Neurological Medical Diseases for Neurosurgeons

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Abstract: A deep understanding of neurological medical diseases is very important for a neurosurgeon. It is essential during clinical assessment, radiological evaluation, and surgical decision-making to identify when one should not operate on a multiple sclerosis or motor neuron disease patient. Many of these neurological medical diseases are under trial for neuro stem cell therapy. In this chapter, we will briefly discuss important and frequent neurological medical diseases. We will discuss encephalitis, acute demyelinating encephalomyelitis, multiple sclerosis, transverse myelitis, peripheral neuropathy, Guillain–Barré syndrome, chronic inflammatory demyelinating neuropathy, myasthenia gravis, hereditary muscular disorders, and Wilson's disease.

Abbreviations

AChR	acetylcholine receptor	ADEM	acute demyelinating encephalomyelitis
ADL	adrenoleukodystrophy	AIDP	acute inflammatory demyelinating polyneuropathy
ALS	amyotrophic lateral sclerosis	AMAN	acute motor axonal neuropathy
AMSAN	acute motor sensory axonal neuropathy	ATM	acute transverse myelitis
BAEP	brain stem auditory evoked potential	CIDP	chronic inflammatory demyelinating polyneuropathy
CIS	clinically isolated condition	CK	creatine kinase
CMT	Charcot–Marie–Tooth	CNS	central nervous system
CSF	cerebrospinal fluid	CT	computed tomography
EDSS	extended disability status score	EEG	electroencephalogram
EMG	Electromyography	FSH	Facioscapulohumeral
GBS	Guillain–Barré syndrome	HAART	highly active antiretroviral therapy
INO	internuclear ophthalmoplegia	IVIG	intravenous immunoglobin
LGMD	limb girdle muscular dystrophy	LMN	lower motor neuron
MAC	membrane attack complex	MD	muscular dystrophy
MFS	Miller Fisher syndrome	MG	myasthenia gravis
MND	motor neuron disease	MRI	magnetic resonance imaging
MS	multiple sclerosis	My D	myotonia dystrophica
NCS	nerve conduction study	NMDA	N-methyl D-aspartate
OCN	oligoclonal band	PCR	polymerase chain reaction
PEG	percutaneous endoscopic gastrostomy	PML	progressive myelo leukoencephalopathy
PNS	peripheral nervous system	PPMS	primary progressive multiple sclerosis
RRMS	relapsing and remitting multiple sclerosis	SMA	spinal muscular atrophy
SOD	superoxide dismutase	SSEP	somatosensory evoked potential
UMN	upper motor neuron	VER	visual evoked response
VLCFA	very long chain fatty acid		

1. Encephalitis

1.1. Introduction

Inflammation of the brain is encephalitis. When the meninges and the brain are affected at the same time, the condition is known as meningoencephalitis. In Western nations, there are 7.4 new instances of acute encephalitis for every 100,000 individuals each year. The incidence in tropical nations is 6.34 per 100,000 individuals annually. In 2015, encephalitis is thought to have killed 150,000 people worldwide and afflicted 4.3 million people. Viruses are typically the cause of encephalitis. The incidence of herpes simplex encephalitis is 2–4 per million people per year. Encephalitis is predisposed by immunosuppression or immunodeficiency. The degree of severity may vary and could even result in death (Vos et al. 2016; Meningitis and Encephalitis Information Page 2017; Wikipedia contributors 2022).

1.2. Signs and Symptoms

- In adult patient:

- Fever of acute onset;
- Headache;
- Confusion;
- Seizures (sometimes).

- In infants or children:
  - Irritability;
  - Restlessness;
  - Poor appetite;
  - Fever.
- Neurological examinations
  - Drowsiness, confusion, stupor, or coma;
  - Memory disturbances;
  - Stiff neck, or other signs of meningism (meningoencephalitis) (NHS 2015; Wikipedia contributors 2022).

1.3. Causes

1.3.1. Viral

Viral encephalitis may affect patients as a direct result of an acute infection or as a sequalae of a latent infection. Most cases of viral encephalitis have an unidentified/unknown cause.

- Common viruses:
  - Herpes simplex infection (the commonest identifiable cause);
  - Rabies virus;
  - Measles virus;
  - Poliovirus.
- Rare viral causes:
  - Arboviral flavivirus (West Nile virus and St. Louis encephalitis);
  - Bunyavirus (La Crosse strain);
  - Reovirus (Colorado tick virus);
  - Arenavirus (lymphocytic choriomeningitis virus);
  - HIV infection;
  - Henipavirus infections;
  - Powassan virus.

1.3.2. Bacterial and Other Etiologies

- Bacterial infection (such as bacterial meningoencephalitis);
- Syphilitic encephalitis;
- Lyme disease encephalitis.

Mycoplasma and Rickettsial Encephalitis

- Parasitic:
  - Cysticercosis;
  - Malaria;
  - Toxoplasmosis;
  - Primary amoebic meningoencephalitis.
- Autoimmune:
  - Anti-NMDA receptor encephalitis;
  - Rasmussen encephalitis;
  - Limbic encephalitis.
- Idiopathic:
  - Encephalitis lethargica (Roos and Tyler 2015; Fisher et al. 2015; Kennedy 2004; Wikipedia contributors 2022).

1.4. Investigations

Only those who have experienced lethargy, a change in personality, or a lowered or altered level of consciousness for longer than 24 h should be considered to have encephalitis. Several tests are used to determine whether someone has encephalitis:

- MRI of the brain—detect inflammation;
- EEG—abnormal signal;
- CSF study—routine study, culture, PCR test, and antibody detection (anti-NMDA receptor);
- Blood test;
- Urine analysis (Venkatesan et al. 2013).

1.5. Treatment

The ideal medication for treating brain infections should have the following characteristics: small size, moderate lipophilicity at pH 7.4, low plasma protein binding level, distribution volume of 1 liter per kilogram, and weak affinity for binding with P-glycoprotein or other efflux pumps on the blood–brain barrier. Certain medications have high blood–brain barrier penetration, including isoniazid, pyrazinamide, linezolid, metronidazole, fluconazole, and some fluoroquinolones.

Here is the course of therapy (based on supportive care):

- Antiviral drugs (if virus is the etiology);
- Antibiotics (if the etiology is bacteria);
- Steroids are utilized to decrease brain edema;
- Sedatives (in restlessness);
- Anticonvulsants;
- Acetaminophen as an antipyretic;
- Decompressive craniotomy (very rare);
- Occupational and physical therapy;
- Pyrimethamine-based continued treatment is frequently utilized to manage toxoplasmic encephalitis;
- HAART (highly active antiretroviral therapy)—in HIV infection;
- Intravenous immunoglobulin (IVIG)—autoimmune encephalitis (Wikipedia contributors 2022).

1.6. Prognosis

Status epilepticus, thrombocytopenia, and cerebral edema are indicators of poor prognosis. On the other hand, early diagnosis with a normal encephalogram is connected with good survival rates (Wikipedia contributors 2022).

2. Demyelinating CNS Diseases

2.1. Acute Disseminated Encephalomyelitis (ADEM)/Post-Infectious Encephalomyelitis

2.1.1. Introduction

It is an immune-mediated demyelinating disease with an acute onset that is dispersed throughout the central nervous system (CNS) as small demyelinating foci in perivenous locations. Lesions do not exceed multiple sclerosis (MS) size and demyelination is restricted to perivascular regions. Most lesions have a diameter of 0.1 to 1.0 mm. ADEM may develop after viral upper respiratory or gastrointestinal tract infections, viral exanthematous diseases (measles, rubella, chickenpox, etc.), or vaccination (influenza or rabies). The most frequent cause of ADEM is measles, succeeded by varicella zoster (chickenpox) (Lindsay et al. 2011).

2.1.2. Clinical Features

After the viral infection has subsided for a few days or weeks, fever, headache, nausea, and vomiting start to appear. Drowsiness plus multifocal neurological symptoms and signs, including hemispheric, cerebellar, brain stem, spinal cord, and optic nerve involvement, come after meningeal symptoms (neck stiffness and photophobia). Myoclonus is frequent.

The predominant forms are spinal, cerebral, or cerebella; however, the situation is typically mixed. Optic neuritis is a symptom of optic nerve involvement. Rarely are the peripheral nerves involved (Greenberg 2010).

2.1.3. Diagnosis

There is no diagnostic test. Total protein and globulin levels in the CSF are elevated. Diffuse, slow wave activity is visible on an electroencephalogram (EEG). The CT scan is normal. The same level of acuteness of all very small focal white matter alterations seen on an MRI are shown by their simultaneous enhancement with contrast (unlike MS).

When there is a clear-cut prior viral infection or immunization, the diagnosis is simple. It is frequently impossible to distinguish viral infection from acute encephalitis when it quickly precedes it. It could be challenging to distinguish it from acute MS. ADEM is indicated by fever, meningeal symptoms, increased CSF protein > 100 mg per ml, and cell count > 50 per mm^3 (Lindsay et al. 2011; Greenberg 2010).

