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Disorders of neuromuscular transmission: myasthenia gravis and Lambert-Eaton myasthenic syndrome

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NEUROLOGIC DISEASES THOUGHT TO BE AUTOIMMUNE

Type or site of dysfunction	Disease
Neuromuscular junction	Myasthenia gravis; Lambert Eaton myasthenic syndrome
Neuropathies/Neuronopathies	AIDP; CIDP; Mononeuritis multiplex (vasculitis); Neuropathies with various antibodies: gangliosides sulfatides MAG; Neuropathies with dysproteinemias; Sensory neuropathy: with Sjogren´s syndrome paraneoplastic; Isaac´s syndrome; Motor neuron disease?
Myopathies	Polymyositis; Dermatomyositis; Inclusion body myositis
Demyelinating Diseases	Multiple sclerosis; Optic neuritis; Transverse myelitis; Acute disseminated encephalomyelitis
Paraneoplastic syndromes	Cerebellar degeneration; Limbic encephalitis; Opsoclonus-myoclonus; Plasmocytoma-myeloma neuropathy; POEMS syndrome; Others listed above
Retroviral related	HTLV associated myelopathy (HAM, TSP); HIV associated neuropathy, myelopathy, etc.

MYASTHENIA GRAVIS: EPIDEMIOLOGY

- Estimates of the annual incidence of myasthenia gravis per million population vary from a low of 2 to 5 to a high of 10.4. Estimates of prevalence vary from 25 to 125 per million.
- The ratio of female to male patients is 6:4. The disease presents at any age. The female incidence peaks in the third decade and the male incidence in the sixth or seventh decade of life. The mean age of onset is 28 years in females and 42 years in males

MYASTHENIA GRAVIS: ETIOLOGY AND PATHOGENESIS

- **Antibodies to ACh receptor** protein have been found to be present in approximately 85 % of patients with generalized myasthenia and in 60 percent of those with ocular myasthenia. The level of receptor antibodies in serum does not correlate precisely with the severity of the myasthenia; the absence of measurable Ab in 15 % of patients remains unexplained. What is not known is what stimulates the production of these antibodies and where they are formed.

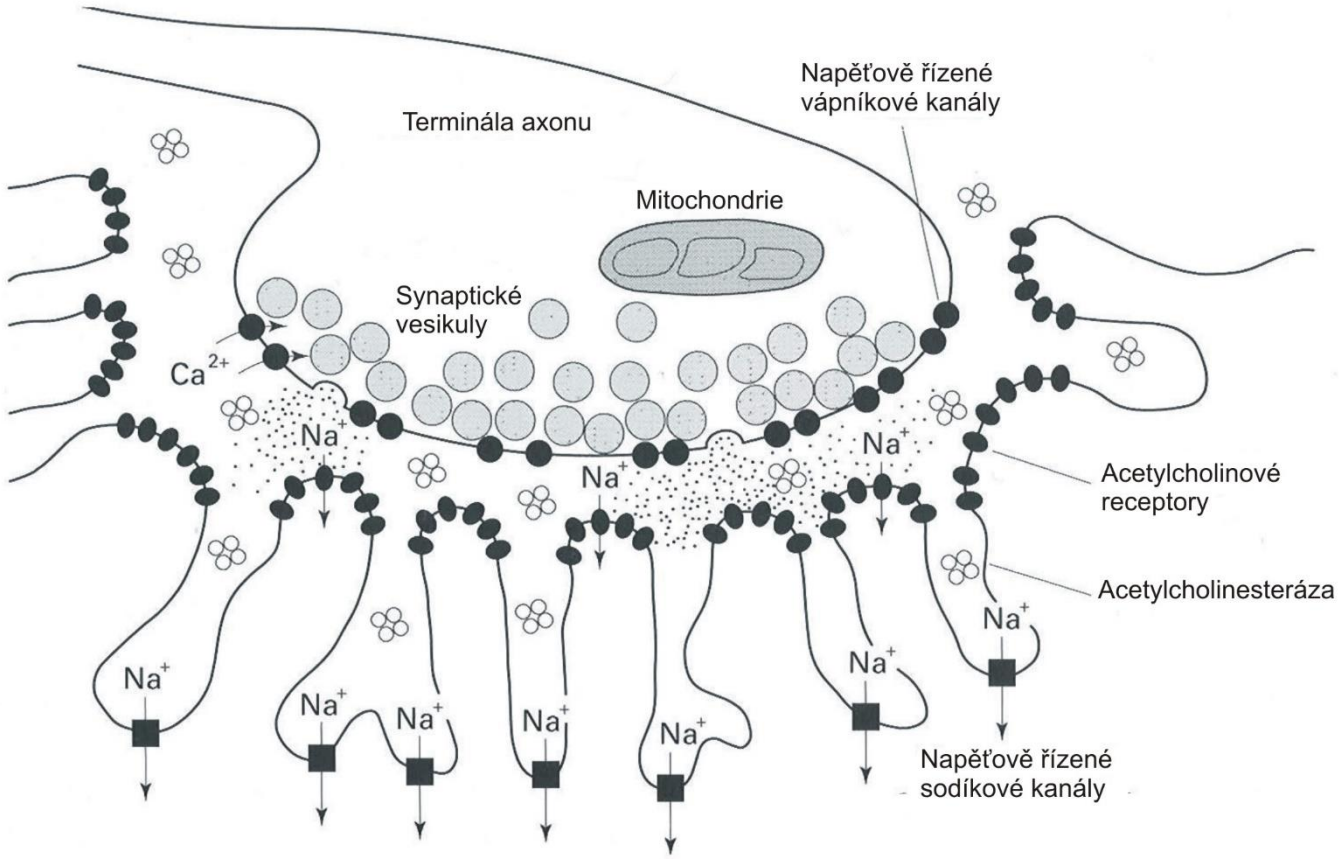
- **Autoantibodies directed against acetylcholine receptors** decrease the number of available receptors by at least three mechanisms: (1) by accelerating the degradation of acetylcholinreceptors; (2) by blocking the receptors´ active sites; (3) by acting with complement, damaging the acetylcholine receptors and their junctional surface membrane.

