Evaluation of Peripheral Neuropathy

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Evaluation of Peripheral Neuropathy - Introduction

- A very common complaint in the clinic
  - Presentation is variable
  - Multiple causes
  - Requires a logical and systematic approach of evaluation and treatment
  - Most can be categorized by subtype and etiology following completion of history, examination, EDX, and appropriate lab work
  - Classification allows for more reasonable assessment of prognosis and treatment options based upon type of peripheral neuropathy.
Evaluation of Peripheral Neuropathy - Epidemiology

• Prevalence is 2400/100,000 (2.4%), but 8% in patients older than 55 years
  – Most common etiology in the industrialized world is DM2
    • Prevalence is increasing in US as obesity epidemic worsens. Expected to continue worsening.
  – Leprous neuritis is an important cause of neuropathy in Asia, India, Africa, S/C Americas (and Louisiana)
  – Other systemic causes: metabolic disorders, infectious agents, vasculitis, toxins, drugs, malabsorption (GI bypass)
  – Dysimmune neuropathies (CIPD, MMN, paraproteinemic neuropathies)
  – Inherited (Charcot-Marie-Tooth)

Evaluation of Peripheral Neuropathy - Diagnosis

• Presentation is often variable & can include
  – Altered sensation, pain, tingling, muscle weakness and atrophy, and even autonomic dysfunction
  – Accurate diagnosis requires skillful interpretation of the patient’s clinical presentation as well as electrodiagnostic evaluation
    • EDX provides data allowing for establishment of distribution, type (axonal vs. demyelinating), chronicity
    • Subtype classification is critical for accurate diagnosis and for an appropriate therapy plan.
Evaluation of Peripheral Neuropathy - Mononeuropathies

- Focal lesions of an individual peripheral nerve
  - Trauma, focal compression, entrapment
  - Carpal tunnel syndrome is most common followed by ulnar nerve entrapment at the elbow
  - EDX provides objective data required for an accurate diagnosis
    - Localization of lesion
    - Severity of lesion

Evaluation of Peripheral Neuropathy - Mononeuropathies

- Caveat: Focal neuropathies can be associated with more generalized metabolic or toxic neuropathies (ie. diabetic polyneuropathy)
- EDX of a suspected mononeuropathy may uncover findings that support a mononeuropathy multiplex as can be seen in vasculitis, sarcoidosis, amyloidosis, or HNLPP
Evaluation of Peripheral Neuropathy – Mononeuropathy Multiplex

- Involvement of multiple individual, noncontiguous nerves
  - Can occur simultaneously or serially
  - Random pattern, multifocal, typically rapidly evolving
  - Urgency of assessment since patients may have a vasculitis associated with systemic disease (polyarteritis nodosa, Churg-Strauss, Sjogren Syndrome, RA)
    - Confirmed vasculitis cases usually require therapies including immunosuppression with steroids or more potent therapies with immunomodulating drugs

- Other conditions that can present with a MM include sarcoidosis, lymphoma, carcinoma, amyloidosis, leprosy, Lyme disease, HIV, and cryoglobulinemia
  - Patients should be considered for nerve biopsy, typically either the sural or superficial peroneal nerves
    - The nerve selected for biopsy should ideally be one that produced abnormal results on nerve conduction
  - About 1/3 of MM cases will have findings on NCS consistent with multifocal demyelination, usually secondary to CIDP or CIPD variant like MMN
Evaluation of Peripheral Neuropathy – Polyneuropathy

• Most common is a distal symmetric polyneuropathy
  – Length dependent (distance from the parent nerve cell body of either DRG or anterior horn)
    • Toes & soles first affected
    • DM2 is the most common cause, but can be seen in other metabolic disorders, acquired systemic diseases, and exogenous toxicities
    • Typical progression proximally; reduced or lost ankle and patellar reflexes; dorsiflexion weakness; proprioception loss

Evaluation of Peripheral Neuropathy – Polyneuropathy

• A thorough history is critical to accurately classify the polyneuropathy
  – Ask about chronic medical conditions, systemic diseases, recent illnesses (especially viral), recent vaccinations, new medications, OTC supplements, EtOH use, heavy metals or solvents exposure, gastric bypass, and family members with similar complaints
    • Gastric bypass: Vitamins A, K, E, B1, B2, B6, B9, B12 / MMA, copper, selenium, and zinc
Evaluation of Peripheral Neuropathy – Polyneuropathy

・ A thorough history is critical to accurately classify the polyneuropathy, continued:
  – Duration (acute vs. chronic) and course
    • Most will progress slowly and symmetrically
    • If rapidly progressive then urgent assessment is necessary since symptoms may represent a serious illness (Guillain-Barré, exposure to toxins, vasculitis)

Evaluation of Peripheral Neuropathy – Polyneuropathy

・ Most involve both small and large fiber nerves though one fiber type may be predominately affected
  – Associated weakness and atrophy is indicative of large fiber involvement since all motor axons except gamma efferent fibers to muscle spindles are large fibers
  – Vibration, proprioception and the efferent arcs of DTRs are all carried by large fiber sensory fibers
  – Pain, temperature, and peripheral autonomic functions are all governed by small fibers
  – Exclusively small fiber neuropathies should not affect the patient’s strength or DTRs
    • DM > idiopathic (middle aged adults) > HIV or amyloidosis
Evaluation of Peripheral Neuropathy – Polyneuropathy

