Evaluation of Peripheral Nervous System Dysfunction

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Disclosures

Nothing

Peripheral Nervous System

- Anterior Horn Cell
- Root
  - Monoradiculopathy
  - Polyradiculopathy
- Plexus
- Multiple levels
- Peripheral Nerve
  - Mononeuropathy
  - Polyneuropathy
  - Mononeuritis multiplex
  - Large fiber
  - Small fiber
- Neuromuscular Junction
- Muscle
Clinical Questions to be Addressed

• Are the symptoms due to neuropathy?
  – If so, is the neuropathy due to cancer pathology, cancer treatments, or something unrelated?
• Are the symptoms severe enough to require intervention?
  – If so, what options do we have?
• Is modification of the present cancer treatment necessary?

Assessment of Neuropathy

• Patients who develop new symptoms during treatment

• Clinical trials of new agents
  – Potential trials of neuroprotective agents

• Clinical assessment
• Neurophysiologic testing
  – Large fiber testing
    • NCS/EMG
  – Small fiber testing
    • QST, QART, sympathetic skin responses, TST, autonomic testing, laser-evoked potentials, current perception threshold testing
• Laboratory testing
• Imaging
• Nerve and skin biopsy
• Toxicity grading systems/Composite scales
No Gold Standard

Challenges

- Lack of standardization
- Poor correlation between objective findings and patient symptoms and severity
- Limited resources across institutions
- Use of objective measures to assess subjective symptoms, i.e. pain, sensory disturbance

History & Physical Examination
H & P

- Pre-existing or previous neuropathies, associated co-morbidities, family history of neuropathy, EtOH use
- Temporal profile of cancer treatments
  - Duration/frequency of administration and dose
  - "Coasting" phenomenon
- Distribution of signs/symptoms
  - Distal, symmetric, sensory > motor
  - Predominantly sensory, UE > LE
- Clinical features
  - Sensory, Motor, Pain, Autonomic, Reflexes, Functional impairment

Coasting

- Symptoms are seen after cumulative exposure
- Symptoms appear or worsen between treatment cycles
  - Including 2-3 months after cessation of treatment

H & P

- Sensory examination
  - "Neuropathic" description of symptoms
    - Large vs. Small fiber
  - Distribution of symptoms
  - Autonomic symptoms: bowel/bladder dysfunction, orthostasis, impotence, arrhythmias, etc.
H & P

• Light touch – A-beta
• Vibration – A-beta
• Proprioception – A-beta
• Pin-prick – A-delta
• Temperature – A-delta, C

Clinical Assessment

• Deep tendon reflexes
• Motor – A-alpha
  – Weakness
  • Distribution, severity
  – Atrophy
  – Fasciculations
  – Tone
• Associated musculoskeletal findings
  – Hammertoes, pes cavus

Physical Examination

• Understand segmental and peripheral innervation patterns
• Test muscles innervated by each cervical/lumbosacral segment
• Test muscles innervated by the same segment, but different peripheral nerves when necessary
Manual Muscle Testing (upper extremity)

- Deltoid (C5-6, axillary nerve)
- Biceps (C5-6, musculocutaneous)
- Wrist Extensors (C6-7, radial)
- Digit Extensors (C6-7, radial)
- Triceps (C6,7,8, radial)
- Finger Flexors (C8-T1, median)
- Dorsal Interossei (C8-T1, ulnar)

Manual Muscle Testing (upper extremity)

- Other Useful Muscles
  - Pronator Tertius (C6-7, median)
    - A non-radial nerve C7 muscle
  - Extensor indicis proprius (C7-8, radial)
    - Most distal radial nerve innervated muscle
    - Non-median or ulnar innervated C8 muscle
  - Abductor pollicis brevis (C8-T1, median)
    - Affected in severe carpal tunnel syndrome
  - Flexor pollicis longus (C8-T1, median)
    - Anterior intersosseous branch of median nerve

Manual Muscle Testing (lower extremity)

- Iliopsoas (L2-3, femoral nerve)
- Quadriceps (L3-4, femoral)
- Hamstrings (L5-S1, sciatic)
- Anterior tibialis (L4-5, deep peroneal)
- Extensor hallucis longus (L5, deep peroneal)
- Gastrocnemius (L5-S1, tibial)
Manual Muscle Testing (lower extremity)

