Survey of Neurology

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WAPA
1/26/13
A 48 y.o. male presents with gradual progressive weakness of his proximal legs and arms without sensory loss. The exam confirms the weakness, reflexes are reduced, and no fasciculations are seen.

The best anatomical localization is?

A. Brain
B. Muscle
C. Motor neuron
D. Spinal cord
E. Peripheral nerve
A 26 y.o. female presents with subacute weakness of her legs, bladder urgency, and sensory loss in the legs. Arms, speech and swallow are fine. The exam confirms the weakness, leg reflexes are increased, and a T10 sensory level is present.

The best anatomical localization is?

A. Brain  
B. Muscle  
C. Motor neuron  
D. Spinal cord  
E. Peripheral nerve
Neurological “Levels”

- Brain
- Brainstem
- Spinal cord
- Motor neuron
- Peripheral nerve
- Neuromuscular junction
- Muscle
- Often unilateral
- Motor and/or sensory
- Language
- Consciousness
- Memory
- Behavior
- Vision
- Seizures
- Movement d/o
Level: Brainstem

- Often unilateral
- Motor and/or sensory
- Consciousness
- Cerebellar
- Movement d/o
- Cranial nerves
  - Diplopia
  - Vertigo
  - Face
  - Swallow
  - Tongue
Level: Spinal Cord

- Often bilateral
- Motor and/or sensory
- Head OK
- Bowel, bladder and erectile
Level: Motor Neuron

- Asymmetric bilateral
- Motor
- Proximal and distal
- Insidious onset
- Fasciculations
- Symmetric or focal
- Sensory > motor
- Cranial nerves 3-12
- Often distal
  » Stocking-glove
- If proximal think
  » Demyelinating (UE + LE)
  » Cauda equina (LE)
Level: NMJ

- Asymmetric bilateral
- Motor only
- Proximal and distal
  - Eyes involved in myasthenia gravis
- Fatigable weakness
  - Myasthenia gravis
- Progressive weakness
  - Lambert-Eaton myasthenic syndrome
Level: Muscle

- Symmetric bilateral
- Motor only
- Usually proximal
This is a 22 yo woman with sensory loss in the right hand that spread to her right trunk and leg over 2 weeks. No weakness. Last year she had numbness in her left face for 4 weeks. Her exam reveals the sensory loss to pinprick.

What test is likely to confirm your diagnostic suspicion?

A. Brain MRI
B. Spinal fluid evaluation
C. Lumbar MRI
D. Electrodiagnostic testing
E. Tibial evoked potentials
Multiple Sclerosis

- CNS disease
- Primarily demyelinating
  - Axonal loss is also present
- Females/white > males/non-white
- Sex 2-3:1 = F:M
- Prevalence 5-250/100,000 population
- Associated with Vit D deficiency and EBV exposure
MS: Types

- Relapsing-remitting MS (RRMS)
  - 60-80%
  - Secondary progressive
  - Progressive relapsing

- Primary progressive MS (PPMS)
  - 20-30%
  - Older, cervical disease
MS: Clinical

- Optic neuritis
  - Blurry, color desaturation
  - Painful eye movement
- Weakness, spasticity
- Sensory
  - most common initial presentation
- Ataxia, tremor
- Cognitive
- Lhermitte’s sign
- Fatigue
- Heat and exercise intolerance
- Bladder
- Sexual dysfunction
RRMS: Clinical

- Exacerbations over hours to days
  » > 24 hrs.
- Resolution over days to months
- 2 events separated in time and space
  » Time: one month
  » Space: clinical or paraclinical (MRI, CSF, EPs)
PPMS: Clinical

- Chronic symptoms > 6 months
- No other explanation
- Testing positive
MS: Testing

- MRI
- CSF (Oligoclonal bands)
- Evoked potentials
MRI

- 90-95% sensitive at first presentation
- Visual detection of plaques
  - Demyelination
  - Gliosis
  - Inflammation
- Location
  - Periventricular
  - Corpus callosum
  - Cerebellum
  - Brain stem
- Acute lesions enhance (Gd+)
- MacDonald Criteria
MRI

Axial flair  Coronal T1 with Gad  Sagittal flair
CSF

- Detects immune changes inside the blood-brain barrier
- Oligoclonal bands
  - Sensitivity
    - 85-90% RRMS
    - 60% PPMS
  - Specificity 60%
- Elevated IgG index
- Normal glucose
- Protein <100
- Cells <50
Evoked Potentials

