Patient 1: History-I

- 40 year-old man referred for stiffness slowed movement in his legs
- Competitive basketball in high school, but told he had a “funny” walk
- 2001-slow running, tripping over toes, stiffness in legs-attributed to age
- No medications

Patient 1: History-II

- No difficulty swallowing, altered speech, emotional lability
- No difficulty with cognitive tasks at work (engineer)
- Seeing urologist over the past year for 12 episodes of urinary incontinence and impotence

Patient 1: Family History

[Family tree diagram showing genetic inheritance]
Patient 1: Examination

- High-arched feet; no spinal deformity
- MS, CN, Sensory-normal
- Motor
  - Spastic tone in the arms and legs; scissors gait
  - Clonus knees/ankles; hyperactive arm reflexes
  - Slowed foot taps and fine finger movements
  - Flexor plantar responses

Patient 1: Investigations

- Brain MRI without/with gad – normal
- C/T-spine MRI – normal
- Urodynamic testing-spastic bladder
- HIV negative

Medical Myelopathy-Working Definition

Myelopathies that are not amenable to surgical intervention or defined by neuroimaging alone

Table I – Etiology of Medical Myelopathies

- Infection – viral, bacterial, fungal, parasitic
- Vascular – dural AVM, arterial occlusion
- Acute-Subacute Idiopathic Transverse Myelitis
- Hereditary – Hereditary spastic paraplegias (HSP)
- Multiple Sclerosis
- Acquired Metabolic – vitamin B₁₂ deficiency, portosystemic shunting, hyperparathyroidism, hyperthyroidism
Table I – Etiology of Medical Myelopathies (cont.)

Connective Tissue Disease – rheumatoid arthritis, Sjogren’s syndrome, lupus, scleroderma
Environmental – radiotherapy, decompression illness, electrical injury, toxins
Miscellaneous – sarcoid, paraneoplastic, necrotic myelopathy, arachnoiditis, postinfectious or postvaccination

Q1: What is the least likely cause of the neurologic examination findings in this patient?
A. HTLV-I myelopathy
B. Hereditary myelopathy
C. Vitamin B12 deficiency
D. Primary lateral sclerosis

Patient 1: History III

• No history of skin rash, oral ulcers, genital ulcers, dry eyes, dry mouth, organomegaly, arthritis, arthralgias, Raynaud’s, hematuria
• No fever, sweats, weight loss, foreign travel
• No relapsing-remitting symptoms
• Focal alteration of vision, sensation, power coordination

Retroviral Myelopathy

• Insidious, motor > bladder > sensory
• HIV Myelopathy-advanced HIV infection
• HTLV-I/II Myelopathy
  – “Slow” epidemic outside the USA
  – < 2% infected develop myelopathy
  – Transmission via breast milk-may appear to run in families
Q2: Which of the following can appear to present with a spastic paraparesis?

A. Friedreich’s ataxia
B. Metachromatic leukodystrophy-adult
C. Familial ALS
D. Dopa-responsive dystonia
E. All can appear to present with apparent spastic paraparesis

Genetic Causes of Adult-Onset Motor Myelopathy

- Hereditary spastic paraparesis
- Adrenomyeloneuropathy and ALD trait
- Friedreich’s Ataxia
- Metachromatic Leukodystrophy
- Familial ALS
- Dopa-responsive dystonia

ALD – Heterozygous Females

- Peroxisomal membrane protein involved in oxidation of VLCFA (↑C24, C26)
- X-linked recessive; Xq28
- Manifesting carriers due to Lyonization
- Spastic paraparesis about 20%
- CNS MR imaging is unremarkable!
- Elevated VLCFFA in 85%; molecular genetic testing in at-risk women

Friedreich’s Ataxia, MJD, Familial ALS, and Spastic Paraparesis

- Friedreich’s –compound heterozygotes – spastic paraparesis; +/- ataxia and no posterior column involvement
- Machado-Joseph dz-Occasionally presents with spasticity as the predominant finding
- ALS-UMN presentation early
Dopa-responsive dystonia

- Can present in children with stiff legs and with “striatal” great toes (“CP”)
- Can be confused with parkin mutations
- Can be referred as “motor myelopathy of unknown cause”
- Respond to dopamine agonists; lose responsiveness if a parkin mutation

Adult-Onset Metachromatic Leukodystrophy (MLD)

- Reduced arylsulfatase-A activity
- Presentation as spastic paraparesis – 10%
- Most common presenting symptoms in adults – aggressiveness, irritability, inappropriate behavior
- Confluent demyelination on brain MRI
- Sulfatide accumulation in tissue (brain, sural nerve, urinary sediment)

MLD MR Imaging

Patient 1: Management

- Athena-Frame shift mutation at nucleotide pos 218-219 in the SPG4 gene (Spastin)
- Genetic counseling
- Baclofen/tizanidine; baclofen pump?
- Urologic management impotence and urinary incontinence
Q3: Which statement is false regarding genetic counseling?

