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Acute disseminated encephalomyelitis: Treatment guidelines

Alexander M., J. M. K. Murthy¹

Department of Neurological Sciences, Christian Medical College, Vellore, ¹The Institute of Neurological Sciences, CARE Hospital, Hyderabad, India

For correspondence:

Dr. Alexander Mathew, Professor of Neurology, Department of Neurological Sciences, Christian Medical College, Vellore, Tamil Nadu, India

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Introduction

Acute disseminated encephalomyelitis (ADEM) is a monophasic, postinfectious or postvaccinal acute inflammatory demyelinating disorder of central nervous system (CNS).^[1,2] The pathophysiology involves transient autoimmune response directed at myelin or other self-antigens, possibly by molecular mimicry or by nonspecific activation of autoreactive T-cell clones.^[3] Histologically, ADEM is characterized by perivenous demyelination and infiltration of vessel wall and perivascular spaces by lymphocytes, plasma cells, and monocytes.^[4]

The annual incidence of ADEM is reported to be 0.4–0.8 per 100,000 and the disease more commonly affects children and young adults, probably related to the high frequency of exanthematous and other infections and vaccination in this age group.^[5-9] There seems to be no gender predominance.^[10]

Clinical Features

In ADEM, neurologic deficits develop 3–6 weeks following an antecedent event. The onset can be abrupt or may evolve over a period of several days. Prodromal illness may precede the neurologic symptoms.^[10] ADEM can affect any part of the neuraxis and thus the clinical presentation is variable and usually polysymptomatic [Box 1]: altered mental status, pyramidal dysfunction, cerebellar ataxia, brainstem syndromes, optic neuritis, myelitis, and rarely myeloradiculopathy and extrapyramidal syndromes.^[11,12] Seizures are not uncommon, can be focal or generalized. Encephalitic illness is more common in children younger than 3 years. [Box 2]^[12] Rarely ADEM may present with features

of intracranial space occupying lesion, with tumefactive demyelinating lesions.^[13-17]

Certain clinical presentations may be specific with certain infections: cerebellar ataxia for varicella infection, myelitis for mumps, myeloradiculopathy for Semple antirabies vaccination, and explosive onset with seizures and mild pyramidal dysfunction for rubella.^[18,19] Acute hemorrhagic leukoencephalitis and acute necrotizing hemorrhagic leukoencephalitis of Weston Hurst represent the hyperacute, fulminant form of postinfectious demyelination.^[20]

Diagnosis

Cerebrospinal fluid (CSF) is abnormal in about two-thirds of patients and shows a moderate pleocytosis with raised proteins.^[21] Oligoclonal band in CSF is usually absent in ADEM

Box 1: Acute disseminated encephalomyelitis: Clinical syndromes

Most common—polysymptomatic presentation
Site restricted syndromes
Acute cerebellar ataxia
Transverse myelitis
Brainstem syndromes
Optic neuritis (bilateral)
Myeloradiculitis

Box 2: Common clinical and laboratory features of ADEM

Clinical
Mostly monophasic
Antecedent infection/vaccination
Abrupt onset with prodromal symptoms
More common in children and no gender preference
Polysymptomatic
Encephalopathy features are more common
Laboratory
Mild to moderate lymphocytic pleocytosis
Oligoclonal band usually uncommon or transient

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whereas it is a common finding in the CSF in patients with multiple sclerosis (MS).^[22]

Magnetic resonance imaging (MRI) is the imaging modality of choice to demonstrate white matter lesion in ADEM and MS. A recent study in children suggested the presence of any 2 of the MRI features: (1) absence of bilateral diffuse pattern; (2) presence of black holes; and (3) presence of 2 or more periventricular lesions help to differentiate MS from ADEM. The sensitivity and specificity of these criteria was 81% and 95%, respectively. In this study the total number of lesions did not differentiate ADEM from MS but periventricular lesions were more frequent in MS.^[23] A study done to compare the MRI pattern of lesions, which could help to differentiate ADEM from MS found the following characteristics: solitary lesion, unilateral large lesion, cortical lesions, and subcortical grey matter (basal ganglia and thalamus) involvement.^[24] Other studies suggested that bilateral thalamic lesion may be diagnostic of ADEM.^[15,16,25-28]

Differential Diagnosis

Monophasic ADEM has to be differentiated from the first attack of MS. In the absence of a biological marker, the distinction between ADEM and MS cannot be made with certainty at the time of first presentation.^[15] However, certain clinical features are more indicative of ADEM [Box 1 and

Table 1: Differential diagnosis: Acute disseminated encephalomyelitis vs multiple sclerosis

Features	Acute disseminated encephalomyelitis	Multiple sclerosis
Antecedent events	Infections or vaccination	No recognizable infection or vaccination
Clinical characteristics	Meningism, stupor focal signs	Focal signs
Course	Nonprogressive, monophasic	Relapsing and Remitting and/or progressive
MRI features	Diffuse, bilateral symmetrical lesions	Periventricular black holes
Prognosis	Recovery is rapid and often complete	Recovery variable

Table 1].^[15,16] In addition, MRI features may be diagnostic of MS or ADEM. Differentiating ADEM from the first attack of MS is of therapeutic importance as early institution of disease modifying drugs will modify the course of MS.

Site restricted syndromes of ADEM may have to be differentiated from Clinical Isolated Syndrome (CIS) [Table 2]. CIS is characterized by the occurrence of a single, clinical (monofocal presentation), demyelinating event with no clinical evidence of MS lesion in space and time. The most common presentation includes optic neuritis, partial myelitis, brainstem syndromes, or multifocal abnormalities.^[29]

The patient with a CIS would have sustained a first ever clinical demyelinating event, and has 2 clinically silent lesions on T2-weighted brain MRI, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial in the first imaging. The revised MS diagnostic criteria are of great value as it enables one to make an earlier diagnosis of MS, based on the development of new lesions on MRI brain, despite the absence of a new clinical event. The MRI brain can predict the conversion to clinical definite MS (CDMS) one cohort study had shown that 88% of patients with an abnormal scan experienced a second event, whereas only 19% of patients with a normal initial scan converted to MS.^[30] Most patients with CIS develop either CDMS or new brain MRI-confirmed lesions within a very short period of 18 months, and the presence of gadolinium-enhancing lesions or meeting MS MRI diagnostic criteria further increases this likelihood.^[31] The diagnostic criteria of CIS are heavily weighted on imaging features.

In the Optic Neuritis Treatment Trial, the risk of conversion to MS at 10 years is 22% in patients who have a normal imaging of the brain, and 56% in patients with an abnormal brain imaging. O' Riordan *et al* found that in patients presenting with optic neuritis, transverse myelitis, and brain stem syndromes, along with an abnormal MRI of brain, had a risk of 83% going on to develop MS at 10 years, while those with a normal brain MR had only a 11% risk.^[32]

CSF oligoclonal bands (OCBs) in CIS showed a sensitivity of 91.4% and specificity of 94.1%.^[33] Masjuan *et al* found that 32/33 patients with OCBs went on to develop MS in 6 years, whereas only 3/19 patients without OCBs went on to develop MS.^[31]

Table 2: Site restricted syndromes of acute disseminated encephalomyelitis and clinically isolated syndrome

Acute disseminated encephalomyelitis	Clinically isolated syndrome
Postinfectious/vaccineal	No antecedent events
Polysymptomatic	Mostly monosymptomatic
Restricted forms can occur	Restricted form
Bilateral optic nerve involvement	Unilateral optic nerve
PNS involvement	No PNS involvement
Long segment of spinal cord involvement	Restricted partial cord
CSF: lymphocytic pleocytosis with raised Protein	Not often
Usually monophasic	Risk for subsequent MS is high
Could have relapse/recurrence (multiphasic ADEM)	Risk for MS

PNS, Peripheral nervous system; ADEM, Acute disseminated encephalomyelitis; Bilateral, CSF, Cerebrospinal fluid.

Treatment

Spontaneous improvement has been documented in patients with ADEM.^[34] However, the recovery is incomplete in patients with ADEM not receiving any form of immune modulation treatment. No therapy has been established by controlled trials in ADEM. Use of high-dose steroids, plasma exchange, and intravenous immunoglobulin are based on the analogy of pathogenesis of ADEM with that of MS.^[35,36]

Treatment of ADEM includes: (1) supportive, and (2) specific—high-dose intravenous methyl prednisolone, intravenous immunoglobulin (IVIg), and plasma paresis, and (3) physical and rehabilitation therapy [Figure 1].

Supportive Care

Supportive care includes airway protection in patients with altered mental status and mechanical ventilation if required. Patients with cervical myelitis may require mechanical ventilation. Other supportive includes: antiepileptic medication in patients with seizures, correction of fluid and electrolyte disturbances, and prophylactic anticoagulation for prevention of deep vein thrombosis in patients with high risk.

Immunomodulation

Intravenous methyl prednisolone is the first-line drug (10–30 mg/kg/day, up to a maximum of 1 g/day) for 3–5 days are being used (Class IV).^[3,4,12,37,38] With this modality of treatment, full recovery has been reported in 50%–80% of patients. Methylprednisolone-treated patients had significantly better outcome with respect to disability status when compared with those treated with dexamethasone.^[39] Oral corticosteroid treatment is continued with gradual tapering over 6 weeks to reduce the risk of relapses. However, these regimens are not based on controlled randomized trials. The role of corticosteroids in patients presenting late in the course of the disease is questionable. Any type of vaccination should be avoided during the first 6 months following recovery.

If high-dose corticosteroids fail, the next step will be plasma exchange (PE) and there is Class Ib evidence for PE.^[40-42] A course of 4–6 PEs have been shown to be associated with moderate to marked and sustained improvement. One could remove a large volume of plasma per exchange if there are no problems of autonomic dysfunction. Predictors associated with improvement include male sex, preserved reflexes, and early initiation of treatment.^[39,40] In centers that do not have this facility for conventional PE, one could modify and improvise to do a small volume manual plasma exchange—by doing a phlebotomy, centrifuging the blood, remove 250–300 mL of plasma and return the cells. One could do this twice a day for 7–10 days.^[43]

Intravenous immunoglobulin (IVIg) (0.4 gm/kg/day for 5 days) is another option, but there is a constraint of high cost and the evidence for this modality of treatment in ADEM is Class IV.^[44] The improvement is seen within 2–3 days.^[45-47] In the absence of randomized controlled trials and with the available evidence, either plasma exchange or IVIg, could be

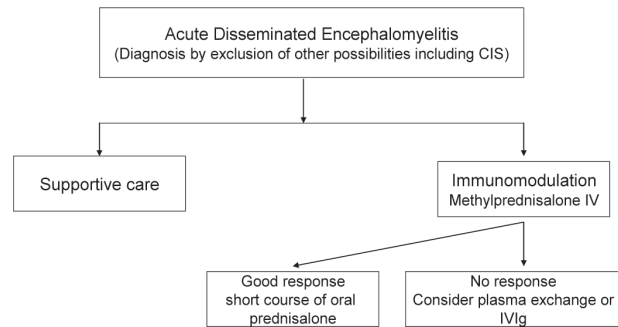


Figure 1: Treatment algorithm- acute disseminated encephalomyelitis

the second-line treatment, when corticosteroids fail. The choice of second-line treatment should be individualized, depending on the severity of the disease, complications, and comorbidities. For example, autonomic dysfunction and hypotension would preclude the use of PE.^[42] Anecdotal reports suggest that IVIg may be more effective in patients with peripheral nervous system involvement and PE in patients with tumefactive demyelination. Methyl prednisolone along with IVIg has been successfully used in patients with atypical features and could be tried for fulminant, aggressive, and atypical disease.^[48]

Cyclophosphamide^[10] and hypothermia^[49] have been used with success in patients with fulminant ADEM. Decompressive hemi-craniectomy has been reported to be life saving in patients with massive life-threatening cerebral edema refractory to conventional medical management.^[50,51]

Relapsing/Recurrence/Multiphasic Acute Disseminated Encephalomyelitis

Although ADEM is typically a monophasic illness, occasionally it can have biphasic or multiphasic course. Different terminologies have been used for an event that occurs within 4 weeks of treatment or within the first 3 months, relapsing ADEM. However, some researchers view new event temporally related to the initial disease process, and thought to be related to early steroid withdrawal and hence terminology steroid dependent or pseudo-relapsing ADEM.

If there is another event 4 weeks after steroid withdrawal or 3 months after the first episode, and if both clinically and radiologically, the same site is involved, this entity is called recurrent ADEM.^[52] But there needs to be a prerequisite that this patient was in complete remission or as in a stable plateau phase of incomplete remission. If one or more ADEM relapses occur, including encephalopathy and multifocal deficits occur, involving new areas of the neuraxis on MRI and neurologic examination, this entity is multiphasic ADEM.^[53] If only the imaging criteria are used these entities would fulfill the criteria for MS and hence these patients need to be referred to a tertiary center with expertise in management of these problems. The present evidence suggests that these episodes are probably related to the ongoing active disease and the autoimmune disease is probably due to persistent antigen/epitope progression and these episodes occur in relation to the initial episode.

Prognosis

Earlier studies reported a mortality rate of 20% with a high incidence of neurologic sequelae in those who survived probably it was related to high incidence of postmeasles ADEM.^[8] However, recent studies suggest a favorable prognosis.^[2,24,54] Prolonged altered mental state was associated with both mortality and morbidity. Multiple or single extensive lesions on MRI lesions may be associated with disability.^[18]

The long-term prognosis of this entity depends on the etiology, with postmeasles patients having a higher mortality rate and significant morbidity in survivors. The prognosis of nonmeasles cases is favorable and most studies report a full recovery in 50%–75% of patients, in a period of 1–6 months after the illness.^[3,4] The most common sequelae are focal motor deficits, could range from mild ataxia to hemiparesis. The principal determinants for the extent of neuronal and axonal damage are duration and severity of inflammation in brain and spinal cord. A hyperacute onset, severe neurologic deficits as a result of aggressive disease, and unresponsiveness to steroids are poor prognostic indicators.

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AIAN guidelines for management of common neurological disorders

Why guidelines? This may be the question many people would ask. The fact is many common neurological diseases are commonly treated by primary care physicians, eg. Stroke, headache, Neuroinfections, Parkinson's disease, etc. Often, it is not possible for them to keep up with the changing trends, both in the diagnosis and management. It would benefit both the patients and treating physicians if they have updated information with the current practice guidelines. With this thought in mind, it was planned, during my tenure as President of IAN, to bring out the "Guidelines for management of common neurological disorders." Fortunately, IAN already has subsections in various disciplines, wherein a group of dedicated people have taken interest in the topic and are updated with the advances. The guidelines have been contributed by experts in respective fields. The guidelines for epilepsy are already published by Indian Epilepsy Society as "Guidelines for Epilepsy Management in India" (Gemind). Hence, this topic is not covered here. I thank all the contributors for their cooperation, interest and the hard work they have put in bringing out this issue. I thank all the convenors of subsections - Drs. Madhuri Behari, J M K Murthy, U K Mishra,

Kameshwar Prasad, Ravishankar and Uday Muthani. The Editor of AIAN, Dr. Sanjeev Thomas, has been kind enough to give the finishing touches to the various articles and bring it up as per the requirement of the journal. I also thank Dr. C Meshram, Honorary Secretary of IAN, for his cooperation and interest in bringing out this issue.

The entire guidelines are being published as a special issue which can be a ready reckoner for the practicing neurologists and physicians. Finally guidelines remain just that – as guidelines – not as a gospel truth! They only guide the physician to take appropriate decision for that individual patient.

H. V. Srinivas

Supplement Editor

Sagar Hospital, 30th Cross, Tilaknagar, Jayanagar,
Bangalore 560 041. Email: hvsrinivas@vsnl.com

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Assessment and management of orthostatic hypotension in Parkinson's disease

The autonomic nervous system controls vital body functions, namely, the heart rate, blood pressure, bladder and genital functions, through the sympathetic and parasympathetic nervous systems. Dysfunction of the autonomic nervous

system in Parkinson's disease (PD) presents as postural or orthostatic hypotension (OH) or impaired urinary, genital, bowel or sweating functions. OH is the hallmark of failure of the sympathetic nervous system. The sympathetic nervous system maintains the blood supply to the brain by keeping the blood pressure (BP) against gravitational stress while standing. Autonomic failure occurs in different Parkinsonian disorders, namely, PD, multiple system atrophy and diffuse Lewy body disease.

Definition of Orthostatic Hypotension

OH is defined as fall in systolic blood pressure (SBP) of 20 mm Hg or more or diastolic blood pressure (DBP) of 10 mm Hg or more on standing or head-up tilt to at least 60°. Measuring BP in supine position alone can be misleading, as patients with OH can misleadingly have supine hypertension.

Clinical Profile

OH occurs in 50.3% of PD patients with the Posture and Gait instability (PIGD) phenotype. It is also common in older patients taking large doses of dopaminergic medications. Parkinsonian patients with OH should be asked for presence of bladder and erectile dysfunction. Patients with OH complain of postural dizziness and light-headedness because of transient fall in cerebral blood flow, but these orthostatic symptoms are poor indicators of OH in PD. This makes it mandatory that all PD patients should undergo BP recording in lying and standing positions even when they do not complain of orthostatic symptoms.^[1] OH in PD is often asymptomatic as autonomic failure possibly because it develops gradually.

Drugs used to treat PD including L-Dopa and other dopaminergic medications can both cause or worsen BP falls in the supine [Levodopa-induced Supine Hypotension (LISH)] and standing positions [Levodopa-induced orthostatic hypotension (LOH)].

Testing

OH is tested at the bedside by recording a change in BP of the patients while they are standing for 3 minutes after they are in the supine position for 3 minutes.^[2] If the patient has difficulty to stand, change in BP can be checked on changing from supine to sitting positions. OH is tested in the laboratory using a tilt table. OH is defined as a fall of SBP by >20 mm Hg or DBP by >10 mm Hg or both. An increase in heart rate in the presence of OH suggests a normal parasympathetic nervous system.

Management^[3]

It is important to recognize and manage OH as doing this Parkinson's Disease reduces morbidity and mortality in PD. It is essential to educate patients, their family, and caregivers to reduce falls occurring because of OH. In patients with mild OH, non-pharmacological methods like avoiding sudden standing after prolonged rest in the supine position might be enough. Elderly PD patients should be advised not to pass urine while standing. Alcohol and medicines might worsen OH; therefore, it is important to check all medicines they are taking. They should avoid foods rich in carbohydrates. It is helpful to increase the head end of bed by 20° while sleeping. Taking small meals at frequent intervals will avoid postprandial OH. Patients with OH should take 5 g of common salt divided through the day. Exercising the calf muscles by walking or cycling can help to prevent BP falls. In the presence of severe OH, calf muscle exercises using a reclining bicycle can be helpful. Elastic stockings are helpful but could be uncomfortable in warm weather.

Pharmacological methods

It is essential to check and adjust dopaminergic medicines as they can worsen OH. The first choice of drug to use is Fludrocortisone. The next choice is sympathomimetic drugs like ephedrine or midodrine. It is important to start them at a low dose and increase the dose slowly.

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Bell's palsy: Treatment guidelines

J. M. K. Murthy, Amrit B. Saxena

Department of Neurology, The Institute of Neurological Sciences, CARE Hospital, Hyderabad, India

For correspondence:

Dr. J. K. Murthy, The Institute of Neurological Sciences, CARE Hospital, Hyderabad - 500034, India. E-mail: drjmk@sol.net.in

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The most common cause of acute onset unilateral peripheral facial weakness is Bell's palsy. The incidence of Bell's palsy is 20-30 cases for 100,000^[1] and accounts for 60-70% of all cases of unilateral peripheral facial palsy.^[2] Either sex is affected equally and may occur at any age, the median age is 40 years. The incidence is lowest under 10 years of age and highest in people over the age of 70. Left and right sides are affected equally.^[3]

Clinical Characteristics

Bell's palsy is an acute peripheral facial weakness of unknown cause and the diagnosis can be established without difficulty in patients with unexplained unilateral isolated facial weakness. The onset is sudden and symptoms typically peak within a few days. Additional symptoms may include pain in or behind the ear, numbness or tingling in the affected side of the face usually without any objective deficit on neurological examination, hyperacusis and disturbed taste on the ipsilateral anterior part of the tongue.^[1] Bilateral idiopathic facial palsy occurs less frequently than unilateral involvement. About 7% of patients with history of Bell's palsy may experience recurrence. The mean interval to first recurrence is reported at 9.8 years after the first episode.

Diagnosis

The first step in the diagnosis is to determine whether facial weakness is central or peripheral. Peripheral facial palsy involves all the facial muscles ipsilateral to the side of facial nerve involvement where as central weakness involves lower facial muscles contralateral to the lesion in the brain stem above pons and cerebral hemisphere.

Bell's palsy is differentiated from other causes of facial palsy such as diabetes mellitus, human immunodeficiency virus (HIV) infection, Lyme disease, Ramsay Hunt syndrome

(peripheral facial palsy with zoster oticus), sarcoidosis, Sjogren's syndrome, parotid-nerve tumors, leprosy, polyarteritis nodosa and amyloidosis, by its rapid onset over several hours. Facial palsy secondary to other causes progresses over days to months.

Diagnostic Workup

Diagnosis of Bell's palsy in a patient with unilateral peripheral facial weakness of unknown cause is purely clinical. However, electrodiagnostic testing done within 14 days of onset may provide prognostic information.

The *nerve excitability test* determines the excitation threshold by recording the minimum electrical stimulus required to produce visible muscle contraction. A difference greater than 3.5 mA between affected and unaffected sides is considered to be significant in terms of poorer outcome. Measuring the peak-to-peak amplitude of the evoked compound action potential of the involved side compared to the normal side has prognostic importance. If there is a 90% or greater reduction in the amplitude of the affected side, the prognosis is poor.^[4]

Currently the *trigeminal blink reflex* is the only test to measure intracranial pathway of the facial nerve and also useful test to study various postparalysis sequelae such as synkinesis and hemifacial spasms. With recovery of facial function the ipsilateral R1 latency becomes less prolonged and the amount of initial prolongation of this response correlates with greater loss of facial motor function.

Gadolinium contrast magnetic resonance (MRI) study reveals enhancement of internal acoustic meatal segment on the affected side; however, this is a non-specific finding. MRI should not be done routinely and should be the investigation to look for other possible causes for acute facial paralysis especially if there is little or no recovery of function.

Treatment

The aims of treatment in the acute phase of Bell's palsy include strategies to speed recovery and to prevent corneal complications. Eye care includes eye patching and lubrication, lubricating drops should be applied frequently during the day and an eye ointment should be used at night.^[5] Strategies to speed recovery include physical therapy, corticosteroids and antiviral agents [Figure 1].

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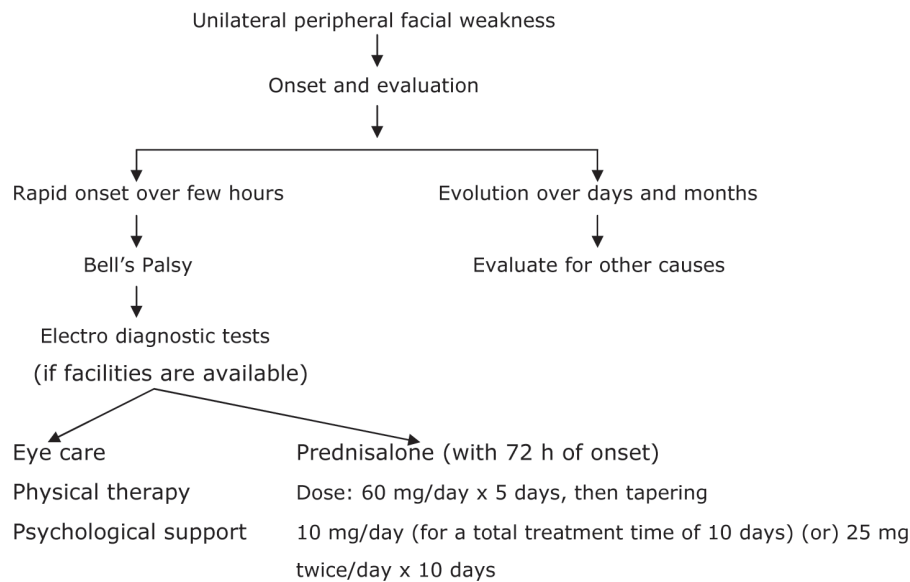


Figure 1: Bell's Palsy: Treatment algorithm

Prednisolone

The rationale for the use of corticosteroids in acute phase of Bell's palsy is that inflammation and edema of the facial nerve are implicated in causing Bell's palsy and corticosteroids have a potent anti-inflammatory action which should minimise nerve damage and thereby improve the outcome.

Randomized, double-blind, placebo-controlled trials have provided compelling evidence that treatment with prednisolone improves outcome in patients with Bell's palsy and shortens the time to complete recovery.^[6-8] Prednisolone should be used in all patients with facial palsy of less than 72 h duration who do not have contraindications to steroid therapy. The prednisolone dose used was 60 mg per day for 5 days then reduced by 10 mg per day (for a total treatment time of 10 days)^[8] and 50 mg per day (in two divided doses) for 10 days.^[7] The reported adverse rates were low. Treatment with prednisolone is likely to be cost-effective.^[9]

Antiviral Agents

The rationale for the use of antiviral agents is the evidence that the inflammation of the facial nerve in Bell's palsy might be related to the herpes simplex virus (HSV). In an autopsy study latent HSV type-1 has been isolated from the majority of the geniculate ganglia samples.^[10] HSV-1 genome was detected in 79% of facial nerve endoneurial fluid in patients with Bell's palsy, but not in the controls.^[11] However, the benefit of acyclovir or valacyclovir, either as single agents or in combination with prednisolone in Bell's palsy has not been definitively established.^[6-8,12,13] Thus with the available evidence acyclovir or valacyclovir should not be routine and treatment with acyclovir is highly unlikely to be considered cost-effective.^[9]

Physical Therapy

In Bell's palsy various physical therapies, such as exercise, biofeedback, laser, electrotherapy, massage and thermotherapy are used to hasten recovery. However, the evidence for the

efficacy any of these therapies, is lacking. Cochrane systemic review of the efficacy of physical therapies, electrostimulation and exercises, on outcome of Bell's palsy concluded that there was no significant benefit or harm from any of these physical therapies for Bell's palsy. There was limited evidence that improvement began earlier in the exercise group.^[14] Another systematic review examined the effects of facial exercises associated either with mirror or electromyogram/biofeedback with respect to complications of delayed recovery in Bell's palsy and concluded that because of the small number of randomized controlled trials, it was not possible to analyze if the exercises, were effective.^[15] However, that the possibility that facial exercise reduces time to recover and sequelae needs confirming with good quality randomised controlled trials.^[14]

Prognosis

About 71% of patients with Bell's palsy have motor function recovery completely within 6 months without treatment.^[16,17] By 6 months all patients with Bell's palsy should show some improvement.^[17] Poor prognostic factors include: old age, hypertension, diabetes mellitus, impairment of taste and complete facial weakness.^[18] About one-third of patients may have incomplete recovery and residual effect. Among the residual effects include post-paralytic hemifacial spasm, co-contracting muscles, synkinesis, sweating while eating or during physical exertion. The two most common abnormal regeneration patterns are: 'crocodile tears' - lacrimation of the ipsilateral eye during chewing and 'jaw-winking' - closure of the ipsilateral eyelid when the jaw opens.

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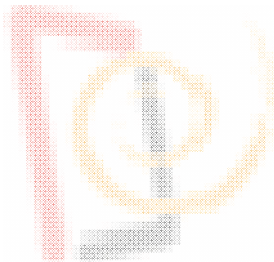
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Cerebral malaria and bacterial meningitis

U. K. Misra, J. Kalita, S. Prabhakar¹, A. Chakravarty², D. Kochar³, P. P. Nair

Department of Neurology, SGPGIMS, Lucknow, ¹PGIMER, Chandigarh, ²Vivekananda Institute of Medical Sciences, Kolkata, ³Department of Medicine, S.P. Medical College, Bikaner, Rajasthan, India

For correspondence:

Dr. UK Misra, Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareilly Road, Lucknow- 226 014, India E-mail: drukmisra@rediffmail.com / ukmisra@sppgi.ac.in

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Malaria is one of the most common treatable and preventable infectious diseases in the world; and 300–500 million malaria cases occur annually, leading to 1.5–2.7 million deaths in tropical countries. About one-third of these cases occur in Asia. In hyperendemic area, most of the children acquire infection by the age of 5 years. Children younger than 6 months enjoy immunity from their mothers. In India the disease occurs in all the agegroups.

Most clinicians would consider any manifestation of cerebral dysfunction in a patient with malaria as cerebral malaria. These manifestations include impairment of consciousness (confusion, delirium, obtundation, stupor, or coma), convulsions, focal neurologic deficit, and psychosis. These abnormalities can as well be due to hypoglycemia or high fever only. Hence a precise definition has been recommended, which has been summarized in Box 1.

Clinical Picture

The mean incubation period is 12 days but it may be as short as 6–12 h in children and non immune person. The prodrome comprises of malaise, headache, and myalgia; chill usually precedes the fever. High fever of 104–105°F, shaking chills, rigors, and sweating are typical of malaria but the patient may have irregular pattern or continuous fever as well. Rarely a patient may have hypothermia due to shock and endotoxemia. Fever in *P. falciparum* malaria occurs every 3rd day but may not be obvious because of multiple exposures and several cycles of parasitemia. Nausea, vomiting, abdominal pain, tachycardia, arthralgia, weakness, muscle tenderness, hepatosplenomegaly, and chest rales may occur in some patients. Seizures may be focal or generalized, occurring more commonly in children

(70%) compared to adults (20%), and some patients may have status epilepticus. Rarely meningismus, focal neurologic signs (aphasia, hemiplegia, ataxia, chorea, and tremor), and neuro-ophthalmologic signs (gaze deviation, oculomotor palsy, nystagmus, and ocular bobbing) may be present. Retinal hemorrhage may occur in 15% of patients. The systemic manifestations of severe malaria complicate the clinical picture and include severe anemia, renal failure, jaundice, pulmonary edema, adult respiratory distress syndrome, hypoglycemia, hemoglobinuria, secondary infection, and septicemia. The presence of multi-organ dysfunction adversely affect the prognosis.

The cerebral malaria has a mortality of 20%–50%, which is higher in children. Poor prognostic predictors are the level of consciousness and presence of other organ dysfunction. Recurrent seizures, absent corneal reflex, decerebration, retinal hemorrhage, age < 3 years, heavy parasitemia, (>20%), peripheral leukocytosis presence of pigmented polymorphonuclear leucocytes (>5%), lactic acidosis, elevated CSF lactate and serum transaminase, and low antithrombin III level are associated with poor prognosis. Those who survive usually have complete recovery. Transient neurologic sequelae occur in 10%–18% being higher in children and include ataxia, hemiparesis, memory disturbance, visual field defects, cognitive impairment, and behavioral abnormalities, which

Box 1: Definition of cerebral malaria

Practical definition

Any impairment of consciousness or convulsion in a patient of malaria.

Research definition (requires 1 – 3 ± 4).

1. Unarousable coma, Glasgow Coma Scale < 10/14 in adults and Blantyre coma scale < 2 in children (and not after a generalized convulsion and not reversed by correction of hypoglycemia.)
2. Asexual forms of *P. falciparum* in blood smear.
3. Exclusion of other causes of coma by history (eg, encephalitis, metabolic encephalopathy, septic encephalopathy, intracranial mass lesion, toxicity, and trauma) by cerebrospinal fluid (CSF) and other relevant examinations.
4. Fatal cases only: confirmation of typical brain histopathology sequestered infected RBCs in postmortem needle biopsy.

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generally reverse in 4–8 weeks. A postmalaria neurological syndrome characterized by acute onset of confusion, seizure, ataxia, myoclonus, tremor, and aphasia is described in patients successfully treated for cerebral malaria in the absence of parasitemia. This syndrome is attributed to immunologic mechanisms as it responds to corticosteroids.

Diagnosis

Diagnosis of cerebral malaria requires demonstration of asexual form of *P. falciparum* in peripheral blood smear, in thick and thin blood smear films stained by Giemsa stain. Absence of parasites in some patients may be due to sequestration of parasitized RBCs in cerebral circulation or earlier treatment with antimalarial drugs. In such a situation, at least 3 smears 6 h apart should be examined. At least 3 smears should be negative before excluding cerebral malaria. The rapid diagnostic test (antigen detection test) and PCR may be helpful.

CSF examination is necessary to exclude other causes of febrile encephalopathy. CSF is generally normal in cerebral malaria, however, mild pleocytosis (10–50 cells/mm³) and protein rise up to 200 mg/dL may be seen. CT and MRI are usually normal or show edema and cortical or subcortical infarcts in watershed zone in 15%–20% patients. EEG shows nonspecific abnormalities, such as diffuse slowing, spike wave discharges, and burst suppression pattern. Cerebral malaria may occur rarely with negative blood smear; therefore a high index of suspicion is required.

Treatment

Cerebral malaria is a neurologic emergency requiring urgent intervention. In endemic area, treatment should be started without waiting for confirmation of the diagnosis. The treatment includes specific antimalarial therapy, supportive therapy for multiorgan dysfunction, and management of associated complications. The drug of choice for cerebral malaria is parenteral artemisinin derivatives or quinine because of widespread resistance to chloroquine. Artesunate has been reported to reduce mortality by 34.7% compared to quinine in a randomized controlled trial in Asian adults. It also reduced the occurrence of convulsion, coma and hypoglycemia. The dose schedule of antimalarial drugs is presented in Box 2. In patients with cardiac disease and in older people, QTc interval should be monitored and quinine should be discontinued if QTc interval exceeds 25% of the basal value. Once the patient can swallow orally he can be switched to oral therapy. In renal and hepatic dysfunction the dose of antimalarial should be reduced after 48 h. In patients undergoing hemodialysis or hemofiltration, dose adjustment is not necessary.

Artemether and artesunate are advantageous because of low toxicity, ease of administration, and greater efficacy. Artesunate, which is water soluble has the advantage of i.v. or i.m. administration and does not produce hypotension or hypoglycemia. In cerebral malaria mefloquine is not preferred because of neuropsychiatric complications. In patients with hyperparasitemia more than 20%, exchange transfusion is recommended.

Complications of malaria, such as adult respiratory distress syndrome, renal failure, convulsions, jaundice, severe anemia,

hypoglycemia, disseminated intravascular coagulation, and shock, need special attention. Corticosteroids are not beneficial and although phenobarbitone reduces the seizures, it increases mortality specifically in children. Intensive care management using artificial ventilation, hemofiltration or hemodialysis may significantly improve the outcome.

Bacterial Meningitis

Acute bacterial meningitis (ABM) refers to inflammatory response to bacterial infection of pia-arachnoid and CSF of the subarachnoid space. In view of the continuity of subarachnoid space over the brain, spinal cord, nerve roots, and nerves, these structures may also be affected. ABM occurs throughout the world, although its precise figures are not available in various Asian countries, its mortality and morbidity is likely to be higher in the developing countries. Worldwide there are 3 main pathogens responsible for ABM: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, which account for 75%–80% patients with ABM after the neonatal period. During the neonatal period, the major pathogens responsible for ABM are group B streptococci, *Escherichia coli*, and other enteric bacilli and *Listeria monocytogenes*.

The most common organisms causing bacterial meningitis are *S. pneumoniae*, *S. meningitidis*, and *H. influenzae*, which spread by droplet or exchange of saliva. Microbial adherence to mucosa, invasion of mucosal barrier, bacteremia, tissue tropism, and host defence mechanisms determine the invasive nature of the microbial disease. The pathogens colonizing the nasopharynx when cause bacteremia and breach the blood–brain barrier, it results in bacterial meningitis. Meningitis can also occur due to parameningeal infection, after traumatic or surgical disruption of blood–brain barrier and rupture of cerebral

Box 2: Treatment of severe falciparum malaria (WHO 2010)^[1]

- Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment (artesunate or quinine) should be started without delay.
- For adults, artesunate 2.4 mg/kg (reconstitute with 5% bicarbonate immediately before infusion) IV or IM given on admission, then at 12 h and 24 h, then once a day. Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg IM given on admission then 1.6 mg/kg per day; or quinine 20 mg salt/kg on admission (IV infusion given in 4 hrs), then 10 mg/kg every 8 h.
- Once the patient can take oral therapy the further treatment should be as below
 - Patient receiving parental quinine should be treated with oral quinine 10mg/kg three times a day to complete a course of seven days along with doxycycline 3mg/kg/day for 7 days (Doxycycline is contraindicated in pregnant women and children under 8 years of age and they should receive clindamycin 10mg/kg every 12 h for 7 days).
 - Patient receiving artemisinin derivative should get full course of oral ACT (artemether plus lumefantrine, or artesunate plus sulfadoxine-pyrimethamine) for 3 days.
- In pregnant women IV quinine is drug of choice for first trimester whereas IV artesunate is drug of choice in 2nd and 3rd trimester.

abscess into the subarachnoid space. The leptomeningeal inflammation results in hyperemia of meningeal venules and capillaries and increases permeability of these vessels, resulting in exudation of protein and migration of neutrophils into pia- and subarachnoid spaces.

Clinical features

The classical clinical picture of adult bacterial meningitis includes headache, fever, neck stiffness, and often with cerebral dysfunction in 65% patients. Nausea, vomiting, myalgia, and photophobia are also common. The meningeal signs (neck stiffness, Kernig's or Brudzinski's) are present in 50% adult patients and less commonly in neonates and older people. Absence of meningeal signs does not rule out the diagnosis of bacterial meningitis. Cerebral dysfunction manifests with confusion, delirium, and declining consciousness ranging from lethargy to coma. Seizures occur in 40% patients. Focal neurologic deficit (hemiparesis, monoparesis, or aphasia) may develop due to cortical or subcortical infarction or ischemia, increased intracranial pressure (ICP), or associated subdural empyema. Neurologic deficit and seizures are more common in pneumococcal compared with *H. influenzae* or meningococcal meningitis. Papilledema is rare and should suggest an alternative diagnosis, such as brain abscess. In neonates, classical features of meningitis may be replaced by listlessness, shrill cry, refusal to feed, irritability or other nonspecific manifestations. In older people, the onset may be gradual with lethargy and obtundation with or without meningeal signs or fever. A high index of suspicion and low threshold for performing lumbar puncture is recommended.

Certain clinical features suggest specific diagnosis, such as prominent rash in extremities in meningococcemia, *Staphylococcus aureus*, *Acinetobacter* spp., and rickettsioses. Pneumonia and otitis media or sinusitis is found in 30% patients with pneumococcal or *H. influenzae*. *S. pneumoniae* is the causative organism for bacterial meningitis due to CSF rhinorrhea or otorrhea. *Listeria*, gram-negative bacilli and group B streptococci may result in encephalitis in extremes of age.

Diagnosis

Diagnosis of bacterial meningitis is based on CSF examination. Prompt blood culture and CSF examination are indicated in all the patients with suspected meningitis. Cranial CT scan before lumbar puncture is indicated when focal findings, altered sensorium, or evidence of raised intracranial pressure are present. When CT scan is not available, blood culture should be drawn and empiric antibiotic therapy should be started.

CSF examinations

Bacterial meningitis reveals raised CSF pressure (20–50 cm of water); protein (100–1000 mg/dl), marked pleocytosis (1000–10,000/mm³, >60% neutrophils) and reduced glucose (<40% of serum glucose). CSF Gram stain is positive in at least 60% of patients and CSF culture in 75%, which may be reduced to 5%–40% if antibiotics were administered before lumbar puncture. For rapid specific diagnosis, latex particle agglutination or counter immunoelectrophoresis may be used if available. A careful Gram stain of CSF is usually sufficient and should be encouraged in developing countries where PCR and other tests may not be available.

CT or MRI may be normal or reveal meningeal enhancement, cerebral edema, communicating or obstructive hydrocephalus, infarction or venous sinus thrombosis.

The patients with bacterial meningitis should be differentiated from viral, tubercular, fungal or parasitic meningitis, subarachnoid hemorrhage and carcinomatous meningitis. If the meningeal signs are less prominent cerebral or epidural abscess, subdural empyema and viral encephalitis should be considered.

Treatment

Antibiotic therapy should be started promptly because delay results in poor outcome of ABM. The selection of antibiotics depends on local resistance pattern, clinical setting in conjunction with allergies, and CSF results. When lumbar puncture is delayed or Gram stain results are inconclusive, empiric therapy is indicated, which is presented in Table 1. Ampicillin, penicillin G or third-generation cephalosporin are typical first-line agents. Ampicillin covers most pneumococcus, meningococcus, and *Listeria* and third-generation cephalosporins cover gram-negative organisms and ampicillin-resistant *H. influenzae*. In patients with head injury or after neurosurgical procedures, vancomycin should replace ampicillin. Ceftazidime should be reserved for pseudomonas meningitis. When the CSF Gram stain or culture reports are available, the specific antibiotic should be started. If *S. pneumoniae* is of unknown antibiotic sensitivity, vancomycin should be added to third-generation cephalosporin to overcome the emerging penicillin-resistant pneumococcus. Gram-positive cocci are treated with vancomycin and third-generation cephalosporins, gram-negative cocci with penicillin G, gram-positive bacilli with ampicillin and aminoglycoside, and gram-negative bacilli with third-generation cephalosporins and aminoglycoside. The duration of therapy is 7–10 days for meningococcal and *H. influenzae*, 10–14 days for pneumococcal, 14–21 days for *L. monocytogenes* and group B streptococci, and 21 days for gram-negative bacilli other than *H. influenzae*.

