CCM Specialty Board Tutorial
Neurological emergency

17th Dec 2013

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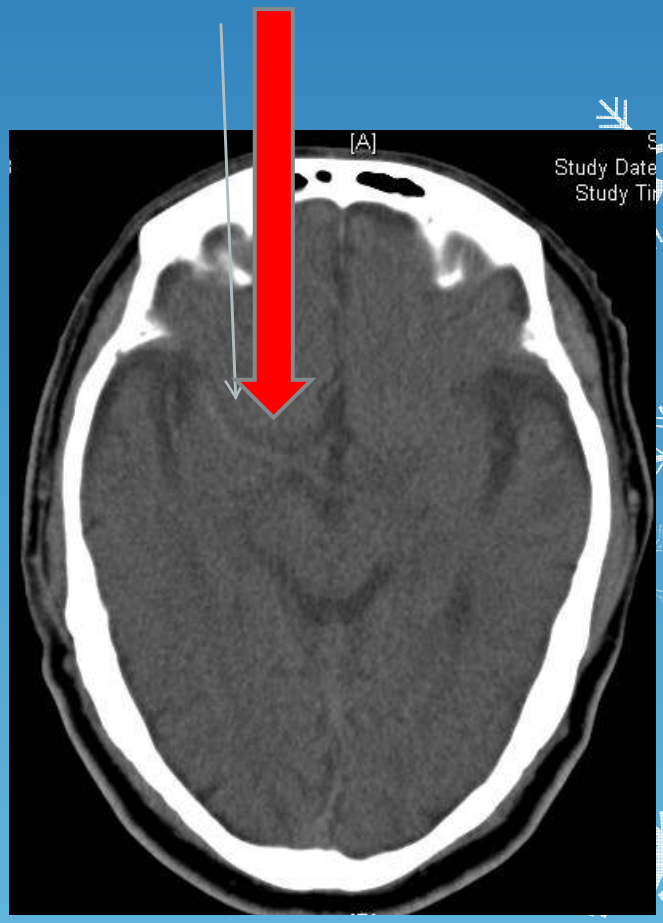
Case 1

- F/69
- Walks unaided, ADL independent
- Known DM, IHD on aspirin
- Sudden onset L sided weakness at 10am
- Arrived AED around 70 mins from symptom onset

- E4V4M5
- Dense L hemiplegia, power 1/5
- Gaze deviated to right side
- Neglect to left side

- Stroke
  - Right hemisphere problem

Dense MCA signal

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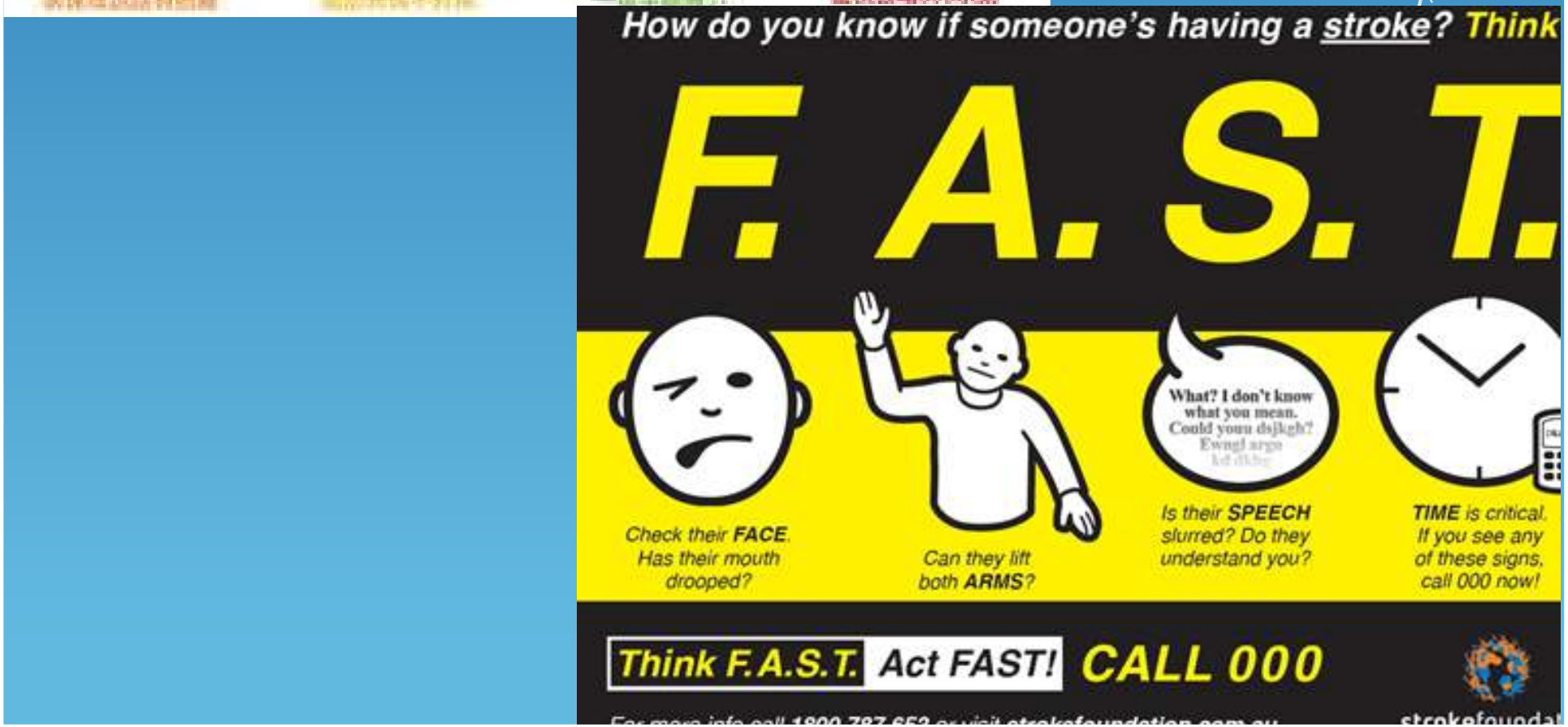

How do you know if someone's having a stroke? Think
F. A. S. T.
Check their FACE. Has their mouth drooped?
Can they lift both ARMS?
What? I don't know what you mean. Could youu dsjkgh? Ewwgl argo
Is their SPEECH slurred? Do they understand you?
TIME is critical. If you see any of these signs, call 000 now!
Think F.A.S.T. Act FAST! CALL 000

AHA/ASA Guideline

- Acute ischemic stroke presented within 3 hours should receive rtPA
  (Class I. Level A)
- Eligible patients should receive rtPA as soon as possible, within 60 mins of hospital arrival
  (Class I. Level A)
- Acute ischemic stroke presented within 3-4.5 hours from onset, should receive rtPA
  (Class I. Level B)

Emergency triage and evaluation

- Same as myocardial infarction
- Chain of survival concept
- Standardized stroke protocol and use of NIHSS

	Time frame
Door to ED physician	< 10 min
Door to stroke team	< 15 min
Door to CT initiation	< 25 min
Door to CT evaluation	< 45 min
Door to needle	< 60 min
Door to ASU admission	< 3 hours

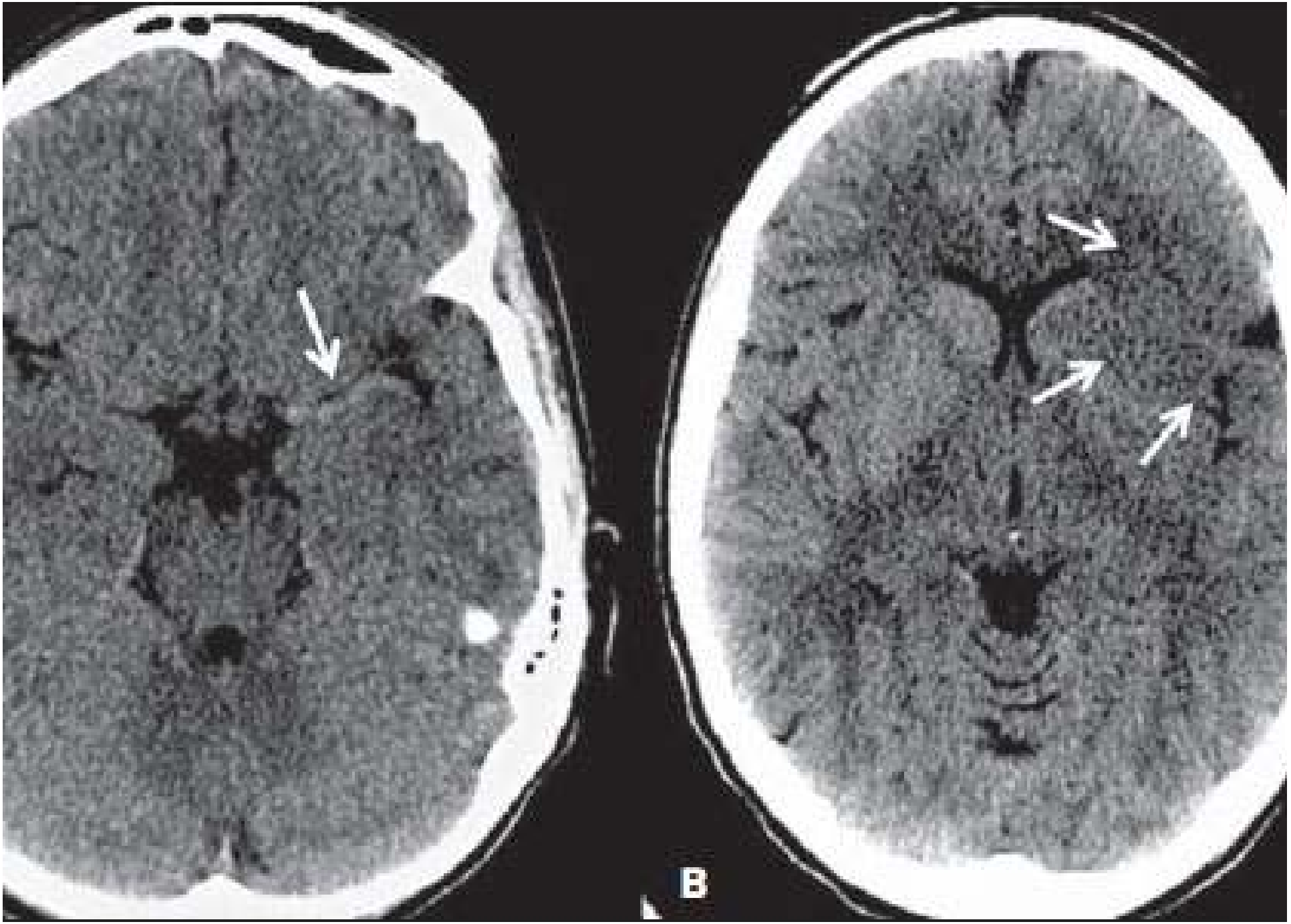
- Baseline blood tests, ECG, CXR are preferable but should not delay thrombolysis treatment

Neuroimaging

- Plain CT brain in most circumstances provides essential information for thrombolytic Rx
- To exclude hemorrhage, brain tumour etc.
- Helpful in predicting outcome and response to thrombolytic treatment

