"...I need to rest every few minutes"

Case 2, Year 1

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Key Concepts

- Neuromuscular junction & signaling transduction.
- Mechanisms interfering with nerve signals across neuromuscular junction.
- Mechanisms underlying muscle contraction.
- Use of basic sciences in interpreting patient's symptoms and signs.
- Use of evidence in refining hypotheses.
- Pharmacology of drugs used in treatment of myasthenia gravis.

Learning Objectives:

This PBL package (tutorials one and two) targets the following objectives:

- Discuss the structures involved in the neuromuscular junction and the process of signaling transduction in a normal nerve and muscle.
- Discuss the different possible mechanisms by which interference may occur with the conduction from nerve fibres to muscle fibres.
- Discuss the mechanisms by which skeletal muscle fibres contract.
- Understand the role of investigations in confirming the diagnosis of neuromuscular junction dysfunction (myasthenia gravis).
- Discuss the pharmacology of drugs used in the management of myasthenia gravis.
- Use knowledge learnt from physiology and histology to interpret the patient's symptoms and signs.

Trigger

(40 Minutes)

Rachel Mendoza, a 30-year-old Phillipine librarian-assistant comes in to see a local general practitioner, Dr Amany Shenwan, because she feels tired, particularly after midday. Rachel works in a major hospital library in Riyadh and she is responsible for placing books back to bookshelves. She has been doing this job for about 7 years with no problems but recently she noticed that she is unable to continue putting books and she has to take rest every few minutes in order to be able to continue. She also noticed drooping of her eyelid usually near the end of her work shift.

Discussion Questions:

- Are there any difficult words you do not understand?
- List the key information about Rachel.
- Identify Rachel's presenting problems.
- For each problem make a list of how it may be caused (generate hypotheses).
- What further information would you like to know to help you differentiate between your hypotheses? (What questions would you like to ask Rachel?)

Trigger

(40 Minutes)

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New Terms

Drooping: to hang downward, pulled down from its normal place.

Hypotheses

1. **Feels tired (usually after midday):**

- Muscle problem (e.g., muscle fatigue, myopathy, muscle inflammation, muscle tear).
- Nerve problem (e.g., inflammation, nerve lesion).
- Neuromuscular junction dysfunction (e.g., problem with receptors, problem with chemical transmission).
- Depression/anxiety/worries/stressed.
- Lack of sleep.
- Low blood glucose level.
- Heart/lung/liver/kidney problems.
- Anaemia.
- Does not like her job/ not happy at work.
- Overloaded with tasks at home and at work.
- Mental tiredness.

Hypotheses

2.Unable to continue:

- Associated Pain.
- Muscle fatigue.
- Muscle tear.
- Ligament problem.
- Decreased oxygen supply to muscles.
- Accumulation of lactic acid etc in the muscle fibers
- Nerve problem.
- Muscle problem.
- Neuromuscular junction problem.
- Heart/lung/liver/kidney problem.
- Anaemia
- Not used to do this job for long hours (unlikely)

Hypotheses

3. Drooping of her eyelid:

- Nerve problem (e.g., nerve tear, nerve lesion, inflammation)
- Muscle problem (e.g., myopathy, inflammation, fatigue).
- Neuromuscular problem:
  - Nerve axon.
  - Synaptic vesicles (chemical transmitter).
  - Nicotine acetylcholine receptors.
  - Sarcolemma membrane.

Facilitation Questions

Do you think Rachel's inability to continue doing her work is normal?

Tutor: *Students might answer by saying "yes", others may say "no". In both cases, you need to ask them to justify their views.*

Not normal (justification):

- She used to do the same job for 7 years with no problems.
- She noticed ptosis of her eyelids.
- She needs to have rest every few minutes to continue her work.

These changes require more assessment before making a final decision.

Facilitation Questions

How can you explain muscle fatigue on prolonged exercises?

A number of physiological changes occur in skeletal muscles on prolonged exercise and could be responsible for the development of fatigue. These changes include:

- Accumulation of metabolites within muscle fiber.
- Decreased oxygen supply to muscles.
- Decreased energy to fuel contraction.
- Decreased adenosine triphosphate (ATP), glycogen, and creatine phosphate.
- Increased intracellular ADP, reactive oxygen species, and magnesium.
- Increased intracellular sodium.
- Changes in intracellular pH (accumulation of lactic acid).

Facilitation Questions

What are the anatomical structures and functions do we need for normal skeletal muscle function?