Treatment of bacterial meningitis sometimes may extend to include family members, medical personnel, and other

Table 1: Treatment of bacterial meningitis

Age group	Etiology	Antibiotics
0–12 weeks	Group B streptococci <i>Escherichia coli</i> <i>Listeria monocytogenes</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i>	Ceftriaxone 150 mg/kg/d 6 hourly + Ampicillin 50–100 mg/kg/d 4–6 hourly
3 mo to 50 y	<i>S. pneumoniae</i> <i>Neisseria meningitidis</i> <i>H. influenzae</i>	Ceftriaxone 100 mg/kg/d i.v. 12 hourly + vancomycin 1 g 8 hourly, for children 60 mg/kg/day in 4 divided doses.
>60 years	<i>S. pneumoniae</i> <i>L. monocytogenes</i> <i>Aerobic gram-negative bacilli</i>	Ceftriaxone 2 g 12 h + ampicillin 3 g 4–6 hourly + vancomycin 1 g 8 hourly
Postsurgical or post-head injury	<i>Staphylococcus aureus</i> <i>Aerobic gram-negative bacilli</i> <i>S. pneumoniae</i>	Ceftazidime 2 g 8 hourly Vancomycin 1 g 8 hourly

contacts who may require chemoprophylaxis and notification to authorities.

Despite the modern antibacterial therapy, the morbidity and mortality of bacterial meningitis is unacceptably high. Corticosteroid has a beneficial effect in bacterial meningitis as it inhibits the synthesis of proinflammatory cytokines at mRNA level, decrease CSF outflow resistance, and stabilize blood–brain barrier. If the organism is known, corticosteroid co-administration results in greater survival and lower morbidity, especially in *H. influenzae* and pneumococcal meningitis in both children and adults. In a recent meta-analysis, adjunctive dexamethasone in the treatment of ABM, however, did not seem to significantly reduce death or neurological disability. There were no significant treatment effects in any of the prespecified subgroups. The benefit of adjunctive dexamethasone for all or any subgroup of patients with bacterial meningitis thus remains unproven. Seizure and status epilepticus should be promptly treated with phenytoin, lorazepam, or diazepam.

Tuberculous Meningitis

Tuberculous meningitis (TBM) is the most severe form of tuberculosis and is an important cause of death and disability in adults and children, especially in HIV-infected patients. The diagnosis of TBM is based on clinical, CSF, and radiological (CT/MRI) findings, evidence of extra-CNS TB, and additional laboratory findings.

The clinical findings of TBM are nonspecific in the early stage and include fever, headache, irritability, neck stiffness, vomiting, and focal neurologic signs. Altered sensorium, cranial nerve palsies, and limb paralysis are more commonly found in advanced disease. The symptom onset to the time of presentation ranges from 7 to 30 days. History of close contact with TB or extrapulmonary TB should be considered suggestive of TBM.

The diagnosis of TBM depends on CSF examination but CT scan should be done before lumbar puncture if a patient has papilledema, focal signs, altered sensorium, or history of seizure to exclude a pressure cone and avoid possible herniation. CSF in TBM is typically clear, has lymphocytic pleocytosis (10–1000 cells/mm³ with lymphocytic predominance), elevated protein (0.5–3 g/L), and low glucose (CSF to plasma glucose ratio < 50%).

CT or MRI findings are commonly seen in stage 2 and 3 of TBM. Basal meningeal enhancement, hydrocephalus, granuloma, and infarction are common findings and are found in various combinations.

Evidence of extra-CNS TB is obtained by a radiograph of the chest, or a cervical or abdominal lymphadenopathy (on abdominal ultrasonography). Diagnostic sampling of lung, lymph node, liver, bone marrow, ascitic fluid, and gastric aspirate add confidence to the diagnosis of TBM. HIV serology should be undertaken in all patients with TBM.

Other diagnoses, such as cryptococcal meningitis (CSF India Ink and cryptococcal antigen), *treponema pallidum* (*treponema pallidum* hemagglutination assays), cytologic tests for

malignancies, malaria, and toxoplasma should be excluded in appropriate clinical settings.

Treatment

Four-drug antitubercular treatment with RHZE (rifampicin, isoniazide, pyrazinamide, ethambutol) should be initiated as soon as the diagnosis of TBM is suspected. One should start the therapy without waiting for confirmation [Table 2].

In adults ethambutol and in children streptomycin may be preferred. Ethambutol is preferred to streptomycin because of ototoxicity in adults. Four drugs are recommended for initial 2 months; and INH and rifampicin for a total of 9–12 months. In patients who come late or have had incomplete treatment may be treated for 12–18 months. Some patients with tuberculoma may need longer treatment. DOTS (Directly observed therapy short course) has not been sufficiently evaluated in TB meningitis.

Corticosteroids are recommended on the basis of randomized controlled trial (RCT) and meta-analysis. Corticosteroids are recommended in patients without HIV infection. A large RCT-recommended dexamethasone treatment for 4 weeks (0.4 mg/kg/day for 1 week, 0.3 mg/kg/day in week 2, 0.2 mg/kg/day in week 3, and 0.1 mg/kg/day in week 4) followed by oral taper (4, 3, 2, and 1 mg/day for 1 week each). Thus patients received 2 months of corticosteroids. Lower doses of prednisolone 40 mg/day, tapered after 1 month may also be considered. But before administering corticosteroids one must be sure of the diagnosis (exclude cryptococcal, syphilis, toxoplasma, and partially treated septic meningitis) and exclude the patients with HIV, diabetes, bedsores, septicemia, and so on.

Baseline investigations

All the patients after the diagnosis of TBM should be tested for HIV and if positive, CD4 count should be done. High-risk individuals for hepatitis should undergo serology for hepatitis B and C. Baseline serum bilirubin, liver enzymes, platelet, and creatinine should be done. Patients on ethambutol should undergo vision testing and red–green color discrimination test. On subsequent follow-up, routine liver and renal function tests are not needed unless there are baseline abnormalities or symptoms related to liver dysfunctions. On monthly follow-up, the patient should be enquired about visual disturbances (blurring or scotoma) and red–green discrimination if patient is on ethambutol therapy for more than 2 months.

Table 2: Chemotherapeutic options of tuberculous meningitis in adults

Drugs	Dose (mg)	Frequency
Low probability of drug resistance		
Isoniazide	300	Daily
Rifampicin	600	Daily
Pyrazinamide	15–30/kg	Daily
High probability of drug resistance		
INH	300	Daily
Rifampicin	600	Daily
Pyrazinamide	15–30/kg	Daily
Streptomycin	1000	Daily
Ethionamide	15/kg	Daily

Surgery

Surgery has limited but definite role in the management of CNS tuberculosis for secondary complications and when diagnosis is not clear.

Hydrocephalus

Mild to moderate hydrocephalus responds well to medical treatment but surgery is indicated when there is raised intracranial pressure, leading to alteration in sensorium. In a patient with hydrocephalus, ventriculoperitoneal shunt is the treatment of choice. Results of shunt surgery in deeply comatose patients who are decerebrating are poor. In such patients, a preliminary trial of external ventricular drainage may help to distinguish the patients who are likely to benefit from surgery.

At times intracranial tuberculoma may require biopsy and surgery when response to ATT is not adequate or diagnosis is in doubt.

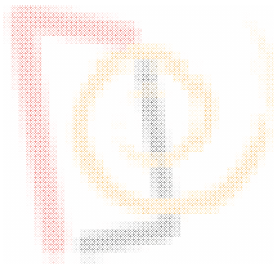
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Constipation in Parkinson's disease

Introduction

Constipation is a common problem in Parkinson's disease (PD),

occurring in about 50–60% of patients and may occur even before the motor symptoms appear.^[1] Various mechanisms causing it are degeneration of neurons in myenteric plexus of colon with presence of Lewy bodies, weakness and incoordinated contraction of muscles of pelvic floor and abdominal muscles which is unable to straighten, anorectal angle preventing passage of stool, dystonic contractions of muscles, megacolon and volvulus.^[2,3]

Principles of management are the following. In early stages, simple measures may be tried, but later on, combinations may be needed.

- Dietary modifications include increased intake of fluids

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(6–8 glasses of water/day), high fiber diet, and plenty of raw vegetables/salads, and bran can be added to increase the bulk.

- Exercise should be increased.
- Medicines that can be helpful include milk of magnesia, Cisapride, Mosapride (5HT₄ agonist/partial 5HT₃ antagonist), enemas, suppositories, stool softeners such as lactulose.

Pain/Dysesthesia in PD

Pain is a common problem in PD and occurs in about 50% of patients. It occurs both in early phase and in advanced stage of disease – more often in off period, but also in on period.^[4,5]

The exact mechanism of pain and dysesthesia is not known, but several mechanisms are proposed. These are:^[6,7] abnormal firing in afferent nerves in dystonic muscles, impaired ability of basal ganglia to modulate sensory information, alteration in serotonergic pathways, decreased activity of dopaminergic fibers on dorsal horn and intermediolateral column of spinal cord and reduced pain threshold due to dopamine deficiency by action on frontal, insular and cingulate gyrus (limbic system) and reduced nociceptive flexion reflex threshold by the same mechanism.

The presentation of pain/dysesthesia includes: painful “frozen shoulder” usually on the side of first symptom, especially before treatment is started (usually early in the disease), off-period limb pain, off-period painful foot dystonia, pain and dysesthesia on chest or abdomen. Some patients may have

mechanical nerve root distribution pain/paresthesia coldness/numbness, arthritis and pain due to bursitis.

The management of these symptoms^[8] is by introduction of dopaminergic therapy with dopamine agonist or levodopa, passive and active exercise and DBS (in advanced stages).

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Dementia in Parkinsonism

Movement disorders originate from malfunctioning of the basal ganglia, whereas dementia is the result of cortical aberrations. Therefore, conceptually, these two disorders are due to involvement of different anatomical areas of brain. But with the passage of time, newer concepts have come up, which eventually explain the co-occurrence of these two seemingly divergent clinical problems. On one hand, with the demonstration of basal ganglia circuit it is now evident that this area has got rich connections with cerebral cortex, particularly prefrontal cortex, through thalamus. On the other hand, newly discovered circuits for cognition have stressed on the role of basal ganglia, particularly the caudate nucleus and thalamus, in different aspects of cognition. The central point in the understanding of dementia in movement disorders is the prefrontal network for attention and the prefrontal cortex, caudate nucleus, and dorsomedial thalamus that form the different components of this network. This network subserves behavioral aspects that require an integration of thought with emotion and motivation, personality, and attention. In terms of the concept of network theory dysfunctions restricted to subcortical components can present with frontal lobe-like features even when the frontal lobe has not been pathologically involved. Apart from this anatomical explanation, there are other possible explanations of dementia in movement disorders. Moreover, biochemically it has been seen that not only are these related to dopaminergic system, but other neurotransmitters, such as acetylcholine and serotonin are also at fault, which explain the cognitive and psychiatric disturbances in movement disorders.

The different parkinsonian syndromes where dementia is a prominent feature include the following:

Parkinson's Disease

When James Parkinson first described the "shaking palsy" in 1817, it was considered as a purely motor system disease. In recent times Parkinson's disease with dementia (PDD) along with dementia with Lewy body (DLB), collectively called Cortical Lewy Body Disease comprises 10%–15% of all degenerative dementia and is only second to Alzheimer's disease (AD) in terms of prevalence.

Lewy body, an intracytoplasmic inclusion containing α -synuclein, is the pathological hallmark of PD and is found in nigral cells. However, it is found in neocortical and paralympic regions in PDD and DLB as well. In contrast to their brainstem counterpart, the neocortical Lewy bodies are smaller, lack

halo, and are difficult to see under routine staining conditions. Moreover, brains of PDD and DLB patients have pathological findings of AD, which is more common than in healthy controls. Biochemically, dopamine deficiency due to nigral degeneration has been implicated for the pathogenesis of dementia. However, loss of noradrenergic input from locus ceruleus and cholinergic input from nucleus of basalis of Meynert are also important for the development of dementia. It is interesting to note that there is more cholinergic deficiency in PDD than AD.

Frequency of dementia in PD varies from 0% to 81% in different studies depending on the associated comorbidity, methodology used, and the criteria used to define dementia. Brown and Marsden in a seminal paper in *Lancet* estimated that it is in the order of 15%–20%, the inordinately high values being attributed to serious methodological flaws.^[1-3] The cognitive disturbances range from specific deficits, demonstrated by formal neuropsychological tests, to overt dementia and there is a continuous spectrum between these two extremes.^[4] There is some evidence of a preclinical phase of dementia, and tests of verbal fluency may be a good predictor of later development of dementia.^[5] The risk factors for the development of dementia in PD are advanced age, treatment-induced visual hallucination, more severe motor symptoms (Unified Parkinson's Disease Rating Scale > 25), development of mania, agitation, disorientation, or psychosis when treated with levodopa, exposure to psychological stress, low socioeconomic status, low education level, and clinical presentation as postural instability gait difficulty variety. Facial masking at presentation has also been observed as a risk factor by some workers.^[6] It has been found that the relative risk of developing dementia with PD is 1.7 as compared with patients without PD. Severity of dementia has been related to bradykinesia, postural and gait disturbances, atypical neurological features of PD, such as early autonomic failure, symmetrical onset, and poor response to levodopa. Some investigators have been able to correlate the severity of disability and the extent of the disease on one hand and the degree of intellectual impairment on the other.^[7-9] Duration of illness has often been implicated in the development of dementia,^[10] although others believe that this is an inconsistent association.^[11] Lieberman *et al*^[7] showed that those who were demented, were at least 5 years older than the nondemented ones, developed the disease later in life and the illness was of brief duration. Importantly, they were poorly responsive to levodopa as well. What emerged from this study was that possibly there are two subsets of patients, where one group suffers predominantly from motor disabilities and are young in age where the progression of the disease is rather slow and the therapeutic response to levodopa is good; the other subset is often termed the motor-cognitive group whose predominant feature is cognitive impairment. Errea *et al* showed that cognitive decline correlated well with low educational level.^[12]

The clinical profile of PDD is one of frontostriatal in nature.^[13,14] Dysphasia, dysphoria, apraxia, and agnosia, which characterize AD, are classically lacking in PDD, while executive dysfunction, visuospatial deficit, large fluctuation in attention, and frequent

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visual hallucination are the significant features. Executive dysfunction is characterized by mental inflexibility and impaired set sifting, whereas visuospatial deficits are in the domain of block designing, picture arrangement, and line orientation.^[15] Visuo-perceptual matching, a feature disturbed in PDD, is retained in AD and selective impairment in the dating of historical photographs is impaired in PD in contradistinction to the inability even to recognize the scenes as well, a feature found in AD.^[16,17] Memory sphere is less involved as compared with AD and when involved it is more of a retrieval deficit in declarative memory and procedural memory. Patients perform better in recognition tasks. Mild language dysfunction may be there and it is characterized by “*tip of the tongue*” phenomenon, decreased naming and fluency, impaired comprehension of syntactically difficult questions and decreased melody of speech.

Dementia with Lewy Body

Cortical Lewy bodies are found in different types of degenerative dementia, which are collectively called as LBD. Clinicopathologically, it encompasses PDD, DLB, and Lewy body variant of Alzheimer's disease (LBV). The last of the three is characterized by cortical Lewy bodies and Alzheimer's type neuropathological changes in the brain and constitutes about 70% of LBD. In different literatures the terms LBD and DLB have been used interchangeably and the term diffuse LBD has been used to denote classical DLB. Because 25%–30% of PD patients develop dementia (PDD) and most DLB patients have parkinsonism, it has been hypothesized that PD, PDD, and DLB are not distinct entities, but may exist along the spectrum of LBD. A DLB/PDD Working Group recently proposed the use of LBD as an umbrella for studying the biology of these disorders, although they also suggested that the three individual terms should be maintained for clinical needs. Consensus criteria artificially divide patients with PDD and DLB by the “*one year rule*” where dementia appears within 1 year of appearance of parkinsonian features in the latter condition.

DLB is the second most common cause of degenerative dementia in the elderly with prevalence up to 30.5% among dementia patients. Pathologically three types of DLB are recognized—brain stem predominant, limbic (transitional), and neocortical.^[18] The areas that are particularly vulnerable to cortical Lewy bodies are hypothalamus, basal forebrain, amygdala, and temporal neocortex. Additionally, A β 42 amyloid plaques are abundant with paucity of tau-positive neuritis as opposed to what is found in AD. Both dopamine and acetylcholine deficiency are implicated in the genesis of dementia in this condition.

DLB consensus criteria has been put forward by McKeith *et al.*^[19] see Table 1.

Impaired visual construction and attention with preserved memory and naming skills distinguish DLB from AD.^[20] Few features are helpful in the diagnosis of probable DLB. Visual hallucination is most specific (90%) for DLB, but its sensitivity is low (22%). Intersecting pentagon test is helpful in mild to moderate dementia (MMSE > 13) to differentiate DLB from AD. Intrusions are more common in DLB.

MRI voxel-based morphometry reveals that DLB has little cortical involvement but does show a discrete cluster of gray matter loss in basal forebrain and dorsal midbrain. Occipital hypoperfusion in SPECT study is found in both PDD and DLB.

Progressive Supranuclear Palsy

It is grouped under the rubric of parkinsonism plus syndrome. The cardinal manifestations are symmetric bradykinesia and rigidity (axial > appendicular) without tremor with predominant vertical supranuclear gaze palsy. Cognitive decline, although less stressed upon, is present in 22% cases at presentation and around 80% in life time. It is predominantly of the frontal subcortical in variety with involvement of executive function and attention.^[21] Executive dysfunction is characterized by impaired set sifting, motor inhibition, verbal fluency, and abstract thinking. Atypical cases are not uncommon who present predominantly with cognitive decline simulating progressive aphasia or frontotemporal degeneration (FTD). Pathologically it is characterized by neurofibrillary tangles, which are composed of aggregates of tau-protein.

Management of Dementia in Parkinsonism

The management of dementia and related problems in Parkinsonism is difficult. One of the chief reasons is that any attempt to ensure mobility with levodopa and related drugs is fraught with the danger of exacerbating mental and behavioral problems and the physician is almost always caught in the cleft stick in order to determine which classes of drugs need to be augmented and which should be restricted so that the subject can lead an optimally healthy life. However, conventional antipsychotics do not work well for the management of the behavioral problems in Parkinsonism and they significantly worsen the motor problems as well.^[22] Of all the atypical antipsychotics clozapine has been shown to superior to others in various placebo-controlled studies. It reduces the positive symptoms of psychosis and there is no worsening of the motor symptoms or global cognition and a recent structured review and meta-analysis concluded that

Table 1: Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)

Central feature (essential for a diagnosis of possible or probable DLB)

- Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but usually is evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.
- Core features (two core features are sufficient for probable and one for possible DLB)
Fluctuating cognition, Recurrent vivid visual hallucination, Spontaneous features of Parkinsonism
- Suggestive features (one core feature + \geq one suggestive feature = probable DLB; \geq one suggestive feature = possible DLB)
REM sleep behaviour disorder
Severe neuroleptic sensitivity
Low dopamine transporter uptake in the basal ganglia

only clozapine can be recommended for the management of drug-induced psychosis in Parkinsonism.^[23-25] Olanzapine, on the other hand, led to significant worsening of the motor symptoms.^[26,27] Trials on quetiapine have not shown any worsening of the symptoms, although some works have doubted the efficacy of this compound for the management of psychosis in Parkinsonism.^[28,29] Aripiprazole, an atypical antipsychotic with partial agonism at D₂ receptors, showed promise as an antipsychotic in Parkinsonism when it was first introduced, but two small open-label studies at varying dosages reported worsening of symptoms or lack of improvement in psychosis.^[30,31] Another recently introduced compound, ziprasidone showed significant overall improvement in total Neuropsychiatric Inventory score and no change in the Unified Parkinson's Disease Rating Scale motor score.^[32]

There is some evidence that cholinesterase inhibitors may have antipsychotic properties for the management of behavioral symptoms in Parkinsonism. A number of open-label studies have documented the beneficial effects of donepezil and rivastigmine in the management of dementia in Parkinsonism. A large placebo-controlled study of rivastigmine found that the rivastigmine group had significant improvement of the neuropsychiatric symptoms than the control group and were less likely to develop hallucinations.^[33] Furthermore, patients who suffered from visual hallucination at the time of initiation of treatment benefited the most.^[34]

The management of psychosis in DLB is equally frustrating and only a prospective randomized study in this regard has been reported to date.^[35] Rivastigmine led to significant improvement in delusions, hallucinations, depression, and apathy; and therefore, cholinesterase inhibitors are now recommended as the first line of management for this condition. Mementine has also been found useful in one small retrospective study.^[36] However, cholinesterase inhibitors can increase tremor in Parkinsonism by their procholinergic actions.^[35]

One of the major problems of management of psychosis and related problems in Parkinsonism is that stopping drugs often lead to worsening of symptoms.^[37] However, some trials show that patients can be switched from clozapine to quetiapine after stability has been earned, provided they responded earlier to the latter agent.^[38]

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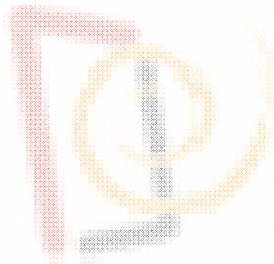
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Guidelines for the use of botulinum toxin in movement disorders and spasticity

Afshan Jabeen, Rukmini M Kandadai, Meena A Kannikannan, Rupam Borgohain

Department of Neurology, NIMS, Punjagutta, Hyderabad, Andhra Pradesh, India

For correspondence:

Dr. Rupam Borgohain, Department of Neurology, NIMS, Punjagutta, Hyderabad, 500082 Andhra Pradesh, India. E-mail: b_rupam@hotmail.com

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Introduction

Botulinum neurotoxin (BoNT) has proved to be a remarkably effective therapy for numerous movement disorders associated with muscle overactivity such as dystonia and related disorders, as well as spasticity [Table 1]. Additional therapeutic benefits accrue from actions such as blockade of acetylcholine release at autonomic nerve analysis as well as the blockade of release of nonacetylcholine transmitters at peripheral nerve endings.

Three broad categories of undesirable side effects are seen with BoNT. These are^[1] diffusion of toxin into neighboring muscles and nerve endings,^[2] sustained neuro-transmission blockade producing effects akin to anatomic denervation, and^[3] development of antibodies to BoNT with subsequent immunoresistance.^[1]

Indications

Most appropriate conversion factor between Botox and Dysport units is less than 3 in cervical dystonia.^[7]

Relative Contraindications

These include any excessive weakness, fixed contractures and neuromuscular disease such as myasthenia gravis, Eaton-Lambert syndrome, and motor neuron disease. Other relative contraindications include pregnancy and lactation and the concurrent use of aminoglycosides.

Assessment

This would include a detailed clinical examination and a video

analysis for later comparative evaluation. Patient education and counseling are essential and treatment goals should be agreed and documented. Consent should be obtained and BoNT should be prescribed. Secondary causes of treatable dystonia such as drugs or Wilson's disease should be ruled out. Physicians administering BTX should have a good understanding of both the anatomy of affected muscles and the resultant movement disorder. EMG monitoring helps diagnose the underlying disorder and identify appropriate muscles for injection.

Goals for Treatment

Dystonia

Treatment of focal dystonia with BoNT is designed to improve the patients' postures and function and to relieve associated pain. BoNT temporarily weakens dystonic muscles, thereby allowing more normal posture and function. The benefits that BoNT conveys to a particular patient depend on the localization and relative degree of severity of the dystonic muscles being injected. The decision to combine injections of BTX-A with other forms of treatment for dystonia is based on associated factors and individual decision.

Blepharospasm

Blepharospasm may be idiopathic or induced by drugs such as l-dopa or neuroleptics. It needs to be differentiated from facial tics in patients with Tourette's syndrome and apraxia of eyelid opening.

The injections are done on an outpatient basis. Intradermal injection with a 27--30-gauge needle is recommended. Typically 3--5 points around each eye are injected. The principle is to avoid the midportion of the upper eyelid to avoid inadvertent diffusion into the levator palpebrae superiors, which would lead to undesirable ptosis.

Focal hand dystonia

Among these, Writer's cramp is the most common form of occupational dystonia. However, these has been described in those professional whose work involves frequent and repetitive movements such as musicians, typists, milkers, cashiers,

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Table 1: Dosage of botulinum toxin for various indications

Indication	Dosage	References
Dystonia		
Blepharospasm	12.5--25 units/eye Botox 50--90 units/eye Dysport	[2-6] [5]
Cervical dystonia (Torticollis)	60--374 units Botox 125--1200 units Dysport 579--19853 units Myobloc	[7-9] [9-11] [9], [12-14]
Oromandibular – facial – lingual dystonia masseters and temporalis	Up to 50 units Botox in each muscle	[15]
Spasmodic dysphonia		
Adductor	15 unilat or 2.5--5 units bilat/TA	[16-20]
Abductor	3.75 units/PCA (unilat) serially	[21]
Focal limb dystonia (including Writer's cramp)	Individualized dosages	[22--28]
Hemifacial spasm	17.5 units Botox 70 units Dysport	[5]
Dystonic tics	Individualized dosages	[29]
Tremors	Hand and neck 50-100 units Botox	[30--32]

cobblers, ticket collectors, and seamstresses. Neurologic evaluation and nerve conduction studies are required to rule out radiculopathy or peripheral nerve involvement such as ulnar neuropathy or median entrapment neuropathy at the rest. Doses used for writer's cramps are 5 U for small muscles and 10–20 U for muscles in the forearm. Benefit has been reported in as many as 80%--90% patients and is usually apparent 5--7 days after injection.

Cervical Dystonia

The movements of the neck – rotation, anterior, and posterior flexion, tilt, and shift in the antero--posterior or lateral planes – can occur in any combination in cervical dystonia. This can be associated with shoulder involvement as well as jerky or tremulous movements and also pain. Muscles involved in the abnormal posturing are isolated using standard anatomic landmarks. The most commonly injected muscles include sternocleidomastoid, trapezius, splenius capitis, levator scapulae, and scalene complex. Usually 2--6 muscles are injected at muscle sites. The BTX should be injected along the belly of the muscle to allow for adequate diffusion. Comella *et al.*^[33] reported a significantly greater magnitude of improvement in those cases where the treated neck muscles were selected by clinical and electromyographic guidance than the cases in which only clinical examination was used.

Oromandibular dystonia

This typically involves the masticatory, lower facial, and tongue muscles and is associated with jaw deviation and spasm. BTX should be injected into the inappropriately contracting muscles in different combinations including masseter, temporalis lateral pterygoids, and submental muscles. The lingual muscles need to be injected carefully.

Laryngeal dystonia

They are three types---adductor spasmodic dysphonia (strained strangled voice), abductor spasmodic dysphonia (whispering voice), and adductor breathing dysphonia (paradoxical vocal fold motion). The thyroarytenoid muscles are located with

EMG guidance, and percutaneous injections of BTX are administered through the cricothyroid membrane. Bilateral injection approach is the most common technique for adductor dysphonia, while for the rarer abductor variety unilateral injections are done serially into the posterior cricoarytenoid muscles.

Hemifacial spasm

This can be a very disabling disease because severely affected individuals are socially handicapped and functionally blind. This can involve any combination of orbicularis oculi, frontalis, risorius, zygomaticus major, and platysma muscles. Injections of BTX are given according to the muscles in spasm which differ from patient to patient.

Palatal Tremor (myoclonus)

This may be idiopathic or symptomatic. BTX injection of the tensor veli palatini muscle may reduce the symptom by reducing the amplitude of myoclonic jerk.

Bruxism

This is an involuntary chewing such as rhythmic jaw movement occurring especially at night, with grinding of the teeth. In this disease, BoNT is injected into the most sore part of the muscle, weakening the most spastic part of the masseter muscle without affecting the ability to chew.

Tics

These can be either motor or phonic tics. Both of these can be simple or complex and also classified as clonic, tonic, and dystonic. BoNT produces significant decrease in both tic frequency and urge to tic. It improves the quality of life as reported by the patients. One has to be cautious of producing hypophonia.

Outcome measurement and follow up

Measurement methods include the use of physical measures, techniques to quantify individual symptoms or benefits, such

as visual analogs scales and verbal scales as well as other rating scales. Follow-up appointment should be at approximately 3–17 weeks post injection using the same assessment as pre injection. It should be assessed again 4–6 months interval.

Spasticity

Symptomatic improvement decreases spasm frequency and relief of pain. There is a reduction of generalized spasticity – it facilitates sitting, and positioning or standing and also allows wearing of orthosis. In functional improvement it improves mobility in terms of speed, quality or endurance of gait, endurance of wheel chair propulsion, improves ease and safety of transfers, dexterity and reaching. There is decrease in burden on care givers such as positioning (e.g., feeding) care and hygiene, e.g., washing and catheterization, dressing, decreases care time to allow quality time. In prevention of complications, it prevents unnecessary use of antispasmodic and others medications, and also prevents pressure sores and contractures. It prevents or delays surgery. Cosmetically, it improves body image.

BoNT injection

BoNT should be offered as a treatment option to reduce muscle tone and improve passive function in adults with spasticity (Level A) and should be considered to improve function (Level B).^[34] Patient should be selected for BoNT depending on the focal spasticity, dynamic spastic component, clearly identified goals for treatment and anticipated functional gains. Patient and their families/care givers should be given adequate information, prior to treatment and should agree goals before treatment is given. Informed consent should be obtained from patients prior to injection. If the patient does not have the mental capacity to concern current policies for obtaining consent should be followed. The maximum dose used in a single treatment should not exceed 1500 mu Dysport (Ipsen), 400 U Botox (Allergan) or 10,000 U Myobloc. The dose of BoNT injected intramuscularly depends on the muscle size. Small muscles such as the open cords receive 0.75 U, whereas larger neck muscles may require 100–150 U and lower limb muscles may require 200–300 U to exert a desirable effect.

Other services

BoNT injection must be a part of rehabilitation program involving postinjection exercise, muscle stretch and/splinting, to achieve an optimal beneficial clinical effect. Clinical should have access to facilities to aid in assessment, selection and treatment planning, e.g., electromyography (EMG). Clinical should familiarize themselves with a single agent to avoid confusion over dose.

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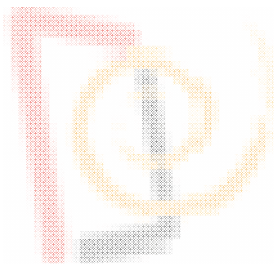
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Guidelines on the diagnosis and the current management of headache and related disorders

K. Ravishankar, Ambar Chakravarty¹, Debashish Chowdhury², Rakesh Shukla³, Sumit Singh⁴

The Headache and Migraine Clinic, Jaslok and Lilavati Hospitals, Mumbai, ¹Department of Neurology, Vivekananda Institute of Medical Science, Kolkata, ²Department of Neurology, G.B.Pant Hospital, New Delhi, ³Department of Neurology, CSM Medical University, Lucknow, ⁴Department of Neurology, Medanta . The Medicity Gurgaon, Haryana, India.

For correspondence:

Dr. K. Ravishankar, A/64, Kalpataru Residency, Sion East, Mumbai . 400 022, Mumbai, India.
E-mail: dr.k.ravishankar@gmail.com

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There are at present no existing guidelines on "headache" that pertain to the Indian setting. With a view to standardizing headache diagnosis across the country and keeping in mind treatment issues peculiar to our setting, these Guidelines have been evolved to help primary care physician's deal with headache patients. These Guidelines have been drawn up by neurologists with a special interest in headache. With limited evidence in literature regarding headache practice and treatment in India, these guidelines are more experience based than evidence based.

All contributors have adhered to the second edition of the International Classification of Headache Disorders (ICHD2-2004). In ICHD2, the first four categories deal with the primary headaches.^[1-5] The next eight categories deal with headaches due to identifiable secondary causes.^[6-13] The last two categories deal with cranial neuralgias and other causes of facial pain.^[14-17]

It is well accepted that no practice guidelines can cover all situations. Some headaches need to be handled by a neurologist but for the most part, primary care physicians are the ones who should be ideally handling headaches and these guidelines are targeted toward that end. These guidelines reflect current clinical practice trends in India. Every chapter has a brief introduction, followed by the salient diagnostic features, the way to investigate and treatment options. A summary of important practice points regarding when to refer

to a specialist has also been included. Common entities have been described in greater detail while rare conditions that are seen less often are only mentioned in passing.

The following is a brief listing of the headache conditions that are included in the second edition of The Classification of Headache Disorders of the International Headache society-ICHD2 (2004). The rubrics employed in all the chapters will be the same that is used in ICHD2.

Quick Reference to the ICHDs

2nd edition-(2004)

- a. Primary headache disorders
 - Migraine
 - Tension-type headache
 - Cluster headache and other trigeminal autonomic cephalalgias
 - Other primary headaches
- b. Secondary headache disorders
 - Headache attributed to head and/or neck trauma
 - Headache attributed to cranial or cervical vascular disorder
 - Headache attributed to non-vascular intracranial disorder
 - Headache attributed to a substance or its withdrawal
 - Headache attributed to infection
 - Headache attributed to disorder of homeoeostasis
 - Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
 - Headache attributed to psychiatric disorder
- c. Cranial Neuralgias and facial pains
 - Cranial neuralgias and central causes of facial pain
 - Other headache, cranial neuralgia central, or primary facial pain

Before going into the actual details, it is important to

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emphasize that the primary physicians should know when to get a neuroimaging in a headache patient to rule out the secondary causes of headache. Also, they should know when to refer the patient to a specialist or higher centre. These have been tabulated in Tables 1 and 2.

Primary Headache Disorders

Migraine

Diagnosis

Migraine is divided into two broad categories, namely migraine without aura and migraine with aura. The spectrum of migraine has now expanded [Table 3]. Most patients suffer from attacks of migraine without aura. The ICHD2 diagnostic criteria for migraine without and with aura are included in Tables 4 and 5. Migraine with aura includes a transient neurological dysfunction that may be visual, sensory or may involve speech and language. Migraine attacks in children are of shorter duration (usually 1–2 h only); the accompanying symptoms are different and may include syndromes such as abdominal migraine or periodic syndromes like cyclic vomiting.

Investigations

Neuroimaging in migraine patients is advocated only when patients present with an unexpected abnormal finding on neurologic examination, when patients present with atypical features, when attacks with migrainous features occur for the first time after the age of 40 years, or when the frequency or

intensity of migraine attacks continue to progress.

Treatment

Management needs to be individualized. The basic principles are as follows. Establish the diagnosis correctly; educate migraine sufferers about their condition and discuss the treatment plan; establish realistic patient expectations by setting appropriate goals; choose the drug treatment based

Table 1: When do we ask for a CTscan/ MR scan in a headache patient?

Neuroimaging should be considered in patients with headache and an unexplained abnormal finding on the neurologic examination.

- In any headache that is worsened by Valsalva maneuver
- With new headaches or progressively worsening headaches
- In patients with atypical headache patterns
- When it is the “first and worst” headache
- Headache that is persistently on the same side
- Headache that is not responding to treatment
- New onset headache in a patient who has cancer or is human immunodeficiency virus (HIV) positive
- Headache with fever, stiff neck, nausea, vomiting.
- Headache associated with papilledema, cognitive impairment, personality change, or seizures.

Table 2: When does one refer or hospitalize a headache patient?

- When a severe headache presents as a medical emergency associated with intractable nausea and vomiting producing dehydration or postural hypotension.
- When backup medications do not work.
- When dealing with migraine complications or variants (e.g. hemiplegic migraine, suspected migrainous infarction, basilar migraine with serious neurologic symptoms such as syncope, confusional migraine, etc)
- When a diagnosis has not been established during a previous similar occurrence.
- When there is a diagnostic suspicion of an infectious disorder involving the central nervous system (e.g. brain abscess and meningitis)

Table 3: Sub-classification of migraine according to the ICHD2 (2004)

- Migraine without aura
- Migraine with aura
- Typical aura with migraine headache
- Typical aura with non-migraine headache
- Typical aura without headache
- Familial hemiplegic migraine
- Sporadic hemiplegic migraine
- Basilar-type migraine
- Childhood periodic syndromes that are precursors of migraine
- Cyclical vomiting
- Abdominal migraine
- Benign paroxysmal vertigo of childhood
- Retinal migraine
- Complications of migraine
- Chronic migraine
- Status migrainosus
- Persistent aura without infarction
- Migrainous infarction
- Migraine-triggered seizure
- Probable migraine
- Probable migraine without aura
- Probable migraine with aura
- Probable chronic migraine

Table 4: Diagnostic criteria of migraine without aura-- ICHD2

- At least five attacks fulfilling criteria B–D
- Headache lasting 4–72 h (untreated or unsuccessfully treated)
- Headache has at least two of the following characteristics:
 - Unilateral location
 - Pulsating quality
 - Moderate or severe pain intensity
 - Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
- During headache at least one of the following:
 - Nausea and/or vomiting
 - Photophobia and phonophobia
- Not attributed to another disorder

Table 5: Diagnostic criteria for migraine with aura--- ICHD₂

- A There have been at least two attacks fulfilling criterion B listed below
- B At least three of the following characteristics are present:
 - There are one or more fully reversible aura symptoms indicating focal cerebral cortical or brain stem dysfunction
 - Either at least one aura symptom develops gradually over more than 4 min, or two or more symptoms occur in succession
 - No aura symptom lasts more than 60 min; if more than one aura symptom is present, accepted duration is proportionally increased
 - Headache follows aura with a free interval of less than 60 min (it may also begin before or simultaneously with the aura)
 - No evidence of organic disease history, physical examination, and diagnostic tests exclude a secondary cause

on the frequency and severity of attacks and the presence of associated symptoms such as nausea and vomiting; consider comorbid and coexisting conditions when choosing drugs for prophylaxis; encourage patients to identify and avoid triggers.

Migraine-abortive treatment

The basic principles of abortive treatment of migraine are as follows. Tailor the treatment choice to suit individual needs (e.g. based on their severity of illness, co-morbidity / co-existing conditions and prior response to medications); use migraine-specific agents (ergotamine, dihydroergotamine (DHE), triptans) in patients with more severe migraine and in those whose headaches respond poorly to non-steroidal anti-inflammatory drugs (NSAIDs) or combination analgesics such as aspirin plus acetaminophen or caffeine; select a non-oral route of administration for migraines associated with nausea or vomiting; guard against medication overuse headache (MOH) (rebound headache). Frequent use of acute medications like ergotamine, opiates, triptans, simple analgesics, and combination analgesics containing caffeine/codeine are thought to cause rebound headache; preventive therapy given simultaneously will help reduce the need for repeated acute medications.

Nonspecific medications for acute treatment

Antiemetics

Oral antiemetics such as metoclopramide and domperidone are an adjunct to treat nausea associated with migraine.

NSAIDs, nonopiate analgesics, and combination analgesics
NSAIDs (oral) and combination analgesics containing caffeine are a reasonable first-line treatment choice for mild to moderate migraine attacks or severe attacks that have been responsive in the past to similar NSAIDs or nonopiate analgesics. Overuse of combination medications is considered to be one of the most prominent causes of rebound headache. Fortunately, analgesics containing butalbital and opioids are not easily available in our country and so their overuse is limited.

Opiate analgesics

Parenteral opiates should only rarely be used as rescue therapy for acute migraine. The risk of sedation and habituation will have to be addressed.

Specific medications for acute treatment

Ergot alkaloids and derivatives

Ergotamine oral 1 mg (available in combination with caffeine) may be considered in the treatment of patients with moderate to severe migraine. Rectal suppositories are not available in India. Safe usage limits the consumption to between 6 to 10 mg per week but ergotamine should not be used on a long-term basis. DHE, a nonselective 5-HT₁ receptor agonist, is effective in relieving headache when used intramuscularly or intravenously. Unfortunately, DHE is not available in India.

Triptans (5 HT_{1B/1D} receptor agonists): As of 2011, sumatriptan, rizatriptan, naratriptan, and zolmitriptan are the only four triptans available in India. Initial treatment with any triptan is a reasonable choice when the headache is moderate to severe. The recommended starting dose for sumatriptan is 25 mg orally. If needed one may increase the dose in increments of 50 mg to a

maximum of 100 mg per dose to a maximum of 300 mg per day. Patients with nausea and vomiting may be given subcutaneous (SC) sumatriptan. A SC injection of 1/2 cc = 6 mg may be used for severe attacks with vomiting. Both sumatriptan injection and intranasal sumatriptan are available in India. Sumatriptan should not be taken within 24 h of the administration of DHE or ergotamine. Caution must be exercised when using sumatriptan in patients with cardiac risk factors, cardiac disease, or uncontrolled hypertension. Rizatriptan is given orally in a dose of 5 or 10 mg to treat attacks of moderate severe migraine. A lower dose is recommended for patients who are on betablockers. Naratriptan is long acting and is used in a dose of 1 mg or 2.5 mg. Recurrence is less with naratriptan.

