MYASTHENIA GRAVIS

INTRODUCTION

- Most common primary disorder of neuromuscular transmission
- Usually due to acquired immunological abnormality
- Also due to genetic abnormalities at neuromuscular junction.

EPIDEMIOLOGY

- Most common age of onset :

  women : 2nd & 3rd decades

  men : 5th & 6th decades
- < 40 yrs , females are affected 2 to 3 times as often as males.
- Later in life, incidence is higher in males.
- Of pts with thymomas, majority are older (50 – 60 yrs) & males.

CLINICAL PRESENTATION

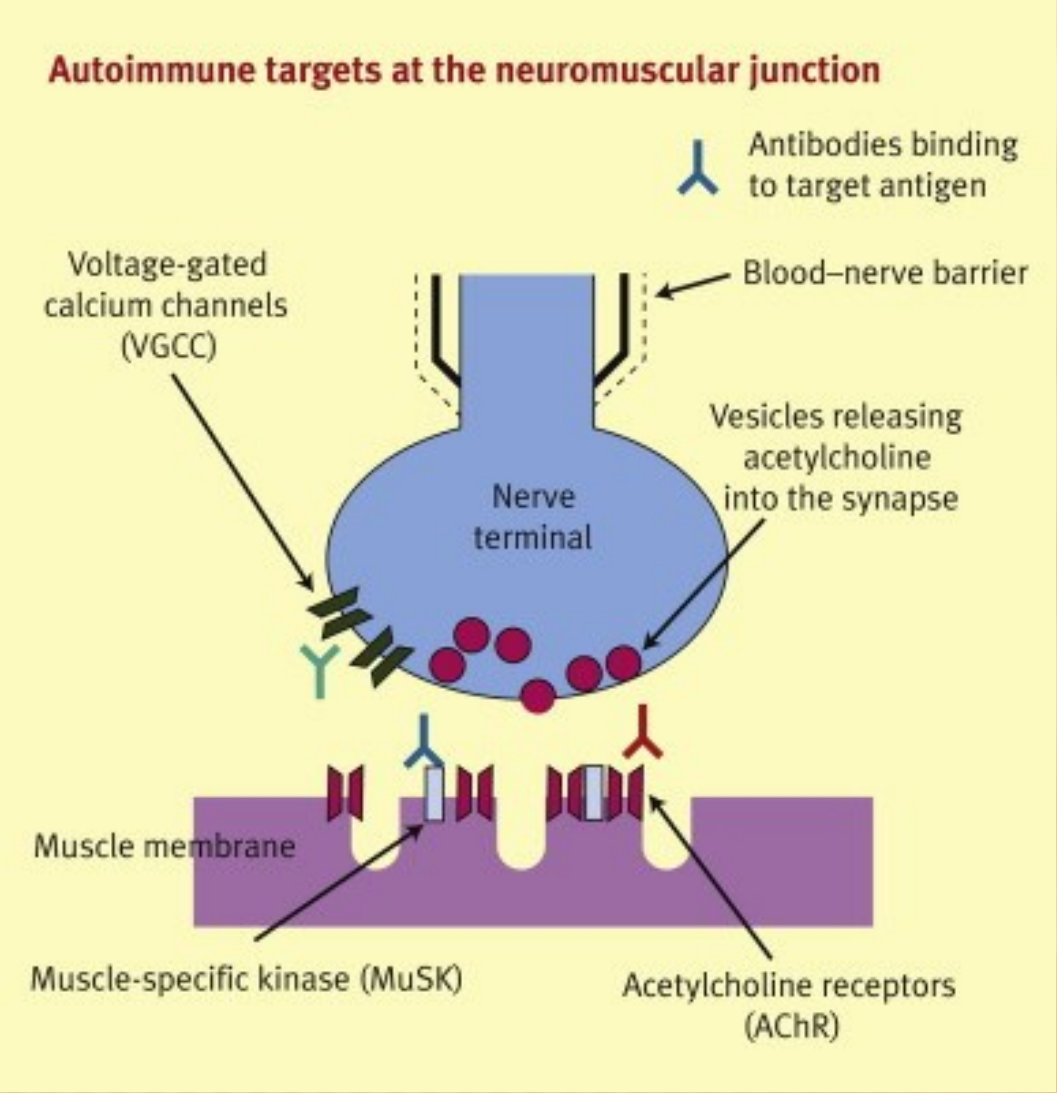
Between patients, the disease varies widely in severity and pattern of progression