- Normal nerve fibres (connected to spinal cord and the brain areas).
- Normal skeletal muscles.
  - Normal actin, myosin, trponin, trepomyosin molecules.
  - Normal Ca2+ concentration.
  - Normal adenosin triphosphate, glucogen, creatine phosphophate.
- Normal neuromuscular junction.
  - Normal vesicles and chemical transmitters.
  - Normal receptors/ availability of normal receptors.
- Normal muscle origin, insertion, bones, ligaments, joints, arterial /venous supply etc.

Facilitation Questions

What could possibly go wrong to each of these structures and produce problems with muscle contraction?

- Normal nerve fibres → inflammation, injury,
- Normal skeletal muscles → injury, tear, inflammation,
  - Actin, myosin, trponin, trepomyosin molecules → decreased sensitivity to Ca, malstructure/function.
  - Ca2+ (ion concentration) → interference with the release of Ca2+, lack of sensitivity to released calcium.
  - Adenosin triphosphate, glucogen, creatine phosphophate → exhaused, decreased.
- Normal neuromuscular junction.
  - Vesicles and chemical transmitters → damaged vesicles, lack of chemical transmitter, rapidly destroyed.
  - Receptors/ availability of normal receptors → lost receptors/damaged, occupied by other substances or antibodies).
- Muscle origin, insertion, bones, ligaments, joints, arterial /venous supply etc → pathological problem (fracture, anomaly, tear, injury, blocked arteries etc).

Further Questions

- Any history of associated pain in muscles/joints?
- Any history of tingling or numbness anywhere?
- Any problems with her vision or swallowing?
- Any history of muscle weakness in the morning?
- What does she mean by being tired?
- Any stress at home or work?
- Are there any other symptoms?
- Any past investigations or treatment?
- Any family history of a similar problem?

Please Read The History

History

Rachel feels that she is having trouble completing her daily work. She says, "my arms seem to become weak after placing a few books on bookshelves. I have to stop every few minutes and take some rest in order to regain strength and become able to continue putting books on shelves. I do not know what is wrong with my arms. In the morning when I walk up I am much better, but as I start carrying things and using my arms I feel they are weak and I need some rest before I become able to carry things. I feel this particularly when I need to raise my arms like when I put books on shelves, hang clothes out on clothesline, or comb my hair.

Rachel also finds it difficult to climb the stairs. She has to take some rest before being able to continue. She does not have shortness of breath or pain. These changes made her feel down and frustrated as she does not know what is wrong with her.

On further questions from Dr Shenwan, Rachel says, "I believe the weakness has been coming gradually over the last 9-12 months. I have no pains in my arms, legs or anywhere else." Recently she noticed drooping of her right eyelid, usually this occurs around the end of her daily work. She has no problems with swallowing and does not have tingling or numbness.

History (Continue)

Past Medical History

Never admitted to hospital.

Allergy and Medication

Nil

Family History

Nothing significant

Tobacco and Alcohol

Nil

Social History

She has been working as a librarian-assistant for over 14 years, and in the last 7 years in Saudi Arabia. She is happy in her workplace and has no problems with her colleagues. She likes her work. Rachel is married and has one child aged 10 years. Her husband is with her and works as a nurse in the same hospital. They have no financial problems and happy as a family.

Discussion Questions

- Are there any difficult words you do not understand?
- List the key information in this progress.
- Identify any new problems and add to your list.
- For each new problem make a list of how it may be caused (generate hypotheses).
- What body system would you like to examine to help you in refining your hypotheses?

New Words

- Tingling or numbness.
- Frustrated.

New Problems

- Have trouble with her daily work for the last 9-12 months.
- Arms seem to become weak after placing a few books on shelves.
- She has to stop every few minutes and take some rest in order to regain strength.
- In the morning she is much better.
- She experience similar trouble when she hang clothes out on clothesline or comb her hair.
- She has difficulty to climb the stairs. No shortness of breath.
- No pain anywhere.
- Drooping of her right eyelid, usually at about the time leaving home.
- No tingling or numbness.
- No problem with swallowing.
- She does not drink or smoke.
- Happy at work. No problems at home.

