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CHAPTER 85

Advances in Epilepsy Management and Current Perspectives

Man Mohan Mehndiratta, Natasha Singh Gulati, Vasundhara Aggarwal

Abstract

Epilepsy is a common neurological disorder attended in Neurology clinics accounting for ~1% of the global disease burden across all ages. Neurologists worldwide now aim at seizure remission in patients with epilepsy because recurrent seizures lead to significant morbidity and mortality and also affect the quality of life (increased health-care use, unemployment, or even sudden death) of the patient and the caregiver. The first step toward accurate diagnosis, therapy, and prognostication of epilepsy is adequate knowledge of its definition and classification. After the appropriate diagnosis is made the two key questions are what and when to start pharmacological treatment and when is non-pharmacological treatment required. Activity modification and restrictions also play an important role in customized treatment. This chapter provides a useful insight into the current perspectives and recent advances in management of epilepsy.

Introduction

Major advances in epilepsy management have surfaced in recent years. In recent years there have been many improving definitions, guidelines, diagnostic, and treatment protocols that have come to the fore. The causes and consequences of epilepsy have been more deeply explored. It is very important to fine tune our knowledge and keep updated. It’s rightly said “Staying Updated Is Our Commitment to Our Patients.”

Definition and Classification—Recent Changes

The first step toward accurate diagnosis, therapy, and prognostication of epilepsy is adequate knowledge of its definition and classification. One of the most eminent international organizations dedicated to epilepsy care, education, and research is the International League Against Epilepsy (ILAE). Table 1 describes the 2014 ILAE Epilepsy Operational (practical) definition.

Seizure is defined as "occurrence of transient signs and/or symptoms due to abnormal excessive or synchronous neuronal activity within the brain.”

ILAE published “position papers” on the latest classification of epilepsies and seizures, as well as an “instruction manual” for use of seizures operational classification in 2017. Position paper of the “ILAE Commission for classification and terminology 2017” states a new multilevel Classification (Fig. 1), which requires a diagnosis at all three levels. First of all it is assumed that the patient is having epileptic seizures as defined by the latest 2017 ILAE Seizure Classification. It starts with Level 1: Seizure type diagnosis. The next step is Level 2: Epilepsy type diagnosis, including focal epilepsy, generalized epilepsy, combined generalized, and focal epilepsy, and also an unknown epilepsy group. The next is Level 3: Epilepsy syndrome diagnosis.

It also incorporates and emphasizing the requirement to considering etiology at each step of diagnosis. The etiology is broken into six subgroups (Fig. 2), keeping in
TABLE 1  2014 ILAE operational (practical) definition of epilepsy

| Epilepsy: A disease of the brain defined by any of the three following conditions |
|---|---|---|
| At least two unprovoked (or reflex) seizures which occur >24 h apart | One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (i.e., at least 60%) after two unprovoked seizures, which can occur over the next 10 years | An epilepsy syndrome diagnosis |
| Epilepsy is considered to be resolved for individuals who have past the applicable age and had age-dependent epilepsy syndrome or individuals who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years |

Fig. 1: New multilevel classification of approach to diagnosis of epilepsy
mind the possible therapeutic consequences. It lays special emphasis on diagnosing a genetic cause of epilepsy. It also emphasizes to consider comorbidities including depression, anxiety, migraine, cognitive impairment, etc., which can affect the progression and management. There are certain drugs to be preferred and avoided in epilepsy with comorbidity. The understanding of etiology and comorbidities will help targeted therapies to the specific type of disease and etiology.\(^2,4\)

**New Regarding the Classification of Epilepsy\(^4\)**
- Combined generalized and focal epilepsy type added (it cannot be just focal or generalized)
- “Benign” are now termed “self-limiting” or “pharmacoresponsive” (where therapy can spontaneously resolve it)
- New term added epileptic encephalopathy and developmental and epileptic encephalopathy
- Psychosocial and other comorbidities included

**New Regarding the Classification of Seizures\(^3-5\)**
- Newly added types and terms in ILAE 2017 classification:
  - New focal seizure types include automatisms, autonomic, cognitive, behavior arrest, emotional, sensory, hyperkinetic, and focal to bilateral tonic–clonic seizures. Atonic, clonic, myoclonic, epileptic spasms, and tonic seizures, which can be either generalized or focal.
  - New generalized seizure types include epileptic spasms, absence with eyelid myoclonia, myoclonic–tonic–clonic, myoclonic–atonic, and myoclonic absence.
- The discontinued terms are:
  - Simple/complex partial
  - Convulsions
  - Dyscognitive
  - Psychic
  - Secondarily generalized

**Approach to Management of Epilepsy**

**Pharmacological Management\(^6-8\)**
The mainstays of treatment are anti-epileptic drugs (AEDs). Two key questions "When and What to Start"??

**When to Start Antiepileptic Drugs: Treatment Indicated??**

**Definitions\(^7\)**
- Unprovoked seizure can have an unknown etiology or can occur in relation to a preexisting brain lesion or progressive nervous system disorder. In the later cases, it is often referred to as a remote symptomatic seizure.
- Provoked seizures has an acute condition, which provokes seizure such as a head trauma, toxic, or metabolic disturbance or acute stroke (also called acute symptomatic seizures).
**First Unprovoked Seizure**

- Decision must be individualized and guided by following factors:
  - High seizure recurrence risk of to meet criteria for epilepsy according to ILAE
  - High risk clinical variables
  - Remote symptomatic cause revealed by clinical history or neuroimaging, e.g., brain tumor, head injury with loss of consciousness brain malformation, prior infection of central nervous system, or prior brain injury or brain surgery scar
  - Prior brain insult
  - Epileptiform abnormalities on electroencephalogram (EEG)
  - Significant abnormality on brain imaging
  - Nocturnal seizure
  - Abnormal focal findings and intellectual disability on neurologic examination
  - Significant side effect profiles in individual patient comorbidities and age
  - Social consequences

**What to Start:** Which and How Many Antiepileptic Drugs

Start with a single AED introduced at a small dose (except status epilepticus or frequent seizures). Monotherapy advantages being:

- avoids drug interactions
- decreases the likelihood of adverse effects
- less cost than polytherapy

The dose is then gradually increased to the lowest effective maintenance dose.

The drug is to be tailored to factors such as disease related factors, drug related factors and individual person characteristics—No single AED that is ideal for all patients.

First generation AEDs remain valuable first-line therapies, which are discussed in Table 2.

Second generation AEDs (Table 3) offer advantages in terms of drug resistance, fewer drug interactions, and improved tolerability and tailoring treatment (Table 3).

AEDs can also be divided based on their mechanisms as given in Table 4.

**Example:** If first generation AED carbamazepine fails to control the seizures then second generation AED like lamotrigine, topiramate, tiagabine, gabapentin, levetiracetam, oxcarbazepine, pregabalin, and zonisamide can be considered (new anticonvulsants are generally considered second-line therapy, however, can be used as first-line therapy in some patients).

If seizures persist on the first AED despite optimal up-titrination to the maximally tolerated dose, exclude non-compliance and reappraise the diagnosis and treatment.

If an AED change is required switch to an alternative monotherapy.

Polytherapy is usually offered after failure of two or three sequential monotherapies (except in a difficult to treat form of epilepsy unlikely to respond fully to monotherapy).

**Drug Resistant Epilepsy:** ILAE defines drug-resistant epilepsy as “failure of adequate trials of two tolerated,
appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained freedom from seizures."

Factors Influencing Choice of AEDs

Disease-related Factors: Anticonvulsants for Specific Seizure Types

- Ethosuximide—For absence seizures alone
- Valproic acid or lamotrigine, or topiramate—If other seizure types along with absence seizures (e.g., generalized tonic–clonic seizures, myoclonic seizures)
  (Caution: Drugs may exacerbate absence seizures—carbamazepine, gabapentin, or tiagabine)
- Broad-spectrum AEDs—Lennox-Gastaut syndrome with seizures
- Adjunctive therapy with rufinamide, clobazam, extended-release topiramate, cannabidiol and stiripentol—Seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex
- Valproic acid, lamotrigine, and topiramate—Juvenile myoclonic epilepsy JME and myoclonic seizures—(JME has a high recurrence rate)
- Levetiracetam—As adjunctive therapy of JME
- Valproic acid, topiramate, or lamotrigine and adjunctive therapy with Levetiracetam, perampanel—Primary generalized tonic–clonic seizures
- Valproate should remain the drug of first choice for generalized and unclassified epilepsies except in women of childbearing age
- Monotherapy with carbamazepine, cenobamate, lacosamide, lamotrigine, oxcarbazepine, and topiramate adjunctive therapy with levetiracetam, tiagabine, gabapentin, pregabalin, lacosamide, cenobamate, or ezogabine—Focal-onset seizures
- Lamotrigine—First line in elderly subjects (patients aged ≥60 years)

Standard and New Antiepileptic Drugs (SANAD) Trial

The largest individual randomized trial examining different antiseizure drugs as monotherapy for the initial management of epilepsy (Fig. 3).

Drug-related Factors

See Box 1.

Individual-related Factors

Specific patient populations and conditions-related considerations

### TABLE 4 AEDs based on mechanism of action

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs Blocking repetitive activation of the sodium channel</td>
<td>Phenytoin, oxcarbazepine, carbamazepine, eslicarbazepine, topiramate, lamotrigine, cenobamate</td>
</tr>
<tr>
<td>Drugs Enhancing slow inactivation of the sodium channel</td>
<td>Lacosamide, rufinamide</td>
</tr>
<tr>
<td>Drugs blocking N-methyl-D-aspartic acid (NMDA) receptor</td>
<td>Felbamate</td>
</tr>
<tr>
<td>Drugs enhancing Gamma-aminobutyric acid (GABA)-A receptor</td>
<td>Phenobarbital, clobazam, and benzodiazepines</td>
</tr>
<tr>
<td>Drugs blocking T-calcium channel</td>
<td>Ethosuximide, valproate</td>
</tr>
<tr>
<td>Drugs blocking Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor</td>
<td>Perampanel and topiramate</td>
</tr>
<tr>
<td>Drugs modulating H-current</td>
<td>Gabapentin and lamotrigine</td>
</tr>
<tr>
<td>Drugs blocking N- and L-calcium channel</td>
<td>Lamotrigine, zonisamide, topiramate, and valproate</td>
</tr>
<tr>
<td>Drugs Blocking unique binding sites</td>
<td>Gabapentin, perampanel and levetiracetam</td>
</tr>
<tr>
<td>Neuronal potassium channel ( KCNQ [Kv7]) opener drugs</td>
<td>Ezogabine</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors drugs</td>
<td>Topiramate, zonisamide</td>
</tr>
<tr>
<td>Other anticonvulsants</td>
<td>Cannabidiol, stiripentol</td>
</tr>
</tbody>
</table>

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Box 1: Drug-related factors influencing choice of AEDs

- Comparative efficacy
- Dosing frequency
- Drug interactions
- Aging
- Neuro-cognitive side effects
- Hypersensitivity reactions; Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
- Suicidality
- Weight loss or gain
- FDA indications
- Cost of medications

- Neonates and children:
  - Adjust doses per kg body weight
  - Tend to metabolize the drugs quicker
  - Rapid rise in the total volume of distribution

Elderly patients: Need less initial dose and maintenance doses because of slow hepatic metabolism, decreased renal clearance and decreased volumes of distribution.

- Women on oral contraceptive pills:
  - AEDs that induce hepatic enzyme decrease the efficacy of oral contraceptive pills—carbamazepine, phenytoin, primidone, felbamate, phenobarbital, lamotrigine, topiramate, and oxcarbazepine.
  - High-dose estrogen-progesterone contraceptive can be administered to counteract this effect.
  - Can use alternative method of contraception.

Women of childbearing age and pregnant women:

- Obstetric complications, changes in seizure frequency, teratogenesis, vitamin K, folic acid, blood levels of AEDs, and breastfeeding are nicely covered in 2009 new guidelines for the management of antiepileptic drugs (AEDs) during pregnancy by the American Academy of Neurology and the American Epilepsy Society.
- Not recommended: Switching medications during pregnancy and polypharmacy.
- Drug serum levels should be obtained frequently.

Renal insufficiency:

- Gabapentin, zonisamide, oxcarbazepine, levetiracetam, lacosamide, and pregabalin doses should be altered as they are excreted mostly by means of renal clearance.
- Nephrolithiasis could be associated with topiramate and zonisamide.

Hepatic disease:

- In patients with chronic liver disease, levetiracetam, pregabalin, gabapentin, and vigabatrin as they do not undergo hepatic metabolism.
Phenytoin, valproic acid, carbamazepine, and felbamate should be used with caution as they have been associated with acute hepatic injury.\textsuperscript{5,8}

**Post-stroke epilepsy:** Consider impact of the antiseizure drug on post-stroke functional recovery and the potential for drug interactions with warfarin and salicylates.

**Brain tumors:** Consider possible drug interactions with chemotherapeutic agents and increased possibility for allergic cutaneous reactions during radiotherapy.

**Psychiatric disorders:**
- Depression correlates more strongly with a poor quality of life than the frequency of the seizures.
- Some AEDs also appear to have mood stabilizing properties while some AEDs cause or exacerbate a depressed mood.

**Migraine:** Valproate, gabapentin, and topiramate are antiseizure drugs that have demonstrated efficacy for migraine prevention in placebo-controlled trials.

**Osteoporosis risk:** AEDs in chronic use have been associated with bone loss. Moreover seizures are also associated with falls and associated bone fractures. Monitor bone density, routinely supplement vitamin D, and calcium. A consistent exercise regimen is also required.\textsuperscript{7}

**Discontinuing AEDs**
After an individual has been seizure free for typically 2–5 years, many consider discontinuing AEDs. Patients with juvenile myoclonic epilepsy (JME) have high recurrence rate (of about 80–90%) during adulthood.

**Risks of Seizure Recurrence**
After drug discontinuation, risk of relapse increase if there are:
- Abnormalities on imaging such as on brain MRI scan and epileptiform or foci abnormalities on an EEG
- Higher number and frequency of seizures
- Longer duration of epilepsy before the seizures-free period
- Specific seizure type, e.g., tonic or atonic seizures
- Shorter duration of freedom from seizure

During tapering AEDs and for at least for first 3 months after discontinuation of AEDs, advise patients to observe strict activity and lifestyle precautions (e.g., not to drive, etc.)

**Non-pharmacological Therapy**
There have been rapid advances in surgical technology and neuroimaging and parallel understanding of developments in epilepsy neurobiology.

**Surgical Procedures**
The types of surgery performed in patients for refractory epilepsy include:

**Anterior temporal lobectomy (ATL):** Most common surgical procedures performed in temporal lobe epilepsy in adolescents and adults.

**Extratemporal resection:** In early childhood, this is the most common type of surgery performed with etiologies being cortical development malformations, vascular malformations, and tumors.

**Lesionectomy:** Lesionectomy involves the resection of circumscribed epileptogenic lesions, including tumors, vascular malformations, and well-delineated malformations of cortical development.

**Hemispherectomy:** When little or no functional cortex remains and the entire hemisphere is considered epileptogenic. For example, in Rasmussen’s encephalitis, Sturge-Weber syndrome or large hemispheric infarction.

**Corpus callosotomy (CC):** The procedure is performed in patients with symptomatic generalized epilepsy who are poor candidates for resective surgery. Occasionally done in frequent secondary generalized tonic–clonic, tonic and atonic seizure leading to falls and injuries.

**Multiple subpial transection (MST):** Occasionally used in focal epilepsy arising in or around eloquent areas.

**Thermal ablation:** Minimally invasive type of laser surgery. Laser destroys the small well-defined focal point of seizure in brain tissue without damaging the surrounding tissue.

**Devices for Brain Stimulation**

**Intracranial systems (implant device):** Deep brain stimulation (DBS) and Responsive neurostimulation (RNS)

**Extracranial systems:**
- Focal cooling and uncaging
- RTM—Repetitive Transcranial Magnetic Stimulation
- TDC—Transcranial Direct Current Stimulation
- TNS—Trigeminal Nerve Stimulation
- VNS—Vagus Nerve Stimulation

**Devices Detecting Seizures**

Helps in alerting the individual and their caregivers and thus helps in monitoring and managing the seizure behavior. However, these devices also have their own limitations:

- Wearable device—Accelerometer, Medpage ST-2, SeizAlert, Protective Headwears
- Sensor implant device—BrainGate ™ Neural Interface System
- Mobile-phone-based device—Epdetect and Epilert
- Watch-based device—SmartWatch Alert
- Software-based multichannel sensor device—NeuroPort System
- Cortical stimulators and mapping—Rehabilicare
- Working mats—Safety Place Mat

**Devices for Surgery**

Include Cyber knife®, Functional MRI, Gamma knife®, High-resolution brain Single-photon emission computed tomography (SPECT), Magnetoencephalography, Near-Infrared Spectroscopy (NIRS), Signal Modeling For Real-Time Identification And Event Detection (SIGFRIED), and Tractography and diffusion tensor imaging.

Responsive neurostimulation (RNS) (Fig. 4) is the first generation “closed loop” device using Brain Computer interface (BCI). The device is set to particular EEG (depending on the patients individual EEG) and whenever there is a seizure the implant helps to detect and record the EEG pattern. It then sends an electrical signal to disrupt that pattern of seizure activity. The FDA in November 2013, approved the NeuroPace RNS System for the controlling seizures in patients with drug-resistant epilepsy particularly partial-onset epilepsy.

Transcranial magnetic stimulation (TMS) is another method for brain stimulation magnetic field induced brain currents were introduced with the help of magnetic stimulator coil from a safe distance to stimulate focally and deeply in the brain tissues.

Vagal Nerve Stimulation (VNS) is FDA approved in patients above 12 years of age to treat medically refractory focal-onset epilepsy. Candidates for VNS should meet the following criteria:

- Adequate trials of at least 2 or 3 AEDs (preferably with different mechanism of action).
- Exclusion of nonepileptic events.
- Not a good candidate for epilepsy surgery.

If the patient is a good candidate for focal resective surgery, then it should be preferred over VNS, as this procedure has a superior seizure free rate.

The noninvasive brain stimulation technique of VNS is transcutaneous vagus nerve stimulation (tVNS). It uses a bipolar electrode (external device) to stimulate the left auricular branch of the vagus nerve at the ear conch. It is a newly developed CE (Cerbomed GmbH, Erlangen, Germany) certified tVNS (NEMOS®) device.

**Radiosurgery**

Radiosurgery is also an alternative to drug resistant epilepsy and other epilepsy surgeries. For example, CyberKnife® and Gamma Knife®. However, due to the radiosensitivity, the safety of the normal tissues around the lesion is at risk.

**Diet Therapy**

*Ketogenic diet (KD):* In patients with drug-resistant epilepsy and where surgery is not feasible, Ketogenic diet
consisting of high fat and low carbohydrates and proteins, i.e., 3:1 or 4:1 (fat:carbohydrate and protein) ratio by weight can be given.

**Modified atkins diet (MAD):** It is a modified traditional KD. Here diet consists of approximately 1:1 (fat:carbohydrate and protein) weight ratio. It is preferred as it is more palatable and less complex compared to KD. Efficacy in children with drug resistant epilepsy is similar to KD.

**Software**

Analysis of user defined seizure events logged in a database over a given time period and converting it into reports and graphs leading to high-tech seizure pattern analysis. Many software tools are presently available. For example, include EpiTrax, eemagine EEG, Epivista, Epilexia, iPlan Net, IdentEvent, Leonardo Brainmap, Neuroport Software System, NeuroScore NeuroGuide Deluxe QEEG 2.5.5, Net Station 4.3 and many more.9

**Activity Modification and Restrictions**

**Seizure Lifestyle Precautions**

**Driving Motorized Vehicles**

Driving laws vary from country to country. Generally it is not advisable for persons with epilepsy to drive during the first 2 years of treatment. The USA permits a person to drive if she/he is seizure free between 3 and 18 months. In the UK, a driving license can be granted if a person is seizure free for 1 year. In Australia, driving licenses are issued to those who’ve been seizure-free for a period of 6 months to 2 years. As of today, the Government of India has no provision to issue special driving licenses to People with Epilepsy (PWE), no matter how long they have been seizure free.10

**Water Precautions**

PWE should not swim alone, have adult lifeguard while swimming, and wear a lifejacket on a boat. Even a simple task of taking bath may be risky.

**Heights, Fire, and Power Tools**

Use of safety devices for example. Having automatic shut-off switch in operating these tools is recommended.8

**Epilepsy and Law**

A book was published jointly by the Indian Epilepsy Association and the Indian Epilepsy Society in 2017.10

**Conclusion**

Epilepsy is a complex neurological disorder with complex pathogenesis. Understanding the updated definitions and classifications and the advanced pharmacological and non-pharmacological approach for its treatment will definitely improve the patient care. Introducing activity modification and restrictions in the treatment protocol will help in customized care of clinical condition of the patient. What we know till date is just the tip of the iceberg. Despite all the ongoing researches, any definitive curative treatment is still a remote possibility. We have miles to go before we relax.

**References**

Abstract

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein present on the surface of myelin sheath. It accounts to only 0.5% of the central nervous system (CNS) myelin sheath and is present only in the CNS. It is considered to have a role in regulating microtubule stability of oligodendrocytes, mediate complement cascade and also help in adhesion of myelin fibers. In spite of its very low concentration, its highly immunogenic nature and presence on surface of myelin sheath make it an easy target to antibodies in CNS autoimmune responses.

MOG antibodies were a topic of interest for past three decades and their role in CNS inflammatory diseases has been supported by their detection in sera and cerebrospinal fluid (CSF) of multiple sclerosis (MS) patients using ELISA and Western blot. Thus, these were thought to be involved mainly in MS pathophysiology. These techniques used denatured MOG peptides as antigens. However, recent techniques using cell based assays showed strong association of antibodies to intact, full length human MOG protein with recurrent optic neuritis, myelitis and brainstem encephalitis like presentations than with classic MS. This has led to the recognition of a new entity, MOG antibody disease (MOG-AD) in patients who have clinical phenotype not fitting into either classic MS or Neuromyelitis optica (NMO), but testing positive for MOG-IgG antibodies. While NMOSD is an astrocytopathy, MOG-AD is a disorder of oligodendrocytes wherein astrocytes are typically spared. Though there is significant clinical and radiological overlap between (MOG-AD) and other related CNS demyelinating disorders like MS and Aquaporin 4 positive NMO, it is important to distinguish these in view of different therapeutic and prognostic implications.

Introduction

We, as treating physicians, are well acquainted with acquired inflammatory demyelinating disease called multiple sclerosis (MS). However, there has been a sea change in our present understanding of demyelinating disorders due to emergence of newer entities, especially Myelin oligodendrocyte glycoprotein associated disease (MOG-AD). It is important to identify this as a distinct clinical entity in view of its different therapeutic and prognostic implications.

Clinical Significance

MS and MOG-AD have considerable features in common like relapsing course, certain radiological features, and in fact in adults with MOG-AD, about 33% meet McDonald’s criteria for MS at least once during disease course, leading to misdiagnosis and thus have serious therapeutic consequences as many drugs used for MS are ineffective and at times leads to clinical worsening in a case of MOG-AD. Thus, patients with suspected MS with worsening on treatment need to be screened for MOG-IgG. Early identification of MOG-AD is important because:

- Few drugs approved in MS (interferon beta, natalizumab, fingolimod) can actually be harmful in MOG-AD.
- Immunopathogenesis for MOG-AD is different from MS.
- MOG-AD requires high dose steroids and careful and slow steroid taper (high risk of flare up).
In MOG-AD, for:
- **Acute attacks**: antibody depleting treatments are very effective (plasma exchange; IVIG in children).
- **Long term**: B-cell targeted therapy (Rituximab).

**Evolution Spectrum of Demyelinating Disorders of CNS (Fig. 1)**

Based on site of involvement, clinical, radiological and serological findings, central nervous system (CNS) demyelinating disorders are classified as:

Types of acquired demyelinating diseases are depicted in Flowchart 1.

**MOG-AD: Pathophysiology**

MOG is a glycoprotein of immunoglobulin superfamily presents exclusively in CNS and many of its epitopes are highly immunogenic. Several studies revealed that T cell/B cell cooperation is an important factor in pathogenesis of CNS autoimmunity. During ongoing inflammation, immune cells enter CNS and recognize CNS MOG and export antigen recognition and expose these antigens to peripheral immune system while draining to cervical lymph nodes. This results in MOG antibody production by peripheral B cells, which further trigger new waves of CNS infiltration. Pathologically, there is inflammation and myelin destruction with astrocytes being spared (unlike in NMOSD), as evidenced by CSF analysis (elevated MBP, absence of GFAP). Brain biopsy showed demyelinating lesions with marked infiltration of T cells and macrophages (with myelin degradation products) with preserved astrocytes and axons along with B-cell infiltration and IgG and complement deposition consistent with pattern II MS lesions.

**Prevalence**

The exact incidence and prevalence of MOG-AD is yet to be elucidated. However, studies showed that it constituted 7.4% of all NMOSD, 6.3% of inflammatory demyelinating diseases of CNS. Among AQP4-IgG negative patients with bilateral and recurrent ON, 40% were MOG-IgG positive.

![Fig. 1: Spectrum of acquired CNS inflammatory demyelinating diseases](image-url)
and with respect to LETM, 7.4–23.2% had MOG antibody. The prevalence among children was higher constituting 50% of definite NMO cases and 80% of recurrent optic neuritis.11

**Demographics**

MOG-AD is relatively more common in males compared to NMOSD with a female to male ratio of 2.8:1 vs. 9:1 in NMOSD. It has no predilection to specific ethnic groups; however, few studies showed higher occurrence among Caucasians. It is more common among children and young adults (third decade), although any age can be affected.

**Clinical Phenotype**

Most of MOG antibody positive patients have optic neuritis, encephalitis with brain demyelinating lesions and/or myelitis, which lead to a new term MOG-IgG-associated ON, encephalitis, and myelitis (MONEM). ON is the most common phenotype (41–63%), followed by LETM (29–31%), NMO (6–24%), and encephalomyelitis (2–6%). Also, concomitant occurrence of both ON and transverse myelitis is more common in MOG-AD than AQP4-IgG patients. Overall, MOG-AD patients have a favorable prognosis compared to MS and AQP4-NMOSD patients (Fig. 2).