2.1.4. Treatment

Despite the lack of controlled trials, steroids are used. In the acute phase, large doses are advised. In refractory situations, cyclophosphamide may be utilized (Lindsay et al. 2011).

2.1.5. Outcome

Usually, the sickness manifests in one phase. The death rate is 20%, and 50% of patients fully recover. The severity of the deficiency and a sudden start are linked to a poor prognosis (Lindsay et al. 2011).

2.2. Multiple Sclerosis

2.2.1. Introduction

Multiple sclerosis (MS) is the most common disabling non-traumatic illness to affect young adults (Kobelt et al. 2017). It is a white-matter-only, idiopathic, demyelinating illness involving the spinal cord, optic nerves, and brain (particularly corticospinal tracts and the posterior columns). The peripheral nerve myelin is not affected (Greenberg 2010). Its basic reason is yet unknown. MS is a complicated disease; numerous genes as well as a number of known environmental factors, including vitamin D or ultraviolet B light exposure, Epstein–Barr virus infection, obesity, and cigarette smoking, all modestly increase disease risk (Ascherio 2013; Dobson and Giovannoni 2018). Most cases begin between the ages of 10 and 59, peaking between 20 and 40. The female and male sex ratio is 2:1. Near the equator, prevalence is less than 1 per 100,000 people and varies with latitude (Lindsay et al. 2011).

2.2.2. Pathology

Plaques are small, dispersed lesions with a greyish color that range in size from 1 millimeter to several centimeters and are found in the white matter of the CNS. The lesions have a perivenous distribution and are in close proximity to veins (particularly, postcapillary venules) (Lindsay et al. 2011).

2.2.3. Pathogenesis

Immune deficiency: There has been talk of immune insufficiency. Deviations in normal immune status may be the cause of "relapses and remissions", and this may explain the possibility of a latent virus persisting. Plaques' T lymphocytes and macrophages may become sensitive to myelin antigens.

Genetic and hereditary factors seem to be important. Multiple sclerosis seems to run in families. As a result, histocompatibility antigens have been studied (HL-A). MS has been linked to A3, B7, B18, and DW2/DRW2, according to research. A total of 30% of monozygotic and 5% of dizygotic twins have concordance. More often than affected males, affected women pass MS to their children, indicating that mitochondrial genes play a role in inheritance.

Viruses: The establishment of MS may be influenced by viruses; infection may take place in a genetically or immunologically predisposed host. Varicella zoster, rubella, measles, and herpes simplex have all been linked to elevated serum as well as CSF antibody titers after recurrence.

Biochemical: A biochemical effect has not been observed. Myelin looks normal prior to disintegration, and the suggested excess of lipids in the diet or malabsorption of polyunsaturated fatty acids remain untested.

In conclusion, the cause is likely complicated and multifactorial (Lindsay et al. 2011; Dobson and Giovannoni 2018).

2.2.4. Clinical Categories

1. Relapsing and remitting: This stage is experienced by 70% of MS patients. With every assault, recovery is almost complete. This stage of the sickness could last for years. There is no established reason why relapses occur.

2. Secondary progressive and relapsing/remitting secondary progressive: Relapsing and remitting MS (RRMS) events are eventually succeeded by an additive loss of function with disability as well as an incomplete recovery. A total of 20% of all patients are currently in the chronic progressive stage. Six to ten years after the onset of symptoms, the condition typically switches from relapsing and remitting to secondary progressive.

3. Primary progressive MS (PPMS): This kind, which affects 15% of all patients, is typical in late-onset MS (>45 years). Relapses are typically absent in the context of gradual progression, and symptoms and signs are typically spinal.

4. Benign: 10 years after commencement, this condition is defined as low-disability (extended disability status score—EDSS 3). The real frequency of these situations is impossible to estimate, and individuals could eventually become severely disabled. The sporadic, unintentional discovery of MS in autopsies lends credence to a benign variety.

It is crucial to recognize the various MS phases when choosing patients to receive novel disease-modifying therapies. Specific scales, like the Kurtzke score/EDSS, can be used to quantify the degree of disability.

[EDSS is a ten-point, non-linear score scale where 1 = no symptoms/signs, 6 = requires a walking aid to achieve a short distance, 8 = restricted to bed or wheelchair, and 10 = death due to MS (Lindsay et al. 2011; Dobson and Giovannoni 2018; Greenberg 2010)].

2.2.5. Clinical Features

An exploration of the symptomless, prodromal, and symptomatic phases of MS is required to understand the condition. When a patient manifests with a clinically isolated condition (CIS), MS is often assumed. Depending on where the eloquent lesion is, this may be mono- or polysymptomatic. Optic neuritis, spinal cord, and brainstem syndromes are the most often observed presentations; nevertheless, a wide range of less-frequent presentations occur, encompassing cortical presentations like dominant parietal lobe syndromes.

Relapses of MS classically start off slowly over the course of a few hours to a few days, hit a plateau after a few weeks, and then slowly recover. In the early stages of MS, the gross clinical recovery after relapses frequently seems complete; yet, most relapses leave some injury behind. For instance, after acute optic neuritis, gross visual acuity may improve, but defects in contrast sensitivity, color vision, and depth perception are still present. As the neuronal reserve is gone, relapse recovery becomes imprecise, neurological abnormalities mount, and a chronic handicap results.

Approximately 10 "asymptomatic" lesions are observed on MRI for every clinical incident. Location and size play a role in symptomatology; a very small lesion in an eloquent area is more likely to result in symptoms. Lesions that are seen on an MRI are solely the tip of the iceberg; there are a lot more lesions that are microscopic in size and many more in deep or cortical grey matter.

After the onset of RRMS, secondary progressive MS often appears 10 to 15 years later and gradually progresses from sporadic relapses to a progressively worsening condition. Instead of a clear transition between disease categories, relapses take place against a background of slow progression until progression becomes dominant. Early MS symptoms like cognitive decline and MRI atrophy suggest that neurodegeneration has been present since the disease's clinical beginning.

Primary progressive onset (PPMS), which often involves one dominant neural system and gradual accumulation of progressive impairment, occurs in 5%–15% of cases. The most typical PPMS manifestation is a progressive spastic paraparesis, but other well-known PPMS subtypes include cerebellar ataxia, sensory ataxia, cognitive loss, and progressive visual loss.

There are fewer people who have PPMS now than there were previously. This raises ethical concerns regarding the classification of MS into different subtypes and is likely linked to the fact that there are no approved therapies for PPMS. Cases may be classified as experiencing relapsing MS after receiving treatment. The pharmaceutical industry used this fictitious categorization of MS into distinct disorders to obtain interferon beta approval under the Orphan Drug Act in the USA.

With a maximum recorded incidence of 2.9/100,000 people, pediatric MS is much less common than adult-onset MS. Treatment is decided based on recurrent demyelination events that are spatially and temporally

isolated. As pediatric MS may be multicentric at onset, it might be challenging to differentiate it from acute disseminated encephalomyelitis. Although relapse rates may be higher, physical recovery is frequently more thorough. In cases where the diagnosis is suspected, referral to a pediatric neurologist with experience in demyelinating illnesses is advised because only a few therapies are approved for use in children.

According to the 2013 changes to the clinical course of MS, MS can be conceived of as a single disease living within a continuum ranging from relapsing ('inflammatory dominant') to progressive ('neurodegeneration dominant'). Currently, false distinctions among the cases with progressive and the cases with relapsing disease are made in MS definitions. Instead, it is preferable to think of these categories as locations along a disease continuum that also includes prodromal (or radiologically isolated) disease.

Symptoms at Onset

1. General symptoms, such as fatigue, headaches, sadness, and aches in the limbs, may indicate psychoneurosis.
2. In a young patient, trigeminal neuralgia may be the first sign of multiple sclerosis.

Motor Symptoms

Among motor symptoms, monoparesis and paraparesis are more prevalent. Quadriparesis and hemiparesis are less frequent. Increased muscle tone, hyperactive deep tendon reflexes, an extensor plantar reflex, and a lack of abdominal reflexes are all warning signs.

Sensory Symptoms

Due to demyelination of the posterior column, numbness and paresthesia can be frequent, frequently mild, and temporary. Lesions to the posterior column affect the ability to feel joint position and vibration. When the cervical posterior column is involved, Lhermitte's sign occurs, and sudden neck flexion causes the limbs to feel "shock-like." Dysesthesia is a disagreeable sensation of burning, coldness, or warmth caused by spinothalamic tract lesions.

Loss of Vision

Acute optic neuritis (Retrobulbar neuritis): Loss of vision typically accompanied by a central scotoma, followed by weeks of recovery. This frequently happens to young adults. The loss of vision happens gradually over several days and is frequently accompanied by pain while moving the eyes (irritation of the dura around the optic nerve). Only color vision is compromised in milder instances. Usually, only one eye is damaged, but sometimes both eyes may be affected at the same time.

Visual impairment can range from a modest central scotoma to total blindness. In up to 50% of patients, a fundoscopy reveals swelling caused by papillitis. The difference between papilledema and papillitis is reduced visual acuity.

Investigation: VERs (visual evoked responses) show delayed conduction. High-resolution MRI confirms the presence of plaque.

