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Advances in the Treatment of Peripheral Neuropathy

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ADVANCES IN THE TREATMENT OF PERIPHERAL NEUROPATHY

Peripheral neuropathies are caused by deranged function and structure of peripheral motor, sensory and autonomic neurons. This manifests clinically as either a mononeuropathy, mononeuritis multiplex (multiple non contiguous nerves) or a polyneuropathy[1].

MONONEUROPATHY

This presents clinically as focal involvement of an individual peripheral nerve. The clinical presentation and findings vary depending on the nerve involved, e.g. foot drop in common peroneal nerve palsy, wrist drop with radial nerve involvement.

Causes

- Compression/entrapment: Carpal tunnel syndrome
- Traumatic
- Vascular lesions
- Infiltrative: Neoplastic

MONONEURITIS MULTIPLEX

This is due to simultaneous or sequential involvement of multiple non contiguous nerves; the disease process can involve either the axon or the myelin of the peripheral nerves.

AXONAL

- Infective: Hansens, HIV
- Vasculitis
- Sarcoidosis
- Diabetes mellitus

DEMYELINATING

- MADSAM (Multifocal autoimmune demyelinating sensory and motor neuropathy)
- HNPP (Hereditary neuropathy with liability to pressure palsies)
- MMN (Multifocal motor neuropathy with conduction blocks)
- Multiple compression neuropathies: Diabetes, hypothyroid

POLYNEUROPATHY

Symmetric involvement of multiple peripheral nerves with sensory symptoms (numbness, tingling paresthesias, sensory ataxia) or distal weakness or both.

Axonal Neuropathies

1. Endocrine: Diabetes, hypothyroidism
2. Metabolic: Chronic renal failure, liver disease, etc.
3. Infections: HIV, HTLV, leprosy, Lyme disease
4. Connective tissue diseases: SLE, rheumatoid arthritis, Sjögren's syndrome.
5. Vitamin deficiency: Vitamin B_{12}, Vitamin E
6. Drugs and toxins:
   - Alcohol, chemotherapeutic agents: Vincristine, cisplatinum
   - Phenytoin, statins, antibiotics: Metronidazole, dapsone, etc.
   - Antiretroviral medications, etc.
7. Paraneoplastic
8. Paraproteinemia: Myeloma, Waldenstrom's macroglobulinemia, MGUS, amyloidosis

9. Inherited: Charcot-Marie-Tooth (CMT) type II, porphyria, HSAN.

Demyelinating Polyneuropathy

1. Immune mediated: AIDP, CIDP
2. Infective: Diphtheria
3. Paraprotein associated: IgM MGUS
4. Hereditary: CMT I, III and X, Refsum's disease, leukodystrophy

NEURONOPATHY

Patients have sensory ataxia, generalized areflexia and near normal power.

Causes

- Toxins: Doxorubicin, pyridoxine excess
- Paraneoplastic
- Sjögren's syndrome
- Idiopathic

Small Fiber Neuropathies

Patients with this type of polyneuropathy present with burning pain, painful dysthesias and autonomic dysfunction.

- Diabetes mellitus and impaired glucose tolerance
- Amyloidosis (primary and familial)
- HIV
- Fabry's disease
- Tangier disease
- Hereditary sensory and autonomic neuropathies
- Chronic idiopathic small fiber sensory neuropathy
- Sjögren's syndrome.