- Other useful muscles
  - Hip adductors (L3-4, obturator)
  - Hip abductors (L5-S1, superior gluteal)
  - Posterior tibialis (L5-S1, tibial)
  - Peroneus longus (L5-S1, superficial peroneal)

Sensory Exam

- C4 = acromioclavicular joint
- C5 = lateral antecubital fossa
- C6 = thumb
- C7 = middle finger
- C8 = pinky
- T1 = medial antecubital fossa

Sensory Exam

- L1 = anterior proximal thigh
- L2 = midanterior thigh
- L3 = medial femoral condyle
- L4 = medial malleolus
- L5 = foot dorsum at 3rd toe
- S1 = lateral heel
- S2 = popliteal fossa
- S3 = ischial tuberosity
- S4-5 = perianal area
Be aware of peripheral nerve overlay

- **Upper extremity**
  - Carpal tunnel syndrome: test C6 on dorsal thumb (radial nerve)
  - Radial neuropathy: test C7 on volar middle finger (median)
  - Ulnar neuropathy at wrist: test C8 on dorsal pinky (dorsal ulnar cutaneous nerve)

- **Lower extremity**
  - Femoral neuropathy affects the medial calf (saphenous nerve)
  - Deep peroneal nerve = first web space
  - Superficial peroneal nerve = skin of the foot dorsum
  - Lateral femoral cutaneous nerve

Reflexes

- **Upper extremity**
  - Biceps C5-6
  - Brachioradialis C5-6
  - Triceps C7
  - Pronator teres C6-7
  - Finger flexors C8

- **Lower extremity**
  - Knee L4
  - Ankle S1
  - Medial hamstring L5
  - Adductor L3

Lower Motor Neuron Signs

- Weakness
- Atrophy
- Fasciculations
- Reduced/flaccid tone
- Reduced/absent reflexes
Clinical Signs & Symptoms

- Subjective symptoms alone have relatively poor diagnostic accuracy
  - Multiple symptoms are more accurate than single symptoms

- Clinical signs are better predictors of neuropathy
  - Multiple signs on exam are more accurate than a single sign

Electrodiagnostics

- Nerve Conduction Studies/Needle electromyography (NCS/EMG)
  - Functional assessment of the peripheral nervous system
    - Extension of the history and physical examination
  - Invaluable tool in the assessment of neuropathy
    - Large fibers: A-alpha, A-beta
Purpose of NCS/EMG

- Confirmation
- Rule out
- Detection of subclinical disease
- Localization
- Severity, acuity
- Pathophysiology
- Prognosis/Response to treatment/Guide further testing

Limitations of NCS/EMG

- Requires subspecialty expertise
- Does not assess small diameter fibers
- Inferring symptoms and neuropathic deficits
  - EMG severity ≠ clinical severity
  - NCS/EMG changes may lag behind symptom onset
- Inferring underlying anatomical, biochemical or other pathophysiologic derangements

EMG + H & P

- Provides the most accurate diagnosis of neuropathy
- EMG should not be used alone to diagnose neuropathy
  - Imperfect sensitivity and specificity
Quantitative Sensory Testing

- Utilized in the evaluation of small fiber neuropathies
  - Various tests involving sensory modality thresholds
    - Thermal: small fiber, Vibration: large fiber
- Commonly used for diagnosis confirmation, serial measurements in neuropathy treatment trials
- Relatively high sensitivity and reliability
- Limited Class II evidence: QST is possibly useful in demonstrating sensory abnormalities in chemotherapy induced neuropathy (Level C recommendation)

Quantitative Sensory Testing Pitfalls

- Requires subspecialty expertise
- Psychophysical test
  - Subjective report
  - Requires patient cooperation
- CNS dysfunction can result in abnormal QSTs
- Patients must be tested in appropriate environment
- Lack of normative values
- Poor reproducibility

Laboratory Testing
Laboratory Testing

- Performed to evaluate for other causes of neuropathy
  - Glucose, HgbA1C, BUN, Cr, serum B12, folate, TSH, RF, ANA, ENA (anti-Ro, anti-La), ESR, CRP, SPEP w/ immunofixation, cryoglobulins
  - Vit B6, Lyme, RPR, HIV, heavy metals, etc.
  - Paraneoplastic panel (anti-Hu, anti-Yo, anti-Mag)
  - CSF studies if leptomeningeal disease, AIDP suspected
  - Tumor markers
    - Assessment of disease response to therapy
  - Genetic testing