Treatment: IV or oral steroid.

The incidence of repeated optic neuritis is greater when oral steroids are used. Within the following two years, it becomes apparent that intravenous steroids decrease the likelihood of later developing MS. Most patients (90%) regain their vision. The ocular neuritis study group observed that, within 2 years, clinically confirmed MS had manifested in 12% of individuals. After then, the annual risk was 5–6%.

Acute, double-sided optic neuritis is less frequent than one-sided illness and the likelihood of developing MS is lower. A transverse myelitis may occasionally follow (neuromyelitis optica). Leber's hereditary optic neuropathy can be distinguished from other conditions by testing mitochondrial DNA.

Disturbance of Ocular Movement

Demyelination that affects the third, fourth, or sixth cranial nerves' brain stem pathways can cause diplopia. When supranuclear or internuclear connections are implicated, abnormal eye movements can occur with or without diplopia. Internuclear ophthalmoplegia (INO), which originates from a lesion in the medial longitudinal fasciculus, is pathognomonic of MS in young people. Other symptoms include nystagmus (rare), pupillary

abnormalities, involvement of the III nerve, or involvement of the II nerve due to sympathetic engagement in the brain stem (Horner's syndrome).

Other Clinical Features

Ataxia of gait and limb incoordination (cerebellar or sensory type), intention tremor and dysarthria (cerebellar involvement), sphincter disruption, and impotence are some other conditions that can cause vertigo of the central type, as can emotional instability, paresthesia, dysarthria, pain, ataxia, photopsia (visual scintillations), depression or euphoria, dysarthria, dysarthria, ataxia, and epilepsy (Lindsay et al. 2011; Dobson and Giovannoni 2018; Greenberg 2010).

2.2.6. Investigations

Neurophysiological Testing

May detect a second asymptomatic lesion.

1. Visual evoked potential (VEP) detects visual pathway defects;
2. SSEP (somatosensory evoked response) may identify central sensory pathway pathologies;
3. BAEP (brain stem auditory evoked potential) may find brain stem pathologies.

Cerebrospinal Fluid (CSF) Study

On rare occasions, a moderate pleocytosis, primarily lymphocytes, is discovered. The total protein level can be higher. In 50–60% of instances, gamma globulin levels rise.

Agar or acrylamide electrophoresis of CSF reveals distinct bands that are absent from serum. Up to 95% of individuals with a diagnosed condition and 50–60% of patients following the initial incident have these bands. In contrast to other inflammatory neurological illnesses, OCBs (oligoclonal bands) are not unique to MS and do persist forever (Lindsay et al. 2011).

MRI of Brain and Spine

Longer relaxation times and a stronger signal on T2W are results of myelin degradation. Gliosis causes alterations that are comparable. The presence of periventricularly distributed white matter abnormalities is suggestive but not definitive of MS. Gadolinium's paramagnetism will reveal any active inflammation. If both the MRI and CSF (oligoclonal band) results are negative, MS will be ruled out. Following a single bout of demyelination, MR may be able to predict the long-term consequences (e.g., transverse myelitis or optic neuritis). People who have abnormalities in their cranial MR will relapse earlier than people who do not. MRI findings do not correlate enough with disability; however, newer methods may be more accurate indicators of illness development.

Diagnosis demands the absence of alternative illnesses and the occurrence of two or more events of symptoms attributed to demyelination, at least thirty days apart at separate sites in the CNS. For clinical investigations that integrate clinical elements with research findings, research criteria have been devised. According to the McDonald criteria (McDonald et al. 2001), a diagnosis can be made following a single clinical episode based on MRI evidence of the occurrence of new lesions.

After a year of increasing deficit, primary progressive MS can be identified by the presence of CNS plaques, oligoclonal bands in CSF that are not matched, and the elimination of other diagnoses (Lindsay et al. 2011; Greenberg 2010).

2.2.7. Differential Diagnosis

Due to MS's wide range of potential signs and symptoms, practically all other illnesses that might produce localized or diffuse CNS dysfunction are included in the differential diagnosis. Conditions that, both clinically as well as on diagnostic tests, may appear to closely resemble MS include the following (Greenberg 2010):

1. ADEM: Usually a single time event. May also have a CSF-Oligoclonal band. Corpus callosum engagement is rare;
2. CNS lymphoma;
3. Other closely linked demyelinating diseases, like Devic's syndrome;
4. Vasculitis;

5. Encephalitis: individuals are generally very ill;
6. Chronic white matter alteration: found in elder patients.

2.2.8. Treatment

Symptom management will frequently require an integrated multi-specialty approach, especially when the disease advances.

Acute Relapse

Methylprednisolone 3 gm i.v. over 3 days. It can also be administered orally.

Modification of Natural Course

Relapsing and remitting MS: Beta interferon and glatiramer acetate decrease the relapse frequency by approximately 30%.

A monoclonal antibody called natalizumab lowers the relapse rate by more than 60% and lessens disability, but it also increases the danger of getting PML-progressive multifocal leucoencephalopathy (01 in 1000). It is, therefore, only offered to people with severe illness.

Mitoxantrone is a chemotherapeutic drug that can be utilized in cases of aggressively severe disease but carries a risk of leukemia and cardiotoxicity.

Trials for a variety of other agents are ongoing.

Primary and secondary progressive MS: Currently, no efficacious disease-modifying agents are available (Lindsay et al. 2011; Dobson and Giovannoni 2018; Greenberg 2010).

2.3. Acute Transverse Myelitis

2.3.1. Introduction

Acute transverse myelitis (ATM) indicates inflammation of the spinal cord, and the etiologies encompass infectious/post-infectious, idiopathic, and autoimmune.

2.3.2. Etiology

Many so-called "causes" remain unproven. Generally agreed etiologies include the following (Greenberg 2010):

1. Infectious and post-infectious
    (a) Primary infectious transverse myelitis
        (i) Viral ATM: myelitis with viral encephalomyelitis, poliomyelitis, herpes zoster, and rabies;
        (ii) Bacterial ATM: encompassing tuberculoma of the cord;
        (iii) Spirochetal ATM: syphilitic myelitis;
        (iv) Fungal (blastomycosis, cryptococcosis, and aspergillosis);
        (v) Parasitic (echinococcus, paragonimiasis, schistosomiasis, and cysticercosis).
    (b) Post-infectious ATM: includes post-exanthematous and influenza
2. Post-traumatic
3. Physical agents
    (a) Decompression sickness;
    (b) Electrocaution;
    (c) Radiation.
4. Paraneoplastic syndrome: the commonest primary is lung; however, ovary, prostate, and rectum malignancy may cause ATM.
5. Metabolic
    (a) Pernicious anemia;
    (b) Diabetes mellitus;
    (c) Chronic liver disease.
6. Toxins

(a) Cresyl phosphates;
(b) Spinal anesthetics;
(c) Intra-arterial contrast materials;
(d) Myelographic contrast dye;
(e) After chemonucleolysis.

7. Arachnoiditis
8. Autoimmune

(a) MS (particularly Devic's syndrome);
(b) Post vaccination (rabies and smallpox).

9. Collagen vascular disease

(a) Mixed connective tissue disease;
(b) Systemic lupus erythematosus.

2.3.3. Clinical Presentation

ATM affects just 1–8 people per million each year. Age of onset range: 15–55 years. Patients may have a viral-like prodrome. Clinical features may include the following (Sherrell 2022):

- Backpain or radicular pain;
- Progressive muscle weakness;
- Paralysis, often starting in the legs;
- Diminished touch and temperature sensations;
- Numbness, tingling, and burning;
- Sexual malfunction;
- Raised urinary incontinence or urgency;
- Fatigue;
- Constipation.

The thoracic level is the most common sensory and presenting level. ATM is rarely the initial symptom of MS.

2.3.4. Progression

Progression is generally fast, with most attaining maximal neuro-deficit by 24 h, but the interval between the first symptom and highest deficit varies from 2 h to 14 days (Berman et al. 1981).

2.3.5. Evaluation

CSF Study

Normal during acute phase, but there may be elevated protein or pleocytosis levels or both.

MRI of Spine

In an individual developing acute paraplegia/myelopathy, particularly when ATM is considered a possibility, the initial investigation should be an urgent MRI. It excludes hemorrhage and other compressive myelopathy. MRI may be normal, however, there may be fusiform-shaped cord swelling with T2W signal changes at the involved level.

2.3.6. Treatment

High-dose steroid therapy (methylprednisolone). In nonresponsive cases, plasma exchange or intravenous immunoglobin (IVIG) can be tried (Absoud et al. 2017).

2.3.7. Prognosis

Good recovery takes place in 30% of patients. Death due to respiratory failure is rare (5%) (Lindsay et al. 2011).

2.4. Leukodystrophies

The normal development of myelin may be hampered by inborn metabolic abnormalities. Although certain genetic illnesses occasionally show their initial symptoms in adulthood, they typically first appear in infancy or youth.

The varieties have been identified:

- Metachromatic leukodystrophy;
- Adrenomyeloneuropathy or adrenoleukodystrophy (ADL);
- Globoid cell leukodystrophy.