Other medications

Corticosteroids (dexamethasone or hydrocortisone) are options for rescue therapy in patients with status migrainosus.

Migraine-preventive treatment

The basic principles of abortive treatment of migraine are as follows. Preventive therapy should be employed in those patients in whom migraine has a high frequency, severity, substantial impact, and in those who have not responded to acute care. Use the least amount of the medication with the fewest side effects to gain control of the symptoms until preventive treatment can be reduced or stopped. Initiate therapy with medications that have the highest level of efficacy. Increase the dose slowly until clinical benefits are achieved without adverse events. Give each drug an adequate trial of at least 2 to 3 months. Use a long acting formulation, it will help improve compliance. Monitor the patient's headache frequency using a headache diary. Select a drug that will treat the coexistent condition and migraine. When using prophylactics, direct special attention to women who are pregnant or desire to conceive. Preventive medications may have teratogenic effects.

Beta-blockers

Not all beta-blockers are effective in migraine. Those that are efficacious include propranolol, atenolol, and metoprolol. Beta-blockers are contraindicated in patients with asthma, chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, heart block or failure, or peripheral vascular disease. When prescribing beta-blockers, start with a low dose and titrate upward as required. Once the attacks are controlled, the medication should be tapered. Propranolol can be started in a dose of 10 mg twice daily and gradually increased to a maximum of 80-120 mg per day. Doses in Indian patients are much less than in the western population.

Calcium-channel blockers

Of the available agents in this group, flunarizine is most commonly used for migraine prophylaxis. Flunarizine is useful as a first line prophylactic and can be started in a smaller dose of 5 mg at night and gradually increased to 10 mg daily. This will help avoid sedation. Flunarizine is to be avoided in patients with depression. Calcium-channel blockers are contraindicated in patients with hypotension, congestive heart failure, or arrhythmia.

Tricyclic antidepressants

Amitriptyline is useful in migraine, especially in patients

with associated TTH. 10 mg orally each night should be given at first, followed by an increase of 10 mg every week, up to 25-50 mg/day; a higher dosage may be required in the presence of comorbid depression. Contraindications include cardiac, kidney, liver, prostate and thyroid disease, glaucoma, hypertension, seizure disorder, and use of monoamine oxidase inhibitors. Tricyclic drugs should be used with caution in elderly patients because of anticholinergic side effects.

Anti-epileptic drugs

Sodium valproate, valproic acid, divalproex sodium, and topiramate have been found to be effective for migraine prophylaxis. Side effects of divalproex include nausea, alopecia, tremor, and weight gain, and their use has been associated with hepatotoxicity, particularly in children. They may also cause neural tube defects and should not be given to women who are pregnant or considering pregnancy or young women with polycystic ovarian disease (PCOD). Divalproex is started in a small dose of 250-500 mg per day and the dose is gradually increased up to 1500 mg per day with continuous monitoring for side-effects. Topiramate should be started in a small dose of 25 mg per day in adults and the dose should be gradually increased in 25 mg weekly increments to a maximum of 100 mg twice daily. Doses of topiramate for migraine in Indian patients are less than that in westerners. Topiramate should not be used in the presence of glaucoma, renal stones and tingling and numbness, diarrhea, and confusional state are some of the temporary side effects. Topiramate has the advantage of weight loss and can be used in preference to divalproex when treating obese patients.

Non-Pharmacologic Therapy

Nonpharmacologic treatment may be combined with preventive therapy to achieve additional clinical improvement for migraine relief. Behavioral treatments are classified into three broad categories: relaxation training, biofeedback therapy, and cognitive-behavioral training (stress-management training). Physical treatment includes acupuncture, cervical manipulation, and mobilization therapy.

Specific situations that warrant different treatment strategies

Migraine in children and adolescents

The only analgesics with evidence of efficacy for the acute migraine treatment in childhood and adolescents are ibuprofen 10 mg/kg body weight and paracetamol 15 mg/kg body weight. Domperidone is the antiemetic of choice in children. Ergot alkaloids should not be used in children and adolescents.

Menstrual migraine

Different drug regimes have been studied to treat this menstrual migraine. Naproxen sodium (250 mg twice daily) has been shown to reduce pain including headache in menstrual migraine. In patients who have clearly predictable menstrual cycles, one can plan a short 8-day course of peri-menstrual prophylaxis starting 5 days prior to and for 3 days during periods.

Migraine in pregnancy

Most migraine drugs are contraindicated in pregnancy.

Fortunately, most pregnant migraineurs experience less or even no migraine attacks. When migraine attacks occurs during pregnancy, only paracetamol should be administered. NSAIDs can be given in the second trimester. Triptans and ergot alkaloids are contraindicated. Propranolol and amitriptyline are the prophylactics that can be used if necessary

When to refer to a specialist?

The patient should be referred to a specialist when migraine transforms to a chronic daily headache or becomes refractory, when migraine is comorbid with severe depression or other psychiatric comorbidity, when there is associated medication overuse, and parenteral treatment becomes necessary.

Tension type headache

Diagnosis

TTH are recurrent episodes of headache lasting minutes to weeks. The pain is typically pressing or tightening in quality, of mild to moderate intensity, and bilateral in location, and does not worsen with the routine physical activity. Nausea and vomiting is usually absent, but photophobia or phonophobia may be present.

The diagnosis of TTH is essentially clinical and relies only on symptoms and signs [Table 6].

TTH has been divided into two forms, *episodic* (ETTH) and *chronic* (CTTH) in ICHD 2. Episodic tension type headache has been divided into two groups, namely *infrequent* and *frequent*. TTH is the least distinct of all headache types. Diagnosis is based chiefly on negative features (i.e. the absence of symptoms that characterize other primary or secondary headaches). However, many of the secondary headaches such as MOH chronic posttraumatic headaches, sinus/ eye disease related headaches, temporo-mandibular joint disorder related headaches, brain tumor related headaches, psychiatric disorder-related headaches, and cervical spondylosis may mimic TTH at some stage of their clinical evolution. Therefore, atypical history or abnormal clinical examination in patients of suspected TTH indicates the need for further investigation.

Treatment

Acute abortive treatment

- Simple analgesics and NSAIDs are the mainstays in the acute therapy.

Table 6: Tension type Headache---core features

Duration	30 min to 7 days
Two out of four following headache features	Bilateral location Pressing/tightening quality (non-pulsating) Mild to moderate intensity Not aggravated by routine physical activity
Associated symptoms	No nausea and vomiting (anorexia may occur) No more than one of photophobia or phonophobia
Not attributed to by another disorder	Other disorders to be excluded by clinical history and examination or by suitable investigation if necessary

- Care should be taken to avoid overuse.
- Opiates should be avoided.
- Nonpharmacologic treatment in the form of relaxation training can be of benefit in recurrent ETTH

Preventive treatment

- Tricyclic antidepressants: Amitriptyline has been found to be most effective for the treatment of CTTH. Amitriptyline should be started on low dose (10 mg to 25 mg per day) and titrated by 10-25 mg weekly till the therapeutic effect or the side effects appear. The common side effects of the drug are dry mouth and drowsiness. Serious side effects like cardiac arrhythmias, precipitation of glaucoma, and urinary retention can occur in predisposed, especially elderly subjects.
- Mirtazepine: can be given in situations where amitriptyline is either ineffective or contraindicated. Other antidepressants like SSRI and tetracyclics have been found to be not so useful.
- Recently, Botulinum Toxin Type A injection has been tried in CTTH with variable results. Currently, this is reserved for refractory patients.
- Relaxation training and biofeedback training are also helpful.
- Usually, preventives are continued for 6 months following which withdrawal is attempted. Upon withdrawal, some patients continue to remain headache free while others start to have headaches again. These patients usually require long-term treatment.

Patient education

Many patients of frequent ETTH and CTTH have grave concerns about possibility of a serious disease such as a brain tumor. Correct explanations can allay these concerns. Physicians should refrain from using such terms like "psychosomatic" or "depression" which might be perceived negatively by the patient.

Headache diary

This often is very helpful for the physicians. They can measure the progression of the frequency and severity.

When to refer to a specialist?

The patient should be referred to a specialist when the diagnosis is uncertain (Multiple headache diagnoses possible), when there is a recent change in character and response pattern in a diagnosed patient, with refractory headaches that are unresponsive to first and second line drugs, with medication overuse problems including opioid dependence, with depression and anxiety not responding to standard drugs, when non-pharmacological treatment like relaxation training, and biofeedback training are required.

Cluster Headache and Trigeminal Autonomic Cephalgias

Trigeminal autonomic cephalgias (TACs) are uncommon, most often primary headache disorders which are usually short lasting and associated with cranial autonomic features. The general diagnostic characteristics of this group are unilateral head pain predominantly affecting the first division of trigeminal nerve, namely the eye, periorbital region, and forehead associated with

cranial autonomic symptoms with increased parasympathetic and decreased sympathetic activity. The TACs include the following individual headache entities: cluster headache (CH); paroxysmal hemicranias (PH); short lasting neuralgiform headache with conjunctival injection and tearing (SUNCT).

Cluster Headache

Diagnosis

An important feature of CH is the circadian periodicity with attacks occurring in a clustered form daily exactly at nearly the same time for several days and with variable periods of remission in between--hence the name CH. Severe head pain that is unilateral and orbital, supraorbital or temporal in location, lasting for 15--180 min duration if untreated. The headache may be associated with one of the following symptoms: ipsilateral conjunctival injection and/or lacrimation; ipsilateral nasal congestion/rhinorrhea; ipsilateral miosis, ptosis; ipsilateral eyelid edema; ipsilateral forehead and facial sweating; sense of restlessness, or agitation during headache. Attack frequency may range from 1 to 8 per day. CH may be classified as episodic or chronic depending on duration.

Investigation

Although most cases of CH seen in practice are primary in nature, CH may be a rare manifestation of an underlying space-occupying lesion, (especially pituitary tumors). Hence neuroimaging studies of all cases of CH are recommended.

Treatment

Abortive treatment

To terminate the acute attack.

- SC sumatriptan: Given as ½ cc = 6 mg SC injection. The injection is available in a preloaded autoinjector format which the patient himself can administer. If the injection is not available, sumatriptan can be given as a nasalspray containing 20 mg per puff.
- Oxygen: Inhalation of 100% oxygen at 6-7 L/min for 15 min is effective in 60% cases. Higher flow rate (12 L/min) may benefit some patients
- DHE: Dihydroergotamine injection or nasal spray is also effective but the drug is not available in India

Preventive treatment

To reduce the frequency and severity of the attacks.

- Verapamil: Pretreatment ECG is essential and this drug should be avoided in conjunction with beta-blockers. It is given in a starting dose of 120 mg long acting daily increased to three times daily. Constipation is the main side effect.
- Lithium: Given in a starting dose of 300 mg to be gradually increased to a max of 900 mg. Pre-check of thyroid and renal profile is necessary and lithium levels need to be monitored periodically.
- Steroids: Prednisolone in a dose of 60 mg daily to start with followed by gradual tapering. Normal precautions as while administering steroids.
- Ergotamine: Useful as adjunctive therapy. For reasons still unknown, ergotamine when used in CH on a daily basis does not usually lead to MOH.

Surgical Options

Surgery as a treatment option for CH is to be considered only in medically intractable situations when there is no improvement with verapamil, lithium, and methysergide.

Paroxysmal Hemicrania

Diagnosis

Paroxysmal hemicrania (PH) is similar to CH clinically but differs from CH in that it occurs predominantly in females, the attack duration is shorter, number of attacks is more per day, and this headache is exquisitely responsive to indomethacin. The gender bias for PH is the reverse of CH. (M: F 1:2.4). The usual onset is 20–50 years (range 6–81 years). Most cases are primary. The attacks are of 2–30 min duration. PH has been divided along the same lines as CH into two categories: episodic and chronic PH.

Investigations

Neuroimaging is seldom needed unless unusual features occur and an underlying secondary structural cause needs ruling out. Indomethacin responsiveness must be tested in all cases of suspected PH to differentiate from CH and SUNCT.

Treatment

Oral indomethacin is the drug of choice—starting at 25 mg TID and increasing to 75 mg TID if GI symptoms do not occur. Gastroprotective agents may be used concurrently. Withdrawal of indomethacin once every 6 months may be attempted.

Short Lasting Neuralgiform Attacks with Conjunctival Injection and Tearing

Diagnosis

The attacks are associated with severe to very severe pain that is strictly unilateral, neuralgic in character (short and sharp) located in the ophthalmic–trigeminal distribution attack, duration is short and in seconds (5–200), attack frequency is very high (1/day – 60/h). Autonomic features are dominant—lacrimation, conjunctival injection are usually seen. Other features may or may not be present and include rhinorrhea, nasal blockage, eye lid edema, ptosis, facial flushing, and facial sweating. There is no refractory period in between attacks. Rarely SUNCT may be caused by posterior fossa tumors and pituitary adenomas. SUNCT needs to be differentiated from trigeminal neuralgia (TN).

Treatment

- Lamotrigine (100–400 mg/day); Topiramate (50–400 mg/day); Gabapentin (600–3600 mg/day) and IV Lidocaine in intractable cases (1.3 – 3.3 mg/kg/h).
- Greater occipital nerve blockade may also help in some. Hypothalamic deep brain stimulation is now being evaluated as a preventive measure.

Other Primary Headaches

Primary stabbing headache

Diagnosis

This entity is characterized by transient and localized stabs of

pain in the head that occur in the absence of organic disease of underlying structures or of the cranial nerves. Stabs last for a few seconds and there are no accompanying symptoms, exclusively or predominantly in the distribution of the trigeminal nerve (orbit, temporal, parietal). These headaches are not accompanied by autonomic symptoms. Migraine is a common association.

Treatment

Indomethacin in a 25–50 mg per day dosage is the most effective treatment option.

Primary Cough Headache

Diagnosis

The headache is sudden, short, and bilateral and brought on by coughing or straining and generally not present at other times. Headache induced by cough or straining may be primary (or benign) and secondary. Most cases of symptomatic or secondary cough headaches are due to Arnold–Chiari Malformation Type 1 (herniation of cerebellar tonsil through the foramen magnum). Intracranial neoplasms or vascular diseases including aneurysms may also cause symptomatic cough headache.

Investigation

Primary cough headaches must occur in the absence of an intracranial pathology and hence neuroimaging (preferably MRI) must be done in all cases.

Treatment

Smoking should be stopped. Some patients respond well to indomethacin.

Primary Exertional Headache

Diagnosis

Any form of exercise precipitates the headache. The headache lasts from 5 to 48 h.

Primary Headache Associated with Sexual Activity

Diagnosis

These are headaches precipitated by sexual activity usually start as a dull bilateral ache as sexual excitement increases and suddenly become intense at orgasm. The headaches occur in the absence of any intracranial disorder. At presentation, the causal relationship to sexual activity (often suppressed by patients) must be elicited for diagnosis.

Investigation

It is known that sexual activity may cause an intracranial bleed (aneurysmal subarachnoid hemorrhage or even intracerebral hemorrhage) and hence a detailed history must be obtained.

Other conditions must be excluded by appropriate investigations (neuroimaging or CSF study), with any “thunderclap” headache where exclusion of subarachnoid hemorrhage is of paramount importance.

Treatment

Some may obtain relief with indomethacin (50 mg) prior to the sex act.

Hypnic Headache

Diagnosis

Attacks of dull headache (sometimes severe) occur at night often awakening the patient from sleep. The headache may occur several times per month, generally lasting for 15--30 min after waking. There are no accompanying autonomic features (differentiation from CH).

Investigations

Exclusion of intracranial disorder is important and hence the need for neuroimaging.

Treatment

- A hot cup of strong coffee at bedtime helps many patients.
- Some patients benefit from may need lithium carbonate 300 mg at night or flunarizine 10 mg at bedtime.

Primary Thunderclap Headache

Diagnosis

High intensity headache of abrupt onset mimic that of ruptured cerebral aneurysm. "True" primary thunderclap headaches are uncommon. Aneurysmal rupture must be excluded. Other conditions include bleeding from cerebral AVM, cerebral venous sinus thrombosis, and pituitary apoplexy.

Treatment

All cases of thunderclap headaches must be referred urgently to specialized units for full work-up and treatment.

Hemicrania Continua

Diagnosis

Hemicrania continua (HC) is a strictly unilateral headache responsive to indomethacin, usually unremitting, but rare cases of remission have been reported. The diagnostic criteria for HC are as follows. Unilateral pain without side shift; pain is daily and continuous, without pain free periods; moderate severity, but with exacerbations of severe pain; autonomic features occurring during exacerbations and ipsilaterally to the pain side include conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea and ptosis and/or miosis. Complete response to therapeutic doses to indomethacin confirms the diagnosis.

Treatment

Indomethacin in a progressively increasing dose of up to 100 mg daily orally gives complete response. Maintenance doses of indomethacin are smaller.

Secondary Headache Disorders

Eight categories deal with *headaches due to identifiable secondary causes*.^[5-12] These are detailed as follows.

Headache Attributed to Head And/Or Neck Trauma

Post-traumatic headache

Post-traumatic headache (PTH) may be accompanied by somatic, psychologic, or cognitive disturbances. It can simulate the clinical characteristics of several primary headaches and is defined as a new onset headache resulting from injury to the brain, head, and neck.

Diagnosis

PTH can present after mild, moderate, or severe head injury. If headache, without any typical characteristics, develops within 7 days after head trauma or after regaining consciousness following head trauma and resolves within 3 months or 3 months have not yet elapsed, it is termed "acute PTH." If it persists for more than 3 months after head trauma, it is termed "chronic PTH." The distinction of 3 months between acute and chronic PTH is rather arbitrary and not based on any clear clinical or biological evidence.

Investigation

- The investigation of choice for PTH is cranial computed tomography (CT) with bone window images.
- Cranial magnetic resonance imaging (MRI) is more sensitive for detecting non-hemorrhagic focal contusions.
- With accompanying neck injury, plain x-rays cervical spine on flexion and extension are necessary to identify fracture, subluxation, or ligamentous injury of spine.

Treatment

Treatment guidelines are based on clinical experience and there are few controlled studies.

Pharmacological

- Abortive treatment for acute PTH provides short-term relief and includes NSAIDs (naproxen 500 mg bd, ibuprofen 400 mg tds). Use of these drugs should be limited to prevent rebound.
- Preventive treatment should be considered if there are more than two attacks of headache per week or headache severity or duration are high. Tricyclic antidepressants (amitriptyline 10-75 mg hs, nortriptyline 25-75 mg hs).
- The chronic, frequent use of opioids or benzodiazepines should be avoided because of the potential for habituation.
- Management of PTH should be tailored to the class of non-traumatic primary headache (chronic tension-type, migraine, etc) into which it fits.

Non-pharmacological

- Psychological evaluation is a generally accepted intervention to identify factors for delayed recovery and for cognitive assessment.
- This along with patient education, reassurance, trigger identification, biofeedback, physical therapy, joint manipulation therapy, and other occupational therapy may be considered if functional overlay is documented.

Headache Attributed to Whiplash Injury

Acute and chronic whiplash injury (WI) headaches are new

diagnostic entities in the ICHD2 classification. WI is produced when acceleration and deceleration forces act on the neck, resulting in hyperextension, hyperflexion, and occasionally hyperrotation of the cervical spine. Rear end or side-impact motor collisions are responsible for about 85% of all WI. Up to 80% of patients complain of headaches following a WI.

Diagnosis

If headache, without any typical characteristics, develops within 7 days after whiplash injury (sudden and significant acceleration/deceleration movement of the neck) and resolves within 3 months or 3 months have not yet elapsed, it is termed "acute headache attributed to whiplash injury." If it persists for more than 3 months after whiplash, it is termed "chronic headache attributed to whiplash injury."

Investigation

Plain x-rays of cervical spine on flexion and extension are necessary to identify fracture, subluxation, or ligamentous injury of spine. CT scan has improved sensitivity for detecting fracture and has been shown to be faster and cost-effective in moderate and high risk trauma patients. 3D CT images are of excellent quality. A cervical spine MRI is indicated in patients with abnormal neurological examinations suggesting the possibility of radiculopathy or myelopathy. CT scan/myelography may be more sensitive than MRI in some cases for nerve root compression. Electromyogram and nerve conduction studies may provide evidence of radiculopathy or brachial plexopathy.

Treatment

Pharmacological

- Short-term use of simple analgesics (acetaminophen 1000 mg, aspirin 500--1000 mg), muscle relaxants (tizanidine 2-8 mg tds), or NSAIDs (naproxen 500 mg bd, ibuprofen 400 mg tds) is recommended.
- Headache due to greater occipital neuralgia may respond to local anesthetic blocks with or without an injectable corticosteroid.
- Persistent headaches and neck pain may benefit from tricyclic antidepressants (amitriptyline 10--75 mg hs, nortriptyline 25--75 mg hs).

Non-pharmacological

- Short-term active exercise and physiotherapy are recommended.
- Soft collar, immobilization, and more than 3 to 5 days of rest should not be advised

Headache Attributed to Cranial or Cervical Vascular Disorders

When a new headache occurs for the first time in close temporal relation to a vascular disorder, it is coded as a secondary headache attributed to the vascular disorder. A diagnosis of headache attributed to vascular disorder usually becomes definite only when the headache resolves or greatly improves within a specified time after its onset. These include many entities of which the ones that are important to recognize are described in the following.

Headache Attributed to Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is by far the most common cause of intense and incapacitating headache of abrupt onset (thunderclap) headache and remains a serious condition (50% of patients die following SAH, often before arriving at hospital and 50% of survivors are left disabled). 80% of patients with SAH have saccular aneurysms. SAH or the warning leak for saccular aneurysm or AVM should be suspected in any patient with abrupt and new onset, severe, and unremitting headache. This suspicion is heightened when headache is associated with neck rigidity, vomiting, and altered mentation.

Investigation

- CT head scan (without contrast): It is the initial investigation of choice to detect SAH with a sensitivity of >90% during first 24 h. The pattern of hemorrhage can also suggest the location of the ruptured aneurysm.
- MRI (Flair) is more sensitive than CT scan from 3 to 14 days after the hemorrhage.
- Cerebrospinal fluid examination is advised if neuroimaging is normal and the suspicion for SAH is high. RBCs are present in nearly all the cases but usually clear from 4 to 21 days. Xanthochromia is present due to the presence of oxyhemoglobin, methhemoglobin, and bilirubin. Oxyhemoglobin is released from the breakdown of RBCs after 2 to 12 h of the SAH and degrades into bilirubin by 3rd to 4th day.
- Angiography: Digital subtraction angiography (DSA), MRA, and CT angiography are required for detection and demonstration of the aneurysm. DSA is essential preoperatively to know the morphology.

Treatment

- Complete bed rest is advised, any kind of exertion should be avoided, and stool softeners should be given.
- Headache should be treated with opioids or acetaminophen and mild sedation. NSAIDs are relatively contraindicated because of the risk of gastrointestinal bleeding.
- Vasospasm is treated or prevented by the "triple H" therapy (hydration, hypertension and hemodilution) along with nimodipine.
- Surgical clipping or endovascular coiling of the aneurysm to prevent re-rupture is the definite treatment, and allows measures to prevent and treat vasospasm.
- SAH is a neurosurgical emergency. The patient should be referred as soon as possible to a specialist when the diagnosis is suspected.
- The mortality is 45% in the first month even in hospitalized patients and 50% of survivors are left with serious neurological complications.

Headache Attributed to Giant Cell Arteritis

Among the arteritides and collagen vascular diseases, giant cell arteritis (GCA) is most conspicuously associated with headache (which is due to inflammation of cranial vasculature, mostly branches of the external carotid artery). It is seen after the fifth decade. GCA has variable clinical manifestations. Recent repeated attacks of amaurosis fugax associated with headache are very suggestive of GCA. Any recent persisting headache in

a patient over 60 years of age should suggest GCA and lead to appropriate investigations. Patients may have swollen tender scalp artery. Steroids should be started promptly without waiting for the biopsy. The major risk is of blindness due to anterior ischemic optic neuropathy, which can be prevented by immediate steroid treatment.

Investigation

- The ESR and C-reactive protein are high. It is used to monitor disease activity during corticosteroid therapy.
- The diagnosis is confirmed by a biopsy of the temporal artery. Since involvement of the vessel may be segmental, positive yield is increased by obtaining a biopsy segment of 3–5 cm together with serial sectioning of biopsy specimens.

Treatment

- Treatment should be started immediately without waiting for the biopsy result.
- Typically prednisolone is started in a dose of 40–60 mg/day and continued for a month.
- Many cases of GCA are chronic and may require steroids for many years.
- The disease activity is monitored by ESR and clinical assessment.

Headache Attributed to Primary Central Nervous System Angiitis

Headache is the dominant symptom in central nervous system (CNS) angiitis (either primary or secondary). It is present in 50–80% of cases. Nevertheless, it has no specific features and is therefore of little diagnostic value until other signs are present such as focal deficits, seizures, altered cognition, or disorders of consciousness. The pathogenesis of the headache is multifactorial: inflammation, stroke (ischemic or hemorrhagic), raised intracranial pressure, and/or SAH.

Investigation

- Complete blood count: TLC is greater than 10,000/mm³ without eosinophilia in 50% of case.
- ESR is normal or mildly elevated.
- CSF often shows lymphocytic pleocytosis and elevated proteins.
- Neuroimaging shows nonspecific multifocal ischemia.
- Cerebral angiography is abnormal in 75% of cases but is not pathognomonic. It shows segmental narrowing of the medium sized vessels.
- Meningeal and brain biopsy is abnormal in only three-fourths of cases due to patchy involvement. Primary CNS angiitis is the diagnosis of exclusion which is confirmed on meningeal and the brain biopsy.
- ANA or other markers are absent.

Treatment

Patients are treated with the combination of prednisone 40–60 mg/day and cyclophosphamide 100 mg/day. The response to the treatment is far less dramatic than giant cell arteritis.

Headache Attributed to Secondary CNS Angiitis

First step is to diagnose CNS angiitis in a patient known to have

one of the many conditions that can cause angiitis. Second step is to find the underlying condition (inflammatory, infectious, malignant, toxic) in a patient presenting with CNS angiitis.

Investigation

Investigations are directed to establish systemic vasculitis. It is imperative to make the diagnosis of the CNS angiitis as well etiological diagnosis of the underlying systemic vasculitis.

Treatment

Treatment is directed toward the management of the underlying systemic vasculitis e.g. corticosteroids and immunosuppressant (azathioprine and cyclophosphamide).

Headache Attributed to Cerebral Venous Thrombosis

Headache is the most frequent and the most common presenting symptom of cerebral venous thrombosis (CVT). It has no specific characteristic. It is usually accompanied by focal neurological deficit, seizures, or signs of raised intracranial tension. Headache resolves within 1 month after appropriate treatment

Investigation

- The single best non-invasive diagnostic tool is MRI along with MRV, and in doubtful cases invasive venography should be done.
- Etiology of the CVT is established by investigations relevant to the clinical setting. In general, investigations include complete blood count, coagulation profile, anti-phospholipid antibodies, protein C, protein S, etc.

Treatment

- Intravenous heparin should be started as possible. It is safe even in the presence of hemorrhagic infarct. Weight-adjusted heparin nomograms for patients with venous thromboembolism are available.
- An initial bolus of 5000 units or 80 units/kg of unfractionated heparin followed by an infusion of 18 units/kg/h is given.
- Treatment with oral anticoagulants (warfarin/acitrom) is started along with heparin. When PT/INR value in the range of 2–3 is achieved, heparin is discontinued. Warfarin is continued indefinitely, if there is underlying coagulopathy, otherwise stopped after 3 to 6 months.
- When present, seizures are controlled with anticonvulsants.
- Intracranial hypertension is treated with mannitol, diuretics, and acetazolamide.
- Adequate hydration should be maintained
- Appropriate antibiotics are given in cases of septic thrombosis..

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Cerebral Autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant (with some sporadic cases) small artery disease of the brain characterized clinically by recurrent small deep infarcts, subcortical dementia, mood disturbances, and migraine with aura. It is due to mutations of Notch-3 gene. Attacks of migraine with aura, with or without other neurological signs are present.

It is a progressive disorder and presents with migraine with aura and stroke. As a rough guideline, migraine appears in third to fourth decade, stroke in the fourth to fifth decade and dementia in sixth to seventh decade.

Investigation

- MRI is always abnormal with striking white matter changes on T2WI.
- The diagnosis is made on a simple skin biopsy with immunostaining of Notch-3 antibodies. The disease involves the smooth muscle cells in the media of small arteries and it is due to mutations of Notch-3 gene.
- Genetic testing for Notch-3 gene mutation can also be done.

Treatment

- The treatment is largely symptomatic.
- Patients are treated as for migraine. Triptans and ergotamine should however be avoided because of their vasoconstrictive property.
- Antiplatelet agents are used for lacunar infarcts.

Headache Attributed to Non-Vascular Intracranial Disorder

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is the persistent increase in intracranial pressure in the absence of any intracranial lesions such as intracranial tumor, hydrocephalus, intracranial infections, dural sinus thrombosis or hypertensive encephalopathy. The term benign intracranial hypertension is not used anymore because the development of the disease can entail complications like vision loss. IIH is a diagnosis of exclusion. Careful detailed history is essential. IIH most commonly occurs in young obese women. It can occur along

Table 7. Conditions associated with IIH

Obstruction to venous drainage
Cerebral venous sinus thrombosis
Jugular vein tumor
Superior vena cava syndrome
Increased right heart pressure
Endocrine disorders
Addison's disease
Hypoparathyroidism
Obesity, recent weight gain
Exogenous agents
Amiodarone
Cytarabine
Corticosteroids (particularly withdrawal)
Cyclosporine
Growth hormone
Levothyroxine (children)
Lithium carbonate
Levonorgestrel (Norplant)
Tetracycline and related compound
Minocycline
Doxycycline
Vitamin A
Vitamin supplements, liver
Infectious or post-infectious conditions
HIV infection Lyme disease
After varicella

with a primary headache disorder or in close temporal relation to a non-vascular intracranial disorder. A majority of patients have papilledema, but IIH without papilledema is also observed. Other symptoms may include tinnitus, transient visual obscurations, and diplopia.

The various conditions that can be associated with IIH are enumerated in Table 7.

Diagnosis

Progressive headache with at least one of the following characteristics and fulfilling criteria C and D: (1) Daily occurrence, (2) diffuse and/or constant (non-pulsating) pain, (3) aggravated by coughing or straining. Intracranial hypertension fulfils the following criteria. Neurological examination is normal or demonstrates any of the following abnormalities: papilloedema; enlarged blind spot; visual field defect (progressive if untreated); sixth nerve palsy. Increased CSF pressure (> 200 mm H₂O in non-obese, > 250 mm H₂O in obese) is measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring. Normal CSF chemistry (low CSF protein is acceptable) and cellularity. Headache improves after withdrawal of CSF to reduce pressure to 120--170 mm H₂O and resolves within 72 h of persistent normalization of intracranial pressure.

Investigation

- Ophthalmologic assessment is done to look for papilledema and atrophy. Visual field charting and assessment (perimetry) are performed to chart the blind spot.
- CT scan or MRI is done to show normal cranial and cerebral characteristics and exclude a venous thrombosis. A high quality ≥ 1.5 T MRI and MRV are mandatory to rule out mass lesions, dural venous sinus thrombotic occlusion, and dural and parenchymal arterio-venous, fistula or AV malformation.
- If required, a DSA may be performed to rule out a vascular malformation.
- CSF examination is done by lumbar puncture after excluding the possibility of an intracranial space occupying lesion as it is imperative to measure CSF pressure.

Treatment

- Primary goal is to prevent vision loss and symptom control. Patients without papilledema are not at risk of visual loss.
- Papilledema improves over a period of 6 months after reduction of ICP.
- No treatment is required if the patient has minimal symptoms and visual function is normal. However, all patients require serial monitoring of visual function, especially field charting for signs of visual impairment.
- Weight reduction---weight loss improves papilledema by reduction of intracranial pressure. Weight loss may also be beneficial for comorbid medical conditions like hypertension and sleep apnea.
- Reduction of CSF pressure:
 - Drugs---Medical treatment includes carbonic anhydrase inhibitors (e.g. acetazolamide and topiramate) and loop diuretics such as furosemide. The usual dose of acetazolamide is 250--500 mg tds (up to 4 g/day may be needed) alone or in combination with a loop diuretic

such as frusemide 40–120 mg/day. Corticosteroids are reserved for urgent management of patients with visual loss and should not be used for the routine treatment of IHH.

- Lumbar puncture---Repeated LPs have been used to lower ICP but have not been systematically studied. The procedure is uncomfortable, and usually not acceptable to the patient.
- Surgery---Surgery should be considered when medical treatment fails or when visual function deteriorates. The main procedures performed include lumbo-peritoneal shunt, ventriculo-peritoneal shunt, optic nerve sheath fenestration, and venous stenting.
- Tricyclic antidepressants, valproate, and calcium channel blockers should be used cautiously because of the fear of weight gain and fluid retention. Simple analgesics/NSAIDs are adequate for patients with only symptom is headache. Serial LPs may also be performed for relief of headache.

When to refer to a specialist?

A patient needs to be referred to a headache specialist or a neurologist if there is no improvement of headache after withdrawal of CSF to reduce pressure between 120 and 170 mm H₂O within 72 h, persistent headache despite adequate medications or progressive visual loss.

Spontaneous Low Pressure Headache

This condition was first recognized in 1930s. More has been learned about it since the early 1990s when MRI became widely available and after pachymeningeal gadolinium enhancement was seen in MRI of headache patients. A much broader clinical and imaging spectrum of the disease is now recognized and a substantially larger number of patients are diagnosed. Headache that occurs upon standing and is relieved by lying down occurs typically in low pressure headaches. It remains commonly misdiagnosed when there is no history of a spinal tap. Headache aggravated by valsalva maneuver is suggestive of spontaneous low pressure CSF headache. It should be considered an important and relatively frequent cause of new daily persistent headache in young and middle aged individual. However, it is important to note that not all orthostatic headaches are due to CSF leak and not all CSF leak headaches are orthostatic. Cervical or interscapular pain may precede orthostatic headache (by days or weeks). Lingering non-orthostatic headache may precede orthostatic headache (by days, weeks, or months). CSF rhinorrhea and CSF otorrhea do not cause positional headache.

Investigation

- CSF examination: opening pressure is typically low, sometimes unmeasurable. CSF protein---normal or elevated up to 100 mg/ kg and normal glucose and cells.
- CT brain scan is usually normal.
- MRI may show the following signs: diffuse pachymeningeal enhancement and descent (sagging/ sinking) of brain (cerebellar tonsils)

Treatment

- Bed rest and avoidance of upright position.
- Adequate hydration should be maintained.

- Oral or intravenous caffeine and theophylline have also been used by the virtue of their constrictive effect on intracranial arteries, leading to increased CSF pressure and reduction in headache.
- One to two cups of coffee provide good amount of caffeine.
- Epidural blood patch is given in patients who have failed initial treatment.
- Epidural infusion of dextran, fibrin glue, or intrathecal fluid infusion has also been tried.
- Surgery is considered when conservative and less invasive approaches fail.

Medication Overuse Headache

MOH is an interaction between therapeutic agents used. MOH should be suspected in a patient not responding to standard prophylactic drugs. Diagnosis is important as both acute and prophylactic drugs become ineffective as long as patient is overusing these analgesic medications. Maintenance of a headache diary is important for diagnosis, and both physicians and patients need to be educated about its use.

Diagnosis

According to the IHCD2 criteria, the diagnosis of MOH can be made in any patient who is having headache for more than 15 days per month and is regularly overusing medications for more than 3 months. Overuse is said to be present, if ergots, triptans, opioids, and combination analgesics are taken for more than 10 days per month. For simple analgesics the duration has to be more than 15 days per month. The diagnostic criteria of MOH are based on the number of tablets taken per month as well as the number of days per month for which the drug is used. They are difficult to use in our country as very few patients are in the habit of maintaining a diary.

Treatment

- Patient education and proper counseling is very important as it helps to motivate the patient for withdrawal of overused medication, to tolerate the withdrawal symptoms, and also prevent the patient from returning back to the overused drug.
- The next step is to discontinue the offending medication. It can be done either suddenly or gradually either as an outpatient or inpatient. Abrupt withdrawal is the treatment of choice. Withdrawal symptoms usually last 3–4 days. They include withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness.
- Bridge therapy is required to treat withdrawal symptoms. NSAIDs, chlorpromazine, valproate, steroids, or clonidine may be used. Most experts recommend steroids for outpatient withdrawal, while IV sodium valproate can be used for in-patient withdrawal. Oral steroids 60–100 mg have been used for 5–6 days in a tapering dose. IV DHE 1–2 mg 8 hourly is preferred as it has a very low likelihood of development of medication overuse but unfortunately this drug is not available in India.
- Patient should be instructed about the proper use of acute medications. He should be advised to take it only if he has severe headache. They should be told not to take the drug in anticipation. NSAIDs such as naproxen are preferred as they rarely cause MOH.

- Migraine preventive medications are an important component of withdrawal treatment strategy and should start as soon as possible during the withdrawal process. Topiramate and divalproex sodium have been shown to be beneficial.
- Relapse following successful withdrawal is a major problem.
- Prevention of development of MOH can be done by using drugs which rarely cause MOH such as NSAIDs or have a low probability of causing MOH such as aspirin, acetaminophen, and triptans and these should be preferred for acute treatment. Use of combination analgesics, tranquilizers, and opioids should be avoided in the treatment of headache. Adequate prophylaxis can help to reduce the overuse of acute medications.

Headache Attributed to Substance Withdrawal

Headache may be produced on withdrawal of few substances after chronic use like caffeine, opioid, and estrogen. They may be diagnosed if there is temporal relationship between headache and withdrawal of substance known to produce withdrawal headache.

Headache Attributed to Withdrawal From Chronic use of Other Substances

It has been suggested but without sufficient evidence that withdrawal of the following substances may cause headache: corticosteroids, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), NSAIDs.

Investigation

- No specific investigations are needed as the diagnosis is based on history of temporal relation between headache and withdrawal of offending agent.
- If there is any doubt about diagnosis then investigations are required to rule out a secondary cause.

Treatment

- Treatment is directed toward total withdrawal of the offending drug because after total withdrawal headache subsides within 1 week period.
- Acute symptomatic drugs like NSAIDs may be used if headache is problematic. Specific treatment for the opioid withdrawal should be undertaken.

Headache Attributed To Infection

Headache is a common accompaniment of intracranial infections and systemic viral infections. It is also common with sepsis and rarely may it accompany other systemic infections. In intracranial infections, headache is usually the first and the most frequently encountered symptom. The occurrence of a new type of headache which is diffuse, pulsating, and associated with a general feeling of illness and fever should raise the suspicion of an intracranial infection even in the absence of a stiff neck.

Headache Attributed to Bacterial Meningitis

Bacterial meningitis usually presents with a triad of headache, fever, and altered sensorium.

Diagnosis

Headache is the most common and may be the first symptom of bacterial meningitis. Fever and vomiting may be associated. The history is usually of short duration. There may be associated history of an ear discharge, or throat infection.

Investigation

- The hemogram shows polymorphonuclear leucocytosis and positive acute phase reactants indicative of infection
- A cerebrospinal fluid examination (CSF) is the confirmatory test.
- CSF exhibits polymorphonuclear leucocytosis with markedly decreased sugars and increased proteins.
- CSF samples should also be sent for gram stain, culture, and sensitivity to look for the causative organism.
- Chest x-ray, blood culture, and culture from throat, ear discharge, skin lesions (if any) should also be done.
- Imaging of the brain with a CT scan or MRI is not usually required for confirmation.

Treatment

- Systemic antibiotics are the mainstay of treatment and the choice of antibiotics depends upon the causative organism grown on the CSF culture/blood culture.
- In many cases, culture reports are either not contributory or are negative, in which case empirical antibiotics [Table 8] are started assuming the most common organism (depending upon the age of the patient).
- The incidence of resistance to antimicrobials is gradually increasing and therefore patients should be closely monitored, and if there is no clinical response observed in the first few days, antibiotics should be changed.

Table 8: Antimicrobials in bacterial meningitis

Age	Likely organism	Antimicrobial drug
0--12 weeks	Group B Streptococcus, Listeria	III Generation cephalosporin + Ampicillin
3 months--50 years	<i>S. pneumoniae</i> , <i>H. influenzae N. Meningitidis</i>	III Generation cephalosporin ± Vancomycin
50 years	<i>S. Pneumonia</i> , Listeria, gram-negative Bacilli	As above + Ampicillin
Skull fractures	<i>S. aureus</i> , <i>S. pneumoniae</i>	As above
Post surgery	As above	Vancomycin + Ceftazidime
Dosage of antibiotics	Ceftriaxone 4 g/day Cefotaxime 8--12 g/day Ceftazidime 8 g/day Vancomycin 3 g/day Ampicillin 12 g/day	

- Steroids are not indicated in acute bacterial meningitis except in children or in conditions where patients develop septicemic shock.