MYASTHENIA GRAVIS: ETIOLOGY AND PATHOGENESIS

Further auto-antibodies:

- Antibodies against striated muscles - **titin, ryanodin receptor, aktinin**; MG: in 30%; > 60 years: in 55%, MG + thymoma: in 75%; more severe weakness, myopathic changes in EMG
- **Antibodies against MuSK** (tyrozin kinase receptor in muscles): younger MG patients, in 30-70% AChRAb negative cases; worse therapeutic response

MYASTHENIA GRAVIS: ETIOLOGY AND PATHOGENESIS



MYASTHENIA GRAVIS: ETIOLOGY AND PATHOGENESIS 2

- The complex **relation of the thymus to MG** - the frequent association between MG and either thymic hyperplasia or thymoma, and the greatly increased chance of permanent remission or improvement following thymectomy - suggests that this organ may play an important part in both the origin and the maintenance of the autoimmune process.

- The basic abnormality is a **reduction in the number of available acetylcholin receptors at neuromuscular junctions**, resulting in impaired neuromuscular transmission and hence weakness and fatigue.

MYASTHENIA GRAVIS: CLINICAL MANIFESTATION

The most important clinical feature of MG is weakness, that exhibits several striking characteristics:

- fluctuating nature (increase at the end of the day);
- fatiguability (weakening during activity and quick restoration after rest);
- distribution (particularly muscles innervated by motor nuclei of the brainstem are involved, i.e., ocular, masticatory, facial, deglutitional, and lingual);
- dramatic improvement in strength following the administration of anticholinesterase drugs.

MYASTHENIA GRAVIS: CLINICAL MANIFESTATION 2

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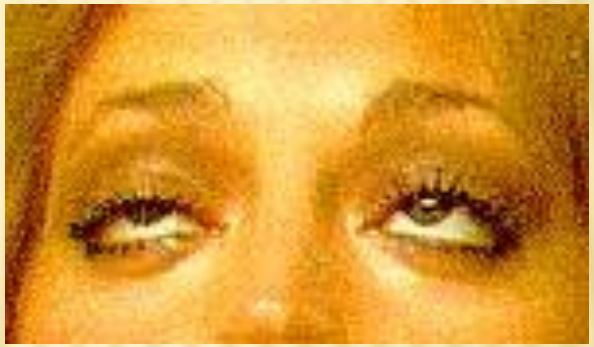
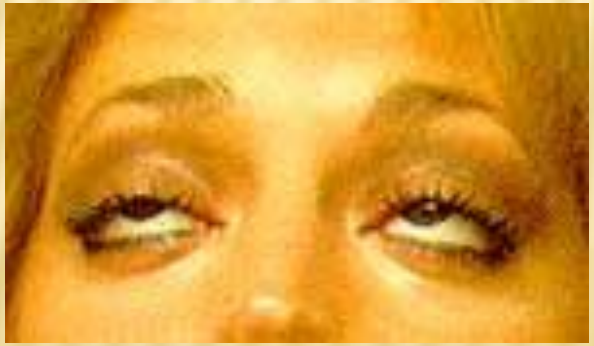