ADEM, Acute disseminated encephalomyelitis; AQP4-NMOSD, Aquaporin 4 positive neuromyelitis optica spectrum disorder; LETM, Longitudinally extensive transverse myelitis; MY, Myelitis; ON, Optic neuritis

**Clinical Features**

A preceding infectious prodrome occurs in many cases in the form of fever, malaise, cough, and rhinorrhea. Though most of cases occur without any predisposing events, post-infectious demyelination after HSV, Borrelia,
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Emerging Concepts in Anti-MOG Syndrome

and EBV have been seen. Studies have described cases of LETM after influenza infection, vaccination, and ADEM after infectious mononucleosis. However, whether these are causative or silent bystanders are yet to be established.

Some patients have a monophasic illness while others may have a relapsing course. Relapse occurs in 44–83% of patients and is mostly optic neuritis. Studies have shown that MOG-AD has higher percentage of single attacks and few relapses compared to AQP4-NMOSD. Also, median time for second attack was longer in MOG-AD (11.3 years vs. 3.2 years in AQP4-NMOSD). Common clinical manifestations of MOG-AD include:

- **Optic neuritis:**
  - Though unilateral ON is a more common presentation, 30–50% of MOG-AD patients have bilateral ON (bilateral ON is less common in AQP4-NMOSD, rare in MS).
  - Characteristic feature is significant optic disc edema in almost 86% of cases with more than 50% optic nerve affection (anterior part) and relative sparing of optic chiasma.
  - It has better visual outcomes compared to AQP4-NMOSD, though recurrence of ON is more frequent in MOD-AD.
  - Some patients may develop steroid dependent optic nerve involvement called chronic relapsing inflammatory optic neuropathy.

- **Myelitis:**
  - Typically causes LETM (involving >3 vertebral segments) in almost two-thirds of cases. Short segment involvement is seen in one third of cases especially in elderly. Usually, motor symptoms predominate. Severity of myelitis is more than MS but less than AQP4-NMOSD.
  - Preferential involvement of thoracolumbar and Conus (explains disproportionate sphincter and erectile dysfunction) region occurs.
  - Central/lateral cord lesion.
  - Clinically may resemble enterovirus associated acute flaccid myelitis.
  - Recurrent LETM is rare (<2%).
  - TM at onset is the most important predictor of long term disability.

  - **ADEM/ADEM like:**
    - More common in children. Can occur at onset in up to 18% of patients.
    - MOG antibodies are present in almost 50% of all multiphasic ADEM patients.

- **Brainstem syndrome:**
  - Area postrema syndrome presenting as intractable nausea and vomiting is less common than in AQP4-NMOSD.
  - Can be seen in 6–15% of cases.

- **Cortical encephalitis:**
  - It is a less common presentation and is usually due to unilateral mild edematous cortical lesion best seen on FLAIR sequences.
  - Patient may present with seizures, abnormal behavior or focal symptoms and it has a very good prognosis (Fig. 3).

**Diagnosis**

**Imaging: MRI**

- **Optic nerve:**
  - During ON, orbital MRI with coronal T2 fat suppressed images shows extensive anterior optic nerve segment T2 hyperintensity (sparing optic chiasma and retrochiasmatic parts) with evidence of optic disc edema.
  - Inflammation and enhancement of perioptic nerve sheath is seen in one third of cases (Figs. 4A and B).

- **Spinal cord:**
  - During myelitis, may show evidence of LETM (T2 hyperintensity involving ≥3 vertebral segments lengthwise and >50% of the axial section of the medullary cord). Cloud like heterogeneous enhancement may be noted.
**Fig. 3:** Comparative patterns and sites of involvement. AQP4-NMOSD: Bilateral, long segment, posterior optic nerve involvement involving optic chiasma; central/gray mater, complete, LETM, thoracolumbar cord involvement. MOG-AD: Bilateral, long segment, anterior optic nerve involvement including optic nerve head, sparing optic chiasma; central/lateral, complete, LETM, conus involvement is characteristic. MS: Unilateral, short segment optic nerve involvement, frequent chiasmal involvement; peripheral, short, partial, multiple cord lesions.

**Figs. 4A and B:** MOG-AD patient with bilateral optic neuritis. (A) Bilateral optic nerve swelling, (B) Longitudinally extensive ON with optic nerve head swelling (arrows)

- Short lesions involving less than 2 vertebral segments can be seen especially in elderly. Conus involvement is highly specific for MOG-AD.\(^{16}\)
- Lesions are usually central and associated with cord swelling.

**Brain:**
- It is abnormal in 45% of cases at onset of disease.\(^{16}\) Lesions are usually bilateral and fluffy.
- Thalamic and pontine lesions are common, subtentorial (brainstem) in one third of cases.
Emerging Concepts in Anti-MOG Syndrome

Dawson’s fingers, U shaped ovoid lesions close to body of lateral ventricle are less common (**Figs. 5A to C**).

**CSF**

CSF findings during an acute attack are variable:
- 50% of the patients have elevated white cell counts (in 5–10%, lymphocyte count can be 100–300 cells/μL) and an elevated CSF protein (>1 g/L in 10%).
- 10% of patients have an elevated protein with normal white cell count.
- Oligoclonal bands are less common (6–17% of patients).1

**Serum**

- IgG MOG antibody tests should be done only in selected patients with clinical and paraclinical features of MOG-AD, in view of chance of false positivity.

- A cell based assay using full length human MOG as target antigen is preferred.

**Biopsy**

Biopsy findings suggestive of pattern II MS lesions can be noted, but not commonly performed.

**Diagnostic Criteria** *(International Panel of Experts—Jarius et al.)* 17,18

MOG-related disorders should be diagnosed in patients who meet all of the following criteria:
- Monophasic or relapsing acute ON, myelitis, brainstem encephalitis, or any combination of these symptoms.
- MRI or electrophysiological (visual evoked potentials in patients with isolated ON) findings compatible with CNS demyelination.
Seropositivity for MOG-IgG as detected by means of a cell-based assay employing full length human MOG as target antigen.

**Treatment-related indications for testing:** Particularly good response to antibody depleting therapies (PEX), immunoadsorption (IA), and B-cell depleting therapies (rituximab, ocrelizumab, and ofatumumab), but relapse immediately after reoccurrence of B cells.

**Special Features**

MOG-AD has some differences compared to AQP4-NMOSD:

- Optic nerve involvement more than spinal cord. Optic nerve involvement is bilateral commonly and caudal spinal cord (conus) affection is characteristic.  
- Mostly monophasic or may have few relapses. Has a relatively less female preponderance.
- More brainstem and cerebellar involvement with few supratentorial lesions.
- Has a wider spectrum and is less commonly associated with other autoimmune disorders.

**TABLE 1** When to test for MOG antibody

<table>
<thead>
<tr>
<th>Test if</th>
<th>Retest if</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Clinical/paraclinical features are suggestive of MOG-AD (2018 International Recommendations)</td>
<td>- MOG antibody positive, but clinical/paraclinical features not suggestive of MOG-AD (red flags)</td>
</tr>
<tr>
<td>- Diagnosis of MS is made, interferon beta or natalizumab has been started, but efficacy is unexpectedly poor and clinical/paraclinical features are compatible with MOG-AD</td>
<td>- Clinical/paraclinical features continue to be suggestive of MOG-AD, but MOG antibody is negative</td>
</tr>
<tr>
<td>- Likelihood of further events is sought, after diagnosis of MOG-AD</td>
<td>- Likelihood of further events is sought, after diagnosis of MOG-AD</td>
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</table>

**TABLE 2** ‘Red flags’—conditions that suggest probable false positive result and thus should be retested with a different cell-based assay

<table>
<thead>
<tr>
<th>Disease course</th>
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</thead>
<tbody>
<tr>
<td>- Chronic progressive disease (rare in MOG-AD), including SPMS (especially SPMS without relapses) and PPMS</td>
</tr>
<tr>
<td>- Sudden symptom onset e.g., &lt;4 h from onset to maximum (ischemic cause), or continuous worsening over weeks (tumor, sarcoidosis, etc.)</td>
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<table>
<thead>
<tr>
<th>MRI</th>
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<tbody>
<tr>
<td>- Lesion adjacent to lateral ventricle that is ovoid/round or associated with an inferior temporal lobe lesion, or Dawson's fingers</td>
</tr>
<tr>
<td>- Active brain MRI over time with silent increase in lesion burden between relapses</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>CSF</th>
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<tbody>
<tr>
<td>- Bi or trispecif MRZ reactions (MS)</td>
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<table>
<thead>
<tr>
<th>Serology</th>
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</thead>
<tbody>
<tr>
<td>- MOG-IgG levels at or just barely above the assay-specific cut-off, especially if clinical picture is atypical</td>
</tr>
<tr>
<td>- Positive MOG-IgM and/or MOG-IgA result with negative MOG-IgG (? significance)</td>
</tr>
<tr>
<td>- MOG-IgG positivity in the CSF but not in the serum (MOG-IgG is produced extrathecally)</td>
</tr>
<tr>
<td>- AQP-4 IgG/MOG-IgG “double-positive” test results (extremely rare; should retest for both antibodies)</td>
</tr>
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<table>
<thead>
<tr>
<th>Others</th>
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<tbody>
<tr>
<td>- Clinical or paraclinical findings suggesting diagnoses other than MOG-EM, NMOSD, or MS (e.g., neurotuberculosis, neuroborreliosis, neurosyphilis, neurosarcoaidosis, Behcet syndrome, SACD, Leber's hereditary optic neuropathy, vasculitis, CNS lymphomma, gliomatosis cerebri, paraneoplastic neurological disorders, PRES, PML, and evidence for CNS infection)</td>
</tr>
<tr>
<td>- Combined central and peripheral demyellination (MOG is not expressed in the PNS)</td>
</tr>
</tbody>
</table>

MRZ, Measles, Rubella, Zoster virus
Responds to B-cell depleting agents and has a better prognosis with good recovery after attacks and minimal disability.16

**Treatment**

Currently, there are no controlled treatment trials in MOG-AD and consensus regarding preferred drug, candidates for immunosuppression and duration of therapy is still uncertain.

**Acute Treatment**

During acute phase, high dose IV methylprednisolone (1–2 gm/day for 3–5 days), is usually effective with partial or no response in 50%. In steroid resistant cases, plasma exchange (3–5 cycles) results in improvement in around 40% of cases.3

**Disease Modifying Treatment**

Several studies have shown that long-term immunosuppression reduces annual relapse rate in MOG-AD patients. The optimal duration of initial immunosuppression after first attack is not clear. However, since relapse risk is maximum early after disease onset, it is reasonable to continue low dose prednisolone (10 mg) for 6 months after 1st attack (change to steroid sparing agent if side effects occur). MOG antibody should be retested after 6 months and if negative, prednisolone should be gradually withdrawn since disappearance of MOG antibody indicates remission. If antibodies are persistently present, since relapses usually occur only in these patients, immunosuppression may be continued up to 12 months.16

However, not all patients with persistent antibodies relapse. Possible risk factors for relapse include: initial...
severe attack and persistent MOG antibody. If relapse occurs, steroid sparing agents like azathioprine, methotrexate, mycophenolate mofetil, maintenance IVIG, and rituximab may be started with gradual tapering of steroids.\(^6\) Rituximab however may cause a temporary rise in B-cell activating factor and autoantibody levels (Flowchart 2).\(^3\)

**Conclusion**

MOG-AD constitute a group of acquired inflammatory demyelinating disorders of CNS, which share clinical and radiological features with MS and AQP4-NMOSD, but their distinct pathophysiology and certain specific features delineate them from their counterparts, and hence considered a separate disease entity by themselves with distinct therapeutic and prognostic implications. The diagnosis of MOG-AD relies on presence of suggestive clinical and paraclinical features with positive MOG-IgG antibody. It is important to identify them early because few conventional therapies used in MS can be harmful in MOG-AD and their early diagnosis and treatment aids in improving recovery and minimizing disability.

**References**

Abstract

Rapidly progressive dementia (RPD) is a rapid decline in one or more cognitive functions which interfere with independent daily living within a period of 1–2 years from symptoms onset. Most of the causes of RPD are treatable and early diagnosis is essential to prevent irreversible neurological injury. Serum vitamin B12, thyroid function test, and MRI brain are the investigations recommended by American Academy of Neurology in any patients with typical dementia apart from routine blood investigations. But the diagnostic workup in RPD needs additional investigations based on clinical profile and stepwise diagnostic approach should be followed including invasive biopsy.

Introduction

Rapidly progressive dementia (RPD) is a group of neurological disorders, which behave quite differently from the slowly progressive neurodegenerative dementias requiring an appropriate diagnostic workup and management. There is no classical definition for the time frame for the onset of dementia; however, these constitute a group of conditions in which first onset symptom to dementia progress in less than 1–2 years, but commonly over weeks to months.1,2 RPDs often cause distress to the patients and caretakers but presents a real challenge to the clinicians as an array of investigations and nimble decisions on management has to be made to protect as much as viable neural tissue. As many of these conditions can be treated and cured, a prompt and accurate diagnosis of the disease causing the dementia is mandatory. Various etiologies have been contributing to this entity are listed in Table 1.

The differential diagnoses of RPD are numerous; nevertheless, a meticulous approach is required to arrive at the accurate diagnosis. A precise history entailing the time course of progression of events is very important.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Etiologies of rapidly progressive dementia</th>
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<tbody>
<tr>
<td><strong>Etiologies of RPD</strong></td>
<td></td>
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<tr>
<td>CJD and other spongiform encephalopathies</td>
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<tr>
<td>Vascular disorders</td>
<td></td>
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<tr>
<td>Autoimmune and paraneoplastic encephalopathies</td>
<td></td>
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<tr>
<td>Malignancies</td>
<td></td>
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<tr>
<td>Metabolic, endocrine, and toxic disorders</td>
<td></td>
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<tr>
<td>Subacute central nervous system infections</td>
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</table>

The use of the mnemonic VITAMINS (Vascular, Infectious, Toxic-Metabolic, Autoimmune, Malignancy, Iatrogenic, Neurodegenerative, and Systemic) will help us consider the manifold etiologies, evaluating a case of RPD.2 The prototype is the prion disease, Creutzfeldt-Jakob disease (CJD).

Diagnostic Approach

Diagnostic workup of a case of RPD should primarily involve ruling out delirium and its causes. A complete blood count with differential, basic metabolic screening
(calcium, sodium, magnesium, phosphorus), liver function tests, rapid plasma reagin, rheumatologic screening (ANA, ESR, CRP), thyroid function tests, vitamin B12 level, HIV, medication levels according to treatment history (e.g., lithium, phenytoin levels), urine analysis should be done as a part of initial evaluation. Cerebrospinal fluid (CSF) analysis for cell count, protein, glucose, IgG index, oligoclonal bands, VDRL, neuron specific enolase ELISA, 14-3-3 protein western blot, total tau enzyme linked immunosorbsent assay, real-time quaking induced conversion test, cryptococcal antigen, viral antibodies, cultures and PCR, bacterial, fungal, acid fast bacilli cultures, and stains are the recommended screening for diagnostic evaluation of a case of RPD. MRI with or without contrast is the initial imaging modality of choice. It should include T1, T2, fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging, apparent diffusion coefficient map, and hemosiderin sequences. EEG should also be done, as epilepsy, nonconvulsive status, transient epileptic amnesia should be contemplated when working up a case of dementia. Screening for mood disorders, assessment of hearing loss, sleep dysfunction, and medication overuse should be always kept in mind and ruled out, as these conditions are potentially reversible. The stepwise investigations in approaching RPD are described in Flowchart 1.

Neurodegenerative Disease with Rapid Course

Most of the neurodegenerative diseases presenting as dementia is marked by their tardy course of progression, however, can present as RPDs occasionally. Alzheimer’s disease (AD) has a median survival rate of 12 years can present occasionally as RPDs, especially in association with amyloid angiopathy. Although the CJD is the commonest cause of RPD, AD represented one among frequent non CJD causes of RPD.5 Frontotemporal lobar degeneration (FTLD) was yet another common cause for RPD, which presents earlier in life than AD and an overlapping FTLD–motor neuron disease and FTLD–parkinsonism syndromes often predispose a faster progression.

Flowchart 1: Stepwise investigations in rapidly progressive dementia
progression of the disorder. The tau-related pathologies like corticobasal degeneration and progressive supranuclear palsy (PSP), was reported as cause of RPD by multiple studies.\(^1,^3,^4\) Dementia with Lewy bodies mimics CJD, and progress as RPD, although it lacks its classical MRI imaging properties and single photon emission computed tomography with 123I-ioflupane can aid the diagnosis.\(^3\)

**Creutzfeldt-Jakob Disease**

CJD can present with rapid cognitive decline (in weeks or months) associated with gait disturbances, visual hallucinations and behavioral disturbances, myoclonus and extrapyramidal symptoms.\(^5\) It is caused by the transformation of the normal neuronal prion protein, resulting in its abnormal accumulation within the neurons. The disease presents as a sporadic form (sCJD), a familial/genetic form and a variant form (vCJD) of which the sCJD is the commonest, accounting for approximately 85% of cases. sCJD usually has late presentation at 50–70 years of age and affecting both sexes identically. Prognosis is often worse with survival rate of 15% at end of 1st year. Mutations of the prion protein gene are accountable for the genetic forms of CJD and include familial CJD, Gerstmann–Sträussler–Scheinker and fatal familial insomnia. Even though they have a similar clinical presentation, the progression is often slower. The EEG is often characterized by focal or diffuse slowing in the initial period but as with the disease progression, pseudo-periodic and, eventually, periodic 1–2 Hz triphasic sharp waves characterize the picture which is highly pathognomonic, even though late in appearance. Normocytic CSF with elevated protein is often seen with 14-3-3, tau proteins and neuron specific enolase having specific diagnostic values.\(^6\) Hyperintensities involving the striatum (caudate and Putamen) and thalamus in the FLAIR and DWI sequences are seen earlier in the disease with “cortical ribboning” (hypersignal delineating the cortex) in the parietal, temporal, and frontal cortices is of statistical importance (sensitivity and specificity of 92% and 94%, respectively) in diagnosing the disease and can be seen even before the EEG findings. However, a definitive diagnosis requires demonstration of prions in the brain. The clinical criteria for probable sCJD require progressive dementia with at least two of the following: pyramidal and/or extrapyramidal symptoms, visual or cerebellar symptoms, myoclonus, akinetic mutism, and positivity in at least one out of three tests (EEG, 14-3-3protein, and MRI). No effective treatment is found for delaying this fatal condition and only palliative treatment for controlling seizures and myoclonus seems to be beneficial.\(^3\)

**Toxic-Metabolic**

Complete treatment history, occupational, and home environmental exposure history are important in analyzing the toxic causes of encephalopathy. Lithium (iatrogenic) can cause encephalopathy. Inorganic lead causes peripheral neuropathy and organic lead is more noxious and can cause cognitive and behavioral symptoms. Mercury (organic and inorganic forms) can cause psychological disturbances. Bismuth toxicity, due to inappropriate use for gastrointestinal disorders, can cause RPD and is reversible if detected early.\(^7\) A few reversible causes like vitamin deficiencies, and endocrinological disorders should also be definitely ruled out. Niacin deficiency (vitamin B3) can cause subacute cognitive impairment and is encountered mostly in nutritionally deprived and in association with systemic disorders like diabetes mellitus, chronic malignancies, and chronic gastrointestinal disorders. Thiamine (vitamin B1) deficiency causes Wernicke encephalopathy and needs urgent thiamine replacement. Vitamin B12 deficiency, folate deficiency, etc. are other potentially reversible causes. Endocrine abnormalities involving thyroid, parathyroid, and adrenal should be screened in any case of rapid progression of dementia. Serum electrolyte levels including sodium, potassium, calcium, and magnesium should also be included in the diagnostic evaluation. Uremic encephalopathy, portosystemic shunt encephalopathy, acquired hepatocerebral degeneration, hypoxia or hypercarbia, hyperglycemia, or hypoglycemia are some other etiologies for RPD. Screening for porphyria and mitochondrial diseases should also be done.

**Vascular**

Vascular conditions like strokes, especially thalamic or callosal infarcts, multi infarcts, cerebral amyloid angiopathy, venous sinus thrombosis, dural arteriovenous fistulas, posterior reversible encephalopathy syndrome (PRES), CNS vasculitis, hypertensive encephalopathy account for other primary causes of RPD.\(^1,^3\) Diffusion-weighted imaging, and gradient echo MRI, vascular
imaging like CT angiography, magnetic resonance venography (MRV), magnetic resonance angiography (MRA) aid in the diagnostic workup of dementia.

**Infections**

Infectious causes for a rapid cognitive decline include herpes simplex encephalitis, AIDS, and its associated CNS conditions like (toxoplasmosis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy), Lyme disease, Whipple’s disease, fungal infections like CNS aspergillosis and rare local infections like Balamuthia mandrillaris and neuroleptospirosis. In endemic regions, neurosyphilis should also be considered as a close differential. Infectious causes usually present with specific symptoms like fever, pleocytosis, and meningeal signs and have relatively acute onset.

**Malignancy**

Neoplastic causes like primary CNS lymphoma and intravascular lymphoma may present with a sudden deterioration of cognition and may present a challenge for the physician. The clinical presentation may mimic Creutzfeldt-Jakob disease and imaging with MRI may not be yielding, as it may not always present with a space occupying lesion or mass lesion. Other metastases/neoplasm related causes that should be considered in the differentials include lymphomatosis granulomatosis, lymphomatosis cerebri, gliomatosis cerebri, metastatic encephalopathy, carcinomatous meningitis, etc.

**Autoimmune Dementia**

At present autoimmune encephalopathies are thought to be the cause for a relatively fair amount of RPDs. A good number of these encephalopathies are treatable, and hence the importance of prompt diagnosis. The pathognomonic features include rapid and fluctuating course, presence of autoantibodies in the peripheral blood and inflammatory markers in CSF. Clinical presentation may be in the form of limbic encephalopathy with disorders of short-term memory behavioral alterations, depression, and temporal lobe seizures. Limbic encephalopathy may be often paraneoplastic, even preceding the diagnosis of the underlying malignancy, in many cases the neurological disorder is non-paraneoplastic. Anti-Hu antibody is the most common cause of limbic encephalopathy, associated with small-cell lung carcinoma, whereas Anti-CV2 antibodies can be associated with small cell lung carcinoma and thymoma. N-methyl D-aspartate receptor (NMDA) antibodies are usually associated with paraneoplastic encephalitis, occurring in young women with ovarian teratoma. Autoantibodies against neuronal VGKC may be related to lung cancer or thymoma, but most cases are not paraneoplastic, especially in the absence of other paraneoplastic autoantibodies. The former has even shown association with acquired neuromyotonia (Isaacs’ syndrome). The clinical spectrum may be of limbic encephalitis combined with neuromuscular hyperexcitability.

Antiglutamic acid decarboxylase (anti-GAD) antibodies are seen associated with conditions like type 1 diabetes and stiff person syndrome and occasionally, cause subacute encephalitis with RDP, ataxia, autonomic instability, and myoclonus, which responds well to immunosuppressive therapy. Autoimmune RPDs can even mimic CJD, both clinically and radiologically, especially limbic encephalopathy with anti VGKC antibodies (LGII antibody subtype) exhibiting cortical ribboning in MRI scans. Hyponatremia due to SIADH is more common in VGKC antibody complex encephalopathy.

A steroid responsive encephalopathy with high-serum titers of antithyroid (anti-thyroglobulin antibodies [anti-TG] and anti-thyroid peroxidase antibodies [anti-TPO antibodies) brings into the picture of Hashimoto’s encephalopathy. The disorder usually affects middle aged women and the presentation may be of stroke like relapsing and remitting episodes or of an RPD. There are reports of systemic autoimmune disorders like SLE and Sjogren’s syndrome presenting as RPDs rarely in the literature. The later may be due to antibody mediated vasculitis or direct antibody attack to the CNS parenchyma as in case of SLE. Despite its propensity for affecting the peripheral nervous system Sjogren’s can present as RPDs with cognitive decline and mood disorders often mimicking multiple sclerosis with recurrent attacks and focal symptoms. The presence of antiphospholipid antibody can aid as a clue to the situation. Neurobechet’s, neurosarcoidosis, and celiac disease worth mention as they present as RPDs rarely with cognitive decline, behavioral alteration, and spinal cord lesions. Primary or secondary vasculitis due to Wegener’s granulomatosis and polyarteritis nodosa can cause encephalopathy resembling RPDs. These
conditions often prompt the requirement of extensive workup with inclusion of serum ACE levels, perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies, antigliadin, antitissue transglutaminase, and anti-endomysial antibodies and even a cerebral angiogram in the armory of evaluation panel, depending on appropriate clinical picture.3

Secondary Causes of RPDs

Normal pressure hydrocephalus also rarely presents as RPD. The complete clinical gamut of memory loss, gait ataxia, and urinary incontinence may not always manifest. High-resolution structural MRI with orthogonal reconstructions will delineate the cause. Diagnosis can be confirmed by means of CSF pressure measurement and improvement following a drainage lumbar puncture. These patients benefit from a ventriculoperitoneal shunt.

Systemic disorders like sarcoidosis, mitochondrial disorders can clinically present with rapid cognitive impairment. Drugs also may precipitate a steep decline of cognitive function. Narcotics, anticholinergic medications, and benzodiazepines are commonly implicated.

Pseudodementia is a diagnostic possibility of exclusion. Patients with history of major depression may present with rapid decline of cognitive functions and often get misdiagnosed as RPDs. A thorough evaluation and ruling out of the neurological and systemic causes will aid in considering the possibility.

Conclusion

Considering the wide range of clinical conditions, which can present as RPDs, the clinician should always give emphasis on enquiring on the natural progression of the disease with particular attention in eliciting the relevant clinical signs. The exact pattern of the cognitive decline and association of psychiatric and neurological symptoms should be enquired in detail with an interrogation into the association of inherited familial conditions, systemic diseases, and causes including metabolic, drugs, and toxins.

The investigation armory should not be restricted to the routine panel of hemogram, electrolytes, liver, renal, and thyroid function testing, a screening for rheumatological disease and malignancy, CSF analysis including a search for oligoclonal bands and MRI, and rather it should be structured and staged. The use of a systematic approach in diagnosis like “VITAMINS” is often rewarding and aid in rapid diagnosis of reversible conditions. However, if the first stage of interrogation is absurd, one should always open eyes to wide array of differentials and impetuous enough to consider a second stage of investigation including a paraneoplastic workup, CT thorax and abdomen, whole body PET, or immunoassays for specific pathogens if required. A blind alley should prompt to consider even brain biopsy.

References

CHAPTER 88

Approach to a Patient with Acute Muscular Weakness

Lakshmi Narasimhan Ranganathan, Namrata Jayaharan, Rini George, Guhan Ramamurthy, Shrivarthan R

Abstract

The approach to a patient with acute muscular weakness chapter deals with the discussion of various causes of muscular weakness, its clinical features, recommended diagnostic testing, and management. Advancements in genetic testing, imaging studies, and laboratory diagnostics offer better understanding about the disease pathogenesis and its course. New molecular markers developed in myopathy help in clinical prognostication and guide treatment. The care of the patients with acute muscular weakness can be challenging. Treatment must be individualized and effective patient participation is necessary for effective management.