Sex-related ADL is marked by adrenal hypofunctions and abnormal myelin in the CNS and peripheral nerves. A failure in the beta oxidation of very long chain fatty acids (VLCFA), which accumulate in the blood as well as skin fibroblasts, is the cause of the clinical presentation, which is quite varied. Lorenzo's oils, a dietary supplement, decrease them and may halt the advancement of this fatal disease. Female heterozygote carriers may have symptoms of a progressive myelopathy with late onset (Lindsay et al. 2011; Greenberg 2010).

3. Motor Neuron Disease (Amyotrophic Lateral Sclerosis)

3.1. Introduction

Motor neuron disease (MND)/amyotrophic lateral sclerosis (ALS) is a progressive neurodegeneration condition involving of upper and lower motor neurons. A total of 2 per 100,000 people are affected per year, with a prevalence of 6 per 100,000. Familial ALS is responsible for 5% of cases of MND and is generally inherited as a dominant trait. The male/female ratio is 1.5:1. The average age of onset is 55 years. Average survival after diagnosis is 03 years. Pathologically, various levels of the CNS and peripheral nerves may be affected:

1. Atrophy of the primary motor cortex;
2. The corticobulbar tract;
3. Nuclei of the cranial nerve;
4. The corticospinal pathway;
5. Neurons of the anterior horn.

Microscopically, there is a loss of neurons in the primary motor cortex, anterior horns, and cranial nerve nuclei. There is evidence of downsizing of corticospinal and corticobulbar fibers. There is no inflammatory response in the involved areas (Lindsay et al. 2011; Gaudette et al. 2000).

3.2. Etiology

The cause of MND is unknown. It seems that cell bodies of motor neurons (upper and lower) die spontaneously. Mutations in the SOD1 gene (superoxide dismutase enzyme producer) may be the cause in some familial ALSs (20%). These are responsible for about 2% of cases with ALS. However, other possible causes include viral infection, toxins, or mineral deficiencies (Lindsay et al. 2011).

3.3. Clinical Presentation

3.3.1. At Onset

A total of 75% of people have asymmetrical limb weakness and atrophy.

Clinical characteristics that are bulbar or pseudobulbar: dysphagia or dysarthria (25%).

The crucial element in both bulbar-onset as well as limb-onset diseases is the involvement of both lower and upper motor neurons together with normal sensation. Approximately 3–5% of instances of dementia include frontal dementia. Emotional instability can happen (Lindsay et al. 2011; Greenberg 2010; Arora and Khan 2022).

3.3.2. Limb-Onset ALS

Corticospinal pathways and anterior horn cells are affected in ALS with limb-onset. Increased muscle tone, exaggerated tendon jerks, extensor plantar reflex, and an asymmetrical occurrence of weakness are all symptoms of corticospinal tract degeneration. A slowly progressing type of MND that only affects the cortical spinal tract is primary lateral sclerosis. Involvement of the anterior horn cells causes muscular atrophy, weakness, and fasciculations. Muscle cramping could occur. The degree of weakness does not indicate that weakness is as bad

as bulbar-onset disease. Possible hand wasting can occur (Lindsay et al. 2011; Greenberg 2010; Arora and Khan 2022).

3.3.3. Bulbar-Onset Disease (Progressive Bulbar Palsy)

Bulbar-onset disease has a mixer of corticobulbar plus lower cranial nerve motor nuclei degeneration, which results in difficulty chewing, an expressionless face, nasal regurgitation, and an exaggerated jaw jerk.

As the pathology advances, the motor system is affected at all levels. Individuals with limb-onset get bulbar features, and vice versa. Weakness of respiratory muscles finally happens and is the frequent etiology of death.

Rare clinical scenarios are dyspnea from respiratory muscles dysfunction, recurrent chest infections from cryptic aspiration, or significant weight loss (Lindsay et al. 2011; Greenberg 2010; Arora and Khan 2022).

3.3.4. Rare Clinical Types and Differentials

1. Primary lateral sclerosis is an asymmetrical upper motor neuron condition that progresses relatively slowly.
2. The "flail arm" variety refers to severe weakening and atrophy of the arms with solely mild weakening of the legs. Typically, this progresses more slowly.
3. Progressive muscular atrophy (may mimic multifocal motor neuropathy along with conduction block, spinal muscular atrophy, limb girdle dystrophy, lead neuropathy, or diabetic amyotrophy).
4. ALS like syndrome:

    - Hexosaminidase deficiency;
    - Paraproteinemias;
    - Lymphoproliferative disease;
    - HIV infection;
    - Lead poisoning;
    - Hyperparathyroidism and hyperthyroidism (produce hyperreflexia and muscle wasting);
    - Pseudobulbar palsy in cerebrovascular disease or multiple sclerosis.

3.3.5. Never in MND

- Bladder is never involved;
- Sensory deficits do not occur;
- Ocular muscles are never involved (Lindsay et al. 2011; Greenberg 2010; Arora and Khan 2022).

3.4. Investigations

Common investigations:

- Nerve conduction studies show normal results;
- EMG shows fibrillation;
- MRI (to excludes compression of spinal cord or foramen magnum);
- Thyroid hormones and calcium studies rule out metabolic or endocrine disease;
- In certain cases, screening for paraproteinemia, lymphoreticular disorders, and hexosaminidase deficiency.

Investigation of suspected MND:

- Mixed upper and lower motor neuron (ALS) syndrome:

    - Electromyography and nerve conduction studies (NCSs).
    - MRI of the brain and spinal cord.
    - Routine blood tests, serum electrophoresis, and thyroid function.
    - HIV test, if there are risk factors.

- Pure lower motor neuron syndrome:

    - Genetic investigations (if slowly progressive, indicating spinal muscular atrophy).
    - Electromyography/NCSs for conduction block.
    - Routine blood tests, serum electrophoresis, and thyroid function.

- Pure upper motor neuron syndrome:

    - MRI of the spinal cord and brain.
    - Folate/B12.
    - Central motor conduction time (utilizing transcranial magnetic stimulation techniques, rarely available).

- Lumbar puncture (Lindsay et al. 2011; Greenberg 2010; Arora and Khan 2022).

3.5. El Escorial Criteria for Diagnosis of MND/ALS

Existence of the following:

- LMN signs in at least two extremities;
- UMN signs in at least one area (cervical/bulbar/ lumbosacral);
- Advancement of disease.

Absence of the following:

- Neurogenic sphincter disturbance;
- Sensory signs;
- Other clinically present PNS/CNS disease;
- Rule out ALS-like syndromes (Brooks 1994; Lindsay et al. 2011).

3.6. Treatment

The main goal of treatment is to control symptoms while providing the patient, and their family, with support as they worsen and their requirements change.

To fully comprehend the ailment and its natural history, counseling is necessary. Meeting the difficulties of each stage of sickness with the help of a nurse professional is essential, and it is ideal to discuss feeding concerns and ventilatory support options in advance so that informed decisions can be made. With medical, legal, and ethical constraints, providing patients with complete care can be difficult.

3.6.1. Symptomatic Treatment

Dysarthria and anarthria—speech evaluation and communication assistance when required.

Dysphagia and aspiration—PEG (percutaneous endoscopic gastrostomy).

Nutrition—calculate calorific components and supplement nutrition with vitamins.

Muscular weakness—walking aids, physiotherapy, splints, etc.

Respiratory failure—Respiratory failure is unavoidable when critical capacity declines. When this goes under 75% or orthopnea begins in patients who do not have extensive bulbar involvement, noninvasive ventilatory support should be taken into account. Recent studies show that this can enhance quality of life. It is less clear what function invasive mechanical ventilation will serve. Rarely, ALS can begin with initial respiratory failure prior to talking about therapy options. This poses a serious managerial conundrum.

3.6.2. Disease-Modifying Agent Treatment

Riluzole is an energy-buffering and anti-glutamate agent. A 100 mg/day dose is safe with a minimal effect, prolonging life by 02 months (Lindsay et al. 2011; Greenberg 2010; Arora and Khan 2022).

4. Inherited Motor Neuron Disorders

4.1. Spinal Muscular Atrophies (SMAs)

The second commonest fatal autosomal recessive illness in Caucasians is spinal muscular atrophy (after cystic fibrosis). The anterior horn cells' deterioration defines the disease. There is symmetrical muscular atrophy and weakening here.

Three forms of recessive SMA are distinguished based on the age of onset, the extent of muscular damage, and the duration of survival (all varieties mapped to the 5q12.2-q13.3 gene locus).

The odds of a parent passing SMA on to their children are 1/10,000, or just under 1%.

4.1.1. Type I—Werdnig–Hoffmann Disease (Acute Infantile SMA)

The incidence of this autosomal recessive condition is 01:25,000 live births.

Clinical characteristics include decreased fetal movements in the final stages of pregnancy along with newborn hypotonia and weakness.

Every motor developmental milestones is postponed, and 95% of cases pass away by 18 months.

