VOLUME - 11, ISSUE - 11, NOVEMBER - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medicine

PERIPHERAL NERVOUS SYSTEM DISORDERS: A DIAGNOSTIC APPROACH

Dr. Ajay Kotwal	Assistant Professor Post Graduate Department of Medicine, Acharya Shri Chander College of Medical Sciences and Hospital Jammu, Jammu and Kashmir 180017
Dr Ranjana Duggal	Post Graduate Department of Physiology Govt Medical College and Hospital Jammu, Jammu and Kashmir
Dr Vanita Sharma	Associate Professor Post Graduate Department of Physiology Govt Medical College and Hospital, Jammu, Jammu and Kashmir
Dr Abhinav Gupta	Professor Post Graduate Department of Medicine Acharya Shri Chander College of Medical Sciences and Hospital Jammu, Jammu and Kashmir 180017
Dr Anil K Gupta	Professor and Head Post Graduate Department of Medicine Acharya Shri Chander College of Medical Sciences and Hospital Jammu, Jammu and Kashmir 180017

ABSTRACT Peripheral neuropathy though a common neurological illness has complex aetiology and several different presentations. The term peripheral neuropathy includes symmetric polyneuropathy, single and multiple mononeuropathy, and radiculopathy. Further classification depends on a mixture of phenomenological, pathological, and genetic or other aetiological features. It is heterogeneous in aetiology, diverse in pathology, and varied in severity. Managing a case of perpipheral neuropathy brings along numerous challenges include identifying a case of peripheral neurophy and differentiating it from mimicks, working up for etiology and treatment based on aetiology. Patients can present with either positive or negative symptoms (or both) linked to motor and sensory systems or with autonomic disturbances in some neuropathies. A detailed history and physical examination provides information regarding onset, course and progression of the disease and the type of involvement like generalized, distal or proximal, symmetric or asymmetric, also the type of fibre involvement like large myelinated or small unmyelinated and may give clues to neuro anatomic localization of the disease. The diagnosis can be confirmed through a appropriate investigation for the neuropathic pattern like blood tests, Cerebrospinal fluid (CSF) analysis, MRI Brain, Ultrasound (USg). These test along with Electro diagnostic investigations like Nerve Conduction Studies (NCS), needle electromyography (EMG) can narrow down differentials and possible aetiologies, However in significant cases etiology remain undiagnosed. Genetic testing is most diagnostic in carefully selected cases. Sometimes nerve biopsy and skin biopsy may be needed to confirm the etiologies.

KEYWORDS :

INTRODUCTION

Neuropathy, often called peripheral neuropathy, indicates a problem within the peripheral nervous system.Early recognition and management of symptoms of treatable etiologies is the key to rapid functional recovery. A cost and time effective approach to patients with varied presentation and etiology is needed .

Epidemiology

Worldwide the prevalence of peripheral neuropathy in general population is 2.4% and increases with age to about 8% in those older than 55 years[1]. In India, various epidemiological community-based studies have shown prevalence ranging from 5 to 2400 per 10,000 population[2].

Anatomy of Peripheral Nervous System

Peripheral nervous system includes nerve roots (radicals), rami, cranial nerves (except optic nerve), spinal nerves, nerve plexus (Brachial and Lumbosacral) and peripheral nerves. Afferent dorsal and efferent ventral roots fuse to form the spinal nerves which again divide into the posterior primary rami and the anterior primary rami forming cranial and spinal nerves. Autonomic fibres may traverse multiple nerves to reach target organ [3]. Pathology of the neurological structures may cause distinctive patterns of motor weakness, sensory disturbances, deep tendon stretch reflex changes, autonomic disturbances or combination of these[4] .

Approach To Patient

A rational approach with an adequate history, relevant clinical examination and appropriate investigations may help in identifying a particular pattern and reaching a diagnosis [5,6,7] . History should enquire about sensory abnormalities, motor symptoms, autonomic abnormalities (Table 1), their mode of onset and progression.

Table1. Type of nerve structures involved and related Symptoms and physical findings observed

Sensory	Negative	Numbness or loss of sensation, Unsteady gait and falls
	Positive	Pain, tingling, burning feet, Allodynia.
Motor	Weakness of muscle strength, Loss of muscle mass	
	Muscle twitching, Muscle cramps	
Autonomic	Postural dizziness and syncope, Orthostatic hypotension, Sexual dysfunction: erectile dysfunction, retrograde ejaculation, Bladder involvement, Skin changes, Abnormal sweating patterns Dryness of mouth, eyes, and skin, Hyperaemia or pallor, Easy satiety, constipation, or diarrhoea	
Trophic	Nail changes, Skin thinning and colour changes, Loss of hair and skin ulcers. Callus formation, Painless ulcers in neuropathic joints,	

Work Up Planning of The Case

While making a diagnosis, certain questions need to be considered including:

1. Does it localize to the peripheral nervous system?

2. If a LMN syndrome, is there any evidence of upper motor neuron involvement
3. Can it be localized to a single named peripheral nervous system structure; viz.neuropathy, radiculopathy, plexopathy, peripheral nerves, neuromuscular junction or muscles?
4. Which systems are involved; motor, sensory, autonomic, combination?