Headache Attributed to Lymphocytic Meningitis

A variety of organisms cause a lymphocytic reaction on infecting the subarachnoid space and cause lymphocytic meningitis. Headache is a common manifestation of these conditions. Causes of lymphocytic meningitis include: infections: tuberculosis, viral infections, borrelia, brucella, amoebic meningoencephalitis, toxoplasmosis, fungal meningitis; malignancy: leukemic meningitis, systemic cancer with meningeal seedlings; chemical meningitis: drug induced, contrast material induced; and systemic causes: vasculitis/connective tissue disorders

Diagnosis

Headache, photophobia, and nuchal rigidity are the main symptoms of lymphocytic or non-bacterial meningitis. Fever may or may not be an accompanying feature to begin with, but is almost invariably seen at some time during the course of the disease. Headache is usually generalized, associated with stiffness of the neck and altered sensorium in advanced cases. The onset of the symptoms may be acute as in viral infections or may be subacute or gradual as in chronic situations like fungal meningitis, tuberculosis, or toxoplasmosis. In chronic meningitis, patients usually have a history of prolonged constitutional symptoms like weight loss, malaise, and evening rise of temperature. A history of prolonged immunosuppression, steroid intake, diabetes could be contributory in some patients. Patients with viral meningitis have an acute onset of these symptoms but the clinical course of the disease is milder and recovery can be spontaneous.

Investigation

- The hemogram might be normal or may show a lymphocytic pleocytosis with a raised ESR.
- X-ray of the chest might reveal tuberculosis which might be clinically silent; it may show evidence of vasculitis or sarcoidosis.
- Unlike in acute meningitis, here imaging of the brain is usually the first investigation.
- The contrast enhanced CT scan head in patients with chronic meningitis shows evidence of basal exudates usually in the cisternal spaces, and/or evidence of vascular compromise of perforator arteries due to these exudates causing infarcts.
- CT scans also show tuberculomas, cryptococcomas, and toxoplasma granulomas which are evident as ring enhancing lesions on imaging. Evidence of hydrocephalus if present can also be seen.
- MRI of the brain is required in cases where it is difficult to differentiate between various inflammatory granulomas in the brain.
- MRI of the spine is needed if there is a suspicion of arachnoiditis.
- CSF examination is required in all cases. All patients with lymphocytic meningitis show lymphocytic pleocytosis in the CSF. Depending upon the cause the CSF sugars might be normal (chemical meningitis, lymphocytic meningitis,

toxoplasmosis, systemic vasculitis), mildly reduced (tubercular meningitis, viral meningitis) or significantly reduced (cryptococcal meningitis). Proteins in the CSF are high in almost all cases except with chemical meningitis and cryptococcal meningitis.

- The CSF should also be evaluated for cryptococci using India ink and for cryptococcal antigens (in cases of suspected fungal meningitis), acid fast bacillus (TB meningitis), PCR (TB meningitis, viral meningitis), toxoplasma antigen (toxoplasmosis). Specialized investigation are required as and when needed according to the individual case.
- HIV serology should be done in all patients with lymphocytic meningitis as it has an important bearing on the management.

Treatment

- The treatment of various forms of lymphocytic meningitis is individualized.
- There are no specific guidelines for many of these treatments and there are no studies in the Indian population to decide what regimen is ideal and correct.

Tubercular Meningitis

- Patients with tubercular meningitis (TBM) require anti-tuberculous drug treatment in the standard doses. Treatment should ideally be started as early as possible for better results.
- There are no studies to recommend which drug combination is ideal. Rifampicin (R) (15 mg/kg), isoniazid (H) (10 mg/kg), pyrazinamide (Z) (30--50 mg/kg), ethambutol (E) (15--20 mg/kg), streptomycin (1.25 mg/kg) (M) are the usually prescribed drugs. At least four drugs should be given at the start of the treatment (RHEZ/RHEM).
- It is recommended that these four drugs be given for at least 3 months and thereafter at least three drugs be continued for at least 1 year or 15 months.
- In the initial phase of treatment steroids (dexamethasone---2 mg/kg or prednisolone 1 mg/kg) are strongly recommended. Steroids need to be given for at least a month before tapering them off.
- Periodic checks of liver function tests should be carried out in all patients as the chances of developing drug induced hepatitis after starting anti-tuberculous treatment (ATT) in patients with TBM is very high.
- Patients should be reassessed periodically for improvement. If they fail to show improvement or develop persistent headache or start worsening or show focal neurological deficits, a repeat evaluation including neuroimaging should be done. Hydrocephalus needs to be managed by doing a ventriculoperitoneal shunt.
- Drug resistance is frequently observed with TBM and needs to be managed by giving second line drugs like capreomycin, kanamycin, or quinolones. If patients develop features of non-responsiveness or worsen in their clinical condition they are best referred to specialists for further management.

Fungal Meningitis

- Cryptococcal meningitis is the commonest fungal meningitis. They should be treated with antifungals. Amphotericin B, flucytosine, fluconazole are the ones that can be used.

- When diagnosed correctly, such patients are better managed at major hospitals with adequate experience in the management of fungal meningitis.

Viral Meningitis

Viral meningitis is almost always self limiting and except in some cases no specific treatment apart from general treatment is required. Some patients with extremely severe meningitis with herpes simplex virus might require acyclovir.

Headache Attributed to Encephalitis

Most common causes of encephalitis are the viral infections. Herpes simplex virus, arbovirus, and mumps are known causes of encephalitis. Except for HSV encephalitis, the causative virus is identified in fewer than half of cases of encephalitis even at referral centers.

Diagnosis

Patients with encephalitis usually present with high grade fever, headache, and altered sensorium. The headache is like any other intracranial infection and the fever is usually high grade with chills and rigors. Patients with encephalitis characteristically do not have neck rigidity. Behavioral problems are common, particularly in patients with herpes simplex encephalitis who present with apathy, aphasia, or generalized irritability. Seizures are common in viral encephalitis.

Investigation

- The CSF in encephalitis demonstrates a lymphocytic pleocytosis with normal or mildly reduced sugars and normal proteins.
- Herpes virus antigen can be detected in the CSF and PCR for viral DNA may be positive; however these tests are available only in referral centers.
- The CT scan may show changes with hypointense areas in the temporofrontal region.
- MRI is a better modality of investigation and shows areas of hypointensity in the frontotemporal region, even in cases where the CT scan may be normal.
- EEG shows abnormal lateralized discharges in the region of the frontotemporal region.

Treatment

- Acyclovir is the drug of choice and is given in 10 mg/kg every eight hourly for at least 14 days or till the CSF PCR comes negative (whichever is earlier).
- If the treatment begins in time the response to treatment can be very rewarding and a clinical cure might be expected.
- Antiepileptics might be required if there are associated seizures.

Headache Attributed to Brain Abscess

Headache is a common finding in patients with brain abscess. The presence of a febrile encephalopathy with focal neurological deficits is indicator of an evolving brain abscess. The presence of an associated ear discharge, frontal sinusitis,

head injury, or history of recent head surgery should heighten clinical suspicion. The most common organisms causing brain abscess include streptococcus, *Staphylococcus aureus*, bacteroides species, and enterobacter.

Diagnosis

- Headache is the most important feature.
- Fever may or may not be present, and if present is usually associated with chills.
- Patients may have focal deficits on neurological examination depending upon the area of the brain where the abscess is located.
- Approximately 50% will have seizures and vomiting and nausea, more so in the morning.
- Neck rigidity is usually not seen.
- Predisposing factors include infections of paranasal sinuses, ears, jaws, teeth or lungs.

Investigation

- Routine hemogram might be normal; CSF examination is contraindicated in suspected or proven brain abscess.
- Imaging of the brain clinches the diagnosis.
- In the early stage of cerebritis, the abscess appears as an area of hypodensity in the CT scan or hyperintensity on an MRI scan.
- In later stages, the abscess presents as a ring enhancing lesion with a thick ring which enhances on contrast scans.

Treatment

- Intravenous antibiotics are required in all, and surgery in most cases with brain abscess.
- A judicious combination of antibiotics, depending upon the likely organism, is to be given for a long time. Most regimens include penicillin or a third-generation cephalosporin and metronidazole. In case the abscess follows a surgery, or head injury, vancomycin should be added to the regimen.
- Antibiotics should be continued for at least 6 to 8 weeks. In non-responders, or in patients with multiloculated abscesses or in patients with large abscesses, early surgery is recommended.
- Surgery might be in the form of a thick needle aspiration or a decortication of the abscess.
- Anticonvulsants are usually given for about 3 months after surgical excision. Recurrence is common and therefore repeat imaging after 6 months after a successful treatment of the brain abscess is recommended.

Headache Attributed to Subdural Empyema

Subdural empyema is often secondary to sinusitis or otitis media. It may also be a complication of meningitis, osteomyelitis of the bones of the skull, or head injury.

Diagnosis

Patients usually present with headache which evolves acutely.

Investigation

- Early diagnosis is best made by CT or MRI which demonstrates pus accumulating in the subdural space.

Treatment

- Untreated subdural hematomas are uniformly fatal.
- Combined medical and surgical treatment is definitely required. Posterior fossa empyemas usually require a craniotomy, others might benefit with burr hole evacuation.
- Antibiotics should be given for at least 6–8 weeks.

Headache Attributed to Systemic Infection

Headache in systemic infections is usually a relatively inconspicuous symptom and diagnostically unhelpful. These conditions are mostly dominated by fever, general malaise, and systemic symptoms. Nevertheless, some systemic infections, particularly influenza, have headache as a prominent symptom along with fever and other symptoms.

Headache Attributed to HIV/AIDS

Headache in patients with HIV infection could be manifold. At the time of seroconversion, patients with HIV infection may have associated aseptic meningitis. These patients, because of diminished immunity, are prone to many cranial infections—like tubercular meningitis, cryptococcal meningitis, toxoplasmosis, etc. Effective treatment of these infections usually resolves the headache. Prophylaxis might be required in most such infections, if the CD 4 count is low in AIDS patients.

Diagnosis

Headache is dull and bilateral, reminiscent of tension-type headache. The confirmation of HIV infection is essential to discriminate headache caused by additional intracranial condition that are associated with HIV infections (e.g., cryptococcal meningitis). Therefore, it is crucial to obtain neuroimaging studies and CSF examination to distinguish between headache as a general symptom of systemic HIV infection and one that is caused by CNS infection or conditions that accompany HIV disease. Headache in AIDS can also be caused by CNS tumors like primary CNS lymphoma and metastatic systemic lymphoma.

Treatment

- The pain of HIV/AIDS usually responds to routine analgesics.
- Management of other primary headaches remains the same in patients with HIV.
- Opportunistic infections in AIDS should be managed accordingly, and this results in improvement of the headache of HIV patients.

Headache Attributed to Disorder of Homeostasis

Included in this segment are headaches attributed to abnormal blood circulation in the brain. Previously these were called as *Headache associated with metabolic or systemic disease*. Headaches can be caused by sudden alteration in the arterial pressure as in pheochromocytoma, and by myocardial ischemia are included in this section. In addition, disorders of homeostatic mechanisms affecting a variety of organ systems, including altered arterial blood gases, volume disturbances as in dialysis, and disorders of endocrine function, are covered in the ICHD2.

Since there are disorders not commonly seen in practice and therefore they have not been discussed in detail.

Headache or Facial Pain Attributed to Disorder of Cranium, Neck, Eyes, Ears, Nose, Sinuses, Teeth, Mouth or Other Facial or Cranial Structures

The disorders of the structures in and around the neck and head region have long been held responsible for headache. Degenerative disorders of the cervical spine, temporomandibular joints, and diseases of the paranasal sinuses are so commonly reported to be “associated” with headaches that headache is often said to be caused by these disorders. These associations have not been supported by evidence as many people who have these disorders do not have headaches and vice versa. Therefore they are not discussed in detail here.

Headache Attributed to Disorder of Eyes

Headache attributed to acute glaucoma

Acute angle closure glaucoma presents with a painful red eye with blurring of vision and occasionally sudden blindness. A closure of this angle due to any reason tends to precipitate an attack of acute glaucoma as the intra-ocular pressure increases to very high levels in a few hours. Pain is severe, boring, and located in or around the eyes.

Diagnosis

Pain in the eye and behind or above it, fulfilling criteria C and D. Raised intraocular pressure, with at least one of the following: conjunctival injection; clouding of cornea; or visual disturbances. Pain develops simultaneously with glaucoma. Pain resolves within 72 h of effective treatment of glaucoma

Investigation

- High index of suspicion in a patient with red fiery eye
- Raised intraocular pressure in excess of 28 mmHg

Treatment

- Pilocarpine or other mitotic drugs—to make the iris cornea angle wider
- Mannitol to reduce intraocular pressure.
- Steroids.
- Surgery when condition stabilizes.

Headache Attributed to Refractive Errors

Refractive errors are very commonly thought to be associated with headache, to the extent that in every individual with any type of headache a visual acuity testing is advised. It is actually a misconception since refractive error is an uncommon cause of headache. Patients rarely complain of headache, they usually have a heaviness of the head or eye soreness on times when they are awake and watching events like television or reading.

Headache Attributed to Ocular Inflammatory disorder

Ocular inflammations are categorized in a variety of ways

including by anatomic location (cornea, iris, sclera, choroid, etc), type of inflammatory response found (e.g., nongranulomatous or granulomatous), temporal profile of symptoms (acute, subacute, chronic), and cause (e.g., viral, bacterial, fungal, autoimmune)

Diagnostic Criteria

Pain in the eye and behind or around it, fulfilling criteria C and D. Ocular inflammation diagnosed by appropriate investigation. Headache develops during inflammation. Headache resolves within 7 days after relief of the inflammatory disorder

Treatment

- Treatment of the underlying cause---antiviral, antibacterials.
- Steroids in cases of autoimmune uveitis.
- Systemic steroids in severe cases.
- Cycloplegics to abolish the associated ciliary spasm.

Referral

The patients should be referred to an ophthalmologist as soon as the diagnosis is made, as most of these conditions can be severe and require expert management.

Headache Attributed to Rhinosinusitis

Headache is commonly attributed to diseases of the nose and paranasal sinuses. As the nerve supply of the nasal sinuses is the same as that of the frontal and temporal regions, the pain of the sinuses is often referred to the skin in the region of the scalp and face. Infection/inflammation of the nose and the nasal sinuses tend to worsen the primary headaches. The diseases of the following structures can cause headache

Diseases of the Nose

- Nasal Septum-Deviation of the nasal septum may cause acute disease of the nasal sinuses that causes facial pain. Acute or chronic sinusitis can complicate the picture.
- Septal Hematoma and Septal Abscess-presents with a purulent and swollen nasal septum, pain is localized and severe, marked sensitivity to local pressure, reddening of the tip of the nose. Seen in granulomatous disease, polychondritis, or other autoimmune disorders.
- Inflammatory Rhinosinusitis-rhinorrhea, elevated temperature, pain affecting the middle part of the face and the area of distribution of the first and second trigeminal branches, and symptoms of an infection of the upper respiratory tract are the symptoms.
- **Allergic Rhinitis**---does not cause primary pain but facial pain may occur as a secondary development. It is typically seasonal presenting with nasal obstruction, nasal pain, and rhinitis.
- **Vasomotor Rhinitis**---is due to excessive reactivity of the mucous membrane. The nasal discharge is clear, and the nasal mucous membrane is swollen and displays a slight reddening compared with inflammatory rhinitis.
- **Atrophic Rhinitis**---there is reduced reactivity of the nasal mucous membrane. Mucous production is reduced, and the nasal mucous membrane is dry, encrusted, inflamed, and irritated.

Diseases of the Paranasal Sinuses

Acute Sinusitis

- Inflammation of the nasal membrane, sinuses, and their vicinity cause the symptoms of sinusitis.
- Purulent discharge and headache develop with acute nasal sinusitis, following an upper respiratory tract infection.
- Nasal polyps can also cause similar symptoms due to obstruction of the meatus of the sinuses. Maxillary sinusitis also may be caused by inflammations of dental gin, such as periapical abscesses, or of iatrogenic origin as a result of dental surgery.
- Allergies, hypothyroidism, cystic fibrosis, immune suppression, and diabetes mellitus predispose to the development of sinusitis. Trauma to the nasal sinus with fractures also may give rise to nasal sinusitis.
- Maxillary sinusitis-pain felt over the sinuses may radiate to the ear and teeth. Skin over the sinuses is tender to percussion. There is purulent discharge from the middle meatus with mild anosmia.
- Frontal sinusitis-Pain is behind the eyes and in and around the centre of the head. Maximum on getting up in the morning and improves on ambulation. There is tenderness over the sinus and the supraorbital nerve, and there is purulent discharge from the nasofrontal duct.
- Ethmoidal and sphenoidal sinusitis-the pain in both the cases is poorly localized but is usually retro-orbital and the eyes are sensitive to pressure. There is presence of post-nasal discharge.
- Chronic Sinusitis-chronic inflammation of the nasal sinus mucous membranes, which become hypertrophy and cause a permanent disturbance of nasal ciliary action and altered function of the mucous glands.

Diagnosis

- Frontal headache accompanied by pain in one or more regions of the face, ears or teeth, and fulfilling criteria C and D
- Clinical, nasal endoscopic, CT and/or MRI imaging and/or laboratory evidence of acute or acute-on-chronic rhinosinusitis;^[1,2]
- Headache and facial pain develop simultaneously with onset or acute exacerbation of rhinosinusitis
- Headache and/or facial pain resolve within 7 days after remission or successful treatment of acute or acute-on-chronic rhinosinusitis

Investigation

- Polymorphonuclear leukocytosis raised ESR.
- Culture from the pus/purulent discharge to isolate the organism responsible
- A transillumination examination can reveal pus levels in sinusitis.
- Plain radiographs of the nasal sinuses may show shadows or fluid levels. It is not possible to differentiate chronic from acute sinusitis by means of radiologic examination; this must be done on the basis of clinical features and the examination findings.
- A CT or magnetic resonance tomogram may be helpful in differentiating between a cystic and a solid lesion or a fluid level.

Treatment

- Antibiotics and oral decongestants—depending upon the organism and the sensitivity of the cultures.
- Decongestants to be given for not more than 3 days.
- Steam inhalation, warm compresses.
- Irrigation of the sinuses by saline and by antibiotics.
- Removal of the obstruction, like polyps, deposits can be cleared surgically.
- Drainage improved surgically by increasing the size of the orifices draining the sinuses.
- Correction of the deviated nasal septum.

Headache Attributed To Psychiatric Disorder

Patients with psychosis seldom complain of headache, in fact it is considered that these patients perceive lesser pain than normal individuals. Patients who have a delusion that they have a lesion in the brain like a space occupying mass, or a delusion that someone has implanted a machine inside their head which causes the headache is an example of the condition when headache can occur in patients with psychosis.

Cranial Neuralgias and Central Causes of Facial Pain

Diagnosis

Neuralgias are defined as sharp, intense, electric shock like pain abrupt in onset and termination limited to the distribution of one or more divisions of a cranial nerves or cervical roots or nerves. The facial pain syndromes have the common denominator of pain in the face which may be localized to either one or more divisions of trigeminal nerve. Unlike neuralgias, they are diffused and are more long-lasting. These diverse conditions can be divided into three broad groups as follows.

- Primary neuralgias
- Pain of cranial and cervical nerve origin other than primary neuralgias
- Central pain in the face and head
- Primary Neuralgias

Trigeminal Neuralgia

Diagnosis

Trigeminal neuralgia is a unilateral disorder characterized by electric shock like pains, abrupt in onset and termination (seconds to up to 2 min), limited to the distribution of one or more divisions of trigeminal nerve. Most commonly, the second and third divisions of trigeminal nerve get affected. In less than 5% of patients, the first division is affected. Pain is commonly evoked by trivial stimuli including washing, shaving, smoking, talking, and/or brushing the teeth which are known as trigger factors. Frequently, however, it occurs spontaneously. Trigeminal neuralgia runs a chronic course; the pains usually remit for variable periods of time to recur again. Despite severe pain, clinically no neurologic (sensory) deficit is seen in primary trigeminal neuralgias.

Etiology

Compression of the trigeminal nerve by a blood vessel at root entry zone is the cause of trigeminal neuralgia in majority of patients. In many, no cause can be found. There may be

other causes of compression of trigeminal nerve leading to symptomatic trigeminal neuralgias in 5% to 7% of patients. These groups of patients are classified as symptomatic trigeminal neuralgias. In these cases, clinically some atypical features may be found such as the presence of sensory impairment, bilaterality (like in MS), and the presence of non-paroxysmal pain.

Investigation

- All patients of trigeminal neuralgia should undergo MRI, preferably using 3D reconstruction techniques to assess the relationship of nerve with the neighborhood blood vessels and to rule out causes other than the vascular compression.

Treatment

The management of trigeminal neuralgia includes pharmacotherapy and neurosurgical intervention through various neuroablative procedures.

Pharmacotherapy

- Carbamazepine was tested by many double-blind placebo-controlled randomized trials and has been found to be efficacious in 75% of patients.
- Treatment is usually started with low dose carbamazepine (100-200 mg/day), which is then up-titrated gradually. Usually the maintenance dose of 400-1200 mg per day is required.
- Physicians have to be cautious about various side effects of carbamazepine especially in the elderly patients.
- Other second line drugs used for treating trigeminal neuralgia include oxcarbazepine, phenytoin, baclofen, lamotrigine, and gabapentin [Table 9].

Surgical Treatment

- Surgical intervention is required for patients who are refractory to medical treatment and continue to have significant pain despite adequate trial of medications. Also, specific secondary causes may be amenable to surgical treatment such as tumors.
- Following surgical options are available for refractory primary (classical) trigeminal neuralgias.
- Micro-vascular decompression (MVD) is the most definitive treatment for trigeminal neuralgia in younger patients. In MVD, the trigeminal nerve is exposed, the offending blood vessel(s) identified, and decompressed. Most common finding is a segment of superior cerebral artery compressing the nerve at the root entry zone. After decompressing it, the operator places a piece of felt between it and the nerve to ensure a permanent separation.
- Pain relief following MVD is almost always immediate and its long-term results are impressive.
- Around 80% of patients remain pain-free up to 2 years and up to 64% patients remain pain-free up to 10 years post-MVD. In expert hands, operating complications are low.
- For elderly patients or those with medical complications where MVD is not possible, percutaneous radiofrequency thermocoagulation of trigeminal nerve sensory root as it leaves the Gasserian ganglion is the procedure of choice.
- Alcohol block of the peripheral branch of the division of the trigeminal nerve that is painful can be attempted. Initial pain relief is good but the recurrence rates are high within 6 months to 1 year. The procedure can be repeated.

Table 9: Drugs for trigeminal neuralgia

Drug	Initial dose	Maintenance dose	Important and common adverse effects
Carbamazepine	100-200 mg	600-1200 mg	Sedation, dizziness, mental slowing, rash, hyponatremia, drug interactions
Oxcarbazepine	150-300 mg	600-1200 mg	Better tolerated than Carbamazepine but hyponatremia is slightly more. Spectrum of adverse effect is same
Gabapentin	100-300 mg	600-2400 mg	Sedation, memory impairment, peripheral edema
Phenytoin	100- 300 mg	300-400 mg	Sedation, ataxia, dizziness, mental slowing, rash, drug interactions, gum hypertrophy, lymphadenopathy, folate deficiency, osteopenia, acne
Lamotrigine	25-50 mg	200-400 mg	Rash, sedation, ataxia, dizziness
Baclofen	10 mg	30-80 mg	Sedation, ataxia, fatigue, GI symptoms, muscle weakness.

- Other upcoming procedures for refractory trigeminal neuralgia include percutaneous balloon compression of the trigeminal ganglion and stereotaxic radiosurgery with gamma knife. However, early recurrences are still a problem.

Glossopharyngeal Neuralgia

Diagnosis

- Glossopharyngeal neuralgia is a severe transient stabbing pain experienced in the ear, in the base of tongue, in the tonsillar fossa, or beneath the angle of jaw.
- The pain is therefore felt in the distribution of the auricular and the pharyngeal branches of the vagus and glossopharyngeal nerves.
- It is commonly provoked by swallowing, talking, coughing, and may remit and relapse similar to trigeminal neuralgia.
- Glossopharyngeal neuralgia is in many ways similar to trigeminal neuralgia.
- The diagnosis of glossopharyngeal neuralgia is essentially clinical, based on the history of characteristic paroxysms of lancinating or aching pain.
- Neurologic, dental, and imaging studies are normal.

Treatment

- Pharmacotherapy of glossopharyngeal neuralgia includes similar drugs as those used in trigeminal neuralgia. Carbamazepine, oxcarbazepine, baclofen, phenytoin, gabapentin, and lamotrigine either alone or in combination have been used.

Other Cranial Neuralgias

Occipital neuralgia

Diagnosis

It refers to paroxysmal stabbing pain with or without persistent aching between the paroxysms in the distribution of greater or lesser and/or third occipital nerve, sometimes accompanied by diminished sensation or dysesthesias in the affected area. It is commonly associated with the tenderness over the nerve concerned and is blocked by local anesthetic injection of the nerve. The frequency of attacks varies from 4 to 5 per day to 2 to 7 per week. Intervening pain-free periods may last up to days weeks or months. Because of the associated feature of lacrimation and ciliary injection and periodicity, this pain syndrome can be confused with cluster like headaches. Occipital localization and neuralgic character distinguish it from cluster like headaches. In most cases, the abnormalities found to compress the C2 and its roots include single or

densely interwoven dilator veins, U-shaped arterial loops, or angiomas. Neuroimaging including x-rays, CT, myelo-CT, and MRI usually are reported to be normal. The most important diagnostic procedure is the complete relief of pain following local anesthetic blockade of the C 2 spinal nerves.

Treatment

- Pharmacotherapy is usually known to be non-rewarding in C2 neuralgia.
- Surgical approach remains the definitive treatment. Decompression of the entrapped nerves (due to scarring) can be done.

Rare cranial neuralgias

- Nervous intermedius neuralgia (brief paroxysms of pain are felt deeply in the auditory canal).
- Superior laryngeal neuralgia (pain paroxysms in throat, submandibular region and under ear and is relieved by local anesthetic block of superior laryngeal nerve).
- Nasociliary neuralgia (touching the outer aspect of one nostril causes stabbing pain lasting minutes to hours on that side of nose radiating up to the medial frontal region),
- Supra-orbital neuralgia (pain in the region of supraorbital notch and medial aspect of forehead).
- Nummular neuralgia pain in a rounded or elliptical area of about 2-6 mm diameter, most commonly in the parietal region that is now considered to be localized terminal branch neuralgia of the trigeminal nerve.

Pain of Cranial and Cervical Nerve Origin other Than Primary Neuralgia

Acute Herpes zoster

It results from reactivation of latent infection by varicella virus. Essentially it is a disease of dorsal root ganglia characterized by vesicular eruptions in the affected dermatome. About 13% of the patients have involvement of trigeminal nerve. The ophthalmic division is affected in majority (80%) of these patients.

Diagnosis

The onset of acute Herpes zoster is usually heralded by pain which precedes the vesicular eruption by a few days. The condition becomes evident once the visible eruption is seen. The initial rash of herpes zoster may mimic that of herpes simplex. The vesicles usually dry out within about 1 week and within a month they heal. The most important complication is post-herpetic neuralgia which may occur in about 10% to 15% of patients.

Treatment

- Acute herpes zoster is treated by using anti-viral agents such as acyclovir, valacyclovir, or famciclovir. Anti-viral therapy also decreases the subsequent incidence of post-herpetic neuralgia by about 80%.
- In addition to the anti-viral agents, tramadol (an opioid derivative), and tricyclic antidepressants like amitriptyline have been found to relieve the residual pain.
- Systemic steroids, particularly for ophthalmic herpes have been used. They usually do not reduce the pain but may improve the quality of life.

Post-herpetic neuralgia

Post-herpetic neuralgia is a neuralgic pain that persists in the affected dermatome long after the vesicular eruption of acute herpes zoster has healed. The pain is typical of neuralgia. Jabs of shooting, lancinating pain on a background of constant burning, or aching pain are characteristically reported. The skin of the affected dermatome is hypoaesthetic. However, the zones of hyperesthesia from which the attacks of pain may be triggered by light touch or brushing are present around the hypoaesthetic zone.

Treatment

- Tricyclic antidepressants, pregabalin, gabapentin, opioids are effective in postherpetic neuralgia.
- Of these, amitriptyline and related tricyclic antidepressants have been most widely used and most thoroughly studied agents for the treatment of post herpetic neuralgia.
- For pain resistant to tricyclic antidepressants and gabapentin, opioids may be tried.
- Intravenous lidocaine and intravenous morphine may be used in an attempt to interrupt the persistent pain unrelieved by other medications.
- There are many surgical interventions that have been used for trigeminal post-herpetic neuralgia. These include trigeminal rhizotomy, avulsion, alcohol injection, or cryoinjection of the supraorbital nerve, alcohol injection of the trigeminal ganglia, and trigeminal tractotomy. While some of these procedures may be useful in an individual patient, none has been found to produce consistently good results for achieving prolonged pain relief.

Tolosa Hunt Syndrome and Painful Ophthalmoplegia

Diagnosis

One or more episodes of unilateral orbital pain persisting for weeks if untreated associated with paresis of one or more of the third, fourth, and/or sixth cranial nerves and/or demonstration of granuloma by MRI or biopsy suggests diagnosis of Tolosa Hunt Syndrome. Paresis usually coincides with the onset of pain or follows it within 2 weeks. Pain and paresis resolve within 72 h when treated adequately with corticosteroids. This condition is however should be considered as only one of the etiologies out of many diverse conditions which have been grouped under the broad heading of "painful ophthalmoplegia."

Investigation

- Clinical examination alone is not sufficient to find out the

causative lesion of painful ophthalmoplegia.

- As a first step, neuroimaging, preferably contrast enhanced MRI, is required to detect cavernous sinus and other pathologies.
 - This is then followed up by various tests like blood chemistry (ESR, blood sugar, connective tissue profile, serology for various infections), CSF studies, cerebral angiography and biopsy depending on suspected etiology.
- 2 For example, if a glaucomatous lesion is seen in cavernous sinus, further investigations for various infections by serology and CSF studies are indicated. In contrast, if a lesion suspicious of aneurysm is seen, angiography is indicated.

Ophthalmoplegic Migraine

This is now considered to be a rare disorder. Recurrent attacks of headache with migrainous characteristics associated with paresis of one or more ocular nerves (commonly the third nerve) in the absence of a demonstrable intracranial lesion on MRI define the clinical syndrome. Only finding on MRI at times may be the enhancement of third cranial nerve with gadolinium. The diagnosis is that of exclusion. All other causes of painful ophthalmoplegia need to be excluded.

Central Pain in the Face and Head

Characteristically, central pain is constant and spontaneous, although they can be evoked. Occasionally, paroxysmal pain can also occur. Central pain may have a predominantly dysesthetic character. The term thalamic pain denotes pain due to lesions or dysfunction of thalamus. Pseudothalamic *central pain* is sometimes used for central pain caused by extrathalamic lesions. Central post-stroke pain is the central pain resulting from a cerebrovascular lesion affecting the quintothalamic pathways or thalamus. Anesthesia dolorosa consists of persistent painful anesthesia in the distribution of the trigeminal nerve or one of its divisions or of occipital nerves. Despite the sensory loss, the patients feel pain which may become unbearable. Persistent idiopathic facial pain is of unknown cause occurring predominantly in middle-aged females and is a diagnosis of exclusion. The pain is usually unilateral, occasionally can be bilateral and is commonly felt around chin or nasolabial fold which may spread to wider areas of face and neck. They are usually deep, poorly localized, occur continuously throughout day and night, and worsen with time. Although many patients have overt depression, not all are depressed. Burning mouth syndrome is a condition characterized by burning sensation in the mouth without a medical or dental cause. Oral mucosa is normal on examination. Occasionally pain may be limited to tongue only (glossodynia).

Etiology of Central Pain

Vascular lesions in the brain and the spinal-cord, multiple sclerosis, spinal injuries, and neurosurgical procedures like cordotomies are common conditions causing central pain. In contrast brain tumors and traumatic brain injuries seldom cause central pain.

Diagnosis

- The diagnosis of central pain rests on the total clinical picture, in which history, symptoms, and signs indicate disease process in the CNS and the pain characteristics of which are compatible with central pain.
- The pain usually starts after the onset of the CNS disease and often the onset is delayed. Pain occurs in a regional distribution and is usually lateralized in contrast to dermatomal or nerve distribution.
- Characteristically, the pain is burning, aching, pricking, lacerating, or lancinating type. Quite often, patients report a mixture of such types of pain occurring simultaneously. Clinical examination usually reveals sensory abnormalities in the form of hypoaesthesia, hyperaesthesia, and dysesthesias.
- Non-sensory symptoms and signs may or may not be present. Central pain is almost always chronic usually lasting for many years.
- Anesthesia dolorosa is most commonly seen as a surgical complication of rhizotomy and thermocoagulation done to treat trigeminal neuralgia.
- Persistent idiopathic facial pain and burning mouth syndrome are diagnoses of exclusion.

Treatment

Current treatment of central pain includes pharmacotherapy and neurostimulation.

Pharmacotherapy

- The first group of drugs is those which reduce CNS hyperactivity. These include carbamazepine, lamotrigine, gabapentin, pregabalin, clonazepam, and baclofen.
- The second group of drugs increases the activity of endorphin-related pain inhibiting systems by influencing the reuptake of serotonin and noradrenalin. The classic example is antidepressant drug, amitriptyline.
- The third group includes alpha-2-agonist like clonidine and direct opiate receptor antagonists.
- Sometimes, intravenous lidocaine and intravenous morphine may be used in an attempt to interrupt the persistent pain unrelieved by other medications.

Neurostimulation

- Transcutaneous electrical stimulation has been found to be effective in central pain syndrome.
- Thalamic stimulation also appears promising.
- Excellent results have been reported following surface stimulation of the motor cortex in central post-stroke pain. All these however require expertise and are usually available in larger centers.

When to refer to a specialist?

- When the diagnosis is uncertain.
- When there is a neuralgias with atypical features
- When there is neuralgia with prominent neurological deficits.
- Refractory neuralgias and headaches unresponsive to first

and second line drugs.

- When surgical treatment is contemplated.

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Guidelines for management of essential tremor

Pramod Kumar Pal

Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, India

For correspondence:

Dr. Pramod Kumar Pal, Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, India.

E-mail: palpramod@hotmail.com

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Essential tremor (ET) is a common movement disorder, and approximately 50% of the cases are inherited as an autosomal dominant trait.^[1] The incidence of ET increases with age, may manifest at any age (childhood to adulthood), and those with a positive family history have an earlier age of onset.^[2] The tremor involves mainly the upper limbs distally and is postural or kinetic type. The less common parts involved with tremor are the head, lower limbs, voice, tongue, face, and the trunk. The tremor amplitude increases with time, and patients experience difficulty in writing, eating, holding objects and doing fine motor tasks, dressing, and speaking.^[3] Although ET usually does not reduce life expectancy or cause other symptoms, many patients have severe psychosocial disability.^[3] Tremor often increases with anxiety, stress, and in situations involving interaction with others. Patients with head and voice tremor often suffer severe embarrassments, and may develop depression.

ET should be differentiated from the other types of tremors, especially tremor of Parkinson's disease, tremor associated with hyperthyroidism, and dystonic tremor of head in patients with isolated head tremor. Once a diagnosis is made, the severity of functional and psychosocial disabilities should be assessed by objective scales, which will help to determine the need for pharmacotherapy.

The management of a patient with ET includes (a) behavioral techniques and physical therapy, (b) medical therapy, and (c) surgical treatment. The patient should be explained about the disease, the long-term outcome, and what the therapies can achieve. All therapies are essentially symptomatic and will not cure or change the course of the disease. If there is minimal functional disability, the patient need not take treatment. Even if the tremor is controlled by medical therapy, stress and anxiety

can increase the symptoms. An outline of the management of ET is given in Figure 1.

Behavioral Techniques and Physical Therapy

Not all patients with ET will need treatment with drugs. Treatment depends on the severity of tremor, the body part affected, and the occupation of the patients. It is also determined by the degree of social disability. In patients with less disabling tremor, certain behavioral techniques and physical therapy may be useful. These include relaxation therapies and reducing emotional stress, using the less disabled hand to write or eat, using wrist weights^[2] and minimizing exposure to tremorogenic foods (eg, caffeine) and drugs (eg, sympathomimetics).

Medical Treatment

Treatment schedules

When it is decided to start medical treatment, it can be of 2 types:

1. Intermittent treatment: *On an as-needed or scheduled basis*. This is recommended when the patient is distressed mainly in social gatherings or prior to an important social activity. A half to 2 tablets of propranolol (20 mg) can be administered 30 min to 1 h before a social activity or the anxiety-provoking event, which increases tremor. Alternatively, a benzodiazepine, such as lorazepam or clonazepam can be administered prophylactically. However, as the benzodiazepines can cause central nervous system adverse events and also have abuse potential, they need to be administered judiciously. Although routine use of alcohol is not recommended, in patients with alcohol responsive tremors, judicious use of a small amount of alcohol prior to select social activities, such as social dinner, can be considered.
2. As long-term suppressive therapy: In patients who need long-term therapy, the following drugs have proved to be useful with varied efficacy and levels of recommendations, based on the class of evidence.

Drugs of choice

β -Blockers, most commonly propranolol, and primidone are the drugs of choice for treatment of ET. Both these agents have level

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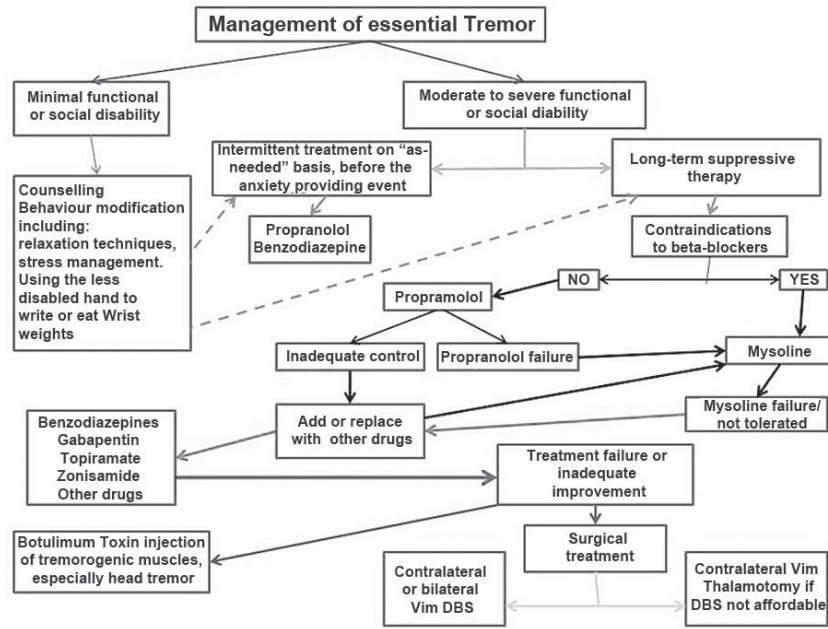


Figure 1: A flow chart showing the steps in the management of essential tremor

A recommendation, and either can be used for initial treatment of ET,^[4] depending on the concurrent medical conditions, and potential side effects.

Propranolol (β-2 blocker)

Treatment should be initiated at 10 mg once daily and gradually titrated (eg, every 3–7 days) to 20 mg twice daily. Elderly individuals may need a lower dose (eg, 10 mg twice daily), while for those who are tolerating well, propranolol can be increased up to 240 mg/day in divided doses. Improvement occurs in approximately 50%–60% of the patients, the greatest improvement being for hand tremor, and the least for head or voice tremor. Long-acting preparations of propranolol also have a similar efficacy. Ten to 15 percent of the responders may develop tolerance after a year of treatment.^[5] Side effects include light headedness, fatigue, impotence, bradycardia, and reduced blood pressure. Relative contraindications to propranolol are severe heart failure, conduction blocks, hyperactive airway disease, depression, and diabetes.