4.1.2. Type II—Kugelberg–Welander Disease (Late Infantile or Juvenile SMA)

Pathology is akin to Werdnig–Hoffmann disease.
Clinical pictures includes:

- The involved muscles are limb girdle muscles.
- It progresses slowly. Median age of death: 12 years. The dominant form is the one that progresses through childhood.

4.1.3. Type III—Adult-Onset SMA

Occurs between second and fifth decade where progressive weakness of limb girdle muscles is seen.
Differentiation from progressive muscular atrophy form of ALS is difficult. A benign clinical course suggests the former.

4.1.4. Scapuloperoneal and Distal Forms

Distinction from Charcot–Marie–Tooth (CMT) disease types I and II as well as scapuloperoneal dystrophy is clinically challenging and differentiation may solely be attained on neurophysiological and histological grounds.

4.1.5. Spinal and Bulbar Muscular Atrophy/Kennedy's Syndrome

It is an X-linked, adult-onset neurogenic muscle atrophy with late distal and bulbar involvement (Gene Locus: Xq11-q12). At over 40 years old, fasciculations begin, followed by muscular atrophy and weakening. Both facial fasciculations and bulbar symptoms are typical. The Babinski sign is unfavorable. A long lifespan is possible.

4.1.6. Management of SMAs

There is nothing specific. Supportive care and genetic counselling are needed (Lindsay et al. 2011; Greenberg 2010; Arora and Khan 2022; Teoh et al. 2017).

5. Peripheral Neuropathies

5.1. Introduction

Diffuse peripheral nerve lesions that cause weakness, sensory disturbance, and/or altered reflexes are referred to as peripheral neuropathy. A single nerve condition known as mononeuropathy is frequently caused by entrapment or trauma. The involvement of two or more nerves, typically as a result of a systemic disorder, is referred to as mononeuropathy multiplex (like vasculitis, arteritis, or diabetes mellitus) (Greenberg 2010).

5.2. Etiology

Diabetes mellitus, alcoholism, and Guillain–Barré are responsible for 90% of cases. Other causes encompass vasculitis/arteritis, monoclonal gammopathy, acute idiopathic polyneuritis, hepatitis-C-virus-linked cryoglobulinemia, Sjogren's syndrome, etc. (Table 1) (Greenberg 2010).

Table 1. Mnemonic for etiologies of peripheral neuropathy—"GRAND THERAPIST".

Guillain–Barré syndrome	**T**raumatic
	Hereditary (e.g., Charcot–Marie–Tooth)
Renal (uremic neuropathy)	**E**ndocrine or **E**ntrapment **R**adiation
	Alcoholism
Amyloid or **AI**DS	**P**orphyria or **P**sychiatric or **P**araneoplastic or
	Pseudoneuropathy or **P**MR
Nutritional (B6 and B12 deficiency)	**I**nfectious/post-infectious (like Hansen's disease)
	Sarcoidosis or "**S**ystemic" **T**oxins [such as
Diabetes or **D**rugs	heavy-metal toxicity (plumbism)]

Source: Authors' compilation based on data from Greenberg (2010).

5.3. Clinical Features

Peripheral neuropathies may present as a deficiency of sensation, pain, incoordination, weakness, and as difficulty in ambulating.

5.4. Evaluation

Work-up for peripheral neuropathies of unknown cause:

1. Blood work: Hb-AlC, ESR, TSH, and vitamin B_{12};
2. EMG and NCS;
3. MR nervogram.

5.5. Treatment

Treatment is provided according to etiology.

6. Guillain–Barré Syndrome (GBS)

6.1. Introduction

Acute demyelinating polyneuropathy Guillain–Barré syndrome (GBS) was initially reported in 1859. It has ascending motor weakness, sensory dysfunction, and autonomic dysfunction, all of which are commonly followed by prodromal disease (generally a gastrointestinal or respiratory infection). It is believed that it has an autoimmune foundation. GBS was once regarded as a singular clinical entity. Acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor–sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome (MFS) are the four primary clinical and electrophysiological subgroups of GBS. AMAN is restricted to pure motor involvement, AMSAN is a more serious disease with motor–sensory involvement, and AIDP is characterized by demyelination.

6.2. Incidence and Etiopathogenesis

About two incidents occur for every 100,000 people annually. It typically happens 1 to 3 weeks following a viral illness or other infection, or following immunization. GBS can develop following viral infections, such as varicella zoster, mumps, and cytomegalovirus (CMV). Additionally, Mycoplasma, Campylobacter infections, vaccinations with vaccines and antitoxins, surgery, trauma, and sometimes malignancy and immunodeficiency are associated with it. Responses to peripheral nerve myelin are cell- and antibody-mediated. In some patients, a T-cell-mediated attack on the myelin basic protein is developed; others develop antibodies to myelin gangliosides or glycoproteins. If segmental demyelination is severe, it might cause subsequent axonal damage. Peripheral nerves and nerve roots experience lymphocyte infiltration within the perivascular space. Cytokines, which are released by lymphocytes and macrophages, harm Schwann cells and myelin. Regeneration is not possible after nerve cell loss and axonal damage (Lindsay et al. 2011).

6.3. Clinical Features

6.3.1. Symptoms

GBS has a variety of clinical characteristics. The most frequently presenting symptoms are weakness and sensory disruption. Typically, a progressive ascending motor weakness, ranging from difficulty walking to paralysis, begins in the lower limbs. Respiratory failure could result from the weakening progressing to the respiratory muscles. There may also be ophthalmoplegia and concomitant bulbar paralysis in cases of facial nerve palsies.

The sensory sensations of paresthesia, numbness, and discomfort are possible. Lower-back pain is frequently felt and can be very severe. In 80% of patients, paresthesia and numbness begin distantly and progress in a manner comparable to motor weakness (Pascuzzi and Fleck 1997; Tandel et al. 2016; Lindsay et al. 2011; Greenberg 2010).

6.3.2. Signs

The results of a clinical examination reveal a flaccid areflexic paralysis. Within 2 weeks after the initiation of symptoms, muscle atrophy can start and can be severe. Arrhythmias, blood pressure swings, urine retention,

paralytic ileus, and hyperhidrosis are all symptoms of autonomic dysfunction, which is a prevalent condition. If severe, this might be related to unexpected death (Pascuzzi and Fleck 1997; Tandel et al. 2016; Lindsay et al. 2011; Greenberg 2010).

6.4. Clinical Types of GBS

6.4.1. AIDP

The most prevalent type, known as acute inflammatory demyelinating polyneuropathy (AIDP), affects 85 to 90% of patients and is identified pathologically by demyelination, lymphocytic infiltration, and macrophage-mediated removal of myelin. Clinical signs include hypo- or areflexia together with symmetrical, ascending motor weakening. Myelin sheaths wrapping peripheral nerve axons are inflamed and destroyed by activated macrophages as part of the underlying pathogenic process. This causes the conduction of peripheral nerves to slow down and become blocked, which weakens muscles. In severe cases, axonal damage could develop later. Antibody binding occurs after nerve terminal axon damage in AIDP, and this route typically results in membrane attack complex (MAC) development with the breakdown of the terminal axonal cytoskeleton as well as mitochondrial injury.

6.4.2. Acute Motor Axonal Neuropathy (AMAN)

AMAN is more prevalent in young people and during the summer in China and Japan. There is a connection to previous Campylobacter jejuni infection.

6.4.3. MFS

Miller Fisher syndrome (MFS) includes ataxia, areflexia, and ophthalmoplegia but usually not weak limbs. Characteristics are serum IgG antibodies against a particular ganglioside (anti-GQ1B antibodies).

6.4.4. AMSAN

It is a GBS variety that can be proven through electrophysiological investigations that involves both motor and sensory fibers. It is more severe and is accompanied by a protracted or even limited recovery. AMAN-like clinical traits are present; however, there are additional sensory symptoms. The fundamental pathogenic mechanism is identical to that of AMAN (i.e., antibody mediated axonal injury).

Chronic inflammatory demyelinating polyneuropathy, a chronic variant of GBS, has been identified. The clinical characteristics resemble those of AIDP; however, they proceed more slowly or recur more frequently (Hughes and Cornblath 2005; Greenberg 2010; Lindsay et al. 2011).

6.5. Investigations

Most patients have high CSF protein levels, although this does not happen until the second/third week of sickness. Normally, cells are missing; however, in 20% of cases, up to 50 cells per mm^3 can be observed (Lindsay et al. 2011).

6.5.1. Nerve Conduction Studies

These can be typical if they are conducted early on in the illness. Multifocal demyelination findings are quickly followed by decreased motor conduction, conduction block, and extended distal motor latencies.

6.5.2. Ancillary Tests

These are carried out to find any triggering infections and can include bacterial and viral tests. Electrolytes are examined for immune complex glomerulonephritis and improper antidiuretic hormone secretion.

Clinical history, CSF analysis, neurophysiological testing, and the elimination of acute spinal cord illness, myasthenia gravis, and porphyria all contribute to the diagnosis.

A number of subtypes of antibodies have been linked to them:

- AMAN: anti-GD1a and GM1;
- Acute sensory neuropathy: anti-GD1b.