- What is the distribution of weakness? Distal versus proximal and distal; focal/ asymmetrical versus symmetrical
- What is the nature of the sensory involvement? Pain/burning or proprioceptive loss and what is the distributionof sensory abnormalities?
- Is it focal, multifocal or generalised? In generalised disorders recognising the patternis important, such as, whether the weakness and numbness are distal or proximal, whether symptoms are symmetric between limbs, or whether cranial or autonomic nerves are involved.

5. What is the temporal evolution; acute, subacute, chronic?
6. Is there any evidence of hereditary neuropathy; family history, skeletal deformity, lack of sensory symptoms despite sensory signs?

Some Peripheral Lesions have concomitant Central Nervous System involvement.

UMN involvement is suggested by Motor weakness (antigravity muscles) with increased tone, brisk reflexes in an affected limb and extensor planter reflex.

Motor Features suggesting a Peripheral Localisation are Flaccid Weakness with Diminished muscle stretch reflexes and muscular atrophic changes in an affected limb while the sensory involvement produces neuropathic features in distinct dermatomal or nerve(s) distribution.

Approach To Peripheral Nerve Disorders

1. Based on duration of symptoms: Acute (less than 4 weeks), Subacute (4 -8 weeks) orChronic (more than 8 weeks)

Most of the acute neuromuscular disorders are related to trauma, such as a peripheral nerve injury while some causes like infectious, inflammatory, and toxic processes may present sub acutely, developing over hours to days e.g Infectious neuropathy, Guillain–Barre syndrome (GBS), Acute porphyric neuropathy, Toxic neuropathy, Vasculitis [8] etc . Differential diagnosis include Botulism and Tick paralysis. Causes of chronic polyneuropathy are Inherited neuropathies, Mitochondrial disorders, Infectious, Connective tissue diseases, Sarcoid neuropathy, Paraproteinemia, Immune-mediated neuropathies, Metabolic (diabetes, hypothyroid, celiac disease)[4,5] and nutritional causes (Vitamin B1, B6, B12, E, copper deficiency) etc. Alcohol use, Heavy metal (lead, thallium, arsenic) exposure[9] and certain Medication (nitrofurantoin, lithium, phenytoin, etc.), Vitamin B6 toxicity can also cause chronic neuropathy[10,11,12].

2. Based on location of symptoms: Focal or Multifocal

1) Focal Pattern:

Sometimes a single or discrete named nervous system structure(s) can explain the sensory and motor signs and symptoms.

a. Radiculopathy

It has radicular pain and sensory disturbances in dermatomal area along with muscle weakness in myotomal distribution. Sensory symptoms often precede motor symptoms. Causes are complications of intrathecal chemotherapy or radiation therapy near the spinal roots[13].

Spinal nerve root compression[14] by intervertebral disk herniation and spondylosis, discitis, bony malignant disease, epidural hematoma, infectious radiculitis, or infiltrative disease of the meninges. MRI of spine identifies these diseases. NCS/EMG helps in diagnosis[15].

b. Plexopathy

Asymmetrical LMN type motor weakness or sensory abnormalities corresponding to distribution of different nerves with multiple root of origins presentation. The brachial and lumbosacral plexus are susceptible to trauma, structural abnormalities, neoplastic infiltration, or inflammatory processes [16,17,18]. Pain predominant presentation more likely suggests Tumour infiltration [19].

c. Mononeuropathy

Acute trauma by ischemia, compression/entrapment or invasion by tumor, infection, irradiation, or injury can cause focal nerve injury[20]. Causes of motor predominant neuropathies are Porphyria, Lead poisoning, Multifocal motor neuropathy (MMN), GBS (in AIDP and AMSAN) etc [19].Mimics of motor predominant neuropathy are Amyotrophic lateral sclerosis, Spinal muscular atrophy including Kennedy disease, Distal myopathies [21] .

2) Multifocal Pattern

Often cases present with multifocal pattern which may be unilateral or bilateral. Some examples are given in the table 3.

