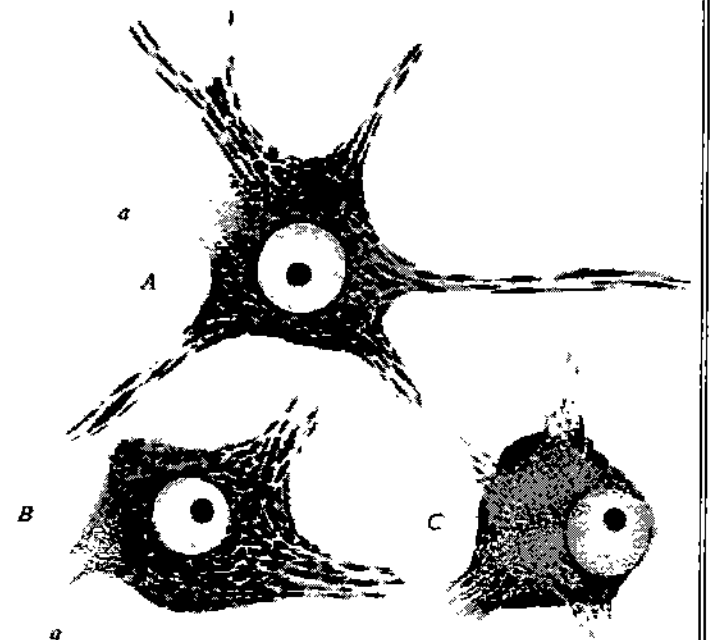
Neuromuscular

MOTOR SYNDROMES

Differential diagnosis
Hereditary

- Amyotrophic lateral sclerosis
  - Hereditary
  - Sporadic
- ALS variants
  - EOM & Extrapyramidal change
  - Primary lateral sclerosis (PLS)
  - Primary muscular atrophy (PMA)
  - Western Pacific ALS
- Amyotrophy
  - Lower extremity, benign
  - Monomelic
- Diabetic amyotrophy
- Hand weakness
- Hopkins
- Infections
- Insulinoma
- Mitochondrial: SCO2
- Motor Neuron Disorders
  - Hereditary
  - Bulbar
  - Lower motor neuron
  - Upper motor neuron
  - Asymmetric
  - Symmetric
- Motor Neuropathy
  - Distal: Acquired & Hereditary
    - Hereditary
    - IgM vs GM1 ganglioside
    - IgM vs GalNAc-GD1a ganglioside
  - Multifocal motor neuropathy (MMN)
- Myopathies
- Painful
- Paraneoplastic
  - Lymphoma
  - Breast
- Poliomyelitis & Post-polio syndrome
- Rapid onset
  - Acute Axonal Motor Neuropathy
  - Poliomyelitis
  - Porphyria
- Spinal muscular atrophy: Hereditary
  - SMN (5q)
  - Androgen Receptor (Bulbar SMA)
  - Distal SMA (Distal HMN)
  - Hexosaminidase A (Tay-Sachs)
  - Scapuloperoneal
  - Spinal muscular atrophy 2
  - X-linked Infant SMA & Arthrogryposis
- Spastic paraparesis
- Toxic



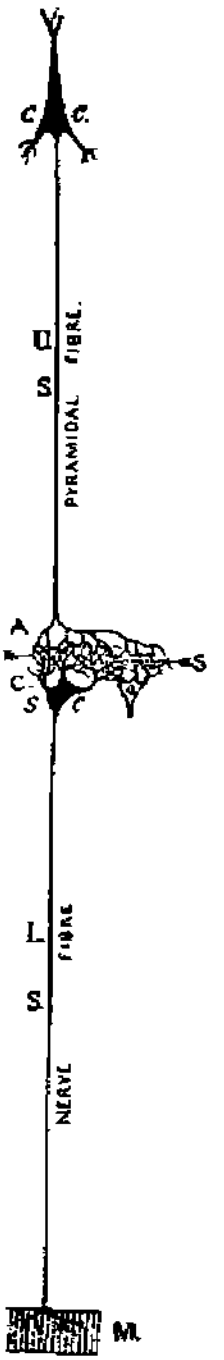
Nerve-cells stained by Nissl's method, with toluidin blue. Magnified 750 diameters. (Schäfer.)
***A*. From anterior horn of spinal cord, monkey.**
***B* and *C*. From facial nucleus, dog.**
***C*. Shows Nissl degeneration, consequent on section of the facial nerve 15 days previously. *a. a.* axons.**