Neuroimaging

- Subtle early signs of vessels thrombosis: dense MCA sign, dot sign
- Early sign of ischemia: lenticular obscuration, insular ribbon sign, cortical ribbon sign, effacement of grey-white matter, sulcal effacement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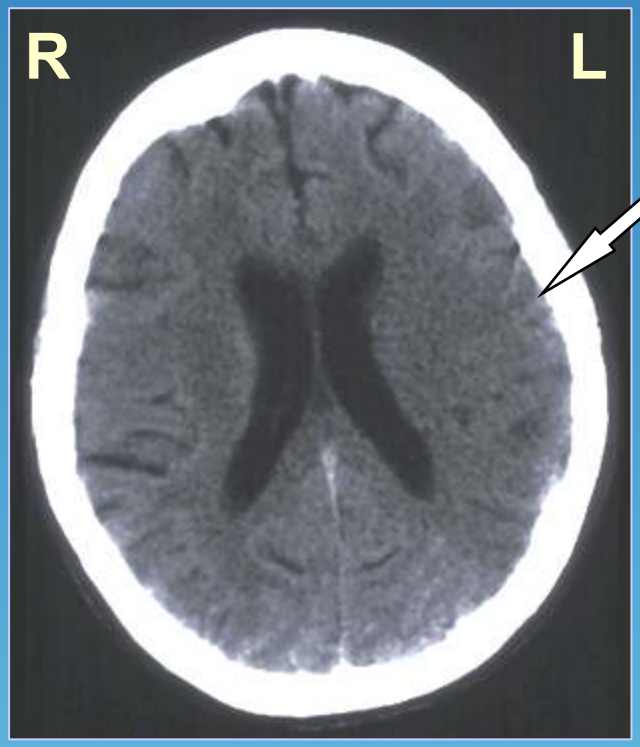
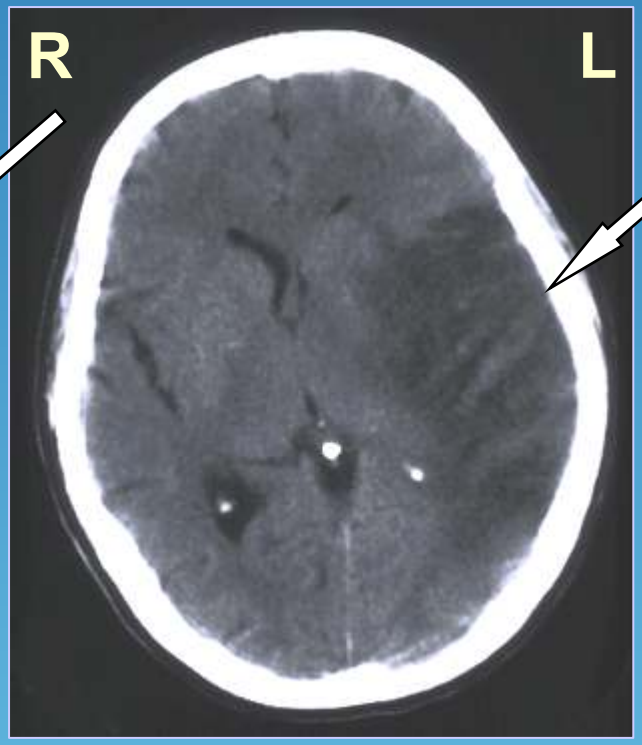
STROKE EMERGENCY BRAIN IMAGING:
NONCONTRAST CT SCAN

Acute (4 hours) Infarction



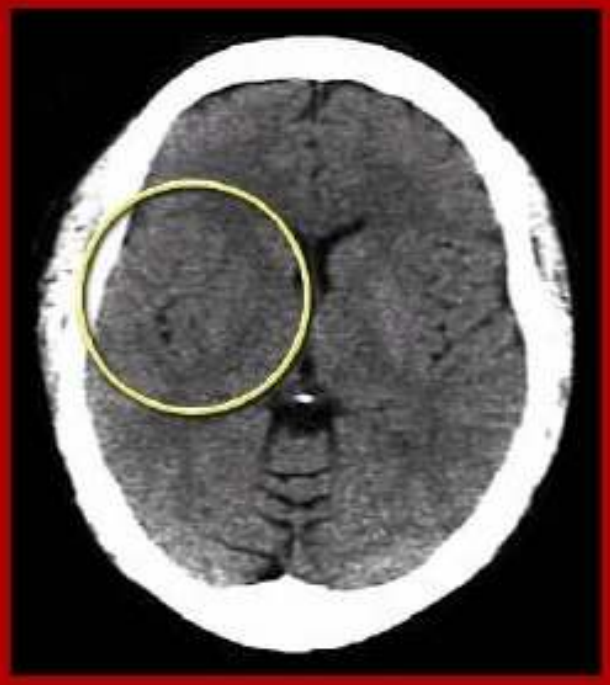
Subtle blurring of gray-white junction & sulcal effacement

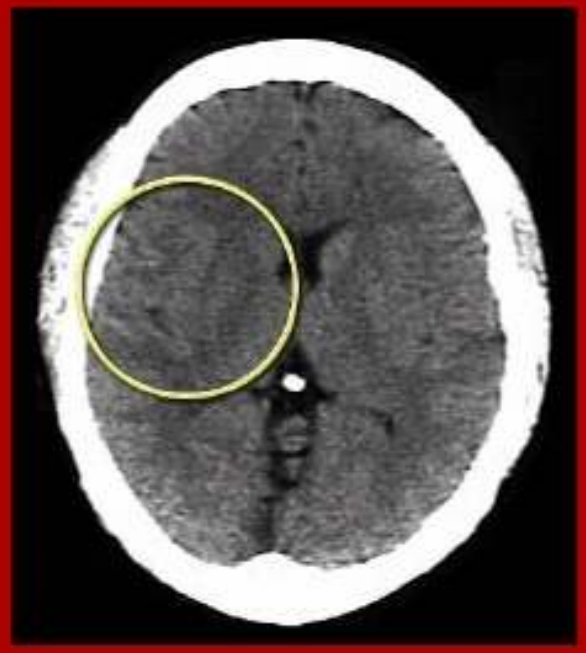
Subacute (4 days) Infarction



Obvious dark changes & “mass effect” (e.g., ventricle compression)

The scan exhibits subtle, hyperacute ischemic changes, including effacement of the insular ribbon and lentiform nucleus edema of the right hemisphere.





NINDS Study

The NEW ENGLAND JOURNAL of MEDICINE

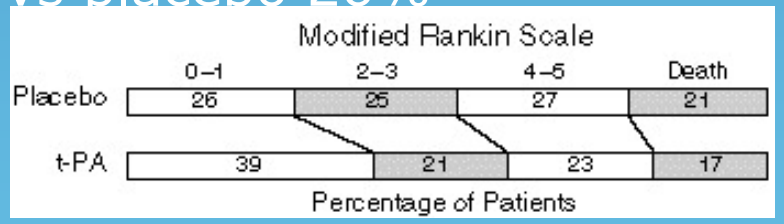
Tissue Plasminogen Activator for Acute Ischemic Stroke

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group

N Engl J Med 1995; 333:1581-1588 | December 14, 1995

- 624 subjects
- Age >18 with clinical diagnosis of ischaemic stroke causing a measurable neurological deficit up to 3 hrs of stroke onset
- Alteplase (rTPA) 0.9mg/kg

- Excellent stroke outcome (mRS 0-1) at 3 months: rTPA 39% vs placebo 26%
- Absolute benefit 13%
- **NNT = 7**



ECASS III Study

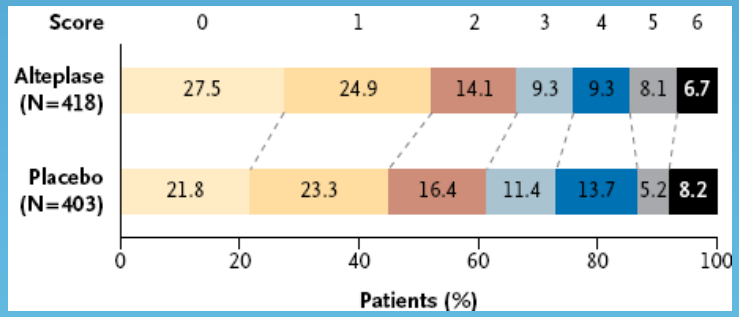
The NEW ENGLAND JOURNAL of MEDICINE

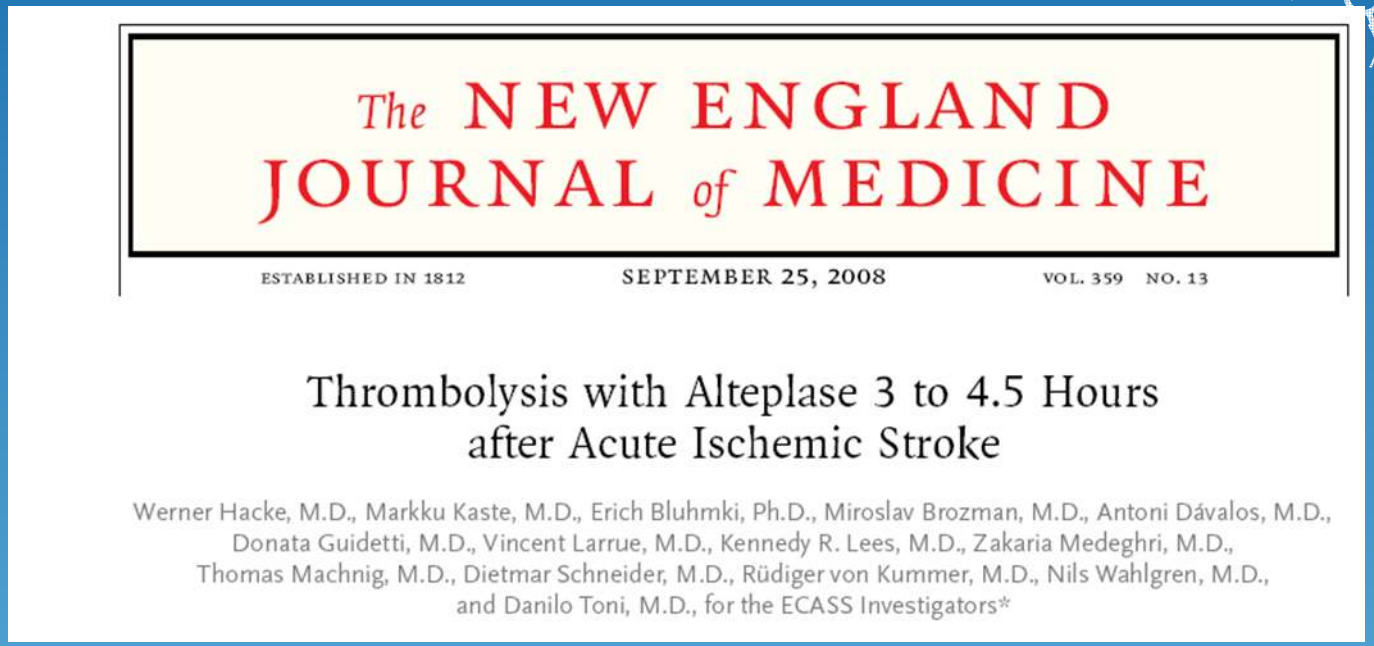
ESTABLISHED IN 1812 SEPTEMBER 25, 2008 VOL. 359 NO. 13

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

- 821 ischaemic stroke patients, with onset between 3 to 4.5 hrs, randomized to receive rt-PA or placebo
- Favourable stroke outcome (mRs 0-1) at 90 days
  rt-PA 52.4% vs placebo 45.2%, p = 0.04
- Absolute benefit = 7.2%, NNT = 14

Conclusion:
Intravenous rt-PA administered between 3 and 4.5 hrs after onset significantly improved outcomes in patients with ischaemic stroke





The NEW ENGLAND JOURNAL of MEDICINE

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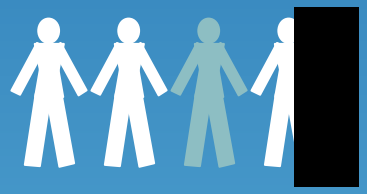
Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghri, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*

- IV rtPA at 3-4.5 hours
  - Additional exclusions criteria
    - age >80
    - Warfarin (regardless of INR)
    - NIHSS>25
    - Diabetes and stroke history
    - 1/3 MCA ischemic change

Number needed to treat

< 90 mins



NNT =3.5

≤ 3 h

NNT = 7

3-4.5 h

NNT= 14

What about patients with stroke onset >4.5 hrs?