Table 3. MULTIFOCAL NEUROPATHIES

Category	Example and electrophysiological finding	
Hereditary	Hereditary neuropathy with liability to pressure palsy(HNPP)	Demyelinating
Ischemic	Systemic vasculitic neuropathy, Ischemic monomelic neuropathy, Cryoglobulinemia, Diabetes mellitus	Axonal
Inflammatory	Multifocal motor neuropathy (MMN), Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)	Demyelinating
	Acute brachial plexopathy (monomelic)	Axonal
Infiltrative	Sarcoidosis, Amyloidosis, Neurolymphomatosis, Leprosy, Neurofibromatosis	Axonal

3) Generalised symptom (Polyneuropathy) Pattern.

Most polyneuropathies present with mixed sensory and motor symptom pattern with prominence of distal sensory loss. Next step is establishing the pattern of illness, whether the symptoms are sensory or motor, or both; whether they are proximal or distal, or both; and whether they are symmetric or asymmetric and if any autonomic features are present.

A. Bilateral Assymmetrical Patttern

A. Asymmetric Proximal And Distal Motor Weakness With Sensory Loss

This pattern is usually seen in polyradiculopathy, or polyradiculoplexopathy or plexoneuropathy[3] Few common causes are Diabetic radiculoplexus neuropathy[6], Diptheria, lymes disease, Guillain Barre syndrome, CIDP variants Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM or Lewis–Sumner syndrome), Toxins (Arsenic, n-Hexane, Amiodarone), Paraneoplastic syndromes, Idiopathic [19].

This pattern is also seen in Multifocal motor neuropathy (MMN), Meningeal disorders (such as carcinoma, lymphoma, sarcoidosis, or infections), Vasculitic neuropathy Sarcoid neuropathy, Amyloidosis, hereditary neuropathy with liability to pressure palsies-HNPP) [5,8].Mimics of asymmetric polyneuropathy are Amyotrophic lateral sclerosis, FSHMD with asymmetric limb weakness

B. Asymmetric Distal Motor Weakness With Sensory Loss
This pattern is seen in confluent mononeuritis multiplex, Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) variant of CIDP [22] , Hereditary neuropathy with liability to pressure palsies (HNPP) [23], Rarely Mononeuropathies and radiculopathies can some time have this presentation

C. Asymmetric Distal Motor Weakness
Asymmetric Distal weakness may suggest Multifocal motor neuropathy (MMN) [21],In ALS [19] Hirayama disease, or monomelic amyotrophy, [24] and some Non neurogenic disorder including inclusion body myositis [8].

D. Asymmetric Proximal And Distal Motor Weakness
Sometimes motor neuropathies, MMN, ALS, paraneoplastic syndromes may have some proximal and distal motor weakness

B. Bilaterally Symmetrical Pattern
Symmetric distal sensory motor neuropathy is the most common presentation, further assessment is based on the relative sensory and motor involvement.

A) Symmetric Polyneuropathy With Distal Sensory Loss
Distal symmetric polyneuropathy, with predominant sensory involvement and lesser motor and autonomic involvement is most common presentation with a chronic time course a slow progression [25] This is also known as length dependent pattern. Symptoms starts in the toes and feet move proximally with disease progression. It is seen in many metabolic disorders, Toxin exposures etc

B) Symmetric Distal Polyneuropathy With Predominant Motor Weakness
Symmetric predominant distal motor weakness is seen in Hereditary motor sensory neuropathy alias Charcot-Marie-Tooth disease (CMT), Distal acquired demyelinating symmetric (DADS) neuropathy variant of CIDP [26] .

C) Symmetric Proximal And Distal Motor Weakness And Sensory Loss
This pattern suggests polyradiculoneuropathy pattern as seen in Acute inflammatory demyelinating poly radiculoneuropathy (AIDP) and Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [27].

D) Symmetric Proximal Predominant Motor Weakness
Proximal greater than distal symmetric weakness is usually due to a myopathy or neuromuscular junction transmission defect. Some radiculoneuropathies (AIDP or CIDP) or motor neuropathies (Progressive muscular atrophy, Spinal bulbar muscular atrophy, Spinal muscular atrophy (SMA) type 1, 2, 3, or 4 and sometimes ALS can have similar presentation[19,21].

E) Symmetric Distal Motor Weakness
Distal symmetric weakness is most commonly due to Axonal forms of CMT and Hereditary motor neuropathies [26]. Amyotrophic lateral sclerosis and Juvenile forms of ALS are important consideration, Distal spinal muscular atrophy has distal motor weakness [21].Non-neuropathic conditions include Distal myopathies and myotonic dystrophy type 1.