Hypotheses

1. **Feels tired (usually after midday):**

- Muscle problem e.g., muscle fatigue, myopathy, muscle inflammation, muscle tear. o/+
- Nerve problem e.g., inflammation, lesion. ?/+
- Neuromuscular junction dysfunction (e.g., problem with receptors, problem with chemical transmission). ?/++
- Depression/anxiety/worries/stressed. o/o
- Lack of sleep. o/o
- Low blood glucose level. ?/+
- Heart/lung/liver/kidney problems./o
- Anaemia. +/o
- Does not like her job. /o
- Overloaded with tasks at home and at work. ?/o
- Mental tiredness. ?/o/+

Hypotheses

2.Unable to continue:

- Pain. /o
- Muscle fatigue. ?
- Ligament problem./o (does not explain problem in legs, arms and eyelids)
- Muscle tear. /o (does not explain problem in legs, arms, and eyelids)
- Decreased oxygen supply to muscles. ? (she has no pain)
- Accumulation of lactic acid etc in the muscle. ?/o (she has no pain)
- Nerve problem. (does not explain proximal weakness)
- Muscle problem. ? /+
- Neuromuscular junction problem. ?/+
- Heart/lung/liver/kidney problem. o/oo
- Anaemia ? / o
- Not used to do this job for long hours (unlikely)

Hypotheses

3. Drooping of her eyelids:

- Nerve problem (e.g., nerve tear, inflammation) /o
- Muscle problem (e.g., myopathy, inflammation, fatigue). /o/+
- Neuromuscular problem:
  - Nerve axon. ?/o
  - Synaptic vesicles ?/o
  - Chemical transmitter ?/+ (can explain weakness after repeated exercise)
  - Nicotine acetylcholine receptors. ?/+ (can explain weakness after repeated exercise)
  - Sarcolemma membrane. /?o

Please Read The Clinical Examination

Clinical Examination

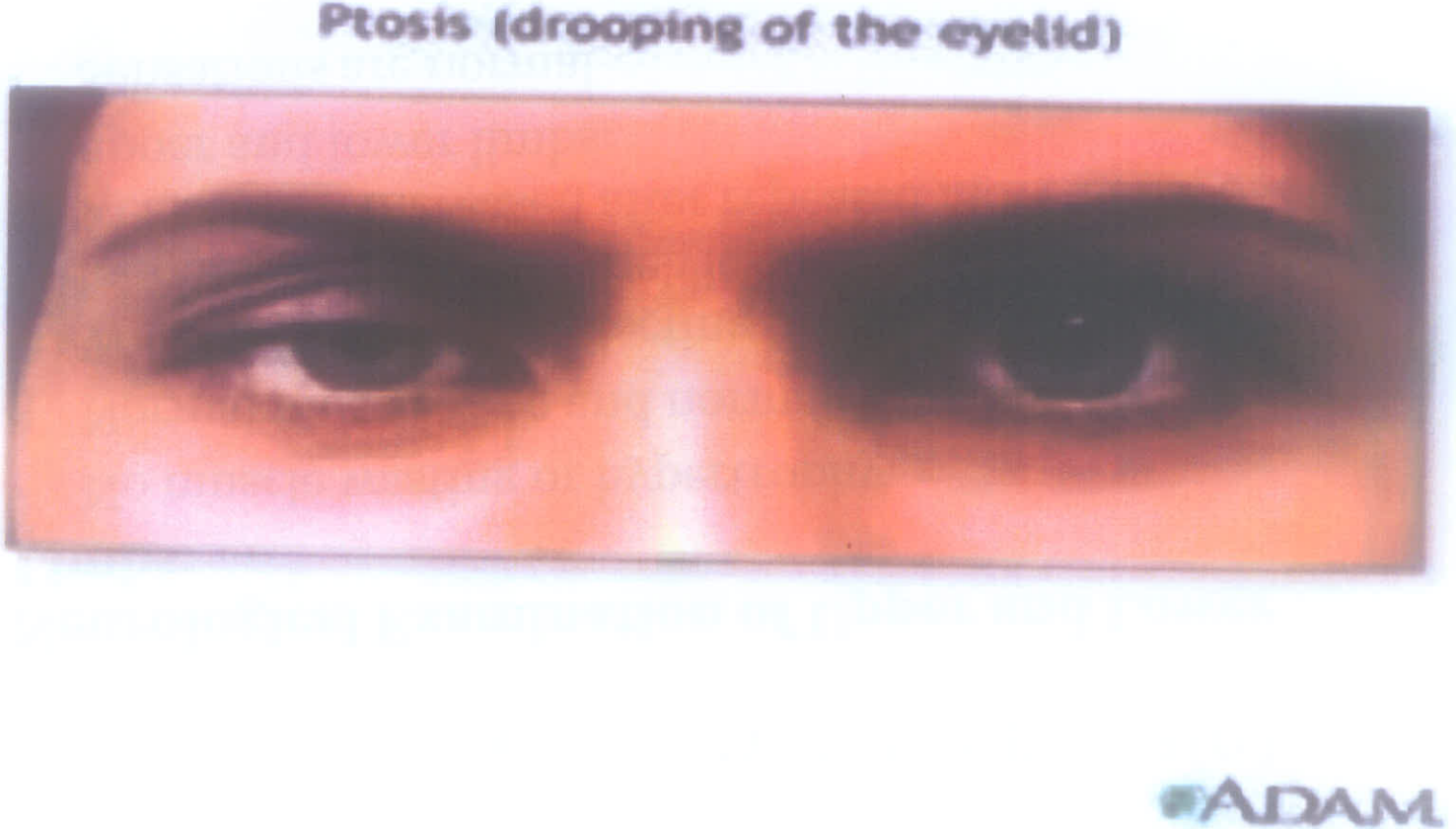
Rachel looks well. She has no pallor.