From: Quain

Motor Neuron Disorders: Differential Diagnoses

- **Asymmetric**
  - Upper + Lower Motor Neuron Signs
    - Amyotrophic Lateral Sclerosis (ALS)
      - Sporadic ALS
      - Hereditary ALS
        - Superoxide Dismutase; Chromosome 21; Dominant
        - Other ALS: Recessive & Dominant
    - Sporadic motor neuron disorders with dementia
      - Western Pacific ALS
      - Frontal Dementia followed by motor system disease
        - Upper motor neuron: Especially bulbar
        - Lower motor neuron: Fasciculations; Mild weakness
        - ? Atypical Creutzfeld-Jacob syndromes
    - Multi-system disorders
      - ALS with Ophthalmoplegia & Extrapyramidal Disorders

        - Polyglucosan body disease
        - Motor neuronopathy with cataracts and skeletal abnormalities
        - Multiple system atrophy
        - AAA syndrome
    - Lower Motor Neuron Signs only (Asymmetric)
        - Distal Lower Motor Neuron (LMN) Syndrome
            - IgM vs GM1 ganglioside
            - IgM vs GalNAc-GD1a ganglioside
            - Also see: Multifocal motor neuropathy
        - Proximal Lower Motor Neuron Syndromes
            - Brachial amyotrophic diplegia
            - ? Associated with IgM vs asialo-GM1
            - Rare: Upper > Lower limbs with anti-Hu antibodies
        - Lower Motor Neuron Syndrome without antibodies (PMA)
        - ALS variants
            - Hereditary
            - Sporadic
        - Focal motor neuron disease
            - Monomelic Amyotrophy
            - Paraspinous muscle amyotrophy
            - Cervical amyotrophy
        - Paraneoplastic motor neuro(no)pathy
            - Mild weakness: With lymphoma
            - Severe weakness: With breast cancer
        - Hopkins' syndrome: Acute post-asthmatic amyotrophy
        - Polio & Post-polio syndrome
        - SMN2 (SMN^C) deletions
        - Neurofibromatosis, Type 2[5]
- **Symmetric & Proximal**: Hereditary Spinal Muscular Atrophy
    - SMN: Chromosome 5q; Recessive
    - Androgen Receptor (Bulbo-spinal Muscular Atrophy): X-linked; Recessive
    - Hexosaminidase A (Tay-Sachs): Chromosome 15; Recessive
- **Hand weakness**
    - Motor neuron disease & motor neuropathies
    - Myopathies: Distal; Myotonic Dystrophy; Inclusion Body Myositis
    - Myasthenia Gravis
    - Peripheral nerve lesion
        - Median: Recurrent motor branch; Anterior interosseus
        - Ulnar: Guyon canal
        - Radial: Posterior interosseus
    - Brachial Plexopathy
    - Distal SMA
- **Bulbar involvement**
    - Bulbo-spinal Muscular Atrophy
        - Androgen Receptor: X-linked
        - Dominant
    - Amyotrophic Lateral Sclerosis (ALS)
        - Sporadic ALS
        - Hereditary ALS
        - ALS with Bulbar onset, Benign course & Bunina bodies
    - Hereditary Bulbar syndromes
        - Brown-Vialetto-van Laere
        - Fazio-Londe
    - Congenital Bulbar syndrome
        - Worster-Drought syndrome: Congenital suprabulbar