C. Pure Sensory Symptom Pattern
Sensory dysfunction without significant weakness can occur with involvement of the spinal cord sensory tracts, the dorsal root ganglia, the sensory nerves and lesion anywhere will produce corresponding symptoms. Most clinically significant lesions will cause static sensory loss in a fixed distribution.

A) Symmetric Proximal And Distal Sensory Loss
Proximal and Distal sensory involvement can occur symmetrically with Polyneuropathies due to toxic, metabolic syndromes [8] .This presentation is also seen with Disruption of dorsal columns and the spinothalamic tracts from trauma, disk disease, infection .

B) Ataxic Neuropathy (proprioceptive Sensory Loss) Without Weakness.
This pattern can affects all sensory modalities including proprioception and pain. It produces gait and limb ataxia, pseudoathetosis and hypoactive or absent deep tendon reflexes.

Few causes are Sensory neuronopathies (dorsal root ganglia disease) as a result of certain infections (HIV), sjogrens syndrome, Miller Fisher syndrome, pyridoxine overdose, paraneoplastic syndrome (small cell lung cancer, lymphoma) [28]. Similar presentation is seen with Chronic immune sensory polyradiculoneuropathy (CISP) [29].

C) Painful Small Fiber Polyneuropathy
It affect small unmyelinated nerve fibers carrying pain and temperature sensation but spares position sense. It has preserved muscle strength and deep tendon reflexes. Painless injuries may occur. Some causes are Diabetes Mellitus, alcohol use, Sjogren's syndrome, Fabry's disease, Tangier's disease, Amyloidosis, Paraproteinemia, Hereditary sensory and autonomic neuropathy, Vasculitis, Toxins (arsenic, thallium), HIV, etc [5,8].

D. Neuropathieswith Prominent Autonomicsymptoms
It includes Infectious diseases (HIV), Diabetic autonomic neuropathy, amyloidosis, Guillain–Barre syndrome, Hereditary neuropathies (HSAN), Paraneoplastic and immune-mediated neuropathies (lupus, rheumatoid arthritis, Sjögren's syndrome etc) [4,5,7,8].

E. Focal Midline Proximal Symmetric Weakness
This pattern with weakness of facial or bulbar muscles, Neck muscles or spine may be seen in GBS variats, Motor neuron disease (Bulbar onset motor neuron disease) etc [30].Some myopathies (occulophyangeal muscular dystrophy, Fascioscapular humoral dystrophy) and Neuromuscular junction transmission disorders are important non neuropathic causes.

Diagnostic Testing
Blood tests, Cerebrospinal fluid (CSF) analysis, electro diagnostic studies (EDX), imaging, and tissue biopsy all serve an additional role in the workup for peripheral nervous system syndromes guided by history and physical examination.

A. Blood Testing
1. Traumatic Mononeuropathy and radiculopathy usually do not need blood testing.
2. Distal symmetric polyneuropathy needs testing for Diabetes [31], metabolic syndrome, multiple myeloma/ paraproteinemia (Serum protein electrophoresis and serum immunofixation, Vitamin B12 deficiency [5,8].
3. In presence of systemic symptoms, rapid onset of neuropathy, motor predominance, or a non–length-dependent pattern certain tests are considered including Thyroid function test, Erythrocyte Sedimentation Rate, folate, antinuclear antibodies, Venereal Disease Research Laboratory (VDRL), etc.
4. Fabry disease has deficient α-galactosidase A in plasma and leukocytes [32].
5. In distal symmetric polyneuropathy test for Diabetes paraproteinemia, toxin [5,31].
6. Asymmetric Proximal and distal motor pattern as in Mononeuritis multiplex and nontraumatic plexopathies need evaluation for vasculitis[8,33].
7. Testing for Serologic Markers guided by clinical pattern

a. Anti-ganglioside (GM1 IgM) antibodies are sought in patients with suspected MMN [34].Proximal motor pattern requires more extensive testing, including anti-ganglioside antibodies (GM1, GD1a, neurofascin (NF155, NF186), contactin-1, Caspr1, and anti-myelin associated glycoprotein (MAG) antibodies[5,8].

b. In patients with small fibre neuropathy , serological testing for vasculitis (Angiotensin converting enzyme (ACE), antinuclear antigen (ANA) profile, rheumatoid Arthritis (RA) factor, anti-Ro/SSA, anti-La/SSB, anti- neutrophil cytoplasmic antigen antibody (ANCA) profile, cryoglobulins), for immune-mediated neuropathies (anti-ganglioside-antibodies, anti-Caspr1/2, anti-LGI 1, anti-ganglionic acetylcholine receptor antibodies) and infectious serology (Hepatitis B, and C, HIV, borreliosis) are recommended in addition to ATTR, Amylodosis , Paraneoplastic screen [35].