Lees KR et al. Lancet 2010;375:1695-1703.

IV tPA: Pooled analysis of outcome vs. onset to treatment (OTT) time

Six randomized controlled IV tPA trials

2775 patients

0-6 h OTT

0.9 mg/kg (except ECASS I - 1.1 mg/kg)

Median NIHSS = 11 (moderate deficit)

The ATLANTIS, ECASS and NINDS rt-PA Study Group Investigators, Lancet 2004

Continued . . .

OTT	Odds Ratio for normal at 3 mo.	Hemorrhage
0-1.5 h	2.81	3.1%
1.5-3 h	1.55	5.6%
3-4.5 h	1.40	5.9%
4.5-6 h	1.15	6.9%

The ATLANTIS, ECASS and NINDS rt-PA Study Group Investigators, Lancet 2004

AHA Guideline Recommendations

IV tPA is recommended for selected patients who may be treated within 3 hours of symptom onset of ischemic stroke

- *Class I, Level A*

AHA Guideline Recommendations

IV tPA should be administered for those who can be treated 3-4.5 hours after symptom onset with similar exclusionary criteria as for within 3 hour window + age > 80, oral anticoagulant use, NIHSS > 25, history of stroke + DM

- Class I, Level B

Thrombolysis in the Elderly

Main worry is the risk of ICH

- Systematic review of 6 cohort studies found similar likelihood of symptomatic ICH OR 1.22 (95% CI 0.77-1.94)

- Three times higher odds of dying after thrombolysis for those > 80

Protocol for rtPA administration

- Informed consent
- Calculate total dose as 0.9mg/kg (not>90mg)
- Give 10% as bolus dose over 1 minute
- Rest over 1hour as infusion
- Maintain SBP <185mmHg and DBP <110mmHg

- Be alert for signs of ICH
  - Sudden increase SBP, deline in mental or neurostatus, severe headache
  - Repeat CT scan

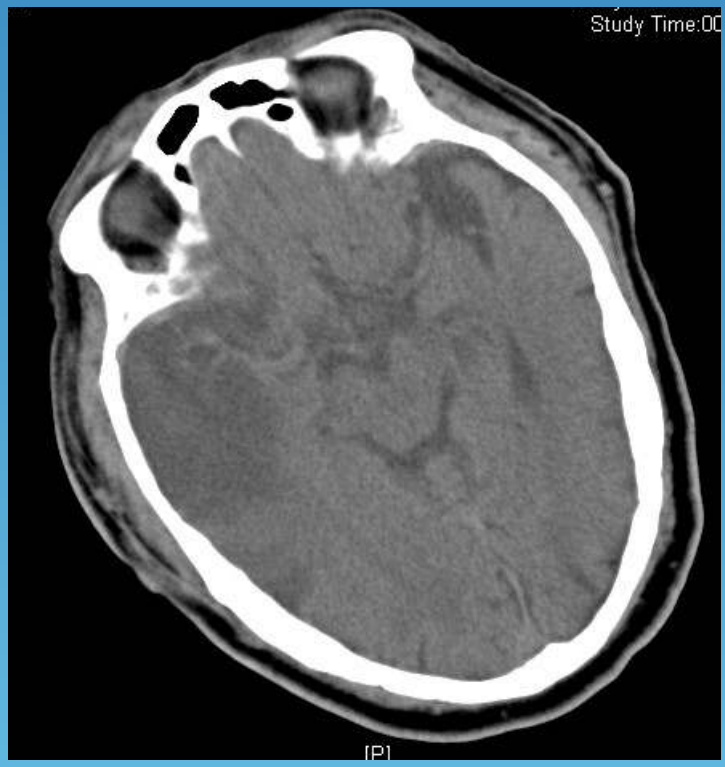
Key exclusion criteria for IV rtPA

- Stroke or significant head trauma <3 months
- GI/urinary tract hemorrhage <21 days
- Major surgery <14 days
- Arterial puncture at noncompressible site<7 days
- Hisotry of prior ICH
- Symptoms of SAH
- Active internal bleeding or acute trauma
- bp<>185/110 or requiring aggressive anti-HT agents
- Clear and large hypodensity on head CT
- INR >1.7, plt count <100

Post rtPA

- Good recovery
- Able to walk unaided at 3 months
- mRS 1

- Eventually found to have AF
- Started on dabigatran



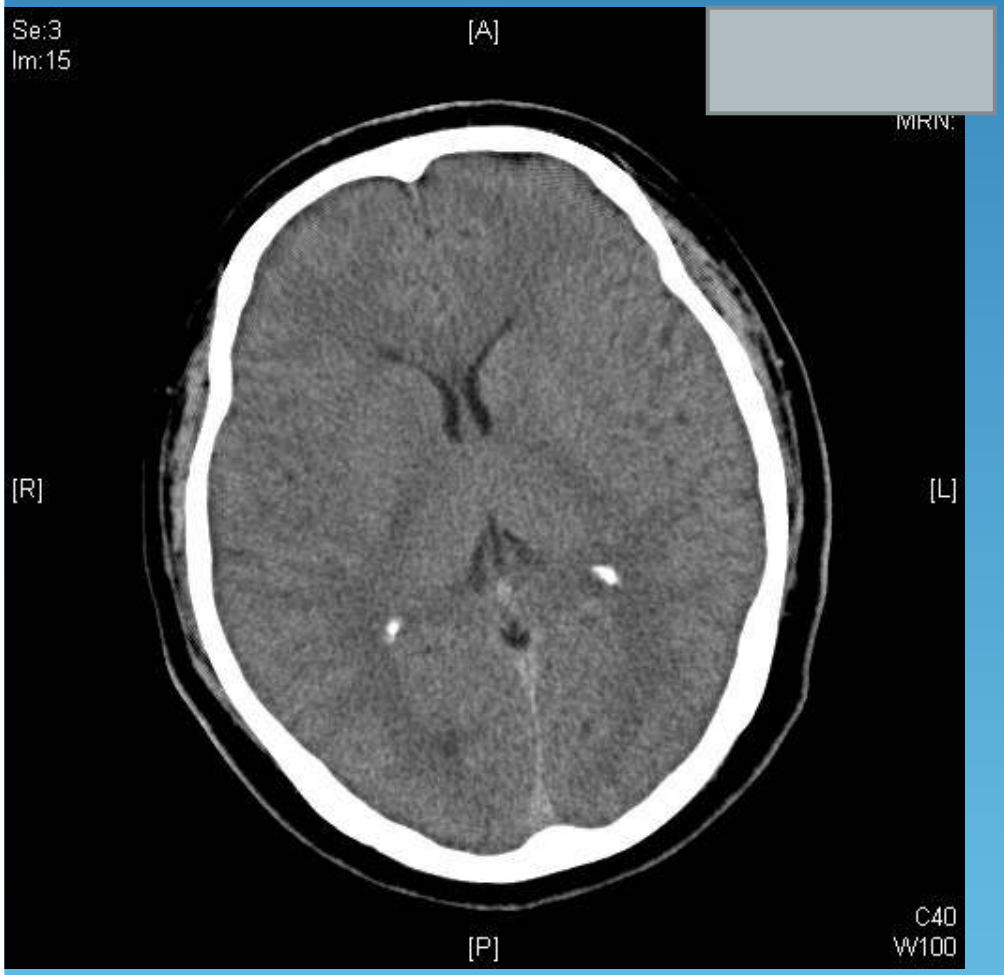
Case 2

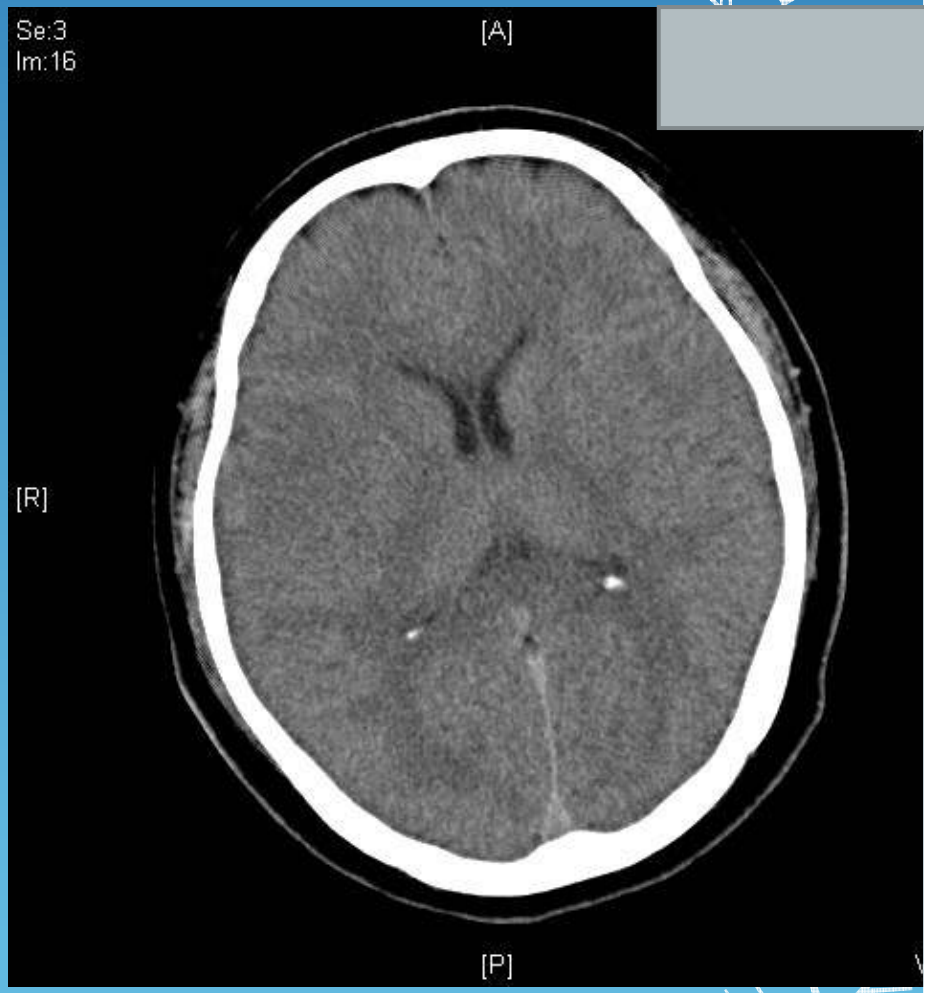
M/75

Chronic smoker DM HT

NIHSS 15

Needle time 145 min





Progress

- During infusion of rTPA, patient has surge of blood pressure of systolic>190mmHg with confusion
- What will you do?