Introduction

Acute onset paralysis of the limbs and bulbar musculature is a neurological emergency. It may be caused by a wide variety of disorders. Some of these conditions may have associated respiratory muscle involvement requiring mechanical ventilation. A detailed history, general physical and neurological examination demonstrating the pattern of involvement can help in narrowing the differential diagnosis. Salient features to be noted in history, physical, and neurological examination are summarized in Table 1.

When evaluating a patient presenting with acute onset weakness of limbs, it is imperative that the following factors be considered. The Flowchart 1 helps in providing a structured approach to a patient presenting with acute muscular weakness.

- The mental status of the patient should be ascertained—a depressed sensorium suggests central nervous system (CNS) pathology.
- The history of the temporal course and progression of the illness is noted—whether it is acute, subacute, chronic, progressive, relapsing, and remitting. Acute onset weakness occurs in Guillain-Barré Syndrome (GBS), porphyria, diphtheria, tick paralysis, inflammatory myopathy, periodic paralysis, to name a few. Fluctuating weakness is seen in myasthenia gravis and Lambert Eaton myasthenic syndrome. Episodic weakness occurs in periodic paralysis.
- On examination of the motor system we can determine the limbs involved—whether the weakness is symmetrical or asymmetrical. The involvement of all four limbs with a definite sensory level on the torso indicates the presence of a high-cord lesion.
- The presence of sensory symptoms or sensory level helps in diagnosis. The sensory symptoms can be attributed to early polyneuropathy. A definite sensory level on the torso is seen in myelopathy.
- The history of bowel, bladder involvement, and other autonomic signs should be enquired. Early bladder involvement occurs in myelopathy.
- It should be examined whether the weakness is proximal or distal: A proximal weakness occurs in myopathy. In polyradiculoneuropathy the weakness
TABLE 1  Assessment of a patient with acute muscle weakness

<table>
<thead>
<tr>
<th>Assessment of a patient with acute muscle weakness</th>
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<tbody>
<tr>
<td><strong>History</strong></td>
</tr>
<tr>
<td>• Onset and progression and duration</td>
</tr>
<tr>
<td>• Distribution of weakness</td>
</tr>
<tr>
<td>• Presence of sensory symptoms</td>
</tr>
<tr>
<td>• Recent history of fever and diarrhea</td>
</tr>
<tr>
<td>• Exposure to drugs/toxins</td>
</tr>
<tr>
<td>• Similar history of weakness in the past</td>
</tr>
<tr>
<td>• Positive family history</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
</tr>
<tr>
<td>• Look for the presence of skin findings of dermatomyositis (Gottron papules, heliotrope rash, shawl sign, holster sign)</td>
</tr>
<tr>
<td>• Thyromegaly and thyroid eye disease</td>
</tr>
<tr>
<td>• Eye signs in myasthenia - Curtain sign, see saw ptosis, peek sign, Cogan’s lid twitch</td>
</tr>
<tr>
<td>• Bulbar involvement</td>
</tr>
<tr>
<td>• Evaluation of respiratory reserve—coughing ability, single breath count of 30, Forced vital capacity, negative inspiratory force</td>
</tr>
<tr>
<td><strong>High yield - Neurological examination</strong></td>
</tr>
<tr>
<td>• Pattern of weakness</td>
</tr>
<tr>
<td>• Bulk, Tone, reflexes</td>
</tr>
<tr>
<td>• Sensory examination</td>
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</table>

is initially proximal followed by distal weakness. The involvement of both proximal and distal muscles occurs in polyradiculoneuropathy.

- Early wasting points toward an axonal rather than a demyelinating etiology.
- Bulbar symptoms can occur in GBS, myasthenia gravis, inflammatory myopathy.
- The hereditary nature of illness is determined by associated family history.
- History of associated medical illness like thyroid disease, connective tissue disease.
- H/o drug/toxin exposure should be looked into. Arsenic poisoning, barium carbonate poisoning mimic GBS with systemic symptoms.

It is essential to localize to the most probable site in the motor unit and the possible etiology that has caused the acute muscle weakness. The various causes of acute muscle weakness are summarized in Table 2. The discussion of all the disorders presenting with bilateral muscular weakness is beyond the scope of this chapter. A few common conditions are elaborated below.

**Guillain-Barré Syndrome**

It is an immune-mediated, rapidly progressive, ascending, predominantly motor polyneuropathy leading to bulbar and respiratory compromise. It has a monophasic course. All age groups can be affected. Antecedent respiratory/gastrointestinal illness is found in 60% of cases. Campylobacter jejuni is the most common infection associated with the AMAN variant. Assisted ventilation may be required in up to 25% of cases.1

**Clinical Features**

- Acute flaccid symmetrical quadriplegia. Around one third of patients remain ambulant throughout the course of the illness.
- Early areflexia.
- Distal paresthesia involves the toes and fingers simultaneously (unusual in other causes of polyneuropathy).
- Bifacial weakness occurs in 50% of cases.
- Bulbar weakness with dysphagia and dysarthria are common.
- Back pain and radicular pain are seen in 25% of patients.
- Autonomic dysfunction can occur. It does not progress beyond 4 weeks. Most individuals have a peak deficit by the first week of illness.

The subtypes of GBS include:

- Acute demyelinating polyneuropathy (AIDP). Most common in North America and Europe (90%).
- Acute motor axonal polyneuropathy (AMAN)—Accounts for 30–47% of cases. It is now classified as a nodopathy.2 It reaches nadir quickly. It is strongly associated with antibodies to GM1, GD1a. The binding of antibodies to the nodal axolemma leads to activation of complement and formation of membrane attack complex. The binding of antibodies alone leads to a functional disruption in conduction, whereas axonal degeneration occurs with the destruction of the nodal protein by the membrane attack complex. Recovery can occur at rates compatible with AIDP depending on the stage in pathogenesis, with functional disruption being associated with a better prognosis.
- Acute motor and sensory axonal polyneuropathy (AMSAN)—It is essential to screen these patients for porphyria. It is the most severe phenotype with rapid
Flowchart 1: Approach to a patient with muscle weakness

TABLE 2 Causes of acute muscle weakness

<table>
<thead>
<tr>
<th>Causes of acute muscle weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute conditions affecting the spinal cord – Infections (HIV, TB, Syphilis, CMV, EBV), Acute</td>
</tr>
<tr>
<td>transverse myelitis, Vascular (Ischemia, hemorrhage)</td>
</tr>
<tr>
<td>• Anterior Horn cell—Polioymyelitis, West nile virus infection</td>
</tr>
<tr>
<td>• Polyradiculoneuropathy—GBS, HIV infection, Zika virus, COVID-19</td>
</tr>
<tr>
<td>• Polyradiculopathy—Disc disease, Cytomegalovirus infection, neoplasm, hematoma</td>
</tr>
<tr>
<td>• Plexus—Acute Brachial Plexopathy, Acute Lumbosacral Plexopathy</td>
</tr>
<tr>
<td>• Nerve—Mononeuritis multiplex, Diphtheria, Lyme disease, Acute intermittent porphyria, critical</td>
</tr>
<tr>
<td>illness neuropathy, Paralytic seafood poisoning</td>
</tr>
<tr>
<td>• Neuromuscular Junction—Organophosphate poisoning, botulism, tick paralysis, myasthenia gravis</td>
</tr>
<tr>
<td>• Muscle—Inflammatory myopathy, infectious myopathy, acute periodic paralysis, toxic myopathy,</td>
</tr>
<tr>
<td>critical illness myopathy</td>
</tr>
</tbody>
</table>
onset and complete paralysis. It is strongly associated with antiganglioside antibodies GM1 and GD1a. Other variants and their associated antiganglioside antibodies.

- Miller Fisher Syndrome: GQ1b, GD1b, GT1a
- Acute sensory ataxic neuropathy: GD1b
- Pharyngo-cervical brachial variant: GD1a, GT1a, GD1b
- Multiple cranial neuropathies
- Facial diplegia with a parasthesias
- Paraplegic variant
- Acute pandysautonomia

**Diagnosis**

*Lumbar puncture* showing albuminocytological dissociation is the hallmark of Guillain-Barré syndrome. This is an elevated CSF protein with a normal cell count. This occurs mainly in the second week of illness.

**Nerve Conduction Study**

- It is normal early in the course of the illness.
- Abnormalities depend on the variant.
- AIDP: Prolonged distal latencies, reduced conduction velocity, prolonged F-wave latency, conduction block, temporal dispersion.
- AMAN/AMSAN: decreased motor and/or sensory amplitudes in the absence of demyelinating features.
  - The electrophysiological findings in AMAN can at times show a conduction block, which leads to misdiagnosis with AIDP. Conduction block occurs with functional disruption due to antibody binding to the nodal axolemma which is termed as reversible conduction failure. Serial electrophysiology is therefore required to differentiate between the variants.

**Antiganglioside antibodies:** Their role in diagnosis has not yet been established.

- *Serum potassium levels:* Hypokalemia can mimic GBS.
- *Other blood tests:* Sodium, potassium, phosphate, magnesium, CPK, white cell count, CRP.
- *MRI spine with contrast:* Nerve root enhancement is visualized.

**Treatment**

- It requires a multidisciplinary approach.
- Intravenous immunoglobulin (IVIg) and plasmapheresis are FDA approved for the treatment of GBS.
- IVIg is administered at a dose of 2 g/kg over 5 days in patients with severe illness and presentation within 2 weeks of disease onset.
- Plasma exchange: From 5–6 cycles at 1–1.5 times the plasma volume.
- Regular monitoring is required for respiratory dysfunction, autonomic dysfunction.
- Prevention of complications like deep vein thrombosis, decubitus ulcers is important.

**Inflammatory/Autoimmune Myopathy**

It a heterogeneous group of disorders which include:

- Dermatomyositis
- Immune-mediated necrotizing myopathy
- Anti tRNA synthetase syndromes
- Polymyositis
  - They can be differentiated by characteristic clinical features, serological tests, and findings on muscle biopsy.

**Clinical Features**

- Proximal muscle weakness of the upper and lower limb manifested clinically as difficulty in getting up from squatting position and difficulty in raising the arms overhead
- Distal muscles are relatively spared
- Truncal weakness
- Neck muscle weakness
- Dysphagia due to pharyngeal weakness

**Dermatomyositis:**

- *Gottrons papules:* Scaly erythematous lesions on the extensor surfaces of the fingers
- *Shawl sign:* Erythematous rash over the shoulders
- *Heliotrope rash:* Periorbital violaceous eruption
- *Holsters sign:* Poikiloderma of the upper outer thigh
- *Calcinosis:* Painful lumps on the skin surface
- There may be the development of malignancy like adenocarcinoma either before or after the onset of weakness.

**Immune-mediated necrotizing myopathy:**

- H/o statin exposure
- Progressive symptoms are noted despite stopping statins, thus differentiating it from statin-induced myopathy
- It is not associated with extramuscular features
**Antisynthetase syndrome**: Is associated with: Raynaud’s phenomenon, arthritis, mechanics hands (hyperkeratotic lesions on the radial and palmar surfaces), interstitial lung disease, myositis.

**Polymyositis**: These patients present with proximal muscle weakness without associated dermatological manifestations. Prior to biopsy, there is a probability for misdiagnosis with conditions like dermatomyositis sine dermatitis, inclusion body myositis, limb-girdle muscular dystrophy.

**Extramuscular involvement**:
- Interstitial lung disease
- Joint disease
- Cardiac involvement

**Diagnosis**
- Creatinine kinase, LDH, AST, ALT, aldolase are elevated
- EMG: Small polyphasic motor unit potentials are seen
- Spontaneous activity may reveal complex repetitive discharges in dermatomyositis

**Muscle Biopsy**
- Dermatomyositis: Perifascicular atrophy, perivascular infiltrate with B cells, plasmacytoid cells, dendritic cells.
- Immune-mediated necrotizing myopathy: Muscle fiber necrosis
- Antisynthetase syndrome: Perifascicular necrosis
- Polymyositis: Inflammatory infiltrates in the non-necrotic muscle fibers

**Serological Tests**
See Table 3.

**Treatment**
- IV/oral steroids are useful depending on the severity.
- Immunosuppressants: azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus as maintenance therapy.
- Refractory cases: IV immunoglobulin, Rituximab

**Critical Illness Polyneuropathy**
It is an acute axonal sensorimotor polyneuropathy leading to muscle weakness with difficulty weaning from the ventilator. It is often associated with critical illness myopathy represented by the acronym CRIMYNE (critical illness myopathy and neuropathy). It is considered that both entities have a common pathophysiological mechanism. Around 70–80% of the patients admitted to ICU develop CIP. Difficulty in weaning the patient from the ventilator despite normal mental, pulmonary, and cardiovascular function, and correction of the metabolic, infectious causes of respiratory failure.

**Risk Factors for Critical Illness Polyneuropathy**
Sepsis/SIRS, multiorgan failure, female sex, prolonged illness, renal failure and renal replacement therapy, TPN, hypoalbuminemia, vasopressor use, hyperglycemia, hyperosmolarity.

**Clinical Features**
- It leads to symmetrical flaccid weakness.
- Proximal and distal weakness with hypotonia and areflexia.
- Muscle atrophy can occur.
- Cranial nerve involvement is very rare. Ophthalmoplegia has been reported in a few instances. If there is cranial nerve involvement, other causes of acquired muscle weakness like Guillain-Barré syndrome should be ruled out.

**Treatment**
Treatment is not effective.
Prevention
Nutritional intervention, antioxidants, testosterone derivatives, growth hormones, immunoglobulins, treatment of sepsis, intensive insulin therapy (maintaining blood glucose between 80–110 mg/dL; risk of hypoglycemia).5

Periodic Paralysis
They are a group of autosomal dominant disorders involving muscle ion channels. They are characterized by episodic muscle weakness and areflexia. These are triggered by changes in behavior and diet. Primary periodic paralysis includes hypokalemic periodic paralysis, hyperkalemic periodic paralysis, Andersen-Tawil syndrome. There is an overlap with other disorders causing myotonia and episodic weakness like paramyotonia congenita. Differences between hypokalemic and hyperkalemic periodic paralysis is given in Table 4.

Hypokalemic Periodic Paralysis
It is associated with mutations in the calcium channel (CACNA1S) in 60–80% or mutations involving the sodium channel (SCN4A) in 20%.6

Clinical Features
Symptoms occur at weekly/monthly intervals. There may be sensory symptoms prior to the onset of weakness—fatigue, myalgia. Usually, there are no cranial nerves or respiratory symptoms. Initial attacks are associated with complete recovery. With time, progressive muscle weakness develops.

Diagnosis
- It may be made clinically from the clinical history and associated features.
- The serum potassium levels are reduced, but never below 2 mM. With lower potassium levels, gastrointestinal, renal, adrenal causes should be ruled out.
- ECG: Features of hypokalemia such as prolonged PR interval, absent T waves and prominent U waves may be present.
- Thyroid function tests should be done in all cases to rule out thyrotoxic periodic paralysis.
- A glucose challenge test with 2–5 mg/kg of glucose may precipitate an attack.
- EMG during an attack reveals short polyphasic motor unit potentials.
- Genetic testing for calcium channel mutations has now largely replaced the need for biopsy.

Treatment
Acute attacks are treated with oral/IV potassium depending on the severity.

Prophylaxis
- Carbonic anhydrase inhibitors like acetazolamide can reduce the frequency and duration attacks. Dichlorphenamide can be used in cases not responding to acetazolamide.
- Other drugs like potassium-sparing diuretics, ACE inhibitors can also be used to prevent attacks.

Myasthenia Gravis
It is an autoimmune disorder with antibodies directed against the nicotinic acetylcholine receptor (AChR). The amount of acetylcholine released is normal, but the availability of acetylcholine receptors is reduced leading to smaller endplate potential.

Clinical Features
The patient presents with extraocular, bulbar, respiratory, and proximal limb weakness. Extraocular weakness may mimic III, IV, VI nerve palsy with sparing of the pupils.7 Bulbar weakness may present with difficulty

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Distinguishing features of hypokalemic periodic paralysis and hyperkalemic periodic paralysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
<td>Hours to days</td>
</tr>
<tr>
<td>Precipitating factors</td>
<td>Rest after exercise, carbohydrate load</td>
</tr>
<tr>
<td>Severity</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Associated myotonia</td>
<td>Absent</td>
</tr>
</tbody>
</table>
in swallowing, speaking, and nasal regurgitation. Limb weakness is proximal, resembling myopathy. These patients characteristically have diurnal variations with fatigue. Anti-MUSK (muscle specific kinase) myasthenia presents with ocular, bulbar, neck, and respiratory muscle weakness. Myasthenic crisis is when a respiratory failure occurs as a result of weakness. A precipitating event like an infection, surgery, and change in medications is often present.

**Diagnosis**

Repetitive nerve stimulation is abnormal in 50–70% of patients with myasthenia gravis. In MG, there is a decremental response of 10% in the CMAP with slow RNS, which is not seen in normal subjects. The decremental response is the electrophysiological correlate of fatigable weakness.

*Tensilon test:* Edrophonium is short-acting acetylcholinesterase injected intravenously under cardiac monitoring. The patient is observed for improvement in symptoms, particularly of the extraocular muscles and ptosis.

*Ice pack test:* It is a nonpharmacological test. It can be used in patients in whom edrophonium is contraindicated. The placement of an ice pack over the ptotic lid leads to improvement.

*Serological tests:* Anti-acetylcholine receptor antibody

*Anti MUSK antibody:* Anti titin, actin, myosin, ryanodine receptor, and other striated muscle antibodies are positive in patients in early-onset thymomatous myasthenia gravis.

*CT/MRI chest:* To rule out the presence of a thymoma.

**Treatment**

- Symptomatic treatment with acetylcholinesterase inhibitors
- Rapid-acting immunomodulation with IVIG or plasmapheresis.
- Long-lasting immunosuppression with steroids and immunosuppressants.
- Surgical treatment in cases with thymoma.

**Conclusion**

Acute muscular weakness may be caused by a wide variety of etiologies. The pattern of weakness may vary depending on the etiology. The weakness may be proximal or distal, symmetrical, or asymmetrical. There are characteristic features that help in arriving at a diagnosis. Careful attention should be given to the presence of respiratory, bulbar weakness, which warrants intensive care since acute onset weakness is a neurological emergency.

**References**

**Abstract**

Opening a blocked artery remains the prerequisite to ensure reperfusion of the critically perfused brain. The “science of thrombolysis” in acute ischemic stroke is built on robust twin pillars of good clinical practice and sound science. It is imperative that patients are immediately triaged, imaged, and judged whether they have viable tissue, which could recover with reperfusion. Thereafter, through the evidence gathered over time, it is identified whether the patients meet the strict criteria for thrombolysis. Patients often fall in grey areas, outside these strict established guidelines, who, however, may be salvaged with thrombolysis with expert clinical acumen. The “art of thrombolysis” is to identify these patients. Thrombolysis is the most validated and valuable tool for physicians in their arsenal against acute ischemic stroke and only smart patient selection can expand its repertoire further, providing best chances of a positive functional outcome.

**Introduction**

Acute ischemic stroke (AIS) is a heterogeneous disorder with varied etiology and complex pathology. Major trials have confirmed the benefit of thrombolysis in the acute stage, irrespective of the stroke subtype. Based on a very simple algorithm that “time is brain” and “unblocking” a “blocked” artery remains the quintessential prerequisite to ensure reperfusion of the critically perfused brain, the “science” of “thrombolysis” in AIS is built on robust twin pillars of good clinical practice and sound science. It is imperative that patients are immediately triaged, imaged, and judged whether they have viable tissue, which could recover with reperfusion.

The evidence gathered over several decades is used to identify patients who fulfill the current guidelines and inclusion criteria for thrombolysis. However, in clinical practice, patients are often encountered who fall outside established guidelines, those in whom thrombolysis is “absolutely” contraindicated, those who do not benefit with thrombolysis (failed thrombolysis) and those who lie within “grey areas” but may nonetheless be salvaged with thrombolysis with expert clinical acumen.

The “art” of thrombolysis is to identify patients in the above categories.

**Approach**

Precise history taking and proper structured evaluation are imperative for decision-making with regards to acute stroke management. The points that have to be noted include the time of symptom onset, age, baseline vitals and blood sugar and stroke severity (graded by NIHSS) (Table 1).

Neuroimaging is undertaken after clinical assessment, with the aim of establishing a clinical diagnosis as promptly as possible. The choices for the same include NCCT or MRI. The former is frequently used because it distinguishes a hemorrhagic from an ischemic stroke and may reveal early ischemic changes. These are graded on the ASPECTS scale (Fig. 1) (Scores >7).
TABLE 1 | NIHSS scoring

<table>
<thead>
<tr>
<th>Tested item</th>
<th>Title</th>
<th>Responses and scores</th>
</tr>
</thead>
</table>
| 1A          | Level of consciousness | 1-Alert  
2-Drowsy  
3-Obtunded  
4-Coma/Unresponsive |
| 1B          | Orientation questions (2) | 0-Answers both correctly  
1-Answers one correctly  
2-Answers neither correctly |
| 1C          | Response to commands (2) | 0-Performs both tasks correctly  
1-Performs one task correctly  
2-Performs neither |
| 2           | Gaze | 0-Normal horizontal movements  
1-Partial gaze palsy  
2-Complete gaze palsy |
| 3           | Visual fields | 0-No visual field defect  
1-Partial hemianopia  
2-Complete hemianopia  
3-Bilateral hemianopia |
| 4           | Facial movement | 0-Normal  
1-Minor facial weakness  
2-Partial facial weakness  
3-Complete unilateral facial palsy |
| 5           | Motor function (arm)  
• Left  
• Right | 0-No drift  
1-Drift before 10 seconds  
2-Falls before 10 seconds  
3-No effort against gravity  
4-No movement |
| 6           | Motor function (leg)  
• Left  
• Right | 0-No drift  
1-Drift before 5 seconds  
2-Falls before 5 seconds  
3-No effort against gravity  
4-No movement |
| 7           | Limb ataxia | 0-No ataxia  
1-Ataxia in one limb  
2-Ataxia in two limbs |
| 8           | Sensory loss | 0-No sensory loss  
1-Mild sensory loss  
2-Severe sensory loss |
| 9           | Language | 0-Normal  
1-Mild aphasia  
2-Severe aphasia  
3-Mute or global aphasia |
| 10          | Articulation | 0-Normal  
1-Mild dysarthria  
2-Severe dysarthria |
| 11          | Extinction or inattention | 0-Absent  
1-Mild loss (1 sensory modality lost)  
2-Severe loss (2 sensory modalities lost) |

Total score: 42. Higher score corresponds to higher stroke severity.

Multimodal imaging (CT/MRI) (Table 2) provides added information about the vascular status (primary and collaterals), perfusion status, and extent of ischemic insult. These take between 10–15 minutes to perform and are required in guiding thrombolysis decisions in special situations like unknown time of onset and wake-up strokes. Small infarct core with higher salvageable penumbra or DWI hyperintensities without corresponding ones seen on T2-FLAIR are usually taken as markers to thrombolyse patients in these situations.

Treatment

The primary therapeutic goal of acute stroke treatment is the prompt restoration of blood flow in the occluded vessel. The following factors must be considered to guide patient selection for the same:

- Age
- Time of symptom onset
- Baseline:
  - NIHSS
  - ASPECTS

Within the Standard Guidelines

Intravenous alteplase (0.9 mg/kg body weight; 10% dose given as an intravenous bolus, with the remaining infused over 1 hour; maximum dose—90 mg) and tenecteplase (0.25 mg/kg body weight; given as a bolus dose) are the thrombolics approved for use. They can be used up to 4.5 hours of stroke onset, the greatest benefit found with earlier treatment [The NNT increases from 2 (treatment 0–1.5 hours) to 7 (treatment 1.5–3 hours) to 14 (3–4.5 hours)]. The standard guidelines for the same are discussed as follows.

Inclusion criteria:

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <4.5 hours since treatment initiation
- Age ≥18 years

Exclusion criteria:

- Significant head trauma or prior stroke in the past 3 months
- Symptoms suggestive of subarachnoid hemorrhage
- Arterial puncture at a non-compressible site in the past 1 week
**TABLE 2** Multimodal imaging

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Functions</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP</td>
<td>Information about infarct core and penumbra</td>
<td>Quicker than multimodal MRI</td>
<td>Additional exposure to radiation and contrast agents</td>
</tr>
<tr>
<td>CTA</td>
<td>Extent and location of arterial occlusion/stenosis/dissection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTV</td>
<td>Detection of CVT</td>
<td></td>
<td></td>
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<tr>
<td>Multimodal MRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI</td>
<td>Location, age, and extent of ischemia</td>
<td>More accurate in determining posterior circulation stroke</td>
<td>Longer time to perform, not widely available, expensive, cannot be used in cases with ferromagnetic implants</td>
</tr>
<tr>
<td>PWI</td>
<td>Location and extent of hypoperfused area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2-FLAIR</td>
<td>Exclusion of stroke mimics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRA</td>
<td>Location and extent of arterial occlusion/stenosis/dissection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRV</td>
<td>Detection of cerebral venous thrombosis</td>
<td></td>
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</tr>
</tbody>
</table>

- History of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation or aneurysm
- Recent intracranial or intraspinal surgery
- Active internal bleeding
- Elevated blood pressure (systolic >185 mm Hg, diastolic >110 mm Hg)
- Acute bleeding diathesis, including but not limited to:
  - Platelet count <100,000/mm³
  - Heparin received in the past 48 hours resulting in abnormally elevated aPTT above the upper limit of normal
  - Current use of anticoagulant with INR >1.7 or PT >15 seconds
  - Current use of direct thrombin or direct factor Xa inhibitors
Blood glucose <50 mg/dL
CT demonstrates multilobar infarction (hypodensity in >1/3 of cerebral hemisphere)

Relative exclusion criteria:
- Minor or rapidly improving stroke symptoms
- Pregnancy
- Seizure at onset with post-ictal residual neurological impairments
- Major surgery or serious trauma within the previous 2 weeks
- Recent gastrointestinal or urinary tract hemorrhage in the past 3 weeks
- Recent myocardial infarction in the past 3 months

*Relative contraindications for thrombolysis between 3-4.5 hours:
- Age >80 years
- Diabetes mellitus
- NIHSS >25
- History of oral anticoagulant intake irrespective of INR

Outside the Standard Guidelines
The standard guidelines for thrombolysis were set based on the findings of the pivotal trials (NINDS, ECAS III, and ATLANTIS). These trials excluded many patients to limit complications, who could potentially benefit from thrombolysis. These include patients mentioned under the relative contraindications section.