Vital signs	Rachel	Normal range
Pulse rate	88	60-100 /min
Blood pressure	120/80	100/60- 135/80 mmHg
Temperature	36.8 °C	36.6-37.2 °C
Respiratory rate	18	12-16/min

Eye Examination:

- She has ptosis of her right eyelid (upper eyelid sits lower than normal).
- Her ptosis increases when asked to follow with her eyes the doctor's examining finger moving up and down in front of her face.
- Eye movements: normal.

Clinical Examination



Source of image: http://nanda-nursing.blogspot.com/2011/05/nursing-care-plan-for-myasthenia-gravis.html

Clinical Examination (continue)

Neurological Examination of Upper and Lower Limbs:

- No muscle wasting or hypertrophy.
- Normal muscle tone and normal reflexes.
- Weakness is mainly affecting her proximal muscles (shoulder girdle) and (pelvic girdle) muscles. The weakness is increased after repeated movements of her upper and lower limbs.
- Sensations are normal

Examination of the Cardiovascular and Respiratory Systems:

- Normal

New Terms

- Ptosis.
- Muscle wasting.
- Muscle hypertrophy.
- Muscle tone.
- Muscle reflexes.
- Proximal muscles.

Discussion Questions

- List the key information in this progress.
- Identify any new problems and add to your list.
- For each new problem make a list of how it may be caused (generate hypotheses).
- What are your learning issues?

Refining Hypotheses

Most likely:

The presence of proximal muscle weakness on repeated exercise together with ptosis (occur a few hours after activity) as well as the lack of evidence for a nerve or muscle problem suggest the diagnosis of myasthenia gravis (neuromuscular junction problem).

Less likely:

- Nerve lesion/nerve inflammation.
- Spinal or central nervous system problem.
- Muscle tear.
- Muscle fatigue.
- Muscle inflammation.
- Myopathy
- Familial muscle disease.
- Joint problem.
- Ligament problem.
- Vascular problem.

Learning Issues

Learning Issues

- What are the possible causes for her inability to continue her work?
- Structures involved in the neuromuscular junction and the process of signaling transduction in normal nerves and muscles.
- The different possible mechanisms by which interference may occur with the conduction from nerve fibres to muscle fibres.
- The mechanisms by which skeletal muscle fibres contract.
- The role of investigations in confirming the diagnosis of neuromuscular junction dysfunction (myasthenia gravis)- reversibility of weakness.
- Pharmacology of drugs used in the management of patients with neuromuscular problem (e.g., myasthenia gravis).
- How can we interpret the patient's symptoms and signs.

Tutorial Two

TUTORIAL TWO

Students will discuss their learning issues for 50 minutes. Then:

- What do we mean by proximal muscles?
- What is your refined hypothesis? Justify your view.
- Discuss the pathogenesis of Rachel's problem.
- What further investigations would you like to order to confirm your final hypothesis?