paralysis
- **Painful**: Diabetic amyotrophy
- **Rapid Onset**
  - Acute Axonal Motor Neuropathy (with Campylobacter jejuni or serum IgG vs GM1)
  - Poliomyelitis
  - Porphyria
    - 4 types cause neurologic attacks
      - Acute intermittent
      - Variegate Porphyria
      - Coproporphyria
      - δ-amino-levulinic acid dehydratase deficiency
    - Urine: During attacks
      - All types produce increased δ-amino-levulinic acid
- **Acquired**
  - **Toxic**: Lead; Dapsone; Botulism; Tick Paralysis
  - **Infections**
    - Polio
    - West Nile
    - Central European encephalitis
    - Creutzfeld-Jacob
      - Amyotrophy
      - Polyneuropathy (± Demyelinating)
- **Other**
  - **Distal SMA**
  - **SMA & motor neuron syndromes: Other hereditary**
  - **Multifocal Motor Neuropathy (MMN)**

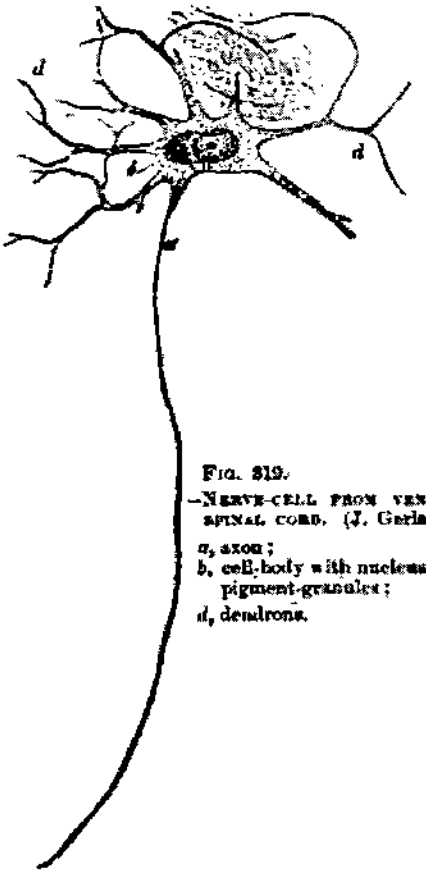
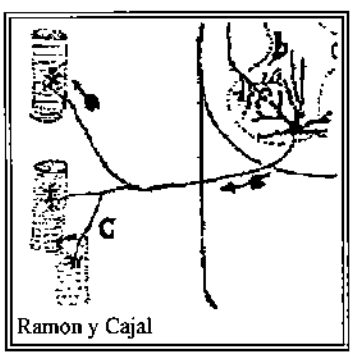


FIG. 319.—NERVE-CELL FROM VENTRAL HORN OF SPINAL CORD. (J. Gerlach.)

a, axon;
b, cell-body with nucleus and clump of pigment-granules;
d, dendrons.

From: Quain

Paraneoplastic Motor Neuropathy



Ramon y Cajal

- Onset: After diagnosis of tumor
- Epidemiology: Majority male & > 50 years
- Clinical
  - Weakness
    - Asymmetric; Arms > Legs
    - Mild
    - Lower motor neuron only
    - Normal bulbar
  - Cramps: Painful
  - Painless in some patients
  - Course: Progressive then stabilizes or improves
- Associated with
  - Non-Hodgkin Lymphoma
  - Also other lymphomas & myeloproliferative disorders[4]
- Laboratory
  - CSF: No cells; Mildly increased protein
  - MRI: Spinal cord normal
  - ? Neuronopathy
- Animal model: Similar disorder in mice 2° murine leukemic virus
- Also see: Paraneoplastic Lower Motor Neuron Syndrome

Paraneoplastic Lower Motor Neuron Syndrome[8]