Treatment of Peripheral Neuropathies

1. *Painful neuropathies:* Neuropathic pain may be spontaneous or provoked by any stimulus. The neurobiological events leading to neuropathic pain are not well understood, but there is probably an increased expression of sodium channels and increased glutamate activity at N-methyl-D-aspartate (NMDA) receptors. Pain is characteristic of small fiber neuropathies, but even in large fiber neuropathies a sufficient number of small fibers may be damaged to cause pain (Vasculitic neuropathy, diabetes, HIV associated, etc). Symptomatic management of painful neuropathy can be both difficult and rarely provides complete relief. Various drugs have been tried to alleviate neuropathic pain; a rational polytherapy is needed in most of these patients starting with a low dose to avoid side effects.
   - *Topical agents*[2]: *Capsaicin cream* (extract of chili peppers, 0.025%) acts by depleting substance P in the unmyelinated nociceptive fibers. Any improvement may be preceded by an intense burning sensation after its application. *Lidocaine patches* are used for pain in post herpetic neuralgia.
   - *Ticyclic antidepressants (TCAs): Amytriptyline,* nortriptyline or desipramine. This class of drugs block reuptake of norepinephrine and serotonin and also inhibit the sodium channels. Treatment with amytriptyline is initiated with low dose (10 mg) and increased if need to 75- 150 mg. Common side effects are sedation, dry mouth, urinary retention and orthostatic hypotension.
   - *Anticonvulsants:* These are preferred for sharp shooting, lancinating pain. Carbamazepine (600-1000 mg), Gabapentin (900-3600 mg) and phenytoin are the drugs used. Gabapentin is also useful in burning dysthesias. The most common side effects observed are sedation and dysequilibrium.
   - *Pregabalin (150- 600 mg):* binds to $\alpha 2\delta$ subunit of the calcium channel and blocks calcium influx. It is considered a more potent successor of gabapentin.
   - *Venlafaxine* (*37.5- 225 mg*) also blocks the reuptake of norepinephrine and serotonin, but has a better safety profile than the TCAs.
   - Others like mexiletine, tramadolol, dextro-methorphan (low affinity NMDA receptor antagonist) and narcotic analgesics (oxycodone, levorphanol) can also be used for refractory neuropathic pain.
   - *Non-pharmacological treatments* like relaxation techniques (meditation, yoga), biofeedback, hypnosis, low intensity transcutaneous electric nerve stimulation (TENS), acupuncture and henna application to the feet have provided variable relief from neuropathic pain.
2. *Demyelinating neuropathies:*

   AIDP (Acute inflammatory demyelinating polyradiculo-neuropathy): Guillain-Barre' syndrome and its variants. The proposed pathophysiologic mechanism is immune damage either to the myelin or axon due

to molecular mimicry as a result of shared epitopes by the peripheral nerve and the antecedent infection/ vaccination.

The current recommendations are the use of either IVIg (400 mg/kg/day for 5 days) or plasmapheresis (30-50 ml/kg on alternate days for 3- 5 cycles) within the first two weeks of the onset of AIDP in patients who cannot walk independently or worse. Though IVIg is convenient to administer as compared to plasmapheresis, it is not devoid of side effects. Notably anaphylaxis in IgA deficient individuals, aseptic meningitis, CCF, thrombotic complications (Stroke, MI) and transient renal failure has been described with IVIg administration. Patients should be carefully observed for respiratory compromise and autonomic storms. Other issues include physiotherapy, prevention of DVT, pressure sores and pressure palsies of the common peroneal and ulnar nerves.

CIDP (Chronic Inflammatory demyelinating polyradiculoneuropathy): Patients present with a progressive or relapsing motor and sensory neuropathy of more than 2 months duration. Though molecular mimicry is implicated like in AIDP; there are few differences:

- There is a chronic low level antigenemia responsible for the immune dysregulation leading to a more protracted clinical course.
- A preceding infection/vaccination are rarely observed.

Patients are treated with steroids, IVIg or plasmapheresis depending on the clinical severity. However, unlike AIDP, CIDP usually relapses. Certain other immunomodulators have been used for refractory CIDP or their steroid sparing properties: Azathioprine (2-3 mg/kg/day) (routine blood count monitoring is needed), Mycophenolate mofetil (1000 mg BID), Rituximab (anti CD20 antibody), Cyclosporine A (5 mg/kg in two divided doses/day), monthly infusions of Cyclophosphamide (1gm/m^2) and Interferon-α (3 million IU SC three times a week for 6 weeks).