- Highest yield of abnormalities:
  - Blood glucose
  - Serum B12
    - Methylmalonic acid
    - +/- Homocysteine
  - SPEP

Imaging

- Performed to identify neuroanatomical derangement
  - Compressive vs. non-compressive etiologies
- Guided by clinical and electrophysiologic assessment

Imaging

- MRI
  - Modality of choice
  - Radiculopathies
  - Plexopathies
  - Large mononeuropathies

Imaging

- Ultrasound
  - Novel use for an old modality
  - Cheaper, more readily available than MRI
  - Useful in entrapment syndromes, nerve sheath tumors
  - Nonspecific findings in polyneuropathy
    - Fatty infiltration of denervated muscle
    - Peripheral nerve inflammation
  - Role is still undefined and poorly evaluated
Biopsy

Nerve Biopsy

- Rarely performed

- Peripheral sensory nerves
  - Sural, superficial radial
  - High sensitivity in the diagnosis of vasculitic neuropathies
    - Amyloidosis (fat pad biopsy preferred), hereditary neuropathies, inflammatory neuropathies, malignancy (rare)

Skin Biopsy

- Skin
  - Assessment of small fiber neuropathies, sensory neuropathies
  - Measurement of intraepidermal fiber density
  - Assessment of distal and proximal sites
  - Changes appear earlier than on sural nerve biopsy

- Easy to perform, well tolerated
- Reliable
Skin Biopsy

- Limitations
  - High specificity, relatively low sensitivity
  - Cannot identify etiology of neuropathy
  - Limited availability of histological processing and evaluation

Grading Scales

- Help assess severity of neuropathy
- Determines levels of impairment related to neuropathy
- Guides decision making about continuing treatment
Grading Scales

- World Health Organization
- Eastern Cooperative Oncology Group
- Ajani Sensory and Motor
- Total Neuropathy Score
- Patient Neurotoxicity Questionnaire
- Oxaliplatin-associated Neuropathy Questionnaire
- EORTC QLQ-CIPN20 (my personal favorite…)
- * National Cancer Institute – Common Terminology Criteria for Adverse Events (v4.03)

CTCAE 4.03

**Peripheral Motor Neuropathy**
- Grade 0: Normal
- Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate symptoms; limiting instrumental ADLs
- Grade 3: Severe symptoms; limiting self care ADLs; assistive device indicated
- Grade 4: Life threatening consequences; urgent intervention indicated
- Grade 5: Death

CTCAE 4.03

**Peripheral Sensory Neuropathy**
- Grade 0: Normal
- Grade 1: Asymptomatic; loss of deep tendon reflexes or paresthesia
- Grade 2: Moderate symptoms; limiting instrumental ADLs
- Grade 3: Severe symptoms; limiting self care ADLs
- Grade 4: Life threatening consequences; urgent intervention indicated
- Grade 5: Death

CTCAE 4.03

- In general:
  - Grade 0-1: no dosage adjustment
  - Grade 2-3: decrease dosage 20-50%
  - Grade 3-4: discontinue treatment
  - Grade 5: """"

Grading Scales - Criticisms

- Mixed assessment of symptoms and signs
- Lack sensitivity to slight changes in neuropathy
- High inter-examiner variability
  - Evaluation parameters not clearly defined
    - Especially w/ respect to function
- Do not take pre-existing conditions into account
- ? Pain ?

Recommendations
NCCN Task Force Recommendations Assessment

• Baseline neurological assessment prior to treatment
  – By the oncologist
  – Identify pre-existing conditions

• Routine assessments during treatments
  – Evaluate motor, sensory, pain, and function

NCCN Task Force Recommendations Assessment

• Refer to specialist (i.e. Dr. C) if patient has
  – Atypical or severe signs/symptoms
  – Pre-existing neuromuscular conditions
  – Significant functional deficits
• Specialist scheduling should be done in parallel with oncologic visits
  – Avoid unnecessary delays in treatments

• Communication is key

NCCN Task Force Recommendations Assessment

• Neurophysiologic testing, lab testing, imaging not routinely recommended
  – Not sufficiently reliable to be used alone for clinical decision making
  – Can be useful as an adjunct for confirming or ruling out a diagnosis

“I never learn anything talking. I only learn things when I ask questions.”
- Lou Holtz