MYASTHENIA GRAVIS: CLINICAL MANIFESTATION
GORELICK SIGN

MYASTHENIA GRAVIS: CLINICAL MANIFESTATION
SEMAN'S SIGN (MYASTHENIC DYPHONIA AND DYSARTRIA

MYASTHENIA GRAVIS: CLINICAL MANIFESTATION 2

- The onset is usually insidious, but there are instances of fairly rapid development, sometimes initiated by an emotional upset or infection.
- Symptoms may first appear during pregnancy or the puerperium, or in the response to drugs used during anesthesia.
- Ocular palsies and ptosis are present in 90 % of cases. In generalized MG the proximal muscles are more affected than distal ones.
- Tendon reflexes are not altered, muscle atrophies are absent, sensitivity is normal.
- Normal pupillary responses to light and accommodation in the face of weakness of extraocular muscles and orbicularis oculi are virtually diagnostic of MG.
- The peak age of onset in women is between 20 and 30 years, while the male incidence peaks in the sixth of seventh decade.

MYASTHENIA GRAVIS: CLINICAL CLASSIFICATION

Osserman´s classification:

1. Ocular myasthenia
2. A. Mild generalized myasthenia with slow progression; no crises; drug responsive

   B. Moderate generalized myasthenia: severe skeletal and bulbar involvement, but no crises; drug response less then satisfactory
3. Acute fulminating myasthenia; rapid progression of severe symptoms with respiratory crises and poor drug response; high incidence of thymoma; high mortality
4. Late severe myasthenia, same as (3), but progression over two years from class 1 to 2.

MYASTHENIA GRAVIS: PATHOGENETIC CLASSIFICATION

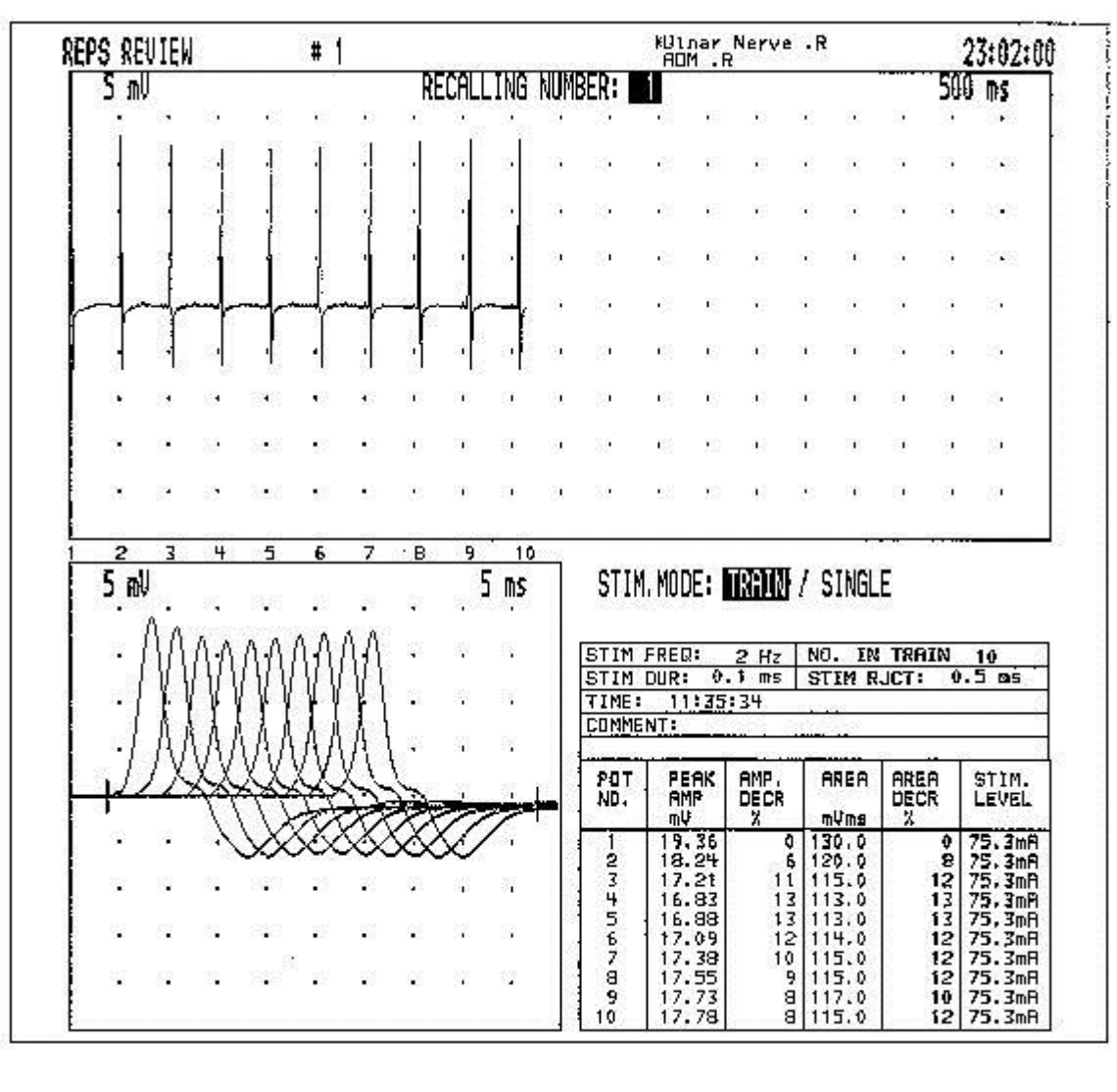
Pathogenetic classification:

1. Early onset MG (up to 40 years of age); female preponderance; thymus hyperplasia; association with HLA-B8 and D/DR 3;
2. Late onset MG (over 40 years of age); male preponderance, thymus atrophy
3. MG associated with thymoma (about 10%)
4. Ocular MG
5. MG with no detectable AChR Ab

MYASTHENIA GRAVIS: DIAGNOSIS

- Typical clinical symptoms and signs
- Positive pharmacological tests (acetylocholinesterase inhibitors Edrophonium or Neostigmin improve the muscle strength);
- Electrophysiological tests showing disturbance of neuromuscular transmission of postsynaptic type: repetitive stimulation, single fiber EMG);
- Measurement of ACh receptor antibodies in blood

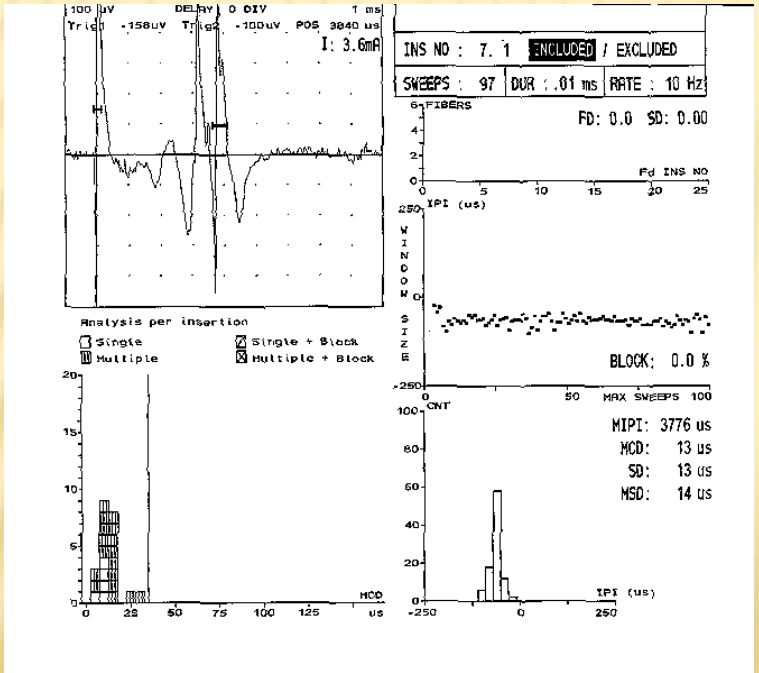
REPETITIVE STIMULATION OF MOTOR NERVES



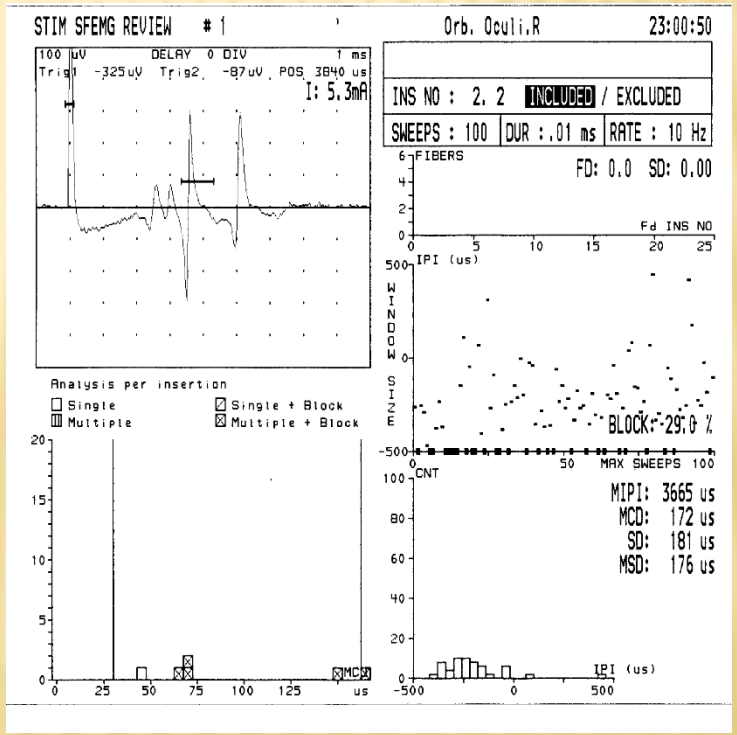
POT NO.	PEAK AMP mV	AMP. DECR %	AREA mVms	AREA DECR %	STIM. LEVEL
1	19.36	0	130.0	0	75.3mA
2	18.24	6	120.0	8	75.3mA
3	17.21	11	115.0	12	75.3mA
4	16.83	13	113.0	13	75.3mA
5	16.88	13	113.0	13	75.3mA
6	17.09	12	114.0	12	75.3mA
7	17.38	10	115.0	12	75.3mA
8	17.55	9	115.0	12	75.3mA
9	17.73	8	117.0	10	75.3mA
10	17.78	8	115.0	12	75.3mA