6.6. Treatment

The best probability of a successful result is supportive care in an HDU or ICU with the exclusion of respiratory and autonomic problems. Impending respiratory failure symptoms call for voluntary intubation for ventilation. Tracheotomy should be performed when the need for breathing support is likely to last longer than two weeks.

Where the degree of immobility renders thrombosis a potential risk, low-molecular-weight heparin (subcutaneous) must be administered with supporting stockings.

In order to hasten recovery and enhance results, both plasma exchange (PE) and intravenous immunoglobulin (IVIG), 0.4 g/kg/day for 05 days, are equally beneficial. Blood is circulated via an extracorporeal cell separator during plasma exchange. Human albumin solution or fresh frozen plasma (FFP) is used to replenish the blood's plasma fraction. During the procedure, anticoagulants are given.

Plasma exchange is used to get rid of antibodies linked to the underlying autoimmune response. Due to its simplicity of administration, IVIG is the favored treatment; however, there are several drawbacks, vasomotor instability, including flu-like symptoms, congestive heart failure, thrombotic events (including myocardial ischemia and strokes), temporary renal failure, and allergy. There is a very slight chance of infection. Treatment is typically delayed in milder instances and provided to patients who are unable to walk. There is no need for steroids (Tandel et al. 2016; Hughes and Cornblath 2005; Pascuzzi and Fleck 1997; Lindsay et al. 2011; Greenberg 2010).

6.6.1. Intravenous Immunoglobulin

GBS can be effectively treated with intravenous immunoglobulin (IVIG), which has been shown to hasten recovery in a manner analogous to plasma exchange. When given within 02 weeks of the start of symptoms, it is most helpful. IVIG is superior to plasma exchange in a number of ways. It has fewer adverse effects, is more readily accessible, and requires less labor. IVIG indications include respiratory depression and muscular weakness.

By inhibiting Fc receptors, IVIG, which is made up of pooled donor IgG antibodies, may lessen the degree of autoimmune inflammation in GBS. This stops the Fc component of antibodies from binding, hence stopping antibody-mediated cell death. Additionally, complement activation is changed. IgA deficiency and prior allergic reactions to IVIG are examples of contraindications (linked to anaphylactic reactions to blood products). IVIG side effects can range from mild to severe and include nausea, headaches, fluid overload, abnormal liver function tests, acute renal failure, venous thromboembolism, and anaphylaxis. Dermatological diseases like erythroderma and fluid overload are also possible side effects. There is no proof that additional rounds of therapy are helpful (Tandel et al. 2016; Hughes and Cornblath 2005; Pascuzzi and Fleck 1997; Lindsay et al. 2011; Greenberg 2010).

6.7. Outcome

The death rates is 2%. A total of 10% of those who advance to respiratory failure are moderately impaired and 20% are severely disabled. In milder diseases, the result is fantastic. The recurrence rate is 3% (Lindsay et al. 2011).

7. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Unlike Guillain–Barré, it rarely affects the respiratory function or cranial nerves and has a gradual or variable course from weeks to months. Segmental demyelination followed by remyelination (onion bulb development) and sparse mononuclear inflammatory change are pathological features. All neuropathies have a 3% prevalence and a five per million incidences.

The age of onset is 35 years on average (fluctuating course in younger patients; progressive course in older patients).

In about two-thirds of patients, IVIG, plasma exchange, or steroids are effective. Steroids should be administered first in moderate/severe cases (cost and convenience of usage), followed by IVIG, and then PE if the response is insufficient. Immunosuppressive medications (such as azathioprine, cyclosporin, or cyclophosphamide) are used in resistant instances despite minimal evidence (Lehmann et al. 2019; Lindsay et al. 2011).

Outcome with Therapy

Thirty percent are symptom-free, 45% are mildly disabled, and 25% are severely disable (Lehmann et al. 2019; Lindsay et al. 2011).

8. Neuromuscular Junction Disorder: Myasthenia Gravis (MG)

8.1. Introduction

MG is a neuromuscular transmission disease characterized by weakness and fatigability of some or all muscle units, as well as weakness that worsens with prolonged or frequent effort or that is eased by rest toward the end of the day. The nicotinic postsynaptic receptors for acetylcholine are destroyed by an autoimmune process, which causes this disease.

A total of 5 cases out of 100,000 are myasthenia gravis, making it a rare disease. An immunological basis for the disease is suggested by the rise in autoimmune diseases in both patients and first-degree relatives, as well as by the relationship of the condition with particular histocompatibility antigens (HLA-B7, B8, and DR2) in the body.

8.2. Etiology

Antibodies attach to the receptor sites, destroying them (complement mediated). Ninety percent of patients have acetylcholine receptor antibodies (AChR antibodies), which can be detected by radioimmunoassay in their serum.

The thymus's function: In 80% of cases, thymic abnormalities are present. The thymus' primary job is to influence the development of T-cell lymphocytes, which take part in immunological responses. Numerous conditions, such as systemic lupus erythematosus, that may be related to myasthenia gravis have thymus dysfunction.

8.3. Pathology

Alterations are seen in the thymus as well as in muscles.

Muscle biopsies may demonstrate abnormalities:

- Lymphocytic infiltration linked to very small necrotic foci of muscle fiber injury.
- Muscle fiber atrophy.
- Diffuse muscle necrosis plus inflammatory infiltration (when linked to thymoma).

A biopsy of a motor point may reveal aberrant motor endplates. Terminal nerve branching that is excessively lengthy and crooked is visible after supravital methylene blue staining. ACh receptors are destroyed by light and electron microscopy, and the secondary folds of the postsynaptic surface are simplified.

8.4. Clinical Features

Up to 90% of cases present in early adult life (less than 40 years of age). The female–male ratio is 2:1. The disease may be selective, involving particular groups of muscles.

Several clinical varieties are identified:

- CLASS I—solely ocular muscle (20%);
- CLASS II—mild generalized weakness;
- CLASS III—moderate generalized and mild to moderate ocular-bulbar weakness;
- CLASS IV—severe generalized and oculo-bulbar weakness;
- CLASS V—myasthenic crisis.

CLASSES II–V comprise 80% of cases. Nearly 40% of CLASS I will ultimately become widespread. The rest exist purely in an ocular manner throughout the course of the disease. Respiratory muscle engagement is associated with serious illness.

8.4.1. Cranial Nerve Symptoms and Signs

- Ptosis and muscular paresis are brought on by ocular involvement.
- A weak jaw might cause the mouth to hang open.
- Face muscles that lack strength appear expressionless.

- When patient smiles, a characteristic smile is produced by buccinator weakness (myasthenic snarl).

Bulbar engagement may lead to dysphagia, dysphonic dysarthric speech, nasal regurgitation, and nasal intonation to speech.

The presence of fatiguing is valuable in attaining a diagnosis as well as in following up the response to therapy.

Fatiguing of other bulbar muscles can be shown by:

- Blowing out cheeks against pressure.
- Counting as far as possible in one breath, etc.

The tongue occasionally demonstrates the characteristic triple grooved appearance with a two lateral plus one central furrow.

8.4.2. Limb and Trunk Symptoms and Signs

The head may droop if the muscles in the neck are weak. Muscles in the proximal limbs are most frequently impacted. Moving against a persistent opposition can reveal fatigue. On repeated testing, limb reflexes frequently become overactive and wear out. A total of 15% of instances result in muscle wasting. The weakness is made worse by anxiety, illness, pregnancy, medicines that affect neuromuscular transmission, and stress.

8.5. Differential Diagnosis

Distinguish from the following:

- General debility/weakness (like chronic fatigue syndrome) as well as functional weakness.
- Progressive ophthalmoplegia (like oculopharyngeal dystrophy and mitochondrial myopathy).
- MS—dysarthria, fatigue, and diplopia with a remitting and relapsing course.
- Lambert–Eaton myasthenic syndrome.

8.6. Natural History

10%—long period remission;
20%—short period remission (1 to few months);
30%—progress to death;
40%—varying degree of disability worsen by exercise.

8.7. Investigation

8.7.1. Pharmacological Testing

Anticholinesterase drugs are utilized to finalize a diagnosis.

Tensilon (edrophonium)—To combat the side effects of muscarinics, a short-action, 2–4 min injection of 2–10 mg was slowly combined with atropine pretreatment (nausea and bradycardia—resuscitation facilities should be available). When objective testing reveals a definite improvement in a deficiency, this is encouraging. A saline injection control with a blinded monitoring person can be helpful. The Tensilon test can result in a false positive in Lambert–Eaton syndrome and a negative result in ocular myasthenia.

8.7.2. Serological

A total of 90% of patients have anti-AchR antibodies, which are almost exclusively specific to this illness. Only 60% of cases of ocular myasthenia display antibodies. The severity of the disease is correlated with titer magnitude. A percentage of patients who do not have anti-AchR antibodies have anti-Muscle-Specific Kinase (anti-MUSK) antibodies.

There is overlap with other autoimmune illnesses, as evidenced by the occurrence of other antibodies, such as microsomal, colloid, rheumatoid factor, and gastric parietal cell antibodies. A total of 90% of patients with thymoma and 30% of all patients have anti-striated muscle antibodies.

