A Tale of Five Demyelinating Neuropathies

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Objectives

• Demonstrate different clinical presentations of demyelinating neuropathies
• Demonstrate importance to recognize clinical subtypes of demyelinating neuropathies since treatments differ
• Learn current understanding and the “state of art” regarding these conditions

Case 1: A tale of slowly wasting hand in a young woman

• 33 year old Caucasian female, a lawyer by profession, noticed slowly progressive weakness of the hand grip and pinch over the past one year
• Her right hand has become atrophy, especially in the thenar and hypothenar muscles
• She denies any muscle twitches, weight loss, numbness, tingling or pain
• There is no family history of neurological or neuromuscular disease

Tale 1: Slowly wasting hand in a young woman

• Examination shows moderate pure motor weakness in the distribution of the median nerve and radial nerve on the right and mild weakness of the left ulnar nerve innervated muscles
• Deep tendon reflexes are unaffected; sensory examination is normal
• No laboratory abnormalities on blood and urine testing, including negative HIV and serum immunofixation

Tale 1: Slowly wasting hand in a young woman

• Nerve conduction shows normal sensory responses
• Motor nerve conduction showed demyelinating changes in the median, ulnar and radial nerves on the right and left median and ulnar
• Prominent conduction blocks present in the right median and right radial, and left ulnar motor nerves
• CSF was acellular and without protein elevation

Conduction Blocks
Tale 1: Diagnosis
The most likely diagnosis in this young woman is:
1. CIDP
2. POEMS syndrome
3. Cervical radiculopathy
4. Multifocal motor neuropathy (MMN)
5. Lewis-Sumner syndrome (MADSAM)

Tale 1: Slowly wasting hand in a young woman
- Asymmetry argues against CIDP or POEMS syndrome
- Pure motor changes argues against cervical radiculopathy or MADSAM
- Slow progression with little atrophy and presences of multiple conduction blocks is strongly suggestive of MMN

Tale 1: Treatment
The best treatment option for Case 1 is to:
1. Refer for decompressive surgery
2. Initiate corticosteroid therapy
3. Initiate IVIG therapy
4. Refer for stem cell transplant
5. Expectant therapy

Tale 1: Discussion
- Multifocal motor neuropathy (MMN) is an acquired immune neuropathy, with asymmetric motor weakness
- Antigenic target is probably ion channels at the nodes of Ranvier
- 20% cases are associated with an IgM gammopathy
- 50-65% have elevated monoclonal IgM antibodies to GM1 antigen
- Treatment of choice is IVIG
  - Recently concluded IVIG trial done by Baxter shows a significant improvement and IVIG is now FDA-approved for use in MMN
  - Alternates include cyclophosphamide and Rituximab

Tale 2: The mysterious footdrop in a Gymnast
- 13 year old M.Y. is an avid gymnast who spends more than 3 hours a day stretching and in gymnastics and for the past one year has been bothered with back pain
- She developed an insidious painless right foot drop over the last one month
- A spine surgeon diagnosed her with anterolisthesis at right L5 and suggested surgery
Tale 2: The mysterious footdrop in a Gymnast

- Examination shows right foot drop with grade 4- strength in the right tibialis anterior, extensor hallucis longus and peroneus longus but normal “inverter (tibialis posterior)”
- Sensory loss along the peroneal nerve distribution
- MRI of LS Spine clearly shows anterolisthesis
- A diagnostic test was performed

The most likely diagnosis in this young woman is:
1. Lumbosacral radiculopathy (L5)
2. CIDP
3. Sciatic nerve tumor
4. Hereditary neuropathy with liability to pressure palsies (HNPP)
5. Lewis-Sumner syndrome (MADSAM)

Tale 2: The mysterious footdrop in a Gymnast

- Clinically this is a peroneal neuropathy and not an L5 radiculopathy (given that the tibialis posterior and gluteus medius muscles were normal)
- Asymmetry would argue against CIDP but may suggest MADSAM – however, MADSAM affects upper extremities more than lower extremities
- Distribution is purely in the peroneal distribution and argues against a sciatic neuropathy

What should we do next in terms of management
1. Nerve biopsy of the right sural nerve
2. Sequencing analysis for PMP-22 mutations
3. MRI of the right knee to look for nerve entrapment
4. Decompressive surgery of the LS spine
5. Initiate IVIG treatment

Tale 2: Discussion

- HNPP is a genetically determined autosomal dominant demyelinating neuropathy
- Presents as recurrent pressure palsies with almost complete recovery in between attacks
- Some patients may present with symmetric sensory-motor neuropathy
- Genetic cause is a deletion in PMP-22 gene
- MRI shows focal nerve enhancement at the site of entrapment
- Treatment is conservative and precaution against entrapments
Tale 3: The Creeping Platelet Count

- 33 years old man referred for evaluation and management of a demyelinating neuropathy for the past 1 year
- Symptoms included foot drop and mild sensory symptoms
- Examination shows exclusively symmetric distal weakness of the legs, loss of deep tendon reflexes globally and mild length-dependent sensory loss

NCS showed slow motor nerve conductions (median 35 m/sec with normal amplitudes; ulnar 32 m/sec with normal amplitudes)

Sensory NCS showed reduced amplitudes

CSF was acellular; protein was 280 mg/dl

Treatment was started with IVIG with no response; IV solumedrol was added to the regimen with no benefit

Patient continue to worsen neurologically; he developed generalized hyperpigmentation.