Primidone

The efficacy of primidone for managing ET appears to be similar to propranolol^[5] and it can be an initial therapy, although most often this is started after the failure of propranolol to control ET satisfactorily. Currently, this drug is not easily available in India. The treatment is initiated at the lowest possible dose and gradually titrated up to avoid side effects, which often appear. When a 50 mg tablet or an oral suspension preparation (50 mg/mL) is available (not available in India), it can be started at 12.5 mg at bedtime and slowly titrated upward (increments by 12.5 mg every week) to the dose when desirable tremor control is achieved without significant side effects. Most patients achieve an optimal tremor control at 250 mg/day, although higher doses up to 750–1000 mg/day may sometimes be required. When a patient requires a lower dose, once daily dosing may be adequate; with higher dosage, the drug should be given

in 3 divided dosages. In India, since only 250 mg tablets are available, the treatment is usually started with one-quarter of a tablet (or even smaller if feasible) at bedtime, and gradually increased by one-quarter every week, till the tremor control is achieved (the final dose may be given in 3 divided dosages). When the patient cannot tolerate any increment of dosage, he may continue the previous dosage for a longer time, and then try further increment of dosage.

The most common side effect of primidone is sedation and drowsiness, and the other common side effects being nausea, vomiting, dizziness, ataxia, confusion, vertigo, and acute toxic reaction. Patients on primidone should have a complete blood count before starting the treatment and again every 6–12 months, as it has been reported, although rarely, to cause red cell hypoplasia, aplasia, agranulocytosis, and megaloblastic anemia. It is contraindicated during pregnancy, lactation, and in patients having porphyria and hepatic and renal dysfunctions.

Combination therapy

When monotherapy with propranolol or primidone does not adequately control limb tremor, these 2 drugs can be used in combination. It has been shown that there may be an added beneficial effect without an increase in side effects.^[4]

Other drugs

The following drugs have lower level (level B or C) recommendations for treating ET, and should be tried (add on or monotherapy) in patients not adequately responding to propranolol or primidone, or when there are prominent side effects:

Benzodiazepines

This group of drugs, which probably augments GABA activity, can be used as add-on treatment for ET. Alprazolam (0.125–3 mg/day), clonazepam (0.5–6 mg/day), lorazepam (1–10 mg/

day), and diazepam (1–10 mg/day) can be considered in patients with significant worsening of tremor due to anxiety or emotional stress. Clonazepam may be particularly useful for treatment of orthostatic tremor, a rare variant of ET.^[6] The drugs should be used with caution because of their abuse potential, side effects of drowsiness and fatigue, and possible withdrawal symptoms following abrupt discontinuance.

Gabapentin

Gabapentin (structure similar to GABA) can be used as a monotherapy or as an add-on therapy for treatment of ET.^[7-9] It is started at 300 mg 3 times daily, and titrated up to 1200–1800 mg/day. The drug is usually well tolerated with few side effects (sedation, irritability, ataxia, weight gain).

Topiramate

Topiramate (blocks sodium channels and potentiates GABA activity) has been shown to be effective in reducing ET (monotherapy or add-on therapy).^[10-12] It is started at 25–50 mg at bedtime and titrated up to 400 mg/day. Side effects include suppression of appetite, weight loss, and paresthesias. Further studies are required to prove its efficacy in ET.

Zonisamide

Zonisamide (acts on sodium and calcium channels) has been reported to be useful in ET, especially for tremors of voice, face, tongue, and head.^[13] It is initiated at 25 mg at bedtime and gradually increased to 200 mg/day. Side effects include sleepiness, fatigue, headache, and paresthesias. The drug can be used as monotherapy or add-on therapy of ET in those who have unsatisfactory response to other antitremor medications at maximally tolerated dosage. Further studies are required to determine the efficacy of zonisamide in ET.

Other drugs

There are reports of possible beneficial effects of pregabalin (starting at 50 mg/day and escalated to 600 mg/day), atenolol (50–150 mg/day), sotalol (75–200 mg/day), nadolol (120–240 mg/day), clozapine (6–75 mg/day), and nimodipine (120 mg/day) in ET. Clozapine is recommended only for refractory cases of limb tremor in ET^[14,15] and patients should be monitored for agranulocytosis. Further studies are required to prove the efficacy of these drugs.

Botulinum Toxin

In medically refractory cases of ET, injections of Botulinum Toxin-A in the tremorogenic muscles (preferably under electromyographic guidance for selecting the muscles) may be useful^[4]. The injection has been shown to be useful for limb, head, and voice tremor.^[16-20] Side effects include temporary weakness of the injected muscles and breathlessness, dysphagia, and hoarseness following treatment for voice tremor. Botulinum toxin injection should be performed only by a trained and experienced neurologist.

Surgical Treatment

Surgical treatment for ET is reserved for those selected patients who have severe tremor not adequately controlled by medical

therapy. Contralateral thalamotomy (VIM nucleus) or deep brain stimulation (DBS) of the thalamus are highly effective in reducing tremor.^[21-22] In India, the choice between thalamotomy and DBS is primarily dictated by the availability of expertise and the cost of DBS. Bilateral thalamotomy is not recommended due to its adverse side effects. Therefore, in those who cannot afford DBS, unilateral thalamotomy contralateral to the most severely affected side is recommended. In patients who can afford DBS, bilateral DBS is recommended to suppress tremor of both sides. There is contradictory evidence that bilateral DBS may be useful for suppressing head and voice tremor. Side effects are more frequent with bilateral DBS.

In summary, ET is a disorder, which can lead to a significant morbidity in some patients, especially functional disability. The approach to management should be guided by the severity of tremor, the parts of the body involved, occupation of the patient, and physical and social disability.

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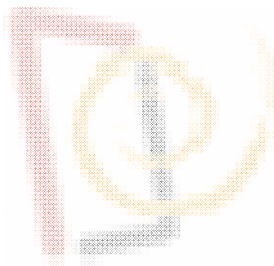
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Initiation of treatment in early PD (evidences based)

Treatment of early Parkinson's disease (PD) may be divided into neuroprotective therapies, symptomatic therapies and various non-standard pharmacologic or non-pharmacologic therapies. Practical guides to direct treatment depend on the patients' symptoms, the degree of functional impairment, the expected benefits and risks of available therapeutic agents. The treatment of PD needs to be individualized, since patients often present with a unique set of signs and symptoms, response to medications and a multitude of other non-socioeconomic factors.

In this communication, we shall present the different agents which have been used in PD subjects with level of evidence of efficacy in different research studies. Then, we shall put our recommendation at the end.

Neuroprotective Therapies of PD

Neuroprotective therapy in PD implies that it would delay decline of motor symptoms and preserve the quality of life. In practical sense, one has to judge the effect of neuroprotective therapy by clinical markers. Potential clinical surrogate markers include ratings of motor impairment, general disability, quality of life measures, delay for the initiation of symptomatic therapy and time to a specific event, motor fluctuations, or death.

Potential neuroprotective therapies include the following.

Vitamin E

Although one unblinded and nonrandomized study without independent assessment suggested a slower rate of progression in early PD patients treated with vitamin E (3200 IU/day) combined with vitamin C (3000 mg/day),^[1] another randomized, blinded study with 800 patients treated with 2000

IU of vitamin E/day or placebo (with or without selegiline) and followed for 14 ± 6 months did not show any difference between the vitamin E and placebo groups in the average time to require levodopa (hazard ratio 0.91, 95% CI 0.74–1.12).^[2]

Coenzyme Q10

Several open and controlled pilot studies on the symptomatic effects of coenzyme Q10 (CoQ10) revealed inconsistent results. The study of the Parkinson Study Group investigating possible protective effects of CoQ10 in early PD demonstrated that high doses of CoQ10 slow the progressive deterioration of functions in PD measured by the total score on the Unified Parkinson's Disease Rating Scale (UPDRS), but neither improve motor functions nor postpone the initiation of levodopa treatment.^[3] Due to the lack of a washout phase and the fast and predominant effects of CoQ10 on activities of daily living (ADL) scores, it is not yet fully clear whether these effects might be a consequence of functional or antidepressive effects rather than neuroprotective actions.^[3-5]

Riluzole

A single Class I, randomized, double-blind, placebo-controlled, 6-month trial evaluated riluzole 50 mg BID compared to placebo with a primary outcome of change in UPDRS. This pilot and extension study showed that riluzole (100 mg/day) was well tolerated in patients with early PD. No evidence of symptomatic effect of riluzole was observed. Because of the exploratory nature of the design and small size of the study, it was not possible to determine whether riluzole affected the natural history of PD.^[6]

MAO-B inhibitors

Selegiline

The Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study^[7] examined the ability of selegiline to delay the need for levodopa therapy in 800 patients with early PD who were not taking any PD medication. After 1 year, 97 subjects (24%) receiving selegiline versus 176 subjects (44%) not receiving selegiline experienced disability significant enough to require levodopa therapy. In addition, patients in the selegiline group had significantly better motor function scores compared with those taking

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placebo. Given the observed symptomatic effect of selegiline, however, conclusions could not be drawn regarding any disease-modifying effects of the drug. Dry mouth was the only adverse event that occurred more commonly with selegiline than with placebo.

Rasagiline

In early monotherapy for PD patients (TEMPO) study,^[8] a 26-week study of rasagiline in early PD, patients were randomized to receive 1 mg rasagiline daily, 2 mg rasagiline daily, or placebo. Motor function significantly improved with both doses of rasagiline compared with placebo. After the first 6 months of the study, those receiving placebo were switched to rasagiline 2 mg daily and patients in the initial rasagiline groups (1 or 2 mg daily) remained on their initial rasagiline doses for an additional 6 months. Significantly better motor function scores were noted in those initially treated with rasagiline than in those who were treated with placebo followed by 6 months of rasagiline.^[9]

Long-term follow-up of 306 of the 360 subjects who completed the initial 6-month study indicated that after up to 6.5 years, the group that initially received rasagiline continued to have significantly better motor function scores compared with the delayed-start group (16% difference between groups).^[10] Results of a larger, 9-month delayed-start study that was designed to further investigate this finding showed that early treatment with rasagiline at a dose of 1 mg per day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline at a dose of 2 mg per day did not. Because the two doses were associated with different outcomes, the authors concluded that the study results must be interpreted with caution.^[11]

Dopa Agonists

Pramipexole

A randomized controlled trial (RCT) of 301 patients with early PD assessed treatment effects of levodopa versus pramipexole. Fewer patients receiving initial treatment for PD with pramipexole developed dopaminergic motor complications than with levodopa therapy. Despite supplementation with open-label levodopa in both groups, the levodopa-treated group had a greater improvement in total UPDRS compared with the pramipexole group making it inconclusive to say that pramipexole has any neuroprotective effect in PD.^[12] In a study of dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression, eighty-two patients with early PD who were recruited were randomly assigned to receive pramipexole, with levodopa placebo (n = 42), or carbidopa/levodopa, with pramipexole placebo (n = 40). Clinical severity of PD was assessed using the UPDRS 12 hours off anti-PD medications.^[13] The primary outcome was change in UPDRS score and change in SPECT with 2-beta-carboxymethoxy-3beta(4-iodophenyl)tropane (beta-CIT) labeled with iodine 123. At 46 months, there was no difference in the change from baseline in the UPDRS scores between the two treatment groups. At 46 months, a reduction of beta-CIT uptake of 16 ± 13.3 (pramipexole) versus 25.5 ± 14.1 in levodopa-treated patients ($P = 0.01$) was seen. However, many of the patients on pramipexole had concomitant levodopa treatment. The lack of a clinical

correlate, the absence of a placebo control and the potentially different regulatory effects of levodopa or dopamine agonists (DAs) on the imaging marker preclude conclusions on any disease-modifying effects of pramipexole on the progression of PD.

To find out long-term effect of initiating pramipexole versus levodopa in early PD, the policies of initial pramipexole and initial levodopa use followed by open-label levodopa use resulted in similar self-reported disability, 6 years after randomization. Persistent differences favoring initial pramipexole were seen in the rates of dopaminergic motor complications, with less severe somnolence favoring initial levodopa.^[14] This study also ruled out any neuroprotective effect of pramipexole.

Ropinirole

A pilot study examined 45 subjects in a prospective cohort treated with up to 1200 mg of levodopa and ropinirole up to 24 mg/day, followed for 2 years, and evaluated with fluorodopa Positron Emission Tomography (PET), which revealed no difference between the two groups. Completion rate was 82%.^[15]

REAL-PET was a parallel-group prospective levodopa-controlled 2-year RCT conducted to assess the effect of ropinirole in 186 untreated patients with early PD. The primary endpoint to measure disease progression was percent reduction in bilateral putaminal uptake of levodopa on fluorodopa PET.^[16] One hundred and sixty-two patients eligible for analysis were treated with ropinirole (up to 24 mg/day) or levodopa (up to 1000 mg/day) for up to 24 months. Both the groups could also be supplemented with levodopa or with stable doses of amantadine or anticholinergics throughout the study. Completion rate was 63%. The reduction in the ropinirole group was 13.4% as compared to 20.3% in the levodopa group ($P < 0.001$), but the same limits as discussed for the pramipexole study preclude any firm conclusions on the effect of ropinirole on PD progression.

Other DAs

There are several DAs such as bromocryptine, pergolide, apomorphine, cabergoline, lisuride, piribedil, and rotigotine. Among these, bromocryptine and cabergoline are available in India. Both are ergot derivatives. Bromocryptine is the weakest clinically in relation to others. Cabergoline is costly. Choosing a DA depends on how much it can be tolerated by the patients and its efficacy. Adverse effects may be the deciding factor regarding a selection. Non-ergot compounds should be preferred to ergot derivatives because of fibrotic adverse reactions and the risk of restrictive heart valve changes.

Levodopa

A randomized, double-blind, placebo-controlled ELLDOPA trial^[17] evaluated 361 patients with early PD who were assigned to receive carbidopa-levodopa at a daily dose of 37.5 and 150 mg, 75 and 300 mg, or 150 and 600 mg, respectively, or a matching placebo for a period of 40 weeks, and then to

undergo withdrawal of treatment for 2 weeks. The primary outcome was a change in UPDRS scores at baseline and at 42 weeks. Neuroimaging studies of 142 subjects were performed at baseline and at week 40 to assess striatal dopamine transporter density with the use of ^{123}I β -CIT uptake [*imaging of the presynaptic dopamine transporters using (^{123}I) beta-CIT used as a diagnostic marker for nigro-striatal degeneration*]. Patients randomized to all levodopa doses had significantly better UPDRS scores than patients on placebo, with the greatest improvement seen on the highest dose. Change in UPDRS on placebo was 7.8 (SD \pm 9), at a dose of 150 mg levodopa was 1.9 (SD \pm 6), at 300 mg was 1.9 (SD \pm 6.9), and at 600 mg was -1.4 (SD \pm 7.7). These results suggest that patients on a higher dose of levodopa had sustained functional improvement compared to their baseline even after a 2-week washout. However, it is possible that this washout period was not sufficient to exclude a persistent symptomatic effect. Patients on the highest dose of levodopa did develop more dyskinesias, but it is unclear whether this reflects a dose effect or disease progression. There was no significant difference in beta-CIT uptake across the groups. In a *post-hoc* analysis that included only patients with abnormal baseline beta-CIT scans, patients on high dose levodopa had greater reduction on beta-CIT uptake. These results are inconsistent and do not allow one to conclude definitely on the impact of levodopa on PD progression.

Other neuroprotective therapies

Due to nonrandomized design and nonindependent outcome assessment, the potential role of thalamotomy^[18] and amantadine^[19] as neuroprotective agents is difficult to assess. There are certain trophic factors which promote survival of DA neurons, such as glial cell line-derived neurotrophic factor (GDNF) and neuroimmunophilins. Inflammations mediated neurodegeneration by the production of cytokines and prostaglandins have been advocated in PD and role of minocycline as an anti-inflammatory agent has not been found effective. Certain agents have been used as apoptotic agents, but have not been successful in the experimental stage.

Symptomatic Therapies for PD

Amantadine

Rigorous analysis of the six randomized controlled trials of amantadine reveals insufficient evidence of its efficacy and safety in the treatment of idiopathic PD.^[20] Amantadine is more helpful in managing dyskinesia associated with dopaminergic therapy.

Anticholinergics

As monotherapy or as an adjunct to other antiparkinsonian drugs, anticholinergics are more effective than placebo in improving motor function in PD. Neuropsychiatric and cognitive adverse events occur more frequently on anticholinergics than on placebo and are a more common reason for withdrawal than lack of efficacy. Results regarding a potentially better effect of the anticholinergic drug on tremor than on other outcome measures are conflicting and data do not strongly support a differential clinical effect on individual Parkinsonian features. Data are insufficient to allow comparisons in efficacy or tolerability between individual anticholinergic drugs.^[21]

MAO-B inhibitors

Selegiline^[22] and rasagiline^[8] have both been compared with placebo in good quality RCTs and they were seen to improve parkinsonism better than placebo. They can therefore be considered efficacious.

Dopa agonist as monotherapy

A meta-analysis of RCTs of DA as monotherapy for the early treatment of PD showed superior efficacy but more frequent adverse events compared to placebo. However, the clinical benefit is often delayed and the potency is lower than l-dopa. The use of DA is an effective treatment option for the treatment of early PD.^[23]

Levodopa

Standard levodopa has been tested in a placebo-controlled RCT, which confirmed its long-established antiparkinsonian efficacy in early PD.^[17]

Apomorphine

It is being only used subcutaneously and has never been tested as monotherapy for the treatment of PD at this early stage.

COMT inhibitors

These drugs are only active when combined with levodopa and are therefore not efficacious as monotherapy in the treatment of untreated patients with early PD.

DAs versus levodopa

On up to 2 years of open extended follow-up of the CALM-PD subjects,^[14] it was concluded that the policies of initial pramipexole and initial levodopa use followed by open-label levodopa use resulted in similar self-reported disability, 6 years after randomization. Persistent differences favoring initial pramipexole were seen in the rates of dopaminergic motor complications, with less severe somnolence favoring initial levodopa.

Two recent meta-analyses^[23,24] confirm that motor complications are reduced with DAs compared to levodopa, but also establish that other important side effects are increased and symptom control is poorer with agonists. Larger, long-term comparative trials assessing patient-rated quality of life are needed to assess more reliably the balance of benefits and risks of DAs compared to levodopa.

Controlled release levodopa versus levodopa

Despite the progressive nature of PD, both the immediate-release and sustained-release carbidopa/levodopa formulations maintained a similar level of control in PD after 5 years compared with baseline in a blinded randomized parallel study of 618 patients in 36 centers worldwide. Additionally, the low incidence of motor fluctuations or dyskinesia was not significantly different between the treatment groups and may be partly attributed to the relatively low doses of levodopa used throughout the 5-year study.^[25]

Agonist Monotherapy versus Another Agonist

There is no convincing evidence of clinically relevant differences in the efficacy of the currently available DAs when used for the treatment of early PD.

Levodopa/Carbidopa/Entacapone versus Levodopa/Carbidopa

One recent multicenter, randomized, double-blind study^[26] investigated whether treatment with levodopa/carbidopa/entacapone when compared with levodopa/carbidopa improves the quality of life in PD patients with no or minimal, nondisabling motor fluctuations. One hundred and eighty-four patients on three to four equal doses of 100/25 to 200/50 mg levodopa/carbidopa or levodopa/benserazide, 0–3 hours of nondisabling OFF time over a 48-hour period and no dyskinesia were randomized to levodopa/carbidopa/entacapone or levodopa/carbidopa treatment for 12 weeks. The primary outcome measure was quality of life as assessed by the PDQ-8. Secondary outcome measures were the UPDRS parts I–IV and the wearing off card. Treatment with levodopa/carbidopa/entacapone resulted in significantly greater improvements in PDQ-8 scores compared to treatment with levodopa/carbidopa (mean difference 1.4 points, $P = 0.021$). Statistically significant improvements were seen predominantly in nonmotor domains (depression, personal relationships, communication, stigma, all $P < 0.05$; dressing $P = 0.056$). Patients who were randomly assigned to levodopa/carbidopa/entacapone also showed significantly greater improvement in UPDRS part II scores ($P = 0.032$), with UPDRS part III scores showing borderline significance. Differences in UPDRS part I and IV and wearing off card scores were not significant. They concluded that treatment with levodopa/carbidopa/entacapone results in improved quality of life compared with levodopa/carbidopa in PD patients with mild or minimal, nondisabling motor fluctuations. But long-term studies are required to evaluate the potential long-term benefits of this treatment strategy.

Various Non-standard Pharmacologic or Non-pharmacologic Therapies of PD

Use of complementary medication and treatment is common in patients with PD; 40% of patients in the United States and 54% of patients in the United Kingdom use treatments such as herbs, vitamins, massage and acupuncture.^[27,28]

Among these, food therapy,^[29-34] vitamin therapy,^[35-37] acupuncture therapy,^[38] manual therapy,^[39-41] exercise therapy,^[42,43] and speech therapy^[44,45] have been tried in various trials.

For patients with PD, exercise therapy may be considered to improve the function (Level C), but this effect persists as long as the patient continues with exercise. For patients with PD complicated by dysarthria, speech therapy may be considered to improve speech volume (Level C).

Indian Guidelines for Treatment of Early PD

Based on the above evidences, Indian guidelines for treatment of early PD are as follows.

Until agents with proven neuroprotective or disease-modifying effects become available, the choice of initial treatment must be tailored to each patient's requirements. Several factors should be considered when determining whether to initiate treatment and which treatment option to use. These factors

include functional disability, disease severity, age, employment status, lifestyle, cognitive and psychiatric status, handedness, predominantly affected side, the presence of comorbid conditions and economic status. Once the decision has been made to start symptomatic treatment, the best choice for each individual patient must be identified. Moreover, drugs available locally are also important.

However, in an ideal situation, an effective evidence-based guideline will be as follows:

1. At this point of time, there is no definite neuroprotective therapy available for PD.
2. Mild symptoms and signs without functional impairment should be observed till mild functional impairment starts appearing.
3. In a patient with mild functional impairment, it is preferable to initiate with an MAO-B inhibitor (Level 1 evidence).
4. If or when MAO-B inhibitor is insufficient or symptoms worsen, the subject should be switched to or add levodopa/carbidopa or non-ergot dopa agonist (pramipexol or ropinirole).

In a patient older than 65 years, who has cognitive or psychiatric issues, or significant comorbidities, initiation of a low dose of levodopa and carbidopa preparation which is to be slowly increased as clinically necessary is recommended with or without an MAO-B inhibitor.

In a patient younger than 65 years, the choice is a DA or anticholinergics or amantidine which could be initiated or added to an MAO-B inhibitor. Dose is to be escalated as required and tolerated. Then, l-dopa and carbidopa preparation should be added when agonist monotherapy becomes insufficient or is not tolerated (Level 1 evidence).

1. Use of anticholinergics and amantidine in early PD has however lower level of evidence.
2. Evidence is still required to recommend starting levodopa/carbidopa/entacapone instead of levodopa/carbidopa when indicated.

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Motor fluctuations and dyskinesias (diagnosis and management)

Motor complications appear in approximately 50% of patients on levodopa (LD) therapy for more than 5 years. Chase *et al*^[1] reported that 28–84% of LD-treated patients develop motor fluctuations after an average of 4.1 years after starting LD therapy. These occur as a result of progression of the disease process (increased neuronal degeneration) and the cumulative effect of prolonged treatment with dopaminergic drugs, especially LD.

The Motor Complications include

- a. Motor fluctuations
 - i. Wearing off effects (end-of-dose deterioration): This is the most common initial manifestation of motor fluctuation. The patient starts to feel the reappearance of motor symptoms before the next dose. It is predictable and occurs 2–4 h after a dose of LD.^[2] In the initial stages, the symptoms great promptly alleviated after the same dose of dopaminergic medications. However, later the dose needs to be increased or another medicine for PD needs to be added.
 - ii. "ON" and "OFF" phenomena which can be predictable or unpredictable: Gradually, the patient starts having "OFF"

periods when not on medications or after the effect of medicine goes away, and a predictably good "ON" response about 45 min to an hour after intake of LD (or other dopaminomimetics).

However, as the disease progress, the "ON" response may be suboptimal or erratic, and patient can develop unpredictable "ON"–"OFF" motor fluctuations. These "motor shifts" occur as a result of loss of presynaptic dopamine terminals and from fluctuating neurotransmitter level.^[1]

- iii. *Nighttime deterioration*: In moderate to advanced disease, patients wake up in the night with motor symptoms, difficulty in rolling over in bed, muscular discomfort, and frequent urination.
 - iv. *Early morning deterioration*: This can often be associated with painful foot dystonia.^[3]
- b. Dyskinesias/ dystonias.

These can be of the following types:^[3,4]
 - i. At peak-dose, more often dyskinesias
 - ii. During "OFF" periods, more often dystonias
 - iii. A combination of peak-dose and "OFF" period (biphasic), patients often cycling in these two phases

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Diagnosis

- a. Diagnosis is based on meticulous history from the patient and caregivers. Patients need prolonged observation before and after a dose of medications for PD. Patients are often not concerned about the minor dyskinesias and therefore may deny this symptom. However, the caregivers are in a better position to confirm the presence of dyskinesias.

- b. When in doubt about the presence or degree of motor complications, patients should be given 24 h diaries to be completed at home, marking the OFF, ON stages, time and severity of dyskinesias, and temporal relationship with the medications. If necessary, patients and caregivers should be shown video clippings of patients with dyskinesias.
- c. Finally, patients may need a short admission in the hospital and evaluated in OFF and ON stages with UPDRS scales and scales for dyskinesias.

Principles of Management

- a. Suboptimal clinical response, wearing-off phenomenon, delayed "ON" or no "ON" without dyskinesias or minimal dyskinesias
 - i. Optimize the current dosage of anti-PD medications (increase the strength of each dose or give more frequently) without causing side effects.
 - ii. If already on optimal dosage of levodopa-carbidopa (LD) preparation only, try
 1. adding COMT-inhibitor-entacapone (200 mg with each dose of LD, up to 1600 mg/day,^[5,6]
 2. changing over to controlled-release (CR) preparation of LD or add CR preparation to the standard LD preparation (especially a bedtime dosage of 200/50 mg CR preparation of LD for nighttime wearing-off),^[7,8]
 3. adding MAO-B inhibitor, e.g. selegiline (5 mg at morning and afternoon) or rasagiline (0.5 mg at morning, later can be increased to 1.0 mg at morning),^[9]
 4. adding amantadine, 100 mg once daily, increased to twice a day,^[10]
 5. adding a dopamine agonist (e.g. ropinirole or pramipexole).^[3]
 - iii. If already on an optimal dosage of dopamine agonist only, try
 1. switching over to another agonist (e.g. from pramipexole to ropinirole and vice versa)
 2. adding LD preparation (immediate or CR preparation)
 3. adding MAO-B inhibitor or amantadine
 - iv. redistribute dietary protein
 - v. consider surgery for PD
 - b. Nighttime deterioration: The following strategies may be tried:
 - i. A CR preparation of LD at bedtime
 - ii. An extra dose of standard LD around midnight when patients wakes up
 - iii. Addition of dopamine agonist or entacapone if patient is not on these drugs.
 - c. Early morning deterioration: Often patients are relieved by a standard preparation of LD, which can be given crushed and with carbonated drink or on empty stomach, if patient can tolerate.
 - d. Patients with disabling dyskinesias
 - i. Choreiform dyskinesias
 1. Peak dose dyskinesias: The following strategies can be tried:
 - a. If patient is on CR preparation of LD, switch over to immediate release one^[11]
 - b. Reduce individual dose of LD and give more frequent
 - c. If patient is on a COMT inhibitor, stop the drug
 - d. Reduce the total daily dose of LD and add a dopamine agonist (ropinirole or pramipexole) or increase the dose of dopamine agonist if patient is already taking one
 - e. Reduce dosage of LD and add amantadine. The dose of amantadine need to be 300-400 mg/day and the benefits tend to be short lived^[12]
 - f. Reduce LD and add anticholinergic drugs (e.g. trihexyphenidyl)
 - g. Remove selegiline or rasagiline
 - h. Continuous drug delivery such as subcutaneous apomorphine or duodenal LD may be considered^[13]
 - i. Atypical neuroleptics such as clozapine may be of help^[14]
 - j. Consider surgery for PD (deep brain stimulation of bilateral subthalamic nucleus is most preferred target)^[3]
 2. Biphasic dyskinesias: It is difficult to treat this condition, but the following strategies may be tried.^[11]
 - a. If patient is on a CR preparation of LD, change over to immediate release one
 - b. Increase the total dose of LD
 - c. Restrict use of LD to several early and/or mid-day doses
 - d. Add or increase the dose of dopamine agonist
 - e. subcutaneous apomorphine injections can be tried at selected times
 - f. Try continuous drug delivery (as mentioned above)
 - g. Assess for psychiatric problems and treat when present
 - h. Try behavioural management
 - i. Consider surgery for PD
 - ii. Dystonias
 1. Peak-dose dystonia
 - a. Reduce dose of LD
 - b. Add or increase dose of dopamine agonists
 - c. Consider surgery for PD
 2. Early-morning / OFF-period dystonia
 - a. Add CR preparation of LD at bedtime
 - b. Add dopamine agonist at bedtime
 - c. Add COMT inhibitor
 - d. Early morning immediate release LD may be tried 1--2 h before getting up from bed
 - e. Other drugs such as baclofen, diazepam, or anticholinergic drugs can be tried
 - f. In focal dystonia, injection of botulinum toxin type A in the dystonic muscles can be tried
- e. Unpredictable "ON-OFF" periods: The following options may be considered.
 - i. Adjust time and dose of LD
 - ii. Add dopamine agonist

- iii. Add COMT inhibitor
 - iv. Add rasagiline
 - v. Change to liquid preparation of LD:^[15]
Daily liquid preparation of LD needs to be prepared by crushing ten tablets of standard (immediate release) 100/25 levodopa/carbidopa, 2 g of ascorbic acid and dissolving in 1 L of water. This solution need to be administered every 60-90 min intervals, the dose being adjusted according to the response and side effects.
 - vi. Redistribute dietary protein
 - vii. Subcutaneous apomorphine
- f. Freezing (motor blocks)
- i. Only in "OFF" state
 - 1. Management strategies as like in patients with wearing-off
 - 2. Manage anxiety, if present, by appropriate drugs or behavioural therapy and nonpharmacologic techniques that involve the use of sensory or mental imagery, cues, or devices.^[11,16]
 - ii. Both in "OFF" and "ON" stages
 - 1. Increase LD to make optimal "ON"
 - 2. Sensory cues
 - 3. Assistive devices
 - 4. Manage anxiety, if present, by appropriate drugs or behavioural therapy
 - iii. Only "ON" freezing

It is very difficult to manage and patients sometimes benefit by reducing the dose of LD.

In summary, medical management of motor fluctuations in PD is challenging. Surgical treatment of PD may be a better option for carefully selected patients.

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Parkinson's disease

Madhuri Behari, Kalyan Brata Bhattacharyya¹, Rupam Borgohain², Shyamal Kumar Das³, Bhaskar Ghosh⁴, Asha Kishore⁵, Syam Krishnan⁵, K Rukmini Mridula², Uday Muthane⁶, Pramod Kumar Pal⁷, Charulata Sankhla⁸, Garima Shukla

Department of Neurology, All India Institute of Medical Sciences, ¹Amrapali Point, Kolkata, ²Nizam's Institute of Medical Sciences, ³Bangur Institute of Neurosciences, Kolkata, ⁴BR Singh Hospital and Center for Medical Education and Research, Kolkata, ⁵Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, ⁶Parkinson and aging research Foundation, Bengalure, ⁷National Institute for Mental Health and Neurosciences, Bengalure, ⁸PD Hinduja National Hospital, Mumbai

For correspondence:

Prof. Madhuri Behari, Department of Neurology, All India Institute of Medical Sciences and Technology, New Delhi, India.

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The diagnosis of Parkinson's disease (PD) is clinical and there are no biological markers to confirm it during life.^[1] Confirmation is possible only post mortem. There are no accepted neuropathological criteria for PD^[2] and there is an ongoing debate on whether PD is a single entity.^[3,4] This is because of the description of genetic forms of PD with clinical features typical of sporadic PD but pathological features distinct from it.^[5] Early accurate diagnosis of PD may be important for institution of disease course-modifying treatments when they become available, for prognostication and for research purposes.^[6] Recognizing early PD is not easy. It is also well known that in the early stages of the disease, PD and other forms of degenerative parkinsonism share common features and clinical distinction may be difficult.^[7] The certainty of diagnosis increases as the disease advances and in specialist clinics.^[8] Even though PD is considered as a predominantly motor disorder, non-motor symptoms occur at all stages of the disease^[9] and may even antedate it.^[10,11] However, the diagnosis of PD rests on motor signs. The three cardinal motor manifestations of PD which are essential to make a diagnosis are rest tremor, rigidity, and bradykinesia.

Rest tremor (4-6 Hz) tremor occurring when the limb is fully supported). It can be brought out by mental stress, during walking, or while performing alternating finger taps with the opposite hand. Some patients have postural tremor but appears only after a latency of seconds to a minute of assuming the outstretched posture of arms (re-emergent tremor).^[12] This feature, if present, helps to differentiate PD tremor from postural tremor due to other causes, e.g. essential tremor (ET) in which

tremor appears immediately on assuming the posture. Typically, rest tremor of the hands in PD has a pill rolling appearance and abates during action. In the head region, tremor occurs in the lips, chin, and jaw but is infrequent in the neck. About 75% of PD patients have tremor during the course of their illness.^[13]

Rigidity (resistance offered to passive flexion-extension or rotation movement of major joints with the patient sitting relaxed. It does not include cog-wheel rigidity caused by tremor). Rigidity in PD is lead pipe-like, is present throughout the range of movement, and is not velocity dependent. In PD, rigidity involves both neck and limbs while in progressive supranuclear palsy (PSP) there is a disproportionate axial preponderance of rigidity.^[14]

Bradykinesia (slowness of initiation of voluntary movements with progressive reduction in speed and amplitude of repetitive actions). It is tested by asking the patient to do repeated finger taps, alternate pronation and supination of forearm, opening and closing of fist and foot taps. Look for speed, regularity, arrests of ongoing movement and slowness. Fatiguing or gradual reduction in amplitude during continued activity and arrests are typical of true bradykinesia.

Postural instability (not due to cerebellar, vestibular, posterior column or visual dysfunction). In the clinic this may be demonstrated by the "pull test." This is assessed from the response to the sudden strong posterior displacement produced by a pull on shoulders while the patient stands erect with eyes open and feet slightly apart. The patient is prepared for the test and can have a few practice runs. Many experts do not consider postural instability by itself for the early diagnosis of PD as it is seldom present in early stages and is nonspecific. Onset with postural instability and gait disturbance (PIGD) tends to be more often due to atypical parkinsonism.^[15]

Although several clinical criteria have been proposed for PD, most have not been evaluated for reliability and validity. The United Kingdom Parkinson's disease Society Brain Bank Clinical Diagnostic Criteria^[16] [Table 1] is based on a retrospective clinico-pathological study and has been tested

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in autopsy confirmed cases and found to have an accuracy of around 75% to 80%.^[17] The misdiagnosis in the remaining cases was from conditions such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), vascular parkinsonism and Alzheimer's disease. These criteria are useful for improving diagnostic accuracy but may not be useful in monosymptomatic and early stages of PD.^[18] Early PD can have a wide variety of presentations including non-specific symptoms like generalized stiffness, pain and paresthesia, reduced appetite, constipation, sleeplessness, shoulder pain, and reduction in volume of voice or more specific ones like tremor during anxiety, sense of inner tremor, reduced arm swing, reduced facial expression, personality changes noticed by others, slowness, monotonous speech, micrographia, problems with fine motor task, dragging of leg, dystonia of limbs (especially in young onset PD due to Parkin mutations), mood changes, decreased smell, and increased salivation.^[19-21] Response to treatment may support the diagnosis. Excellent response to levodopa and levodopa-induced chorea are seen more often in PD but can occur in MSA^[22] where it wanes with time. Orofacial dystonia, spontaneous or levodopa induced, is often seen in MSA. Partial response to levodopa can be seen in PSP^[23] and other atypical parkinsonism.

In order to address the issue of improving the early diagnosis of PD, Calne *et al.* proposed a designation of escalating levels of diagnostic confidence [Table 2].^[24] Three categories were defined.

1. Clinically possible: Presence of any one of tremor, rigidity, or bradykinesia could qualify for clinically possible PD. Impairment in postural reflexes was not included. Tremor must be of recent onset and may be rest or postural.
2. Clinically probable: Two of the cardinal features of rest

tremor, rigidity, bradykinesia, or impaired postural reflexes are required to make this diagnosis. Alternatively, asymmetrical rest tremor, asymmetrical rigidity, or asymmetrical bradykinesia alone may be sufficient.

3. Clinically definite PD: A combination of three of the features - rest tremor, rigidity, bradykinesia or impairment in postural reflexes - is required to make the diagnosis of PD clinically definite. Alternatively, two of the features are sufficient if one of the first three displays asymmetry. Laboratory support for the diagnosis could be applied to each category. However, these criteria have not been validated in pathologically confirmed cases.

There are certain conditions which are commonly mistaken for PD, especially in the early stages of PD. ET can have rest tremor^[25] and also cogwheel type of rigidity. ET can be asymmetric; however, long-duration asymmetric postural tremor is more likely to be due to PD than ET.^[26] The distinguishing features between the tremor of PD and ET are shown in Table 2. The other conditions producing rest tremor include dystonic tremor (tremor in a dystonic body part, irregular and abolished in certain positions), tardive tremor related to neuroleptic exposure, and Wilson's disease. The slowness of activities seen in hypothyroidism may be mistaken for bradykinesia. The slowness of activities and reduced facial expression in depression can resemble PD. Slowness of activities, slow gait, instability, and hypomimia of the elderly may also resemble PD. Diagnosis of PD should be made carefully in very old people in whom the presence of a rest tremor may be the most specific sign.^[27]

PD needs to be differentiated from the secondary causes of parkinsonism. Vascular parkinsonism results from infarcts

Table 1: UK Parkinson's disease society brain bank clinical diagnostic criteria^[16]

Inclusion criteria	Exclusion criteria	Supportive criteria
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) And at least one of the following: Muscular rigidity 4-6 Hz rest tremor Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction	History of repeated strokes with stepwise progression of parkinsonian features. History of repeated head injury History of definite encephalitis Oculogyric crises Neuroleptic treatment at onset of symptoms More than one affected relative Sustained remission Strictly unilateral features after 3 years Supranuclear gaze palsy Cerebellar signs Early severe autonomic involvement Early severe dementia with disturbances of memory, language, and praxis Babinski sign Presence of cerebral tumor or communicating hydrocephalus on CT scan Negative response to large doses of levodopa (if malabsorption excluded) MPTP exposure	(Three or more required for diagnosis of definite PD) Unilateral onset Rest tremor present Progressive disorder Persistent asymmetry affecting side of onset most Excellent response (70--100%) to levodopa Severe levodopa-induced chorea Levodopa response for 5 yr or more Clinical course of 10 yr or more

Table 2: Distinguishing features between tremor of Parkinson's disease and essential tremor

Feature	PD	ET
Tremor type	Predominantly rest; re-emergent postural tremor	Predominantly postural (immediate)
Tremor frequency	4-6 Hz	8--12 Hz
Tremor characteristics	Supination--pronation	Flexion--extension
Unilateral/bilateral	Usually unilateral to begin with	Usually bilateral
Areas involved	Head and voice tremor not usually seen	Head and voice tremor are usually seen
Response to alcohol	No	Common
Positive family history	Rare (less than 10%)	Usual (17--100% of patients in various series)

involving frontal lobe, deep subcortical white matter, and basal ganglia. The patients are more likely to present with gait difficulty and postural instability rather than tremor. They usually have a history of stroke and report risk factors for stroke. Focal signs like pyramidal signs and vascular dementia may co-exist. The patients usually have a more upright posture, wide based stance, and well-preserved arm swing compared to PD. Response to levodopa therapy is usually poor.^[28] A variety of drugs including neuroleptics, dopamine receptor blocking agents, dopamine depletors (tetrabenazine), and calcium channel blockers can cause drug-induced parkinsonism (DIP). This could develop 1 to 3 months after introduction of a D2 receptor blocker neuroleptic or an increase in dose and generally resolves in weeks to months after discontinuation. Freezing and festination are rare in DIP. DIP is often difficult to differentiate from PD; useful clues for differentiation include parkinsonism associated with tardive dyskinesia or akathisia, symmetric signs, action greater than resting tremor and presence of a low-frequency, high-amplitude jaw tremor ("Rabbit syndrome").^[29-31] The classical features of normal pressure hydrocephalus include gait disturbance, urinary incontinence and cognitive changes; however the triad is seen only in advanced cases.^[32] Bradykinesia of upper limbs is seen in around 50% and frank parkinsonism, usually symmetrical, in less than 15% of patients.^[33] Rest tremor and upper limb rigidity are rare. Gait is more wide-based and apractic in NPH. Gait difficulty is not usually overcome by stepping over examiners foot as it happens in PD. Wilson's disease is yet another cause for parkinsonism; most cases also have other signs like coarse "wing beating" tremor, dystonia, a "mixed" dysarthria, and neurobehavioral disturbances. Investigations like serum copper and ceruloplasmin measurement, slitlamp examination for Kayser-Fleischer ring, 24 h urinary free copper estimation, and liver biopsy are helpful in establishing the diagnosis in suspected cases. Infections (SSPE, mycoplasma pneumonia, HIV, viral encephalitis), metabolic disturbances (hyperparathyroidism), toxins (MPTP, manganese, carbon monoxide, cyanide, methanol), anoxia, and structural lesions (frontal, temporal, brainstem and posterior fossa space occupying lesions causing hydrocephalus) are relatively rare causes of secondary parkinsonism.