8.7.3. Electrophysiological

The decrementing response is a reduction in the amplitude of the compound muscle action potential produced by repeated supramaximal nerve stimulation. Different stimulation rates—even those as low as 3/second—can result in a decrementing response.

Single-fiber electromyography is a more accurate indicator of neuromuscular function and is typically increased (95% of mild instances are abnormal). It measures "Jitter", which is the time interval variability of action potentials from two single muscle fibers of the same motor unit.

8.7.4. Additional

A significant mediastinal mass will be shown on a chest X-ray, although a minor thymoma cannot be ruled out. All recently diagnosed cases should have a chest CT scan.

8.7.5. Treatment

Protecting respiration with intubation and, if required, ventilation is the top priority in critically ill patients.

Anticholinesterase Drugs

This is a well-established form of therapy. Anticholinesterase medications prevent the enzyme cholinesterase from degrading acetylcholine, which enhances receptor activation. More acetylcholine is, hence, accessible to influence neuromuscular transmission.

To combat side effects (vomiting, nausea, muscle fasciculations, diarrhea, and increasing weakness), atropine, a muscarinic inhibitor, may be needed. Anticholinesterases seldom completely relieve symptoms, and high doses can cause cholinergic crisis.

Cholinergic crisis:

- Deteriorating weakness;
- Increased salivation, sweating, and bronchial secretions;
- Miosis;
- Ultimate respiratory failure.

Atropine can veil initial warning symptoms of this potentially life-threatening condition.

Steroids

Steroids are a sensible choice in generalized and profound ocular disease (rare) since this disorder is immune-mediated. The first dose of prednisone is 60 mg/day. Before improvement, there may be a brief period of decline. As a result, low-dose regimens are frequently favored, starting cautiously with prednisone 25 mg every other day. When a reaction happens, the dose is decreased.

Immunosuppressants (Other than Steroids)

These drugs (cyclosporine and azathioprine) are applied in individuals who do not respond to steroids or who need an unacceptably large dose of a steroid for maintenance.

Thymectomy

There are two indications for thymectomy:

1. Presence of a thymoma;
2. When MG is widespread and the utility of surgery outweigh the dangers.

A trans-sternal approach is preferred over a supra-sternal approach as it provides more chance of total removal.

Within 5 years of surgery, 70% of cases stay in remission.

Plasmapheresis

Plasma filtration has a short-term benefit by removing antibodies and other circulating components (4–6 weeks). Over a period of 6–8 days, 1.5–2 liters of plasma are swapped 3–5 times. The method is costly and fraught

with risks (metabolic disturbance, hypotension, and thrombo-embolism). It is employed to stabilize refractory cases and, in severe illness, to prevent thymectomy.

Immunoglobulin (IVIG)

Administered intravenously daily for 5 days at a dose of 400 mg/kg in place of plasmapheresis. Acetylcholine receptors may be blocked by the mechanism. A favorable reaction lasts for two to three months in 75% of individuals. The cost of treatment is high, and complications and long-term implications are unknown. Anticholinesterases should not be necessary for the full duration of the sickness. These medications may be stopped after the disease is under immunological control.

8.7.6. Emergency Treatment—Myasthenic/Cholinergic Crises

- Find and manage the precipitating etiology, e.g., drug interaction, infection, or overdose;
- Position the patient at 45°, clean airway, give O_2, and, if in obvious respiratory failure, intubate plus ventilate for the duration, as needed.

Myasthenic Crisis

- Neostigmine IV, 08–12 mg/day;
- Inj. atropine 0.5 mg 8 hourly;
- Prednisolone 100 mg/day;
- Consideration for IVIG or plasmapheresis;
- Switch to oral anticholinesterases when patient is able to swallow.

Cholinergic Crisis

- Discontinue all anticholinesterases;
- Regularly check for respiratory function (especially vital capacity);
- Wean from ventilation at the right time;
- Restart oral anticholinesterases at a low dose followed by a gradual increase (Trouth et al. 2012; Gilhus et al. 2019; Lindsay et al. 2011; Greenberg 2010).

8.7.7. Neonatal Form of MG

This happens in a group of infants or mothers with MG.

- Indicated by poor sucking /crying as well as floppy extremities.
- Become symptomatic within 48 h of birth and may exist until the end of the third month.
- Occurs due to passive transplacental transfer of IgG (acetylcholine receptor antibodies).
- Therapy with anticholinesterases is needed until spontaneous resolution occurs. Remission takes place after exchange transfusion. This can occur even when the infant's mother has been in remission for many years (Trouth et al. 2012; Gilhus et al. 2019; Lindsay et al. 2011; Greenberg 2010).

8.7.8. Congenital Myasthenias

Pre-, post-, and mixed synaptic abnormalities are the cause of these non-immunologic illnesses. Although onset might be postponed until adulthood; they typically manifest in infancy. Muscle groups in the extremity (with concomitant skeletal anomalies when early age of onset), bulbar, ocular, and respiratory systems are particularly susceptible to fatigue. Electrophysiological evaluation is complicated, there are no AChR antibodies, and some patients respond to anticholinesterases or 3,4-diaminopyridine as supportive therapies (Trouth et al. 2012; Gilhus et al. 2019; Lindsay et al. 2011; Greenberg 2010).

9. Inherited Myopathies

9.1. Inherited Muscle Disorders

The muscular dystrophies (MD) are gradually deteriorating muscle illnesses that are genetically determined and characterized by cycles of fatty tissue replacement and muscle regeneration. Defects in the dystrophin-related glycoprotein complex are linked to a variety of diseases. Congenital myopathies have a more favorable prognosis

and are characterized by morphological muscular defects without necrosis. The metabolic myopathies exhibit aches and weariness.

9.1.1. Xp2.1 Dystrophies (Duchenne and Becker Muscular Dystrophy)

Xp2.1 is where the dystrophin gene is found. While deletions inside the middle rod domain are linked to the milder Becker Dystrophy, point mutations and deletions involving the terminal domains are more frequently linked to the serious clinical phenotype of Duchenne.

Duchenne Muscular Dystrophy

Clinical Features: The prevalence of Duchenne muscular dystrophy is 01:3500 male births. It is characterized by delayed motor development in the early years, which is often seen between 1 and 3 years of age. Contractures, scoliosis, and eventually loss of ambulation occur around the age of 12. Although it occurs in 80% of cases, pseudohypertrophy of muscles, especially the calf, is not a pathognomonic sign.

The child is unable to climb steps or get out of a low chair, and when they try to get up from the ground, Gower's placard warns that he will "climb up him" (not diagnostic; however, implicative of pelvic muscle weakness).

Investigations: A diagnosis may be made through gene testing of serum. Due to the size of the dystrophin gene, many procedures only screen a small portion of it. Therefore, a "negative test" does not exclude it, necessitating a muscle biopsy and immunological investigations. This shows that dystrophin is not present. By using PCR, female carriers may be found.

Creatine kinase (CK): Markedly increased (several thousand times). At birth, the enzyme is increased, and female carriers have higher levels.

Electrocardiogram: In 80% of electrocardiograms, conduction problems are visible together with tall precordial R waves with deep left precordial Q waves. To identify developing cardiomyopathy, repeat echocardiography should be performed occasionally.

Electromyography—demonstrates serious myopathic change.

With the utilization of scoliosis surgery, active treatment of contractures, and noninvasive ventilation, the expected lifespan has increased from late teens to late 20s or early 30s. Although the ideal regimen is still unknown, corticosteroids decrease development and delay the onset of impairment. Death occurs due to a lack of oxygen in the lungs, an infection, or "suddenly" (possibly due to a heart condition). Coordinating long-term care for afflicted people should be performed in advance rather than in response to the progression of the illness.

Becker Dystrophy

From Duchenne dystrophy to the milder illness Becker dystrophy, abnormalities in the dystrophin gene may be linked to a range of manifestations. The incidence of Becker muscular dystrophy is lower than that of Duchenne muscular dystrophy (1:35 000), and it typically manifests later in life with limb girdle involvement and pseudohypertrophy. Some female bearers of the mutation may also experience these later, lesser manifestations. Cardiac involvement, which is unrelated to the mutation or the degree of limb muscle dysfunction, may cause symptoms in up to 10% of affected people and female carriers.

With serum DNA analysis, a diagnosis is made in up to 80% of instances. A diagnosis is made in the remaining cases using a combination of immunohistochemistry evidence of a relatively absent dystrophin, high CK, the clinical type, and pedigree analysis.

9.2. Muscular Dystrophies

9.2.1. Dystrophies with Particular Patterns of Weakness

Facioscapulohumeral (FSH)

A contraction of 3.3 kB repeats at locus 4q35, which is linked to an autosomal dominant disease of varied severity. The prevalence is 1–2:100,000. The exact mechanism through which this mutation results in illness in unknown.

The clinical pictures are:

- Facial muscle weakness (may be asymmetrical or mild);

- Periscapular weakness resulting in winging of the scapula as well as rising up of the scapulae on abduction;
- Humeral muscles weakness;
- A primely proximal lower-limb type of weakness leading to a dromedary or camel-backed gait. Pseudohypertrophy is not a characteristic feature.