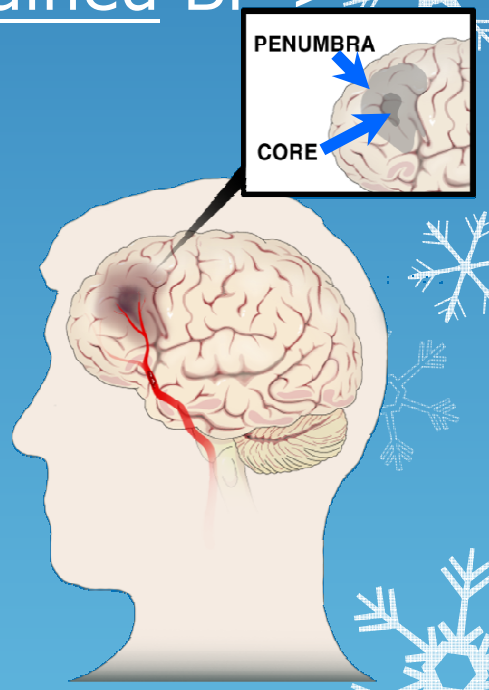
- A Stop rTPA
- B control blood pressure
- C repeat CT scan

MAY LOWER BP SLIGHTLY PRE T-PA

MUST PICK AN UPPER LIMIT TO TREAT—220/120 IS ONE OPTION

If all t-PA criteria met except sustained BP > 185/110:

- Calm patient, empty bladder
  - **SBP > 220 or DBP > 120** } **No BP med, No t-PA**
  - **SBP > 185 and ≤ 220 or DBP > 110 and ≤ 120** } **Lower BP pre-t-PA**



Avoid excessive lowering of BP just to give t-PA—
"Don't kill the penumbra to save the penumbra"

Blood pressure control after rTPA given

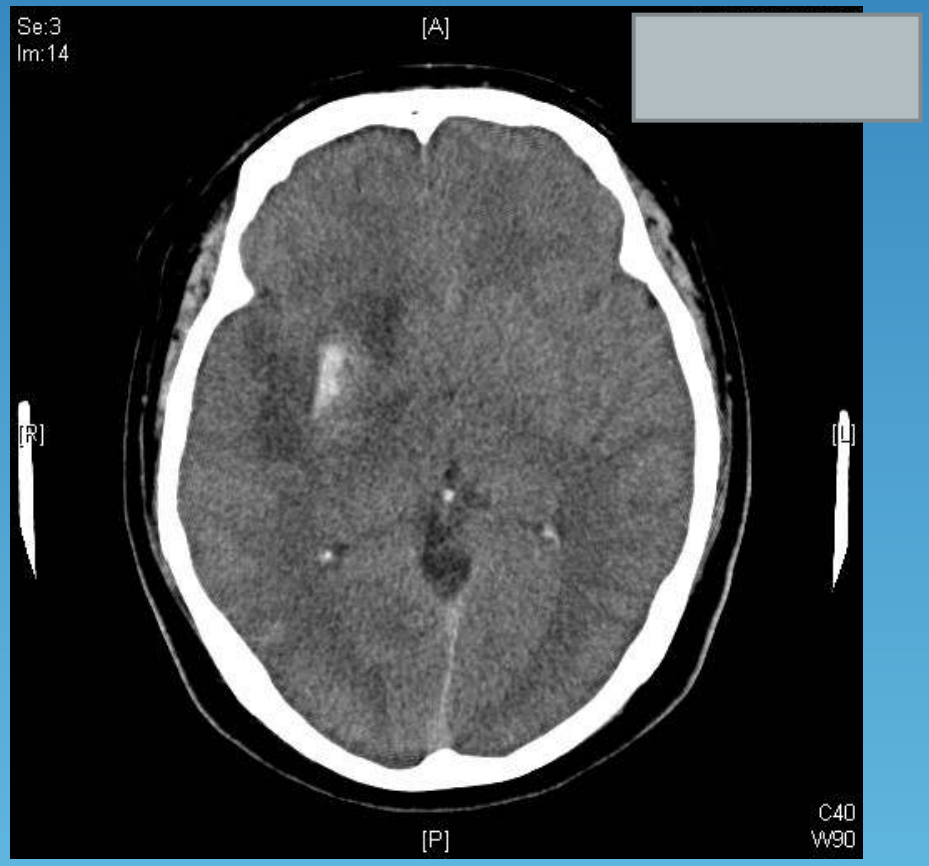
Aim to keep systolic bp<180 and diastolic bp <105

- If diastolic blood pressure 105–120 mm Hg or systolic blood pressure
180–230 mm Hg
  10 mg labetalol over 1–2 min
  May repeat or double the dosage or labetalol every 10 to 20 minutes to a maximum dose of 300 mg or
  continuous labetalol infusion given at a rate of 2–8 mg/min.

- If diastolic blood pressure 121–140 mm Hg or systolic blood pressure
230 mm Hg,
  IV labetalol as aboved
  consider use of infusion of sodium nitroprusside

- If diastolic blood pressure 140 mm Hg, start infusion of sodium nitroprusside at a rate of 0.5 mg/kg/min.

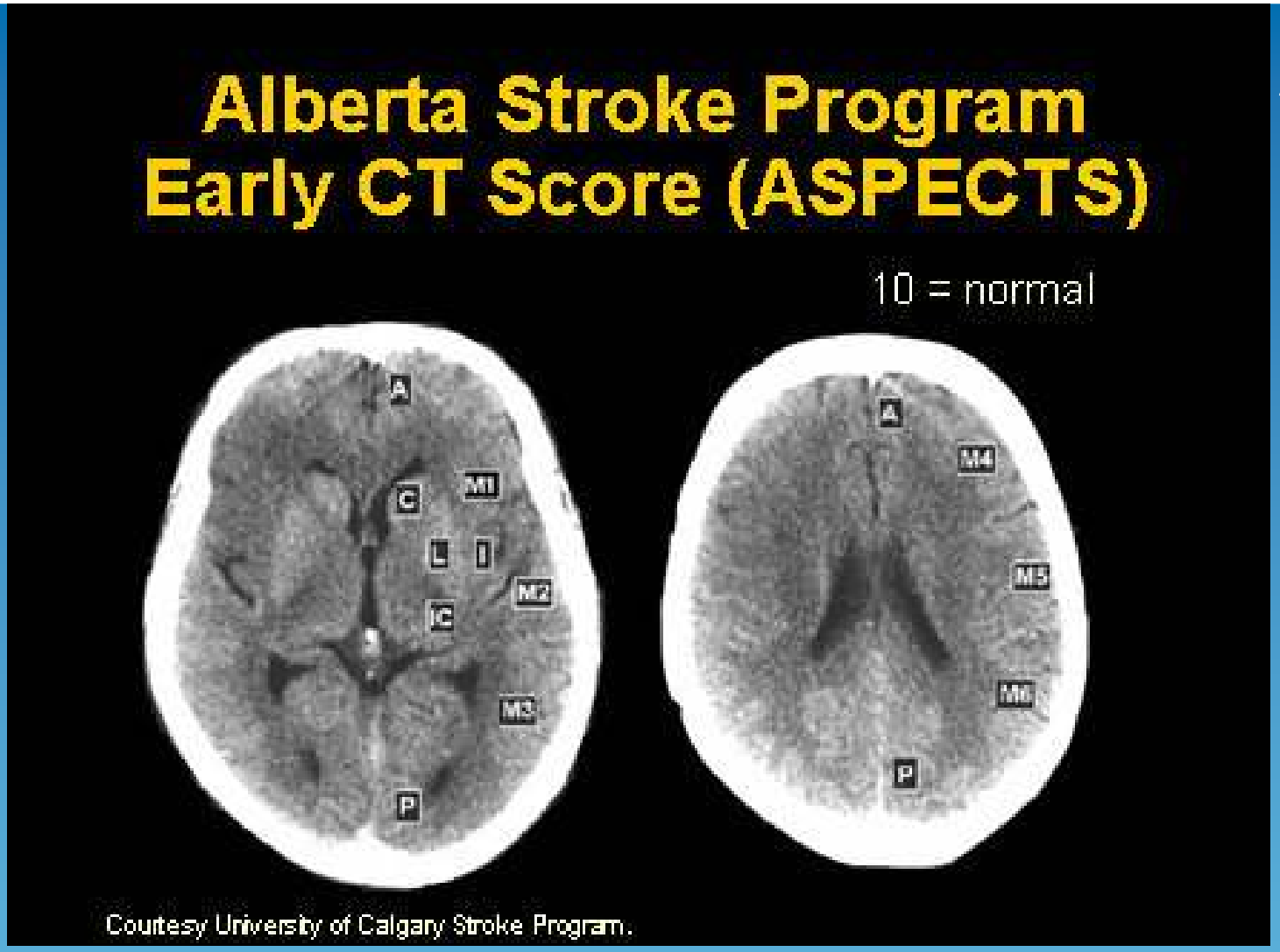
Repeat CT brain



Complications after rTPA Hemorrhagic Transformation

- Hemorrhagic transformation
  - Occur in around 6-7% of patients with symptom
  - Usually occur in the first few hours (half life of rtPA is aproximately 45 minutes
  - Risk factors:
    - symptom severity
    - early infarct signs on admission brain CT
    - advanced age
    - elevated blood pressure
    - longer the time treatment window

Alberta Stroke Program Early CT Score (ASPECTS)



- Use of ASPECT score to determine bleeding risk

  Deduct 1 mark if hypodensity in each region, score <= 7 signify severe ischemia

  - rtPA should be withheld if early infarct sign > 1/3 MCA territory, as risk of hemorrhage is high

Management of hemorrhagic transformation

- Discontinue thrombolytics
- Type and screen
- 4 to 6 unit of FFP with platelet conc
- Possible consider recombinant factor VII or prothrombin complex citrate

24 hour after infusion of rTPA

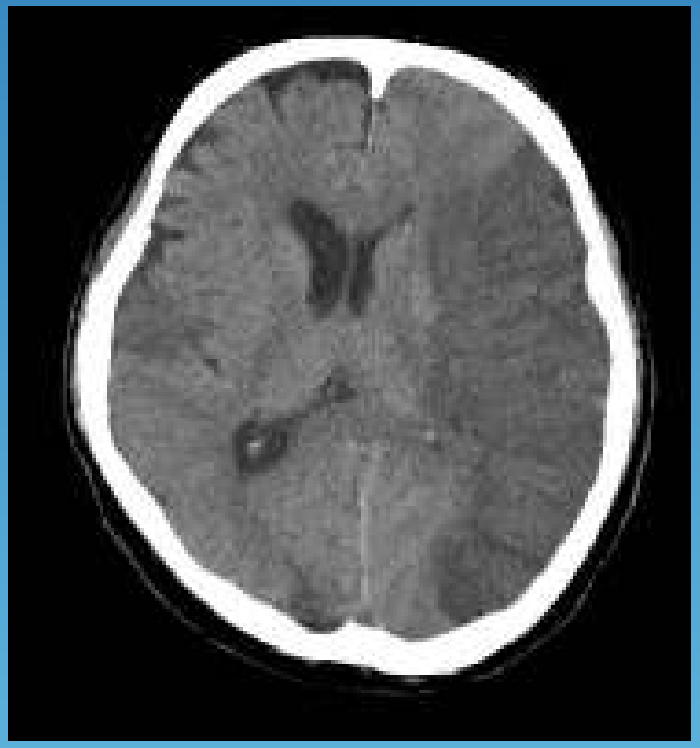
- Blood pressure well control after a dose of labetolol
- GCS remain stable 14/15
- NIHSS 12

Case 3

- F/75
- HT DM
- Last seen well the day before
- Admitted early morning found by relative to have sudden onset decrease conscious status

Case 3

- GCS E4V1M5
- PE showed dense right side hemiplegia (0/5)
- Global aphasia
- Gaze preference to left side
- Developed fever



Management

- rTPA should not be considered
  - Last seen well the night before
  - Extenive involvement of the infarct size

Management

- Admit ASU
  (Class I. Level A)

- Optimize cerebral blood-flow
- Lie flat and bed rest to optimize cerebral blood-flow
- Hypovolemia should be corrected with IV NS *(Class I. Level C)*
- *Bp target< 220/120 if possible, except…….*
  - *Exception:*
  - *Aortic dissection*
  - *Acute myocardial infarction*
  - *Acute pulmonary edema*
  - *Acute renal failure*

Guidelines for the early management of patients with Acute Ischemic Stroke. AHA. 2010