- Detects conduction slowing through CNS
  - Demyelination
- Type: Sensitivity
  - Visual: 70%
  - Tibial: 70%
  - Median: 60%
MS: Treatment

- Symptomatic
- Acute
  » Methylprednisolone 1000mg IV qd x 3-5
- Chronic (Disease modifying drugs)
  » Interferon beta-1b (Betaseron)
  » Interferon beta-1a (Avonex)
  » Interferon beta-1a (Rebif)
  » Glatiramir acetate (Copaxone)
  » Nataluzimab (Tysabri)
  » Fingolimod: oral, new 2011
- Mitoxantrone (worsening RRMS and SPMS)
Pathophysiology

Lymph Node → Blood Vessel → Brain

T-Cell Maturation → S1P1 → Blood-Brain Barrier

VLA-4

Neuron

Myelin

Myelin Basic Protein

Axon
Treatment: Methylprednisone

Steroids decrease T-cells, reduce inflammation, shore up the BBB, and decrease Ab production.
Treatment: Beta-interferons

Beta-interferons change the balance in favor of more suppressor T-cells.
Treatment: Copaxone

Glatiramer acetate looks like MBP and may work as a decoy for MBP reactive T-cells.
Treatment: Tysabri

Nataluzimab blocks VLA-4 so that T-cells can’t bind to the vessel wall.
Treatment: Fingolimod

Fingolimod is a S1P₁ (sphingosine-1-phosphate) receptor antagonist.
A 56 y.o. man presents with trouble walking, small hand writing, and a resting tremor.

You make a presumptive diagnosis and suggest:

A. Sinemet trial
B. Head MRI
C. Propranolol for essential tremor
D. Stroke work-up
Parkinson’s Disease

- Loss of dopaminergic neurons in the substantia nigra
- Lewy bodies
- Differentiate from broader classification of parkinsonism
- Mean age of onset 55yo
Parkinsonism

- Parkinson’s Disease
- Neuroleptic side effect
- Post-encephalitic
- Toxins (Mn, CO, MPTP)
- Dementia
- Wilson’s disease
- Basal ganglia calcifications

- Parkinson-plus syndromes
  - Progressive supranuclear palsy
  - Corticobasoganglionic degeneration
  - Multisystem atrophy
    - Autonomic
    - Cerebellar
  - Diffuse Lewy body disease
PD: Clinical

- Slow progressive course
- 4 cardinal features
  - Resting tremor
  - Bradykinesia
  - Rigidity (cogwheel)
  - Postural reflex impairment
- Other: dementia, depression, autonomic
PD: Treatment

- **Sinemet = carbidopa/levodopa**
  - Levodopa converts to dopamine
  - Most potent drug for PD
- **Dopamine agonists**
  - Act directly on dopamine receptors
  - Synergy with levodopa
  - Ex. Pramipexole, Ropinirole
- **COMT inhibitors**
  - Block COMT metabolism of levodopa to DA
  - Ex. Entacapone
- **Other**
Levodopa
COMT
AADC
3-OMD
Dopamine

Levodopa
AADC
COMT
Dopamine
3-OMD

3,4-DHPA
MAO-B
COMT

3-MT
MAO-B

Homovanillic acid

COmt = catechol-O-methyltransferase
AADC = amino acid decarboxylase
MAO = monoamine oxidase
OMD = O-methyldopa
DHPA = dihydroxyphenylacetic acid
MT = methoxytyramine
A 32 y.o. male feels dizzy several times a day when he moves his head to the left. He describes a spinning sensation that lasts 1 minute. The exam reveals nystagmus with head maneuvers.

Q. Categorize - treatment?

A. Presyncope - Valium
B. Vertigo - Valium
C. Dysequilibrium - Physical therapy
D. Dysequilibrium - Meclizine
E. Vertigo - Otolith repositioning
Benign Positional Vertigo

**Etiologies**
- Head injury
- Viral
- Idiopathic

**Canalolithiasis**
- Calcium deposit in a semicircular canal
- 90% posterior canal

**Clinical**
- Positional vertigo
- Positional nystagmus
  - Hallpike maneuver

**Treatment**
- Epley maneuver
Utricle and Otoliths
Left Posterior Canal BPV

Hallpike maneuver

Nystagmus: Geotropic torsional Upbeat
A 27 year-old male complains of dizziness starting 3 hours ago that is becoming more severe. He describes a constant spinning. Your exam is remarkable for hearing loss to finger rub in the left ear and horizontal nystagmus to the right no matter which way he looks.