Please Read Progress 1

Progress 1

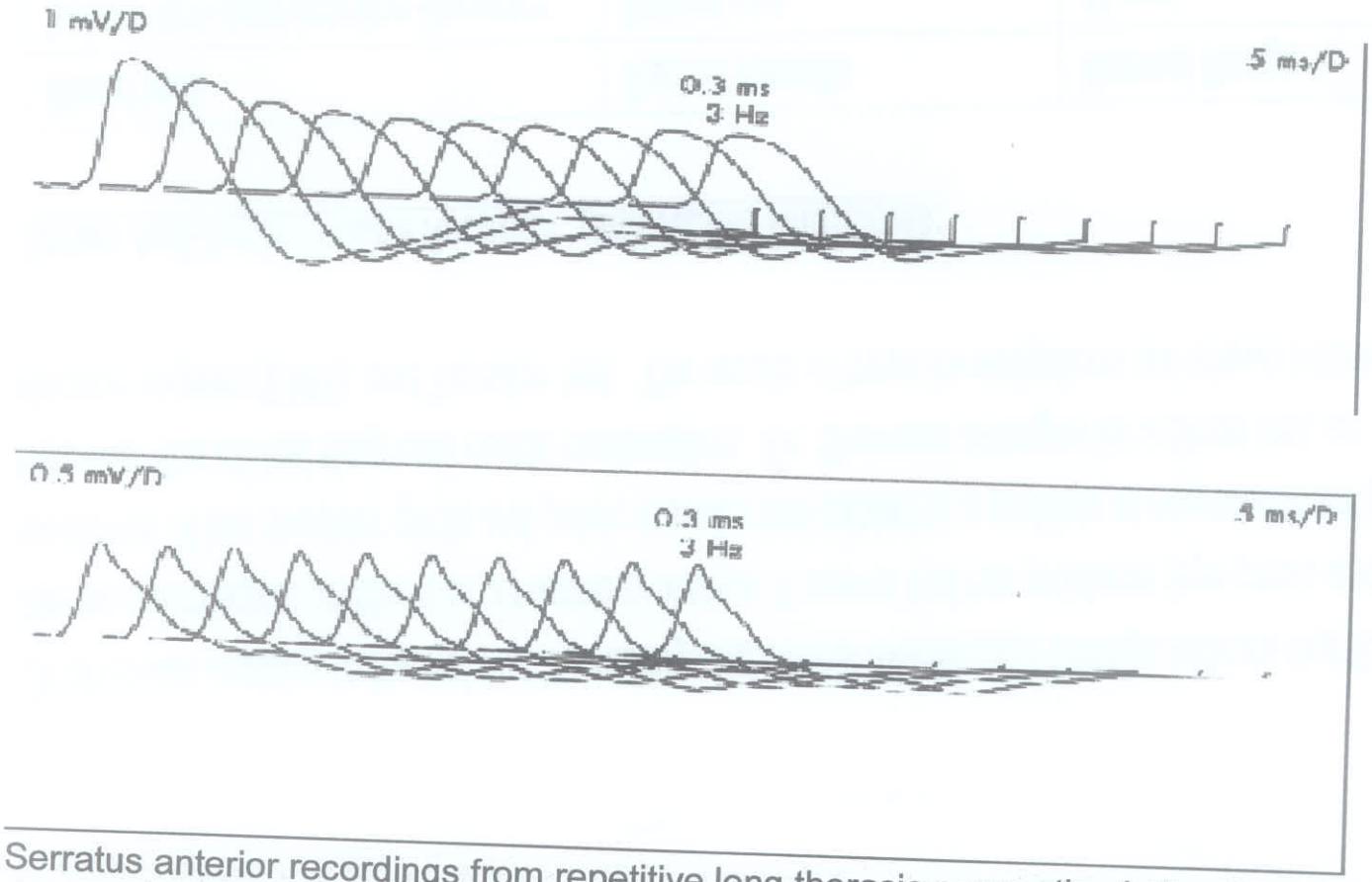
Dr Shenwan explains to Rachel that the history and clinical examination findings indicate that Rachel has no neurological problems or a muscle problems. It seems that her problems (eye ptosis and weakness of her shoulder girdle and pelvic muscles are related to a problem at neuromuscular junction. However, the clinical diagnosis needs confirmation. Dr. Shenwan arranges for a blood test, an electromyogram (EMG), and Tensilon test. The results of these investigations are shown below:

Serum Anti-Acetylcholine Receptor (anti-AChR) Antibodies:

Blood test	Rachel Results	Normal Range
Serum Anti-Acetylcholine Receptor Antibodies	Raised +++	Absent