c. For sensory neuronopathy, test for anti–Sjögren syndrome A (SSA) and anti–Sjögren syndrome B (SSB) antibodies, and Anti HIV Antibodies testing. Other tests include Pyridoxine levels (Vit B6), paraneoplastic autoantibodies (especially anti-Hu antibodies anti-CV2 antibodies), Anti ganglioside antibodies (GD1b, GD2, GD3, GQ1b, GT1a, GT1b), anti FGFR3 [36].

d. For malabsorption anti gliadin, antitransglutaminase-antibodies
e. While with a history for intoxications, blood, urine, hair and nail analysis for toxins and heavy metals e.g. arsenic, lead, mercury, thallium,etc [37].
f. Porphyria screening in suspected patients .
g. If phenotype is suggestive of CIDP or DADS neuropathy, serum protein electrophoresis and immunofixation should be obtained. IgA or IgG paraprotein to screen for POEMS syndrome [5].
8. Blood tests are generally low yield in the workup of motor neuron diseases.

9.In suspected NMJ disorders presence anti–acetylcholine receptor antibodies , voltage-gated calcium channels with response on Repetative nerve stimulation (RNS) may help in diagnosis.

B. CSF Testing

CSF examination is warranted when an inflammatory, vasculitic, paraneoplastic, or infectious cause is suspected in patients presenting with proximal motor pattern, small fibre neuropathy or sensory ataxic pattern.In immune-mediated neuropathies, albuminocytological dissociation is often found, whereas infectious causes result in CSF pleocytosis [38]. Oligoclonal bands can be found in paraneoplastic neuropathy, borreliosis, sarcoidosis, M. Bechet, and some inflammatory conditions [39].

C. Electrodiagnostic Testing

A complete electrodiagnostic evaluation including Sensory and motor Nerve Conduction Study and needle EMG, are useful in certain conditions like large-fiber neuropathy, compression neuropathies or radiculopathies. It can help finding answers like distribution type of nerve fibers involved, underlying pathophysiologic process (Axonal/demyelination, Acute/chronic), severity of disease and temporal study over time and response to intervention. Electrodiagnostic testing has limited role in isolated pain and sensory symptoms, distal symmetric polyneuropathy [40].

The demyelinating neuropathies are characterized by increased distal motor latencies, a significant slowing of nerve conduction velocities, motor conduction blocks, temporally dispersed potentials, and absent or delayed late responses (e.g., F-waves) [41].Some causes of Primary demyelinating polyneuropathy are given below GBS, CIDP or its variants , paraproteinemia, Diphtheria, arsenic, amiodarone, gold etc. Hereditary/ Genetic causes produce unifom demyelination eg are Charcot-Marie-Tooth disease type 1,3,4 and Hereditary neuropathy with liability to pressure palsies (HNPP), Krabbe disease,Metachromatic leukodystrophy, Refsum disease, Cockayne syndrome Some disorders target proteins and ion channels in the nodal region[42], characterized by rapid decline of compound muscle action potential (CMAP) amplitudes, suggesting motor axon loss. The example of nodopathies is the acute motor axonal neuropathy (AMAN) variant of the GBS, Miller Fisher syndrome, Multifocal motor neuropathy (MMN), Marine toxins, phenytoin etc.

Chronic axonal neuropathies are often linked to Drug and toxin exposure like: Alcohol, vincristine, phenytoin, organophosphate, statins, metronidazole, dapsone. Other causes are Leprosy, HIV, Borreliosis, Connective tissue disorders, Hypothyroidism , Diabetes, chronic renal failure, Paraneoplastic syndrome (Ca Lung and ovary), Paraproteinemia, Vitamin B12, Folic acid, Vitamin E deficiency and some inherited causes (CMT 2 and CMT X) [5,37].

D. IMAGING

MRI can detect affection of more proximal nerve segments lesions as nerve roots and surrounding structures. MRI in demyelinating polyradiculoneuropathies such as AIDP, CIDP, and CISP may show hypertrophic or enhancing nerve roots . Dynamic MRI of the cervical spine helps diagnosis of Hirayama disease. Focused MRI of the brachial or lumbosacral plexus may help in identifying lesions. Hyperintense MRI signal along the corticospinal tracts seen with upper motor neuron–predominant disease [43].