- Epidemiology: Single patient, 72 year old female
- Onset: 4 months before diagnosis of tumor
- Clinical
  - Weakness
    - Asymmetric at onset
    - Arms & Legs
    - Severe
    - Lower motor neuron only
    - Bulbar: Hypophonia; Dysphagia; Unilateral facial paresis
  - Painless
  - Course
    - Progressive over months
    - Improvement after tumor removal
    - Long-term residual disability
  - Sensation: Normal
  - Tendon reflexes: Absent
  - CNS: Transient dizziness & Nystagmus
- Associated with
  - Ductal adenocarcinoma of breast
- Laboratory
  - Antibodies
    - Serum binding to βIV spectrin, isoform I (Bands at MW 250kD & 140kD)
    - Serm binding to axon initial segments & nodes of Ranvier in rat brain
  - Electrophysiology
    - EMG: Denervation
    - NCV: Small CMAPs; No conduction block
  - MRI: Spinal cord with high signal spots on T2
  - ? Neuronopathy
- Immunosuppressive treatment: No response
- Also see: Paraneoplastic Motor Neuropathy

HOPKINS' SYNDROME: Acute post-asthmatic amyotrophy

- Age: 1 to 13 years
- Onset
  - After acute asthmatic attack: Latency 1 to 18 days
  - Mild pain: Limb, neck or meningismus
  - Rapid onset weakness
- Weakness
  - Single limb; Asymmetric; May be Proximal > Distal
  - Severity: Mild to severe
  - Arm or leg
- Sensory: Normal
- CSF
  - Pleocytosis
  - Protein: ± Increased
- MRI: May show signal (T2) in spinal cord
- Prognosis: Permanent paralysis

Post-Polio Syndrome

- Diagnostic Criteria: Clinical
  - History of polio
    - Partial or complete neurological & functional recovery
    - Stable function > 15 years
  - Onset of
    - Fatigue
    - Muscle pain
    - Functional loss
      - Usually 2° Musculoskeletal disorder
      - New weakness is rare
  - Neurological examination
    - Lower motor neuron syndrome (confirmed by EMG or MRI)
      - Measurable loss of strength is rare
    - Decreased or absent tendon reflexes
    - No sensory loss
  - Other
    - No other explanation for symptoms
    - Joint pain & cold intolerance may accompany the syndrome
- Laboratory features
  - CK: Elevated
  - Electrophysiology
    - Very large motor units (up to 10 times normal)
    - Some fibrillations & positive sharp waves even in stable patients
  - Muscle pathology
    - Near full recovery of strength & stable
      - Type I muscle fiber predominance
    - Persistent or new weakness
      - 50% type I fibers
      - Angular fibers; Atrophy + hypertrophy
    - New weakness & high CK
      - More small angular fibers
      - Muscle fiber necrosis
- Recommended exercise
  - Mild paresis: Resistance training
  - Moderate paresis: Submaximal endurance
  - Severe paresis: None; Joint bracing

Old Polio
Asymmetric atrophy & weakness
Atrophic right leg (arrow) in patient with paralytic polio 70 years in past

Monomelic Amyotrophy

- Eponyms
  - Hirayama's disease
    - Course: Progressive weakness over 1 to 4 years; Then plateau
  - O'Sullivan-McLeod syndrome
    - Course: Slow progression
- Epidemiology
  - Male > Female: Up to 10:1
  - Family history
    - Usually sporadic
    - Occasional familial occurrence
      - Dominant[13] or Recessive
  - Common in Eastern India[7], Taiwan
  - Association: Heavy physical activity before onset
  - Possible etiologies
    - Neck flexion induced cervical myelopathy
    - Motor neuron disease
- Onset
  - Age: Young adult; 15 to 25 years; Up to 40 years in India
  - Weakness: Distal; Single limb