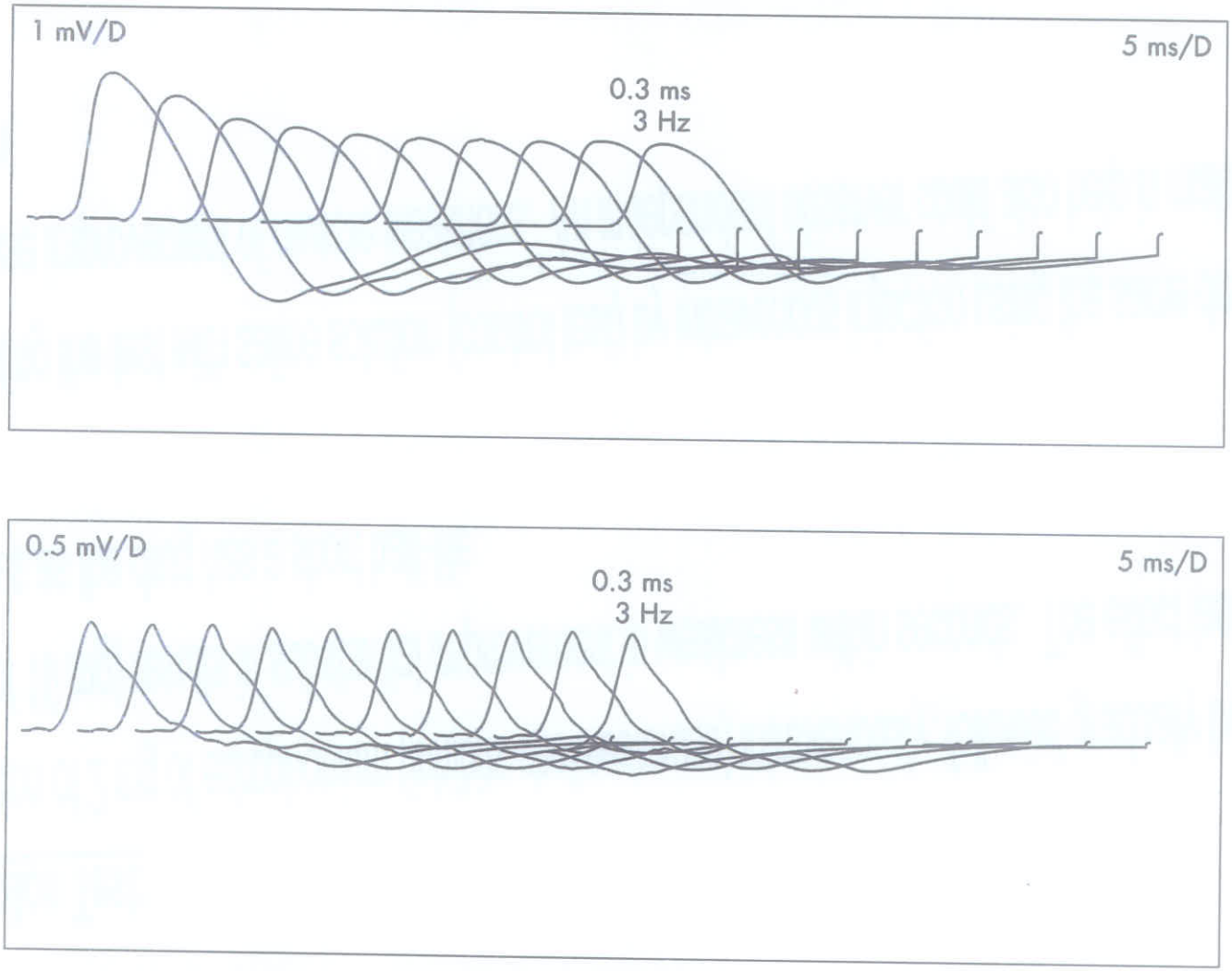
Electromyogram (EMG):

Repetitive stimulation of the long thoracic nerve; an EMG recorded from the serratus anterior muscle shows a decremental response. See recording and report below.



Serratus anterior recordings from repetitive long thoracic nerve stimulation (top trace) and A normal control (bottom trace). There is a decremental response of -33% in the patient compared to -4% in the control. Vertical gain and horizontal sweep are indicated in the tracings.

Serratus anterior recordings from repetitive long thoracic nerve stimulation (top trace) and a normal control (bottom trace).