MADSAM (Lewis Sumner syndrome): Now considered to be an asymmetric variant of CIDP. Treatment is similar to CIDP.

Multifocal motor neuropathy with conduction blocks (MMNCB): Patients have an asymmetric demyelinating neuropathy involving multiple motor nerves. The exact pathogenesis is not known, though an immune dysfunction is believed to be the cause. However, these patients do not respond to steroids or plasma exchange. Treatment in these patients consists of: IVIg (0.4 kg/day for 5 consecutive days) [3], Monthly IV cyclophosphamide (1-g/m^2) for 6 - 8 months preceded on each occasion by two plasma exchanges, Interferon-β and rituximab.

Distal Acquired Demyelinating Sensory Neuropathy (DADS) Patients present with distal sensory symptoms without much of motor involvement (cf CIDP). Treatment with IVIg, plasmapheresis and corticosteroids is ineffective; Rituximab is believed to be of some benefit in these patients.

3. *Diabetic neuropathy:* Management consists of
   - Strict control of diabetes
   - Treatment of neuropathic pain
   - IVIg or methylprednisolone in diabetic lumbosacral radiculoplexopathy (Bruns Garland syndrome)
   - Steroids in diabetic CIDP
   - *Treatment of autonomic neuropathy*
     1. Gastroparesis: Promotility agents like cisapride, domperidone
     2. Diabetic diarrhea: Antibiotics (for blind loop syndrome), loperamide, clonidine
     3. Erectile dysfunction: sildenafil (phosphodiesterase 5 inhibitor)
     4. Orthostatic hypotension: 500 ml of water ingestion on waking[4], increased salt intake, elastic stockings and fludrocortisone (0.1- 0.6 mg daily)
     5. Bladder atonia may require frequent self intermittent catheterisation.
     - *Alpha lipoic acid:* Though trials (ALADIN, NATHAN 1 trials) showed benefit, not of much use in clinical practice.
     - *Aldose reductase inhibitors:* Not used now; were believed to decrease the levels of sorbitol which are implicated in the pathogenesis of diabetic polyneuropathy.
4. *Paraproteinemic neuropathy:* Primarily consists of treatment of the underlying condition (Multiple myeloma, Waldenstrom's macroglobulinemia, cryoglobulinemia). Demyelinating neuropathy associated with MGUS is treated with IVIG, steroids or plasmapheresis.
5. *Vasculitic neuropathy:* Treatment consists of: High dose IV (0.5- 1 g/m2 per month) or oral cyclophosphamide (2 mg/kg) and prednisolone (1 mg/kg) till clinical remission occurs. Cyclophosphamide is then continued for 1 year after the disappearance of all traces of disease activity.
   - Methotrexate
   - Treatment of neuropathic pain similar to diabetic neuropathy