- In the early stages, the weakness can be intermittent. Often the first sign is drooping of the eyelids or double vision
- About 15 percent of patients only ever have eye muscle weakness – this is called **ocular myasthenia**
- Others also have more widespread weakness - **generalized myasthenia**
- These patients can develop weakness of the face, swallowing, and chewing muscles, slurring of speech, and weakness of the limbs and neck. In severe cases, weakness of the breathing muscles can occur. Problems with swallowing or coughing can cause choking

Ptosis (drooping of the eyelid)

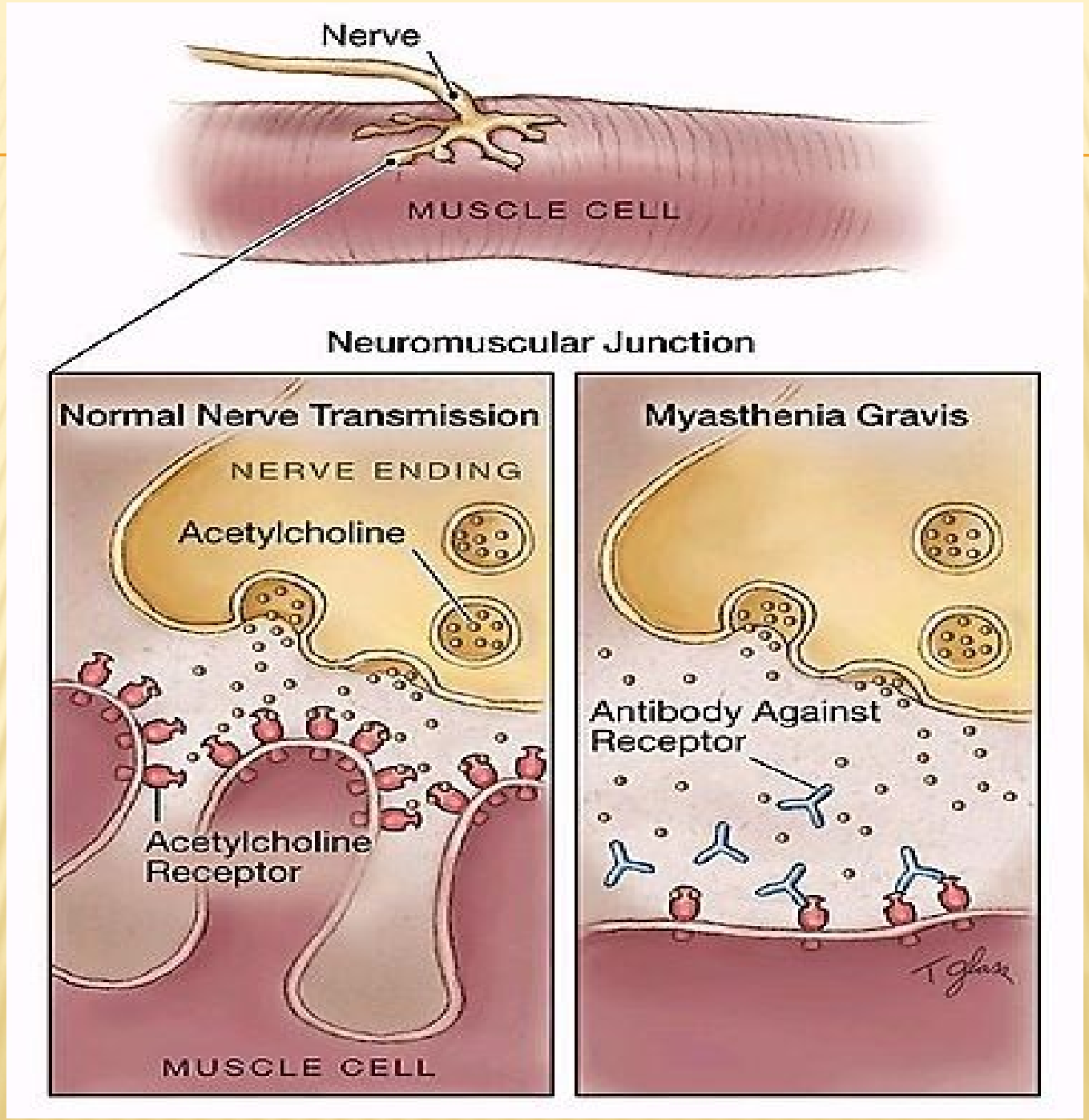
PATHOPHYSIOLOGY

- Nerves, at the synaptic terminal, release a chemical called acetylcholine
- Normally Ach binds to the Ach receptors (AchR) on the muscle membrane
- This causes the muscles to trigger contraction


Autoimmune targets at the neuromuscular junction
Antibodies binding to target antigen
Voltage-gated calcium channels (VGCC)
Blood–nerve barrier
Vesicles releasing acetylcholine into the synapse
Nerve terminal
Muscle membrane
Muscle-specific kinase (MuSK)
Acetylcholine receptors (AChR)

PATHOPHYSIOLOGY

- Myasthenia gravis is an autoimmune disease caused by abnormal antibodies carried in the blood stream
- The commonest antibodies are directed against the muscle acetylcholine receptor (AchR)
- These antibodies interfere with the binding of Ach with the AchR by themselves binding to the receptors