E. Ultrasound Imaging

Ultrasound is painless and thus is better tolerated than EMG, but less useful in assessing deeper structures. It may show asymmetrically increased nerve cross-sectional areas of roots and nerve in immune-mediated neuropathy [44]. USG of muscles may show fasciculations, decreased muscle thickness, and increased muscle echo intensity and echo variance in patients with motor neuron disease.

F. Tissue Biopsy

In correct clinical context, a nerve or skin biopsy may aid in the diagnosis of polyneuropathy

I) Nerve Biopsy

The most commonly biopsied nerves are the sural, radial, or superficial fibular (peroneal) nerves . MRI and ultrasound can help to select target nerve segments. Some indications of nerve biopsy are

1. When vasculitic neuropathy is suspected and all the tests for systemic vasculitis or inflammatory disorders are negative.
2. Mononeuritis multiplex if test for vasculitis, infections, urinalysis, and body imaging are non contributory
3. In Demyelinating immune-mediated neuropathies, (i.e., CIDP) nerve biopsy is done only in case of diagnostic uncertainty .
4. In symmetrical distal sensorymotor neuropathy pattern, with atypical symptoms or if tests suggest an acquired condition (i.e., vasculitis).
5. Severe, rapidly progressive painful polyneuropathy i.e. when vasculitis is suspected.
6. Treatment refractory inflammatory neuropathy to look form imics.

Vasculitides produces pathologic findings including inflammation around and necrosis of the vessel walls. Biopsy of a nearby muscle increases diagnostic sensitivity for vasculitis.

ii) Skin Biopsy

Skin biopsy from a distal and a proximal site in a lower extremity stained with an antibody to PGP 9.5, a panaxonal marker, can measure epidermal fibre density and help diagnose small fibre polyneuropathy in uncertain cases and determine if it is length dependent or diffuse process. Nerve and skin biopsy as well as Bone marrow, salivary gland, or subcutaneous fat with Congo red staining may demonstrate amyloid [45].

G. Genetic Testing

Genetic testing is considered when clinical history or examination suggests a hereditary origin of the peripheral neuropathy. Clinical clues to a hereditary neuropathy are young age at onset, progressive symptoms , prominent wasting with skeletal or foot deformities although late-onset hereditary neuropathy is also known, e.g., axonal CMT or ATTRv amyloidosis [46].

Genetic testing is guided by the mode of inheritance, demyelinating versus axonal pattern, and affected nerve fibre modality [46]. PMP22, MFN2, MPZ, and Cx32 are most often involved . Duplication of the PMP22 gene (CMT1A) is in most of patients with positive family history and demyelinating neuropathy , mutation in MFN2 gene is seen in patients with positive family history and axonal neuropathy, [46].

Genetic testing for POLG1 mutations should be considered in Sensory ataxic neuropathy Depending on the clinical pattern the test results, and the suspected underlying cause, it can sometimes become necessary [47].

H. Newer diagnostic tests have been introduced to assess the progression and prognosis of the peripheral nerve disorders which include Corneal confocal microscopy used in patients of small fiber neuropathy and ganglionopathy, Laser Doppler Imager Flare (LDIF) to assess nerve fibre density, Meissner Corpuscle Density (MC density) at fingertip and Stimulated Skin Wrinkling in sensory neuropathy[5].

I. Autonomic function testing is important for corroborating clinical presentation of autonomic features associated with peripheral neuropathies. J. To perform additional examinations, e.g., to exclude a malignancy by computed tomography of chest and abdomen or positron emission tomography

