Other Neuromuscular Transmission Disorders

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CONGENITAL MYASTHENIAS

- INCIDENCE << incidence of MG.
- *not autoimmune*!

PATHOGENETIC CLASSIFICATION – see p. Mus1 >>

CLINICAL FEATURES

MYASTHENIC SYMPTOMS after neonatal period ("floppy baby") + **FAMILY HISTORY** (autosomal recessive inheritance is most common)

N.B. may present later in life and, in some cases, without family history – diagnosed as serologically-negative autoimmune myasthenia.

- difficulty with feeding, delayed motor milestones, persistent or sometimes progressive limb weakness.
- skeletal abnormalities can result from weakness.
- some syndromes lack ocular involvement!

DIAGNOSIS

- positive **AChR antibody test** excludes congenital myasthenia (negative test is less helpful).
- positive* **edrophonium (Tensilon) test** confirms myasthenic syndrome but does not differentiate congenital myasthenia from MG.

  *may be negative in deficiency of acetylcholinesterase.
- **repetitive nerve stimulation**** → decrement in CMAP.

  **at 10 Hz (vs. MG – at 3 Hz).
- **single-fiber EMG** – as in MG.

Differential Diagnosis

1) mitochondrial myopathy
2) myasthenia gravis / neonatal myasthenia (passive placental transfer of AChR antibodies).

TREATMENT

- **respiratory & bulbar** supportive measures.
- some patients respond to **anticholinesterases**; if not – try 3,4,-DIAMINOPYRIDINE.

EATON-LAMBERT SYNDROME

- autoantibodies against **voltage-gated Ca^{2+}-channels** in peripheral nerves → reduced acetylcholine release* (at *neuromuscular* and *autonomic* synapses).

*number↓ of released ACh quanta.

Disorder of **presynaptic cholinergic cell**

a) 66% **paraneoplastic disorder** (60% patients, esp. men, have small cell lung cancer) - antibodies arise in reaction to tumor.

   Syndrome may predate tumor detection by up to 3 years!
b) 33% associated with **other autoimmune disorders** (thyroid disease, pernicious anemia, vitiligo, type I diabetes mellitus).

N.B. botulism also affects Acch release!

CLINICAL FEATURES

Skeletal muscles: **proximal & limb girdle muscle weakness + hyporeflexia** (esp. knee and ankle) are hallmarks.

respiratory, bulbar*, ocular muscles spared

*pharyngeal weakness (dysphagia) is only cranial weakness regularly encountered.

– lower limbs > upper limbs.

  PROXIMAL MUSCLES OF LOWER LIMBS!
– myalgia may occur.
– general fatigue (precedes weakness).
– gait dysfunction (follows weakness on standing).

N.B. ***repetitive / sustained*** *contraction can improve muscle strength for few seconds*!!! (warming-up phenomenon) – opposite of fatigability!; with continued use muscle fatigability returns.

Autonomic cholinergic (nicotinic & muscarinic) dysfunction: xerostomia, loss of taste, impotence.

– orthostatic hypotension, sluggish pupillary responses, peripheral paresthesias are rare.

DIAGNOSIS

- negative **EDROPHONIUM test**.
- abnormally small CMAP amplitude on **EMG**.
- **repetitive nerve stimulation**: see p. D20 >>, p. D22 >>

  at > 10 Hz* → CMAP increment (2 to 20 times original)!!! – that is the opposite of myasthenia gravis!!!

  * facilitates calcium accumulation in nerve terminal

  at 2 Hz → CMAP decrement.
- search for malignancy: chest X-ray, mammography, pelvic ultrasound.

TREATMENT

- directed to concomitant tumor.
- AMIFAMPRIDINE PHOSPHATE (Firdapse) tablets – FDA approved (11/28/2018).
- to **facilitate ACh release** - combination PYRIDOSTIGMINE + 3-4-DIAMINOPYRIDINE.
- other drugs that facilitate ACh release have had adverse effects:

GUANIDINE - bone marrow depression, cerebellar syndrome.
4-AMINO PYRIDINE - convulsions.

- **IVIG, plasmapheresis** effects are transient.
- **cytotoxic drugs** should be used cautiously.
- optimal treatment of non-neoplastic cases - modest doses of alternate-day PREDNISONE.

BIBLIOGRAPHY for ch. "Neuromuscular, Muscular Disorders" → follow this LINK >>