A. Acute vestibular syndrome  
B. Benign positional vertigo  
C. Meniere’s disease  
D. Central vertigo (e.g. stroke, MS)
Acute Vestibular Syndrome

- Vestibular neuritis
  - Without auditory symptoms
- Labyrinthitis
  - With auditory symptoms
- Clinical
  - Sudden onset
  - Constant
  - Unidirectional nystagmus
  - Fixation helps
  - Days to weeks

- Viral?
  - Valacyclovir* not helpful

- Treatment
  - Steroids* acutely
    - Prednisone 120mg qd with 3 wk taper
  - Valium
  - Scopolamine
  - Anti-emetics

*Strupp, et. al. NEJM 2004;351:354
ARS Question

This 58 year-old man first noticed right hand weakness 4 months ago. Three months ago he developed dysarthria and mild trouble swallowing liquids. One month ago he developed left hand weakness. All the symptoms are progressing. Twitching is present. No pain or sensory loss.

You make a presumptive diagnosis and order what test?

A. B12 level
B. Electrodiagnostic test (EMG)
C. Brain MRI
D. TSH
E. CSF for increased protein
ALS: Clinical

- Upper motor neuron
  - Weakness
  - Increased reflexes
  - Spasticity
  - Pseudobulbar
  - Babinski sign

- Lower motor neuron
  - Weakness
  - Decreased reflexes
  - Atrophy
  - Fasciculations
  - EMG denervation
ALS: Treatment

- Rehabilitative
- Medications
  - Riluzole
  - Symptomatic
- Gastrostomy tube
- Mechanical ventilation
This 64 year-old man began having burning pain in his toes 3 years ago. Slowly, it has moved to the knee. The hands became dysesthetic 1 year ago. Weakness is also present in the feet and he is off balance when walking. Reflexes intact except at the ankles.

What is the most likely etiology?
A. Vasculitis
B. Guillain-Barre syndrome
C. Diabetes mellitus
D. B12 deficiency
ARS Question

This 24 year-old man began having tingling in his toes 3 days ago. Rapidly, it has moved to the whole body accompanied by weakness such that he can’t get out of bed and is having trouble breathing and swallowing. Reflexes are absent.

What is the most likely etiology?
A. Vasculitis
B. Guillain-Barre syndrome
C. Diabetes mellitus
D. B12 deficiency
Peripheral Neuropathy

- Step 1: History and physical
- Step 2: Electrodiagnostics
- Step 3: Putting it all together
Step 1: History and Physical

- True peripheral nerve disorder?
  - Cervical stenosis
  - Fibromyalgia
  - MS (central)
  - Myopathy
  - ALS

- Clinical
  - Usually sensory > motor

- Description
  - Burning
  - Stabbing
  - Allodynia
  - Numb
  - Cold
Describe Features

- Distribution
  - Length-dependent
  - Proximal and distal
    - Think demyelinating

- Acute vs. chronic
Step 2: Electrodiagnostics

- **Upsides**
  - Confirm neuropathy
  - Physiology
    - Axonal vs. demyelinating

- **Downsides**
  - Pain
  - Cost
  - Time
  - Miss small fiber dis.
Step 3: Putting It All Together

- Is a neuropathy confirmed?
- Work-up based on characteristics
- Diabetes mellitus is most common
- Unknown also very common
- Biopsy usually not helpful
Differential: Demyelinating

- Guillain-Barre syndrome (AIDP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- CIDP variants
- Diphtheria
- N-hexane
- Acute arsenic

- Paraproteinemic (monoclonal gammopathy)
  - MGUS
  - Multiple myeloma
  - Waldenstrom
  - POEMS
  - Cryoglobulinemia

- Inherited
  - Charcot-Marie-Tooth type 1
  - Metachromatic leukodystrophy
  - Krabbe
Differential: Large Fiber Axonal

- Diabetes mellitus
- Paraproteinemic
- Paraneoplastic
- Uremia
- Vasculitis
- B12 deficiency
- Vit E deficiency
- Hypothyroid

- Porphyria
- Sarcoid
- Toxins
  - Chemotherapy
  - Pyridoxine
  - Nitrous oxide
  - Lead
  - Mercury

- Inherited
  - Charcot-Marie-Tooth type 2
Differential: Small Fiber Axonal

- Diabetes mellitus
- Paraproteinemic
  » Amyloidosis
- Paraneoplastic
- Cryoglobulinemic
  » Hepatitis C
- HIV
- Leprosy