- In 75 per cent of patients, the abnormal antibody production is associated with abnormalities of a gland in the chest called the thymus, which is part of the immune system. About 10 per cent of patients have a tumour of the thymus (a thymoma) that is usually benign


Nerve
MUSCLE CELL
Neuromuscular Junction
Normal Nerve Transmission
NERVE ENDING
Acetylcholine
Acetylcholine Receptor
MUSCLE CELL
Myasthenia Gravis
Antibody Against Receptor

MYASTHENIA GRAVIS PROFILE @METROPOLIS

- AchR Antibody
- ASKA (Skeletal/Striated Muscle Antibody)
- Anti MuSK (Muscle Specific tyrosine kinase)

ACHR ANTIBODY

- Demonstration of muscle AChR autoantibodies in a patient's serum supports the diagnosis of acquired (autoimmune) MG, and quantitation provides a baseline for future comparisons
- The assay for muscle AChR binding antibodies is considered a **first-order test** for the laboratory diagnosis of MG, and for detecting "subclinical MG" in recipients of D-penicillamine, in patients with thymoma without clinical evidence of MG, and in patients with graft-versus-host disease

ACHR ANTIBODY

Occurrence:

- Adults with generalized MG: 85 to 90%
- Childhood MG: 50%
- Ocular MG: 50% to 70%

Significant role in:

- Diagnosis of Myasthenia gravis

  (The high frequency of anti-AChR Abs in MG patients and their specificity makes their detection a reliable diagnostic test).
- Assessment and patient management following immunosuppressive treatment or plasmapheresis.
- Prognosis of disease progression, particularly in paraneoplastic MG.