Delayed Thrombolysis
The patient selection for this subgroup is largely dependent on the multimodal imaging techniques mentioned previously. With the advent of these, the era of exclusively time-based thrombolysis may finally be over.

The WAKE UP trial enrolled patients with wake-up strokes or strokes whose time of stroke onset was not known, but were last seen normal more than 4.5 hours ago. This was based on the premise that stroke in these patients usually occurs closer to waking up/found not to normal unlike traditional teaching where it was taken from when they were last seen to be normal. Inclusion criteria required the presence of ischemic lesion visible on DWI but no parenchymal hyperintensity on FLAIR (indicating that the stroke had probably occurred in the past 4.5 hours). They found that this approach was associated with a significantly better functional outcome as compared to placebo.

The EXTEND trial enrolled ischemic stroke patients for thrombolysis in the extended window period (4.5-9 hours after stroke onset or wake-up stroke between 4.5-9 hours of sleep), guided by perfusion based imaging. Those patients who were found to have hypoperfused, yet salvageable brain regions by the same were randomly assigned either to receive intravenous alteplase or placebo. Patients were eligible if they had a mismatch between the core of infarction and potentially salvageable brain tissue in the penumbra. They found a higher likelihood of better functional outcome in thrombolysed patients as compared to placebo.

Minor Nondisabling/Recovering Strokes
The AHA/ASA recommend the administration of intravenous alteplase for patients with mild disabling strokes but are indecisive about mild strokes with nondisabling symptoms. This has posed a therapeutic dilemma: treat because they might worsen or do not treat because of risk of sICH? The PRISMS trial helped define the role of intravenous rTPA in this setting. Apart from the excellent outcome in the aspirin group, the overall similar outcomes between the two groups make it unlikely that thrombolysis in patients with NIHSS scores ≤5 with nondisabling deficits would significantly improve their functional outcome. However, the trial does not address the issue of what constitutes a "non-disabling" deficit in its entirety. Ambiguity and lack of consensus in this regard will continue to raise concerns regarding “missing” eligible patients for thrombolysis on the grounds of the deficits being "nondisabling."

Patients with Seizure at Onset
Post-stroke seizures are classified as early (within 1 week of stroke) and late (>7 days post-stroke). Occasionally, these early seizures occur at stroke onset. The inherent difficulty in differentiating Todd’s palsy from ischemic stroke associated weakness makes this situation a relative contraindication for thrombolysis. However, with the advent of multimodal imaging techniques described previously, the decision for thrombolysis can be made with more certainty if there is an ischemic penumbrat that can be salvaged. Both AHA/ASA and ESO recommend thrombolysis, if it can be ascertained with confidence that the focal deficit is due to ischemic stroke, and not a post-ictal phenomenon.
Patients on Anticoagulation

All patients on vitamin K activity based anticoagulation (warfarin/acitrom) need to undergo INR testing prior to anticoagulation, and can be safely thrombolysed if INR <1.7. All patients with an INR above that range cannot be thrombolysed as the risk of bleeding negates the benefit of thrombolysis.7

Ideally, patients on novel non-vitamin K based anticoagulants (direct thrombin inhibitors/factor Xa inhibitors) should not be thrombolysed if the last dose has been taken within the past 48 hours. However, it can be considered if all appropriate laboratory tests: aPTT, PT, clotting time, thrombin time, and factor Xa assay are normal.7

Pregnancy

Ischemic strokes in pregnancy and puerperium are rare and usually of cardioembolic origin (secondary to rheumatic heart disease) in our country. Treatment is challenging because of the potential risks to the mother and teratogenicity to the fetus. The former include antepartum hemorrhage due to abruption placentae, peri-, or postpartum hemorrhage and premature labor.15

No RCTs on thrombolysis have been conducted in this patient population both due to ethical reasons and paucity in numbers. Some case reports/case series have shown beneficial results. The afflicted patient is thrombolysed based on the inclusion and exclusion criteria mentioned previously as the maternal health takes precedence over the fetal health. Also, rTPA does not cross the blood-placental barrier and animal studies till date have not shown any evidence of teratogenicity.

Therefore, the decision regarding thrombolysis should be taken on a case-to-case basis balancing the benefits against potentially unknown harms.

Dementia

Thrombolysis in individuals with dementia remains unaddressed and does not find mention in either inclusion or exclusion criteria for thrombolysis. The higher burden of small vessel disease and/or amyloid angiopathy in this patient population makes most physicians reluctant toward thrombolysis due to the presumed added risk of post-thrombolysis hemorrhage.16,17 However, studies revealed that white matter disease was associated with increased risk of post-thrombolysis hemorrhage but not for poorer outcome at 3 months.18 Another study found no difference in the rates of mortality and intracranial hemorrhage in this patient population compared to those without dementia.19

Caution may be exercised in individuals who are no longer independent for activities in daily living (mRS >3) as not much might be gained from thrombolysis, but should be actively contemplated in the remainder.

Malignancy

There is limited data available on the safety and efficacy of thrombolysis in patients with a malignancy. The presumed risk of symptomatic intracranial hemorrhage makes it a relative contraindication for the same.20 However, a few case series found that it was not a significant independent risk factor for post-thrombolysis morbidity or mortality. Therefore, thrombolysis may be safely considered in patients with malignancies, provided an absence of an intracranial neoplasm or brain metastasis.

Abbreviations

AHA, American Heart Association
ASA, American Stroke Association
ASPECTS, Alberta Stroke Programme Early CT Score
CT, Computerized Tomography
CTA, CT Angiography
CTP, CT Perfusion (study)
CTV, CT Venogram
CVT, Cerebral Venous Thrombosis
DWI, Diffusion Weighted Imaging
ESO, European Stroke Organization
FLAIR, Fluid Attenuated Inversion Recovery
INR, International Normalized Ratio
MRI, Magnetic Resonance Imaging
NCCT, Non-Contrast Computed Tomography
NIHSS, National Institute of Health Stroke Scale
NNT, Number Needed to Treat
PWI, Perfusion Weighted Imaging
RCT, Randomized Controlled Trial
rTPA, recombinant Tissue Plasminogen Activator
sICH, symptomatic Intra-Cranial Hemorrhage
Conclusion

Thrombolysis with rTPA and tenecteplase has dramatically revolutionized acute stroke treatment due to their availability as an effective means of treatment. There is mounting evidence of their benefit not only within but also beyond the standard treatment guidelines. The benefit of thrombolysis can be further extended through smart selection of patients based on a clinico-imaging criterion, which improves response rates and decreases the complication risk. Evidence-based exclusion criteria are invaluable but should be adaptable in the acute setting as stringent additional testing will be counter-productive wasting precious time.

The selection of patients for thrombolysis is both an art and a science. The “art” is dependent on the clinical acumen and experience of the treating physician. This art reassures him that a benefit is expected from the treatment and is not being done for the lack of other better alternatives. The “science” part arises from the analysis of predictive markers determining the response to therapy.

Thrombolysis is the most validated and valuable tool for physicians in their arsenal against ASI and only smart patient selection can expand its repertoire further, providing best chances of a positive functional outcome.

References

Abstract

Stroke imaging is growing by leaps and bounds with every passing year. Since mechanical thrombectomy has become the standard of care in large vessel occlusions. Its imperative that every physician is equipped with the knowledge of stroke imaging to keep up with the latest trends. This chapter briefly outlines the important signs of stroke in imaging starting from non contrast ct brain to advanced imaging evaluations done before a patient is undertaken for mechanical thrombectomy.

Introduction

A clinical diagnosis of stroke even when it is largely accurate by an experienced clinician warrants mandatory neuroimaging. Imaging in stroke patients is the quintessential step before any step in the management of these patients. Furthermore, in stroke there is a rapid shift from time-based approach to tissue-based approach during interventions. Before doing MR imaging, a non contrast CT brain in stroke window will be a cost effective, time saving, and logical first step and in many cases the only investigation that will ever be needed in stroke patients. With the advent of extended stroke interventions with endovascular techniques, CT angio, and CT perfusion imaging will be needed to assess the risk benefit ratio before intervening.

Acute Stroke

Ischemic strokes contribute to almost 85% of stroke cases with hemorrhagic strokes contributing to 10% of cases and the rest by subarachnoid hemorrhage (SAH). Transient ischemic attack is a transient neurological deficit due to focal brain, spinal cord or retinal ischemia that rapidly recovers usually within 1 hour with no infarction or tissue injury.

Intracerebral Hemorrhage (ICH)

Even though MRI brain is the most specific investigation for identifying bleeds in brain, non-contrast CT is the gold standard investigation for ICH. The density of bleed declines by 1.5 HU/day. The location of the bleed may offer some clue to the etiology of the bleed (Table 1).

Hematoma clot expansion in hypertensive patients can be halted by effective blood pressure management and if necessary by rFactor VII administration. Hemorrhage extending into ventricles worsens the clinical outcome in all patients (except in thalamic hemorrhage). Hence, early CT brain helps charter the course in ICH patients and not merely excludes hemorrhage for acute ischemic stroke patients. Some of the important signs of ICH in both NCCT and CT brain are listed in Table 2 and depicted in Figures 1A to C.

Vascular Imaging

Vascular imaging may be necessary in patients with suspected arteriovenous malformation (AVM) induced superficial bleed that can be surgically evacuated or in aneurysmal SAH.
TABLE 1  Location of bleed and its etiology

<table>
<thead>
<tr>
<th>Location</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatocapsular &amp; striatothalamic</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Lobar—more in occipital</td>
<td>CAA</td>
</tr>
<tr>
<td>Lobar—(large irregular shaped from cortex to ventricles)</td>
<td>AVM</td>
</tr>
<tr>
<td>Lobar—with blood fluid level</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Lobar—parietal or temporal</td>
<td>Vein of Trolard or Labbe thrombus</td>
</tr>
<tr>
<td>Lobar -Frontal with SAH (dissecting Jet of bleeding aneurysm)</td>
<td>Aneurysms</td>
</tr>
<tr>
<td>Cisternal bleed/sulcal bleed</td>
<td>Aneurysms</td>
</tr>
<tr>
<td>Parasagittal bleeds/Meningeal based bleed with edema</td>
<td>Dural venous thrombosis/CVT</td>
</tr>
<tr>
<td>Subdural bleed</td>
<td>Coagulopathy or trauma</td>
</tr>
<tr>
<td>EDH</td>
<td>Trauma</td>
</tr>
<tr>
<td>Primary IVH</td>
<td>Cavernoma, AVM, coagulopathy, HT, tumors</td>
</tr>
<tr>
<td>Convexity SAH/ICH</td>
<td>RCVS</td>
</tr>
</tbody>
</table>

AVM, arteriovenous malformation; CAA, cerebral amyloid angiopathy; CVT, cerebral venous thrombosis; EDH, epidural hemorrhage; HT, hemorrhagic transformation; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

TABLE 2  Signs in CT brain indicating active bleed

<table>
<thead>
<tr>
<th>ICH signs in CT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA Spot sign—contrast extravasation into hematoma</td>
<td>Active bleed with poor outcome</td>
</tr>
<tr>
<td>Swirl sign (in NCCT) akin to CTA Spot sign</td>
<td>Acute extravasation of blood into hematoma</td>
</tr>
<tr>
<td>Island sign—multifocal bleed around main bleed</td>
<td>Active hematoma expansion</td>
</tr>
<tr>
<td>Blend sign—blending of hypodense and hyperdense area</td>
<td>Active hematoma expansion</td>
</tr>
<tr>
<td>Black hole sign (hypoattenuating within hyperdense)</td>
<td>Active hematoma expansion</td>
</tr>
</tbody>
</table>

Figs. 1A to C: Some important ICH signs in Plain CT Brain. (A) Plain CT brain Showing central Swirl sign and peripheral island sign. (B) CT brain demonstrating central spot sign. (C) Plain CT brain demonstrating blood fluid level
**MR Imaging**

MR imaging remains as the most accurate investigation for detecting very small hemorrhages. The transition of oxyhemoglobin (diamagnetic) in blood to later derivatives starting from deoxyhemoglobin (paramagnetic) causes local T2 dephasing of the protons from its precessional path and induces rapid signal loss in GRE and susceptible weighted imaging, manifesting as blooming. Whether thrombolysis can be safely done in patients with microbleeds due to hypertensive vasculopathy is a topic of controversy with many deferring thrombolysis when there is more than 10 microbleeds.

**Acute Ischemic Stroke (AIS)**

Aided with an accurate history, an NCCT is the ideal emergency investigation in AIS patients. It conveniently rules out hemorrhage and many of the stroke mimics. Ischemic tissue due to cytotoxic edema appears hypodense on NCCT. Reversible ischemic tissue may appear hypodense and swollen in CT. Very large hypodense lesion portends poorer outcome and high risk of hemorrhagic transformation.

Even in an acute setting almost half the patients with AIS have a normal CT brain. A well trained eyes can pick out some of the early ischemic signs (see Figs. 2A to D) in plain CT (Table 3) so that thrombolysis can be undertaken without delay.

### Table 3: Signs of early ischemia in NCCT

<table>
<thead>
<tr>
<th>Early ischemic changes in NCCT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdense arteries (MCA, PCA, ACA)</td>
<td>Highly sensitive, less specific</td>
</tr>
<tr>
<td>M2 Dot sign</td>
<td>Highly specific, less sensitive</td>
</tr>
<tr>
<td>Basilar artery Dot sign</td>
<td>Very high mortality</td>
</tr>
<tr>
<td>Striatal and lentiform hypodensity</td>
<td></td>
</tr>
<tr>
<td>Loss of insular ribbon sign</td>
<td>One of the earliest changes</td>
</tr>
<tr>
<td>Cortical gray-white differentiation loss</td>
<td></td>
</tr>
<tr>
<td>Hemispherical sulcal effacement</td>
<td></td>
</tr>
<tr>
<td>Focal compression of lateral ventricles</td>
<td></td>
</tr>
</tbody>
</table>

**Figs. 2A to D:** Early ischaemic signs in Plain CT brain. (A) Showing hyperdense left MCA in the sylvian cistern (HMCA sign). (B) Showing Hyperdense Basilar artery in suprasellar cistern (Basilar Dot sign). (C and D) Showing blurring of margins of basal ganglia & Right insular ribbon sign respectively.
ASPECTS Scoring

The Alberta stroke programme early CT score (Anterior ASPECTS) is a 10-point scoring system with CT imaging done in patients with MCA strokes (see Fig. 3).

Anterior ASPECTS

- Two slices are chosen for the analysis—thalamic level (M1 to M3) and just above basal ganglia (M4 to M6) (see Fig. 3).
- Ten segments located within mca distribution. Caudate head, insula, lentiform nucleus, internal capsule, and M1–M6.
- Normal segments—0 point. Ischemic region—1 point. Points are deducted from an initial score of 10 for every region involved
- Maximum is 10 points. Lower scores denotes larger regions of mca infarct. A score of 7 or less indicates 1/3 of mca territory infarct and increased chance of poor clinical outcome.
- Score 7 = 1/3 mca infarct. Score 0 = full mca

Posterior ASPECTS

The posterior ASPECTS just like anterior aspects is the 10-point scoring system where points are lost for each region affected. The pons and the midbrain are worth 2 points each (unilateral or bilateral) (see Fig. 4).

- Thalamus (1 point each)
- Occipital lobes (1 point each)
- Midbrain (2 points)
- Pons (2 points)
- Cerebellar hemispheres (1 point each)

Many accredited stroke centers follow an individualized stroke image algorithm. One such highly recommended algorithm adopted by Massachusetts General Hospital, USA is shown in the Flowchart 1.

Massachusetts General Hospital acute stroke imaging algorithm for triage of patients with severe ischemic
strokes caused by anterior circulation occlusions dictates a Plain CT Brain for all patients followed by CT angiography. The patient is further evaluated with DWI if the patient has an NIHSS score of 10 or above with an occlusion identified at distal ICA and Proximal MCA with accessibility to microcatheter. If the size of core infarct is less than 70 mL in DWI the patient is taken up for endovascular therapy. If the patient is unfit for endovascular therapy, perfusion studies can be done for further guidance of therapy.

**Goals of Acute Stroke Imaging-4Ps**
- Parenchyma—assess early signs of acute stroke, rule out hemorrhage
- Pipes—assess extracranial and intracranial arteries
- Perfusion—assess CBV, CBF, MTT
- Penumbra—assess tissue that can be salvaged

**CT Angiography**

Contrast enhanced CT offers substantial additional value in assessment of cerebral blood volume, CT perfusion studies and in CTA. One of the most important objectives is location of the clot in the distal ICA or proximal MCA so as to undertake intra-arterial therapy. Volume of infarct is an important parameter deciding the use of IAT, with volume greater than 70–100 mL having high chances of hemorrhage. CT angiography may offer great insights into the nature of the thrombus by following assessments.

- **Length of clot**: In MCA strokes, studies have shown that the IVT has no potential to recanalize if the clot length exceeds 8 mm (see Fig. 5). Such patients may greatly benefit from endovascular interventions (Provided with good collaterals). Surprisingly many basilar artery occlusions (BAO) even with high NIHSS scores obtain very good recanalization with IVT even comparable to intra-arterial thrombolysis.
- **CTA source image ASPECTS**: For ASPECTS scoring and collateral assessments. CTA SI being more sensitive offers a distinct advantage in early ischemic strokes when compared to NCCT (see Fig. 6).
- **Residual flow assessment**: Successful thrombolysis and outcome depends upon the ability of the thrombolytic agent to permeate the entire length of the clot. This can be assessed in CTA by means of residual flow grade with residual grade 1 and 2 offering greater chances of opening up of vessels by means of either allowing thrombolytic agent to permeate the clot or by means of good collaterals (see Fig. 7). Another way of analysing residual flow includes calculating proximal and distal clot interface HU ratio. With ratio greater than 2 having poor chances of recanalization.
Terminal Internal carotid artery occlusions: Carotid T and L shaped occlusions theoretically may have less chance of recanalization when compared to Terminal I shaped occlusion because of collateral MCA flow, higher density of the clot and increased lepto meningeal collaterals in the later. Shape of the thrombus also helps interventionalists to plan and decide approach to thrombectomy. (see Fig. 8).

Clot burden score: It is a scoring system to determine the extent of thrombus in proximal anterior circulation by location with scores ranging from 0–10. A score of 10 is normal and a score of 0 indicate multi segment occlusion with a score greater than 6 having greater recanalization rates (see Fig. 9):

- 10—total patency
- 0—occulsion of major vessel
- 2—absence of contrast opacification m1
- 2—distal m1/supra clinoid ica
- 1—each m2
- 1—a1 segment
- 1—infra clinoid ica
- lower cbs—larger, proximal thrombus, large infarct, worse collaterals
- >6 higher recanalization. <6 less rate of recanalization (see Fig. 9)

Collateral score: collaterals that supports the penumbral tissue during ischemia includes convexity leptomeningeal vessels and circle of willis. Decreased flow leads to increased progression of ischemia and absent collaterals is associated with worse clinical outcome.

A modified Tan (see Fig. 10) or Miteff scoring systems is used for angiographic collateral assessment determining the course of AIS.

CT Perfusion (CTP) Imaging

CTP is sensitive to capillary and tissue level blood flow and provides insight into delivery of blood to brain parenchyma. Typical parameters assessed are the following:

cbv: total volume of blood in a given unit volume of brain (mL/100 g)

cbf: volume of blood moving through a given unit volume of brain/unit time (mL/100 g/mt)
mtt: average of transit time of blood through a given brain region

\[ mtt = \frac{cbv}{cbf} \]

In the first few hours after stroke, the final infarct volume in absence of reperfusion is predicted by MTT and TTP. Tissue infarction is represented by reduced CBV due to failure of autoregulatory responses. Ischemic penumbra is then the difference between CBV and MTT and TTP, which in turn denotes viable tissue at risk for infarction.

All three perfusion CT parameters can be depicted either visually—on a color scale—or numerically, using selected regions of interest.
The standard color scale is graded from shades of red and yellow to blue and violet.

With CBV and CBF, perfusion is portrayed in red/yellow/green (highest) to blue/purple/black (lowest).

Normally there is equal symmetric perfusion in the cerebral hemispheres with higher CBF and CBV in gray matter (cortex, basal ganglia) compared to white matter.

MTT shows the most prominent regional abnormalities. Color scales are reversed to emphasize the abnormally prolonged transit time in the ischemic brain. The slower the transit time, the closer to the red end of the scale. Brain with normal transit time appears blue (see Fig. 11).

Important ancillary finding like Luxury perfusion and crossed cerebellar diaschisis may be seen.

**MR Imaging**

Diffusion weighted imaging is one of the most sensitive technique for ischemic core estimation. Studies have shown that a DWI abnormality volume of more than 70 mL is highly specific for a poor outcome.

Diffusion and perfusion weighted imaging offers vast information regarding tissue viability in stroke. Perfusion MRI is applied as a bolus tracking during gadolinium administration (same as CTP) or instead of using an intravascular contrast agent, CASL magnetically labels the blood entering the brain allowing measurement of TTP, MTT, CBV, and CBF. CASL imaging within 24 hours of stroke symptom onset can depict perfusion defects and diffusion-perfusion mismatches.

**DWI/PWI Mismatch**

Ischemic penumbra is depicted as DWI/PWI mismatch in MR imaging. The errors in calculation of core infarct size is because diffusion imaging overestimates core volume by causing restriction in regions of penumbra whereas perfusion imaging overestimates penumbra by including regions with benign oligemia (see Fig. 12).
“Classic” mismatch pattern is where the ischemic core on DWI is embedded within a hypoperfused penumbral brain region on PWI (see Fig. 13).

“Nonclassic” fragmented mismatch pattern is where part or all of the ischemic regions on DWI are dissociated from the hypoperfused region on PWI.

It is very clear that proximal MCA and distal ICA has to have a small core infarct with a disproportionately large penumbra, nearing a DWI/PWI mismatch of 100%. This is also confirmed clinically with the clinical/diffusion mismatch, for example, NIHSS score (≥8) with a small core infarct (≤25 mL).

**DWI Negative Stroke**
- Lacunar infarcts
- Brainstem infarcts
- Clot lysis with recanalization
- Moderately reduced or fluctuating hypoperfusion that is not severe enough to restrict water movement

**MR Angiography**
There are three types of MR angio techniques:
- Time of flight
- Phase contrast
- Gadolinium contrast

Only CE MRI has any use much like CTA in acute ischemic stroke patients.

**MRS**
The use of MRS in AIS patients apart from showing reduced NAA peak and a raised lactate peak does not offer much information and remains to be validated.

**PET/SPECT Imaging**
SPECT has application only in presurgical epileptogenic foci mapping and has negligible role in neuroimaging much less in strokes and is largely superseded by the superior PET imaging in every possible way. PET imaging has research application in strokes patient and is currently out of focus in strokes because of the complexities in metabolic activity of the ischemic tissue.

**Xenon Inhalation CT**
Xenon is inhaled and based on the tissue concentration the CBF data is obtained. The anesthetic properties and difficulty in administration has precluded its routine use.

**Transcranial Doppler Ultrasound/TCCD**
TCD and TCCD are rapidly evolving as auxiliary investigations in stroke patients. Operator dependence and high expertise are the major limiting factor for its routine use.

TCD and TCCD have a role in stroke following settings:
- Continuous monitoring and identify recanalization during or after thrombolysis
- Detection of right to left shunt
- Monitor flow velocities in sickle cell patients to prevent stroke
- Cerebral VMR measurement
- Vasospasm in SAH

**Conclusion**

Imaging in stroke has grown by leaps and bounds and much exciting developments await in the horizon. Both CT and MRI are complementary in stroke imaging and in many patients a detailed evaluation will require both these investigations.

**References**

Abstract
Movement disorder encompasses large number of neurological disorders that share the common clinical feature of involuntary movements of either hypo- or hyperkinetic character. Movement disorders are classified first phenomenologically and then etiologically. In terms of phenomenology, hypokinetic movement disorders include Parkinson’s disease, several other conditions with Parkinsonian features, and rare disorders like stiff-person syndrome. A large number of hyperkinetic movement disorders are divided in several categories including tremors, chorea, dystonia, tics, stereotypies, and myoclonus. The ataxias and movement abnormalities associated with cerebellar system disorders and the large category of gait disorders also fall within this category. This chapter deals with the clinical approach and management of common movements disorders.

Introduction
The term “movement disorder” denotes an abnormality of the form and velocity of movements of the body and is often equated with disorders of basal ganglia. Although some movement disorders are present in pure isolation, many clinical syndromes take form of “mixed movement disorder.” Thorough clinical examination should take front seat in diagnosis rather than adopting a scattergun approach to investigations is critical which in turn is time consuming and costly.

Movement disorders are defined as neurologic syndromes that cause interruption of motor activities by either production of excessive, unwanted and involuntary movements or paucity of normal free flowing movements.

Classification
Broadly, movement disorders can be classified into:
- Hypokinetic Disorders
  - Parkinsonism
- Hyperkinetic disorders
  - Tremors
  - Myoclonus
  - Chorea
  - Ballism
  - Dystonia
  - Tics
  - Athetosis

Parkinsonism
Parkinson’s disorder results from dopaminergic neuronal degeneration in the nigrostriatal pathway. It affects about 1% of population over the age of 50 and is the second most common movement disorder.¹

Differential Diagnosis of Parkinson’s Disease
- PD
- Parkinsonian syndromes
  - Progressive supranuclear palsy
  - Multisystem atrophy (MSA)
Neurology

SECTION 6

- Diffuse Lewy body disease
- Corticobasal degeneration
- Drug induced
- Other Non-Parkinson’s akinetic-rigid syndromes
- Wilson’s disease
- Depression
- Arthritis, polymyalgia, fibromyalgia

Cardinal Features

- **Tremors:** The commonest presentation is rest tremor in one hand which is often accompanied by decreased arm swing and shoulder pain. The tremor is a coarse “pill rolling” movement, fairly rhythmic, from 2–6 Hz.
- **Bradykinesia and rigidity:** More commonly visible on symptomatic side, and midline signs such as reduced facial expression or mild contralateral bradykinesia may already be present. Patients typically develop stooped posture. Poor balance, tendency to fall, and difficulty in walking is seen in patients with Parkinson’s disease.

