Upper Motoneuron (UMN) Diseases

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FAMILIAL (s. HEREDITARY) SPASTIC PARAPLEGIAS

SPG - broad group of disorders characterized by lower extremity spasticity and weakness.

- degeneration of *most distal portions of longest ascending and descending* ***axons*** (esp. corticospinal tracts to legs*, fasciculus gracilis, spinocerebellar tracts).
  *nearly normal in brainstem but show increasing atrophy at more caudal levels in spinal cord ("dying back")
- **neurons of origin** and **PNS** are unaffected.

Type	Genetic Nomenclature	Inheritance	Gene Locus	Population	Product
Complicated	SPG1	X-linked	Xq28		L1CAM (L1 cell adhesion molecule)
"Pure" (uncomplicated)	SPG2	X-linked	Xq28 or Xq21*		Proteolipid protein
	SPG3	AD	14q12-q21	European, North American	?
	SPG4	AD	2p21-24	European, North American	
	SPG5A	AR	8p11-q13	Tunisian	?
	SPG5B	AR	?	Tunisian, European	?
	SPG6	AD	15q11.1	North American	?
	SPG7	X-linked	?	Single family	?
Spastic paraplegia with amyotrophy	ALS4	AD	9q34	Single family	?

*other mutations in same gene cause Pelizaeus-Merzbacher disease!

PREVALENCE – 10 per 100.000

CLINICAL FEATURES

Clinical heterogeneity - some cases are mild and some are severe.

- variability often occur within same family.
- onset in 2-4th decades (infancy ÷ late adulthood).

Uncomplicated ("pure") FSP (more common):

1) slowly progressive **spasticity of lower extremities** (weakness of hip flexion & foot dorsiflexion)
   At onset, disorder is one of coordination; there may be ***no muscle weakness***!
   Spasticity is usually most disabling component!
   - slow, stiff gait, trip easily, unable to run.
   - deep tendon reflexes are pathologically increased (often ≥ grade 4).
   - crossed adductor reflexes, ankle clonus, extensor plantar responses.
   - gait disturbance progresses insidiously and continuously: paraparesis → paraplegia; most patients become nonambulatory at 60-70 yrs of age (respiratory function is spared - long survival).
   - pes cavus may develop (30-50%).
2) mild (!) decrease in proprioception below knees
3) urinary sphincter dysfunction (urgency and incontinence) late in disease.

No abnormalities of **corticobulbar tracts** or **upper extremities** (except possibly brisk deep tendon reflexes).

Complicated FSP - presence of *other neurological problems* (optic neuropathy, retinopathy, extrapyramidal disturbance, dementia, ataxia, ichthyosis, mental retardation, deafness).

DIAGNOSIS

- of exclusion.

Molecular diagnosis - available only to families who have been linked to one of identified loci.

Electrophysiological studies are most revealing:

- ***somatosensory evoked potentials*** of lower extremities - conduction delay in dorsal column fibers (even without clinically evident sensory loss).
- ***cortical evoked potentials*** - reduced conduction velocity and amplitude in lumbar spinal segment muscles (potentials of arms are either normal or mildly slow).
- ***nerve conduction studies*** - normal.

MRI of brain / spinal cord – unrevealing (± spinal cord atrophy).

FSP can mimic treatable disorders:

1) vitamin B_{12} deficiency
2) DOPA-responsive dystonia
3) cervical spondylosis
4) multiple sclerosis

TREATMENT

- to combat *problems associated with chronic paraplegia* (BACLOFEN or DANTROLENE for leg spasticity, OXYBUTYNIN for bladder spasticity).

- **intrathecal** BACLOFEN is gaining favor because gait may improve!

PRIMARY LATERAL SCLEROSIS (PLS)

- **pure UMN component** of ALS (just as spinal muscular atrophy is purely LMN version).
  In theory, ALS may start as purely UMN disorder but that seems truly exceptional.

- selective loss of large pyramidal cells in precentral gyrus → degeneration of corticospinal and corticobulbar projections.
- < 5% of all cases of motor neuron disease.

CLINICAL FEATURES

- "spastic paraparesis of middle life":

1) onset after age 40.
2) slowly progressive spastic leg weakness (gait disorder) → becomes stable* (patients rarely lose ability to walk with cane or other assistance).
3) spastic dysarthria and dysphagia (progressive pseudobulbar palsy).

- no sensory, no sphincter symptoms.

*course may be as aggressive as in ALS!

DIAGNOSIS

MRI - no consistent abnormality (many asymptomatic people > 40 yrs. show white matter lesion in brain!).
CSF - normal (protein content may be increased).
EMG - no signs of denervation (but sometimes does).
Magnetic brain stimulation - ***delayed conduction*** of corticospinal tracts.
Sensory-evoked potentials - ***normal***

BIBLIOGRAPHY for ch. "Spinal Disorders" → follow this LINK >>