- Fabry disease
- Toxins
  » Chemotherapy
  » Thallium
- Inherited
  » Hereditary sensory autonomic neuropathy
Differential: Mononeuropathy Multiplex

- Diabetes mellitus
- Vasculitidies
  - PAN
  - Churg-Strauss
  - Wegener
- Infection
  - Leprosy
  - Lyme
  - HIV
- Connective tissue
  - RA
  - SLE
  - Sjogren
- Inflammatory
  - Sarcoid
- Cryoglobulinemia
Mononeuropathy Multiplex Cont.

- Amyloid
- Hereditary
  - Hereditary neuropathy with liability to pressure palsy (HNLPP)
- Neoplastic
  - Compression
  - Invasion
  - Paraneoplastic
- Trauma
- Radiation
- Auto-immune
  - Multifocal motor neuropathy with conduction block (MMN)
  - Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
  - Multifocal acquired motor axonopathy (MAMA)
Differential: Medications

- Amiodorone (A/D)
- Perhexiline (A/D)
- Chloroquine (D)
- Vinca Alkaloids (A)
- Cisplatin (A)
- Paclitaxel (A)
- ddC, d4T, ddl (A)
- Dapsone (A)
- Isoniazid (A)
- Ethambutol (A)

- Nitrofurantoin (A)
- Metronidazole (A)
- Chloramphenicol ?
- Phenytoin (A)
- Pyridoxine (A)
- Tacrolimus (D)
- Colchicine (A)
- Disulfarim (A/D)
- Procainamide (D)
- Sulfasalazine (A)
- Thalidomide (A)

Diabetic Neuropathy

- Symmetric
  - Distal sensory
  - Autonomic
  - Proximal lower limb
  - Acute cachectic
  - Treatment induced

- Focal
  - Cranial nerve
    - Pupil sparing 3rd
  - Mononeuropathy
    - Limb
    - Trunk
  - Proximal lower limb
AAN Consensus

Conclusion: Patients with distal symmetric sensory polyneuropathy have a relatively high prevalence of diabetes or pre-diabetes (impaired glucose tolerance), which can be documented by blood glucose, or GTT (Class III).

Recommendation: When routine blood glucose testing is not clearly abnormal, other tests for pre-diabetes (impaired glucose tolerance) such as a GTT may be considered in patients with distal symmetric sensory polyneuropathy, especially if it is accompanied by pain (Level C).
First Line Testing for Distal Sensory Neuropathy

- Fasting plasma glucose
  - Impaired fasting glucose: 100-125mg/dl
  - Diabetes: >125mg/dl on 2 occasions
- If fasting glucose okay, consider OGTT
  - Impaired glucose tolerance: 2hr post prandial glucose 140-200mg/dl
  - Diabetes: 2hr post prandial glucose >200mg/dl
- B12, SPEP

Treatment

- DPN = Diabetic peripheral neuropathy

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>2+ RCTs in DPN</th>
<th>Duloxetine, Pregabalin, TCAs, Oxycodone CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 2</td>
<td>1RCT in DPN</td>
<td>Carbamazepine, Gabapentin, Lamotrigine, Tramadol, Venlafaxine</td>
</tr>
<tr>
<td></td>
<td>1+ RCT non-DPN</td>
<td></td>
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<tr>
<td>Topicals</td>
<td></td>
<td>Capsaicin, Lidocaine</td>
</tr>
<tr>
<td>Other</td>
<td>1+ RCT non-DPN</td>
<td>Bupropion, SSRI, Phenytoin Methadone, Topiramate</td>
</tr>
</tbody>
</table>

**Recommendation**

- **Level A**
  - 2+ class 1 studies
  - Pregabalin

- **Level B**
  - 1 class 1 study or 2 class 2 studies
  - Gabapentin, Sodium valproate, Duloxetine, Venlafaxine, Amitriptyline, Tramadol, Opiates, Capsaicin, TENS

- **Level U**
  - No class 1-3 studies
  - Insufficient evidence
  - Topiramate, SSRI, nortriptyline, Lidocaine, Alpha lipoic acid

- **Not helpful**
  - Evidence against
  - Lamotrigine, Oxcarbazepine, Lacosamide, Mexilitine, Laser
ARS Question

This 38 year-old man has SOB, trouble smiling and chewing, and mild proximal arm weakness. Both diplopia and ptosis are present. The symptoms are better in the morning and after rest. They are worse when reading, walking, and lifting.