Antiplatelet

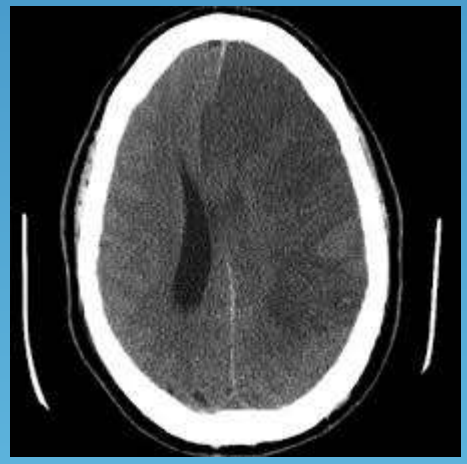
- Administration of oral aspirin (initial dose 325mg) within 24 to 48 hours after stroke onset is recommended
  (Class I. Level A)

- Aspirin as adjunct therapy to IV fibrinolysis is not recommended
  (Class III. Level C)

Guidelines for the early management of patients with Acute Ischemic Stroke. AHA. 20

progress

- On day 4, patient has sudden onset decrease in GCS to V1M3E3
- Repeat CT brain



Malignant MCA syndrome

- Failed recanalization of rTPA
- Large hemispheric infarctions involving the middle cerebral artery territory (malignant MCA syndrome)
- Large cerebellar infarctions
- Mass effect caused by ischemic infarcts typically peaks 3-5 days

Management of raised ICP

- Monro kellie
  - Skull is a rigid container
  - CPP= MAP-ICP
  - ↑ ICP with long duration of ↑ ICP → poor outcome

Malignant infarction

- Aggressive medical measures (e.g. mannitol, hyperventilation) in treatment of malignant brain edema remains not well established *(Class IIb. Level C)*

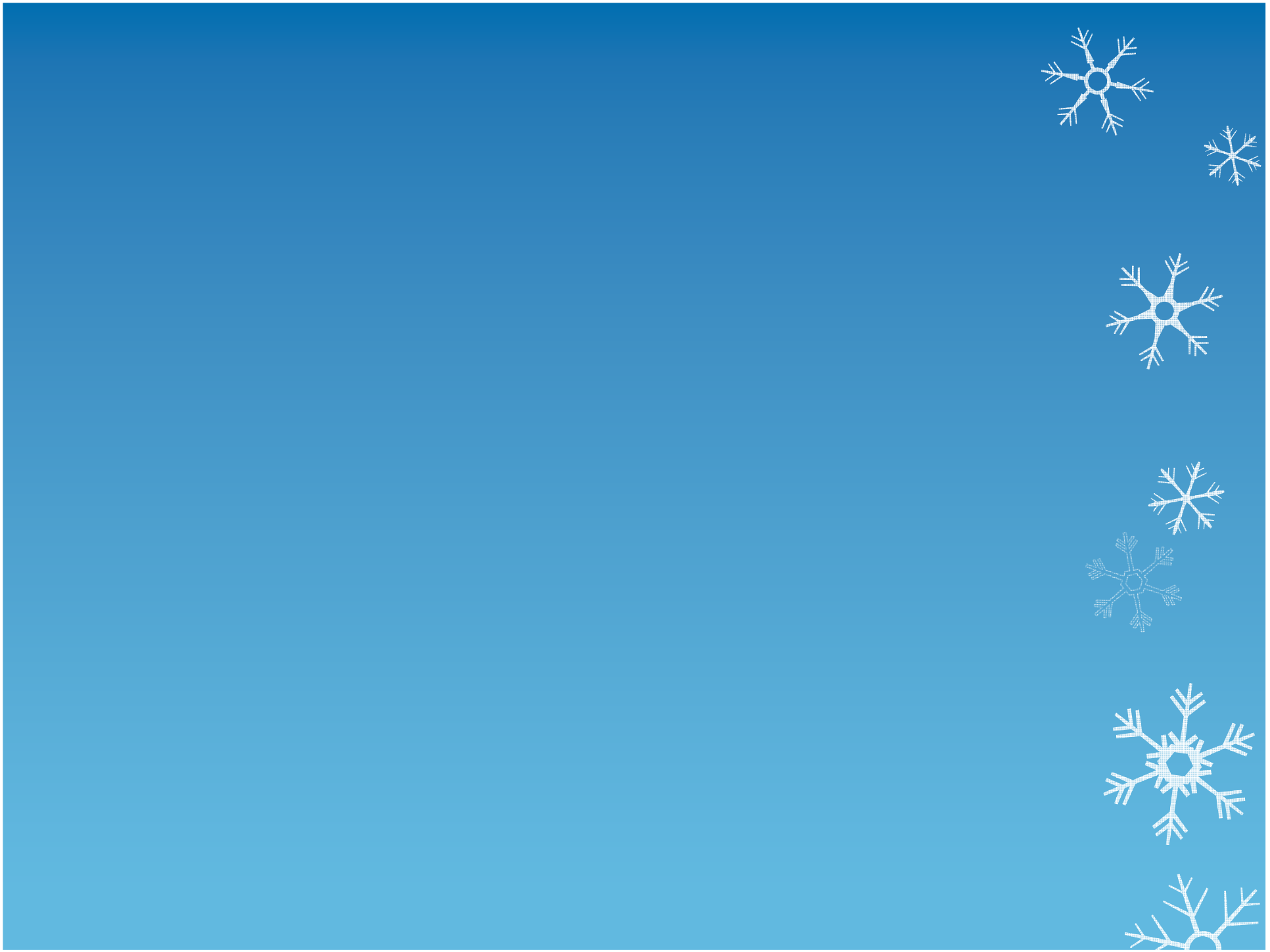
- Decompressive surgery
  - effective for cerebellar infarction to prevent herniation and brainstem compression *(Class I. Level B)*
  - potentially lifesaving for cerebral malignant edema *(Class I. Level B)*

- IVD is useful for acute hydrocephalus *(Class I. Level B)*

Guidelines for the early management of patients with Acute Ischemic Stroke. AHA. 2010

Predictors for decompressive surgery favorable outcome

- Younger age
- Nondominant hemisphere
- Higher initial GCS score and lower ICP
- Early surgery



Case 4

- A 28 year old man presents for progressive difficulty walking
  - Flu symptoms 2 weeks ago
  - Recently developed low back pain and numbness in his feet
  - Difficulty standing and climbing stairs, tripping frequently

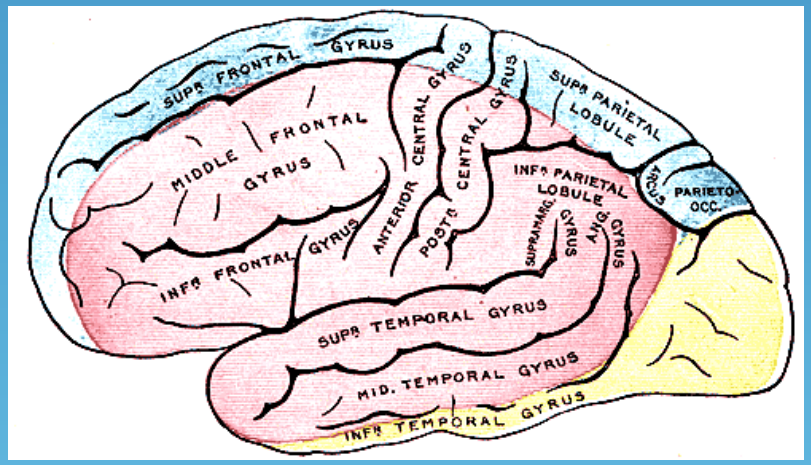
- Physical Examination
  - Vitals stable
  - Cranial nerves normal
  - Mild hypotonia, normal muscle bulk; mild distal LE weakness
  - Distal sensation reduced symmetrically to all modalities but normal in the trunk
  - tendon reflexes absent over upper and lower limbs
  - Slapping gait with bilateral foot drop

Case 4

- Can you localize the lesion?

Localization

Central nervous system

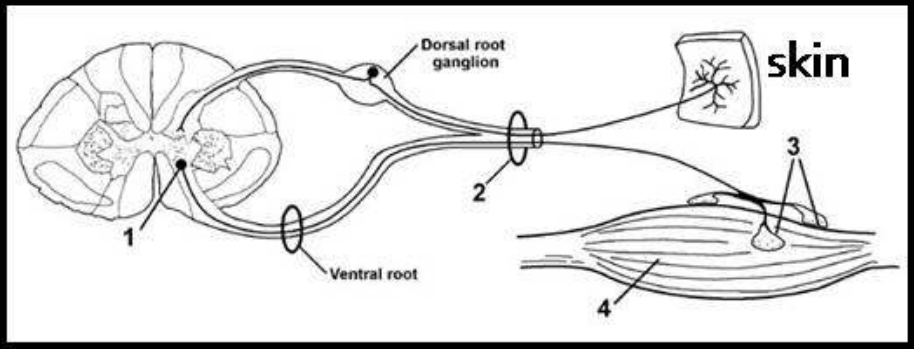


Peripheral nervous system

- Nerve root
- Plexus
- Peripheral nerve
- Neuromuscular junction
- Muscle

The most important step in neurologic localization is differentiating a *central nervous system* lesion from a *peripheral nervous system* lesion

Peripheral nervous system motor disorder



1. Anterior horn cell
2. Peripheral nerve*
3. Neuromuscular junction
4. Muscle

*motor and sensory

Peripheral nervous system motor disorder

- Anterior horn cell disorder
  - Motor neuron disease
  - Spinal muscular dystrophy (Genetic)
  - Polymyelitis (Acquired)
- Peripheral nerve disorder
  - Gullian Barre disease
  - Chronic inflammatory demyelinating disease
    - MGUS IgG/A/M
- Neuromuscular disorder
  - Myasthesia gravis (post-synatic disorder)
  - Lambert Eaton disorder (pre-synatic disorder)
- Muscle disease

Localization

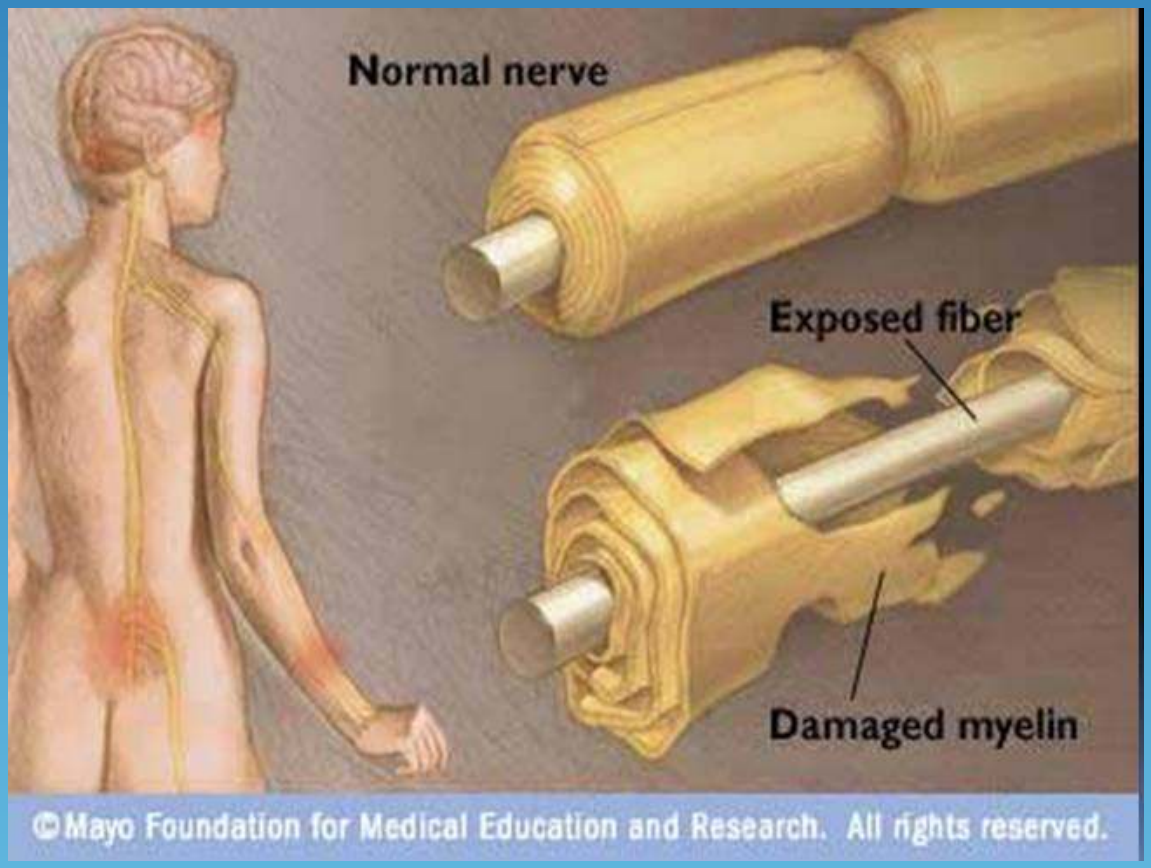
	Neuropathy	Myopathy	Myelopathy	NMJ disorder
Weakness	Distal > proximal	Proximal > distal	Below level of lesion	Fluctuating/ muscle fatigue
Deep tendon reflexes	Severe reduction/ early loss	Mild reduction/ late loss	Increased	Normal or mildly reduced
Sensory	Distal/ ascending	Preserved	Sensory level	Preserved