A. Asymptomatic minors are offered testing
B. Symptomatic minors are offered testing
C. The myelopathy risk in a child is 50%
D. Testing should be offered to the parents and siblings of the patient

Hereditary Spastic Paraparesis-Hx

• 1876-Seeligmuller: progressive leg spasticity with distal axonal degeneration
• 1993-Harding: uncomplicated-simple phenotype
  – Complicated-multiple neurologic features
    -amyotrophy; sensory neuropathy;
    -cerebellar; choreoathetosis/dystonia
    -optic atrophy; macular degeneration
    -mental retardation
    -disorders of skin pigmentation

Hereditary Spastic Paraparesis (HSP)

• Autosomal Dominant -13
• Autosomal Recessive-15
• X-Linked-4
• Clinical tests-refer to www.genetests.org

HSP – Autosomal Dominant

• SPG-4 most common; Spastin
  – 40-45% of AD HSP; Athena test available
  – ¼ asymptomatic or subtle exam findings only
  – ¼ cannot walk independently after age 48 years
• ATPase
  – Chaperone for nuclear protein complexes
  – Normal disassembly of microtubules
HSP Pathogenesis 2004

- Should explain preferential degeneration of long corticospinal tract axons-abnl axonal transport or “fueling” of axonal transport
- Multiple loci and genes for study
- Knockout animal models of disease
- Study functional effect on cells
- Reclass by pathophysiology?

Spastin Pathogenesis 2011-I

- Haploinsufficiency or dominant negative?
- Failure of hexamerization?
- Prevention of ATP binding or hydrolysis?
- Inhibit the cleavage of tubulin?
- Leads to disruption of anterograde and retrograde axonal transport
- Role in ER shaping, endosomes?
HSP – Clinical Implications

- Consider HSP in Ddx of “pure” or “complex” motor myelopathy
  - Consider genetic testing for appropriately screened individuals
  - Clinical tests expanding-www.genetests.org
  - Genetic counseling important
  - Is contributing to our understanding of axonal function in health and disease

Patient 2: History I

18 yo man competing in state basketball championship spring 2011
-Drives game-winning basket and falls to ground-left tib fib fracture (made the layup)
-3/5 ORIF + 3/6 Fasciotomy ant/lat left calf
-3/8 Debridement-found left deep peroneal nerve transected; stump-stump anastomosis

Patient 2: History II

- Burning distal left leg few days post-op
- Circumferential numbness distal calf +foot
- Weakness left distal leg and foot
- Poor ROM at the ankle
- Strength improved somewhat
- PT 3x/wk, no exercising on his own
- Referred 7/11-Candidate for nerve grafting?

Patient 2-Examination-I

-Healed scars lateral and anterior left calf
-Left ankle contracture
-MS, CN, Motor, Sensory all nl except left leg
-Power left leg: TA 4, peronei 4, toe flexors 2, EHL 3, quadriceps 5, hamstrings 5
-Reflexes: 2 left knee + absent left ankle
Patient 2-Examination-II

- Left steppage gait; apparent L foot drop
- L calf atrophy
- Can walk on toes but not left heel
- Allodynia + deep pin sensation over dorsal/plantar foot, inclu first web space
- Decr vibration/position left great toe
- No Romberg sign

Q1: Will nerve grafting be necessary?

1. Yes, immediately
2. Yes, but wait up to 4-6 additional months for recovery
3. Yes, but wait one year
4. No

Indications for Nerve Grafting

- Complete absence of motor function, but motor axons are working: MRC 3-4 (2 TF)
- Grafting sacrifices existing nerve function-cut nerve to make room for the graft
- Usually limit grafting to the first year following injury (window of opportunity)
- Adequate time delay to allow for onset of spontaneous recovery (approx. 3-9 months)

Nerve Grafting Procedure + Principles

- Harvest sural nerve segment to span injured nerve segment to distal nerve sheath
- Leaves a numb patch in sural distribution, but no functional deficit
- The graft creates a microenvironment that promotes nerve regeneration
- Able to identify both proximal and distal nerve sheaths for suturing the graft
Q2: What is the anatomic localization of the neurologic examination findings?