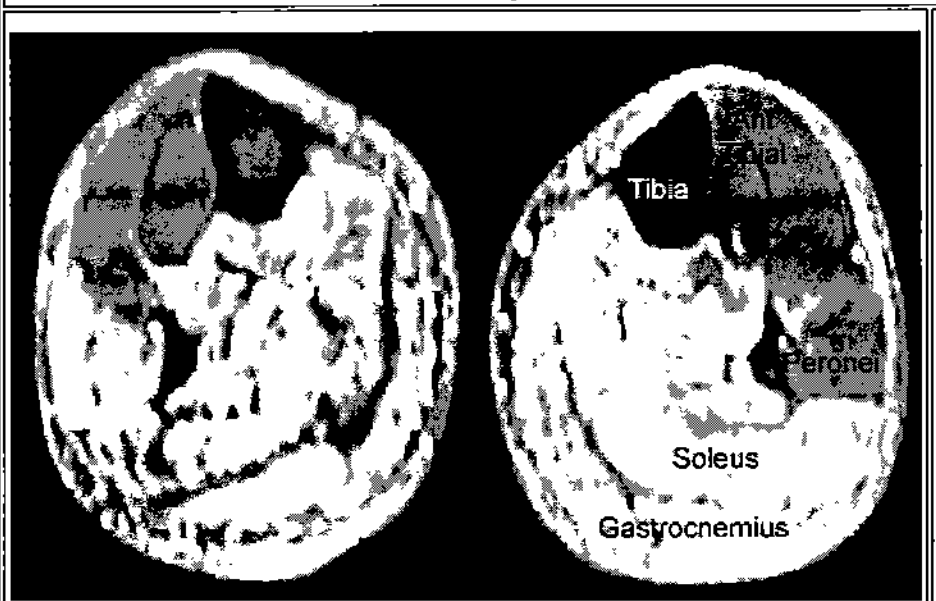
- Clinical
  - Weakness
    - Often confined to a single arm
    - Distal involvement (97%): C7, C8 & T1 innervated muscles; Hand & Forearm
    - Proximal > Distal: 10%
    - Side: Right 1x to 3x Left
  - Atrophy: "Oblique amyotrophy"; Sparing brachioradialis
  - Tremor (80%): On finger extension; Irregular & Coarse (Minipolymyoclonus)
  - Occasional other features
    - Weakness: Other
      - Ipsilateral shoulder
      - Progression to opposite limb
        - Frequency: 18% - 40%
        - Latency: Range 2 to 120 months; Mean 43 months
        - Usually milder weakness than 1st limb
      - Worsening on exposure to cold
    - Fasciculations
      - On affected side (47% to 66%)
      - May not be symptomatic
      - Contractile fasciculation
    - Sensory loss
      - Mild or none in affected limb
      - Rarely prominent on examination
    - Discomfort
      - Cramps & Spasms (30%)
      - Neck pain
    - Autonomic: Hyperhidrosis
  - Tendon reflexes: Usually normal
  - No cranial nerve, leg or pyramidal changes
  - Disease course
    - Typical monomelic amyotrophy[10]
      - Progression: Over 1 month to 5 years; 7% as long as 8 years
      - Static after progression phase: May persist for decades
      - Disability: Mild or none in 73%
    - O'Sullivan-McLeod syndrome[6]: Progression over decades
- Laboratory
  - EMG
    - Location of pathology
      - Most common: C7-T1
      - Occasional: Legs
      - May be present in asymptomatic limbs
    - Chronic denervation
      - In affected limb(s) (100%)
      - Opposite arm or lower extremities: Some patients
      - Signs of acute denervation in 45%
    - Ongoing denervation
  - NCV
    - CMAPs: Small in affected limbs; Especially ulnar nerve
    - Sensory: Normal
  - Sympathetic skin response: May be abnormal
  - MRI
    - Cervical pathology
      - ? Some patients with inelastic dura
        - Spinal cord compression with neck flexion[1]
      - Anterior shifting of posterior dura: Engorged posterior venous plexus
      - Spinal cord atrophy: C6 & C7
      - T2 signal in anterior horns of gray matter
    - Other studies[3]
      - No major spinal anomalies
      - Mild flexion-induced cord displacement

- Differential diagnosis: HMN & Distal SMA

Amyotrophy: Benign Lower Extremity[11]