ASKA (ANTI SKELETAL MUSCLE ANTIBODY)

- These are auto antibodies formed against the contractile elements of striated muscle

Occurrence:

- 30% of adult patients with MG and 80% of patients with thymoma
- May also be detected in patients with Lambert-Eaton syndrome, small-cell lung carcinoma, breast carcinoma, and graft versus host disease in some bone marrow transplant patients

ASKA- CLINICAL UTILITY

- This test is a useful serological aid in the diagnosis of thymoma, especially in patients with onset of myasthenia gravis (MG) younger than 45 years
- It is useful as a screening test for MG in older patients, especially when tests for muscle AChR antibodies are negative
- Serial measurements are useful in monitoring the efficacy of immunosuppressant treatment in patients with MG
- Serial measurements are useful after treatment of thymoma

MUSK ANTIBODY

- MuSK (Muscle specific kinase) is a tyrosine kinase receptor which is required for the formation of the neuromuscular junction (NMJ)
- Antibodies against MuSK cause a decrease in the patency of the NMJ and the consequent symptoms of MG

MUSK ANTIBODY- OCCURRENCE

- In 10–20% of patients with generalised myasthenia gravis and in up to 50% of patients with ocular myasthenia gravis there are no detectable antibodies to the acetylcholine receptor (AChR). In such cases the disease is commonly referred to as **seronegative myasthenia gravis**
- Antibodies to muscle specific kinase (MuSK) are demonstrated in the sera of patients with generalized seronegative myasthenia gravis

MUSK ANTIBODY- CLINICAL UTILITY

- Myasthenia gravis patients with these antibodies have been described as having more prominent bulbar and neck weakness and more respiratory crises
- Anti-MuSK antibodies were not found in seropositive myasthenia gravis

MYASTHENIA GRAVIS PROFILE- REPORT FORMAT

Test Description	Observed Value	Reference range & units
ASKA-Skeletal (Striated) Muscle Antibody, serum	**NEGATIVE**	NEGATIVE

DESCRIPTION OF TEST :

1. Autoantibodies against striated muscles can be an indication of myasthenia gravis
2. **However only high antibody titres are of diagnostic relevance.**

TECHNIQUE :

BIOCHIP slide using combinations of different histological substrates and Hep-2 cells is used.

ASSOCIATED TESTS :

Acetyl choline receptor antibody

MYASTHENIA GRAVIS PROFILE- REPORT FORMAT

Test Description	Observed Value	Biological Reference Interval
ANTI MuSK ANTIBODIES serum by RIA	**3.07**	NEGATIVE : < 0.05 nmol/L

Antibodies against striated muscles (MuSK Antibody) - Muscle specific receptor tyrosine kinase.
Myasthenia gravis is a generalized autoimmune disease which is mainly caused by disorders of the transmission of neuromuscular stimulation as a result of a reversible blocking of the acetylcholine receptors at the motor end plates. Antibodies against acetylcholine receptors can be found in about 90% of patients.
In acetylcholine receptor antibody negative patients, another antibody is identified against MuSK (Muscle specific receptor tyrosine kinase.) .
Antibody against acetylcholine receptor antibody / MuSK are seen in separate patient groups.
ASSOCIATED TEST : acetylcholine receptor antibody

MYASTHENIA GRAVIS PROFILE- REPORT FORMAT

Acetyl Choline Receptor Antibodies serum by R.I.A.	**0.01**	Normal levels : 0.0 to 0.25 nMol/L * Borderline levels : 0.25 to 0.4 nMol/L Positive levels : Above 0.4 nMol/L

1. Autoantibodies to the acetylcholine receptor are responsible for failure of the neuromuscular junction in Myasthenia Gravis .
2. Receptor antibody measurement can be of considerable value in disease diagnosis and follow up.
3. Presence of acetyl choline receptor antibody in the blood of persons who have symptoms of myasthenia gravis supports the diagnosis. However, a lack of these antibodies does not rule out this condition. About 10-15% of people with myasthenia gravis do not have signs of this antibody in their blood.

. .
Associated Test : Anti Musk Antibodies (Muscles specific receptor thyrosine kinase).