Case 4 investigations

- Unremarkable blood result
- NCT
  - Primary demyelination-----2 axonal damage
  - Prolonged distal latencies, conduction velocity slowing, conduction block and temporal dispersion of CMAP are the usual feature
- Elevated CSF protein without pleocytosis (<10 cells/mm3)

GBS

- Most frequent cause of acute flaccid paralysis worldwide
- Most dramatic neurologic emergencies
- Post infectious polyneuropathy
  - Mainly motor also sensory and autonomic
- Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)


Normal nerve
Exposed fiber
Damaged myelin
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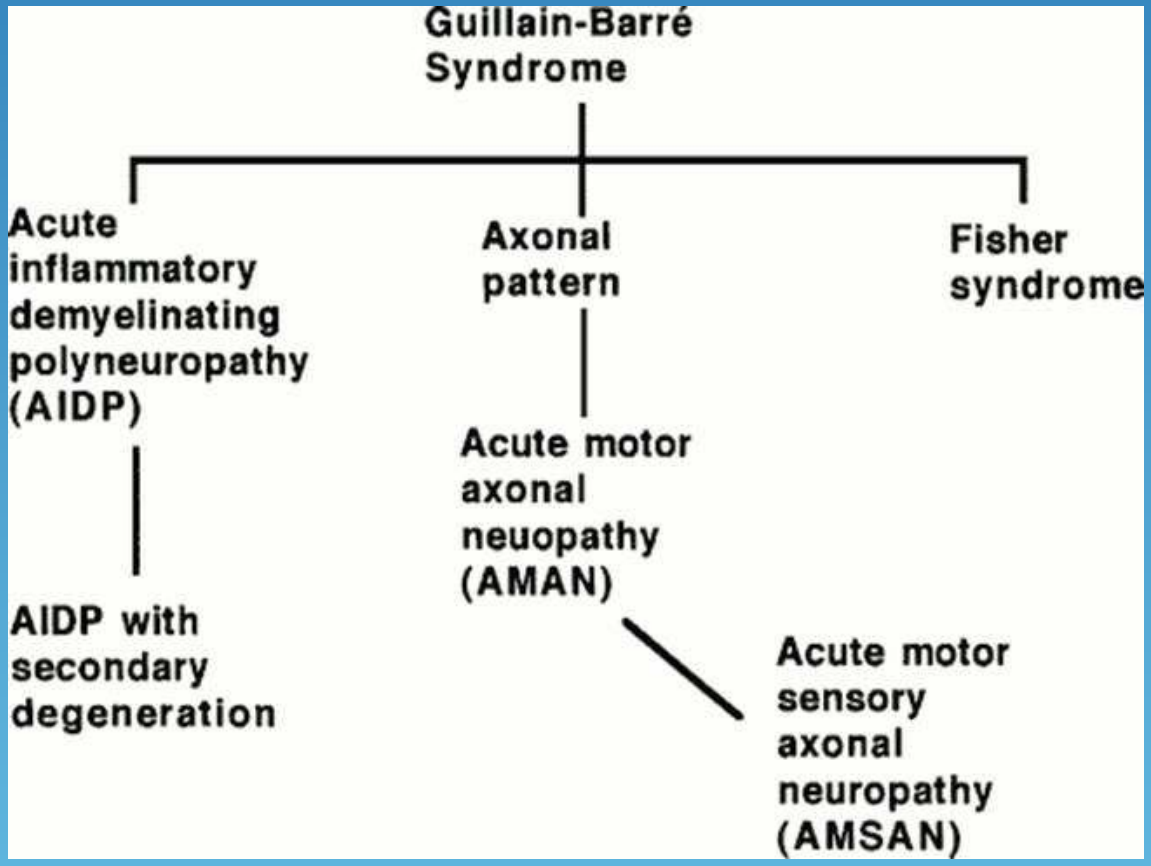

Guillain-Barré Syndrome
Acute inflammatory demyelinating polyneuropathy (AIDP)
Axonal pattern
Fisher syndrome
AIDP with secondary degeneration
Acute motor axonal neuopathy (AMAN)
Acute motor sensory axonal neuropathy (AMSAN)

AIDP	
Atypical forms of AIDP	Pure motor Prominent sensory loss
Regional presentaitons of AIDP	Pharyngo-cervico-brachial
	Facial deiplegia with paresthesia
Pure sensory form	
Pure autonomic form	
Miller Fischer syndrome	
Axonal forms	AMAN
	AMSAN

Levin KH. The Neurologist 2004;10: 61-74

Antecedent infections

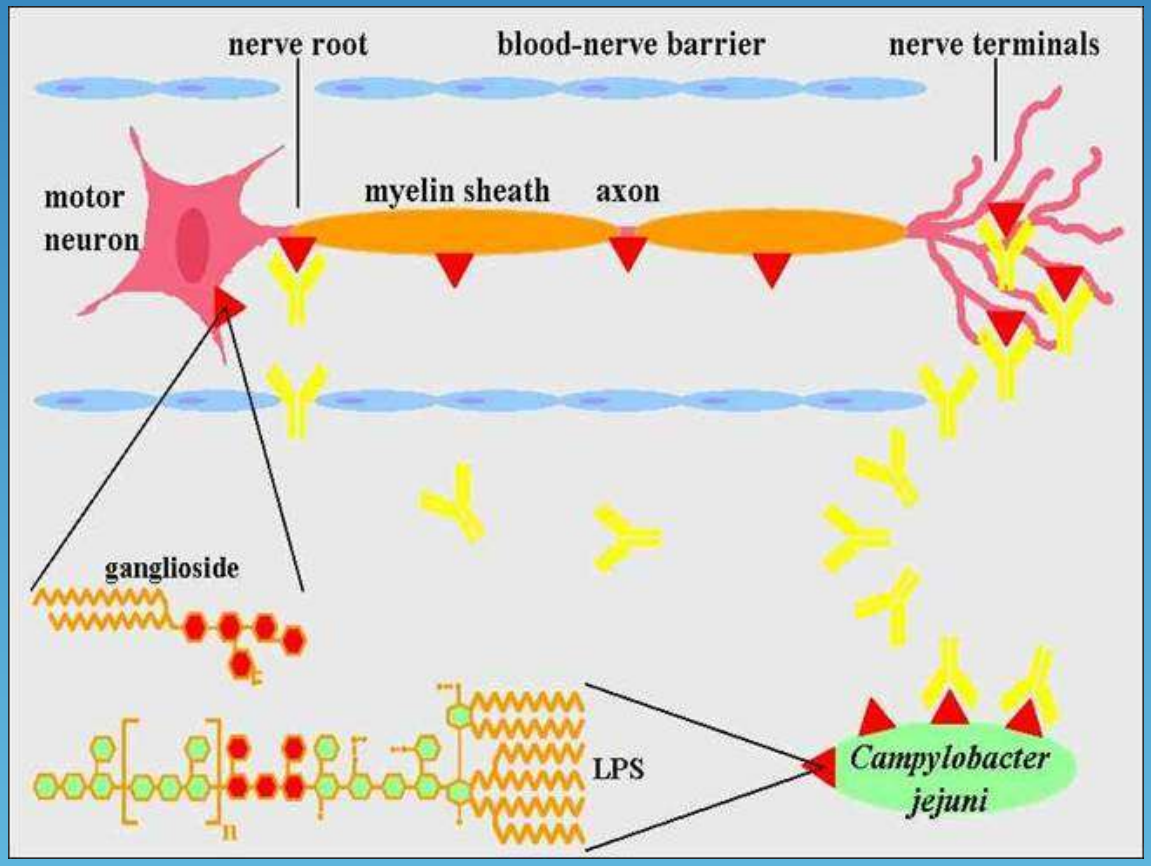
- 60-70% of GBS occur 1-3 weeks after an acute infection, usually respiratory or gastrointestinal
- 20-30% of cases in North America, Europa and Australia are preceded by Campylobacter jejuni infection

Other precipitating factors

Vaccines: Influenze, hepatitis, rabies, tetanus
Lymphoma
Surgery
SLE
HIV seropositivity

Pathogenesis

- All GBS result from immune responses to nonself antigens (infectious agents, vaccines) that misdirect to host nerve tissue through a resemblance of epitope (molecular mimicry) mechanism
- Neural targets: gangliosides
  - Type of ganglioside mimicry determines the specificity of the antibodies and the associated GBS variant


nerve root
blood-nerve barrier
nerve terminals
motor neuron
myelin sheath
axon
ganglioside
LPS
Campylobacter jejuni

Anti-Glycolipid antibodies in GBS

Subtype	Antibody target	Usual isotype
AIDP	No clear patterns, GM1: most common	IgG
AMAN AMSAN	GD1a, GM1, GM1b, GalNAc-GD1a	IgG
MFS	GQ1b (>90%)	IgG

Natural history of GBS

- Definition of GBS
  - Progression of neurological symptom within 8 weeks
- Fifty percent of patients progress to their nadir within 2 weeks, 75% within 3 weeks and more than 90% within 4 weeks of the onset of symptoms
- Rate of improvement is variable

Van der Meche FG et al, Eur Neurol 2001;45: 133-39

Diagnosis

- Clinical findings
- Electrodiagnosis
- CSF findings

Diagnostic Criteria for GBS

Modified from AK Asbury, DR Cornblath: Ann Neurol 1990;27: S21, 1990

Required	
1. Progressive weakness of 2 or more limbs due to neuropathy	
2. Areflexia	
3. Disease course < 4 weeks	
4. Exclusion of other causes (eg: vasculitis, toxins, botulism, diphtheria, porphyria, spinal cord/cauda equina syndrome	
Supportive	
Relative symmetrical weakness	
Mild sensory involvement	
Facial or other cranial nerve involvement	
Absence of fever	
Typical CSF profile	
Electrophysiologic evidence of demyelination	