Differentiation of PD from other neurodegenerative causes of Parkinsonism is important from the treatment and prognostication point of view. MSA is characterized by a combination of varying degrees of parkinsonism, early and prominent autonomic dysfunction, and cerebellar dysfunction. Parkinsonism is predominant in MSA-P and cerebellar dysfunction is more prominent in MSA-C.^[34] Red flags that suggest MSA are disproportionate anterocollis (chin on chest), severe lateroflexion of trunk, head and neck (Pisa syndrome), orofacial dystonia that are spontaneous or L-dopa induced, irregular action and postural tremor of hands, severe hypophonic quivering high pitched dysarthria, emotional incontinence, nocturnal strider, or excessive snoring. Dementia and behavioral changes are not usually seen.^[35] MRI may be supportive. Patients with PSP present with progressive unexplained and unexpected falls or tendency to fall (backwards or in any direction) within 1 year of onset of parkinsonism.^[36] Vertical supranuclear gaze paresis (any downward or moderate to severe upgaze) is characteristic. The parkinsonism is generally symmetric with axial more

than appendicular rigidity, behavioral and cognitive changes, early dysphagia, and dysarthria.^[37] MRI may be supportive. Cortico-basal degeneration (CBD) results in progressive cortical dysfunction such as asymmetric ideomotor or constructional apraxia, alien limb phenomenon, cortical sensory loss, focal myoclonus, apraxia of speech, or nonfluent aphasia. Extrapyrarnidal dysfunction such as asymmetric appendicular rigidity that is levodopa unresponsive and asymmetric appendicular dystonia is also part of the clinical picture.^[38] MRI findings may support the diagnosis. Dementia with Lewy bodies (DLB) is a dementia syndrome associated with visual hallucinations, fluctuating levels of attention, and spontaneous parkinsonism. Dementia precedes motor symptoms or occurs within 1 year. The parkinsonism is symmetric with early gait and postural instability.^[39] Moderate L-dopa response may be seen. In Alzheimer's disease, parkinsonism follows dementia, is symmetric, and rest tremor is rare. Dementia of AD is dominated by early and severe memory impairment. Clinical features which suggest an alternative diagnosis other than PD in a patient presenting with parkinsonism are listed in Table 3.

There is no diagnostic test which can reliably differentiate PD from other causes of parkinsonism. Acute levodopa challenge (with 250 mg/25 mg of levodopa/carbidopa) and assessment for changes in Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) score of 30% or more have a sensitivity of around 70% and specificity of around 80% for predicting an eventual diagnosis of PD.^[40] Around 30% will have false positive or false negative results. Subcutaneous apomorphine challenge (1-4.5 mg of apomorphine given subcutaneously)^[41] has similar utility but apomorphine is not freely available in India. Patients need to be pre-treated with domperidone for 2-3 days to prevent dopaminergic side effects.

Decreased smell in standardized smell identification tests (like the University of Pennsylvania Smell Identification Test - UPSIT) may be useful to discriminate PD from PSP and CBD. The smell is preserved in these conditions unlike PD in which there is moderate to severe impairment of smell. MSA and PD have overlapping levels of impairment.^[42,43]

Significant overlap in levels of impairment does not allow reliable distinction between PD and atypical parkinsonism based on neuropsychological testing, electro-oculogram, sphincter and urethral EMG or autonomic function tests.^[44]

Conventional and advanced MR modalities may help distinguish PD from atypical parkinsonism. However, the

Table 3: Baseline features that suggest an alternative diagnosis other than PD

- Mild or no tremor, particularly absence of rest tremor
- Severe bradykinesia at onset
- Symmetric signs and rapid progression
- Postural instability, gait difficulty and freezing at onset or early in the disease (within 3 years)
- Falls at presentation or early in the course
- Slowing of saccades or supranuclear palsy (other than upgaze restriction)
- Dementia preceding motor symptoms or in the first year
- Hallucinations unrelated to medicines early in the disease
- Severe and symptomatic dysautonomia unrelated to medicines

*A combination of features is more suggestive of an alternative diagnosis than a single odd feature.

evidence is insufficient and MRI has low sensitivity.^[44] Iodine-123 meta-iodobenzylguanidine (MIBG) cardiac imaging is normal in multiple system atrophy and PSP, while it is abnormal in PD.^[45] However, the level of evidence is currently not considered high enough to recommend for routine diagnostic purposes. Hyperechogenicity of substantia nigra detected by brain ultrasonography has been shown to differentiate PD from atypical parkinsonism.^[46-49] Evidence is not strong to recommend it for routine diagnostic purposes. Beta CIT and IBZM SPECT can differentiate PD from ET^[44] but are not freely available.

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Psychosis in Parkinson's disease

Psychosis in Parkinson's disease (PD) appears in the later stages of the disease. It affects 5–8% of the treated patients,^[1] more often as the disease advances. The clinical features include prominent visual hallucinations with clear sensorium and retained insight. The risk factors for the development of psychosis in PD are anti-PD medications (particularly, dopamine receptor agonists), duration of disease, older age, disease severity, sleep disturbance, cognitive impairment, dementia and/or depression.M

The pathophysiology of PD psychosis is now known to involve an interaction between extrinsic, drug-related and

intrinsic, disease-related components. The most important extrinsic factor is use of dopaminergic medication, which plays a prominent role in PD psychosis. Intrinsic factors seen in PD patients with hallucination consist of duration of illness, old age, visual processing deficits such as lower visual acuity, difficulty in recognizing color and contrast, ocular pathology and functional brain abnormalities. Sleep disturbances are reported early and include fragmentation of sleep and vivid dreams. The intrinsic factors include altered neurochemicals (dopamine, serotonin, acetylcholine, etc.) and structural abnormalities involving Lewy body deposition in specific regions of brain. Genetic predisposition such as presence of apolipoprotein E epsilon 4 allele and tau H1H1 genotype may also play a role. Deep brain stimulation surgery resulted in reduction of anti-PD medication, but this failed to improve psychosis, thus leading to some insights to the intrinsic factors where reduction in anti-PD medications to the lowest tolerated dose did not improve psychosis. Initial manifestation of chronic dopaminergic medication may be sleep disturbances in the form of dreams, night terrors. Dreams are vivid, real, featuring people and events from past and nightmares, where the patient screams and thrashes. The patient is commonly unaware of these symptoms but

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disturbs the spouse or companion sharing the bed. Visual hallucinations in PD psychosis take form of people, friends and relatives from past. Solitary figures are seen repeatedly but do not speak. Animals running across floor appearing through closed window or door are seen. Inanimate objects grow legs and walk. Miniature people are seen. Ceiling and floors appear to be in motion. Often hallucinations are benign and nonthreatening. They occur in the evening hours and commonly are visual, rarely auditory, thus differentiating them from other causes such as schizophrenia. Paranoid delusions are common. Anticholinergic drugs produce toxic delirium, confusion, agitation, and are associated with tachycardia, unformed hallucination and lack a theme.

Other behavior manifestations in patients with PD include delusions, punding, hypersexuality, gambling, obsessive-compulsive disorders, euphoria, anxiety, anticholinergics – toxic confusional state.

Treatment of Psychosis

Papapetropoulos *et al.* concluded that virtually all anti-Parkinsonian drugs are able to induce psychotic symptoms.^[2] It is controversial that some of the dopaminergic drugs do have a higher potential to induce psychosis than others. In a study by Aarsland *et al.*, the authors found no correlation at all between anti-Parkinsonian drugs (levodopa and dopamine agonist (DA)) and hallucinations.^[3] Possible correlations between dopaminergic treatment with different drugs and the risk for PD patients to develop psychosis were analyzed. In randomized, double-blind trials investigating different DAs, the incidence of hallucinations was 8.1% for priribedil, 2.8% for bromocriptine, 4% for rotigotine, 5% for ropinirole, 7–9.3% for pramipexole, 4.8% for cabergoline, 3.4% for pergolide, and 0–4.4% for levodopa. All DAs are effective D2 agonists and, to a lower extent, D3 agonists. These drugs also have D4 receptor affinity which may play a role. Levodopa – the drug with the lowest risk for psychosis in the present investigation – has only low affinity to D4 receptors. Dopamine agonists with $\alpha 2$ receptor affinity, such as pergolide, may have higher incidence of psychosis. Cabergoline behaves as a strong antagonist at $\alpha 2$ receptors, whereas ropinirole and pramipexole are mostly inactive. Thus, the treatment of psychosis is focused on withdrawing the drugs which have higher incidence of inducing psychosis and less antiparkinsonian effect. Thus, the following order of withdrawing the offending drugs is suggested, that is tapering and stopping, if necessary, the drugs with the highest risk-to-benefit ratio first. Anticholinergics are stopped first, followed by selegiline, dopamine agonists, amantadine, and finally catechol-O-methyltransferase (COMT) inhibitors,

which have no psychotomimetic action of their own. Finally, levodopa is reduced. If the hallucinations still persist on withdrawing the offending drugs and further reduction in dopaminergic drugs is not possible without hampering the mobility of the patient, then only addition of atypical antipsychotic is considered.

Several atypical antipsychotic agents (i.e. clozapine, olanzapine) have been shown to be efficacious in reducing psychotic symptoms in PD; however, use of clozapine requires regular monitoring due to the side effects such as agranulocytosis, worsening of confusion, tachycardia, dizziness, sweating. Regular WBC monitoring every 2 weeks is required. Olanzapine in smaller doses may help but also has the side effects such as worsening of confusion, somnolence, balance impairment, lipid abnormalities, weight gain, impaired sugar control in diabetics. Caution is warranted in glaucoma, prostatic hypertrophy, seizure disorder, hypovolemia and dehydration. This drug leads to motor worsening in higher doses. Ziprasidone and aripiprazole are proven to be efficacious in open-label trials and have shown limited efficacy. Quetiapine is a common first-line treatment for PD psychosis because of its tolerability, ease of use although it has failed to demonstrate its efficacy in double-blind trials. A common side effect in the elderly is sedation. Cholinesterase inhibitors may prove to be more beneficial than antipsychotics. Donepezil has not shown significant reductions in psychotic symptoms, perhaps due to methodological limitations. However, results from an open-label study and a double-blind, placebo-controlled trial involving PD patients with hallucinations support the efficacy of rivastigmine. Non-pharmacological interventions such as electroconvulsive therapy in isolated case reports have shown the potential to reduce psychotic symptoms and may be considered in cases involving concurrent depression and/or medication-refractory psychosis. Antidepressants (i.e. clomipramine and citalopram) may improve psychosis in some depressed patients.

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Sleep disorders in Parkinson's disease: Diagnosis and management

A large majority (upto 96%) of patients with Parkinson's disease (PD) suffer from various sleep-related problems.^[1,2] Sleep disturbances, as assessed by validated scales like the Parkinson's disease sleep scale (PDSS)^[3] usually correlate with disease severity and the Hoehn and Yahr staging.^[4]

The main factors responsible for disturbed sleep in PD have been classified by Barone *et al.*, into the following four subcategories:^[5] 1) PD-related motor symptoms, including nocturnal akinesia, early-morning dystonia, painful cramps, tremor and difficulty turning in bed; 2) treatment-related

nocturnal disturbances with drugs like levodopa, other dopamine agonists, antidepressants; 3) psychiatric symptoms, including hallucinations, vivid dreams, depression, dementia, insomnia, psychosis and panic attacks; 4) other sleep disorders, including insomnia, rapid eye movement behavioral disorder (REM-BD), restless legs syndrome (RLS), periodic leg movements (PLMS) and excessive daytime sleepiness (EDS). Other common problems among these patients like poor sleep hygiene, nocturia and pain further worsen sleep quality.

Objective Assessment of PD Patients for Sleep Problems

Over the last few years, a bedside scale, the PDSS for sleep disturbances specifically for PD has been developed, validated and employed for screening.^[3] The following sleep-related issues are included in this scale:

- Overall quality of night's sleep (item 1)
- Sleep onset and maintenance insomnia (items 2 and 3)
- Nocturnal restlessness (items 4 and 5)
- Nocturnal psychosis (items 6 and 7)
- Nocturia (items 8 and 9)
- Nocturia motor symptoms (items 10-13)
- Sleep refreshment (item 14)
- Daytime dozing (item 15)

This, along with the widely accepted sleepiness scale, the Epworth Sleepiness Scale is an 'easy to apply' instrument for identifying sleep-related problems in PD.^[6] In addition, for specific assessment for RBD, the RBD clinical questionnaire can be used.^[7] [Table 1]

Table 1: Approach to sleep-related problems in patients with PD

Poor night time sleep/Insomnia	Excessive daytime sleepiness
Sleep initiation problems: Poor sleep hygiene: regular sleep and activity schedules RLS / PLMD: adjust dopaminergics, opioids Hallucinations and psychosis: reduce Levodopa, quetiapine/ clozapine Pain, dyskinesias, dystonia: adjust timing of dopaminergic therapy	• Maintenance of good sleep hygiene • Addressing all causes of disturbed nighttime sleep, especially sleep apnea • Treatment of depression with non-sedating antidepressants, if night time sleep is satisfactory
Sleep maintenance problems: Depression: SSRIs, Bupropion Sleep apnea: CPAP RBD: Clonazepam Nocturia: Oxybutynin, tolterodine Pain: NSAIDs / other analgesics	• Adjusting dosage of dopaminergic therapy • Use of Modafinil

Diagnosis of individual sleep problems and their management

RLS and / or PLMD

RLS is diagnosed by specific criteria laid down by the international RLS study group:^[8]

Essential Criteria:

- Urge to move legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
- Symptoms begin or worsen during periods of rest or inactivity such as lying or sitting.
- Symptoms are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- Symptoms are worse in the evening or at night than during the day or only occur in the evening or night.

The diagnosis of PLMD can be suspected clinically, typically with the bed partner complaining of jerky limb movements occurring periodically every few seconds or minutes. This does, however, need to be confirmed through an overnight polysomnography.^[9]

Treatment:

Although treatment strategies essentially remain the same for RLS and PLMD in PD as in other patients, with dopamine agonists and Levodopa, the main challenge often is to control symptoms, when patients are already on high doses of these agents for PD. Improvement of RLS symptoms following bilateral subthalamic nucleus stimulation in patients with PD, has been reported.^[10]

RBD:

RBD is a disorder manifesting with elaborate motor activity with dream mentation during REM sleep with intermittent loss of REM sleep atonia. The following diagnostic criteria laid down in the International Classification of Sleep disorders (ICSD-R) and criteria B and C are the minimal, required for RBD diagnosis:^[11]

- a. The patient has a complaint of violent or injurious behavior during sleep.
- b. Limb or body movement is associated with dream mentation.
- c. At least one of the following occurs:
 1. Harmful or potentially harmful sleep behaviors
 2. Dreams appear to be "acted out"
 3. Sleep behaviors disrupt sleep continuity
- d. Polysomnographic monitoring demonstrates at least one of the following electrophysiological measures during REM sleep:
 1. Excessive augmentation of chin electromyography (EMG) tone
 2. Excessive chin or limb phasic EMG twitching, irrespective of chin EMG activity and one or more of the following clinical features during REM sleep:
 - a. Excessive limb or body jerking
 - b. Complex, vigorous or violent behaviors
 - c. Absence of epileptic activity in association with the disorder

Upto half of all patients with RBD can progress to develop

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PD and other neurodegenerative conditions (multiple system atrophy, diffuse lewy body dementia) nearly 10-50 years after onset of RBD symptoms.^[12,13]

Treatment:

Treatment of RBD is relatively simple since a vast majority (>90%) of patients show good response to small doses (0.25-3 mg) of Clonazepam.^[14] Another agent which can be useful is melatonin; however, the purity of available preparations of this drug remains an issue.

Sleep apnea

Studies have shown that sleep apnea is not commoner in patients with PD than in the general population.^[15] However, this being a common disorder, especially in the elderly, who may also suffer from cardiovascular comorbidities. The diagnosis is suspected from a history of excessive snoring, excessive daytime somnolence and witnessed apneas and needs to be established by polysomnography studies.

Treatment, as in all patients with obstructive sleep apnea, is with continuous positive airway pressure (CPAP).

Disorders of circadian sleep rhythm

The main problems related to circadian sleep rhythms are irregular sleep wake patterns, mainly resulting from the widely prevalent problem of EDS in patients with PD, which results in multiple naps in the daytime and disrupted and inadequate nighttime sleep. Dopaminergic therapy has been shown to be related with activity rest rhythm alterations, mainly early morning awakenings among patients with PD.^[16] The other rhythm disorder which could be encountered is advanced sleep phase syndrome, in which sleep onset shifts to much earlier than usual with very early morning awakening. This can result from an exaggeration of the propensity for the elderly to develop some advancement in sleep phase.

These problems can be addressed by stressing the need for proper sleep hygiene with fixed sleep schedules and minimal allowance for daytime napping.

Insomnia

Nearly 30% patients with PD may suffer from insomnia, resulting from the general tendency of the elderly to lose a continuous consolidated period of sleep every night, compounded by motor problems of PD, nocturia, medication effect, any other primary sleep disorders and most of all coexistent depression.^[17]

Treatment should be targeted firstly toward improving physical activity with regular sleep schedules, improving sleep hygiene. Simultaneously, a good history should always be taken to look for primary sleep disorders and causes of secondary insomnia, mainly depression.

EDS

EDS in PD can be multifactorial. The various causes which may

cause disrupted nighttime sleep, as discussed above should be the main target. Sleep apnea should especially be looked for.

The following table summarizes a brief approach toward diagnosis and management of sleep disorders:

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Stroke management

Kameshwar Prasad, Subhash Kaul¹, M.V. Padma, S.P. Gorthi², Dheeraj Khurana³, Asha Bakshi

Department of Neurology, All India Institute of Medical Sciences, New Delhi, ¹Nizam's Institute of Medical Sciences, Hyderabad, ²Command Hospital, Central Command, Lucknow, ³Postgraduate Institute of Medical Education and Research, Chandigarh, India

For correspondence:

Dr. Kameshwar Prasad, Department of Neurology, Room No.704, 7th Floor, Neurosciences Centre, Ansari Nagar, AIIMS, New Delhi - 110 029, India. E-mail: drkameshwarprasad@gmail.com

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Introduction

Scope of the guidelines

These National Clinical Guidelines for stroke cover the management of patients with acute stroke and the secondary prevention of stroke. Primary prevention of stroke, rehabilitation and subarachnoid hemorrhage are excluded from the scope of these guidelines. These guidelines cover the management of stroke in adults (over 18 years) from onset to chronic care and focus on patients with a new clinical event (first stroke or recurrent stroke).

Goal and objectives of the guidelines

The primary goal of the guidelines is to continuously improve the quality of care in patients with stroke nationally. Our intention is closing the gap between best practice and actual practice.

The objective of the guidelines is to provide clinicians and administrators with explicit statements, where evidence is available, on the best way to manage specific problems. Local health service facilities (e.g. hospitals, nursing homes, etc.) will need to add detail.

The guidelines are directed primarily at practising clinicians involved in management of patients with stroke. Their aim is to help clinicians, at any level – primary, secondary or tertiary – to make the best decisions for each patient, using the evidence currently available. The focus is on the more common clinical questions faced in day-to-day practice. The guidelines may be used by all health professionals or health care planners involved in the management of the patients with stroke.

The secondary objectives of the guidelines are to identify

areas where gaps in knowledge or lack of evidence exist and to stimulate research in each area.

The guidelines are concerned with the management of patients who present with a new clinical event that might be stroke. Stroke in this context is defined as 'a clinical syndrome characterized by rapidly developing signs and symptoms of focal or at times global loss (as in subarachnoid hemorrhage or brain stem involvement) of cerebral brain functions, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin.'

While appraisal of evidence forms the basis of the development of these guidelines, we wish to clarify some points:

- “ Evidence related to drugs is generally stronger, because it is methodologically easier to study each intervention in contrast to studying complex intervention like occupational therapy, health education or nursing care. These do not necessarily mean that interventions with so called strong evidence are more important than those where the evidence is weak.
- We believe that highest level of evidence is not always required to make strong recommendation. If the intervention is safe, logic is strong and effect is obvious, the level of evidence desirable to make strong recommendation may be lower than the highest.
- “ We recognize that many areas of clinical importance may not have evidence available to construct guidelines, and the recommendations represent a consensus from the working group on such areas.

The working group is aware of recent developments in evaluating levels of evidence and strength of recommendations, and also that the GRADE methodology has been adopted by more than 25 organizations around the world including the WHO. The group endorses the use of GRADE methodology (Guyatt and Oxman)^[1] for this purpose and will incorporate this in the next version of the guidelines.

Context and use

These guidelines should be taken as statements to inform the clinician, not as rigid rules. Practitioners may need to deviate from the guidelines in individual cases but such deviations should be justifiable and justified.

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The guidelines may be used to inform decisions on standards of good practice and are likely to be used for audit of stroke services. Before the guidelines are used as 'standards', it is important to ensure that the relevance and appropriateness of the guidelines are discussed in the context proposed.

These guidelines do not cover specific management of associated illnesses like diabetes mellitus, cardiac problems and others as these may be addressed by guidelines from related organizations or are generally expected from a physician.

Guidelines for Organization of Services for Stroke Care

Stroke care may be organized at three levels - a basic stroke care facility, a primary stroke care facility and a comprehensive stroke care facility. The basic stroke care facility should be the minimum setup at district hospitals; primary stroke care facility should be mandatory for all medical colleges and multispecialty hospitals; and well-equipped hospitals including some medical colleges should develop comprehensive stroke care facilities. The basic stroke facility may not have artificial ventilators, echocardiography and carotid Doppler facility, primary stroke care facilities may have these facilities but not neurosurgery, MRI or angiography. Comprehensive stroke care facilities should have all these facilities.

Recommendations

Patient care services

Acute stroke team

- At a minimum, includes a physician and another health care professional (i.e., nurse, physician). In addition, a physiotherapist is essential for rehabilitation.
- Team personnel should have experience, expertise and special interest in diagnosis and treatment of stroke patients.
- Team should be available 24 × 7 and a member of the team should be at patient bedside within 15 minutes of being called.

Written care protocols

- Protocols should be made available for rt-PA use in acute stroke.
- Protocols for emergency care, diagnostic tests, stabilization of vital functions and use of medication should be made available.
- Protocols should be reviewed and updated at least once a year.

Emergency medical services (EMS) should be developed and upgraded for stroke care at the hospital or district level to include transport and triage of patients from peripheral medical centers.

Emergency department

- ED personnel should be trained to diagnose and treat all types of stroke.
- ED should have good communication with the EMS and the acute stroke team

- ED personnel should undergo educational activities related to stroke diagnosis and management at least twice a year.

Stroke unit

- Should consist of a hospital unit with specially trained staff and a multidisciplinary approach to treatment and care of stroke patients.
- Should be able to admit patients in the unstable phase, monitor the vital and neurological parameters, diagnose the etiology and subtype and discharge patients with advice on physiotherapy and secondary prevention.
- Should transfer severely ill and stuporous patients including those with raised intracranial pressure (ICP) and with unstable cardiopulmonary status to intensive care.
- Should consider using telemedicine to improve access to treatment in rural and remote areas.

Neurosurgical services

- Comprehensive stroke care facilities should have 24 × 7 on call neurosurgeon to evaluate and operate in cases requiring such consultation and neurosurgery.
- A primary stroke care facility should have neurosurgical care available as early as possible (<2 hours). The patient should either be transferred to a neurosurgical care facility or should be able to call in a neurosurgeon within 2 hours.
- A written protocol for transfer plan should be available.
- The hospital with neurosurgical facility should be having 24 hours operating facility and support personnel (anesthesia, radiology, laboratory services, etc.).

Support services

- Neuroimaging: All levels of stroke care facilities should have the capability of performing or access to either a cranial computed tomography (CT scan) or magnetic resonance imaging (MRI) scan within 30 minutes of the order being written with experienced physicians or a radiologist to interpret the imaging reports.
- Laboratory services to perform routine blood tests, coagulation studies, ECG and chest roentgenograms with 24-hour services. The lab results should be available within 45 minutes of being ordered.
- Commitment and Support of the Organization/Institution should be available toward the stroke care facility and the stroke unit should have a designated medical director/incharge with expertise in stroke.
- Educational programs periodically and annual programs for the stroke team should be instituted and public education about prevention, recognition and management of stroke should be carried out.

Evidence: Albers,^[2] Alberts,^[3] Audebert,^[4] Calvet,^[5] Evans,^[6] Intercollegiate Stroke Working Party,^[7] Katzan,^[8] Koton,^[9] LaMonte,^[10] Prabhakaran,^[11] Purroy,^[12] Ronning,^[13] Silva,^[14] Stavem,^[15] Stroke Unit Trialists' Collaboration.^[16]

Acute Phase Care

Admission to hospital

Most patients with stroke should be admitted to a hospital because their neurological condition may worsen over the first

few days, they may develop non-neurological complications (e.g., aspiration pneumonia), and urgent investigations (like CT scan) may be required.

Recommendations

Patients with acute stroke (onset within last 72 hours or altered consciousness due to stroke) should be admitted to hospital for initial care and assessment. Circumstances where a physician might reasonably choose *not* to admit selected patients with stroke include the following:

- Individuals with severe pre-existing irreversible disability (e.g., severe untreatable dementia), or terminal illnesses (e.g., cancer), who have options to be cared at lower level health care facility.
- Alert patients with mild neurological deficits (not secondary to ruptured saccular aneurysm) who are identified more than 72 hours after onset of symptoms, who can be evaluated expeditiously as outpatients, and who are unlikely to require surgery, invasive radiological procedures or anticoagulation;
- Patients with mild neurological deficits in whom a history and examination is consistent with lacunar stroke syndrome, and a CT scan that either is normal or shows old lacunar infarcts. However, they should be evaluated expeditiously as outpatients.

Diagnosis and management of resolved or rapidly resolving acute neurological event

- Patients who are first seen after fully resolved or rapidly resolving neurological symptoms need diagnosis to determine whether in fact the cause is vascular (about 50% are not) and then to identify treatable causes that can reduce the risk of stroke (greatest in first 7-14 days).
- Any patient who presents with transient symptoms suggestive of a cerebrovascular event should be considered to have had a transient ischemic attack (TIA), unless neuroimaging reveals an alternative diagnosis.
- All such patients except those with transient monocular blindness should have imaging of brain, either CT scan or MRI. Patients presenting with transient monocular blindness (amaurosis fugax) must have a complete ophthalmological examination to exclude primary disorders of the eye before diagnosis of TIA.
- Patients who have had a TIA should be assessed as soon as possible for their risk of subsequent stroke using a validated scoring system, such as ABCD² (Refer to Appendix -1).
- All patients with history of TIA should be started on aspirin 150 or 300 mg daily or Clopidogrel (75 mg) once a day in case of aspirin allergy; and those at high risk of stroke (ABCD² score of 4 or above) should be assessed at primary or comprehensive stroke care facility within 24 hours for further management (as indicated under heading 'Secondary Prevention'). Those at lower risk should be assessed within 1 week of onset of symptoms.
- Patients with crescendo TIA (two or more TIAs in a week) should be treated as being at high risk of stroke, even though they may have ABCD² score of 3 or below.
- Patients who have had a TIA but who present more than one week after their last symptom has resolved should be treated as those with ABCD² score of 3 or below.
- All patients with TIA should be managed as indicated under the heading 'Secondary Prevention'.

Evidence: Bray,^[17] Cucchiara,^[18] Lavalley,^[19] Rothwell.^[20]

Diagnosis of acute persistent cerebrovascular event

The aims of emergent evaluation are to:

- “ Separate stroke (a vascular event) from other causes of rapid onset neurological dysfunction (stroke mimics);
 - “ Provide information about pathology (hemorrhage vs. ischemia);
 - “ Give clues about the most likely etiology;
 - “ Predict the likelihood of immediate complications; and
 - “ Plan appropriate treatment.
- It should be recognized that 'stroke' is primarily a clinical diagnosis and that the diagnosis should be made with special care:
 - In the young;
 - If the sensorium is altered in presence of mild to moderate hemiparesis;
 - If the history is uncertain; or
 - If there are other unusual clinical features such as gradual progression over days, unexplained fever or papilloedema.

History, physical examination and common investigations

- “ History should follow usual routine. Special attention should be paid to onset of symptoms, recent stroke, myocardial infarction, seizure, trauma, surgery, bleeding, pregnancy and use of anticoagulation/insulin/antihypertensive, history of modifiable risk actors: Hypertension, diabetes, smoking, heart disease, hyperlipidemia, migraine and history of headache or vomiting, recent child birth and risk of dehydration.
- “ Physical examination should be on usual lines with special attention to ABC (airway, breathing, circulation), temperature, oxygen saturation, sign of head trauma (contusions), seizure (tongue laceration), carotid bruits, peripheral pulses, cardiac auscultation, evidence of petechiae, purpura or jaundice.
- “ Validated stroke scales like NIHSS may be used to determine the degree of neurological deficit.
- “ All patients should have neuroimaging, complete blood count, blood glucose, urea, serum creatinine, serum electrolytes, ECG and markers of cardiac ischemia. Selected patients may require liver function tests, chest radiography, arterial blood gases, EEG, lumbar puncture, blood alcohol level, toxicology studies or pregnancy test.
- “ All patients should have their clinical course monitored and any patient whose clinical course is unusual for stroke should be reassessed for possible alternative diagnosis.

Brain imaging should be performed immediately for patients with persistent neurological symptoms if any of the following apply:

- “ Indication for thrombolysis or early anticoagulation.
- “ On anticoagulant treatment.
- “ A known bleeding tendency.
 - A depressed level of consciousness (GCS below 13).
 - Severe headache at onset of stroke symptoms.
 - Papilloedema, neck stiffness, subhyaloid hemorrhage or fever.

Patients with acute stroke without the above indications for

immediate brain imaging, scanning should be performed within 24 hours after onset of symptoms.

Evidence: Intercollegiate stroke working party,^[7] Wardlaw.^[21]

Immediate specific management of ischemic stroke

All patients with disabling acute ischemic stroke who can be treated within 3 hours (4.5 hours as soon as approved by the Drug Controlling authority) after symptom onset should be evaluated without delay to determine their eligibility for treatment with intravenous tissue plasminogen activator (alteplase).

- Please see Appendix - 2 for detailed recommendation on thrombolytic therapy.
- All acute stroke patients should be given at least 150 mg of aspirin immediately after brain imaging has excluded intracranial hemorrhage (In patients with t-PA, aspirin should be delayed until after the 24-hour post-thrombolysis).
- In patients with large hemispheric infarct (malignant MCA territory infarct), aspirin may be delayed until surgery or decision is made not to operate.
- In dysphagic patients, aspirin may be given by enteral tube.
- Aspirin (at least 150 mg) should be continued until 2 weeks after the onset of stroke symptoms, at which time any antiplatelet or anticoagulant agent is started as indicated in 'secondary prevention'.
- Any patient with acute ischemic stroke who is known to have dyspepsia with aspirin should be given a proton pump inhibitor in addition to aspirin (also see 'secondary prevention').

Evidence: CAST,^[22] ECASS III - Hacke,^[23] Hill,^[24] IST-3 Whiteley,^[25] National Institute for Health and Clinical Excellence,^[26] NINDS.^[27]

Surgery for ischaemic stroke

Patients with middle cerebral artery (MCA) infarction who meet all of the criteria below should be considered for decompressive hemicraniectomy and operated within a maximum of 48 hours:

- Age 60 years or below.
- NIHSS score of above 15.
- Decrease in the level of consciousness to give a score of 1 or more on item 1a of NIHSS, or GCS score between 6 and 13.
- CT scan showing signs of an infarct of at least 50% of the MCA territory, with or without infraction in the territory of anterior or posterior cerebral artery on the same side or diffusion-weighted MRI showing infarct volume >145cm³.

Patients with large cerebellar infarct causing compression of brainstem and altered consciousness should be surgically managed with suboccipital craniectomy.

Symptomatic hydrocephalus should be treated surgically with ventriculostomy.

Evidence: DECIMAL, DESTINY, HAMLET - Gupta,^[28] Jüttler,^[29] Vahedi.^[30]

Hemodilution and neuroprotection:

- Hemodilution therapy is not recommended for the

management of patients with acute ischemic stroke.
 " No neuroprotective drug is recommended outside the setting of randomized clinical studies.

Evidence: Davalos,^[31] Muir,^[32] Shuaib.^[33]

Immediate specific management of intracerebral hemorrhage (ICH)

ICH related to antithrombotic or fibrinolytic therapy

- " ICH related to intravenous heparin requires rapid normalization of a-PTT by protamine sulphate (1 mg/100 U of heparin) with adjustment of dose according to time elapsed since the last heparin dose: For 30 to 60 min : 0.5 to 0.75 mg; for 60 to 120 min: 0.375 to 0.5 mg, for >120 min 0.25-0.3/mg). Protamine sulfate is given by slow i.v. not to exceed 5 mg/min (maximum of 50 mg). Protamine sulfate may also be used for ICH related to use of subcutaneous low molecular weight heparin.
- Patients with warfarin related ICH should be managed with vitamin K, fresh frozen plasma (FFP) and wherever available prothrombin complex concentrate. Vitamin K (10 mg i.v.) should not be used alone because it takes at least 6 hours to normalize the INR. FFP (15-20 ml/kg) is an effective way of correcting INR, but there is risk of volume overload and heart failure. Prothrombin complex concentrate and factor IX complex concentrate require smaller volumes of infusion than FFP (and correct the coagulopathy faster but with greater risk of thromboembolism).
- " Patients with ICH related to thrombolysis should be treated with infusion of platelets and cryoprecipitate as indicated in Appendix-2.

Evidence: Cartmill,^[34] Goldstein,^[35] Huttner,^[36] Fredriksson,^[37] Yasaka.^[38]

Restarting warfarin

- " Patients with a very high risk of thromboembolism (those with mechanical heart valves), warfarin therapy may be restarted at 7-10 days after onset of the index ICH. Those with lower risk may be restarted on antiplatelet therapy.

Evidence: Gubitz 4,^[39] Phan.^[40]

Surgery for ICH

- " Patients with cerebellar hemorrhage (>3 cm in diameter) who are deteriorating neurologically or who have signs of brain stem dysfunction should have suboccipital craniectomy and surgical evacuation of hematoma.
- " Patients with supratentorial ICH causing midline shift and/or herniation with impairment of consciousness or deteriorating neurologically should have surgical evacuation of hematoma within 72 hours of onset of symptoms, unless they were dependent on others for activities of daily living prior to the event or their GCS is <6 (unless this is because of hydrocephalus).
- " Patients with hydrocephalus who are symptomatic from ventricular obstruction should undergo ventriculostomy.

Evidence: Auer 1989,^[41] Mendelow,^[42] Prasad,^[43] Prasad.^[44]

Acute arterial dissection

- Any patient suspected of having arterial dissection should be investigated with appropriate imaging (MRI and MRA).
- People with stroke secondary to arterial dissections should be treated with either anticoagulants or antiplatelet agents. In selected patients, stenting may be indicated.

Evidence: Arauz,^[45] Desfontaines,^[46] Han,^[47] Lyrer.^[48]

Cardioembolic stroke

- Patients with disabling ischemic stroke who are in atrial fibrillation should be treated with aspirin 300 mg for the first 2 weeks before starting anticoagulation.
- In patients with prosthetic valves who have disabling cerebral infarction and who are at significant risk of hemorrhage transformation, anticoagulation treatment should be stopped for one week and aspirin 150-300 mg should be substituted.
- Some experts, despite lack of evidence, recommend starting heparin within 48 hours of onset of cardioembolic stroke, except in patients with large infarctions.

Evidence: Butler,^[49] Evans,^[50] Hart,^[51] Intercollegiate Stroke Working Party,^[7] Scottish Intercollegiate Guidelines Network.^[52]

Cerebral venous thrombosis

- Patients suspected to have stroke due to cerebral venous thrombosis should be investigated by MRI/MRV/CTV only if not diagnosed by CT scan.
- Patients diagnosed with stroke due to cerebral venous thrombosis (with or without hemorrhagic infarct or secondary cerebral hemorrhage) should be given full-dose anticoagulation (initially heparin and then warfarin [INR 2-3]) unless there are contraindications.

Evidence: Boussier,^[53] Stam.^[54]

Physiological Homeostasis (Oxygen, temperature, blood pressure, glucose)

Supplemental oxygen therapy

- Patients should receive supplemental oxygen if their oxygen saturation drops below 95%.

Evidence: Chiu,^[55] Ronning.^[56]

Management of body temperature

Recommendation

- Temperature should be monitored every 4 hours for at least first 48 hours and preferably as long as the patient is in the ward.
- Fever (>37.5°C) should be treated with paracetamol. The search for possible infection (site and cause) should be made.
- Hypothermia <34°C should be avoided as it can lead to coagulopathies, electrolyte imbalance, infection and cardiac arrhythmias.

Evidence: Castillo,^[57] Fukuda,^[58] Hajat,^[59] Reith.^[60]

Management of blood pressure

Ischemic stroke

- In acute ischemic stroke, paraenteral antihypertensive

medication should be recommended only if there is a hypertensive emergency with one or more of the following serious concomitant medical issues:

- hypertensive encephalopathy
- hypertensive nephropathy
- hypertensive cardiac failure/myocardial infarction
- aortic dissection
- pre-eclampsia/eclampsia
- intracerebral hemorrhage with systolic blood pressure (SBP) over 200 mmHg.

“ Antihypertensive medication should be withheld in ischemic stroke patients unless SBP is >220 mmHg or the mean arterial blood pressure (MAP) is >120 mmHg. Lowering by approx 15% during the first 24 hours is recommended.

“ Except in hypertensive emergency, lowering of blood pressure should be slow and with use of oral medications.
 “ Sublingual use of antihypertensives is not recommended.
 “ Blood pressure reduction to 185/110 mmHg or lower should be considered in people who are candidates for thrombolysis.

Intracranial hemorrhage

“ If SBP is >200 mmHg or MAP is >150 mmHg (recorded twice, two or more minutes apart), then blood pressure should be aggressively treated with parenteral antihypertensives (e.g., labetalol or nitroglycerin).

“ If SBP is >180 mmHg or MAP is >130 mmHg (up to 150 mmHg), then a modest reduction is advised with rapidly acting oral or parenteral medication or nitroglycerin patch.

“ Target BP should be 160/90 or MAP of 110 mmHg.

Evidence: Ahmed,^[61] Bath,^[62] Horn,^[63] Schrader.^[64]

Management of blood glucose

Recommendation

“ The blood glucose level should be maintained between 70 and 190 mg/dL. Elevated blood glucose >140 mg/dL should be managed with insulin administration using the sliding scale in the first week of stroke onset.

“ Hypoglycemia should be monitored and accordingly 20% glucose (50 ml bolus) should be administered.

Evidence: Bruno,^[65] Gray,^[66] National Institute for Health and Clinical Excellence.^[67]

Cerebral edema and increased intracranial pressure

Until more data are available

“ Corticosteroids are not recommended for the management of cerebral edema and increased ICP following stroke.

“ In patients whose condition is deteriorating secondary to increased ICP, including those with herniation syndromes, various options include: Hyperventilation, mannitol, furosemide, CSF drainage and surgery. If CT scan (first or repeat one after deterioration) suggests hydrocephalus as the cause of increased ICP, then continuous drainage of CSF can be used.

“ Initial care includes mild restriction of fluids, elevation of head end of the bed by 20 to 30 degrees and correction of factors that might exacerbate increased ICP (e.g. hypoxia,

hypercarbia and hyperthermia).

- Hyperventilation acts immediately (reduction of the pCO₂ by 5-10 mmHg lowers ICP by 25-30%) but should be followed by another intervention to control brain edema and ICP. Hyperventilation can cause vasoconstriction that might aggravate ischemia. An intravenous bolus of 40 mg furosemide may be used in patients whose condition is rapidly deteriorating. If required, furosemide 20 mg (once daily) may be continued for the first week, Acetazolamide 250 mg (BD) may be added in those not responding to other treatment methods.
- Strict intake-output chart must be maintained to avoid dehydration.
- Mannitol (0.5 gm/kg IV given over 20 minutes) can be given every 6-8 hours. If clinically indicated, dose frequency may be increased to every 4 hours, but then the central venous pressure should be monitored and kept between 5 and 12 mmHg to prevent hypovolemia. This may be continued for 3-5 days.

Evidence: Bereczki,^[68] Broderick,^[69] Qizilbash,^[70] Tyson.^[71]

General Early Supportive Care

Position

- Patients should be advised to undertake activities like sitting, standing or walking only with caution. An occasional patient, who deteriorates on assuming sitting or standing posture, should be advised bed rest.
- Non-ambulatory patient should be positioned to minimize the risk of complications such as contractures, respiratory complications, shoulder pain and pressure sores etc.