Which two tests will help confirm your diagnosis?

A. CPK and brain MRI
B. Repetitive nerve stimulation and CPK
C. Repetitive nerve stimulation and brain MRI
D. Ach Rec Abs and brain MRI
E. Repetitive nerve stimulation and Ach Rec Abs
Myasthenia Gravis

- Definition: autoimmune disease of the neuromuscular junction characterized by fatigable weakness
- Antibodies against multiple epitopes on the muscle side
- Failure to generate a muscle action potential
Myasthenia Gravis

- 50-125/million
- Bimodal incidence
  - Female 2nd-3rd decade
  - Male 6th-7th decade

- Types
  - Generalized 85%
  - Ocular 15%
  - Neonatal
    - Abs from mother
Neuromuscular Junction

- Ach release
- Attach to Ach receptors
- Muscle contraction
- Ach detaches
- Acetylcholinesterase

Antibodies:
- Ach receptor 85%
- MuSK 7%
- Unknown 8%
Myasthenia Gravis

- **Clinical**
  - Fatigability
  - Ptosis and diplopia
  - Sensory normal
  - Reflexes maintained
  - Bedside maneuvers

- **Diagnosis**
  - H&P
  - Repetitive stimulation
  - Antibodies
  - Tensilon test
  - Chest imaging
Myasthenia Gravis

- Treatment
  - Thymectomy (not MuSK)
  - Anticholinesterase agents
  - Immunosuppression
  - Immunomodulation (plasmapheresis, IVIG)
This 52 year-old male has painless weakness of his thighs and hands. On exam he can’t pinch, get out of the chair w/o pushing, and has absent knee DTRs. The CPK is 426 (2x normal). A muscle biopsy is likely to show which disease?

A. Polymyositis
B. Dermatomyositis
C. Inclusion-body myositis
D. Becker muscular dystrophy
E. McArdle disease
Myopathy

- Inflammatory myopathy
- Muscular dystrophy
- Metabolic myopathies
- Other
Myopathy

- Inflammatory myopathy
  - Muscular dystrophy
  - Metabolic myopathies
  - Other

- Polymyositis (PM)
  - Prox muscles and neck
  - CPK 5-10x normal

- Dermatomyositis (DM)
  - Prox muscles and neck
  - Skin changes
  - CPK 2-10x normal

- Inclusion body myositis (IBM)
  - Distal forearm, prox thigh
  - Most common after 50
  - CPK 1-5x normal

- Biopsy
Myopathy

- Inflammatory myopathy
- **Muscular dystrophy**
  - Metabolic myopathies
  - Other
- Inherited
  - Progressive weakness and atrophy
    » Variable distribution
- Biopsy and DNA testing
- CPK normal to 100x
- No specific treatment yet
Weakness Patterns in Different Types of Dystrophy

A. Duchenne/Becker dystrophinopathy
B. Emery-Dreifuss
C. Limb-girdle
D. Facioscapulohumeral
E. Distal (myotonic dystrophy also involves the face)
F. Oculopharyngeal

Case: Muscular Dystrophy

This is a 18 year-old female who has had progressive weakness since the age of 15. It is both distal and proximal. No sensory loss is reported. Multiple immunosuppressive drugs have not worked. CPK 20,000.

Exam: Strength 4/5 (using wheelchair)  
Reflexes are reduced  
Sensory normal
Myopathy

- Inflammatory myopathy
- Muscular dystrophy
- **Metabolic myopathies**
- Other

- Glycolysis defect
  » Ex. McArdle’s disease
- Fatty acid defect
  » Ex. Carnitine palmitoyl transferase II deficiency
- Mitochondrial cytopathy
  » Ex. Kearns-Sayer
- CPK increases when metabolic system is stressed
- Myoglobinuria
- Biopsy and DNA testing
Case: Metabolic Myopathy

This is a 18 year-old male who gets weak and has cramping after moderate exercise. Myoglobinuria has been noticed on two occasions. No sensory loss is reported. CPK 343.

Exam: Strength normal
Reflexes are present
Sensory normal
Myopathy

- Inflammatory myopathy
- Muscular dystrophy
- Metabolic myopathies

**Other**

- Drug-induced
  - Steroids
  - Statins
- Infectious
- Sarcoid
- Amyloid
- Paraneoplastic
- Critical illness
- GVHD
END