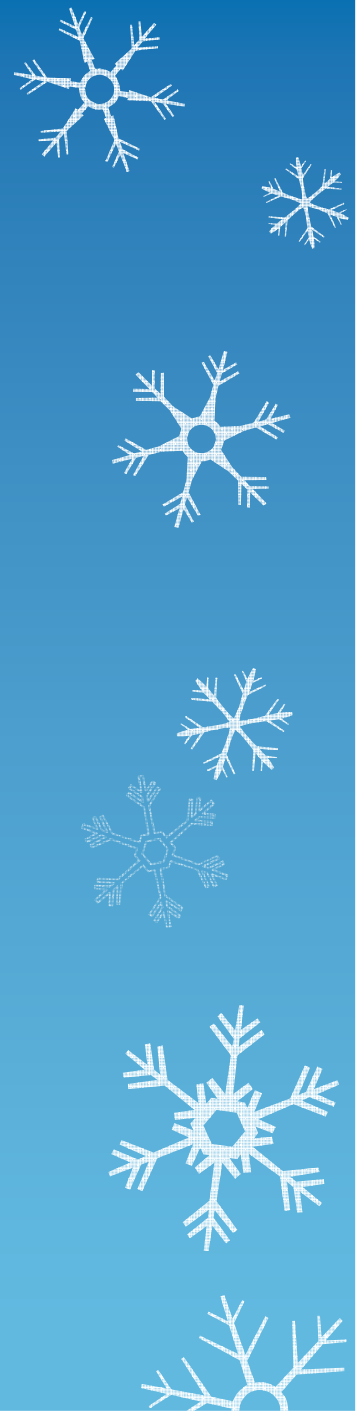
CSF analysis

- Elevated CSF protein without pleocytosis (<10 cells/mm3) is a distinctive finding
- CSF is often normal in the first week. Protein is elevated in 90% by the end of first week
- In MFS, 25% of patients had raised CSF protein in week 1 and 85% in week 3
- No association between protein levels and outcome

Electrodiagnosis

- Electrodiagnostic features are mild or absent in the early stages of GBS and lag behind the clinical evolution
- Essential to subtype various forms of GBS
  - Primary demyelination-----2 axonal damage
    - Prolonged distal latencies, conduction velocity slowing, conduction block and temporal dispersion of CMAP are the usual feature
  - Primary axonal pathology
    - Reduced amplitude (motor/sensory) without conduction slowing or prolongation of distal latencies

Variant of GBS



GBS variants

- Miller Fischer Syndrome
- Acute motor axonal type neruopathy (AMAN)
- Acute motor/sensory type neuropathy (AMSAN)

Miller Fischer Syndrome

- Accouts for about 5% of all GBS cases
- Classic triad of ***ophthalmoplegia, areflexia and ataxia***
- Benign variant
- May present with fragments of classic picture or may have additional feature that overlap with findings in AIDP
  - Unilateral or bilateral facial weakness, abnormal pupillary reactivity and extremity weakness

Miller Fischer Syndrome

- Exact pathogenesis is unclear
- Electrodiagnostic testing may also be normal
- Anti-GQ1b in MFS
  - Present in the serum of about 95% of patients with these syndrome
  - Titers of IgG are highest early in the course of MFS

Differential diagnosis of GBS

- Viral infection
  - Poliomyelitis, Paralytic rabies, Tick paralysis
- Metabolic cause
  - Hypokalemia, hypophosphatemia, hypermagnesesmia
- Acute brainstem syndrome
- Acute myelopathies
- Neuromuscular disorder
  - Myasthenia gravis
  - Botulism, organophopshate poisoning
- Muscle abnormalities
  - Critical illness myopathy

GBS vs ATM

TABLE 5. Distinguishing Features Between Guillain-Barré Syndrome and Transverse Myelitis

Characteristics	Transverse Myelitis	Guillain-Barré Syndrome
Motor findings	Paraparesis or quadriparesis	Ascending weakness LE > UE in the early stages
Sensory findings	Usually can diagnose a spinal cord level	Ascending sensory loss LE > UE in the early stages
Autonomic findings	Early loss of bowel and bladder control	Autonomic dysfunction of the cardiovascular (CV) system
Cranial nerve findings	None	EOM palsies or facial weakness
Electrophysiologic findings	EMG/NCV findings may be normal or may implicate the spinal cord: prolonged central conduction on somatosensory evoked potential (SEP) latencies or missing SEP in conjunction with normal sensory nerve action potentials	EMG/NCV findings confined to the PNS: motor and/or sensory nerve conduction velocity reduced, distal latencies prolonged; conduction block; reduced H reflex usually present
MRI findings	Usually a focal area of increased T2 signal with or without gadolinium enhancement	Normal
CSF	Usually, CSF pleocytosis and/or increased IgG index	Usually, elevated protein in the absence of CSF pleocytosis

Treatment

- Very few randomized controlled trials (RCT) on GBS treatment were published recently
- 3 components of management
  - Monitoring, supportive and critical care
  - Immunotherapy
  - Rehabilitation

Supportive and critical care

- Monitoring vital parameters
- Nutrition
- DVT prophylaxis
- Ventilator assitance
- Autonomic dysfunction
  - potential ileus
  - cardiovascular instability
  - blood pressure change, cardiac arrhythmias
- Chest and general physiotherpy
- Frequent turning
- Management of pain, constipation

Ventilator assistance

- Among severely affected patients about 25% need artificial ventilation
- Indications for intubation
  - VC of 15ml/kg
  - Significant hypercarbia, hypoxia
  - Death is not due to ventilatory insufficiency, but due to intercurrent infection, MI or pulmonary embolism

Prognosis

- Worst outlook in patients with severe proximal motor and sensory axonal damage
- Excellent prognosis in MFS
- AMAN
  - Recovery occurs in about 2 months but the extent of recovery may be less than in AIDP

Poor prognostic factors

- Bulbar dysfunction
- Autonomic dysfunction
- Severe weakness
- Rapid onset to peak (<3 days)
- Age>60
- Reduced median CMAP amplitude
- Pulmonary infections

Prognosis using EGOS

- Erasmus GBS outcome scale (EGOS)
- It is calculated in the first 2 weeks of disease onset using
  - Age, presence of preceding diarrhoea, and GBS disability
- EGOS can accurately predict the chance of independent walking after 6 months

Van Koningsveld R et al. Lance Neurol 2007;6: 589-94

Immunotherapy

- IVIG or plasmapheresis can be initiated, both are equally effective
  - Shorten time to recovery
- Combining these therapies has no additional benefit
- Meta-analysis of RCTs indicates
  - PE reduced need for mechanical ventilation from 27% to 14%
  - Increase likelihood of full recovery at 1 year from 55% to 68%

Hughes RA et al, Brain 2007. 130:2245-2257

Timing of treatment

- Start treatment as soon after diagnosis as possible
- Greatest effect observed when PE was started within the first 2 weeks from onset
  - ~ 2 weeks after first motor symptoms, immunotherapy is only minimally effective

The Gullian Barre Syndrome Study Group. Neurology 1985;35: 1096-104

Plasmapheresis

- A course of plasmapheresis consists of 40-50ml/kg plasma exchange (PE), 4-5 times over 2 weeks
- Should ideally be administered within the first 2 weeks and not later than 4 weeks from clinical onset

French Cooperative Group on PE in GBS. Ann Neurol 1997;41: 298-306

Immunoglobulins

- IVIG as effective as plasmapheresis, at least in the first 2 weeks
- IVIG preferred as initial therapy because of its ease of administration and good safety record
- Doses
  - 5 daily infusions for a total dose of 2g/kg

Hughes RA et al. Cochrane Database Syst Rev 2006;1: CD002063

Treatment

- Steroid (oral, parenteral) alone are not beneficial in GBS

Hughes RA et al, Cochrane Database Syst Rev 2006;2: CD001446

Summary of AAN recommendations for immunotherapy for GBS

Plasma exchange

- Recommended in non ambulant patients with GBS who present within 4 weeks from the onset of symptoms
- Ambulant patients who present within 2 weeks from the onset of symptoms

Summary of AAN recommendations for immunotherapy for GBS

- Intravenous immunoglobulin (IVIg) recommended in non-ambulant adult patients with GBS within two or possibly four weeks from the onset of neuropathic symptoms.
-
- The effects of plasma exchange and IVIg are equivalent.
- Corticosteroids are not recommended in the treatment of GBS.

Summary of AAN recommendations for immunotherapy for GBS

4. Sequential treatment with PE followed by IVIg or immunoabsorption followed by IVIg is not recommended for GBS.

5. Plasma exchange or IVIg are treatment options for treating children with severe GBS.

Case 5

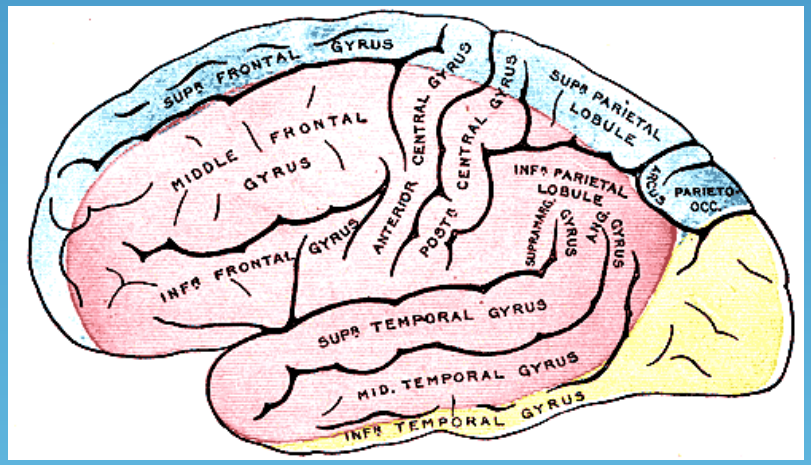
- 35/F
- Good past health
- Progressive weakness over 4 limbs and neck muscle in the previous 3-4 weeks
- Soft speech occasionally seeing double vision

examination

- Tachypnoea, tachycardia
- Bilateral facial nerve palsy
- Bulbar speech nasal tone
- Power 4/5 Ul and LL proximal and distal
- Normal tone and reflex
- No cerebellar sign
- No sensation vibration problem

Localization

Central nervous system



Peripheral nervous system

- Nerve root
- Plexus
- Peripheral nerve
- Neuromuscular junction
- Muscle

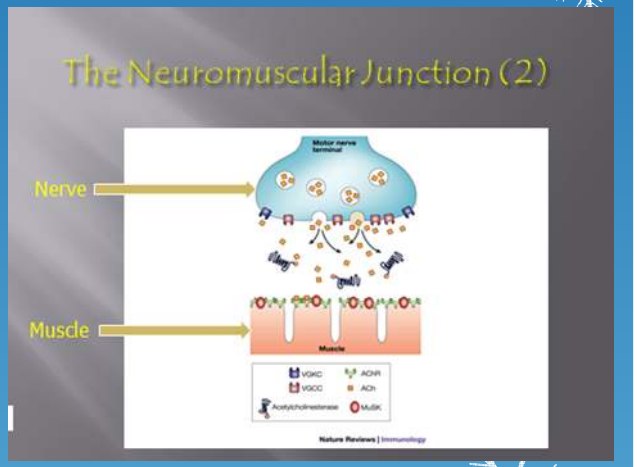
The most important step in neurologic localization is differentiating a *central nervous system* lesion from a *peripheral nervous system* lesion

progess

- Admitted ICU for further management
- Subsequently intubated in view of the respiratory failure
- Further investigation including blood taking and Electrophyisology study confirmed the diagnosis