MYASTHENIA GRAVIS: DIAGNOSIS - JITTER

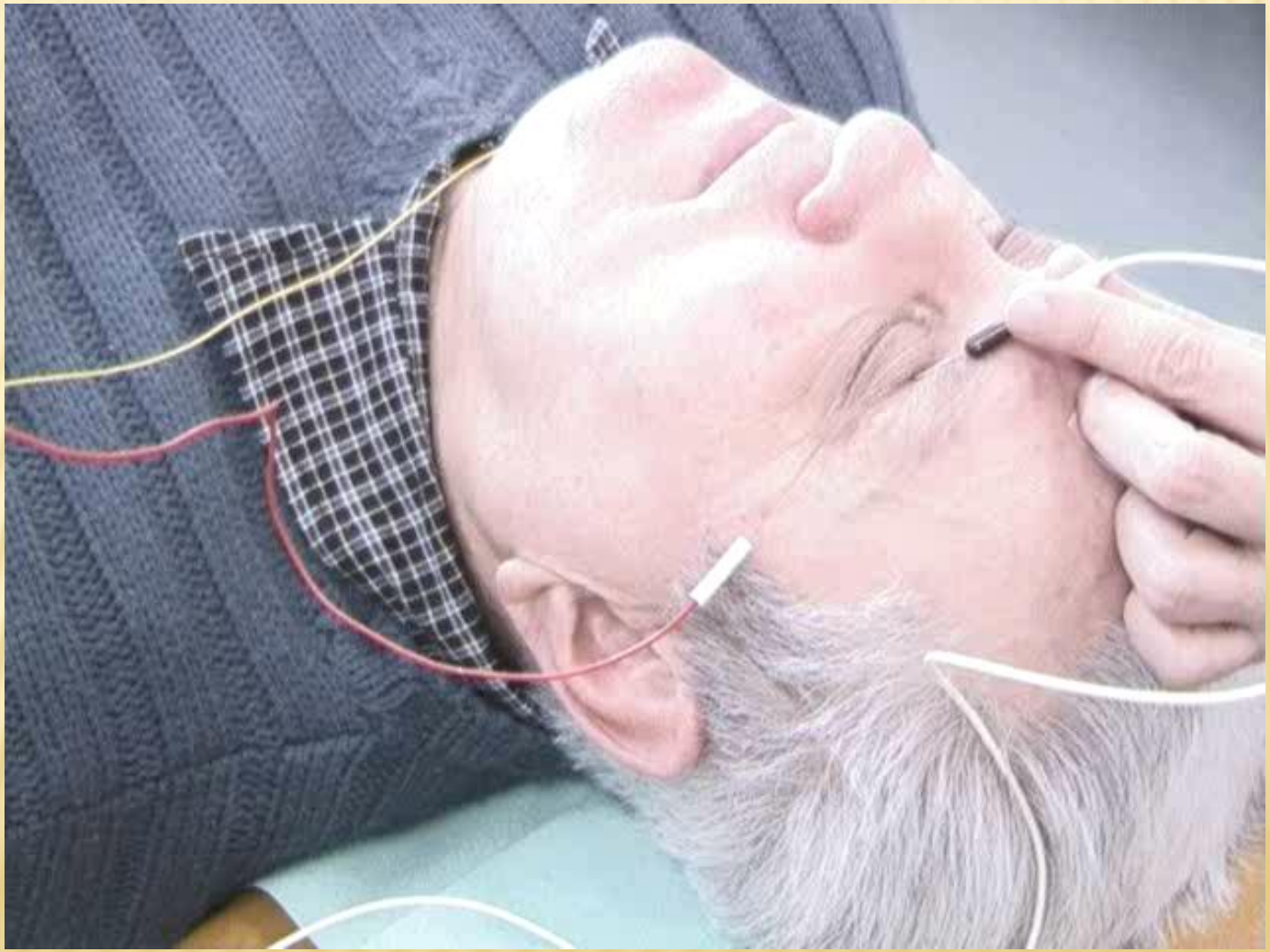
Normal jitter



Abnormal jitter



MYASTHENIA GRAVIS: DIAGNOSIS - JITTER



MYASTHENIA GRAVIS: DIAGNOSIS - JITTER

MYASTHENIA GRAVIS: THERAPY

1. **Anticholinesterase drugs** (inhibitors of acetylcholin-esterase): neostigmine (Syntostigmin, Prostigmin), pyridostigmin (Mestinon, Kalymin) symptomatically counteract myasthenic weakness;
2. **Thymectomy** are recommended in all patients with generalized MG responding poorly to anticholiesterase medication, especially in patients up to 40 years of age, and in all patients with thymoma; the remission occurs usually within 3 years after thymectomy;
3. **Corticosteroids** are proper treatment for moderately severe myasthenic patients, in whom a remission has not been induced by thymectomy;

SIDE EFFECTS OF CORTICOSTEROIDS AND THEIR PREVENTION

Side effect	Prevention	Monitoring
Generalized obesity; abnormal fat distribution with moon facies, buffalo hump, and thinning of extremities	Diet (caloric restriction)	Checking body weight
Impaired glucose tolerance or diabetes mellitus	Diet (low carbohydrate)	Checking blood glucose
Sodium retention; edemas; hypertension	Diet (low salt)	Checking natremia, BP
Hypokalemia	Supplementation (up to 40 mEq daily)	Checking kalemia
Adrenal suppression	Alternate-day regimen	Double any low maintenance dosis during acute periods of stress
Growth retardation in children		
Irregular menses		