REFERENCES

1. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey factsheet: neurology. Centers for Disease Control and Prevention website. http://www.cdc.gov/nchs/data/ ahcd/NAMCS_2010_factsheet_ neurology.pdf. Accessed May 13, 2015
2. Trivedi S, Pandit A, Ganguly G, Das SK. Epidemiology of Peripheral Neuropathy: An Indian Perspective. Ann Indian Acad Neurol. 2017; 20(3):173-184. doi:10.4103/aian.AIAN_470_16
3. London ZN. Resident basic science III: neuroanatomy: all the lesions. Course presented at American Academy of Neurology Annual Meeting; May 6, 2019; Philadelphia, PA.
4. Watson JC, Dyck PJB. Peripheral neuropathy: a practical approach to diagnosis and symptom management. Mayo Clinic Proc 2015;90(7):940–51.
5. Motiwala R. A Clinical Approach to Disease of Peripheral Nerve. Clin Geriatr Med. 2021 May;37(2):197-208. doi: 10.1016/j.cger.2021.01.009. Epub 2021 Mar 23. PMID: 33858604
6. Perkins BA, Olaleye D, Zinman B, et al. Simple screening tests for peripheral neuropathy in diabetes clinic. Diabetes Care 2001;242(2):250–6.
7. Lanier JB, Mote MB, Clay EC. Evaluation and management of orthostatic hypotension. Am Fam Physician 2011;84(5):527–36.
8. Siao P, Kaku M. A Clinician's Approach to Peripheral Neuropathy. Semin Neurol. 2019 Oct;39(5):519-530. doi: 10.1055/s-0039-1694747. Epub 2019 Oct 22. PMID: 31639835.
9. Rubens O, Logina I, Kravale I, Eglite M, Donaghy M. Peripheral neuropathy in chronic occupational inorganic lead exposure: a clinical and electrophysiological study. J Neurol Neurosurg Psychiatry 2001; 71(02): 200–204
10. Yiannikas C, Pollard JD, McLeod JG. Nitrofurantoin neuropathy. Aust N Z J Med 1981;11(04):400–405
11. Johnston SR, Burn D, Brooks DJ. Peripheral neuropathy associated with lithium toxicity. J Neurol Neurosurg Psychiatry 1991;54(11):1019–1020
12. Shorvon SD, Reynolds EH. Anticonvulsant peripheral neuropathy: a clinical and electrophysiological study of patients on single drug treatment with phenytoin, carbamazepine or barbiturates. J Neurol Neurosurg Psychiatry 1982;45(07):620–626
13. Koh S, Nelson MD Jr, Kovanlikaya A, Chen LS. Anterior lumbosacral radiculopathy after intrathecal methotrexate treatment. Pediatr Neurol. 1999 Aug;21(2):576-8. doi: 10.1016/s0887-8994(99)00040-5. PMID: 10465148.
14. Kushchayev SV, Glushko T, Jarraya M, et al. ABCs of the degenerative spine. Insights Imaging 2018;9(2):253–274. doi:10.1007/s13244-017-0584-z.
15. Anderson, Greg; Vaccaro, Alexander R. (2013). *Decision Making in Spinal Care || Cervical Radiculopathy. , 10.1055/b-002-85482(), –.* doi:10.1055/b-0034-84312
16. Shanina E, Liao B, Smith RG. Brachial plexopathies: update on treatment. Curr Treat Options Neurol 2019;21(5):24. doi:10.1007/s11940-019-0562-5.
17. Jones MR, Prabhakar A, Viswanath O, et al. Thoracic outlet syndrome: a comprehensive review of pathophysiology, diagnosis, and treatment. Pain Ther 2019;8(1):5–18. doi:10.1007/s40122-019-0124-2.
18. Gwathmey KG. Plexus and peripheral nerve metastasis. Handb Clin Neurol 2018;149:257–279.doi:10.1016/B978-0-12-811161-1.00017-7.
19. **Continuum (minneap minn)2020;26(peripheral nerve and motor neuron disorders):1130-1160**
20. Hobson-Webb LD, Juel VC. Common entrapment neuropathies. Continuum (Minneap Minn) 2017;23(2, Selected Topics in Outpatient Neurology): 487–511. doi:10.1212/CON.0000000000000452
21. Verschueren A. Motor neuropathies and lower motor neuron syndromes. Rev Neurol (Paris). 2017 May;173(5):320-325. doi: 10.1016/j.neurol.2017.03.018. Epub 2017 Apr 20. PMID: 28434507
22. Ikeda S, Koike H, Nishi R, et al. Clinicopathological characteristics of subtypes of chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Neurosurg Psychiatry 2019;90(9):988–996.doi:10.1136/jnnp-2019
23. Attarian S, Fatehi F, Rajabally YA, Pareyson D. Hereditary neuropathy with liability to pressure palsies. J Neurol 2020;267(8): 2198–2206. doi:10.1007/s00415-019-09319-8.
24. Preethish-Kumar V, Polavarapu K, Nashi S, et al.Hirayama disease/cervical flexion-induced myelopathy progressing to spastic paraparesis: a report on three cases with literature review. Neurol India 2018;66(4):1094–1099. doi:10.4103/0028-3886.236966