6. *Paraneoplastic neuropathy:* Focus is to identify and treat the underlying neoplasm, usually a small cell carcinoma of the lung or breast or ovarian carcinoma.
7. *Vitamin deficiency neuropathy:* Investigate for the cause of the vitamin deficiency and treatment with vitamin supplements. Patients with B12 deficiency and pernicious anemia need injectable vitamin supplements life long. Vitamin E in high doses (100 mg/kg/day) is needed for the treatment of the sensory neuropathy due to vitamin E deficiency.
8. *Chronic renal failure and chronic liver disease:* Neurotoxic drugs should be avoided and early dialysis initiated**.** Renal transplant alleviates the symptoms of uremic neuropathy within 3-12 months. Management of neuropathy associated with chronic liver disease consists of pain management; the role of liver transplant is not yet defined except for those with autonomic neuropathy where an early liver transplant is indicated.
9. *Critical illness polyneuropathy:* This is an axonal polyneuropathy seen in critically ill patients who present as generalized weakness or difficulty in weaning from the ventilator. This neuropathy resolves spontaneously in survivors 3- 6 months following discharge from the intensive care unit.
10. *Toxic neuropathies:*
    - *Arsenic:* In the acute form can mimic GBS, however eventually most of the patients develop an axonal polyneuropathy. In the acute phase treatment is with chelating agents like dimercaprol or D penicillamine to prevent the development of neuropathy. However, the role of these chelating agents in the treatment of neuropathy is not known.
    - *Lead:* The most characteristic presentation is wrist drop due to radial nerve palsy**.** Treatment of lead toxicity is by using dimercaprol or 2,3-dimercaptopropane; again the treatment of the associated neuropathy is not well defined.
    - *OPC (organophosphorous compounds):* Neuropathy may be associated with the intermediate syndrome or as the delayed axonal polyneuropathy. For the intermediate support, ventilatory support is needed for any respiratory muscle involvement. There is no specific treatment for the delayed polyneuropathy.
    - Manifests clinically as a painful polyneuropathy and alopecia. Treatment is the use of IV potassium chloride, forced diuresis and hemodialysis during the acute stages of the poisoning and preventing further toxin exposure.
11. *Drug induced:* Many drugs are implicated to be causative for both small and large fiber neuropathy. Sometimes it may be difficult to ascertain whether the neuropathy is due to the primary disease or he drugs used to treat it (Both HIV infection per se and antiretroviral drugs can cause a painful neuropathy). The treatment in most of the drug induced neuropathies is cessation of the offending drug. However, symptoms may progress even after stopping these drugs due to a phenomenon described as coasting. Patients with an underlying congenital neuropathy (e.g. CMT) may be more vulnerable to develop neuropathy with neurotoxic drugs.
12. *Infections:*
    - *HIV:* Neuropathy in these patients can be due to the primary infection (distal painful sensory neuropathy), opportunistic infections (Cytomegalovirus induced lumbar polyradiculoplexopathy), drug induced or multi factorial. Management consists of identifying the cause of the neuropathy and treating it.
    - *Hansens:* Depending on the bacilli load (Multibacillary/ Paucibacillary); patients are treated with rifampicin, dapsone and clofazimine for either 6 or 12 months. In those with a pre existing neuropathy, steroids (40 mg) are also added for the initial couple of months to prevent neuritis due to drug reversal reactions.
    - *Diphtheritic neuropathy:* In the early stages patients develop palatal palsy and paralysis of accommodation. Patients may also develop a demyelinating sensorimotor neuropathy 3- 15 weeks after the infection. Treatment with diphtheritic anti toxin within 48 hours after the onset of primary infection reduces the incidence and severity of neuropathy.
    - *Lyme disease:* Not common in India. Treatment in the acute stage is with antibiotics (IV ceftriaxone; oral doxycycline or amoxicillin in mild cases).
13. *Hereditary neuropathies:* As definitive treatment is not available for most of these inherited neuropathies, treatment remains mainly symptomatic. Affected individuals are often evaluated and managed by a multidisciplinary team. Daily heel cord stretching exercises to prevent Achilles' tendon shortening is desirable. Special shoes, including those with good ankle support,

may be needed. Affected individuals often require ankle/foot orthoses to correct foot drop and aid walking. Orthopedic surgery may be required to correct severe pes cavus deformity. Some individuals require forearm crutches or canes for gait stability, but fewer than 5% of individuals need wheelchairs. Exercise is encouraged within the individual's capability and many individuals remain physically active. Drugs and medications such as vincristine, taxol, cisplatin, isoniazid, and Nitrofurantoin that are known to cause nerve damage should be avoided.[5]

Patients with porphyria should avoid fasting, alcohol and certain drugs (barbiturates, sulfonamides, analgesics, anticonvulsants and female sex hormones) that can precipitate an attack. Treatment consists of a high carbohydrate diet (400 g/day) and in non-responders IV hematin is used (suppresses the activity of ALA synthetase) (4 mg/kg 12 hourly for 3 days).

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