Other Motor Features:
- Micrographia
- Masked facies
- Reduced eye blinking
- Soft voice
- Dysphagia
- Freezing
- Bradylalia

Non-Motor Features:
- Sensory disturbances
- Mood disorders
- Sleep disturbances
- Autonomic disturbances—orthostatic hypotension, gastrointestinal disturbances, sexual dysfunction
- Cognitive impairment (dementia)

Treatment

Drugs commonly used:
- Management of motor complications (Table 1)
- Management of non-motor complications (Table 2):
- Neuroprotective therapies: See Table 3
- Deep brain stimulation (DBS): DBS is functional neurosurgical approach used to treat motor fluctuations. Indications are:
  - Levodopa responsive Parkinson’s disease
  - Motor fluctuations
  - Age < 70–75 years
  - Adequate trial of dopaminergic medications given

### Table 1: Management of motor complications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting dose</th>
<th>Target dose</th>
<th>Adverse effects</th>
<th>Main benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbidopa-L-Dopa</td>
<td>25/100 mg tid</td>
<td>Up to 50/250 mg</td>
<td>Dyskinesia, hallucination, nausea, confusion</td>
<td>Bradykinesia and tremors controlled</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>0.5 bid</td>
<td>Up to 2 mg tid</td>
<td>Atropinic effects</td>
<td>Tremor reduction</td>
</tr>
<tr>
<td>MAO- inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
<td>5 mg</td>
<td>5 mg bid</td>
<td>Cheese effect</td>
<td>Reduced off time</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>0.5 mg</td>
<td>1 mg daily</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ropinirole</td>
<td>0.25 mg tid</td>
<td>9–24 mg/day</td>
<td>Orthostatic hypotension, confusion, sleepiness</td>
<td>Reduced motor fluctuations</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>0.125 mg tid</td>
<td>0.75–3 mg/day</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>COMT inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entacapone</td>
<td>200 mg</td>
<td></td>
<td>Diarrhea, dyskinesia</td>
<td>Prolonged effect of L-Dopa</td>
</tr>
<tr>
<td>Also- Tolcapone and newer acting Opicapone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>100 mg/day</td>
<td>100 mg bid-tid</td>
<td>Confusion, hallucination, congestive heart failure</td>
<td>Smoothing of motor fluctuations</td>
</tr>
</tbody>
</table>

TABLE 1: Management of motor complications

2
### TABLE 2
Management of non-motor complications

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>SSRIs—Mirtazapine, TCAs</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Anti-psychotics like quetiapine</td>
</tr>
<tr>
<td>Dementia</td>
<td>Cholinesterase inhibitors like donepezil, rivastigmine</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Low dose clonazepam</td>
</tr>
<tr>
<td>Bladder disturbances</td>
<td>Oxybutynin, tolterodine</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>Low dose fludrocortisone, midodrine³</td>
</tr>
</tbody>
</table>

### TABLE 3
Neuroprotective approaches and their mechanism of action

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Potential neuroprotective approach⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative stress and mitochondrial dysfunction</td>
<td>Antioxidants (monoamine oxidase inhibitors, coenzyme Q10, glutathione promoters, inhibitors of α synuclein aggregation⁵)</td>
</tr>
<tr>
<td>Excitotoxicity</td>
<td>Glutamate antagonists (e.g., riluzole)</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Antiapoptotic agents (e.g., mixed lineage kinase inhibitors)</td>
</tr>
<tr>
<td>Trophin deficiency</td>
<td>Neurotrophins</td>
</tr>
<tr>
<td>Caspase activation</td>
<td>Caspase inhibitors as minocycline</td>
</tr>
</tbody>
</table>

- Ablative surgeries:
  - Thalamotomy
  - Pallidotomy
- Newer drugs in development:
  - Istradefylline: Adenosine A2a antagonists which improve motor fluctuations as an add-on drug
  - Remacemide: NMDA channel antagonist delays the absorption of L-dopa

### TABLE 4
Classification of hyperkinetic disorders

<table>
<thead>
<tr>
<th>Regular/predictable</th>
<th>Intermediate</th>
<th>Fleeting/unpredictable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>Dystonias</td>
<td>Fasciculations</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>Myokymia</td>
<td>Myoclonus</td>
</tr>
<tr>
<td>Palatal myoclonus</td>
<td>Athetosis</td>
<td>Chorea</td>
</tr>
<tr>
<td>Palatal myoclonus</td>
<td>Tic</td>
<td>Dyskinesias</td>
</tr>
<tr>
<td>Tic</td>
<td>Stereotypy</td>
<td></td>
</tr>
<tr>
<td>Stereotypy</td>
<td>Myorhythmia</td>
<td></td>
</tr>
</tbody>
</table>

- Whether the movement is suppressible by attention or sensory tricks?
- Whether the movement is present or absent during sleep?

### Tremors
Rhythmic, oscillatory, and involuntary movement produced by alternating, synchronous contractions of reciprocally innervated muscles ([Flowchart 1](#)).

- **Essential tremors (ET):** It is commonest of all movement disorders. ET is often familial. It is an action tremor that affects head, hands, and voice, worsened by anxiety. The neurological examination is otherwise normal.
- **Parkinsonian tremors:** The tremor is slow, coarse, and compound, rate averaging 4–5 Hz. Causes include idiopathic Parkinson’s disease, drugs induced like antipsychotic agents, HIV/AIDS, neurosyphilis, toxoplasmosis, PML or chronic head trauma.
- **Orthostatic tremors:** Orthostatic tremor consists of a high-frequency (14–18 Hz) tremor in the legs during standing. Unaware of the tremor, the patient may complain of unsteadiness or discomfort in the legs that are relieved by leaning against a stationary object, by walking, or by sitting down.
- **Cerebellar tremors:** Cerebellar tremors are slow, absent at rest, and progressively increase with amplitude of movement. A variant known as Holmes tremor is typically present during rest, posture holding, and movement.
- **Hereditary geniospasm:** It is characterized by involuntary vertical movement of the tip of the chin with quivering and mouth movements.
- **Neuropathic tremor:** These are associated with neuropathy diagnosed when other tremorgenic neurologic disorders have been ruled out. The neuropathic tremors are kinetic, usually postural 4–7 Hz in frequency.
**Management of Tremor**

See Table 5.

**Chorea**

Chorea is swift, graceful, semi-purposeful, dance-like non-patterned, involuntary movements involving proximal or distal muscle groups. They are present at rest but are increased by emotional stress, tension, activity, and self-consciousness.

**Huntington’s disease:** It is an autosomal disorder which is progressive and fatal. It is characterized by:

- Involuntary choreiform movements which advances to dystonia, rigidity, myoclonus.
- Cognitive dysfunction: depression with suicidal tendencies, psychosis, and aggression.
- Gait abnormality.
- Oculomotor involvement: Characterized by slowness of both pursuit and saccadic movements and patient is unable inability to make a volitional saccade without movement of the head.

**Management:** Dopamine blocking agents like Tetrabenazine have been approved. More recently, deuterated tetrabenazine has also been approved. Recently, an experimental anti-sense drug successfully lowered the level of mutant huntingtin protein in spinal fluid of affected patients.

**Sydenham’s chorea (aka Saint Vitus Dance):** It is acute in onset, self-limited choreiform movements seen mostly in patients with rheumatic fever.

Paroxysmal chorea is seen in hyperglycemia and hypoglycemia, infections, and vascular diseases.

**Athetosis**

In athetosis (Hammond’s disease), the movements are involuntary, coarse, rhythmic and writhing in character. Movements are slower but more sustained and have larger in amplitude than those in chorea. Any combination of flexion, extension, pronation, supination, and abduction in variable degrees can be seen. The movements are

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**TABLE 5** Medical management of tremors

<table>
<thead>
<tr>
<th>Tremor Syndrome</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential Tremor</td>
<td>First line: Propranolol (up to 320 mg) and Primidone</td>
</tr>
<tr>
<td></td>
<td>Second line: Topiramate, Gabapentin</td>
</tr>
<tr>
<td></td>
<td>Third line: Clonazepam, Botulinum toxin</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>Levodopa and/or Dopamine agonists</td>
</tr>
<tr>
<td>Orthostatic tremor</td>
<td>Clonazepam, Gabapentin</td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>Clonazepam, Baclofen</td>
</tr>
<tr>
<td>Palatal tremor</td>
<td>Phenytoin, Carbamazepine</td>
</tr>
<tr>
<td>Cerebellar tremor</td>
<td>Propranolol, Clonazepam</td>
</tr>
<tr>
<td>Neuropathic tremor</td>
<td>Propranolol, Primidone</td>
</tr>
</tbody>
</table>
intensified by voluntary activity (overflow phenomenon) and disappear in sleep. Athetosis is usually congenital following perinatal injury but can also be acquired following disease, trauma, or drug toxicity. Treatment is exactly like chorea.

**Dystonias**

Dystonia is defined as involuntary, sustained patterned, or repeated muscle contractions often associated with twisting movements and abnormal posture. Voluntary actions worsen dystonia and it is because of overflow muscle activation. Factors that aggravate dystonia are stress and fatigue and relieving factors are relaxation and sensory tricks (geste antagoniste). Classification of Dystonia is given by European Federation of Neurological Sciences (EFNS-2011) (Table 6).

**Management**

- Anticholinergic is the most successful oral medication for the treatment of dystonias, particularly trihexyphenidyl.
- Baclofen: This drug has good response in young patients less than 20 years of age and with mild to moderate dystonia.
- Benzodiazepines: Mainly used for blepharospasm and cervical dystonia with predominant head tremor.

- Botulinum toxin: Treatment of choice for patients with focal or segmental dystonia, like spasmodic dysphonia, blepharospasm, oromandibular, cervical, and lingual dystonia. It can also be used to treat occupational dystonias, like writer’s cramp.
- Physical and occupational therapy.

**Hemiballismus**

Here the movements are wide, flinging, incessant that occur unilaterally. It classically occurs due to hemorrhage or infarction in contralateral subthalamic nuclei. The movements occur incessantly during awake state and disappear only with deep sleep. It is difficult to treat situation, extremely disabling and occasionally fatal too.

**Myoclonus**

It can be defined as single or repetitive, sudden, brief, jerky, arrhythmic, lightning-like, involuntary movement involving part of muscles, entire muscles, or groups of muscles. It appears symmetrically on both sides. Such synchrony is unique to myoclonus. The distribution of myoclonus can be localized, diffuse, segmental, or generalized. On the basis of etiology, myoclonus can be classified into physiological myoclonus (e.g., hypnic jerks), epileptic myoclonus, essential myoclonus (idiopathic or hereditary), myoclonus is secondary to an underlying disorder or psychogenic or symptomatic myoclonus.

It arises in the CNS from cortical, subcortical, and spinal cord levels. Can be provoked by various stimuli like noise or touch but disappears during sleep.

Clonazepam may be helpful in all types of myoclonus. Other drugs that can be used for cortical myoclonus are antiepileptic drugs such as valproate, levetiracetam, and piracetam, but ineffective in other forms of myoclonus.

**Tourette’s Syndrome**

Neurobehavioral disorder which predominately affects males and characterized by multiple motor tics and vocalizations. Such tics may be suppressed for short periods of time or even totally abolish for days to weeks. Onset occurs before the age of 15 years and incidence decreases or even nil during adulthood. Tourette’s syndromes are associated with anxiety, attention deficit hyperkinetic disorder (ADHD), depression, and obsessive compulsive disorder (OCD). Onset in adults is
associated with Parkinson’s disease, dystonia, drugs (e.g., neuroleptics, levodopa), and trauma.

**Tics**
It is a brief stereotyped irresistible repetitive purposeful movement. It can be voluntarily suppressed for a short period.

**Drug-induced Movement Disorders**

**Acute**
They include akathisia, acute dystonic reactions, serotonin syndrome, tremor, neuroleptic malignant syndrome. It occur within minutes to days of drug ingestion.14

**Subacute**
It occurs within days to weeks of drug ingestion.

**Tardive syndromes:** These are drug induced and occur either during exposure or within weeks of stopping a drug and these are present for at least 1 month.15

- **Tardive dyskinesia (TD):** It develops months to years after ingestion of antipsychotic treatment. Characterized by choreiform movements of the mouth, tongue, and lips.
  - Lower risk of TD is conferred by youth and use of atypical antipsychotics. Increased risk is conferred by advanced age, toothlessness, and organic cerebral dysfunction.
  - Roughly one third of TD cases resolve within 3 months of discontinuing the offending drug. Most other patients slowly improve over a course of years.

- **Tardive dystonia:** Chronic neuroleptic exposure leads to this condition and is characterized by rocking motion and axial muscle involvement. Tardive dystonia often persists even after offending medication is weaned off and is often refractory to treatment.

- **Tardive akathisia and Tardive Tourette’s syndrome** are much less common but still associated with chronic antipsychotic exposure.

**Neuroleptic malignant syndrome** is characterized by hyperthermia, rigidity, tachycardia, and renal failure. It usually occurs days to weeks after exposure to medication. It might also be precipitated by discontinuation of antiparkinsonian medications.

**Conclusion**
Movement disorders can manifest in numerous ways, with symptoms ranging from subtle to disabling. In recent years, there has been tremendous increase in new diagnostic information, pharmacological, and neurosurgical treatments for movement disorders, as well as a greater understanding of impaired motor control function. The most important for anyone affected by movement disorder is a dedicated team of specialists who can monitor the progress and support optimal health with the latest therapeutic options available.

**References**

Abstract

Headache poses diagnostic challenges to the physicians for many reasons. It is an extremely common complaint which may be associated with acute illness or serious pathology such as brain tumor or cerebral aneurysm. The majority of patients experiencing recurrent headache in the population suffer either from a variant of tension type headache or migraine. Migraine is more likely to be disabling and becomes the most likely diagnosis for any patient presenting with recurrent headache interfering with function. It is the surround of migraine—the aura, prodrome, and postdrome that can be most challenging and confused with other pathologies.

A basic working knowledge of the common primary headaches and a rationale manner of approaching the patient with these conditions allow a specific diagnosis of migraine to be made quickly and safely. This article discusses about the approach for diagnosis of migraine.

Introduction

Migraine is the most incapacitating disorder of brain, which presents as more severe form of headache with recurrent attacks. The incidence of migraine in women is 15% and whereas in men it is 6%. Approximately 20% of the population experience migraine during their lifetime. Migraine is highly prevalent and is the 7th leading cause of time spent disabled worldwide, yet it has received relatively little attention as a major public health issue. According to "waiting room" survey, 29% of patients encountered at least one migraine headache in a primary care setting within the preceding year. Unfortunately, only 48% of individuals with migraine have received the appropriate diagnosis.

There are many barriers to the diagnosis of migraine, approximately one third of the migraineurs fail to consult the medical care, relaying largely on treatment with over the counter analgesics. This may reflect inadequate access to medical care, ignorance of the availability of the excellent treatment of headache, or reluctance to present with a symptom that society often labels as "benign or nuisance." Even with the evidence of neurological basis of migraine, the stigma of a psychiatric element persists widely in society. Under appreciation by the physician's acts as a barrier for effective diagnosis in clinical settings, magnified by undue emphasis on the serious, but much more uncommon, causes of headache.

Definition

Migraine is defined as intermittent attacks of headache lasting 4–72 hours, with the pain exhibiting two of four specific characteristics (unilateral, throbbing, moderate-severe, worse with activity) and requiring either nausea or photophobia.

Migraine may begin early in childhood, but its prevalence increases at 10–14 years of age and continues to increase until 35–39 years of age, after which it gradually decreases, particularly women after menopause. Migraine affects three times more commonly in women than men.
Classification of Migraine

See Box 1.

Clinical Features

Migraine, which often begins in childhood, adolescent, or early adulthood, can progress through four stages, not everyone who has migraines goes through all stages.

- Premonitory (Prodromal) Phase (50–80%)—A day or two before the onset of migraine, the changes that alert an upcoming migraine attack includes mood changes, neck stiffness, frequent yawning, food cravings, increased thirst, micturation, and constipation.

- Aura (15–20%)—Some people experience aura before or during migraines, which are reversible symptoms of the nervous system, that includes visual symptoms such as flashes of light, scintillations, bright spots, hemianopsia, scotoma, vision loss, auditory phenomena, like hearing noises, pins, and needle sensation of arm or leg, numbness in the face or one side of the body. Each symptom usually begins gradually and progress with time, lasting over 20–60 minutes.

- Headache—If untreated, this phase usually lasts from 4 to 72 hours. Headache characterized by unilateral throbbing/pulsatile headache occasionally affecting both sides, associated with nausea, vomiting, sensitivity to light and sound.

- Post Drome (80%)—This phase lies between resolution of headache and normalization of patient symptoms, during which the patient experiences non-headache symptoms such as limitation of normal functions, which includes easy tiredness, difficulty in concentration, neck stiffness, and irritability.

Triggers of Migraine

Glare, bright light, sound, hunger, physical exertion, hormonal fluctuations during menses, lack or excess of sleep, alcohol intake, barometric pressure changes.

Diagnosis

Why Diagnosis of Migraine is Difficult?

Migraine headaches can be easily diagnosed, but aura may mislead the diagnosis, migraine aura is positive phenomenon, hallucinations associated with migraine are usually elementary instead of complex, but the most common one is unformed visual aura and is characteristic feature of the disease. Investigations in these patients turns out to be normal, even if abnormalities are detected they may be incidental.

Migraine can be differentiated from autonomic cephalgias, but overlap syndromes such as cluster headache also seen, and diseases simulating migraine such as headache from hypertension, giant cell arteritis, reversible cerebral vasospastic syndrome, carotid artery disease, acute glaucoma, intracranial mass lesions, raised intracranial pressure, meningitis and reversible cerebral vasospastic syndrome must not be missed.

Borderline conditions include mitochondrial cytopathies, migralepsy, and migrainous stroke. Importantly migraine is often misdiagnosed for other paroxysmal events mainly cerebrovascular disease and seizures, but also peripheral nervous system disorders, syncope, multiple sclerosis, vestibular disorders, gastrointestinal and cardiac disease, functional and psychiatric illness.

The diagnosis becomes even more difficult when the patient is in transitional or intermediate or having mixed

BOX 1

International Classification of Headache Disorders, Third Edition BETA (ICHD-3 BETA)^5

- Migraine without aura
- Migraine with aura:
  - Migraine with typical aura
  - Migraine with brainstem aura
  - Hemiplegic migraine
  - Retinal migraine
- Chronic migraine
- Complications of migraine:
  - Status migrainosus
  - Persistent aura without infarction
  - Migrainous infarction
  - Migraine aura-triggered seizure
- Probable migraine:
  - Probable migraine without aura
  - Probable migraine with aura
- Episodic syndromes that may be associated with migraine:
  - Recurrent gastrointestinal disturbance
  - Benign paroxysmal vertigo
  - Benign paroxysmal torticollis
features of both tension type headache and migraine, in such patients a headache diary or headache notebook is useful to get necessary information in diagnosing the migraine.

**Diagnostic Evaluation**

**When to Suspect a Migraine?**

It will be most accurate and most efficient, to consider migraine simply as the most common episodic headache presenting to clinician. Acute sinusitis is an easily recognized source of headache, but chronic sinus dysfunction rarely acts as independent source of recurrent headache. Migraine should be the first thought for those patients describing episodic headache that is severe, disabling, or interfering with normal function. A stable pattern, an absence of daily headache or daily analgesic use and a normal neurologic examination will help in diagnosis of migraine. Typical symptoms and signs can be used to provide additional support to the diagnosis. Fundamentally we should “think migraine first” with any clinical presentation of episodic headache, particularly when it is disabling.

Patients with a stable pattern, normal general physical and neurological examinations and a typical migraine presentation do not require further diagnostic evaluation. However, progressive patterns, abnormal examination findings, or atypical presentations including those with daily headaches will need further evaluation.

The “Nasty Nine” (listed in **Box 2**) outlines the nine specific situations necessitating neuroimaging, electroencephalography, lumbar puncture, or serum studies.

**BOX 2** Indications for diagnostic evaluation of headache: “Nasty Nine”

* First/worst severe headache
* Abrupt-onset headache
* Progressive or changing headache pattern
* Headache with neurologic symptoms >1 hour
* Abnormal examination findings in headache patient
* Headaches associated with syncope or seizure
* Headaches in children <5, adults >50 years of age
* Headaches in immunocompromised patients
* Headaches that increase on Valsalva, exertion, and sexual activity

The IHS criteria are helpful in diagnosis of the migraine, and it has made migraine a positive diagnosis rather than a diagnosis of exclusion. Careful questioning of the patient and application of the diagnostic criteria and to carry out a brief, but sensitive and highly focused neurological examination is very helpful.

An abbreviated version of IHS diagnostic criteria is shown in **Box 3**.

**BOX 3** IHS diagnostic criteria for migraine from Headache Classification Committee of The International Headache Society

* Migraine without aura—lasts 4–72 hours
* Has at least two of the following characteristics:
  - unilateral
  - pulsating
  - moderate or severe intensity
  - aggravated by exertion
* Associated with one or more of the following:
  - nausea, vomiting, phonophobia, photophobia

* Migraine with aura—Two or more headache preceded by aura:
  - Aura symptoms usually involving:
    - blurred vision
    - flashing lights
    - missing area of visual field
  - Aura symptoms fully reversible, lasting less than 1 hour.
  - Headache follows aura within 1 hour

**Migraine without Aura**

Migraine without aura previously known as common migraine, where patient complains of episodic headache lasting from hours to days, disabling type accompanied by gastrointestinal symptoms or by increased sensitivity of special senses. With exercise or hard work, tension type headache can be easily distracted but same is not possible in migraine without aura. The duration and frequency of migraine plays vital role in differentiating headache due to medication overuse (MOH) or tension type headache (TTH) where the frequency is more than twice a week, but the same frequency is unlikely seen in migraine without aura (MO).
Migraine with Aura

Migraine with aura previously known as focal or classic migraine, aura progress over time and lasts for several minutes, improves at one aspect and at other it worsens. It is difficult to distinguish between migraine with aura from thromboembolism and epilepsy because here aura sometimes affects sensation, movement, cognition, vestibular function, or consciousness. Sometimes in migraine with aura of recent onset is usually preceded by long standing history of MO, which should be differentiated from “bilious attacks,” “sinusitis” or “normal headaches.”

In middle age group migraine with aura without headache is most common, sudden onset of MA episodes without headache is mistaken as transient ischemic attacks (TIA). In contrast, sudden episodes of MA with headache need to be distinguished from thromboembolism as it is associated with headache of abrupt onset with non-evolving impairment, which is restricted to single vascular territory.

Take a Detailed History

From diagnosis point of view, history taking remains the most important aspect. It is important to allow patients for proper description regarding their attacks and also for clarifying the history by proper questioning with the aim to fill the gaps in the history that the patient has told you spontaneously. The mainstay of diagnosis of migraine depends completely on history, thorough examination of a patient helps to identify other associated problems, which may exacerbate an underlying tendency to migraine.

The questionnaire should begin by asking about the pattern of the pain, including when, and how headaches begin, duration and frequency of episodes with associated exacerbating or triggering factors. The questionnaire should also include nature of pain, its location, character, and severity, and the symptoms, which accompany pain suggesting other primary or secondary headache disorders such as epiphora, nasal and conjunctival hyperemia, ptosis, edema of eyelids, fever, neck stiffness, and sweating.

It is important to know about present and previous treatments that have been tried and on what basis these treatments are taken and the reason for their discontinuation if any and regarding patient’s previous medical history (anxiety, depression, and sleep disorders), current treatment for non-headache diseases, family history (of headache), and social history (regarding occupation, smoking, alcohol, and caffeine consumption).

If structured approach to history taking is strictly followed and proper headache diary is maintained then necessary information that is needed for most probable diagnosis can easily be gathered and gaps in patient’s history can be easily filled without specifically asking patient.

Examination

The main aim of examination is to consider regarding organic brain disease and to screen for accompanying comorbid diseases such as hypertension, depression, etc., and also to reassure the patient and their family regarding disease. A thorough neurological examination assessing cognitive, sensory, motor system along with the fundoscopy for the pappilledema is must.

Investigate Appropriately

Decision about investigation done on migraine patients are driven by two most common cultural myths. The first myth being the brain tumor common cause of headache followed by abnormal blood tests or scan results based diagnosis of migraine. The goal of investigation is to

<table>
<thead>
<tr>
<th>Tests</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with ESR</td>
<td>Temporal arteritis</td>
</tr>
<tr>
<td>CSF analysis</td>
<td>For fever with headache patients</td>
</tr>
<tr>
<td>X-ray PNS</td>
<td>For sinusitis</td>
</tr>
<tr>
<td>X-ray chest</td>
<td>Consider in smokers or with metastatic cancers</td>
</tr>
<tr>
<td>X-ray cervical spine</td>
<td>Cervical spondylosis</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Due to its greater sensitivity and capability of visualizing intracranial structures it is preferred for all subacute and chronic presentations of headache</td>
</tr>
<tr>
<td>CT</td>
<td>Useful in patients presenting with abrupt onset of headache and to find rare brain tumors, subarachnoid hemorrhage, and chronic subdural hematomas</td>
</tr>
<tr>
<td>EEG</td>
<td>Useful in evaluation of patients with headache, loss of consciousness and to diagnose basilar migraine in addition to differentiation of organic headache</td>
</tr>
</tbody>
</table>
exclude other causes of migraine like symptoms not to confirm migraine. The following are the investigations required for those headache patients with unusual signs and symptoms are CBC with ESR, Chest X-ray, X-ray PNS, X-ray C spine, CSF fluid analysis, CT/MRI brain, and EEG (Table 1).

**Differential Diagnosis**

- Tension type headache
- Cluster headache
- Idiopathic stabbing headache
- Medication overuse headache

**Conclusion**

Migraine presents a major diagnostic and therapeutic challenge to general physicians and neurologists. Patients with unstable or progressive pattern headache, an abnormal examination or an association with features unusual for migraine should trigger further evaluation. According to studies there is a general disenchantment of migraine patients with their physician and a widespread problem of analgesic overuse. These problems may be overcome by programs of education for the public, physicians, and neurologists, patient should be made aware of the dangers of the analgesic abuse and of the availability of appropriate and more effective migraine treatments.