Evidence : Turkington,^[72] Tyson.^[71]

Swallowing

- Please see Appendix- 3 for detailed recommendation on bedside swallowing assessment.
- All conscious patients should have assessment of the ability to swallow. A water swallow test performed at the bedside is sufficient (e.g. 50 ml water swallow test)
- Testing the gag reflex is invalid as a test of swallowing.
- Patients with normal swallow should be assessed for the most suitable posture and equipment to facilitate feeding. Any patient with abnormal swallow should be fed using a nasogastric tube.
- Gastrostomy feeding should be considered for patients who are unable to tolerate nasogastric tube.
- Patients with altered sensorium should be given only intravenous fluids (Dextrose saline or normal saline) for at least 2-3 days.

Evidence: Dennis,^[73] Hamidon,^[74] Norton,^[75] Paciaroni,^[76] Smithard.^[77]

Oral care

- All stroke patients should have an oral/dental assessment including dentures, signs of dental disease, etc., upon or soon after admission.
- For patients wearing a full or partial denture, it should be determined if they have the neuromotor skills to safely wear

and use the appliance(s).

- “ An appropriate oral care protocol should be used for every patient with stroke, including those who use dentures. The oral care protocol should address areas including frequency of oral care (twice per day or more), types of oral care products (toothpaste, floss and mouthwash) and specific management for patients with dysphagia.
- “ If concerns are identified with oral health and/or appliances, patients should be referred to a dentist for consultation and management as soon as possible.

Evidence: Brady.^[78]

Early mobilization

- “ Passive full-range-of-motion exercises for paralyzed limbs can be started during the first 24 hours.
- “ All patients should be referred to a physiotherapist/rehabilitation team as soon as possible, preferably within 48 hours of admission.
- The patient's need in relation to moving and handling should be assessed within 48 hours of admission.

Evidence: Fang,^[79] Richards.^[80]

Nutrition

- “ Every patient should have his/her nutritional status determined using valid nutritional screening method within 48 hours of admission.
- “ Nutritional support should be considered in any malnourished patient.

Evidence: Davalos,^[81] Gariballa,^[82] Milne,^[83] National Institute for Health and Clinical Excellence.^[84]

Management of seizures

- Patients with seizure, even single should be treated with loading dose of phenytoin (15-20 mg/kg) followed by maintenance dose 5 mg/kg per day for a period of at least 3 months. If needed, carbamazepine or sodium valproate may be added. Status epilepticus should be treated as per its guidelines. At present there is insufficient data to comment on the prophylactic administration of anticonvulsants to patients with recent stroke.

Evidence: Meierkord,^[85] Passero,^[86] Vespa.^[87]

Venous thromboembolism

Prophylaxis

- “ Patients with paralyzed legs (due to ischemic stroke) should be given standard heparin (5000 units subcutaneous b.d.) or low-molecular weight heparin (with appropriate prophylactic doses as per agent) to prevent deep vein thrombosis (DVT).
- “ For those who cannot tolerate heparin, aspirin given for treatment is of some prophylactic value.
- “ In patients with paralyzed legs (due to ICH), routine physiotherapy and early mobilization should be carried out to prevent leg vein thrombosis.
- “ Early mobilization and optimal hydration should be maintained for all acute stroke patients.
- “ CLOTS trial data does not support the routine use of thigh

length graduated compression stockings for prevention of DVT.

Treatment

- Standard heparin (5000 U i.v.) or low molecular weight heparin (with appropriate therapeutic doses as per agent) should be started initially. When standard heparin is used, a prior baseline complete blood count and a-PTT should be done and a rebolus (80 U/kg/h) and maintenance infusion (18 U/kg/h) should be given (target a-PTT of 1.5 times the control value).
- Anticoagulation (warfarin 5 mg once daily) should be started simultaneously unless contraindicated and the dose should be adjusted subsequently to achieve a target INR of 2.5 (range 2.0-3.0), when heparin should be stopped.

Evidence: Berge,^[88] CLOTS,^[89] Gubitz.^[39]

Bladder care

- An indwelling catheter should be avoided as far as possible and if used, indwelling catheters should be assessed daily and removed as soon as possible.
- Intermittent catheterization should be used for urinary retention or incontinence.
- The use of portable ultrasound is recommended as preferred non-invasive method for assessing post-void residual urine.

Evidence: Thomas^[90]

Bowel care

- Patient with bowel incontinence should be assessed for other causes of incontinence including impacted feces with spurious diarrhea.
- Patients with severe constipation should have a drug review to minimize use of constipating drugs, be given advice on diet, fluid intake and exercise (as much as possible), be offered oral laxatives and be offered rectal laxatives only if severe problems remain.

Evidence: Coggrave^[91]

Infections

- Development of fever after stroke should prompt a search for pneumonia, urinary tract infection or DVT.
- Prophylactic administration of antibiotics is not recommended.
- Appropriate antibiotic therapy should be administered early (after taking relevant culture specimens).

Evidence: Chamorro.^[92]

Discharge planning

- Discharge planning should be initiated as soon as a patient is stable.
- Patients and families should be prepared and fully involved.
- Care givers should receive all necessary training in caring for it.
- Patients should be given information about discharge issues and explained the need for and timing of follow up after discharge.

Evidence: Grasel,^[93] Langhorne,^[94] Larsen.^[95]

Secondary Prevention

This includes measures to reduce the risk of recurrence of stroke in patients who have had TIA or stroke. These guidelines apply to vast majority of patients with TIA or stroke, although some of the recommendations may not be appropriate for those with unusual causes of stroke, like trauma, infections, etc.

Every patient should be evaluated for modifiable risk factors within one week of onset. This includes:

- " Hypertension
- " Diabetes mellitus
- " Smoking
- " Carotid artery stenosis (for those with non-disabling stroke)
- " Atrial fibrillation or other arrhythmias
- " Structural cardiac disease

In any patient where no risk factor is found, consideration for investigating for rare causes may be given. The investigations may include anti-phospholipid antibodies, protein C,S and anti-thrombin III.

Evidence: Coull,^[96] Johnston,^[97] Koton,^[98] Lovett.^[99]

Antiplatelet therapy

" All patients with ischemic stroke or TIA should receive antiplatelet therapy unless there is indication for anticoagulation.

- Aspirin (30-300 mg/day) or combination of aspirin (25 mg) and extended release dipyridamole (200 mg) twice or clopidogrel (75 mg OD) are all acceptable options for initial therapy. The clinician should be guided by his own preference coupled with the affordability and tolerance of the patient.
- " In children, the maintenance dose of aspirin is 3-5 mg/kg per day.
- Combined aspirin-extended release dipyridamole as well as clopidogrel is marginally more effective than aspirin in preventing vascular events.
- " The combination of aspirin and clopidogrel increases the risk of hemorrhage and is not recommended unless there is indication for this therapy (i.e., coronary stent or acute coronary syndromes).
- " Addition of proton pump inhibitor should not be routine and should only be considered when there is dyspepsia or other significant risk of gastrointestinal bleeding with aspirin.

Evidence: CAPRIE,^[100] CHARISMA Bhatt et al,^[101] ESPS,^[102] ESPS-2,^[103] ESPIRIT,^[104] MATCH – Fisher.^[105]

Anticoagulation

" Anticoagulation should be started in every patient with atrial fibrillation (valvular or non-valvular) unless contraindicated, if they are likely to be compliant with the required monitoring and are not at high risk for bleeding. Aspirin also provides some protection if there are constraints to the use of oral anticoagulation. [Table 1].

- Anticoagulation should be considered for all patients who have ischemic stroke associated with mitral valve disease, prosthetic heart valves, or within 3 months of myocardial infarction.
- Anticoagulation should not be started until brain imaging has excluded hemorrhage, and 14 days have passed from the onset of a disabling ischemic stroke (except when a demonstrable intracardiac thrombus is present).
- Anticoagulation should not be used for patients in sinus rhythm unless cardiac embolism is suspected.
- For effective anticoagulation target, INR is 2.5 (range 2.0-3.0) except for mechanical cardiac valves (3.0: range 2.5-3.5).

Evidence: Antithrombotic Trialists' Collaboration,^[106] De Schryver,^[107] ESPRIT,^[104] Hankey,^[108] Ringleb,^[109] Saxena.^[110]

Blood pressure lowering

- Blood pressure lowering treatment is recommended for all patients with history of TIA or stroke. The benefit extends to persons with or without a history of hypertension. The treatment should be initiated (or modified) prior to discharge from hospital in hospitalized and at the time of first medical assessment in non-hospitalized patients.
- An optimal target for these patients is 130/80 mmHg, but for patients known to have bilateral severe (>70%) internal carotid artery stenosis, SBP of 150 mmHg may be appropriate.
- The optimal drug regimen is uncertain; however the available data supports the use of diuretics or the combination of diuretics and an ACEI.

Evidence: ALLAHAT,^[111] Blood Pressure Lowering Treatment Trialists' Collaboration,^[112] EXPRESS – Rothwell,^[113] HOPE,^[114] PROGRESS.^[115]

Carotid intervention

- Patients with TIA or non-disabling stroke and ipsilateral 70-99% internal carotid artery stenosis (measured by two concordant non-invasive imaging modalities or on a catheter angiogram) should be offered carotid endarterectomy or stenting (see below) within 2 weeks of the incident event unless contraindicated.
- Carotid intervention is recommended for selected patients with moderate (50-69%) stenosis in symptomatic patients.
- Carotid ultrasound / angiogram should be performed on all patients who would be considered for carotid endarterectomy or angioplasty.
- Carotid endarterectomy should be performed by a surgeon with a known perioperative morbidity and mortality of <6%.
- Carotid angioplasty and/or stenting should be considered for patients who are not operative candidates for technical, anatomic or medical reasons or when adequate surgical expertise is not available.
- Carotid intervention is not recommended for patients with mild (<50%) stenosis.
- All those with carotid stenosis should receive all secondary prevention measures, whether or not they receive carotid intervention.

Evidence: Cina,^[116] ECST,^[117] Ederle,^[118] Fairhead,^[119] NASCET - Eliasziw,^[120] Inzitari,^[121] Paty,^[122] Rothwell.^[123]

Lipid lowering therapy

- All patients with history of TIA or ischemic stroke should be treated with a statin if they have a total cholesterol of >200 mg%, or LDL cholesterol >100 mg%.
- The treatment goals should be a total cholesterol of <200 mg%, and LDL cholesterol of <100 mg% (<70 mg% for very high risk individuals).
- Treatment with statin therapy should be avoided or used with caution in patients with history of hemorrhagic stroke.

Evidence: Baigent,^[124] Collins,^[125] HPS,^[126] SPARCL - Amarenco.^[127,128]

Lifestyle measures

- All patients who smoke should be advised to stop smoking and to avoid environmental smoke.
- All patients who can do regular exercise should be advised to do so for at least 30 minutes each day. They should be advised to start with low intensity exercise and gradually increase to moderate levels (sufficient to become slightly breathless).
- All patients should be advised to use low fat dairy products and products based on vegetable and plant oils, and reduce intake of red meat.
- Patients' body mass index or waist circumference should be measured, and those who are overweight or obese should be offered advice and support to lose weight.
- All patients, but especially those with hypertension, should be advised to reduce their salt intake by not adding extra table salt to food, using as little as possible in cooking, and avoiding preserved foods, pickles etc. and choosing low salt foods.
- Patients who drink alcohol should be advised to keep within recognized safe drinking limits of no more than three units per day for men and two units per day for women.

Evidence: Brunner,^[129] He,^[130] Hooper,^[131] Lancaster,^[132] Rice,^[133] Silagy,^[134] Toole,^[135] Wang.^[136]

Appendix-1

ABCD and ABCD2 Prognostic score to identify people at high risk of stroke after a TIA. It is calculated based on:

A – age (≥60 years, 1 point).

B – blood pressure at presentation (≥140/90 mmHg, 1 point).

C – clinical features (unilateral weakness, 2 points or speech disturbance without weakness, 1 point).

D – duration of symptoms (≥60 minutes, 2 points or 10–59 minutes, 1 point).

The calculation of ABCD2 also includes the presence of diabetes (1 point). Total scores range from 0 (low risk) to 7 (high risk).

Appendix - 2

Recommendation on thrombolytic therapy

Prerequisites and criteria for inclusion:

1. Diagnosis of acute ischemic stroke.
2. No evidence of hemorrhage on plain CT scan (NCCT) of brain.
3. Measurable neurological deficit (NIHSS 4-25)
4. Neurological deficits of low NIHSS score but significant functional disability:
 - Aphasia
 - Hemineglect
 - Hemianopia
5. Neurological signs should not be clearing up spontaneously in the evaluation period.
6. Onset of symptoms within 4.5 hours of beginning treatment.
7. Absence of major head trauma or major stroke in the previous 3 months.
8. No myocardial infarction requiring hospitalization in the past 3 months (to prevent hemopericardium)
9. No major gastrointestinal or urinary tract hemorrhage in the past 3 weeks.
10. No major surgery in the previous 14 days.
11. No history of previous intracranial hemorrhage due to aneurysm, angioma or arterio-venous malformations.
12. Diagnosed brain tumor.
13. Blood pressure should be less than 185/110 mm Hg.
14. No evidence of acute bleeding from any site or acute fracture on examination.
15. Not taking oral anticoagulants or if anticoagulants are being taken, INR to be ≤ 1.7
16. If receiving heparin in last 48 hours, a-PTT is to be performed and should be normal (< 35 secs).
17. Platelet count to be assessed if there is clinical suspicion of thrombocytopenia. Platelet count should be $\geq 1,00,000/\mu\text{l}$. If there is no clinical suspicion, platelet count test is ordered, but need not wait for result to start thrombolysis.
18. Arterial puncture at a non-compression site < 7 days.
19. Blood glucose concentration ≥ 50 mg % and ≤ 300 mg%.
20. Seizure at onset to be ascertained whether due to stroke. If there is clinical suspicion of non-vascular postictal deficit, magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) to CT with CT angiography (CTA) to be performed to document stroke.
21. NCCT head should not show a large or multilobar hypodensity involving more than 1/3 rd of arterial territory (limited literature suggests increased risk of hemorrhagic transformation).
22. Informed consent from patient or responsible care giver.

Treatment regime for IV thrombolysis with rt-PA in acute ischemic stroke

1. Infuse 0.9 mg/Kg (maximum dose of 90 mg) over 60 minutes with 10% of the dose given as a bolus over 1 minute.
2. Admit the patient to an intensive care unit or a dedicated stroke unit for monitoring.
3. Perform neurological assessments every 15 minutes during the infusion and every 30 minutes thereafter for next 6 hours, then hourly until 24 hours after treatment.
4. If the patient develops severe headache, acute hypertension, nausea or vomiting, discontinue the infusion (if the infusion

is still on) and obtain emergency CT scan.

5. Measure blood pressure every 15 minutes for the first 2 hours and subsequently every 30 minutes for the next 6 hours, then hourly until 24 hours after treatment.
6. Increase the frequency of blood pressure measurements if a systolic blood pressure is ≥ 180 mmHg or if a diastolic blood pressure is ≥ 105 mmHg; administer antihypertensive medications to maintain blood pressure at or below these levels.
7. Delay placement of nasogastric tubes, bladder catheters or intra-arterial (IA) pressure catheters.
8. Obtain a follow-up CT scan at 24 hours before starting anticoagulants or antiplatelet agents.

Catheter-Based or intra-arterial (IA) thrombolysis or reperfusion strategies: IA thrombolysis is still under investigation and should be used in well-equipped centers within a framework of research protocol.

Indications

- “ A significant neurologic deficit expected to result in long-term disability.
- “ Deficits attributable to large vessel occlusion (basilar, vertebral, internal carotid or MCA M1 or M2 branches).
- “ Non-contrast CT scan without hemorrhage or showing well-established infarct
- “ Acute ischemic stroke symptoms with known onset. Treatment initiated within 6-8 hours of established, non-fluctuating deficits due to Anterior Circulation (carotid/MCA) stroke. The window of opportunity for treatment is less well-defined in posterior circulation (Vertebral/Basilar) ischemia and patients may have fluctuating, reversible ischemic symptoms over many hours or even days and still be appropriate candidates for therapy.

Contraindications

1. Intracranial hemorrhage (ICH, SAH, subdural hematoma, etc.)
2. Well-established acute infarct on CT/MRI in the territory to be reperfused ***
3. Major infarction. ***
 - [e.g. $> 1/3$ cerebral hemisphere]
4. CNS lesion with high likelihood of hemorrhage s/p chemical thrombolytic agents (e.g., brain tumors, abscess, vascular malformation, aneurysm, contusion) ***
5. Suspicion of subarachnoid hemorrhage
The items marked with *** are not contraindications for mechanical clot lysis.

Warnings

These conditions may increase the risk of unfavorable outcomes but are not necessarily a contraindication to treatment:

1. Recent surgery/trauma (< 15 days) ***
2. Recent intracranial or spinal surgery, head trauma, or stroke (< 3 months) ***
3. History of intracranial hemorrhage or brain aneurysm or vascular malformation or brain tumor ***

- [may consider IA catheter-based reperfusion in patients with CNS lesions that have a very low likelihood of bleeding such as small unruptured aneurysms or benign tumors with low vascularity]
 - 4. Active internal bleeding (< 22 days) ***
 - [including arterial puncture at a non-compressible site]
 - 5. Platelets less than 100,000/ μ l, PTT > 40 sec after heparin use, or PT > 15 or INR > 1.7, or known bleeding diathesis ***
 - 6. Left heart thrombus documented ***
 - 7. Increased risk of bleeding due to any of the following: ***
 - Acute pericarditis
 - Subacute bacterial endocarditis (SBE)
 - Hemostatic defects including those secondary to severe hepatic or renal disease
 - Pregnancy (relative contraindication)
 - Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions
 - Septic thrombophlebitis or occluded AV cannula at seriously infected site
 - Patients currently receiving oral anticoagulants, e.g., Warfarin sodium and INR > 1.7
 - Advanced age
 - Status - post-full dose IV tPA
 - 8. Life expectancy less than 1 year or severe comorbid illness
- The items marked with *** are not contraindications for mechanical clot lysis.

Prethrombolysis management

1. Start supplementary oxygen if unable to maintain O_2 saturation > 92%. Treat any fever with acetaminophen. NPO for any oral intake (e.g., food, medication, etc.).
2. Do not place Foley, nasogastric tube, arterial line or central venous line unless it is necessary for patient safety.
3. Do not place any femoral catheters (venous or arterial).
4. Do not lower blood pressure unless it is causing myocardial ischemia or exceeds 220/120. Use labetalol iv (5-20 mg iv q 10-20 mins). Monitor with non-invasive cuff pressures every 15 mins or continuous arterial pressure monitoring.
5. Do not administer heparin unless recommended by the Acute Stroke Team.
6. Alert interventional neuroradiology and anesthesia about possible case.
7. Alert neuro-ICU and check for bed availability.
 - Consider bypassing CT Angio if risk is increased (e.g., renal failure, acute CHF) and it is unlikely to change treatment decision. Hold metformin 48 hrs after iodinated contrast.
 - Check MRI exclusions (e.g., Severe claustrophobia, implanted pacemaker, metal fragments, shrapnel).
 - Review CT/CTA with interventionalist and stroke team.
 - Obtain written or verbal informed consent for endovascular procedure and general anesthesia from patient or appropriate caregiver. If no individual is available for consent, consider emergency consent procedures.
 - If time permits, obtain STAT DWI-MR imaging but do not delay time to treatment.

Guidelines for management of blood pressure prior and perithrombolysis:

- Pretreatment

- Systolic > 185 mmHg or diastolic > 110 mmHg
 - Labetalol 10-20 mg IV over 1-2 min
 - If labetalol is not available, oral captopril (12.5 mg) and repeat at intervals of 15 minutes or clonidine (0.1 mg)
- if still elevated,
 - May repeat or double labetalol every 10 min to maximum dose of 300 mg, or give initial labetalol dose, then start labetalol drip at 2-8 mg/min
 - Nicardipine 5 mg/h IV infusion as initial dose and titrate to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h
 - If blood pressure is not controlled by labetalol or nicardipine, consider sodium nitroprusside or rule out other cause of acute hypertension such as hypertensive urgency
- During/after treatment
 - Monitor blood pressure
 - Check blood pressure every 15 min for 2 h, then every 30 min for 6 h, and finally every hour for 16 h
 - Diastolic > 140 mmHg
 - Sodium nitroprusside 0.5 mcg/kg/min IV infusion as initial dose and titrate to desired blood pressure
 - Systolic > 230 mmHg or diastolic > 121 - 140 mmHg
 - Option 1
 - Labetalol 10 mg IV for 1-2 min
 - May repeat or double labetalol every 10 min to maximum dose of 300 mg, or give initial labetalol dose, then start labetalol drip at 2-8 mg/min
 - Option 2
 - Nicardipine 5 mg/h IV infusion as initial dose and titrate to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h; if blood pressure is not controlled by labetalol or nicardipine, consider sodium nitroprusside.
 - Systolic 180 - 230 mmHg or diastolic 105 - 120 mmHg
 - Labetalol 10 mg IV for 1 - 2 min
 - May repeat or double labetalol every 10 - 20 min to maximum dose of 300 mg or give initial labetalol dose, then start labetalol drip at 2 - 8 mg/min

For acute stroke onset during or immediately after diagnostic or therapeutic angiography/ or coronary and cardiac interventions

If a femoral arterial sheath is still in place, DO NOT REMOVE IT. The sheath should remain sutured in place while t-PA is given. Consider IA urokinase if the sheath can be accessed and the Interventional Neuroradiology staff is available. If not, consider giving t-PA i.v. at full dose 0.9 mg/kg. In all cases, leave the sheath in place and check STAT a-PTT. Observe the groin site closely and follow hematocrit and vital signs for evidence of acute blood loss. If a hematoma forms or there is evidence of blood loss, notify vascular surgery and apply pressure until hemostasis is achieved. If bleeding continues, t-PA can be reversed with FFP, cryoprecipitate and platelets. Vascular surgery may choose to surgically repair the artery. If no bleeding occurs, the sheath can be removed after 24 hours. If heparin cannot be held for sheath removal, vascular surgery will surgically close the vessel in the operating room.

Bleeding after t-PA

1. For suspected symptomatic hemorrhage after t-PA or other plasminogen activator has been given:
 - Hold administration of IV t-PA if still infusing until Brain CT completed and shows no evidence of bleeding.
 - Exclude other possible causes of neurologic worsening or acute hemodynamic instability.
2. For confirmed symptomatic hemorrhage on head CT:
 - Consult neurosurgery for possible intervention.
 - Check STAT values: CBC, PT, a-PTT, platelets, fibrinogen and D-dimer.
 - If fibrinogen < 100 mg/dL, then give cryoprecipitate 0.15 units/kg rounded to the nearest integer. If still bleeding at 1 hr and fibrinogen level still less than 100 mg/dL, repeat cryoprecipitate dose.
 - Institute frequent neurochecks and therapy of acutely elevated ICP, as needed.
 - Additional options or considerations.
 - If platelet dysfunction suspected, give platelets 4U.
 - If heparin has been administered in the past 3 hours:
 - Discontinue the heparin infusion and order protamine sulfate. Calculate total amount of heparin received over the preceding 3 hours.
 - If initiated within 30 minutes of last heparin dose: Give 1 mg protamine per 100 U heparin.
 - If initiated within 30-60 minutes: Give 0.5-0.75 mg protamine per 100 U heparin.
 - If initiated within 60-120 minutes: Give 0.375-0.5 mg protamine per 100 U heparin.
 - If heparin stopped greater than 120 minutes ago: Give 0.25-0.375 mg protamine per 100 U heparin.
 - Give by slow IV injection, not to exceed 5 mg/min, with total dose not to exceed 50 mg.
 - Monitor for signs of anaphylaxis; the risk is higher in diabetics who have received insulin.
 - Follow-up with STAT a-PTT q1 hour for the next 4 hours, then q4 hours through 12 hours of hospitalization.
 - Serious systemic hemorrhage should be treated in a similar manner. Manually compress and compressible sites of bleeding, and consult appropriate additional services to consider mechanically occluding arterial or venous sources of medically uncontrollable bleeding.

Laryngeal function	(Aah/ee) (Normal = 1, weak = 2, absent = 3)	[]
Voluntary cough	(Normal = 1, weak = 2, absent = 3)	[]
Stage 1: Give a teaspoon (5 mL) of water three times		
Dribbles water	(None /once = 1, > once = 2)	[]
Laryngeal movement on attempted swallow	(Yes = 1, no = 2)	[]
“Repeated movements” felt?	(None/once = 1, > once = 2)	[]
Cough on swallowing	(None/once = 1, > once = 2)	[]
Stridulous on swallowing	(No = 1, yes = 2)	[]
Laryngeal function after Swallowing	(Normal = 1, weak/wet = 2, absent = 3)	[]
Stage 2: If the swallow is normal in stage 1 (two of three attempts), try 60 mL of water in a glass or beaker.		
Able to finish in seconds		[]
No of sips		[]
Cough during or after swallowing	(No = 1, yes = 2)	[]
Stridor during or after swallowing	(No = 1, yes = 2)	[]
Laryngeal function after swallowing	(Normal = 1, weak/wet = 2,	[]
Do you feel aspiration is present?	(No = 1, possible = 2, yes = 3)	[]

Appendix – 3

Bedside swallowing assessment

Name	Registration No.	
Date	Day	
Conscious level	(Alert =1, drowsy but arousable = 2, response but no Eye opening to speech = 3, response to pain = 4)	[]
Head and trunk control	(Normal sitting balance = 1, sitting balance Not maintained = 2, head control only = 3, No head control = 4)	[]
Breathing pattern	(Normal 1, abnormal =2)	[]
Lip closure	(Normal = 1, abnormal = 2)	[]
Palate movement	(Symmetrical =1, asymmetrical =2, minimal/ absent =3)	[]

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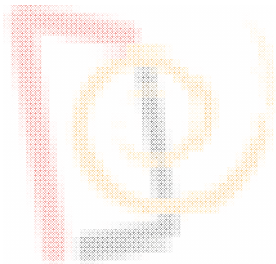
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Treatment of multiple sclerosis

Lekha Pandit, J. M. K. Murthy¹

Department of Neurology, KS Hegde Medical Academy, Nitte University, Mangalore, Karnataka, ¹The Institute of Neurological Sciences, CARE Hospital, Hyderabad, India

For correspondence:

Dr. Lekha Pandit, Professor of Neurology, KS Hegde Medical Academy, Nitte University, Mangalore-575018, Karnataka.
Email: panditmng@gmail.com

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Multiple sclerosis (MS) is a chronic autoimmune inflammatory disorder of the central nervous system (CNS). There has been an increase in the prevalence of MS worldwide. There are no epidemiological studies available from India in the last three decades. The prevalence of 3 per 100,000 for India, quoted by the Multiple Sclerosis International Federation (MSIF), is likely to be a gross under estimation. Natural history studies have shown that 10 years after disease onset, approximately 50% of patients are using a cane to walk and 15% require a wheel chair.^[1] A significant number of patients with "benign MS" develop cognitive dysfunction into the course of their disease.^[2]

Clinical Features

Most of the patients have initial demyelinating events referred to as clinically isolated syndromes (CISs) such as optic neuritis, partial cord syndrome, or an acute brainstem event. If the magnetic resonance imaging (MRI) shows multifocal disease at the time of CIS, nearly half to two-third develop recurrent events and transform into clinically definite MS. Based on the type of presentation, MS is classified into:

1. Clinically isolated syndromes (CISs)
2. Relapsing and remitting multiple sclerosis (RRMS)
3. Secondary progressive multiple sclerosis (SPMS)
4. Primary progressive multiple sclerosis—progressive from the onset (PPMS)
5. Primary relapsing multiple sclerosis (PRMS)

An acute relapse refers to an episode of neurological disturbance, of the kind seen in MS that lasts for at least 24 h, and which was not precipitated by intercurrent infection or stress. Typically relapses evolve over days, reach a plateau, and gradually remit over a variable period of time.

Diagnosis

The core requirements for the diagnosis of MS are dissemination of lesions in space and time [Table 1]. The currently accepted classification for MS is the McDonald Diagnostic Criteria^[3] which is heavily biased in favor of MRI. Evoked potential studies and cerebrospinal fluid (CSF) evaluation have become less important in the diagnosis of MS and are recommended when evaluating a case of CIS or there is clinical or radiological uncertainty [Table 2].

The revised criteria for diagnosis of MS include the following:

- " At least two attacks with objective clinical evidence of at least two lesions.
- " At least two attacks with objective clinical evidence of one lesion plus dissemination in space¹ shown on MRI or two or more MRI lesions consistent with MS plus positive CSF finding or second clinical attack.
- " One attack with objective clinical evidence of at least two lesions plus dissemination in time² on MRI or second clinical attack.
- " One attack with objective clinical evidence of one lesion, plus dissemination in space shown on MRI or two or more MRI lesions consistent with MS plus positive CSF findings and dissemination in time shown on MRI or second clinical attack.
- " Insidious neurologic progression suggestive of MS plus one year of disease progression determined retrospectively or prospectively and two of the following: Positive brain MRI results (nine T2 lesions or at least four T2 lesions with positive visual evoked potential), positive spinal cord MRI results with two focal T2 lesions, and positive CSF findings.

Treatment of multiple sclerosis

Treatment of MS includes treatment of acute relapses, disease-modifying drugs, and treatment of various symptoms and complications associated with MS [Table 3 and Figure 1].

Note

1. The revised MRI criteria for dissemination in space are three of the following: One or more gadolinium-enhancing lesions or nine T2 hyperintense lesions; one or more infratentorial lesions; one or more juxtacortical lesions; or three or more periventricular lesions.
2. The revised MRI criteria for dissemination in time are detection of gadolinium enhancement at least 3 months after the onset of the

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Table 1: Diagnostic criteria for multiple sclerosis (Revised Mc Donald criteria)

Clinical presentation	Additional Data Needed
2 or more attacks 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable and must be consistent with MS)
2 or more attacks 1 objective clinical lesion	Dissemination in space, demonstrated by: <ul style="list-style-type: none"> • MRI <ul style="list-style-type: none"> • 1 Gd-enhancing or 9 T2 hyperintense lesions if no Gd-enhancing lesion • 1 or more infratentorial lesions • 1 or more juxtacortical lesions • 3 or more periventricular lesions • (1 spinal cord lesion = 1 brain lesion) • or a positive CSF and 2 or more MRI lesions consistent with MS • or further clinical attack involving different site
1 attack 2 or more objective clinical lesions	Dissemination in time, demonstrated by: MRI or second clinical attack
1 attack 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space by demonstrated by: <ul style="list-style-type: none"> • MRI • or positive CSF and 2 or more MRI lesions consistent with MS and Dissemination in time demonstrated by: MRI A Gd-enhancing lesion demonstrated in a scan done at least 3 months following onset of clinical attack at a site different from attack, or In absence of Gd-enhancing lesions at 3 month scan, follow-up scan after an additional 3 months showing Gd-lesion or new T2 lesion. or second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	Positive CSF and Dissemination in space demonstrated by: <ul style="list-style-type: none"> • MRI evidence of 9 or more T2 brain lesions • or 2 or more spinal cord lesions • or 4-8 brain and 1 spinal cord lesion • or positive VEP with 4-8 MRI lesions • or positive VEP with <4 brain lesions plus 1 spinal cord lesion and Dissemination in time demonstrated by: <ul style="list-style-type: none"> • MRI • A Gd-enhancing lesion demonstrated in a scan done at least 3 months following onset of clinical attack at a site different from attack, • or • In absence of Gd-enhancing lesions at 3 month scan, follow-up scan after an additional 3 months showing Gd-lesion or new T2 lesion. • or continued progression for 1 year

Attack – neurological disturbance consistent with MS and lasting more than 24 hours. Time between attacks not less than 30days, Positive CSF - Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index, Positive VEP (visual evoked potential)- Delayed but well-preserved wave form. Attack – neurological disturbance consistent with MS and lasting more than 24 hours. Time between attacks not less than 30days, Positive CSF - Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index, Positive VEP (visual evoked potential)- Delayed but well-preserved wave form.

first clinical event or detection of a new T2 lesion appearing at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event.

Treatment of acute relapse

Prevention

Several factors may trigger relapses or may exacerbate existing symptoms and MS patients should be educated about preventive measures. Infections especially of the urinary tract should be anticipated and aggressively controlled. It is safe to vaccinate these patients. Stressful life events and physical trauma may also cause relapse.

Steroids

Not all relapses need to be treated. Steroids are best indicated

for the treatment of disabling relapses such as optic neuritis, significant motor disability, acute ataxia, etc. The exact mechanism of action is not clear, but some of the possible mechanisms include: anti-edema effects, stabilization of blood-brain barrier, reduction of proinflammatory cytokines, and apoptosis of T cells.^[4]

The optic neuritis treatment trial (OPTT) established the standard of care.^[5] High dose intravenous (IV) methyl prednisolone in a dose of 1 g/day for 3 days followed by a short course of oral steroids in tapering dose was shown to be significantly better than oral corticosteroids in the hastening rate of recovery following mono ocular optic neuritis. Time to next relapse was also prolonged in those who received parenteral steroids though this effect was not significant

Table 2: Diagnostic work up for suspected multiple sclerosis

Source	Test	Reason for testing
MRI with contrast	Brain and spinal cord	Diagnosis of white matter disease. In MS, in addition, to establish dissemination in space and time
Blood (essential)	ESR,ANA, ANCA,RF Vitamin B12 Serology for HIV, Syphilis, HTLV1	Vasculitis, Systemic autoimmune disorder Vitamin B12 deficiency
Blood (optional)	ACE Lactate, pyruvate,CK Very long chain fatty acids Arylsulfatase Anti neuronal nuclear antibody 1&11	Sarcoidosis, whipples disease Mitochondrial encephalomyopathy Leukodystrophy Paraneoplastic syndrome
CSF (optional)	IgG index, Oligoclonal bands (paired samples) Lactate,pyruvate PCR for infections	MS, SSPE, HIV, neurosyphilis Mitochondrial encephalopathy HSV, CMV, HTLV1, other
Cerebral angiography (optional)		Vasculitis, vasculopathy,
Biopsy (optional)	Skin Conjunctiva Brain	SLE, Vasculitis Sarcoidosis Atypical (non MS) white matter lesions

ESR- Erythrocyte sedimentation ratio, ANA- Antinuclear antibody, ANCA-Anti neutrophil cytoplasmic antibody, RF-Rheumatoid factor, ACE-Angiotensin converting enzyme, CK-Creatine phosphokinase, HSV-Herpes simplex virus, CMV-Cytomegalo virus, SSPE-Subacute sclerosing panencephalitis

Table 3: Treatment recommendations in multiple Sclerosis

- Acute relapse :
Specific treatment ;Oral or Intravenous methylprednisolone (preferably Intravenous) 1 gram per day for 3 days, not more than 3 times in a year.
- Disease modifying therapy:
RRMS : In all patients newly diagnosed to have RRMS by Mc Donald Criteria
SPMS : In all patients with SPMS and having superimposed relapses during their progressive disease course.
PPMS: Not indicated
Choice of therapy :
RRMS - Either Interferon Beta or Glatiramir acetate can be started. Frequent and higher dosing with Interferon Beta more superior to once a week treatment.
SPMS – Interferon Beta to be started

after the first 10 years following OPN. Most neurologists use IV methyl prednisolone in doses of 1 g/day for 3–5 days.^[6] Oral taper with corticosteroids is a controversial area in MS therapeutics, with many neurologists preferring to avoid it. In some situations when patients do not respond well to initial 3–5 days of parenteral methyl prednisolone, the course may be repeated once again. It is also advisable to give not more than three courses of steroids per year in MS patients.^[7] Transient hyperglycemia and hypertension should be looked out for and so also worsening of preexisting acid peptic disease. The specific precaution to be taken before steroid administration is to exclude infections particularly urinary. Plasmapheresis and intravenous immunoglobulin are not standard recommendations in the treatment of MSrelapse.

Disease-modifying drugs in multiple sclerosis

The disease-modifying drugs (DMDs) [Table 4] are used for the relapsing forms of MS and have multiple benefits:^[8,9]

- (1) decreases in the frequency and severity of relapses or no relapses;
- (2) less development of disability or sustained improvement;
- (3) well maintained or improved quality of life;
- and (4) less MRI lesion burden and less development of CNS atrophy.

Although a variety of DMDs has become available for the treatment in MS, only interferon-beta (IFN-β), glatiramir acetate, mitoxantrone, and the very recently launched Natalizumab (Tysabri) are currently available in India.

Interferon-β

Interferons are produced naturally in human lymphocytes and modulate the immune system by influencing the production of protein products. Avonex and Rebif are forms of interferon β-1a, but the strength of the individual doses and the injection routes differ. Avonex is prepackaged as a 30-mg dose that is given once a week intramuscularly. Rebif is provided in two dose strengths, 22 mg and 44 mg, and is injected subcutaneously three times a week, beginning therapy with the lower dose. Betaseron, interferonβ-1b, is given subcutaneously every other

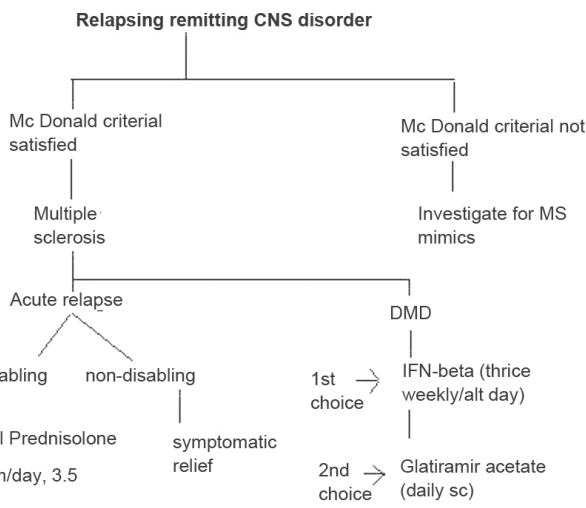


Figure 1: Treatment algorithm for multiple sclerosis

Table 4: Disease modifying drugs in multiple sclerosis

Agent	Dose	Major side effects
IFNB 1b	250 ug SC every other day	Flue like illness, liver function and thyroid function abnormalities
IFNB 1a (IM)	30 ug IM weekly	Same as above
IFNB 1a (SC)	44 ug thrice weekly	Same as above
Glatiramer acetate	20 mg SC daily	Injection site reactions, urticaria, lymphadenopathy
Mitoxantrone	12 mg/m ² IV every 3 months (max 140 mg/m ²)	Cardiomyopathy, leucopenia, treatment-related-leukemia. infections infertility

day. In several class I studies, interferon-β has been shown to reduce the attack rate in RRMS patients and also reduce T2 lesion load on MRI.^[9,10] However, there is little evidence from long-term follow-up studies that it slows down sustained disability progression.

Glatiramer acetate

Glatiramer acetate (Copaxone) is a synthetic drug that interferes with antigen presentation.^[11] It is given as a single, daily, 20-mg subcutaneous injection. In several class I studies, glatiramer acetate has been shown to reduce the attack rate in patients with RRMS, reduce lesion load on T2W MRI and possibly also slows sustained disability progression. It is appropriate to consider glatiramer acetate for treatment in any patient who has RRMS. Although it may be that glatiramer acetate also is helpful in patients with progressive disease, there is no convincing evidence to support this hypothesis.

Mitoxantrone

It is an anthracenedione chemotherapeutic agent (similar to adriamycin) that has been approved for the treatment of relapsing remitting and secondary progressive MS. Three clinical trials including a large phase III study support the use of mitoxantrone in RRMS.^[12-14] However, its use is associated with cardio-toxicity and leukemia in some patients who were in remission five or more years after treatment.^[15] At present the best indication for mitoxantrone would be in patients with aggressive RRMS (more than two relapses in a year or worsening lesion load while on a primary disease modifying agent) and probably patients with poor response to IFN-β. However, in view of dosing limitations, at best, mitoxantrone can be used as an inducer of remission in RRMS.^[16] Maintenance therapy with other DMDs is required. The best combination perhaps would be short course of mitoxantrone combined with a DMD with a good safety profile such as β-interferon or glatiramer acetate. There is no robust evidence to support the use of mitoxantrone in primary PPMS, or in the later stages of SPMR (EDSS > 6).