- Epidemiology
  - 16 cases described
  - Male > Female: 5:1
- Onset: Mean age 41 years
- Clinical
  - Weakness: Posterior legs
    - Usual: Posterior calf; Peronei; Hamstrings
    - Rare: Quads
    - Often bilateral (50%)
      - Clinical or subclinical
      - Asymmetry: Some
  - No sensory, bulbar or upper motor neuron signs
  - Course
    - Insidious onset
    - Slow progression: Few years
    - Stabilization
- Laboratory
  - MRI
    - Loss of muscle with fat replacement
    - Distribution: Lower extremities
      - Distal leg: Posterior compartment
      - Thigh: Long head of biceps
  - EMG: Denervation
  - Muscle biopsy: Denervation; Grouped atrophy

Benign lower limb amyotrophy: MRI



From: M Al-Lozi

Legs: Involvement of posterior muscle groups

From: M Al-Lozi

Thigh: Long head of biceps involvement

"Primary Muscular Atrophy" (PMA)[15]

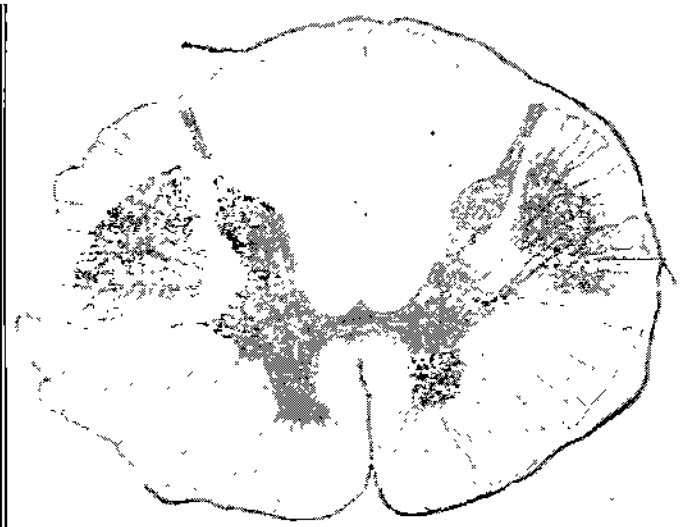
- Epidemiology
  - Frequency: 7% to 11% of ALS-like disorders
  - Male in 74%: vs 55% in ALS
- Lower Motor Neuron Syndrome: Widespread
  - Weakness: Distribution
    - Distal & Proximal: Either may be more prominent
    - Asymmetric
    - Often involves paraspinous & respiratory muscles
    - Often spares bulbar musculature
  - Spontaneous motor activity
    - Cramps: Common in legs, at night
    - Fasciculations
  - Upper motor neuron signs
    - Not present at diagnosis
    - After 5 years: 20%
      - More with younger onset age
      - 50% develop in 1st year after diagnosis
  - Pain: Related to immobility
  - Time course
    - Progressive
    - Survival
      - Mean = 4 years: vs 3 years in ALS
      - Range: Similar to, more rapid, or slower than, typical ALS
      - Overall mortality: 68%
- Laboratory
  - Muscle pathology: Grouped atrophy > Fiber type grouping
  - No serum antibodies
  - No conduction block
- No evidence for response to treatment
- Differential diagnosis
  - Proximal lower motor neuron syndrome
  - ALS
    - Sporadic
    - Hereditary
      - SOD mutations: A4V, Leu84Val, D101N
      - CHMP2B
- Pathology
  - Loss of motor neurons in anterior horn of spinal cord
  - Shrinkage of remaining motor neurons
  - Inclusion bodies: Intracytoplasmic, Hyaline

Gowers

Primary muscular atrophy
Note wasting, including paraspinous muscles.