**References**

Abstract
Vascular dementia is a disease, carrying a great history of understanding, dates back to 19th century, when pathologists identified arteriosclerotic changes in the brain vessels, supplying the gray and white matter of the brain, was contemplated as senile dementia. The main problem was the identification of vascular dementia was submerged in the wide understanding of Alzheimer’s disease (AD), which was dominating the understanding of dementia, along with identification of frontotemporal dementia. In the elderly citizens, who are prone for atherosclerotic changes in the vessels offer great contribution to the development of dementia. Vascular dementia (VAD) is now understood along with vascular cognitive impairment (VCI) not only includes VAD, but also AD with ischemic cerebral lesions and VCI without dementia. The identification of VAD is essential, in the concept of management of dementia, which in other conditions are progressive. The therapeutic amenability of VAD makes it as a distinctive entity in the early stage of the disease. Subcortical vascular ischemia with dementia (SIVD) is identified by the severe degree of occlusion of small vessels that ramify into the white matter, causing occlusion, resulting in multiple lacunar infarctions in the subcortical structures. The differentiating issues with AD and SIVD may by difficult by assessing the cholinergic deficits, but the recent progress of in vivo amyloid imaging studies could relatively identify the separate entity of SIVD, from AD, where in the amyloid plaques are absent in SIVD. The upcoming concepts between VAD/VCI and their clinical concepts give wonderful idea about the management of the SIVD.

Introduction
SIVD is widely identified disease of slowly progressive dementia, in contrast to the classical Alzheimer’s disease and frontotemporal dementia, which are due to development of degeneration and infiltration of amyloidal plaques into the gray matter of the brain, causing shrinkage of the brain matter. There are some distinct identifiable clinical observations between these diseases, and the main benefit of understating the SIVD is its amenability to the treatment. Hence, identification of SIVD become mandatory, and excluding it from other forms of dementia, since other forms of dementia are difficult for management. The identification of subcortical white matter lacunes becomes one of the major components of identification of SIVD, which depending on its location makes the clinical manifestations, as well its volume of affected brain matter. Vascular dementia (VAD), due to CVD, that directly or indirectly damages the neurons associated with cognitive activity. It is also identified that in majority of AD cases, vascular lesions becomes a coexisting factor, contributes heavily in the pathogenesis of dementia, with the existing degenerative brain parenchyma. The recent postulation of vascular cognitive impairment (VCI), which embraces both VAD, AD with CVD—sometimes labeled as mixed dementia. More so, another entity also identified as VCI with no dementia (VCIND). VCI becomes a larger term that would include all the stages of cognitive impairment associated with CVD.
Indian Scenario of Vascular Dementia

VAD is a complex presentation in clinical practice. Varied presentations are observed in clinical practice. Its symptoms are not homogenous, but highly variable. The incidence of VAD is ubiquitous in India, but still now exact incidence is not clearly available, even though quite an amount of data is available in the literature. In a cohort study, where in NINDS-AIREN criteria were used to diagnose VAD. Patients were subtyped into subcortical, cortical, cortical-subcortical, and infarct may be quite tiny, but in a strategic location, may present as dementia. In a study by Suvarna Alladi et al., dementia in developing countries: Does education play the same role in India as in the West? over 42 patients with VAD, subcortical dementia was the most common type (52.4%), followed by cortical-subcortical (26.2%), strategic infarcts (14.3%), and cortical dementia (7.1%). Stroke (81%), hypertension (71.4%), and diabetes (35.7%) were principal risk factors. Small artery disease was the elementary vascular mechanism in 42.9%; intracranial large artery disease, in 16.7%; extracranial disease, in 2.3%; cardioembolism, in 2.3%; multiple mechanisms, in 19%; and unknown, in 16.7%. Subtypes were similar in associated risk factors and neuropsychological features but differed in clinical correlates and vascular mechanisms. The results and clinical presentations is highly dependent on the underlying mechanism, pathology, extent and location of the infarct, which may differ in different ethnic groups.4,5

Pathophysiology

The main issue involving VAD is generated from vascular lesions. These lesions may be large like a major artery occlusion or tiny perforators, causing lacunar infarcts. These lacunar infarcts, even though they are tiny, when happens in multiple areas, and constitute a major brain volume affection, the dementia evolves. More so, tiny infarcts in strategic locations like frontal lobe, temporal lobe, or brain stem do affect the higher mental function critically. Hence, the deciding factors are volume of infarction, or location of the infarction. Once the ischemic process begins, axonal degeneration results, from the neuronal damage, Wallerian degeneration results, especially more in the white matter subcortical lesions. Neuronal interconnections become a gross impediment in the thought process, ranging from minimal cognitive impairment to a progressive dementing illness.

Recent Concepts in VAD and VCI

The following classification is widely adopted among neurologists across the world:
- Multi-infarction dementia,
- Strategic infraction dementia,
- Hemorrhagic dementia,
- Mixed dementia,
- SIVD, and
- Other forms of vascular dementia.6,7

Strategic infarction dementia, hemorrhagic dementia, does develop in a rapid fashion clinically due to acute cerebrovascular diseases. A stepwise progression, inherent fluctuation of clinical presentation of symptoms, and focal neurological signs are suggesting the development of acute VAD. With SIVD, cognitive impairments are often sneaky in its onset, while later decline progressively, like in classical AD.8

Classical motor symptoms is not most often demonstrable clinically, sometimes unnoticeable, further confusing clinicians. Existence of pure SIVD has been reported in studies related to amyloid imaging, where significant subcortical white matter ischemic changes were evident with no trace of deposition of amyloid plaques. Pure SIVD is distinct from AD or mixed dementia, which demonstrate fibrillar forms of amyloid deposition in the brain.9

Various other types of VAD include dementia where in the etiologies are heterogeneous, for example, cerebral amyloid angiopathy, hereditary diseases (such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [CADASIL] and vasculitis.10-12

On the issues of mild cognitive impairment (MCI) due to AD or early phase of AD, it is observed that accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles (NFT) in the brain. These deposits and NFT do hinder the neuronal transmission, interfering with the thought process of the patients suffering from AD. But, the understanding of VCI identifies potentially treatable and preventable components of dementia. It is worth observing that after the establishment of cognitive impairment, the vascular potential risk factors, can be clinically intervened, and there is a chance of rectification of clinical symptoms, and mostly it prevents secondarily in the newly occurring ischemic zones, toward worsening of symptoms in contrast to AD.13

It is also observed that small vessels which are deeper in the brain do have multiple changes due to atherosclerosis,
and also due to various small vessel diseases, causing SIVD, in senior citizens, very commonly which is a finding recently observed, by many workers.\textsuperscript{14}

**Pathophysiology of SIVD**
- Marked ischemic change in the brain, due to discrete and incomplete infarctions which may be tiny in character.
- Hypo or diminished perfusion of blood into the white matter, due to critical occlusion of the perforators and medullary branches of the cerebral vasculature.
- There is a typical white matter lesions resulting in ischemia of neurons, oligodendrocytes, Wallerian degeneration of the myelin sheath and axons. The lacunar infarctions (étatlacunaire) are a result of perforating arteriolar occlusions within the subcortical structures, including basal ganglia, thalamus and external and internal capsules. It is observed that there are decreased auto regulation, BBB disruption, endothelial dysfunction, resistance to blood flow, and dilatation of perivascular spaces.\textsuperscript{15}
- Consequent these vessel changes and subclinical infarctions there is gross disruption of the prefronto-subcortical circuits and thalamocortical circuits due to white matter ischemic lesions and lacunar infarctions.
- These disruptions are the causative factors for the ongoing dementia and cognitive impairment in SIVD. There are some evidences that A-beta plaques, neurofibrillary tangles are visualized in the SIVD, which is also thought to be a consequent issue due to ischemia of the brain structures.\textsuperscript{16}

**Clinical Manifestations of SIVD and Its Associations with Structural and Functional Brain Images**

The mainstay in the SIVD is the cognitive impairment of varying degree, its stepwise development along with the neurological deficits is common. Abnormal behavior disorders like disinhibition and akinetic mutism are common if the prefronto subcortical circuits are damaged directly or as a secondary effect of ischemia.\textsuperscript{17}

Other findings are uncommonly hemiparesis, peripheral speech disorders, pseudobulbar palsy, urinary incontinence, and features of extrapyramidal involvement when the ischemia is in basal ganglia especially in putamen. Impairment of attention, poor verbal fluency may manifests in early phase of SIVD (Table 1).\textsuperscript{18,19}

Still there are studies in progress which can differentiate SIVD from mixed dementia by establishing the clinical, imaging studies, especially from studies available with amyloid PET imaging.

**SIVD Biomarkers**
So far various studies have been observed, without any conclusive evidence of any biomarkers. Many of the recent longitudinal studies have met with results that they proceed ultimately to AD. In VAD, the novel genetic variants discovered could be presumably used as potential biomarker for diagnosis and treatment.

The field of pharmacogenetics is a beacon of hope in VAD for improving drug efficacy and safety. Causal gene identification is highly limited to monogenic form of VAD, while by evidence VAD of sporadic form is less probable. For future research, more homogenous subgroups with a larger and heavier sample sizes are essential. For further genetic investigations in VAD, endophenotypes look as a promising research tool. Apart from genome wide association studies (GWAS) and gene analysis studies, focus on epigenetic modifications and microRNAs are also increasing. The therapeutic implications of the same have to be evaluated in future, depending on the evidences available time of time. BBB (blood brain barrier) disruption is one of the beneficial situations for future analysis. Significant, biodegradation products are

**TABLE 1** Differential diagnosis clinical features between SIVD and AD

<table>
<thead>
<tr>
<th>Higher cognitive functions</th>
<th>Vascular dementia (SIVD)</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Grossly impaired</td>
<td>Mildly impaired</td>
</tr>
<tr>
<td>Language and understanding</td>
<td>Decreased output and fluency</td>
<td>Poor recalling and naming</td>
</tr>
<tr>
<td>Visuospatial orientation</td>
<td>Fair and mild affection</td>
<td>Gross affection</td>
</tr>
<tr>
<td>Memory functions all types</td>
<td>Moderate loss</td>
<td>Gross and severe loss</td>
</tr>
<tr>
<td>Frontal lobe executive functions</td>
<td>Severe loss</td>
<td>Moderate loss</td>
</tr>
</tbody>
</table>
identified, which include increased albumin leakage in CSF. It is also observed that certain metalloproteinases are observed to be available as markers of neuroinflammation, as they disrupt the basal lamina, tight junctions of blood vessels, with disruption of myelin. The levels of metalloproteinases-9, in CSF, are observed to be increased in VAD. The concentration of the neurofilament cytoskeleton, which may give hall mark for white matter disruption of large myelinated axons, observed to be higher in patients with SIVD.20

Several different results have been reported with biomarker studies on VAD/VCI patients. A recent study compared the biomarkers from CSF of four groups, namely MCI group that remained stable as MCI (MCI-MCI); SIVD (MCI-SIVD); mixed dementia (MCI-MD); and MCI group that finally progressed to AD (MCI-AD). It was reported that the levels of phosphorylated and total tau (T-tau) were lower, while that of A\(\beta\) were higher in the MCI-SIVD than the MCI-AD group. In the MCI-MD group, biomarker levels in the CSF were between those levels of MCI-SIVD and MCI-AD group. CSF levels of MD-SIVD were closer to the levels of control group and the MCI-MCI group. The intermediate levels of CSF biomarker levels of tau and A\(\beta\) in the SIVD group as compared to MCI-MD and control groups indicate a common pathology of SIVD with AD. The biomarker levels in the CSF of VAD and AD patients when compared, it is observed that A\(\beta\) levels are lower, while tau levels are higher in AD patients as compared to VAD patients. However, overlaps have been observed between the two. No such differences were observed between the biomarker levels in non-elderly individuals, who had mild, moderate, or severe white matter hyperintensities.

Alternative biomarkers associated with SIVD include those related to BBB breakdown. Albumin leakage can result following BBB breakdown, increasing the protein concentration in the CSF as a result. In view of this, increased albumin levels are supportive as evidence of SIVD. MMPs are attributed as neuroinflammatory markers, as they attack the blood vessel tight junctions and basal lamina, apart from disrupting the myelin. MMP-9 levels were increased in CSF of VCI patients as compared to AD patients. Neurofilament is another important white matter disruption marker. Neurofilament acts as a cytoskeleton in large myelinated axons. In individuals with higher neurofilament levels, SIVD is prominent. In non-demented individuals with severe white matter lesions, similar findings were reported. As described previously, advanced imaging techniques can help serve as potential biomarkers, enabling understanding of underlying pathophysiology of SIVD.

**Imaging in SIVD**

One of the promising diagnostic identification of SIVD is done in imaging studies. MRI imaging appears to be a superb identification tool, than CT of higher resolution, along with the MR angiography to identify the affected territory. Tiny infarcts in common locations like cortical, subcortical, exceeding a volume of more than 50 cc, or any small tiny insignificant volume of infarct in a strategic location, results in high degree of clinical manifestations (Refer Figs. 1 and 2). Hence, it is observed by MRI studies, that it is not the multiplicity, but its location and total volume of gray matter involvement or white matter connect ions, manifests in clinical syndromes. PET scan also observed to be quite useful in identifying ongoing infarct, or preimaging status of the infarcts, which would be useful in assessment of management of the disease. It is almost emphasized as on current state of affairs, more than bio markers, imaging studies are highly efficient in identifying the diseases at an early state.

- Large areas of infarction or hemorrhage post stage with severe brain substance damage, both gray and white matter.
- Decreased diffusion anisotropy in the places of white matter hyperintensities, amyloid PET imaging for routine diagnosis of AD, myloid PET imaging can be clinically useful for differentiating pure SIVD and mixed dementia, which sometime can be challenging to distinguish and would give rise to diagnostic dilemmas.

**Role of Neurophysiological Studies**

It is not the issue that neurophysiological studies like cortical evoked potentials, EEG, and BAER also play an important role in identifying the interrupting pathways well in advance to imaging studies. But it needs heavy and careful scrutiny to identify such subtle changes, to inform the clinicians about the development of SIVD.

**Strategies for Treatment of SIVD**

- Major treatment strategies include improving the obvious clinical symptoms at the same time mitigating the underlying small vessel disease progression.
An important significant factor contributing to cognitive impairment and brain atrophy is microinfarct pathology. By regulating small vessel disease, once can administer antiplatelets agents as a means of secondary stroke prevention.

For the primary prevention of VCI, antiplatelet agents as a means of therapy are not established yet. Due to its vasodilatory effect, nimodipine, a calcium channel blocker, has been found as a potential agent for SIVD treatment. In early clinical trials for VAD, nimodipine was found to be successful, following which an “intention to treat” trial with 230 patients was conducted. The set primary end point was not achieved in the trial, although, positive results were obtained in the mini mental state examination and global deterioration scale, along with improvement in language production.

For managing cognitive symptoms, the uses of cholinesterase inhibitors have been implicated. SIVD associated cholinergic deficits are well defined from the findings that perforating arterioles supply the basal forebrain cholinergic nuclei and that hippocampal CA1 region is highly vulnerable to ischemia.

Deficits in the cholinergic fibers have been identified in CADASIL patients. In view of which, cholinesterase inhibitors have brought in for the treatment of cognitive impairments of VAD, which are linked with deficits of the cholinergic fibers. Beneficial effects on cognitive functioning of cholinesterase inhibitors were observed in a randomized controlled drug trial on CADASIL patients. In another CADASIL study, donepezil, a cholinesterase inhibitor did not show improvement in the primary endpoints. A subgroup analysis on the other hand indicated improvement in the treatment group in executive functions. Associated behavioral changes can be managed by use of atypical neuroleptics while depression can be managed by the use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs). For preventing AD and VCI, modification of cardiovascular risk factors has been suggested. The risk factors include diabetes, hypercholesterolemia, and hypertension. Associated lifestyles changes in diet, physical activity, smoking, obesity, alcohol consumption, etc. may also help manage VCI.

Nimodipine 30 mg once daily, donepezil 10 mg, maintain till the higher cognitive functions become stable.

**Abbreviations**

- AD, Alzheimer’s disease
- SIVD, subcortical ischemic vascular disease
- VAD, vascular dementia
- VCI, vascular cognitive impairment
Conclusion

VAD is a diverse condition encompassing various conditions. SIVD can imitate AD, and as like AD, SIVD also demonstrates a slow progression in cognitive decline. Changes in mood and behavior, along with impairments in frontal executive symptoms can be revealed by carrying out neuropsychological tests and extensive medical histories. Dementia from other causes can be differentiated from SIVD by the help of neuroimaging studies and identifying specific CSF biomarkers. Proper management and early treatment of SIVD along with secondary stroke prevention can be accomplished effectively by clinicians by reviewing carefully a patient’s medical history, his test reports obtained following neurological examinations, structural/functional neuroimaging, biomarker analysis, etc. Means of making the treatment and diagnosis of SIVD more effective and efficient include development of diverse experimental SIVD model for thorough understanding of the pathology. Identifying and corroborating the specific biomarkers will also assist in improving treatment strategies. Maintaining a database of extensively collected details from longitudinal studies, data from imaging and biomarker studies for subcortical vascular MCI and SIVD is required, which can be shared with fellow scientists and researchers for ensuring better management of the disease condition. Standardization methods for vascular lesions in neuroimaging and neuropathologies are underway. However, miles are to be covered before the concept of SIVD can be incorporated in clinical practice and be accepted widely.

References

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated disorder of peripheral nerves and radicles. It is usually a symmetrical, non-length-dependent hyporeflexic neuropathy, involving both proximal and distal limbs, with motor and sensory deficits, progressing over at least 08 weeks. Although a rare entity, it is thought to represent about one-fifth of all initially undiagnosed neuropathies, and is one of the commonest treatable neuropathies worldwide. Pathophysiologically, it is characterized by immune-mediated loss of myelin, resulting in slowed/blocked nerve conduction. Many new paranodal proteins, which may be specific targets of immune attack in some subsets of CIDP, have been described. Clinically, it differs from Guillain-Barre syndrome (GBS) with respect to the onset and duration of symptoms, as well as prominent involvement of sensory nerves. In contrast to GBS, which is monophasic, CIDP is a chronic, relapsing-remitting illness, and requires long-term immunosuppression. Corticosteroids, plasmapheresis, and intravenous immunoglobulin (IVIg) are the recommended first-line therapies, and 50–90% patients respond to one of these. Apart from this, many atypical variants of CIDP have also been described. The EFNS/PNS Criteria 2010 are used to diagnose CIDP on the basis of clinical and electrophysiological data. After the first-line treatment, long-term immunosuppression is usually given in the form of either oral drugs such as azathioprine, methotrexate, mycophenolate, or biologicals such as rituximab. Subcutaneous IVIg has been recently approved as a maintenance therapy for CIDP. Few validated scoring systems are available for objectively documenting the response to therapy. The aim, in the long term, is to balance risk of early relapse with the need to avoid overtreatment and immunosuppression. Overall, CIDP remains one of the few chronic neuropathies that are readily treatable, and early diagnosis and appropriate treatment are crucial to improve the patient’s quality of life.
Epidemiology
CIDP is a disease of adulthood, and its prevalence increases with increasing age. In patients less than 19 years of age, the prevalence is 0.23–1.26 per 100,000; while it increases up to 5.74–14.37 per 100,000 in ages above 60 years. It is 1.6–2.9 times more common in males. It is also more common among diabetics, though exact figures are debatable.

Pathophysiology
CIDP is characterized by immune-mediated loss of myelin, predominantly in the spinal roots, proximal nerve trunks, and major plexuses, but it can also be disseminated throughout the peripheral nerves. This causes slowing of nerve conduction and/or conduction block.

Myelinated axons only allow action potentials at the nodes of Ranvier between the myelinated internodes (saltatory conduction), and they propagate the action potential at rates significantly higher (70–150 m/sec) than in unmyelinated neurons (0.5–10 m/s) (Fig. 1).

Both cell-mediated and humoral mechanisms are involved in pathogenesis of CIDP. It is considered an autoimmune response against some unidentified Schwann cell/myelin antigen. The trigger for this autoimmune response is also unknown.

Cellular mechanisms are implicated on the basis of inflammatory infiltrates in nerve biopsies, changes in the frequencies/function of T-cell subsets, altered expression of cytokines in blood and CSF of patients, and the role of T-cells in experimental autoimmune neuritis (EAN) model.

Deposition of immunoglobulins and complement on the surface of Schwann cells and myelin in sural nerve biopsies, and rapid response to plasmapheresis indicate the role of humoral immune-system.

Proteins in and around the node of Ranvier are also involved. The paranode consists of contactin-1/CASPR-1 (contactin associated protein-1) complexes, which bind to Schwann cell neurofascin-155 (NF155). They are vital for the initial clustering of sodium (Na+) channels, and maintenance of clustering at the node, acting as a membrane barrier to limit diffusion of ion channels essential for saltatory conduction. They undergo immune-attack in several anti-ganglioside-mediated “nodoparanodopathies.” Antibodies against NF155 have been identified in 4% of CIDP cases. An additional subset of CIDP has been identified with autoantibodies against contactin-1/CASPR-1 complex.

Clinical Features
Typically, patients have relatively symmetric proximal and distal weakness (non-length dependent), along with sensory dysfunction in the form of paresthesias, numbness, sensory ataxia, and uncommonly pain. By definition, these symptoms must progress for at least 8 weeks. On examination, profound hyporeflexia/areflexia is characteristic.

Though motor weakness is often more prominent and disabling, sensory loss occurs in up to 90% of patients, and is greater for vibration and proprioception than pain and temperature. Pain is rare initially, but is present in up to 70% of patients in the long term.

Uncommon features:
- Cranial neuropathy—up to 20% cases: facial nerve (10–15%) or oculomotor nerve (5%)
- Back pain—lumbar canal stenosis or cauda equina syndrome can occur rarely if there is marked nerve root swelling or hypertrophy
- Distal neuropathic tremors—up to 50% of patients
- Dysautonomia—mild, limited distribution
- Respiratory failure—extremely rare (<5%), must prompt search for alternate diagnosis

There are also variations in onset and course of CIDP (Table 1).

Acute onset and relapsing forms are difficult to distinguish from Guillain-Barré syndrome (GBS) (Table 2). Patients with GBS-like presentation who progress beyond 8 weeks, or relapse beyond 2 months or more than twice, are considered to have CIDP.
### TABLE 1
Variations in onset and course of CIDP

<table>
<thead>
<tr>
<th>Onset (duration between onset to worst weakness)</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (&lt;4 weeks)</td>
<td>2–16% cases Chronic progressive Around 2/3rd</td>
</tr>
<tr>
<td>Subacute (4–8 weeks)</td>
<td>17–35% Relapsing-remitting Between 18–33% (more common in younger patients)</td>
</tr>
<tr>
<td>Gradual (&gt;8 weeks)</td>
<td>&gt;50% Monophasic Between 10–25% (more common in children)</td>
</tr>
</tbody>
</table>

### TABLE 2
Differences between GBS and CIDP

<table>
<thead>
<tr>
<th>Features</th>
<th>GBS</th>
<th>CIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
</tr>
<tr>
<td>Nadir of weakness (from onset)</td>
<td>&lt;4 weeks</td>
<td>&gt;8 weeks</td>
</tr>
<tr>
<td>Antecedent events (infections, vaccination, etc.)</td>
<td>&gt;70% cases</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Sensory features</td>
<td>Less prominent</td>
<td>More prominent</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>65%, may be severe</td>
<td>25%, may be mild</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Apart from this, there are many other clinical variants of CIDP, which are syndromically distinct (Table 3).

Some clinical conditions may predispose a patient to CIDP. They should be investigated in all patients, because treatment of the primary underlying disease may sometimes lead to improvement of neuropathy (Box 1).17

### Diagnosis
Currently, EFNS/PNS criteria-2010 are the most widely accepted diagnostic criteria (Table 4).18 Maximum emphasis is placed on clinical and electrophysiological evidence of demyelination. All other investigations are supportive. The second revision of these criteria has just started, and further changes are expected.19

### Differential Diagnosis

**Immune mediated:** GBS, MMN, drug-induced demyelinating neuropathy [TNF-alpha inhibitors- (infliximab, etanercept, adalimumab), tacrolimus, checkpoint inhibitors, bortezomib].

**Metabolic:** Diabetic and rarely, uremic neuropathies.

**Systemic diseases:** Amyloidosis, sarcoidosis, lymphoma, paraproteinemia-associated neuropathy, POEMS.

**Infections:** Neuroborreliosis, diphtheria, leprosy, HIV-associated neuropathy or radiculopathy, CMV-radiculopathy.

**Hereditary:** Hereditary neuropathy with pressure palsy, Charcot Marie Tooth disease, Fabry disease, Refsum disease, mitochondrial neuropathies.

### Treatment
Corticosteroids, plasmapheresis and IVIg are approved first-line therapies for the treatment of CIDP.4,5

**Steroids:** Treatment is initiated with high dose/pulse of oral or injectable steroids. Regimens proven in trials include daily prednisolone (1–1.5 mg/kg), dexamethasone pulses, methylprednisolone intravenous or oral pulses. High dose should be maintained for at least 3–6 months, when the disease plateaus, after which gradual taper may be attempted. Relapse rates are unacceptably high; so, a steroid-sparing agent should be added with the initial regimen, so that by the time steroid taper is started, the other immunosuppressant is effective.4,20

**IVIg:** The ICE study established the role of IVIg as a first-line therapy.21 Dose—2 gm/kg divided over 5 days. Maintenance doses may be required every 4–8 weeks.22
**TABLE 3** Clinical variants of CIDP

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis-Sumner syndrome ([Also called multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)]</td>
<td>Strikingly asymmetrical sensory and/or motor deficits in individual nerve distributions, clinical and electrophysiological motor and sensory involvement, (distinguishing it from multifocal motor neuropathy), steroid responsive(^{13,16})</td>
</tr>
<tr>
<td>Chronic Immune Sensory Polyradiculopathy (CISP)</td>
<td>Sensory ataxia due to inflammation restricted to dorsal roots—progressive numbness, ataxia, hyporeflexia, normal power. Nerve conduction studies (NCS) usually normal, but somatosensory evoked potentials (SSEP) shows prolongation. MRI may show enhancing radicles(^{13,16})</td>
</tr>
<tr>
<td>Sensory-Predominant CIDP ([Chronic sensory demyelinating neuropathy])</td>
<td>Prominent sensory ataxia, pain, and paresthesias. Despite the lack of weakness, NCS shows significant motor conduction slowing 10% of CIDP, responds well to IVIg(^{13,16})</td>
</tr>
<tr>
<td>Distal Acquired Demyelinating Symmetric Neuropathy (DADS)</td>
<td>Symmetric, sensory, or sensorimotor starting distally in the lower limbs, without proximal involvement (length-dependent). Slowly progressive, frequently (nearly 2/3rd) associated with IgM paraprotein. Approximately 50% DADS with IgM also have anti-MAG antibodies. Tends to be resistant to standard therapies for CIDP(^{13,16})</td>
</tr>
<tr>
<td>Pure Motor CIDP</td>
<td>Rare (2–5%)—involvement of motor and sparing of sensory fibers. Non-segmental pattern of weakness, lack of bulbar involvement, demyelinating electrophysiological abnormalities, and response to immunotherapy distinguish it from motor neuron disease(^{19})</td>
</tr>
<tr>
<td>Neurofascin antibody-mediated CIDP</td>
<td>IgG(_4) autoantibodies to neurofascin-155(NF155). Younger age at onset, more common sensory ataxia and tremor. Often responsive to B cell depletion therapy (e.g., rituximab), less response with IVIg(^{19})</td>
</tr>
<tr>
<td>Contactin-1 antibody-mediated CIDP</td>
<td>Clinical phenotype not well established, often characterized by advanced age, rapid onset and severe, predominantly motor, and early axonal involvement. May also be responsive to B cell depletion, and refractory to IVIg(^{11})</td>
</tr>
<tr>
<td>CANOMAD ([Chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies])</td>
<td>Similar to the Miller Fisher variant of GBS, though chronic in nature (disialosyl ganglioside is GQ1b). Other associated IgM antibodies include GD1a and GD1b, which cause a sensory-predominant disorder</td>
</tr>
<tr>
<td>Localized variants</td>
<td>Limited chronic focal upper limb variant and chronic inflammatory lumbosacral polyradiculopathy (considered a regional lower extremity variant of CIDP), responsive to IVIg(^{12})</td>
</tr>
</tbody>
</table>

**BOX 1** Conditions associated with CIDP

- Hepatitis C
- Lymphoma
- Monoclonal gammopathy of undetermined significance (MGUS)
- HIV/AIDS
- Organ transplant recipients
- Connective tissue disorders (notably SLE and Sjogren’s syndrome)
- Inflammatory bowel disease
- Melanoma
- Diabetes mellitus

**Plasmapheresis (PLEX):** In a rapidly deteriorating patient, PLEX is the best treatment.\(^{4,5}\) Usually, 5–7 cycles are performed over 2–4 weeks. Improvement begins within days, but relapse rates after stopping are very high (70%, 14 days after stopping PLEX). Therefore, additional immunosuppressive medication must be used. It is preferred, if patients are very weak, rapidly deteriorating, or unresponsive or intolerant to steroid or IVIg.\(^{4,8,12,13,18}\)

**Subcutaneous immunoglobulin (SCIG):** PATH study (2018) comparing low-dose SCIG (0.2 g/kg), high-dose SCIG (0.4 g/kg), and placebo, showed absolute risk reduction (for relapse) of 25% for low-dose, and 30% for high-dose SCIG compared to placebo.\(^{23}\) Therefore, SCIG seems to be a promising agent, but requires further large-scale studies to establish dosing protocols.