25. Callaghan BC, Price RS, Feldman EL. Distal symmetric polyneuropathy: a review. JAMA 2015;314(20):2172–2181. doi:10.1001/jama.2015.13611.
26. Rossor AM, Kalmar B, Greensmith L, Reilly MM. The distal hereditary motor neuropathies. J Neurol Neurosurg Psychiatry 2012;83(1):6–14. doi:10.1136/jnnp-2011-300952.
27. Nobile-Orazio E. Chronic inflammatory demyelinating polyradiculoneuropathy and variants: where we are and where we should go. J Peripher Nerv Syst 2014;19(01):2–13
28. Kuntzer T, Antoine JC, Steck AJ. Clinical features and pathophysiological basis of sensory neuronopathies (ganglionopathies). Muscle Nerve 2004;30(03):255–268
29. Szmulewicz DJ, McLean CA, Rodriguez ML, et al. Dorsal root ganglionopathy is responsible for the sensory impairment in CANVAS. Neurology 2014;82(16):1410–1415
30. Statland JM, Barohn RJ, McVey AL, Katz JS, Dimachkie MM. Patterns of Weakness, Classification of Motor Neuron Disease, and Clinical Diagnosis of Sporadic Amyotrophic Lateral Sclerosis. Neurol Clin. 2015 Nov;33(4):735-48. doi: 10.1016/j.ncl.2015.07.006. Epub 2015 Sep 8. PMID: 26515618; PMCID: PMC4629510.
31. Thaisetthawatkul P, Lyden E, Americo Fernandes J Jr, Herrmann DN. Prediabetes, diabetes, metabolic syndrome, and small fiber neuropathy. Muscle Nerve 2020;61(4):475–479. doi:10.1002/mus.26825.
32. Balendran S, Oliva P, Sansen S, et al. Diagnostic strategy for females suspected of Fabry disease. Clin Genet 2019. doi:10.1111/cge.13694.
33. Robblee J, Katzberg H. Distinguishing Radiculopathies from Mononeuropathies. Front Neurol. 2016 Jul 13;7:111. doi: 10.3389/ fneur.2016.00111. PMID: 27468275; PMCID: PMC4942461.
34. Beadon K, Guimarães-Costa R, Léger JM. Multifocal motor neuropathy. Curr Opin Neurol 2018;31(5):559–564. doi:10.1097/WCO. 0000000000000605
35. Collins MP, Periquet MI. Non-systemic vasculitic neuropathy. Curr Opin Neurol 2004;17(05):587–598.
36. Nishimoto Y, Odaka M, Hirata K, Yuki N. Usefulness of anti-GQ1b IgG antibody testing in Fisher syndrome compared with cerebrospinal fluid examination. J Neuroimmunol 2004;148(1–2): 200–205. doi:10.1016/j.jneuroim.2003.11.017.
37. Staff NP, Windebank AJ. Peripheral neuropathy due to vitamin deficiency, toxins, and medications. Continuum (Minneap Minn) 2014;20(5 Peripheral Nervous System Disorders):1293–1306
38. Breiner A, Moher D, Brooks J, et al. Adult CSF total protein upper reference limits should be age-partitioned and significantly higher than 0.45 g/L: a systematic review. J Neurol 2019; 266(3):616–624. doi:10.1007/s00415-018-09174-z
39. London ZN, Nowacek DG. Does cerebrospinal fluid analysis have a meaningful role in the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy? Muscle Nerve 2019; 60(2):111–113. doi:10.1002/mus.26513
40. AANEM policy statement on electrodiagnosis for distal symmetric polyneuropathy. **Muscle Nerve 2018;57(2):337–339. doi:10.1002/mus.26003.**
41. Joint_Task_Force_of_the_EFNS_and_the_PNS. (2010). European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—First Revision. J Peripher Nerv Syst, 15(1), 1–9.
42. Willison H, Scherer SS. Ranvier revisited: novel nodal antigens stimulate interest in GBS pathogenesis. Neurology 2014;83(2):106Y108. doi:10.
43. Rajagopalan V, Pioro EP. Unbiased MRI analyses identify micropathologic differences between upper motor neuron-predominant ALS phenotypes. Front Neurosci 2019;13:704. doi:10.3389/fnins. 2019.00704
44. Katzberg HD, Bril V, Breiner A. Ultrasound in neuromuscular disorders. J Clin Neurophysiol 2016;33(2):80–85. doi:10.1097/WNP. 0000000000000234.
45. **Gertz MA. Immunoglobulin light chain amyloidosis: 2018 Update on**

diagnosis, prognosis, and treatment. Am J Hematol 2018; 93(9): 1169– 1180. doi:10.1002/ajh.25149

46. Rossor, A. M., Evans, M. R., & Reilly, M. M. (2015). A practical approach to the genetic neuropathies. Practical Neurology, 15(3), 187–198
47. Weiss MD, Saneto RP. Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO) in late life due to compound heterozygous POLG mutations. Muscle Nerve. 2010 Jun; 41(6):882-5. Doi: 10.1002/mus.21636. PMID: 20513108