Osteoporosis; vertebral compression fractures	Supplementation of calcium (1 g daily), vitamin D (50.000 u. once a week), and gonadal hormones, esp. in postmenopausal women and long-term steroid therapy	Monitoring 24-hr urinary calcium and serum 25-OH vitamin levels
Lipolytic action resulting in hyper-lipidemia; rarely fat emboli in the femoral head and aseptic necrosis of the hip; epidural lipomatosis resulting in spinal cord compression		
Steroid myopathy		Diet: high protein intake; isometric training programme
Steroid psychosis		
Behavioral and affective changes (nervousness, irritability, moodiness, insomnia, depression		
Pseudotumor cerebri		
Peptic ulcer ???	Antacids or H2 receptor antagonists	
Skin changes (acne, striae, facial hirsutism, ekchymoses)		
Impaired wound healing		
Posterior subscapular cataract		Regular ophthalmologic exam
Glaucoma		Regular ophthalmologic exam
Herpes zoster and other opportunistic infections		

MYASTHENIA GRAVIS: THERAPY 2

4. **Azathioprine** is proper treatment for the same patients as corticosteroids; it has later beginning of the effect, but less side effects than corticosteroids; it is better for long-term treatment;
5. **Mycophenolate mophetil, cyclosporin:** immunosupressants
6. **Plasmapheresis** may be lifesaving during crisis; it is also useful before and after thymectomy and at the start of immunosupressive therapy; its effect is, however, temporary
7. **Intravenous intravenous human immunoglobulin**