• Acute Polyneuropathies
  – Acute and symmetric presenting with a rapidly progressive paralysis and areflexia and variable sensory involvement
    • Usually a Guillain-Barré variant
    • Urgency of diagnosis because of the risk of progression to respiratory insufficiency
    • Caution because early presentations can involve only minor complaints of distal paresthesias and mild weakness
    • Face, bulbar, and respiratory muscles can be affected
    • Up to 1/3 patients will require intubation and ventilator support
    • Patients presenting to ER should be admitted and monitored with serial NIF assessments

Evaluation of Peripheral Neuropathy – Polyneuropathy

• Acute Polyneuropathies, continued
  – GBS represents a range of autoimmune inflammatory polyradiculoneuropathies
    • Most are demyelinating though some forms are primarily axonal, affect motor nerves, and involve only secondary demyelination
    • Treatment includes either PLEX or IVIg. Both will minimize clinical worsening, hasten recovery, and reduce long term disability
Evaluation of Peripheral Neuropathy – Polyneuropathy

• Acute Polyneuropathies, continued
  – Less common causes include porphyria, diphtheria, tick paralysis, vasculitis, some medications, paraneoplastic syndromes, critical illness polyneuropathy, and poliomyelitis
    • WNV infection can cause a polio-like areflexic paralysis, but the difference is that WNV infections will also present with either meningitis or encephalitis
    • Treatment includes either PLEX or IVIg. Both will minimize clinical worsening, hasten recovery, and reduce long term disability

• Chronic Polyneuropathies
  – Usually evolve over the course of month to years and clinical presentation can be variable
  – Most can be pared down to a few specific etiologies with thorough history and examination and with electrodiagnostic testing
  – Establish the
    • rate and the pattern of disease progression (progressive vs. relapsing);
    • Motor vs. sensory or both
    • Small vs. large fiber or both
    • Axonal vs. demyelinating (EDX)
      – EDX also provides information regarding demyelination (uniform or multifocal)
Evaluation of Peripheral Neuropathy – Polyneuropathy

- Chronic Demyelinating Polyneuropathy
  - Either genetically determined or acquired
    - EDX is very useful since it allows for discovery of uniform and symmetric slowing on NCS (genetic) or multifocal slowing and conduction block on NCS (acquired)
  - Most genetic polyneuropathies are variants of Charcot-Marie-Tooth and about 80% will have a PMP22 gene duplication
    - Commercial genetic analysis is the best way to accurately classify these neuropathies since clinical phenotypes of CMT are so variable and different genetic mutations can produce similar phenotype

Evaluation of Peripheral Neuropathy – Polyneuropathy

- Chronic Demyelinating Polyneuropathy
  - Acquired neuropathies are typically immune-mediated and demyelinating
    - Chronic Inflammatory Demyelinating Polyneuropathy is the most common type
      - Either gradually progressive or relapsing
      - Typically produces a motor neuropathy, but can affect sensory nerves
      - Can affect both distal and proximal muscles
      - CSF protein is almost always elevated
    - Multifocal Motor Neuropathy
      - Similar to CIDP but characterized by partial conduction block seen only in motor axons
      - Typically presents with weakness and atrophy in the forearms and hands (MND mimic)
  - Both respond to immunotherapy, though differently
    - Both respond to IVIg and immunosuppressive drugs but only CIDP responds to steroids and PLEX
Evaluation of Peripheral Neuropathy – Polyneuropathy

• Chronic Axonal Polyneuropathy
  – The most common of polyneuropathies
    • DM is the most common etiology
      – Other causative metabolic disorders include nutritional deficiencies, chronic renal failure, malignancies and their chemotherapy treatments, medications, alcohol abuse
    • CMT2 (axonal)
    • Idiopathic
      – Even after thorough work up as many as ¼ patients with a chronic polyneuropathy will have no discovered cause of their symptoms
      – Most are mild cases and predominantly distal sensory neuropathies in older patients
      – Some may be small fiber; some may be pre-diabetic
        » Remember that the degree of diabetic neuropathy does not correlate directly with glycemic index

Evaluation of Peripheral Neuropathy – Labs

• All patients should receive CBC, CMP, TSH, B12/MMA, folate, SPEP with immunofixation, A1c
  – Add B1, B2, B6, Cu, Zn if h/o gastric bypass)
  – Add heavy metals screen if patient history warrants, remembering that Ar can be elevated after eating sea foods
  – If ddx includes infections, immune-mediated disease, or neoplastic causes then CSF should be analyzed
  – Nerve biopsy should be reserved for cases when diagnosis cannot be determined by less invasive means
  – Genetic analysis is readily available, relatively inexpensive, and should be used in investigations of hereditary neuropathies
Evaluation of Peripheral Neuropathy – Treatments

- Peripheral neuropathies secondary to metabolic derangements should have specific therapy directed at managing the derangements (DM, low B12, hypothyroidism, renal insufficiency, etc).

- Immune mediated neuropathies usually need IVIg or PLEX, and sometimes need immunomodulating therapies.

- Hereditary neuropathies unfortunately may have no treatment.
References