**Biological agents:** Rituximab was shown to be effective in a small retrospective Italian study.\(^{4,5}\) In refractory CIDP, and patients with NF-155 or CASPR-1 associated disease, it has been stated to be an effective drug.\(^{10,11}\) The RECIPE trial, started recently, hopes to shed more light on its role in CIDP.\(^{24}\)
### TABLE 4
EFNS/PNS 2010 criteria for CIDP

**Clinical criteria**

- **Inclusion criteria**
  - **Typical CIDP**
    - Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities
    - Duration ≥2 months
    - Absent/reduced DTRs in all extremities
  - **Atypical CIDP**
    - Predominantly distal (DADS)
    - Asymmetric (MADSAM)
    - Focal (e.g., involvement of the brachial or lumbar sacral plexus, or of one upper or lower limb)
    - Pure motor
    - Pure sensory (including CISP)

- **Exclusion criteria**
  - Neuroborreliosis, diphtheria, drug, or toxin exposure probable to have caused neuropathy
  - Hereditary neuropathy
  - Prominent sphincter disturbance
  - Multifocal motor neuropathy (MMN)
  - Other causes—POEMS, osteosclerotic myeloma, diabetic and non-diabetic lumbar sacral radiculoplexus neuropathy, peripheral nervous system (PNS) lymphoma, amyloidosis

- **Supportive criteria**
  - Elevated CSF protein with leukocyte count <10/mm³
  - MRI: Gd-enhancement and/or hypertrophy of cauda equina, nerve roots, or brachial or lumbar sacral plexuses
  - Abnormal sensory electrophysiology in at least 1 nerve:
    - Normal sural with abnormal median or radial sensory nerve action potentials (SNAP)
    - Conduction velocity <80% of lower limit of normal (LLN) (<70%, if SNAP amplitude <80% of LLN)
    - Delayed SSEP without CNS disease
  - Objective clinical improvement following immunomodulation
  - Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis

**Electrophysiological criteria**

- **Definite:** At least one of the following:
  - Motor distal latency ≥50% above upper limit of normal (ULN) in two nerves (excluding median neuropathy at the wrist), or
  - Reduced motor conduction velocity ≥30% below LLN in two nerves, or
  - Prolonged F-wave latency ≥30% above ULN in two nerves (≥50%, if motor amplitude <80% LLN), or
  - Absent F-waves in two nerves if these nerves have distal motor amplitudes ≥20% of LLN + ≥1 other demyelinating parameter in ≥1 other nerve, or
  - Partial motor conduction block: ≥50% proximal motor amplitude reduction relative to distal, if distal amplitude ≥20% LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve, or
  - Abnormal temporal dispersion (≥30% duration increase between the proximal and distal CMAP) in ≥2 nerves, or
  - Distal CMAP duration increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms) + ≥1 other demyelinating parameter in ≥1 other nerve

- **Probable:** ≥30% amplitude reduction of the proximal CMAP relative to distal, excluding posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve

- **Possible:** As in “definite” but in only one nerve
### TABLE 5  Overall disability sum score

<table>
<thead>
<tr>
<th>Arm disability scale – function checklist</th>
<th>Not affected</th>
<th>Affected but not prevented</th>
<th>Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing upper part of body (excluding buttons/zips)</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Washing and brushing hair</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Turning a key in a lock</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Using knife and fork (/spoon—applicable if the patient never uses knife and fork)</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Doing/undoing buttons and zips</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

#### Arm grade
0 = Normal  
1 = Minor symptoms or signs in one or both arms but not affecting any of the functions listed  
2 = Moderate symptoms or signs in one or both arms affecting but not preventing any of the functions listed  
3 = Severe symptoms or signs in one or both arms preventing at least one but not all functions listed  
4 = Severe symptoms or signs in both arms preventing all functions listed but some purposeful movements still possible  
5 = Severe symptoms and signs in both arms preventing all purposeful movements

<table>
<thead>
<tr>
<th>Leg disability scale – function checklist</th>
<th>No</th>
<th>Yes</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you have any problem with your walking?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Do you use a walking aid?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>How do you usually get around for about 10 metres?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Without aid</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>With one stick or crutch or holding to someone’s arm</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>With two sticks or crutches or one stick or crutch and holding to someone’s arm</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>With a wheelchair</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>If you use a wheelchair, can you stand and walk a few steps with help?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>If you are restricted to bed most of the time, are you able to make some purposeful movements?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

#### Leg grade
0 = Walking is not affected  
1 = Walking is affected but does not look abnormal  
2 = Walks independently but gait looks abnormal  
3 = Usually uses unilateral support to walk 10 metres (25 feet) (stick, single crutch, one arm)  
4 = Usually uses bilateral support to walk 10 metres (25 feet) (sticks, crutches, two arms)  
5 = Usually uses wheelchair to travel 10 metres (25 feet)  
6 = Restricted to wheelchair, unable to stand and walk few steps with help but able to make some purposeful leg movements  
7 = Restricted to wheelchair or bed most of the day, preventing all purposeful movements of the legs (e.g., unable to reposition legs in bed)

Overall disability sum score = arm disability scale (range 0–5) + leg disability scale (range 0–7); overall range: 0 (no signs of disability) to 12 (maximum disability).

For the arm disability scale: Allocate one arm grade only by completing the function checklist. Indicate whether each function is “affected,” “affected but not prevented,” or “prevented.”

For the leg disability scale: Allocate one leg grade only by completing the functional questions.
Other immunosuppressive agents: Methotrexate, azathioprine, and mycophenolate mofetil are common steroid-sparing agents. Cyclosporine and cyclophosphamide are also used as second-line agents.

Strength-training exercises and gradual weight bearing, along with orthotics (when required) are also extremely important for recovery. Symptomatic treatment for neuropathic pain, dysesthesias, tremors, and dysautonomia is given as clinically indicated.

Most patients show maximum benefit from IVIg or steroids by 3rd month. If a clear treatment response is not documented by 3–6 months, the drug, dosage, or diagnosis should be reconsidered. Once maximum benefit is achieved, structured dose reduction or optimization may be attempted. However, the strategy to best taper treatment is unknown. Objective documentation of treatment response may help in such decision-making. INCAT-ODSS (Inflammatory Neuropathy Cause and Treatment-Overall Disability Sum Score) scale for disability assessment, and CDAS (CIDP Disease Activity Status) scheme for disease activity are two such scoring systems (Tables 5 and 6). The aim is to balance risk of early relapse with the need to avoid overtreatment and immunosuppression.

Prognosis

Overall, CIDP is a treatment-responsive neuropathy, and 50–90% patients respond to one of the first-line therapies. Lack of response must prompt search for alternative etiology. Poor prognostic factors are rapidly progressive disease, early axonal changes on NCS, advanced age, delayed initiation of therapy, and high proportion of fibers showing demyelination on biopsy. A recent study also identified certain patterns on nerve ultrasound at the time of diagnosis, which may predict good response to treatment. In the original series by Dyck et al. (1975), 60% were ambulatory, 25% wheelchair or bed-bound, and 10% died. This figure has significantly improved with advances in diagnosis and treatment, and in a recent 14-year study of Danish patients, 53% could discontinue treatment, only 6% had severe morbidity, and 1% died. However, CIDP is a lifelong disease that invariably results in some residual disability even with effective therapies.

Conclusion

CIDP is a treatable immune-neuropathy with variable clinical presentation. Diagnosis is based on clinical phenotype and electrophysiological features. Early and effective immunotherapy can prevent long-term disability accumulation. Regular follow-up with objective monitoring can help in therapeutic decision-making.

References

CHAPTER 95

Autoimmune Encephalitis

Gurinder Mohan, Arvinderpal Singh, Sidhant Sachdeva

Abstract

Autoimmune encephalitis is an upcoming cause of altered mental status with a subacute onset. The most common presentation is limbic dysfunction in patients of autoimmune encephalitis. However, other areas like hindbrain, spine, neocortex, striatum, and peripheral nervous system can also be variably involved depending upon the antibody involved. Paraneoplastic and non-paraneoplastic are the two broad categories of antibody dependent CNS disorders. Anti-NMDA Receptor Encephalitis is the most well defined autoimmune encephalitis syndrome. Detection of specific autoantibodies helps in establishing a definitive diagnosis of autoimmune encephalitis. Treatment is aimed at removal of the antibodies and suppression of the immune system. First line therapy includes intravenous methylprednisolone along with IVIG/plasma exchange. Second line therapy includes rituximab, cyclophosphamide, azathioprine, MMF.

Introduction

Autoimmune encephalitis is an upcoming cause of altered mental status with a subacute onset. It is only a recent addition to the medical literature. However, it is still not considered in the differential diagnosis outside of large tertiary care hospitals.

The term “autoimmune encephalitis” includes a group of disorders that present with closely related clinical features and MRI findings, but can be differentiated by the specific antibody.

The most common presentation is limbic dysfunction in patients of autoimmune encephalitis. However, other areas like hindbrain, spine, neocortex, striatum, and peripheral nervous system can also be variably involved depending upon the antibody involved. Prominent extralimbic involvement can also be seen in a few subtypes.

Subacute onset of impaired memory and cognition is generally seen.

Pathophysiology

Paraneoplastic and non-paraneoplastic are the two broad categories of antibody dependent CNS disorders.

Paraneoplastic disorders are associated with antibodies acting against intracellular antigens. They are associated with cancer and involve T-cell mediated attack against the neurons. This leads to an irreversible neuronal damage. These antibodies act as useful tumor markers.

The other group involves antibodies against extracellular antigens of ion channels and the receptors. The association with cancer tends to be variable. The prognosis in this group is much better. The antibodies are directly pathogenic and cause reversible damage to the neurons without neuronal death.

Clinical Features

Autoimmune encephalitis can have varying manifestations. The typical presentation is altered cognition along with
subacute progressive decrease in consciousness. Memory involvement occurs early in the disease (Table 1).

**Anti-NMDA Receptor Encephalitis**

It is the most well defined autoimmune encephalitis syndrome. The pathogenesis involves IgG autoantibodies acting against the GluN1 portion of the NMDAR. The neuronal dysfunction is reversible initially but may become permanent if untreated due to persistent inflammation and glutamate excitotoxicity mediated by NMDA.

Clinical features:
- Prodromal symptoms like headache, fever, malaise
- Psychiatric symptoms such as bizarre, agitated, anxious behavior, hallucinations
- Insomnia, seizures, memory deficits, decreased consciousness, stupor with catatonic features
- Dyskinesias, autonomic dysfunction

**Diagnosis and differential diagnosis (Table 2):**
- Cerebrospinal fluid (CSF) analysis shows:
  - lymphocytic pleocytosis or
  - oligoclonal bands
- Electroencephalography (EEG) shows infrequent epileptic activity and frequent slow, disorganized activity
- MRI is usually normal or may show transient abnormalities in cortical or subcortical regions. Medial temporal symmetric hyperintensities are most frequent findings (Figs. 1A to D)
- PET scan demonstrates an increased gradient of cerebral glucose metabolism in the frontal-occipital region
- The detection of IgG antibodies against the GluN1 portion of the NMDA receptor is confirmatory of anti-NMDA encephalitis

**TABLE 1  Autoimmune encephalitis syndromes**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Clinical features</th>
<th>Tumor association</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR</td>
<td>Psychosis, insomnia, memory impairment, seizures, dyskinesias, autonomic disturbances</td>
<td>Ovarian teratoma</td>
</tr>
<tr>
<td>LGI1</td>
<td>Myoclonus, hypotension, dystonic seizures</td>
<td>Thymoma in 5% cases</td>
</tr>
<tr>
<td>Contactin-associated protein-like 2</td>
<td>Limbic encephalitis, neuromyotonia, memory loss and confusion, sleep disturbances, autonomic instability, neuropathic pain</td>
<td>Thymoma</td>
</tr>
<tr>
<td>AMPAR</td>
<td>Psychiatric disturbances</td>
<td>70% (various solid tumors)</td>
</tr>
<tr>
<td>GABA-A receptor</td>
<td>Rapidly deteriorating encephalopathy, status epilepticus, epilepsy partial continua</td>
<td>Thymoma (40%)</td>
</tr>
<tr>
<td>GABA-B receptor</td>
<td>Seizures, limbic encephalitis</td>
<td>SCLC</td>
</tr>
<tr>
<td>IgLONS</td>
<td>REM and non-REM sleep disturbances, obstructive sleep apnea</td>
<td>No association with cancer</td>
</tr>
<tr>
<td>DPPX</td>
<td>Encephalopathy, CNS hyperexcitability, hyperekplexia</td>
<td>Rarely B cell neoplasms</td>
</tr>
<tr>
<td>GlyR</td>
<td>Encephalomyelitis, muscle spasms,rigidity,myoclonus,hyperekplexia</td>
<td>H/O carcinoma</td>
</tr>
<tr>
<td>Metabotropic glutamate receptor 5</td>
<td>Encephalitis</td>
<td>Hodgkin's lymphoma* or no tumor</td>
</tr>
<tr>
<td>Metabotropic glutamate receptor 1</td>
<td>Ataxia</td>
<td>Hodgkin's lymphoma or no tumor</td>
</tr>
<tr>
<td>Neurexin 3-alpha</td>
<td>Confusion, seizures, encephalitis, dyskinesias</td>
<td>No cancer association</td>
</tr>
<tr>
<td>D-2 receptor</td>
<td>Involvement of basal ganglia</td>
<td>No cancer association</td>
</tr>
</tbody>
</table>

*Limbic encephalitis and Hodgkin’s lymphoma are together known as Ophelia syndrome.

AMPAR, alpha-aminoc-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2, contactin-associated protein-like 2; CNS, central nervous system; DPPX, dipeptidyl-peptidase-like protein 6; FLAIR, fluid-attenuated inversion recovery; GABA, gamma-aminobutyric acid; GlyR, glycine receptor; LGI1, leucine glioma inactivated 1; mGluR, metabotropic glutamate receptor; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; REM, rapid eye movement.
### TABLE 2  Anti-NMDA receptor encephalitis diagnostic criteria

**Probable anti-NMDA receptor encephalitis**

All three criteria must be present:
- Subacute onset (<3 months) of 4 out of 6 major groups of symptoms:
  - Psychiatric manifestations or cognitive decline
  - Speech involvement
  - Involvement of the autonomic system
  - Seizures
  - Movement disorder
  - Depressed level of consciousness
- One of the following:
  - Abnormal EEG (epileptic activity, slow/disorganized activity, extreme delta brush)
  - Oligoclonal bands or pleocytosis on CSF examination
- Exclusion of other differentials

**Definite anti-NMDA receptor encephalitis**

- Positive IgG antibodies against GluN1 with 1 or more of the 6 major groups of symptoms, along with exclusion of other differentials

*Diagnosis can be made by presence of three groups of symptoms in the presence of ovarian teratoma

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**Figs. 1A to D:** MRI showing T2 hyperintensity in the left inferior temporal lobe (A), cingulate gyrus (B–D), insular cortex (B and C).
Association with tumors: The occurrence of ovarian teratoma is dependent upon the age at which the patient presents. Female patients who are older than 18 years have ovarian teratomas in 50% of the cases, while girls who are younger than 14 years have a teratoma in 9% of the cases. Detection of a tumor is rare in male patients.

Association with HSVE: Herpes simplex viral encephalitis (HSVE) is associated with Anti-NMDA receptor encephalitis. MRI features like asymmetry of temporal lobe hyperintensities may be subtle findings, which may differentiate between the two diseases.

Treatment and prognosis: Treatment options include:
- **Immunosuppression:** Immunosuppression in form of IV methylprednisolone (1 g/day for 5 days) and either IVIG (400 mg/kg per day × 5 days) or PEX (plasma exchange)
- **Tumor resection**
- **Second-line therapies:** Rituximab (375 mg/m² once a week × 4 weeks, or 1 g twice given two weeks apart) and cyclophosphamide (750 mg/m² once a month × 4–6 months). Other agents include Azathioprine and MMF.8

**Anti-LGI1 Encephalitis**
Hyponatremia, myoclonus and fasciobrachial dystonic seizures are most common presentations.9-12 This is a usual cause of rapidly progressive dementia in elderly. Recurrent hyponatremia is also common.

MRI shows features typical of limbic encephalitis. CSF is often normal or only shows oligoclonal bands.

Around 5–10% of cases are associated with thymoma.

Treatment includes glucocorticoids, IVIG, mycophenolate mofetil, and/or plasma exchange.

**Anti-Caspr2-Associated Encephalitis**
Anti-Caspr2 (contactin-associated protein-like 2) associated encephalitis commonly presents as limbic encephalitis, as Morvan syndrome (neuromyotonia, memory involvement and confusion, sleep disturbance, autonomic disturbance), or it can even present as isolated neuromyotonia referred to as Isaacs syndrome.13 The progression of the disease is slower than other autoimmune encephalitis syndromes. It is usually not associated with cancer.

The target antigen, Caspr2, is involved in the normal functioning of voltage-gated potassium channels (VGKC).

Patients with thymoma are more likely to develop Morvan syndrome.

Immunotherapy remains the mainstay of treatment.

**Anti-AMPA Receptor Encephalitis**
Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr) encephalitis presents with purely psychiatric symptoms.

It has a high association with cancer, more commonly in lung, breast, or thymic tumors.

Treatment consists of management of underlying tumor and/or immunotherapy.

**Anti-GABA-A Receptor Encephalitis**
It is characterized by a rapidly progressive encephalitis along with seizures which are refractory to the usual treatment, status epilepticus, or may even present with epilepsy partialis continua.

Tumors, most commonly thymoma, occur in 40% of patients.

Immunotherapy is the mainstay of treatment. Pharmacologic-induced coma may be required for prolonged seizures.

**Anti-GABA-B Receptor Encephalitis**
It is characterized by antibodies against the B1 subunit of the gamma-aminobutyric acid B (GABA-B) receptor. The patients commonly present with limbic encephalitis. Approximately 50% of the cases are associated with small cell carcinoma of lung.

Treatment includes immunotherapy and tumor treatment.

**Anti-IgLON5 Encephalopathy**
Patients present with sleep disorders (REM and non-REM) along with abnormal movements during sleep and features of obstructive sleep apnea.14

Video-polysomnography is essential to define the complex sleep disorder. CSF and imaging studies are normal aside from the presence of IgLON5 antibodies in CSF and serum. Response to immunotherapy is poor.

**Anti-DPPX Encephalitis**
Patients with antibodies against dipeptidyl-peptidase-like protein-6 (DPPX) present with prodromal symptoms of
weight loss and diarrhea, followed by encephalitis with features of central hyperexcitability (agitation, myoclonic seizures, tremors, hyperekplexia).

Treatment consists of immunotherapy.

**Anti-GlyR Encephalopathy**
Antibodies to the α-1 subunit of the glycine receptor (GlyR) have been associated with a syndrome of PERM, acquired hyperekplexia, and stiff-person syndrome.

Most patients respond to immunotherapy.

**Anti-mGluR5 Encephalitis**
Antibodies against the metabotropic glutamate receptor 5 (mGluR5) are associated with features suggestive of limbic encephalitis.

Hodgkin lymphoma (Ophelia syndrome) and SCLC are the tumors most commonly associated with this syndrome.

Treatment consists of immunotherapy and management of the underlying tumor.

**Anti-mGluR1 Encephalitis**
Anti-metabotropic glutamate receptor 1 (mGluR1) encephalitis presents commonly with ataxia (cerebellar).

There is usually no association with cancer. The patients improve with early immunotherapy.

**Anti-Neurexin-3 Alpha Encephalitis**
The common presenting features are severe encephalitis, progressively worsening consciousness, dyskinesias, and hypoventilation.

Treatment consists of immunotherapy.

**Diagnostic Approach**
Detection of specific autoantibodies helps in establishing a definitive diagnosis of autoimmune encephalitis.

Characteristic MRI findings in such patients include hyperintensities on FLAIR or T2-weighted images in affected brain regions commonly medial temporal lobes and/or brainstem.

Nonspecific EEG abnormalities are common and include focal/generalized slowing, epileptiform activity, and periodic lateralized epileptiform discharges (PLEDs).

Patients with N-Methyl-D-aspartate (NMDA) receptor encephalitis have a characteristic EEG pattern called extreme delta brush.

CSF findings include modest elevation of protein usually less than 100 mg/dL, lymphocytic pleocytosis, elevated immunoglobulin G, and/or oligoclonal bands.

The patient should also be evaluated for occult malignancy, with the tumor location being guided by the presenting syndrome.

**Antibody testing:** Paraneoplastic and autoimmune antibody testing should be performed on both serum and CSF.\(^\text{15}\)

General principles to be followed are:
- Test for antibodies in serum and CSF. Testing serum and then, if negative, testing CSF delays diagnosis and can lead to false positive results and is therefore not recommended.
- If the CSF is negative but the serum antibody is positive, the serum result should be considered as a false-positive diagnosis.
- If the clinical findings do not correlate with the antibody identified, the antibody identified may be a false-positive, particularly if the antibodies were identified only in serum.

**Diagnostic Criteria\(^\text{16}\)**
See Table 3.

**Treatment Approach (Flowchart 1)**\(^\text{17}\)
Treatment for autoimmune encephalitis when suspected clinically should be started prior to results of antibody testing after infectious etiology has been ruled out. The results of antibody testing can then be used to refine treatment strategy.

Treatment is aimed at removal of the antibodies and suppression of the immune system.

First-line therapy includes intravenous *methylprednisolone*, for example, 1 gm daily for 5 days in an adult and either intravenous immunoglobulin G, for example, 400 mg/kg per day × 5 days or PEX (plasma exchange) and tumor removal as and when indicated.

Second-line therapies include *rituximab* (either 375 mg/m\(^2\) weekly × 4 weeks, or 1 gm given twice 2 weeks apart) and *cyclophosphamide* (750 mg/m\(^2\) once a month × 4–6 months depending on results). Other agents include Azathioprine and MMF.

Seizures should be treated aggressively with anti-epileptic drugs.
Conclusion

Autoimmune encephalitis is an important differential in patients presenting with altered sensorium of a subacute onset. The two main groups (intracellular directed antibodies and cell-surface directed antibodies) have a considerable overlap. Limbic structures are most commonly involved on neuroimaging. A small percentage of patients have no findings on neuroimaging in spite of profound neurological dysfunction, but antibody testing can ultimately lead to the diagnosis of autoimmune encephalitis in such patients.

References


Abstract

Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular disorder worldwide. It is of paramount importance to understand the pathophysiology of this purely mechanical vestibular disorder. This is because the treatment involves physical therapy and/or repositioning maneuvers, which are dependent on the elicited positional nystagmus that localizes as well as lateralizes the involved semicircular canal. The chapter discusses the pathophysiology, clinical subtypes, diagnostic oculomotor patterns (positional nystagmus), and therapeutic repositioning maneuvers, and physical therapy for the treatment of different subtypes of the BPPV. The YouTube link of videos of diagnostic positional tests and the therapeutic repositioning maneuvers are presented in a tabular form.