LAMBERT-EATON MYASTHENIC SYNDROME: HISTORY AND PATHOGENESIS

- **History**
  - In 1957 Drs. Lambert and Eaton described a myasthenic syndrome associated with malignant tumors.
- **Epidemiology**
  - 3% of SCLC develop LEMS; annual incidence is 5/per million in SCLC related LEMS;
  - It most often occurred in men over 40 (male/female ratio 2:1)

LAMBERT-EATON MYASTHENIC SYNDROME: PATHOGENESIS

- LEMS is a rare condition in which weakness results from a **presynaptic abnormality of acetylcholine (Ach) release** at the neuromuscular junction
- It was first described in association with lung cancer and was initially considered to be a **paraneoplastic syndrome**. Recent developments demonstrate that LEMS results from an **autoimmune attack** directed against the voltage-gated calcium channels (VGCC) on the presynaptic motor nerve terminal
- Approximately **70%** of patients have **small cell carcinoma of the lung** (mostly small cell lung cancer) with the remaining patients having underlying autoimmune diseases. In most cases the syndrome predates the discovery of the tumor.
- A few patients have an **overlapping syndrome** with both MG and Lambert-Eaton myasthenic syndrome as shown by the fact that they have antibodies not only to anticholine receptor but also to voltage-gated P/Q - type calcium channels indicating presynaptic abnormality.

LAMBERT-EATON MYASTHENIC SYNDROME: CLINICAL SIGNS AND SYMPTOMS

- **Weakness** is the predominant symptom and the **proximal muscles of the lower extremities** are predominantly involved, with less involved proximal upper extremities, and to a much lesser extent the cranial musculature. About 50% of these patients have partial bilateral ptosis. Sometimes neck weakness is found. Bulbar and facial weakness are rare however
- **Tendon reflexes** are reduced or absent
- While some develop **fatigue**, it is not as clear cut as the fatigue observed in AM. Strengh may improve after exercise and then weaken as activity is sustained
- The patients also complain of peculiar **leg pains and paresthesias**; the weak muscles may ache and are occasionally tender
- **Autonomic nervous system** is affected producing impotence and dry mouth and much less often other autonomic phenomenon

LAMBERT-EATON MYASTHENIC SYNDROME: DIAGNOSIS

Clinical diagnosis: The disease should be suspected in any patient complaining of proximal weakness. Several clinical tests have been developed: One is to have the patient grip the examiner's hand as hard as he can. The examiner feels an increase in strength over several seconds. In addition the knee jerk amplitude is noted to be augmented after a vigorous contraction of the quadriceps lasting 10-20 seconds.

LAMBERT-EATON MYASTHENIC SYNDROME: DIAGNOSIS 2

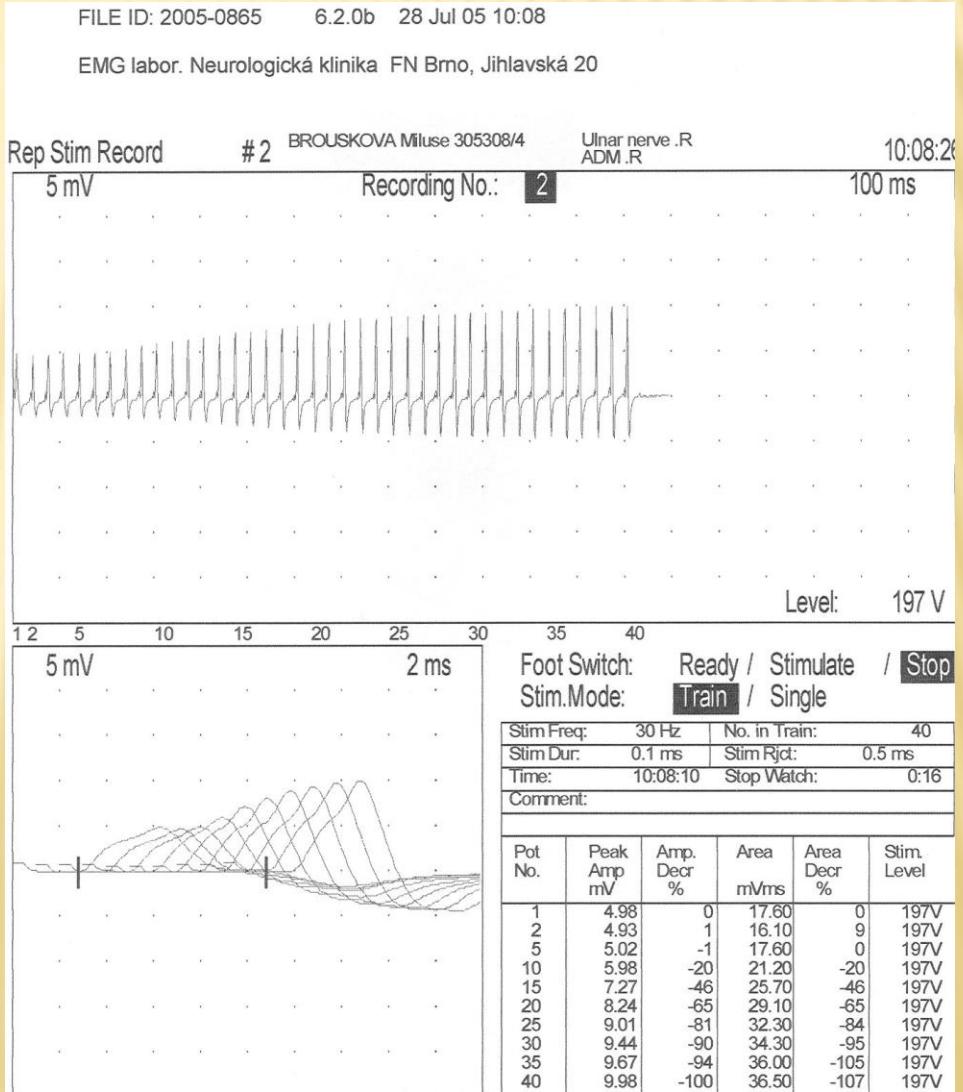
Electrophysiological tests:

- Standard EMG: low amplitude motor revoked responses on EMG with normal nerve conduction studies and normal findings on needle EMG examination.
- Repetitive stimulation of motor nerves: decrement of both amplitude and area of CMAP at frequencies between 1 to 5 Hz; increment (>100%) of CMAP amplitude at frequencies from 20 to 50 Hz
- Single fiber EMG: abnormal jitter and blockings
- The defect is generalized and repetitive stimulation studies or SFEMG can be done on almost any muscle

Serological tests: detection of autoantibodies against voltage-gated P/Q - type calcium channels

LAMBERT-EATON MYASTHENIC SYNDROME: DIAGNOSIS 2

Repetitive stimulation of motor nerves: increment



Pot No.	Peak Amp mV	Amp. Decr %	Area mVms	Area Decr %	Stim. Level
1	4.98	0	17.60	0	197V
2	4.93	1	16.10	9	197V
5	5.02	-1	17.60	0	197V
10	5.98	-20	21.20	-20	197V
15	7.27	-46	25.70	-46	197V
20	8.24	-65	29.10	-65	197V
25	9.01	-81	32.30	-84	197V
30	9.44	-90	34.30	-95	197V
35	9.67	-94	36.00	-105	197V
40	9.98	-100	36.50	-107	197V

LAMBERT-EATON MYASTHENIC SYNDROME: THERAPY

- Extensive search for underlying malignancy $\Rightarrow$ cancer therapy
- Cholinesterase inhibitors
- Guanidine hydrocholride or 3,4-diaminopyridine
- Immunosupression (corticosteroids, azathioprine)
- Plasma exchange
- Intravenous human immunoglobulin

AUTOIMMUNE ETIOPATHOGENESIS OF MYASTHENIA GRAVIS AND LAMBERT-EATON MYASTHENIC SYNDROME

- **Myasthenia gravis (MG)** and the **Lambert-Eaton myasthenic syndrome (LEMS)** are each a distinct pathophysiological entity, but nevertheless have striking similarities.

- Both are **organ-specific autoimmune disorders** that are mediated by **IgG autoantibodies** interacting with **cation channel proteins in plasma membranes of the neuromuscular synapse**.

AUTOIMMUNE ETIOPATHOGENESIS OF MYASTHENIA GRAVIS AND LAMBERT-EATON MYASTHENIC SYNDROME 2

- The principal autoantigens that are the respective targets of these highly specific immunoglobulins are extracellular segments of

  1) the nicotinic acetylcholine receptor (AChR), which is the **Na+/K+ channel in the muscle's postsynaptic membrane** that is **opened by acetylcholine,** and

  2) the motor nerve terminal's voltage-sensitive Ca channel that is **opened by the action potential.**

- Both disorders are significantly **associated with an intrathoracic neoplasm**, **epithelial thymoma** in MG and **primary lung carcinoma**, usually small cell type, in LEMS.