Natalizumab

It is a humanized monoclonal antibody directed against α-integrin, an adhesion molecule expressed on all leukocytes except neutrophils.^[16] The drug has been shown to be effective in suppression of relapses, disability, and MRI lesion

Table 5 Symptomatic treatment of MS

Symptom	Treatment		Non pharmacological
	Pharmacological		
	Drug	Dosage	
Spasticity	Baclofen	10-150 mg/d.	Physiotherapy
	Tizanidine	2-24 mg/d	Treat concurrent infections
	Diazepam	5- 8 mgm/d.	
	Gabapentin	300-3600 mg/d.	
Fatigue	Botulium Toxin		
	Amantadine	200-400 mg/d	Exclude depression
Pain (MS Related)	Modafanil	200-400 mg/d	Exclude Hypothyroidism
	Amitriptylline	25-150 mg/d	Cooling of body
	Carbamazepine	200-1600 mg/d	
	Gabapentin	300-2400 mg/d	
Tremor	Lamotrigine	200-400 mg/d	
	Pregabalin	150-600 mg/d	
Intention	Propranolol	40-120 mg/d	Occupational therapy
	Gabapentin	300-2400 mg/d	Physiotherapy
Cerebellar	Carbamazepine	200-1600 mg/d	
	Topiramate	25-150 mg/d	VIM thalamotomy
Paroxysmal	Clonazepam	3-6mg/d	VIM deep brain stimulation
	Carbamazepine	200-1000 mg/d	
Symptoms	Gabapentin	300-1500 mg/d	
	Lamotrigine	200-400 mg/d	
Cognitive	Donepezil	10 mg/d	Attention training
Impairment			memory training

activity, and the drug is very well tolerated. Natalizumab is given once a month as infusion. The major concern with natalizumab is the development of progressive multifocal leukoencephalopathy (PML).^[17] By February 2011, at the time of writing this article the reported cases were 95, 20 of whom have died. The risk of PML rises with duration of treatment from, <1/1000 in the first year to a little more than 1/1000 after the second year.

Other drugs used in the treatment of MS include azothiapriner,

methotrexate, cyclophosphamide, and mycophenolatemofetil. However, none of them have been established for use by phase III studies.

Pregnancy

During pregnancy relapse rates are low but it definitely increases in the immediate 3 months postpartum.^[18] Ideally women with MS should plan their pregnancy and stop disease-modifying agents 3 months prior to conception and restart the same after breast feeding is over. IFN- β and natalizumab are Category C pregnancy drugs (where potential benefits may warrant the use of the drug in pregnant women despite potential risks), glatiramer acetate is a Category B (no demonstrable side effects in the fetus during any trimester) and mitoxantrone is a Category D (positive evidence of human fetal risk based on adverse reaction data, but potential benefits may warrant use of the drug in pregnant women despite potential risks) drug. There are no contraindications for breast feeding while on DMD.

Role of disease-modifying agents in clinically isolated syndromes

Several placebo-controlled phase III clinical trials (class I evidence) have studied patients with CIS and evidence of silent lesions on MRI. There was substantial reduction in new MRI lesions and risk of subsequent exacerbations in patients treated with interferon β -1a (Avonex or Rebif),^[19] interferon β -1b (Betaseron), and more recently with glatiramer acetate (Copaxone). Patients initially treated with placebo and later converted to active treatment never achieved the magnitude of benefit seen in the patients who received early treatment with disease modifying therapy.

Symptomatic treatment of multiple sclerosis

Spasticity, fatigue, tonic spasms, parasthesia, depression, sexual, and voiding dysfunctions are some of the symptoms that require pharmacological interventions^[20] [Table 5].

Conclusions

The key to successful management of MS is early diagnosis and early initiation of treatment with disease-modifying agents. Creating awareness among primary care doctors especially ophthalmologists, pediatricians, and physicians with interest in neurology, go a long way in achieving an early diagnosis. The exorbitant cost of DMD makes it unaffordable to vast majority of patients with MS in India. The necessity is now to have well-designed clinical trials which could re-examine the role of cheaper drugs such as azathioprine, in the Indian setting.

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Treatment guidelines for Guillain–Barré Syndrome

Meena A. K., S. V. Khadilkar¹, J. M. K. Murthy²

Department of Neurology Nizam Institute of Medical Sciences, Hyderabad, ¹Grant Medical College, Mumbai, ²The Institute of Neurological Sciences, CARE Hospital, Hyderabad, India

For correspondence:

Dr. A. K. Meena, Professor Department of Neurology Nizam Institute of Medical Sciences Hyderabad . 500082
Email: meenaak@hotmail.com

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Introduction

Guillain–Barré syndrome (GBS) is an acute onset, usually monophasic immune-mediated disorder of the peripheral nervous system. The term GBS is often considered to be synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but with the increasing recognition of variants over the past few decades, the number of diseases that fall under the rubric GBS have grown to include axonal variants and more restricted variants, such as Miller Fisher syndrome (MFS) [Table 1].^[1]

Epidemiology

The reported incidence rates for GBS are 1–2 per 100,000 population.^[2-4] The lifetime likelihood of any individual acquiring GBS is 1:1000.^[5] The subtypes of GBS have different incidence rates in different parts of the world. In Europe and North America AIDP is dominant contributing to 90% of the cases. In contrast in China and Japan AMAN being the most common subtype.^[6,7] The picture is intermediate when we look at other population. In Indian series the incidence of AIDP and AMAN are virtually equal although AMAN is more common in younger patients.^[8] There seems to be a slight preponderance of AIDP in studies by Gupta *et al*^[9] and by Meena *et al* (unpublished data from NIMS, Hyderabad). Available Indian literature indicates a peak incidence between June–July and Sept–October.^[10] In western countries, GBS is common in the 5th decade,^[11] but in India it occurs more commonly at a younger age.^[10,12] GBS is equally common in men and women and can occur at any age. There is a male preponderance among the hospitalized population.^[10,12]

Clinical Features

Most often an unremarkable infection, such as upper respiratory infection, often predates the onset of GBS by 14 days.^[2,5] Many antecedent infections have been identified, including *Campylobacter jejuni*, cytomegalovirus (CMV), *Mycoplasma pneumoniae*, Epstein–Barr virus, influenza virus, JEV.^[13,14] Surgery, immunization, and parturition have also been associated with GBS. GBS usually begins abruptly with distal, relatively symmetrical onset of paraesthesias and quickly followed by progressive limb weakness. Progression is rapid, with 50% of patients reaching clinical nadir by 2 weeks and more than 90% by 4 weeks. The current diagnostic criteria include <4 weeks of progression to clinical nadir. Approximately 80%–90% of patients with GBS become nonambulatory during the illness.^[15,16] Pain is prominent in 50% of patients.^[16,17] Neurological examination is characterized by distal and often proximal, relatively symmetrical, weakness. Although GBS is essentially a motor neuropathy, sensory dysfunction is seen in a few patients. It is seen more in a demyelinating form of GBS.^[12,18] Sensory examination is often normal in the early phase of disease. Facial or pharyngeal weakness is commonly seen in GBS. Diaphragmatic weakness due to phrenic nerve involvement is also common. Approximately one third of hospitalized GBS patients require mechanical ventilation due to respiratory muscle or oropharyngeal weakness.^[18,19] Tachycardia is common but more serious autonomic nervous system dysfunction may occur, including life-threatening arrhythmias, hypotension, hypertension, and gastrointestinal dysmotility. The incidence is between 27% and 55% and is more common in demyelinating than axonal form.^[12,20]

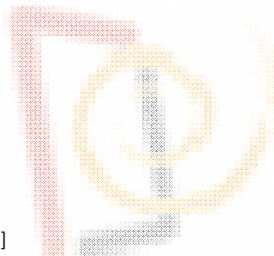
Pathogenesis

Major advances have been made in understanding the mechanisms of some of the subtypes. The histological appearance of the AIDP subtype resembles experimental autoimmune neuritis, which is predominantly caused by T cells directed against peptides from the myelin proteins P0, P2, and PMP22. The role of T-cell-mediated immunity in AIDP remains unclear and there is evidence for the involvement of antibodies and complement. Strong evidence now exists that axonal subtypes of Guillain–Barré syndrome, acute motor axonal neuropathy (AMAN), and acute motor and sensory

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Table 1: Guillain-Barré syndrome—clinical variants

Acute inflammatory demyelinating polyradiculoneuropathy
[Predominantly motor, bilateral facial and pharyngeal, occasional sensory, and autonomic disturbances]
Acute motor axonal neuropathy
[Only motor neuropathy]
Acute motor sensory axonal neuropathy
[Motor and sensory neuropathy]
Miller Fisher syndrome
[Ophthalmoplegia, ataxia, areflexia]
Acute pandysautonomia
[Pure autonomic neuropathy—both sympathetic and parasympathetic]
Pure sensory Guillain Barré syndrome
[Pure sensory neuropathy]
Cervico-brachial-pharyngeal
[Motor weakness predominantly affecting cervico-brachial and pharyngeal muscles]
Bi-brachial
[Motor weakness confining to both the upper limbs with areflexia]
Distal limb variant
[Motor weakness confined to distal muscles of upper and lower limbs with no sensory and cranial nerve involvement]
Oculopharyngeal
[Motor weakness predominantly affecting ocular and pharyngeal muscles]
Paraparetic variants
[Motor weakness predominantly confined to lower limbs]
Pure ophthalmoplegia
[Weakness of bilateral ocular muscles]
Bilateral facial palsy with paresthesias
[Weakness of bilateral facial muscles with paresthesias]
Ropper's variant
[Bilateral sixth and seventh cranial nerve palsy]
Pure generalized ataxia
[Symmetrical limb and axial ataxia]
Polyneuritis cranialis
[Symmetrical or asymmetrical multiple cranial neuropathy]



axonal neuropathy (AMSAN), are caused by antibodies to gangliosides on the axolemma that target macrophages to invade the axon at the node of Ranvier. About a quarter of patients with Guillain-Barré syndrome have had a recent *C. jejuni* infection, and axonal forms of the disease are especially common in these people. The lipo-oligosaccharide from the *C. jejuni* bacterial wall contains ganglioside-like structures and its injection into rabbits induces a neuropathy that resembles acute motor axonal neuropathy.^[21-23] Antibodies to GM1, GM1b, GD1a, and GalNac-GD1a are in particular implicated in acute motor axonal neuropathy and, with the exception of GalNacGD1a, in acute motor and sensory axonal neuropathy.

Diagnosis

Progressive weakness in both upper and lower extremities within 4 weeks along with areflexia is essential requirement for the diagnosis. Supportive ancillary testing for GBS includes CSF analysis and electrodiagnostic testing, both of which may be normal in the early phase of GBS. The limitations of ancillary testing in the early phase combined with the importance of prompt treatment of GBS mandates that the clinician at times make the diagnosis based solely on history and examination. An elevated CSF protein concentration (with normal cell

count) is only found on initial CSF analysis in 50% of patients; elevated CSF protein concentration occurs in more than 90% of patients at the peak of the disease. CSF pleocytosis is an important red flag, which raises the question of infectious (HIV, CMV, Lyme, sarcoid), carcinomatous, or lymphomatous polyradiculoneuropathy [Table 2].

Electrodiagnosis

Electrodiagnostic (EDX) testing is performed to support the clinical impression. EDX testing of GBS patients often demonstrates features of demyelination, such as temporal dispersion, significantly slow conduction velocities, and prolonged distal and F-wave latencies.^[24] Electrodiagnostic testing features of acquired demyelination (eg, conduction block, temporal dispersion, nonuniform slowing of conduction velocities) are particularly helpful because these findings are characteristic of immune-mediated demyelinating neuropathies. In early GBS, prolonged distal compound muscle action potential (CMAP) latencies and temporal dispersion are more commonly demonstrated than are slow motor conduction velocities and conduction block.^[27] Another electrodiagnostic testing hallmark of GBS is the “sural sparing” pattern; that is, the finding of a normal sural sensory nerve response in the

setting of abnormal upper extremity sensory nerve results.^[27] This pattern is very unusual for neuropathies other than GBS. Sural sparing, a marker of demyelinating neuropathy, is more commonly seen in later than in early stages of AIDP. Other electrodiagnostic testing abnormalities are frequently encountered in early GBS but they are less specific to GBS. These include absent H-reflexes, low motor nerve CMAP amplitudes on distal stimulation, and prolonged F-wave responses.^[25-27] It is reported that the H-reflex was absent in 97% of GBS patients within the first week of symptom onset. It should also be pointed out that motor electrodiagnostic testing findings are more often abnormal than sensory nerve results in early GBS. Blink reflex studies are often abnormal when there is facial nerve involvement.^[26] Phrenic nerve conduction studies can be used to predict respiratory failure and the need for ventilation.^[28] Reduced CMAP amplitudes of 0%–20% of the lower limit of normal carry a poor prognosis.^[29]

The diagnostic yield of various neurophysiological criteria may vary in different subforms of Guillain-Barré syndrome, whose prevalence varies in different geographical areas. In a recent study the diagnostic sensitivity of Albers *et al.*,^[30] Cornblath,^[31] Ho *et al.*,^[32] Dutch GBS Study Group,^[33] Italian GBS Study Group,^[34] and Albers and Kelly criteria^[35] were evaluated and correlated with clinical subtypes of GBS, duration, severity, and outcome.^[36] The sensitivity of nerve conduction study in the diagnosis of GBS and in different clinical subtypes of GBS was highest using Albers criteria (88.2%) and lowest using Cornblath criteria (39.2%). As per Ho *et al.*, patients could be categorized into AIDP (86.3%), AMAN (7.8%), and AMSAN (5.9%). Electrophysiological findings necessary to diagnose GBS is in Table 3.

Incidence of antiganglioside antibodies in GBS has varied widely in different published series.^[37,38] Its much more common in AMAN variant than AIDP. The incidence was found to be 58% in a study of 60 patients of GBS by Meena *et al.* (Unpublished data from NIMS, Hyderabad). Although antiganglioside antibodies have been implicated in the pathogenesis of GBS, assaying antiganglioside values in a patient with GBS other than MFS at the present time has no diagnostic value in routine practice.

Variants of Guillain-Barré syndrome

Commonly recognized variants include those with axonal forms, variants based on particular fiber-type involvement (sensory or autonomic), and MFS. Variants with regional or a markedly asymmetric distribution also occur.^[1] There are also differences in abruptness of onset and time to reach nadir, which can complicate diagnosis and decisions about treatment. For example, some patients have clinical features and disease course similar to GBS except for a slower progression (ie, progression that lasts longer than 4 weeks); this disease is sometimes referred to as subacute inflammatory demyelinating polyradiculoneuropathy (SIDP);^[39,40] however, in many respects SIDP is like GBS and often should be treated as such. AMSAN and AMAN are two variants characterized by immune attack directed at axons rather than Schwann cells and myelin.^[41-44]

AMAN occurs in large epidemics during summer in northern

China and more sporadically elsewhere.^[44] It mostly affects children and young people, usually from rural areas. Onset of motor weakness is abrupt. In addition to acute pure motor paralysis, many patients have transient neck and back stiffness early in the course with resolution within day. Recovery usually begins within 3 weeks and is often complete and may take longer. Mortality rate is roughly 3%–5%. Sensory nerve conduction studies are normal and motor nerve studies are remarkable for low or absent CMAP amplitudes with normal conduction velocities. Denervating potentials are seen on needle electromyography.^[6]

AMSAN shares many pathological features with acute motor axonal neuropathy but differs clinically from it in patient age of onset (usually adults rather than children), geographic distribution (can occur anywhere), time of onset (not only summertime), involvement of sensory nerves, course (protracted), and outcome (usually severe residual disability).^[40-44] It has an abrupt onset and rapid progression with most patients requiring mechanical ventilation within a few days of symptom onset. Motor nerves are electrically inexcitable early in the disorder. Sensory nerve conduction studies are also abnormal. Widespread denervation is seen on needle examination. The course is protracted and outcome poor, with only 20% ambulating at 1 year.

Table 2: Guillain-Barré syndrome—red flags raising other diagnostic possibilities

Clinical
<ul style="list-style-type: none"> • Fever at onset • Severe pulmonary dysfunction with limited weakness at onset • Severe sensory signs with limited weakness at onset • Persistent bladder or bowel dysfunction or bladder or bowel dysfunction at onset • Sharp sensory level • Marked persistent asymmetry of weakness
Laboratory
<ul style="list-style-type: none"> • Increased number of mononuclear cells in CSF • Polymorphonuclear cells in CSF

Table 3: Electrodiagnostic findings in Guillain-Barré syndrome^[32]

Electrodiagnostic features suggestive of acquired demyelinating neuropathy
Conduction velocity reduced in two or more nerves
CMAP conduction block or abnormal temporal dispersion in 1 or more nerves
Prolonged distal motor latencies in 2 or more nerves
Prolonged minimum F-wave latency or absent F-wave
Electrodiagnostic features suggestive of axonal neuropathy
No evidence of significant reduction in conduction velocity.
No evidence of abnormal temporal dispersion.
Prolonged distal latency NOT considered demyelination if amplitude < 10% LLN.
Decrease in CMAP (AMAN) and SNAP (AMSAN) to <80% of LLN or inexcitable (absent evoked response) in 2 or more nerves.
CMAP, Compound muscle action potential; AMAN, Acute motor axonal neuropathy; AMSAN, Acute motor and sensory axonal neuropathy; SNAP, Sensory nerve action potential; LLN, Lower limits of normal

MFS: The more recognizable and distinct regional variant of GBS is MFS.^[1,45,46] Like GBS, the onset of MFS often follows an infection, for example *C. jejuni*.^[47] MFS patients classically present with external ophthalmoparesis, areflexia, and ataxia,^[2] although MFS patients often present with fewer components of the classical clinical triad^[1,46,48,49] or with additional clinical features (facial weakness, oropharyngeal weakness, internal ophthalmoparesis, central nervous system involvement). Bickerstaffs brainstem encephalitis (BBE) is a related syndrome in which alteration of consciousness or corticospinal tract signs are seen in addition to ophthalmoparesis and ataxia. Many patients with MFS or BBE also have "overlapping GBS" with flaccid quadriplegia.^[46,50] Anti-GQ1b antibodies are present in 95% of patients with acute MFS^[51] and in approximately two-thirds of patients with BBE. The recognition of various clinical presentations and the high sensitivity and specificity of anti-GQ1b antibody testing suggest rubric name of "anti-GQ1b antibody syndrome."

Anti-GT1a antibody without anti-GQ1b reactivity is found in patients presenting with the pharyngeal-cervical-brachial (PCB) variant of GBS.^[52,53] More than half of MFS patients will have cytoalbuminological dissociation on CSF analysis performed within the first 3 weeks of disease onset.^[54] In MFS, motor nerve conduction studies in the limbs are usually normal or only mildly abnormal with slight reductions in compound muscle action potential amplitudes and conduction velocities.^[55] Conduction block and temporal dispersion are not a feature of MFS. Sensory nerve action potential amplitudes are usually moderately to severely reduced, more so in the upper extremity sensory nerves (eg, median) than the sural nerve. Blink reflex R1 delayed or absent. MRI of the brain frequently demonstrates cranial nerve enhancement (eg, oculomotor nerves) in MFS^[56] and high-intensity abnormalities in the posterior fossa, white matter, or thalami in patients with BBE.^[50] MFS is generally a benign, self-limiting conduction. Almost all treated and untreated patients return to normal activities within 6 months of disease onset, usually with resolution of ophthalmoplegia within 1–2 months and ataxia within 3–4 months.^[57]

Other regional variants of GBS are those that affect other specific areas of the body, such as only the face or the afferent sensory and autonomic systems.^[58]

Management

Patients with GBS who are symptomatic but are able to walk unaided for more than 5 m and who are stable can be managed conservatively at peripheral centers. However, they should be observed for progression of the disease, especially if they are still within the first week of the onset of the disease. Blood pressure and heart rate fluctuations, clinical signs of respiratory failure should be carefully and meticulously monitored. Clinical signs of ileus should be watched. If any of these signs are detected they should be immediately shifted to specialized centers for further management. In the acute phase in bed-bound adult patients require both supportive therapy and immunotherapy can be used taking into consideration the cost factors and the clinical status (staging, complications, and other comorbid conditions) of individual patients.

Supportive Care

Immunotherapy therapy has not reduced the mortality in

GBS. Mortality is due to disease-related issues or secondary complications developed in hospital due to prolonged disease course. Meticulous and attentive care of these patients are essential in reducing the mortality. Supportive care consensus guidelines have been published.^[59]

Management of respiratory failure

GBS is the most common peripheral neuropathy causing respiratory paralysis. Despite advances in respiratory management and immunotherapy, mortality from GBS is as high as 20% for ventilated patients. Mechanical ventilation is usually required by one third of the patients.^[59] Clinical signs like tachypnea, tachycardia, brow sweating asynchronous movements of chest and abdomen and a vital capacity < 20 mL/kg, maximal inspiratory pressures < 30 mm H₂O, maximal expiratory pressure < 40 cm H₂O predicts imminent respiratory failure.^[59] Time from onset to admission of less than 1 week, facial weakness, bulbar paresis, and neck weakness are other factors associated with respiratory failure.^[59,60,61] Simple bedside single breath count, which correlates well with vital capacity than phrenic nerve conduction studies is a good predictor of respiratory failure (Unpublished data by Meena et al from NIMS, Hyderabad). Percutaneous dilatational tracheostomy may be advantageous over traditional tracheostomy by allowing less risk of accidental extubation and a better cosmetic outcome. In general it takes 2–6 weeks to wean out of ventilatory support.^[62] Tracheostomy may be performed 2 weeks following intubation and should be based on status of an individual. It is comfortable and provides airway safety but is associated at times with life-threatening complications and disfiguration.^[59] If pulmonary function is improving, it may be preferable to wait 1 more week to attempt at weaning from ventilator.

Management of Dysautonomia

Acute dysautonomia is a significant cause of death in patients with GBS. Cardiac and hemodynamic disturbance manifesting as hypertension, postural hypotension, and tachycardia occur in a majority of GBS patients.^[69] This is due to excessive sympathetic over activity and parasympathetic under activity. Severe dysautonomia occurs usually in severe cases at the peak of the deficit.^[69] Tachycardia is most common, usually in the range of 100–120/min, which does not require treatment. Approach to inserting a pacemaker for serious bradycardia or sinus arrest has varied widely because of the uncertainty that exists in anticipating such events at the bed side by different ways. However, the presence of tachycardia, increased daily variation in systolic blood pressure, reduced normal respiratory-induced heart rate variation, and first episode of severe bradyarrhythmia reduce the threshold for insertion of pacemaker.^[70,71] Endotracheal suction may provoke bradycardia or systole, and this can be reduced by hyperoxygenation. Hypertension is seen in one third of patients with GBS and can be labile or be followed by hypotension.^[63-65] If hypertension is severe (mean pressure greater than approximately 125 mmHg) and sustained, specific therapy may be necessary. Antihypertensives with short half-lives (labetolol, esmolol, or nitroprusside infusions) should be considered.^[65] Beta-adrenergic or calcium channel blockers should be used with caution, especially if episodes of hypertension alternate with

hypotension. Hypotension can be managed by maintaining intravascular volume and avoid using diuretics. Patients with a risk of hypotension should not be left unattended in a sitting or upright position. Pronounced and persistent hypotension should warrant search for other causes, such as sepsis myocardial infarction and pulmonary thromboembolism or use of narcotics or positive pressure ventilation. Gastrointestinal motility disorders occur in 15% of severely affected GBS patients. Ileus is associated with other features of dysautonomia (tachycardia and hypertension). Dysmotility can be effectively managed by suspension of enteral feeds, nasogastric suctioning, and erythromycin or neostigmine.^[59,69]

Hyponatremia is the common electrolyte abnormality in GBS and is due to SIADH (in majority of the cases) and natriuresis. The treatment is different for both. Both require replenishment of sodium but SIADH need fluid restriction and in case of natriuresis requires intravascular volume expansion. The best way to differentiate these two conditions is by measuring central venous pressure.

Deep vein thrombosis prophylaxis

All patients should be given subcutaneous fractionated or unfractionated heparin and support stockings until they are able to walk independently to prevent deep vein thrombosis.^[69] If a prolonged bedridden period is anticipated and a tracheostomy has already been performed, institute oral anticoagulant treatment with warfarin coumadin.

Pain and sensory symptoms are reported in majority of patients with GBS and should be treated effectively with opioid analogues. Sedation and bowel hypomotility may become a problem. Other drugs, such as gabapentin, carbamazepine acetaminophen, NSAIDs, and tricyclic antidepressants also can be tried.

Nutrition

Nasogastric or gastric tube feeding should be instituted early and slowly. High energy (40–45 nonprotein kcal) and high protein diet (2–2.5 g/kg) have been recommended so has to reduce muscle wasting and assist respiratory weaning. Continuous enteral feeding seems to be better tolerated than bolus feeding in these patients.

Surveillance for infections with weekly or more frequent sputum and urine cultures and blood count may be useful but the use of these tests should be guided by clinical circumstances.

Immunotherapy

Both plasma exchange and IVIg are effective immunotherapies for adult and pediatric patients with GBS if given during the first few weeks of disease.

Plasmapheresis

In a meta-analysis of 6 class II trails comparing plasma exchange (PE) to supportive care alone for adults with GBS, it was found that PE reduced the risk of developing respiratory failure.^[72,73] Patients treated with PE fared significantly better in the following secondary outcome measures: Time to recover walking without aid, percentage of patients requiring artificial ventilation, duration of ventilation, full muscle strength

recovery after 1 year, and severe sequelae after 1 year. Time to onset of motor recovery in mildly affected patients was significantly shortened in the PE group. However, the cost of PE has been shown to be offset by the savings of shorter hospital stay.^[74]

The volume of plasma removed and the optimum number of PE has not been established and it varies in different trials, but many physicians use the protocol of North American trial in which a total of 200–250 mL/kg was exchanged over 7–10 days all over the world.^[75] There is evidence that the number of PE in GBS should be adjusted to disease severity and that also patients with mild symptoms do benefit from PE.^[76]

In mild GBS, two sessions of PE are superior to none. In moderate GBS, 4 sessions are superior to 2. In severe GBS, 6 sessions are no better than 4. In line with these findings, Yuki *et al* reported that at least 2 PE are needed to significantly reduce the circulating immunoglobulin complexes.^[77] In developing countries where cost is the limiting factor, small volume PE may be used. In India small volume PE was used by Tharakan *et al* with comparable results.^[78] They used 15 mL/kg body weight/day to be continued till the progression of the disease got arrested or recovery started. This protocol is still performed in various centers in developing countries with good results.

Type of Plasma Exchange

Continuous flow PE is superior to intermittent flow exchanges. The replacement fluids do not affect the outcome of PE according to the French Study Group.^[79] Although albumin was found to be superior to fresh frozen plasma as the exchange fluid.

When to use PE? A better outcome was demonstrated with PE in French Study Group when compared with North American Study Group.^[79] This is due to the fact that treatment was initiated within 2 weeks in the former study group and within 4 weeks in the latter. Hence PE is more beneficial when started within 7 days after disease onset rather than later, but was still beneficial in patients treated up to 30 days after disease onset.

Who should be offered PE? All patients with mild, moderate, and severe GBS benefit from treatment. Patients who need even minimum assistance for walking, who are steadily progressing and those who are bed- and ventilator-bound should be advised PE. The value of PE in children younger than 12 years is not known.

AAN in 2003 concluded that PE hastens recovery in nonambulant patients who get treatment within 4 weeks of onset, and PE hastens recovery of ambulant patients with GBS who are examined within 2 weeks. PE is usually administered as one plasma volume, 50 mL/kg, on 5 separate occasions over 1–2 weeks.^[72]

Slightly more complications were observed in PE group than the IVIg group. Significant adverse events of PE include hypotension, septicemia, pneumonia, abnormal clotting, and hypocalcemia. Major hemostatic disorders, unstable cardiovascular state, active infection, and pregnancy are contraindications to PE.

Immunoabsorption therapy is an alternative technique to PE. This form of therapy removes Ig from the circulation without the need for replacement with albumin or FFP because of loss of albumin. Evidence says that there is no difference in outcomes between patients treated with immunoabsorption and PE or double filtration plasmapheresis.^[80,81]

Steroids

In a Cochrane systematic review of 6 trials with 587 patients it has been shown that corticosteroid therapy is ineffective for treating GBS.^[82]

Intravenous Immunoglobulins

The first RCT on the use of IVIg was published in 1992, and showed that IVIg is as effective as PE.^[83] Since the publication of these results, IVIg, in a regimen of 0.4 g/kg bodyweight daily for 5 consecutive days, has replaced PE as the preferred treatment in many centers, mainly because of its greater convenience and availability. The Cochrane review on the use of IVIg in GBS contained 4 additional trials.^[84] No difference was found between IVIg and PE with respect to the improvement in disability grade after 4 weeks, the duration of mechanical ventilation, mortality, or residual disability. The combination of PE followed by IVIg was not significantly better than PE or IVIg alone. The combination of IVIg and intravenous methyl prednisolone was not more effective than IVIg alone, although there might be a short-term effect of this combined treatment when a correction is made for known prognostic factors.^[85,86]

In general in patients with renal dysfunction the rate of infusion should be decreased to half of the normal infusion rate.

Timing of treatment

Most RCTs have included only patients who are treated within the first 2 weeks from onset of weakness and who are unable to walk without assistance. If these criteria are met, there is no doubt that patients with GBS should be treated with IVIg or PE. The question remains as to what to do in patients with rapidly progressive limb weakness or impaired pulmonary function but who are still able to walk. Although not proven effective, it seems logical to treat these patients with IVIg.

Treatment of mildly affected patients

These patients are able to walk with some support or no support. A retrospective study showed that these patients often have residual disabilities.^[87] RCTs that have assessed the effect of IVIg have not studied the effect in mildly affected patients. It should be kept in mind that no RCTs have assessed the effect of PE or IVIg in these mildly affected patients with GBS.

Miller Fisher syndrome

No RCTs have studied the effect of PE or IVIg in patients with MFS.^[88] Observational studies have suggested that the final outcome in patients with MFS is generally good. In a large uncontrolled observational study,^[89] IVIg slightly hastened the amelioration of ophthalmoplegia and ataxia. The investigators concluded that IVIg and PE did not influence the outcome of patients with MFS, presumably because of good natural

recovery. Patients with mild or uncomplicated MFS may perhaps be treated conservatively. Patients with more severe or complicated anti-GQIB antibody syndrome, an overlapping GBS, should probably receive immunotherapy.

Treatment of patients who deteriorate in spite of therapy

Some patients with GBS continue to deteriorate after PE or a standard course of IVIg. In these cases, the best option is unknown. Whether these patients need PE after they have been treated with IVIg has not been investigated, but the combination of PE followed by IVIg is no better than PE or IVIg alone. PE after IVIg is also not advised, because PE would probably wash out the IVIg previously administered. A study in a small series of patients investigated the effect of a second course of IVIg in severe unresponsive patients with GBS.^[90] This uncontrolled study suggested that a repeated course of IVIg could be effective. About 5%–10% of patients with GBS deteriorate after initial improvement or stabilization following IVIg treatment.^[91] Although no RCTs have assessed the effect of a repeated IVIg dose in this condition, it is common practice to give a second IVIg course (2 g/kg in 2–5 days). These patients are thought to have a prolonged immune response that causes persistent nerve damage that needs treatment for a longer period of time.^[92] A longer interval between onset and treatment and longer time to nadir may be associated with a greater chance of relapse.

Cost-effectiveness of PE and IVIg in GBS

When faced with restrictions in financial resources, especially in developing countries cost-effectiveness of any treatment becomes a major issue in treatment decision making. This is very true in GBS in which the currently approved treatment has shown equal efficacy. There are a few available cost analysis studies addressing this issue and the results are controversial.^[93,94] However, in developing countries use of small volume PE may bring down the cost when compared to IVIg. Hence the decision to use PE or IVIg must be based on multiple factors. The main limitations for use of PE would be availability of the technical expertise and support. Lack of these, ease of administration, and fewer side effects with IVIg may dictate use of IVIg as the first line of therapy.

Prognosis

GBS has a serious long-term impact on the patients' work and private life, even 3–6 years after the onset of illness. Recovery can be slow and take years. Persistent disability is seen in 20%–30% of adult patients but is less common in children.^[2,95] Severe fatigue is a sequel of GBS in two thirds of adult patients. In an RCT of amantidine, it was not superior to placebo.^[96] Twelve weeks bicycle extensive training program had positive effects on fatigue, anxiety, depression, and functional outcome.^[97]

Conclusions

GBS is a monophasic immune-mediated neuropathy characterized by acute onset of predominantly motor weakness and is a common cause of respiratory paralysis. There are many variants described with different prognosis and manifestations. Electrodiagnosis aids in the diagnosis. Immunotherapy definitely makes a difference in the recovery

of GBS patients and both PE and IVIg are equally effective. IVIg may be preferred because of its low side-effect profile and ease of administration. However, small volume PE can be used with equal efficacy due to cost constraints. Attentive anticipatory supportive treatment is equally important in reducing the morbidity and mortality in GBS.

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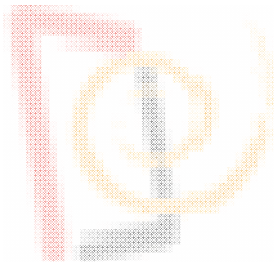
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Treatment in late Parkinson's disease

It is almost 200 years since James Parkinson described the major symptoms of idiopathic Parkinson's disease (IPD). Since then, our treatment armamentarium has slowly increased, providing effective treatment to many patients, but the management of the late stage of the disease is still a huge challenge. Levodopa is the most effective pharmacological treatment available for IPD.^[1] In late stages of the disease, however, it is difficult to maintain a stable therapeutic response with pharmacological therapy. Motor complications such as wearing off fluctuations^[2] and dyskinesias^[3] develop with increasing frequency in patients after 5–6 years of dopaminergic therapy.

Pharmacological Therapy

Motor complications are often managed in the initial stages with adjustment in levodopa dosage. Motor off time can be reduced by the addition of various dopaminergic agonists including pergolide, pramipexole, ropinirole, cabergoline, and drugs such as monoamine oxidase (MAO) inhibitors (rasagiline) and catechol-O-methyl transferase (COMT) inhibitors (entacapone).

^[4] A recent Cochrane review demonstrated that all the three groups of adjuvant drugs – dopaminergic agonists, MAO-B inhibitors (MAOBI) and COMT inhibitors (COMTI) – reduced off time, levodopa dose, and improved Unified Parkinson Disease Rating Scale (UPDRS) scores in Parkinson's disease (PD) patients with motor complications but at the cost of increased dyskinesias and numerous other side effects. In the same review, indirect comparisons suggested that dopamine agonist therapy may be more effective than COMTI and MAOBI therapy. However, there is lack of direct evidence and head to head comparison trials between these drugs.^[5]

Management of troublesome dyskinesias is a major challenge in late stages of the disease. Studies have shown that dyskinesias occur in about 50% of elderly and almost 100% of younger patients under the age of 40 years after 6 years of levodopa therapy.^[6]

The exact pathophysiology of dyskinesias is still not clear. As fluctuations in the dopamine levels may contribute to the appearance of dyskinesias, reducing the dose and increasing the frequency of levodopa, addition of MAOBI or COMTI and addition of dopaminergic agonists can be tried in the initial phases. There is strong evidence that initial therapy with dopamine agonists in early stages of the disease results in delay in the appearance of dyskinesias compared to that with levodopa.^[7,8] However, once levodopa treatment is

initiated, alone or in addition to dopaminergic agonists, the time duration from the onset of levodopa therapy to occurrence of dyskinesias was the same in both groups. Similarly, addition of entacapone to levodopa/carbidopa theoretically should cause less dyskinesias, but the evidence is still lacking. A recent review and guidelines by AAN identified amantadine as a safe and effective pharmacological therapeutic agent for dyskinesias.^[4] Various studies have shown that amantadine significantly reduces dyskinesias by about 50%. However, there are still confounding results on whether the antidyskinetic effect of amantadine wears off after a year or there is a long-standing effect.^[9-11] Though clozapine has also shown reduction in dyskinesias, the side effect profile, especially the occurrence of agranulocytosis, restricts its usage.^[4] Thus, in late stage of PD, there is limited efficacy of medical therapy.

Surgical Therapy

The recent progress in functional neurosurgery probably marks the second most important therapeutic advance in PD after the introduction of levodopa. In the last 15 years, there have been many Class III and Class IV studies suggesting the effectiveness of deep brain stimulation (DBS).^[4] With the results of the recently concluded two large-scale randomized clinical trials involving 156 patients with PD^[12] and 255 patients with PD^[13] with severe motor complications, the evidence has become more robust. DBS is more effective than the best medical therapy in improving "on" time without troubling dyskinesias by 4.6 h/day, motor function in 71% compared to 36% in medical therapy, and quality of life at 6 months after surgery.^[13] There was, however, an increased risk of side effects related to the procedure.^[13] Thus, while DBS is the most effective therapy in patients with motor complications, it is important to select the correct patients who are eligible for the procedure.^[14]

PD patients with at least 5 years disease duration, UPDRS-III off score of 30 or more, H and Y score of ≤ 3 , significant response to levodopa with troublesome dyskinesias and normal cognition are eligible for DBS.^[14] Best results have been reported in patients with advanced PD with at least 5 years of disease duration and (a) excellent levodopa response, (b) younger age, (c) no or few axial non-levodopa responsive motor symptoms, (d) no or very mild cognitive impairment, and (e) absence of or well-controlled psychiatric disease.^[15] Unfortunately, these stringent criteria imply that only a small percentage of PD patients are eligible for DBS.^[16]

Various sites have been proposed but the effect is maximally seen with stimulation of bilateral subthalamic nucleus (STN) and globus pallidum interna (GPi) for most features of IPD. Similar benefits for both STN and GPi DBS have been reported in only a few randomized studies.^[17] The recent co-op study addressed this issue.^[18] Two hundred ninety-nine patients with PD were randomized to STN or GPi DBS with the primary outcome of UPDRS-III assessed in a blinded manner. Similar

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improvements were found at 2-year follow-up for both surgical sites. Dopaminergic medication was decreased more for the STN group but visuomotor processing speed declined less after GPi DBS. Furthermore, subjects who had GPi DBS showed improvement in depression, whereas subjects who had STN DBS worsened. Taken together, both STN and GPi DBS improve motor function, but the target selection should be individualized considering the differences in nonmotor outcomes.^[18] Various complications can occur with DBS, including risk of intracranial hemorrhage (<2%), lead fracture and migration and hardware infection, but the rates have come down markedly with improvement in technology and operative procedures.

Ablative Surgery

Although thalamotomy and pallidotomy have largely been abandoned and replaced by DBS, ablative therapies may yet have a role in certain patients such as those with an increased risk of infection or a history of recurrent infection of their DBS systems, economic reasons and in patients with predominantly unilateral symptoms. Ablative surgeries are not preferred because of significant side effects including dysphagia, dysarthria and cognitive deficits. Disadvantages of ablative surgery include mistargeted lesions with permanent neurological deficits and suboptimal and unilateral benefits even in well-targeted approach.^[19-21]

Newer Treatment Modalities

Continuous dopaminergic stimulation

Intrajunctional constant-rate infusions of levodopa are a newer therapeutic option to provide a constant dopaminergic level in the blood. Studies have shown that with this approach, motor fluctuations, and particularly, the intractable dyskinesias of patients with advanced PD are substantially reversed even as the total daily levodopa dose and corresponding "on" time are increased. The carboxymethylcellulose formulation of levodopa, provided in a gel formulation (duodopa) at a concentration of 20 mg/mL and delivered through an intrajunctional pump system, is approved in most countries of Europe.^[22,23] Studies are being conducted to further validate the results of this procedure and look at its technical liabilities for long-term therapy (e.g., potential percutaneous gastrostomy infections, dislocation, kinking and occlusion of catheters, high cost) to assess the overall efficacy.

Similarly, mini pumps with continuous subcutaneous delivery of the dopamine agonist apomorphine have been shown to reverse fluctuations and dyskinesias.^[24]

Newer molecules like glutamate receptor antagonists (that reduce D1 output), cannabinoid receptor antagonists, α_2 -adrenergic receptor antagonists (that inhibit GPe), adenosine A2A-receptor antagonist, and 5-HT1A-receptor agonists are being evaluated for reducing dyskinesias.^[25]

Conclusions

Late stages of PD are characterized by the development of motor complications including wearing off and dyskinesias.

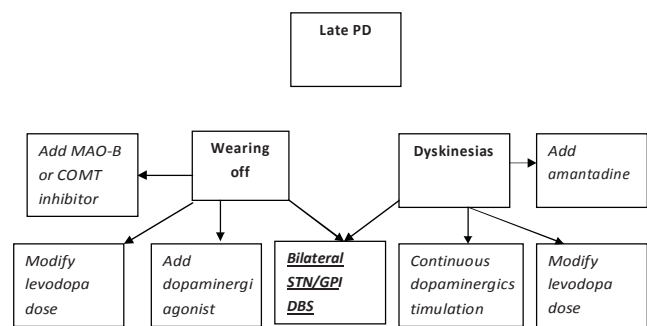


Figure 1: Algorithm for management of late stage PD

Although few patients improve with modifications in levodopa dosage and addition of dopaminergic agonists, MAOBI and COMTI, many develop troublesome dyskinesias. Best therapy available is bilateral DBS of STN or GPi. Continuous dopaminergic stimulation with duodopa or apomorphine may be considered [Figure 1].

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