CONGENITAL MYASTHENIAS

Clinical Features: 1
- 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 late 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 Ca2+ channels in peripheral nerves → reduced acetylcholine release** (at neuromuscular and autonomic synapses).

*Number of released ACh quanta.

Disorder of presynaptic cholinergic cell

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<th>a) 66% paraneoplastic disorder (60% patients, esp. men, have small cell lung cancer) - antibodies arise in reaction to tumor.</th>
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<td>b) 33% associated with other autoimmune disorders (thyroid disease, pernicious anemia, vitiligo, type 1 diabetes mellitus).</td>
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N.B. Botulism also affects Acch release!

Clinical Features
Skeletal muscles: proximal & limb girdle muscle weakness + hyperreflexia (esp. knee and ankle) are hallmarks.

- Respiratory, bulbar*, ocular muscles spared.
- Pharyngeal weakness (dysphagia) is only cranial weakness regularly encountered.
- General fatigue (precedes weakness).
- Myalgia may occur.
- 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 (tachicardia & miosis) dysfunction: xerostomia, loss of taste, impotence.

- Orthostatic hypotension, sluggish pupilary responses, peripheral parasthesias are rare.

Diagnosis
- Negative edrophonium test.
- Abnormally small CMAP amplitude on EMG.

Repetitive nerve stimulation:
- 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.
- 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.
- IVIG, plasmapheresis effects are transient.
- Cytotoxic drugs should be used cautiously.
- Optimal treatment of non-neoplastic cases - modest doses of alternate-day Prednisone.