Lo Y L et al. J Neurol Neurosurg Psychiatry 2003;74:379-381

Tensilon Test:

Injection of 2 mg of edrophonium (inhibits cholinesterase) intravenously, followed gradually by 8 mg (a total of 10 mg) results in substantial improvement in weakness within seconds. The effect lasts for few minutes as the drug has a short half-life.

Repeating the test with saline solution (control test) by intravenous injection using the same dose does not cause improvement of muscle weakness. An independent observer could also help in making the decision.

Discussion Questions

- Are there any terms that you do not understand?
- Summarise the key information that you have obtained from this progress.
- Interpret the changes observed from these three tests.
- Use the results of these investigations and your interpretation to refine your hypothesis.
- What are your management goals and management options?

New Words/Terms

- Ptosis.
- Electromyogram (EMG).
- Serum anti-acetylcholine receptor antibodies.
- Long thoracic nerve.
- Serratus anterior muscle.
- A decremental response.
- Edrophonium.
- Cholinesterase inhibitor.

Facilitation Questions

- How would you interpret her blood test results?
- How would you interpret Rachel's EMG findings?
- How would you interpret the edrophonium test results?
- On the bases of these investigations, what is your final hypothesis?
- What are your management goals and your management options?

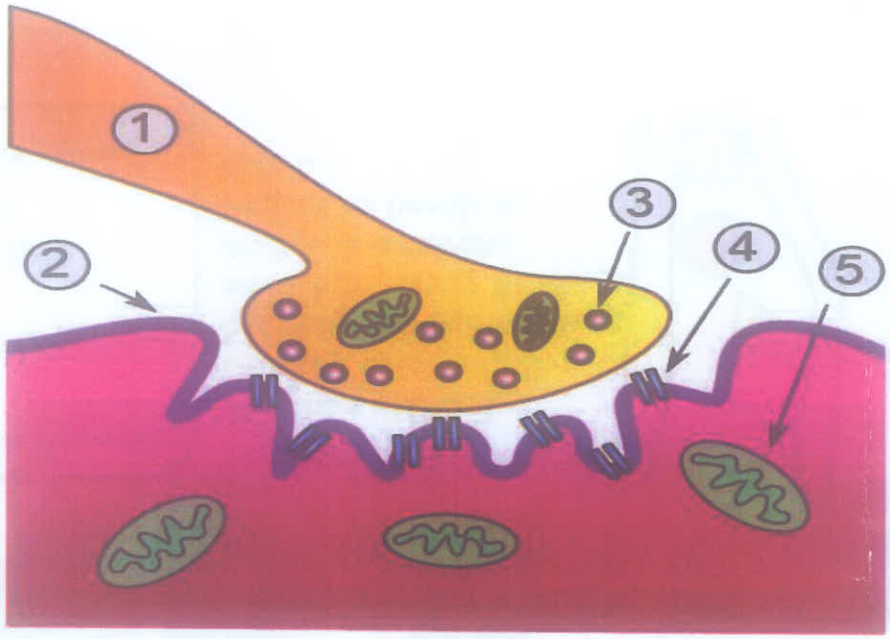
Please Read the Closure

Case Closure

Dr Shenwan explains the results of investigations to Rachel. She says, "the blood test confirms the presence of a high titer (level) of antibodies called Anti-Acetylcholine Receptor Antibodies. These antibodies occupy the receptors (entry doors) at the muscle end (known as acetylcholine receptors). As a result the number of free receptors (entry doors) are less available than normal. This change prevents a chemical substance responsible for conduction of nerve signals (electricity) known as acetylcholine from being attached to free receptors and becoming able to stimulate muscle contraction. Dr Shenwan uses a diagram to explain these changes to Rachel (see below).