A. Tibial nerve  
B. Deep peroneal nerve  
C. Superficial peroneal nerve  
D. All of the above

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Anatomy of Sensory Findings

Intermediate and medial cutaneous nerves of thigh (femoral)

Lateral cutaneous nerve of calf (common peroneal)

Superficial peroneal nerve

Deep peroneal nerve

Saphenous nerve

Sural nerve

Medial and lateral plantar nerves

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COMMON PERONEAL NERVE

SUPERFICIAL PERONEAL NERVE

Deep peroneal nerve

Tibialis anterior

Peroneus longus

Extensor digitorum longus

Peroneus brevis

Extensor hallucis longus

Peroneus tertius

Extensor digitorum brevis

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Gastrocnemius, medial head

Soleus

Tibialis posterior

Flexor digitorum longus

Flexor hallucis longus

TIBIAL NERVE

MEDIAL PLANTAR NERVE to:

Abductor hallucis

Flexor digitorum brevis

Flexor hallucis brevis

LATERAL PLANTAR NERVE to:

Abductor digiti minimi

Flexor digiti minimi

Adductor hallucis

Interossei
Explaining Mechanisms of Nerve Repair to Patients/Referring MDs

The major mechanisms of nerve repair:
1) Remyelination
2) Collateral sprouting with reinnervation
3) Axonal regeneration
4) Combinations of the above

Q 3: Time to onset of functional recovery is typically slowest for axonal regeneration

A. True  
B. False
Repair of Acquired Demyelination

- Recovery over weeks to months
- Arrest underlying ongoing nerve injury (e.g.-autoimmune, diabetes, uremia)

Collateral Sprouting - Before

Collateral Sprouting - After

Role of Collateral Sprouting

- Depends on reserve pool of intact axons
- Onset ~3-4 months after axonal injury
  - Long duration motor units on needle EMG
  - Polyphasic units with early reinnervation
  - Reduced recruitment with muscle activation
Neuropathy – Axonal Regeneration

Optimal rate = 0.5 – 1.0 inches/month
Factors limiting effectiveness:
- ↑ age of patient
- ↑ distance from site of nerve injury to target
- Ongoing nerve injury (i.e. – alcohol intake)
- Disrupted microenvironment (i.e. – scar)

Patient 2: EMG Results 7-11

- Absent distal left peroneal + tibial CMAPs
- Peron CMAPS to TA: L 3.5 mV, R 6.3 mV
- L superficial peroneal absent; surals nl
- Needle EMG:
  - No MUAPs under vol control in EDB + AH
  - Mild-Mod decr recruitment in left TA, peronei
Q 4: Disparity Between Clinical Foot Drop But Preserved Peroneal CMAPs

What is the most likely reason for the preserved peroneal CMAP amplitude from TA (3.0 mV) and observed clinical foot drop?

A. Patient effort
B. Ankle contracture
C. Pain during muscle contraction
D. EMG artifact

Range of Motion is Crucial!

- Can get nerve recovery, but lack of functional recovery if contracture present
- PT not enough—pt must stretch frequently
- Stretch when inactive—sitting, using elastic bands, broom handle, “walking the hand”
- “Frozen shoulder“—from shoulder girdle muscle weakness, pain with movt, or both
- Ankle contx—calf weakness, pain with movt

Patient 2: Clinical/EMG Results 1-12

- Better range of motion at the ankle
- Beginning to play recreational basketball
- Left distal peroneal + tibial CMAPs absent
- Peroneal to TA: L 6.0 mv (vs 3.5 in 7-11)
- Needle EMG:
  - Early polyphasic units seen in AH and EDB
  - Improved recruitment in TA and peronei

UCSF Nerve Injury Clinic

Neurosurgery-Nerve grafting
Dr. Michel Kliot, Director
Neurology-Neurologic exam, EMG
Dr. Jeff Ralph and Dr. John Engstrom
Orthopedic Surgery-Tendon transfers, joints
Dr. Ed Diao and Dr. Lisa Lattanza
Scheduling-Erica Terry (415)-353-2241