DISORDERS OF THE NEUROMUSCULAR JUNCTION

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of *skeletal* muscles.

Etiology and pathology:

- The underlying defect is a decrease in the number of available *acetylcholine receptors* (AChRs) at neuromuscular junctions due to an antibody-mediated autoimmune attack.
- The disease is most commonly caused by autoantibodies to acetylcholine receptors (anti-ACRs) in *the post-synaptic membrane* of the neuromuscular junction. These antibodies block neuromuscular transmission and initiate a complement-mediated inflammatory response.
- A minority of patients have other autoantibodies in particular autoantibodies to a muscle-specific kinase (MuSK).
- About 15% of patients (mainly those with late onset) have a thymoma, and the majority of the remainder has thymic follicular hyperplasia.
  Muscle-like cells within the thymus (myoid cells), which bear AChRs on their surface, may serve as a source of autoantigen and trigger the autoimmune reaction within the thymus gland.

Clinical features:

- The disease usually presents between the ages of 15 and 50 years.
- Women affected more often than men in the younger age groups and the reverse at older ages.
- The cardinal symptom is abnormal *fatigable weakness* of the muscles particularly of *the ocular, neck, facial and bulbar muscles*. The weakness increases during repeated use and may improve following rest or sleep.
- Worsening of symptoms towards the end of the day or following exercise is characteristic.
- The first symptoms are usually intermittent ptosis or diplopia.

- *Bulbar weakness* may develop leading to difficulty in swallowing, nasal regurgitation or aspiration of liquids or food.
- Weakness in chewing is most noticeable after prolonged effort, as in chewing meat.
- Patient may be unable to undertake tasks above shoulder level, such as combing the hair, without frequent rests.
- Respiratory muscles may be involved, and respiratory failure is not uncommon cause of death.
- If weakness of respiration becomes so severe as to require respiratory assistance, the patient is said to be in *crisis* (cholinergic or myasthenic crisis).
- Despite the muscle weakness, *deep tendon reflexes are preserved*. There are *no sensory signs* or signs of involvement of the central nervous system.

Diagnosis and Evaluation:

The suspected diagnosis should always be confirmed by

1-Pharmacological test

The intravenous injection of the short-acting anticholinesterase, *edrophonium bromide* (2mg injected with a further 8 mg given half a minute later, is a valuable diagnostic aid (the *Tensilon test*). Improvement in muscle power occurs within 30 seconds and usually persists for 2-3 minutes.

2-Electrophysiological test

EMG with repetitive stimulation may show the characteristic *decremental* response.

3-***Immunological test***

Anti-acetylcholine receptor antibody (anti-ACRs) is found in over 80% of cases, though less frequently in purely ocular myasthenia (50%). Anti-MuSK antibodies are found especially in AChRA-negative patients.

- In addition to these investigations, all patients should have a *thoracic CT to exclude thymoma*, which may not be visible on plain X-ray examination.
- Screening for other autoimmune disorders, particularly *thyroid disease*, is important.

Management:

a- symptomatic

- The duration of action of acetylcholine at remaining receptors in the neuromuscular junctions is greatly prolonged by inhibiting its hydrolysing enzyme, acetylcholinesterase.
- The most commonly used anticholinesterase drug is *pyridostigmine*, which is given orally in a dosage of 30-120 mg, usually 6-hourly.
- Muscarinic side-effects, including diarrhoea and colic, may be controlled by *propantheline* (15 mg as required) or atropine.

b- Disease modifying therapy

1-Plasma exchange & Intravenous immunoglobulin are normally reserved for *myasthenic crisis* or for *pre-operative preparation.*

2-Corticosteroid treatment can be extremely effective in improving myasthenic weakness and establishing remission.

- Improvement is commonly preceded by marked exacerbation of myasthenic symptoms and treatment should be initiated in hospital.

- It is usually necessary to continue treatment for months or years, often resulting in adverse effects.

3-Other immunosuppressant treatment

- Include azathioprine, cyclosporine, tacrolimus and mycophenolate mofetil, rituximab.
- Immunosuppressant treatment is of value if reducing the dosage of steroids necessary and may allow steroids to be withdrawn.

4-surgical:

- *Thymectomy* in the early stages of the disease leads to a much better overall prognosis, *whether a thymoma is present or not*, in any *antibody-positive* patient *under 45 years* with symptoms not confined to extraocular muscles.

Prognosis:

- Remissions sometimes occur spontaneously.

- When myasthenia is confined to the eye muscles, the prognosis is excellent and disability slight.
- Young female patients with generalised disease have high remission rates after thymectomy.

Lambert-Eaton myasthenic syndrome (LEMS)

- N-M transmition is impaired, often in association with antibodies to *pre-synaptic* voltage-gated calcium channels.

- It is characterized by *muscle weakness which improves after exercise.*

- Patients may have *autonomic dysfunction* (and a dry mouth).

- The cardinal clinical sign is *absence of tendon reflexes*, which can return immediately after sustained contraction of the relevant muscle.

- The condition is associated with underlying malignancy, especially *bronchogenic carcinoma*, in a high percentage of cases, and investigation must be directed towards detecting such a cause.