Primary Lateral Sclerosis[2]

Dominant, Adult onset 4p16 FIG4: 6q21 PLS + FTD Recessive, Childhood onset	

Sporadic, Adult onset	 From Bramwell: Diseases of the Spinal Cord **PLS: "Sclerosis" of pyramidal tracts** (Upper thoracic cord)

PLS : Sporadic, Adult onset

- Nosology: ? Discrete syndrome vs ALS variant
- Genetics
  - Family history: Usually none
  - No mutations in Alsin gene in sporadic cases
- Clinical
  - Onset
    - Spasticity
      - Legs before arms
      - Slowly progressive
    - Age: Most commonly in 5th decade
  - Motor dysfunction
    - Corticospinal ± corticobulbar tract dysfunction
      - Spasticity: Legs > Arms
      - Tendon reflexes: Brisk
      - Plantar reflex: Normal or upgoing
      - Pseudobulbar signs: Especially with disease onset > 45 years
    - Symmetric
    - No lower motor neuron change
  - Sensory: Normal
  - Frontal lobe dysfunction: Mild
  - Progression
    - Gradual
    - Slow
    - > 3 years; Up to 3 decades
  - Bladder function: Normal until late in disease
  - Differences from ALS [14]: PLS has less
    - Bulbar onset
    - Weakness
      - Focal
      - Limb
    - Weight loss
    - Vital capacity reduction
- Laboratory
  - Magnetic stimulation: Absent or prolonged cortical motor evoked latencies
  - MRI: Focal atrophy of precentral gyrus
  - PET scan: Reduced glucose consumption in pericentral region

- Central motor conduction times: Prolonged
- Normal: Serum; CSF; EMG; Spinal cord imaging; Serum CK; CSF protein

- Disease association: ? Breast cancer
- Pathology
  - Corticospinal tract: Axonal loss
  - Normal: Anterior horn cells ± Betz cells
- Differential diagnosis
  - Structural disorders: Spinal; Foramen magnum; Hydrocephalus
  - Hereditary spinal disorders
  - Infections

PLS: Recessive, Juvenile onset[2]

- Alsin (ALS2); Chromosome 2q33; Recessive

- Epidemiology: Cypriot family
- Genetics
  - Mutation
    - Deletion: In Exon 9
    - Homozygous c.2980-2A>G mutation at splice acceptor site of intron 17: Frameshift
  - Allelic with
    - ALS2: Mutations in another region of alsin gene
    - Familial spastic paraparesis, infantile onset (IAHSP)
- Clinical
  - Onset: Childhood
  - Spasticity: Bulbar; Extremities
  - Gaze paresis: Saccadic
  - Normal: Cognition; Sensation
  - Progression: Slow; Some remain ambulatory for decades
- Laboratory
  - Central motor conduction times: Delayed or Unrecordable
  - EMG: No denervation
  - Brain imaging: Normal

PLS: Dominant, Adult onset

- Chromosome 4ptel-4p16.1; Dominant

- Epidemiology
  - Single French-Canadian family
  - Male:Female = 1:1
- Onset
  - Age: 30 to 60 years
  - Spasticity: Leg; Asymmetric
- Clinical
  - Spasticity: Arms & Legs; Asymmetric
  - Strength: Normal
  - Reflexes
    - Tendon: Diffusely increased
    - Plantar: Extensor
  - Dysphagia: 60%
  - Sensation: Normal
- Laboratory
  - EMG: Denervation, mild, distal, chronic
  - MRI: Normal or Spinal cord atrophy, mild

PLS with Frontotemporal dementia[12]

- Sporadic

- Epidemiology: 2 patients
- Onset
  - Age: 6th to 8th decade
  - Dementia
  - Dysarthria
- Clinical
  - Cortical
    - Dementia
    - Aphasia
  - Motor
    - Spasticity
    - Bulbar dysfunction: 1 patient
    - Strength: Normal
    - Tendon reflexes: Brisk
    - Plantar responses: Extensor
  - Course
    - Slow progression
    - Death after 7 years
- Pathology
  - Neuronal loss: Frontotemporal & Motor cortex
  - Inclusions: Ubiquitin & TDP-43 positive cytoplasmic

 Patient information

Return to Polyneuropathy Index

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2/18/2010