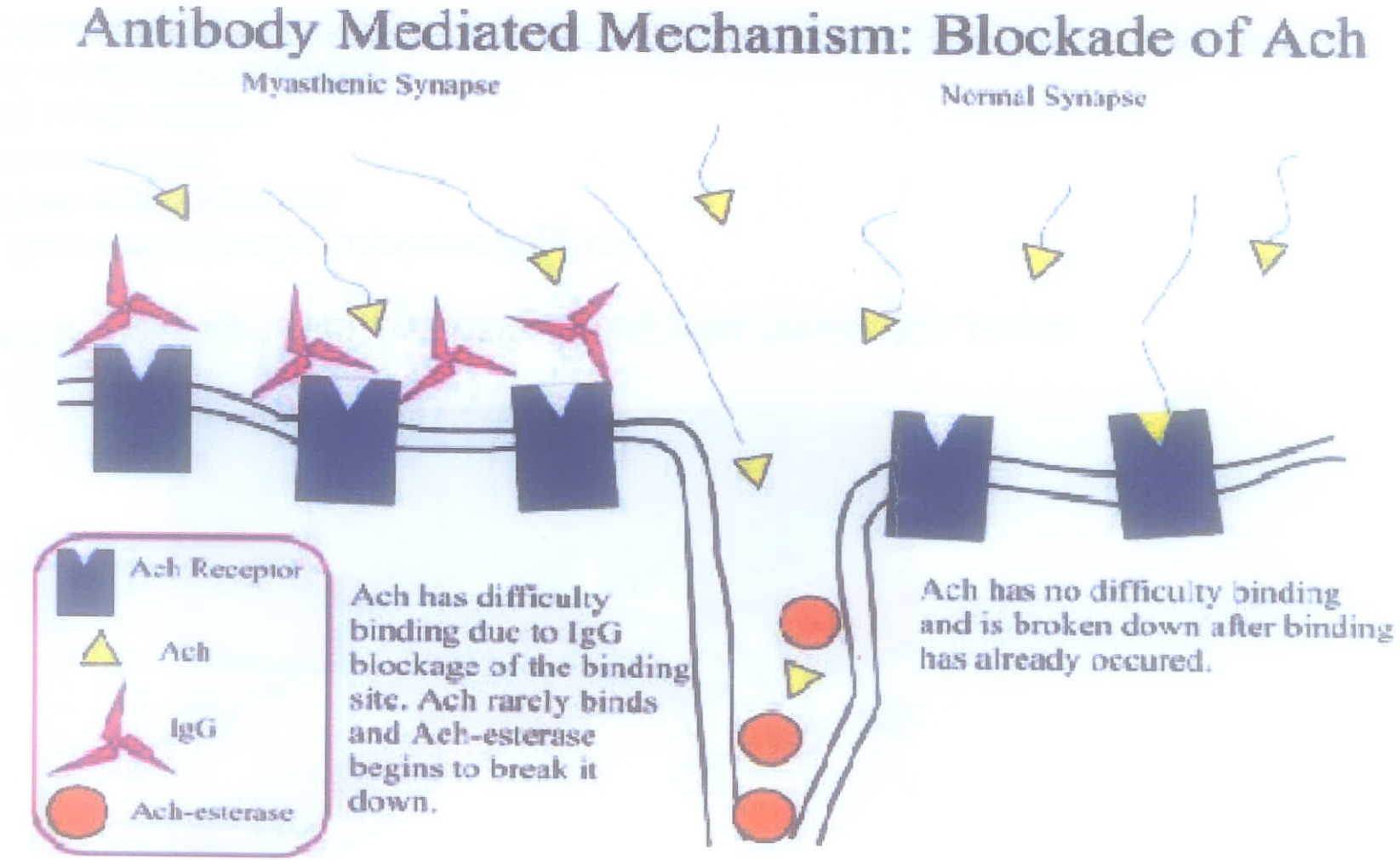
Dr Shenwan adds, "for reasons we do not know, the disease involves the muscles of the eyelids, muscles of swallowing, and muscles forming the shoulder girdle region and pelvic/thigh region. This explains the weakness you have with your arms during activities (e.g., put books on shelves, comb your hair, hang clothes to clothesline) and legs (e.g., climb stairs). Both the Tensilon test and the EMG changes confirm the diagnosis. This disease is known as Myasthenia gravis."

Dr Shenwan commences Rachel on Pyridostigmine (60 mg tablets) every 4 hours. The drug prolongs acetylcholine activity by inhibiting cholinesterase enzyme. The drug is metabolized rapidly (has a short half-life) and hence the need to take the medication every 4 hours. The dose of the drug is adjusted according to the clinical effects observed. Dr Shenwan warns Rachel about the side-effects of the drug including weakness, abdominal colic, and diarrhea. She asks Rachel to review if these symptoms appear.



Source of image: http://en.wikipedia.org/wiki/Myasthenia_Gravis

The neuromuscular junction comprises:
Presynaptic terminal.
Sarcolemma.
Synaptic vesicles.
Acetylcholine receptors.
Mitochondria.



Source of the image: http://www.macalester.edu/psychology/whathap/ubnrp/gravis/MGACH.html