The degree can range from severe childhood types to later-onset, potentially asymptomatic diseases. Only the highest limit of 1.5–2 or normal CK levels may be increased. Although secondary inflammatory change on a biopsy may result in an incorrect diagnosis of polymyositis, muscle biopsy and EMG will demonstrate myopathic abnormalities but lack specific characteristics. Heart involvement is not a characteristic. Some early onset cases (Coat's syndrome) are complicated by high-rate sensorineural deafness as well as exudative retinal telangiectases. The magnitude of respiratory muscle involvement affects the prognosis. Some patients might benefit from ventilator support.

Scapuloperoneal

It is a condition affecting the proximal muscles of the upper and lower limbs that is dominant or recessive. Beginning in maturity, foot drop is succeeded by scapular deltoid, bicep, and tricep weakness. It is challenging to distinguish from inflammatory muscle disease and spinal muscular atrophy.

Distal

Apart from myotonic dystrophy, distal weakness brought on by primary dystrophies is uncommon. It is described that both autosomal dominant and recessive patterns can initially affect the muscles of the upper or lower limbs. Some have been linked to muscle fiber vacuolation.

Emery–Dreifuss

Although uncommon, its cardiac consequences make it significant. There are reports on dominant and X-linked forms. Spinal contractures provide the impression of hyperextension. Early ankle and elbow contractures occur. Scapuloperoneal dispersion may be weak. Virtually all heart abnormalities are life-threatening, yet ventricular tachyarrhythmias do occur sometimes. Patients will need to be paced and may have defibrillators implanted. Having weak respiratory muscles is possible.

Oculopharyngeal

The PABP2 gene on chromosome 14 has a modest GCG trinucleotide expansion, which is responsible for this extremely uncommon pattern of weakness. It is autosomal-dominant in inheritance. It occurs with an average onset age of 50 years and features dysphagia, ptosis, and ophthalmoparesis. Limb weakening could occur. Rimmed vacuoles and filamentous intranuclear inclusions are visible in muscle biopsies.

Limb Girdle Syndromes and Limb Girdle Muscular Dystrophy (LGMD)

Both secondary and primary myopathies frequently appear with slowly worsening proximal weakness. A wide variety of proteins with various activities contribute to the LGMD phenotype. Recessive forms occur more often than dominant types. A variety of conditions, such as non-dystrophic Desmin myopathy; metabolic, toxic, and endocrine myopathies; inflammatory polymyositis, etc., can cause weakness in the limb girdle distribution.

9.2.2. Myotonic Dystrophy (MyD)

A non-coding region at location 19q13.3 has an unstable trinucleotide repeat expansion that leads to myotonic dystrophy, an autosomal dominant multisystem condition. Because of its indirect effects on nearby genes, this expansion is thought to be harmful. It has a 5 per 100,000 incidence and can manifest at any age. While neuromuscular characteristics may not be obvious, the disorder is typically distinguished by the presence of MYOTONIA, which is the inability of muscles to immediately relax once a contraction has ended.

Clinical Presentations

- Cataracts.
- Smooth muscle disorder, constipation, gut motility dysfunction, and bladder emptying malfunction.
- Cardiac muscle disease, dilated cardiomyopathy, and atrio-ventricular block.

- Respiratory failure because of diaphragmatic and intercostals weakness, swallowing impairment, and central sleep apnea.
- Diabetes because of insulin resistance.
- Testicular atrophy and subfertility.

Diagnosis

Clinical diagnosis is simple in situations of classic adult onset when myotonia, frontal baldness, cataracts, and progressive distal plus bulbar dystrophy are present. In mild situations, where cataracts could be the only symptom, clinical diagnosis may be more challenging. DNA diagnosis is made possible through direct measurement of the CTG repeat size using Southern blotting on peripheral leucocytes. Patients contain 50 to several thousand CTG repeats, compared to normal people who have 5 to 37.

The management of problems and genetic counseling place a premium on disorder recognition. The extensive clinical diversity (phenotype) of MyD is caused by the genetic defect instability (number of repeats) between generations. Females run the risk of giving birth to a baby who is critically ill and may not make it through the neonatal period due to respiratory failure. Occasionally, people first present with respiratory failure or sudden death, either spontaneously or after anesthesia.

Two rare, alternative illnesses are taken into consideration when molecular studies are negative while clinical symptoms are suggestive:

1. Dystrophia myotonica type 2;
2. Proximal myotonic myopathy.

9.3. Dystrophies: General Principles and Investigation

9.3.1. General Principles

Despite the fact that some types of dystrophy may be impossible to diagnose or rule out, the following practical concerns are universal:

1. Genetics: It is obvious how different inheritance styles affect the patient's family. Even if molecular diagnosis has not been made but an inherited muscle illness is suspected, assistance from a clinical geneticist should be sought to discuss this. The phenotype of LGMD varies greatly, and isolated occurrences may indicate a novel dominant mutation. Patients should be informed of these issues, as well as those of their spouses.

2. Cardiac disease: Emery–Dreifuss syndrome, in which life-threatening conduction deficits are unavoidable, as well as Xp2.1-related dystrophies and polymyositis exhibit this, which is of utmost importance. ECGs should be performed every 12 months in the absence of a confirmed diagnosis, and echocardiography should be conducted as well if signs of heart failure start to appear.

3. Respiratory failure: Diaphragmatic weakness is associated with respiratory failure, a common symptom of Xp2.1, MD, LGMD; other types of MD; and inflammatory muscular disease. Sleep-disturbed breathing may also result from some congenital myopathies' late degeneration. It is crucial to be aware of this because such patients typically benefit from noninvasive nocturnal ventilatory support.

9.3.2. Investigations

Creatine kinase (CK): The injured muscle membrane releases this sarcoplasmic enzyme. Rhabdomyolysis and muscular dystrophies are associated with high levels, although normal readings do not rule out lesser muscle illness.

Neurophysiology: Normal investigations do not rule out muscle disease, but they may be able to distinguish between neurogenic and myopathic weakness and show indications of muscular membrane damage (such as in inflammatory myopathies).

Muscle biopsy: Some illnesses can be diagnosed with routine staining of frozen material, but others require immunohistochemical analysis and appropriate mutation research (e.g., muscular dystrophies). Deciding between a needle biopsy and an open biopsy is challenging; the former is less unpleasant but simpler, while the latter may be preferred to reduce sample mistakes (González-Jamett et al. 2018; Lindsay et al. 2011; Greenberg 2010).

10. Neurometabolic Diseases: Wilson Disease

10.1. Introduction

It is also known as hepatolenticular degeneration. It is an autosomal recessive disease identified by the storage of intracellular copper with hepatic and neurological dysfunctions.

10.2. Pathology

The putamen and the globus pallidus experience cavitation and neuronal death. The liver displays the symptoms of severe cirrhosis. All organs acquire copper, but the kidney, nail beds, and Descemet's membrane in the eye are particularly susceptible. Ceruloplasmin, a type-2 globulin that typically binds 98% of the copper in plasma and delivers copper to enzymes, is insufficient (cytochrome oxidase). All organs experience deposition due to a rise in loosely bound copper/albumin. Urinary copper levels are higher.

10.3. Clinical Presentations

There are two clinical types:

- Acute:
  - Bradykinesia, behavioral change, involuntary movements, and severe liver dysfunction (common);
  - If not treated, death in 02 years from liver failure.
- Chronic
  - Significant proximal wing-beating tremor;
  - Dysarthria, rigidity, and dystonia;
  - Choreoathetosis;
  - Psychosis, behavioral disorder, and dementia;
  - Liver dysfunction is less severe;
  - If not treated, death within 10 years.

The storage of copper in Descemet's membrane produces a golden brown "Kayser-Fleischer ring" that can be observed by the naked eye or using a slit lamp and is pathognomonic.

10.4. Diagnosis

Biochemical evidence of an aberrant copper metabolism supporting the following, any patient with atypical hepatic and/or neurological characteristics should be evaluated for:

- Decreased ceruloplasmin (<20 mg/dL);
- Increased unbound serum copper;
- Raised urinary copper clearance;
- Liver biopsy and copper metabolism tests with radioactive ^{64}Cu;
- MRI (T2W) demonstrates putaminal and thalamic hyperintensity.

Biochemical studies will find decreased ceruloplasmin in carriers and in patients without symptoms in their families. In copper-transporting ATPase, more than 20 mutations have been found. There is no diagnostic genetic testing available.

10.5. Treatment

Provide a low-copper diet as well as chelating medication, such as penicillamine—1.5–1 g per day. Trientine is a good substitute if patients experience side effects including allergy, skin rash, bone marrow suppression, or glomerulonephritis, which are frequent.

The patient will require therapy for the rest of their lives. Normal life expectancy is compatible with adequate treatment. With time, Kayser–Fleischer rings will vanish (Członkowska et al. 2018; Rodriguez-Castro et al. 2015; Lindsay et al. 2011; Greenberg 2010).

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