His platelet count also gradually rose to ~million/cubic mm

Ophthalmology exam shows papilledema

What is the likely diagnosis in this patient?

1. Lumbosacral canal stenosis
2. CIDP
3. POEMS syndrome
4. Adrenomyeloneuropathy
5. Lewis-Sumner syndrome (MADSAM)

CBC: Hgb 11.1, WBC 2.9 K, Platelet 980,000

IgA lambda monoclonal protein (2.1 g/dl)

Skeletal survey with multiple lucencies in the bones

Bone marrow plasma cell infiltration in the bone marow with more than 9% of cells were plasma cells

Vascular endothelial growth factor (VEGF) >3000 (normal up to 60)
Tale 3: The Creeping Platelet Count

What would you do next?
1. Plasmapheresis
2. Referral to hematology for POEMS work up
3. Initiate IVIG
4. Surgery referral for spinal stenosis surgery
5. Rituxan

Case 3: The Creeping Platelet Count

Discussion
- Lack of proximal muscle involvement and lack of response to IVIG and steroids very concerning for this being not CIDP
- Changing hematologic profile, papilledema and skin changes very strongly suggestive of POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin changes)
- Treatment of choice is high dose cytoablative chemotherapy and bone marrow transplantation with stem cell rescue

Tale 4: The Nordstrom tailor with proximal muscle weakness

- SL is a 50 year old Korean man with 8 month history of proximal leg-arm weakness. He had difficulty getting up from a squatting position
- No sensory or bulbar symptoms
- Denies any muscle pain or skin rash
- Denies any respiratory symptoms
- CK was 660 iu/L and was referred for management of muscular dystrophy

Tale 4: The Nordstrom tailor with proximal muscle weakness

- Examination showed symmetric grade 4- muscle strength in the proximal muscles (deltoids, biceps, triceps, hip flexors, quadriceps)
- Diffuse areflexia
- Minimal sensory deficits
- Gait waddling
Tale 4: The Nordstrom tailor with proximal muscle weakness

What is the likely diagnosis in this patient?
1. Pompe disease
2. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
3. POEMS syndrome
4. Limb-Girdle muscular dystrophy
5. Spinal muscular atrophy type IV

What would you do next?
1. Start IVIG treatment
2. Refer to neurosurgery for laminectomy
3. Muscle biopsy and genetic testing
4. Start Lumizyme therapy
5. Nerve biopsy

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Tale 4: The Nordstrom tailor with proximal muscle weakness

Nerve conduction showed normal distal studies; however, proximal nerve conductions showed marked delay
EMG showed marked neurogenic changes
CSF was acellular but CSF protein was 280 mg/dl and IgG synthesis and index was elevated
MRI showed nerve root enhancement
Responded well to IVIG and treatment was discontinued after 2 years – patient remains in clinical remission 3 years out

Discussion
– For diagnosis of CIDP proximal muscle weakness is a requirement
– Sometimes CIDP can present with pure proximal muscle weakness with no sensory changes and normal distal nerve conductions
– A trial of IVIG or steroids may be worthwhile as a therapeutic challenge
Tale 5: A middle aged man with sensory ataxia

- TK is a 58 year old man with 6 month history of balance difficulty worse at night and with his eyes closed
- Denies any pain or muscle weakness
- Denies any significant sensory symptoms
- Has had multiple falls over the last 3 months
- There is no family history of neuromuscular diseases

- Examination showed normal muscle strength except for mild toe weakness
- Significant large fiber sensory loss
- Unable to stand without support because of severe sensory ataxia (Romberg markedly positive)
- Diffuse areflexia
- No cerebellar signs

- Nerve conduction studies showed normal motor and sensory nerve conductions with no evidence for demyelination
- CSF showed acellular specimen; CSF protein was elevated at 180 mg/dl; CSF IgG synthesis and index was elevated
- SSEP showed delayed cortical potentials
- MRI of the thoracic spine showed marked nerve root enhancement and nerve hypertrophy – neuroradiology called it "CIDP"

What is the likely diagnosis?
1. CIDP
2. Primary CNS lymphoma
3. MMN
4. Amyloidosis
5. Chronic inflammatory sensory radiculopathy (CISP)

What would you like to do next to manage this patient?
1. Genetic testing for PMP-22 mutation
2. Sensory nerve root biopsy
3. DNA testing for Transthyretin (TTR) mutation
4. Plasmapheresis or IVIG
5. Repeat B12 levels
• CISP is a treatable immune neuropathy with the primary immune attack against sensory nerve roots (pre-ganglionic segment)
• Clinical findings with acquired sensory ataxia, minimal or no motor weakness and areflexia. Spinal fluid with increased protein and MRI with nerve root enhancement
• Responsive to IVIG and Plasmapheresis treatments

Demyelinating Neuropathies

• There are many different types of demyelinating neuropathies
• Some are acquired and some are inherited
• Other than family history, important to pay attention to time course, pattern of weakness (proximal vs. distal), pattern of involvement (motor vs. sensory) and symmetry vs. asymmetry
• Treatment differs with different diseases and therefore, important to differentiate the different diseases
  – For instance MMN gets worse with steroids whereas CIDP and MADSAM responds well to steroids

Questions?