Introduction

Benign paroxysmal positional vertigo (BPPV) is a mechanical disorder of the membranous labyrinth and is the most frequent cause of vertigo worldwide. It is caused by vestibular lithiasis, which exists in two forms:

- **Canalolithiasis:** The degenerative otoconial debris gets detached from the utricular matrix and inappropriately enters one of the three semicircular canals namely posterior, horizontal, and anterior in that order of frequency.¹

- **Cupulolithiasis:** The otoconial debris becomes inappropriately adherent to the cupula, making it heavy and gravity sensitive.² Cupulolithiasis exists in two forms, with the otoconial debris getting attached to either canal (Cup-C) or utricular (Cup-U) side of the cupula.³

The chief symptom of BPPV is severe rotational vertigo triggered by changes in the position of head relative to the gravity. The typical situations during which attacks occur are lying on the bed, getting up from supine to sitting, assuming lateral recumbent positions, bending forward (e.g., to tie shoelaces), and pitching the head up (e.g., keeping an object on a high shelf). The associated autonomic symptoms like perspiration, nausea, and vomiting are more common in the horizontal semicircular canal benign paroxysmal positional vertigo (HSC-BPPV).⁴ The head motion normally moves endolymph in the appropriate semicircular canal, bending the cupula to generate the nerve impulse in the vestibular nerve: the latter apprises the brain (via the vestibulo-ocular reflex) in which plane and at what angle the head has moved. Consequently, the brain reflexely generates the corrective eye movements equal in angle but in the opposite direction so that the point of fixation falls on the fovea centralis. If otoconial particles inappropriately enter any of the semicircular canals, they continue to drag endolymph for few seconds (maximum 30 seconds in canalolithiasis⁵ and longer in cupulolithiasis⁶) even after the head movement has ceased, thus causing a sudden severe asymmetry in the resting vestibular tone and a transient severe vertigo. By a similar mechanism, a sudden severe asymmetry of the resting vestibular tone results from a cupula that has been rendered abnormally heavy and gravity-sensitive by the adherent otoconial debris and the consequent positionally triggered vertigo.
Table 1 shows the relative frequency of all patients diagnosed with BPPV at any specialty clinic. Due to its peculiar anatomy, which facilitates the sequestered degenerative otoconial debris to gravitate into the canal, the posterior semicircular canal BPPV (PSC-BPPV) is the most prevalent variant of the disorder. The relatively higher location of the anterior semicircular canal (ASC) within the bony labyrinth restricts the upward movement of the otoconial debris as well as facilitates self-clearance of any debris through its non-ampullary arm, that inadvertently enters it. Therefore, the anterior semicircular canal BPPV (ASC-BPPV) is the least prevalent variant of the disorder. In the upright positions, the horizontal semicircular canal (HSC) is inclined 30-degrees relative to the horizontal plane, its cupular barrier is at a higher location, and it becomes vertical in the supine position. Therefore, any free-floating debris that enters the HSC tends to leave the canal through the utricular exit in its non-ampullary long posterior arm during lateral recumbent positions. The spontaneous remissions of HSC-BPPV reported in a few studies are perhaps responsible for its modest frequency.

**Classification of BPPV**

BPPV can be classified as under:

**Monocanalicular**

- **Posterior Semicircular Canal BPPV (PSC-BPPV):**
  - Geotropic variant (geo-PSC-BPPV)—Otoconia either free-floating in the ampullary arm in the juxtcupular location or adherent to the cupula.
  - Apogeotropic (apo-PSC-BPPV)—Due to free-floating otoconia in the non-ampullary arm.

- **Horizontal Semicircular Canal BPPV (HSC-BPPV):**
  - Geotropic variant (geo-HSC-BPPV)—Due to free-floating otoconia in the long non-ampullary posterior arm (long posterior arm horizontal semicircular canalolithiasis).
  - Apogeotropic Variant (apo-HSC-BPPV)—Either due to free-floating otoconia in the short ampullary anterior arm of the HSC (short anterior arm horizontal semicircular canalolithiasis) or due to cupulolithiasis. The latter exists in two forms with otoconial debris getting adherent to either canal (Cup-C) or utricular side (Cup-U) of the cupula.

- **Anterior Semicircular Canal BPPV (ASC-BPPV):** The ASC-BPPV is due to canalolithiasis, as per the consensus statement of the committee for the classification of vestibular disorders of the Bárány Society. The otoconial debris in the ampullary arm of ASC results in positional downbeating nystagmus during the provocative positional tests. The cupulolithiasis of the ASC and the non-ampullary arm ASC canalolithiasis are not convincingly known to exist.

**Multicanalicular**

- **Single-canal bilateral** involving the same semicircular canal in either of the labyrinths.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>PSC-BPPV (%)</th>
<th>HSC-BPPV (%)</th>
<th>ASC-BPPV (%)</th>
<th>Multiple canals (%)</th>
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<tr>
<td>De la Meilleure et al., 7 1996</td>
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<td>61.8</td>
<td>35.3</td>
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</table>

- Multicanal unilateral involving at least two different semicircular canals (posterior, lateral, or anterior) in one of the labyrinths.
- Multicanal bilateral involving two or more different semicircular canals in both labyrinths.

**Diagnosis**

The clinical features of the BPPV are enumerated in the introduction section of the chapter and it is impossible to localize and lateralize the involved semicircular canals based on the symptomatology alone. Two additional important points about the symptomatology of BPPV are:

- Vertigo in the HSC-BPPV occurs during the lateral movement of the patient's head in the supine position and is less frequent during extension or flexion of the head.20
- A prominent sense of continuous dizziness rather than true rotational vertigo still enhanced with the change of position but, overall, continuous is the hallmark of apo-PSC-BPPV.4

The experiments of Julius Ewald (1855–1921) in pigeons framed the three laws that bear his name, and these laws are fundamental for understanding the pathophysiology of the diagnostic positional tests namely Dix-Hallpike test (DHT), supine roll test (SRT), and straight head hanging test (SHHT), which generate the diagnostic oculomotor patterns for semicircular canals affected by the vestibular lithiasis.21 Ewald (1892) cannulated each of the three semicircular canals and applied negative and positive pressures to observe the intensity and direction of the generated nystagmus. The two main outcomes of his experiments are:

- The generated nystagmus is always directed parallel to the plane of the stimulated canal (Ewald's 1st law).
- The generated nystagmus is stronger when the endolymph moves toward the ampulla (ampullopetal) in the case of the HSC (Ewald's 2nd law), and away from the ampulla (ampullofugal) in case of vertical semicircular canals (PSC and ASC) (Ewald's 3rd law). With this background knowledge of physiology of semicircular canals, the positional tests are discussed below.

**Dix-Hallpike Test**22

The positional nystagmus generated during DHT is always directed parallel to the plane of the stimulated canal as per the Ewald's 1st law. Lowering the 45-degrees rotated head in the yaw plane to the 20-degrees head hanging position during the DHT aligns the PSC with the sagittal plane and places its ampullary end to the superior most position. Consequently, there is an ampullofugal shift of the otoconial debris in the ampullary arm of the PSC, leading to an excitatory cupular deflection (Ewald's 3rd law) and this generates the oculomotor patterns characterized by an upbeating ipsitorsional positional nystagmus.

The patient is placed on the examination table in long-sitting, such that the distance between his bottoms and the head end of the table allows his head to hang during Dix-Hallpike positioning. The patient’s head is held with both hands and is rotated 45-degrees to one side (for example left) in the yaw plane. Thereupon he is positioned supine such that his 45-degrees left rotated head extends 20-degrees on the support of the author’s hands representing the left Dix-Hallpike position (Fig. 1). Left Dix-Hallpike positioning is maintained for at least 60 seconds or until elicited nystagmus lasts. A similar sequence of positioning is done in the right head hanging position if no nystagmus is elicited on the initially tested side. The DHT results can be interpreted as:

- An upbeating ipsitorsional positional nystagmus suggests the most prevalent geotropic variant of the PSC-BPPV (geo-PSC-BPPV). The lateralization is to the side eliciting positional nystagmus in the 20-degrees head hanging position during the DHT (https://youtu.be/MBsbJeYRF7s).
- A downbeating torsional nystagmus suggests either ASC-BPPV or the apo-PSC-BPPV. The lateralization of the ASC-BPPV is suggested by the direction of the torsional component, which is too often little or inconspicuous. The DHT elicits positional downbeating nystagmus in the head hanging position to either side as well as in the deep or enhanced straight head hanging positions in the ASC-BPPV. The positional downbeating nystagmus of apo-PSC-BPPV is not typically crescendo-decrescendo, often lasts longer, and is contratorsional. However, initially, too often it is impossible to differentiate between an ASC-BPPV and apo-PSC-BPPV based on findings of the DHT alone (https://youtu.be/wlb-iYZThzU).
Neurology

**Fig. 1: Dix-Hallpike Test:** The Dix-Hallpike test (DHT) involves moving the patient from a long sitting position on the examination table with the head rotated 45-degrees to a side (left in the figure) to 20-degree below horizontal head-hanging supine position. After a latency of few seconds it produces an upbeating ipsitorsional nystagmus in the PSC-BPPV, and downbeating ipsitorsional nystagmus in the ASC-BPPV. The torsional component is either little or inconspicuous in ASC-BPPV. If positional nystagmus is not elicited on one side even after 60 seconds, the patient is positioned to upright sitting, and an identical sequence is repeated with the head rotated 45-degrees to the opposite side.

**Fig. 2: Supine Roll Test:** A pillow of about 4-inch thickness is placed at the head end of the examination table. The supine roll test is performed with the patient in long-sitting on the examination table. From long-sitting, the patient is shifted to a supine position so that the head is flexed to 30-degrees as the occiput lands on the pillow. The patient’s head is rolled from neutral to one side while the patient is supine. After waiting for any nystagmus or vertigo to subside, the test is performed to the opposite side.

**Supine Roll Test (Head Yaw Test or Pagnini McClure Maneuver)**

A pillow of about 4-inch thickness is placed at the head end of the examination table. The SRT is performed with the patient in long-sitting on the examination table. From long-sitting, the patient is shifted to supine position so that the head is flexed 30-degrees as the occiput lands on the pillow. The patient’s head is rolled from neutral to one side while the patient is supine. After waiting for any nystagmus or vertigo to subside, the test is performed to the opposite side (Fig. 2). The positive test elicits horizontal positional nystagmus, which may be:

- **Geotropic:** Implying that the fast component of the nystagmus is directed toward the lowermost ear. The geotropic positional nystagmus is elicited on the lateral head roll to either side and is attributed to the long posterior non-ampullary arm horizontal semicircular canalolithiasis. The side to which the lateral head roll elicits stronger geotropic nystagmus is the affected side as per the Ewald’s 2nd law (https://youtu.be/jwRgSZ71Ux8Or).

- **Apogeotropic:** Implying that the fast component of the nystagmus is directed away from the lowermost ear. The apogeotropic positional nystagmus is elicited on the lateral head roll to either side and is attributed to the
short anterior ampullary arm horizontal semicircular canalolithiasis or cupulolithiasis. The side to which the lateral head roll elicits weaker apogeotropic nystagmus is the affected side as per the Ewald’s 2nd law. (https://youtu.be/t_Ie7LGcCXQ).

In the geotropic variant of the HSC-BPPV (geo-HSC-BPPV), in which otoconial debris is free-floating in the long posterior non-ampullary arm of the HSC, an ipsilesional lateral head roll in the yaw-axis, during the SRT, produces an excitatory hydrodynamic drag of the endolymph toward the ampulla. This very reason in the variant, during SRT, elicits stronger geotropic nystagmus to the side of lesion than to the opposite side (Figs. 3A and B) (https://youtu.be/-gp7Dol6_jk). In the apogeotropic variant of HSC-BPPV (apo-HSC-BPPV), where otoconial debris is either free-floating in the short anterior ampullary arm of the HSC or is adherent to the cupula, thus making it heavier, the excitatory hydrodynamic drag of the endolymph toward the ampulla occurs when there is contralesional lateral head roll in the yaw axis during SRT. Accordingly, in the apo-HSC-BPPV during the SRT, stronger apogeotropic nystagmus is elicited when the head is yawned to the contralesional side (Figs. 3A and C) (https://youtu.be/v6vmGAJaRDs).

The duration of the positional nystagmus is up to 1 minute in the canalolithiasis and more than 1 minute in the cupulolithiasis. The HSC-BPPV caused by short anterior ampullary arm canalolithiasis presents with apogeotropic positional nystagmus that may last longer than 1 minute. However, if the SRT elicits persistent apogeotropic positional nystagmus lasting more than 1 minute and there are no changes in the direction of nystagmus even after repetitive head roll tests, it is explicable by the horizontal canal cupulolithiasis either on canal-side (Cup-C) or on the utricular-side (Cup-U)19 (https://youtu.be/glT9HiAwFaC).

**Table 2** summarizes the currently known variants of BPPV, the anatomico-physiological correlation between otoconial location and oculomotor patterns generated on the diagnostic positional tests in terms of the direction, latency, and duration of the elicited positional nystagmus. Because the management of BPPV exclusively depends on the repositioning maneuvers and/or physical therapy, it is imperative to localize as well as lateralize the involved semicircular canal by a meticulous execution of Straight Head Hanging Test

The straight head hanging test (SHHT) is carried out with the patient in long-sitting on the examination table such that the distance of the patient’s bottoms from the head end of the table allows the head to hang during supine positioning. The patient’s head is firmly held and is positioned to the supine neutral position with the head 30-degrees or maximally extended (beyond the short edge of the examination table). The patient is held in the enhanced straight head hanging position till positional nystagmus is elicited and lasts or for at least 60 seconds if no positional nystagmus is elicited. The patient is instructed to keep their eyes open even when experiencing vertigo in the head hanging position to observe the pattern of induced positional nystagmus. A SHHT is positive if a downbeating nystagmus is elicited with or without a torsional component (https://youtu.be/Ubwsq9J75c).
## TABLE 2
Synopsis of otoconial location, diagnostic positional test, elicited nystagmus characteristics, and YouTube links in different BPPV subtypes

<table>
<thead>
<tr>
<th>BPPV variant</th>
<th>Otoconial location in upright position</th>
<th>Positional test</th>
<th>Nystagmus direction</th>
<th>Nystagmus latency</th>
<th>Nystagmus duration</th>
<th>YouTube link</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>geo</em>-PSC-BPPV</td>
<td>Juxta-cupular in the ampullary arm of PSC</td>
<td>DHT</td>
<td>Upbeating &amp; ipsitorsional</td>
<td>Brief latency (rarely up to 40 s)</td>
<td>&lt;1 min</td>
<td><a href="https://youtu.be/MBsbJeYRF7s">https://youtu.be/MBsbJeYRF7s</a></td>
</tr>
<tr>
<td><em>apo</em>-PSC-BPPV</td>
<td>Non-ampullary arm of PSC near common crus</td>
<td>DHT &amp; SHHT</td>
<td>Downbeating &amp; contratorsional</td>
<td>Brief or no latency</td>
<td>&gt;2 min</td>
<td><a href="https://youtu.be/Ubwsqx9J75c">https://youtu.be/Ubwsqx9J75c</a></td>
</tr>
<tr>
<td>PSC-BPPV cupulolithiasis</td>
<td>Adherent to cupula of PSC</td>
<td>Half-DHT*</td>
<td>Upbeating &amp; ipsitorsional</td>
<td>Brief or no latency</td>
<td>&gt;1 min</td>
<td>-</td>
</tr>
<tr>
<td>ASC-BPPV</td>
<td>Juxta-cupular in ampullary arm of ASC</td>
<td>DHT &amp; SHHT</td>
<td>Downbeating &amp; ipsitorsional; torsion often too little or absent</td>
<td>Brief or no latency (rarely up to 30 s)</td>
<td>&lt;1 min</td>
<td><a href="https://youtu.be/wlb-iYZThzU">https://youtu.be/wlb-iYZThzU</a></td>
</tr>
<tr>
<td>Long posterior-arm HSC-canalolithiasis</td>
<td>Long non-ampullary posterior-arm of HSC</td>
<td>SRT</td>
<td>Horizontal geotropic</td>
<td>Brief or no latency (rarely up to 2 min)</td>
<td>&lt;1 min</td>
<td><a href="https://youtu.be/-gp7DoIo6_jk">https://youtu.be/-gp7DoIo6_jk</a></td>
</tr>
<tr>
<td>Short anterior arm HSC-canalolithiasis</td>
<td>Short ampullary anterior arm of HSC</td>
<td>SRT</td>
<td>Horizontal apogeotropic</td>
<td>Brief or no latency (rarely up to 2 min)</td>
<td>&lt;1 min</td>
<td><a href="https://youtu.be/v6vmGAJaRDs">https://youtu.be/v6vmGAJaRDs</a></td>
</tr>
<tr>
<td>HSC cupulolithiasis</td>
<td>Adherent to cupula of HSC (Cup-C or Cup-U)</td>
<td>SRT</td>
<td>Horizontal apogeotropic</td>
<td>Brief or no latency</td>
<td>&gt;1 min</td>
<td><a href="https://youtu.be/glT9HTAwaF8">https://youtu.be/glT9HTAwaF8</a></td>
</tr>
</tbody>
</table>

*The patient's head is turned 45° toward the side to be tested: the patient is then inclined 60° backward to one side, instead of 110° so that the cupula of PSC is earth horizontal. Rolling the head 180° to the other side (release position) should reveal a less intense nystagmus beating in the opposite direction, due to ampullopetal deflection of the cupula.

PSC-BPPV, Posterior Semicircular Canal Benign Paroxysmal Positional Vertigo; HSC-BPPV, Horizontal Semicircular Canal Benign Paroxysmal Positional Vertigo; ASC-BPPV, Anterior Semicircular Canal Benign Paroxysmal Positional Vertigo; geo, Geotropic; apo, Apogeotropic; Cup-C, Cupulolithiasis canal side; Cup-U, Cupulolithiasis utricular side; DHT, Dix-Hallpike Test; SHHT, Straight Head Hanging Test; SRT, Supine Roll Test
the provocative positional tests and observing the patterns of the elicited positional nystagmus thereon.

**Management**

The treatment of BPPV with drugs is neither indicated nor successful. In selected patients who develop severe nausea and/or vomiting during the repositioning maneuvers and/or physical therapy, promethazine may be used. Once accurate lateralization of the side and localization of the involved canal is known, an appropriate repositioning maneuver and/or physical therapy is carried out. In general, canalolithiasis is more amenable to treatment with repositioning maneuvers compared to cupulolithiasis. It is important to review the patient at short intervals at least twice, at 1 hour and 24 hours after the repositioning maneuver and/or physical therapy. The improvement is evaluated in terms of extirpation of the positional nystagmus and associated vertigo. The treatment of different BPPV variants with repositioning maneuvers and/or physical therapy is summarized in the Table 3. Figures 4 to 8 illustrate the different maneuvers used in the treatment of the common variants of BPPV. Column four of the Table 3 shows YouTube links to access the videos of the therapeutic repositioning maneuvers and/or physical therapy. After the repositioning maneuver, otoconial debris occasionally refluxes into a canal different from the one originally affected. This phenomenon is known as canal-switch and occurs in 6–8% of patients. The appearance of a different oculomotor pattern on a verifying positional test than the one initially observed, after the patient has been subjected to a seemingly successful repositioning maneuver, is a harbinger of canal-switch. Patients undergoing canal-switch require treatment according to the protocol of the canal involved with the switch phenomenon. The appearance of persistent spontaneous nystagmus following a repositioning maneuver in HSC-BPPV may result from jamming of the otoconia within a canal or between the cupula and the adjacent ampulla wall. The canal jam results in partial or complete obstruction within the canal, resulting in spontaneous nystagmus that persists irrespective of a change in head position. The physicians involved in the physical treatment of patients with BPPV should be aware of these two potential complications of physical therapy, namely the canal-switch and canal jam.

**Copyrights Information**

The educational videos in the YouTube links mentioned in column 7 of the Table 2 and column 4 of the Table 3 are protected by the copyrights of the author. The author has

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**Table 3**

Synopsis of BPPV variants, otoconial location, therapeutic repositioning maneuvers and/or physical therapy, and YouTube links

<table>
<thead>
<tr>
<th>BPPV variant</th>
<th>Otoconial location in upright position</th>
<th>Therapeutic repositioning maneuver and/or physical therapy</th>
<th>YouTube link</th>
</tr>
</thead>
<tbody>
<tr>
<td>geo-PSC-BPPV</td>
<td>Juxta-cupular in the ampullary arm of PSC</td>
<td>Epley Maneuver [22](Fig. 4)</td>
<td><a href="https://youtu.be/JSwRvT453M8">https://youtu.be/JSwRvT453M8</a></td>
</tr>
<tr>
<td>PSC-BPPV cupulolithiasis</td>
<td>Adherent to cupula of PSC</td>
<td>Epley Maneuver [22](Fig. 4) (more sessions required compared to geo-PSC-BPPV [25])</td>
<td><a href="https://youtu.be/JSwRvT453M8">https://youtu.be/JSwRvT453M8</a></td>
</tr>
<tr>
<td>ASC-BPPV</td>
<td>Juxta-cupular in ampullary arm of ASC</td>
<td>Yacovino maneuver [26](Fig. 8)</td>
<td><a href="https://youtu.be/frQ98anQThk">https://youtu.be/frQ98anQThk</a></td>
</tr>
<tr>
<td>Long posterior-arm HSC-canalolithiasis</td>
<td>Long non-ampullary posterior-arm of HSC</td>
<td>Gufoni Maneuver [27](Fig. 6), Lempert’s 360 degrees Barbecue Roll Maneuver [28,29](Fig. 5), Forced Prolonged Positioning (FPP) [30]</td>
<td><a href="https://youtu.be/u_WNOpxG30">https://youtu.be/u_WNOpxG30</a> (Gufoni Maneuver) <a href="https://youtu.be/ZEG-rKEYnZw">https://youtu.be/ZEG-rKEYnZw</a> (Lempert’s 360 degrees Barbecue Roll Maneuver)</td>
</tr>
<tr>
<td>Short anterior arm HSC-canalolithiasis</td>
<td>Short ampullary anterior-arm of HSC</td>
<td>Appiani Maneuver [31](Fig. 7)</td>
<td><a href="https://youtu.be/EUW4GVhPdi">https://youtu.be/EUW4GVhPdi</a></td>
</tr>
<tr>
<td>HSC cupulolithiasis</td>
<td>Adherent to cupula of HSC (Cup-C or Cup-U)</td>
<td>Head-Shaking maneuver (HSM) [32], Cupulolith Repositioning Maneuver [33]</td>
<td><a href="https://youtu.be/pOKOFAqtl(HSM)">https://youtu.be/pOKOFAqtl(HSM)</a></td>
</tr>
</tbody>
</table>
Fig. 4: **Epley maneuver for left posterior semicircular canal BPPV:** The patient is positioned in long-sitting on the examination table and head is rotated 45-degrees to the side (left in this case) to which the Dix-Hallpike test elicited the upbeating ipsitorsional positional nystagmus. Thereupon the patient is positioned supine such that the head hangs 20-degrees below the short edge of the examination table and remains in this position for 1 minute. Then the head is rotated 90-degrees to the patient’s right and is maintained in this position for 1 minute. Then the patient is instructed to assume the right lateral recumbent position and to further rotate head rightward so that his nose orients at the right angle to the surface for another minute. Finally, the patient is positioned to short-sitting keeping the head position unchanged, until he is fully seated with his legs hanging on the examination table.

(Source: Reproduced with permission from Prof. Dr. Thomas Lempert, Chief Physician of the Neurology Department at the Schlosspark Clinic in Berlin)

Fig. 5: **Lempert’s 360-degrees barbecue roll maneuver for right long posterior arm horizontal semicircular canalolithiasis:** **Step 1:** The patient lies on his back on the examination table with his right ear down or the starting position can be right lateral recumbent. **Step 2:** The head is then slowly rolled away from right side until the face is pointing up and remains in this position for 30 seconds or till the vertigo ceases. **Step 3:** The head is then rolled in the same direction until the right ear is up or the patient can be positioned left lateral recumbent and remains in this position for 30 seconds or till vertigo ceases. **Step 4:** The head and body are then rolled in the same direction until they are face down and remains in this position for 30 seconds or till vertigo ceases. **Step 5:** The head and body are then rolled in the same direction until they reach the original position with right ear down and remain in this position for 30 seconds or till vertigo ceases. After 30 seconds the patient then slowly positioned to upright short sitting on the examination table.
Figs. 6A to D: Gufoni maneuver for the left posterior arm horizontal semicircular canalolithiasis. (A) The patient is placed in short sitting on the examination table with lower limbs hanging down. (B) Briskly positioned to the contralesional right lateral recumbent on the examination table and the position maintained for 1 minute. (C) The head is rotated 45-degrees downward in the yaw-axis, and this position is maintained for 2 minutes. (D) Upright short sitting positioning is done. The lower panels a, b, c, and d show the transit of otoconial debris from the long posterior arm of the left horizontal semicircular canal to the utricle during the maneuver.
Figs. 7A to D: **Appiani maneuver for the left short anterior arm horizontal semicircular canalolithiasis.** (A) The patient is placed in short sitting on the examination table with lower limbs hanging down. (B) Briskly positioned to the ipsilesional left lateral recumbent on the examination table and the position maintained for 1-minute. (C) The head is rotated 45-degrees upward in the yaw-axis and this position is maintained for 2 minutes. (D) Upright short sitting positioning is done. The lower panels a, b, and c, show the transit of otoconial debris from the short anterior arm of the left horizontal semicircular canal to the utricle during the maneuver. The possible outcomes of the Appiani maneuver are either the otoconial debris is repositioned to the utricle thus clearing the left horizontal semicircular canal (d-1) or shift of otoconial debris to the posterior arm of the left horizontal semicircular canal thus transforming to left long posterior arm horizontal semicircular canalolithiasis (d-2).

Possible outcomes:
- **Cure after appiani maneuver**
- **Otoconia shift to posterior arm**
SECTION 6
Neurology

Neurology

Fig. 8: Yakovino Maneuver. Step 1: The patient positions in the long-sitting on the examination table. The distance of the patient’s bottoms from the head end of the table is such that it allows the head to hang on positioning supine. Step 2: The head is held in the neutral position, and the patient is positioned supine so that the head extends about 30-degrees or more below the horizontal. This position is maintained for 30 seconds or till the downbeating nystagmus lasts. Step 3: The head is now anteflexed 30-degrees above horizontal so that it attains a “chin to chest position” with vertex approximating the vertical axis. This position is maintained for 30 seconds. Step 4: The head and entire body are brought to sitting position with head in the straight position, and this is maintained for 30 seconds.

Acknowledgments
The author is grateful to Professor Thomas Lempert, Professor of Neurology, Chief Physician of the Neurology Department at the Schlosspark Clinic, Berlin, Germany, for his kindness in providing his illustration (Fig. 4) for this chapter. To Mr. Renith Kurian, who video recorded the diagnostic and therapeutic maneuvers (shown in the YouTube links) and precisely captured the nystagmus during the entire diagnostic and treatment period and to Mr. Ashraf for drawing the Figures 6 and 7 on CorelDraw graphics suite 2019.

Conclusion
Successful treatment of BPPV with repositioning maneuvers and physical therapy has been one of the greatest accomplishments in the field of Otoneurology. This has been possible due to several factors like in vivo demonstration of otoconia in the SCC, application of physical laws to precisely lateralize as well as localize the otoconial debris within the SCC, and conceptualizing the movement of otoconia in the SCC during head movements in the physical models of the labyrinth to develop specific canal clearing maneuvers. A trained vestibular physician’s role in the medical fraternity is to obviate the unnecessary and often expensive neuroimaging studies, which patients of BPPV often undergo due to ignorance of physicians at large to identify and treat this truly benign peripheral vestibular disorder by repositioning maneuvers and physical therapy.

References