Myasthenia Gravis

Anatomy

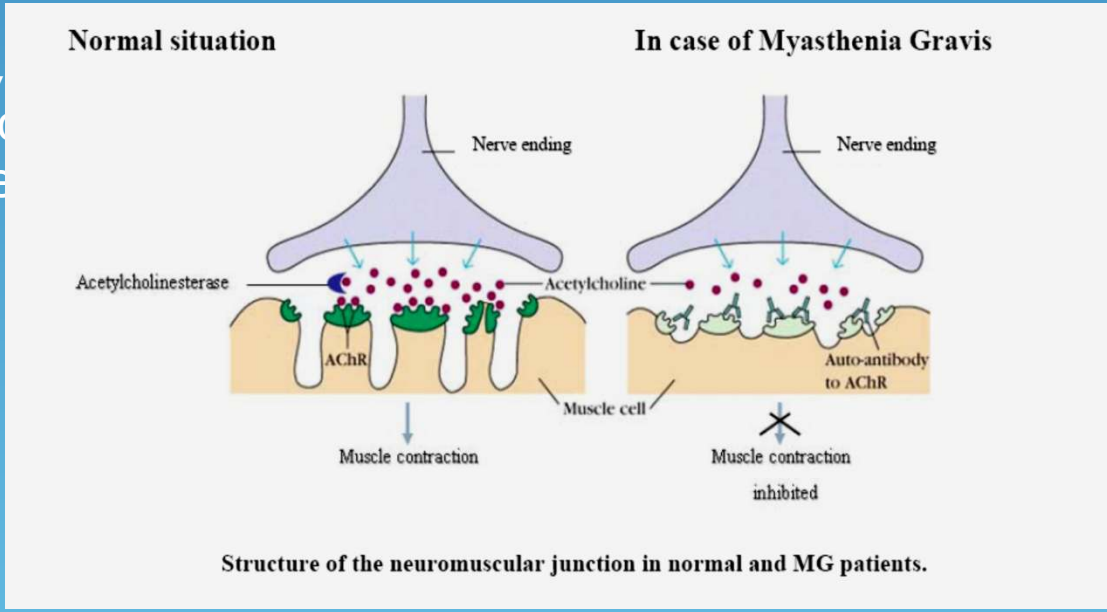


- Neuromuscular Junction (NMJ)
  - Components:
    - Presynaptic membrane
    - Postsynaptic membrane
    - Synaptic cleft
  - Presynaptic membrane contains vesicles with Acetylcholine (ACh) which are released into synaptic cleft in a calcium dependent manner
  - ACh attaches to ACh receptors (AChR) on postsynaptic membrane

Pathophysiology

- In MG,
  recept
  muscle

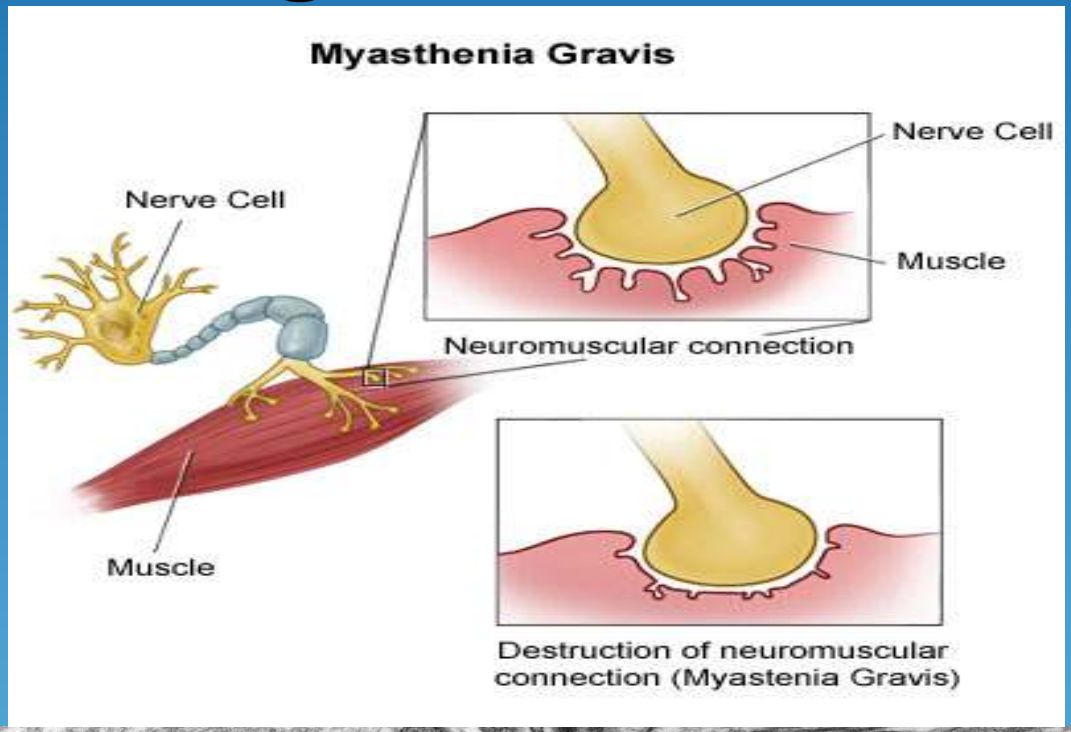
line



Structure of the neuromuscular junction in normal and MG patients.

MG Damages the Muscle Endplate

A.



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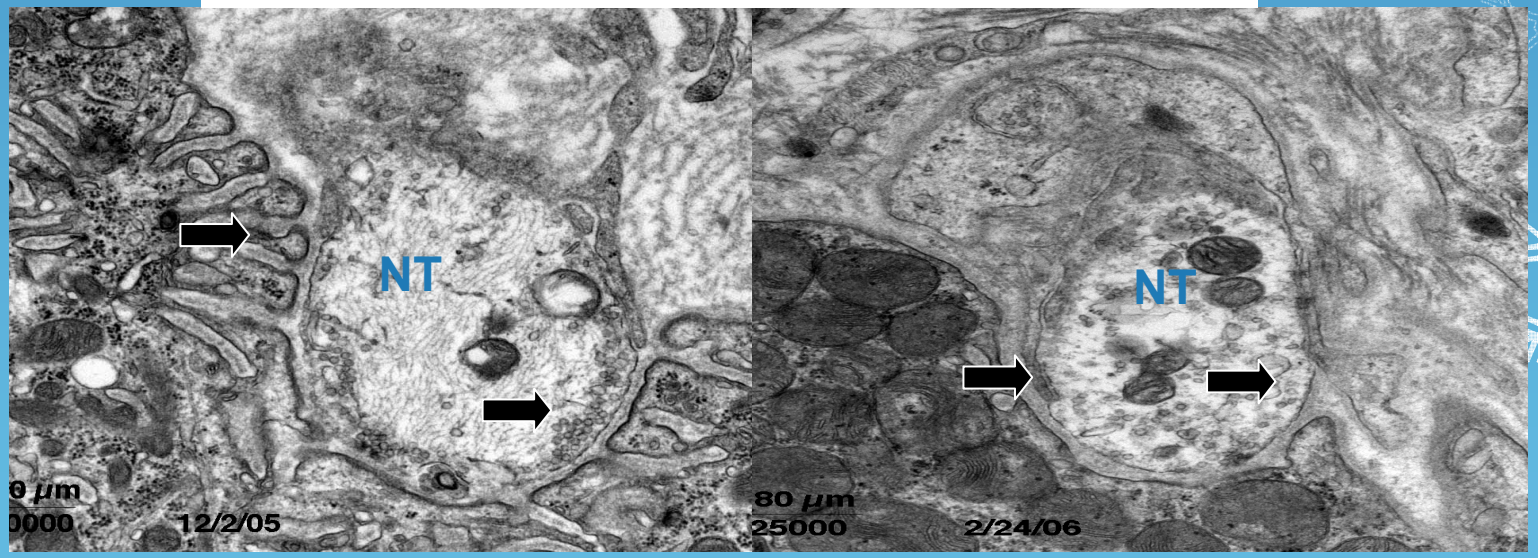
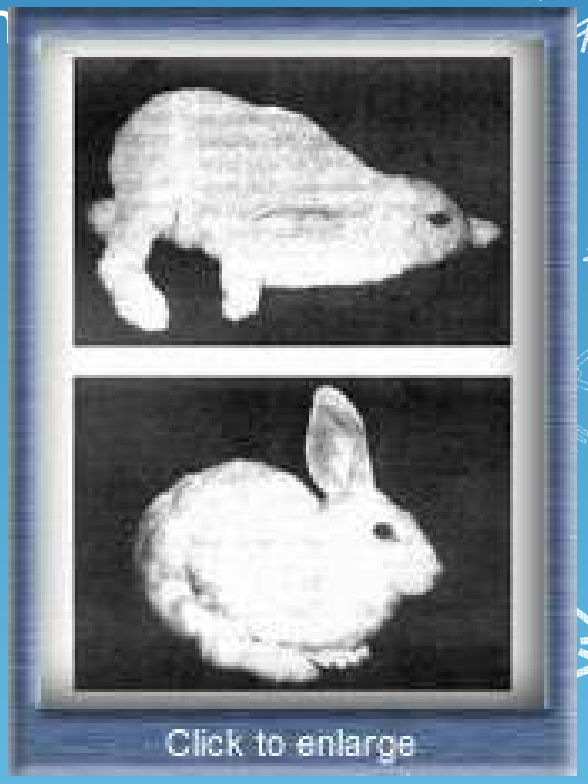


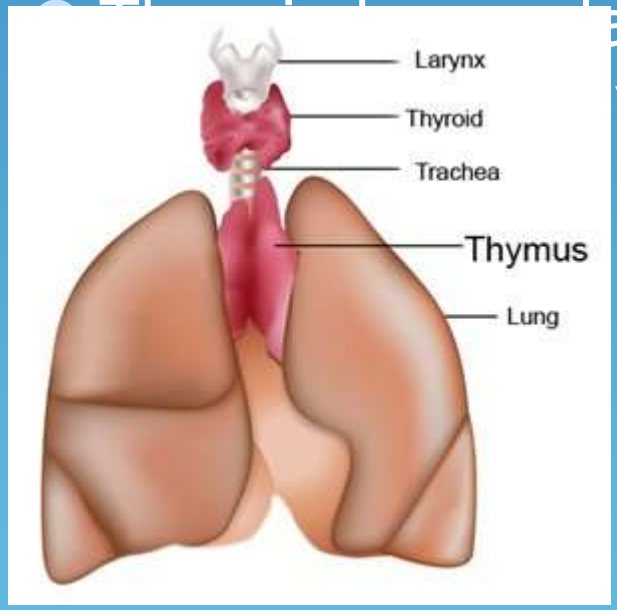
Pathophysiology

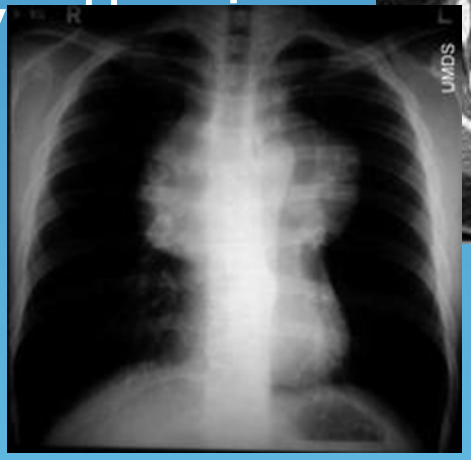
- Anti-AChR antibody is found in 80-90% of patients with MG
  - Proven with passive transfer experiments
- MG may be considered a B cel mediated disease
  - Antibodies

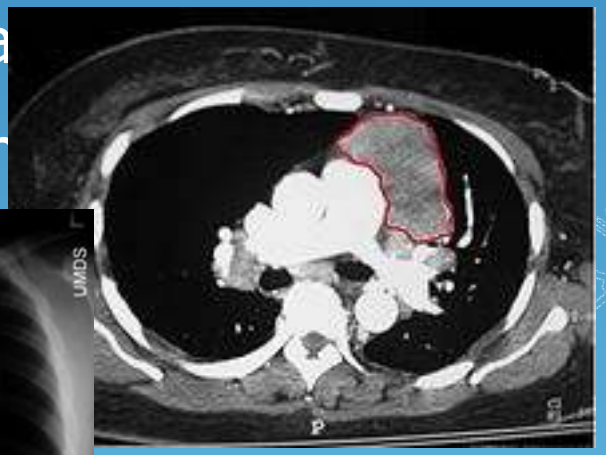


Pathophysiology

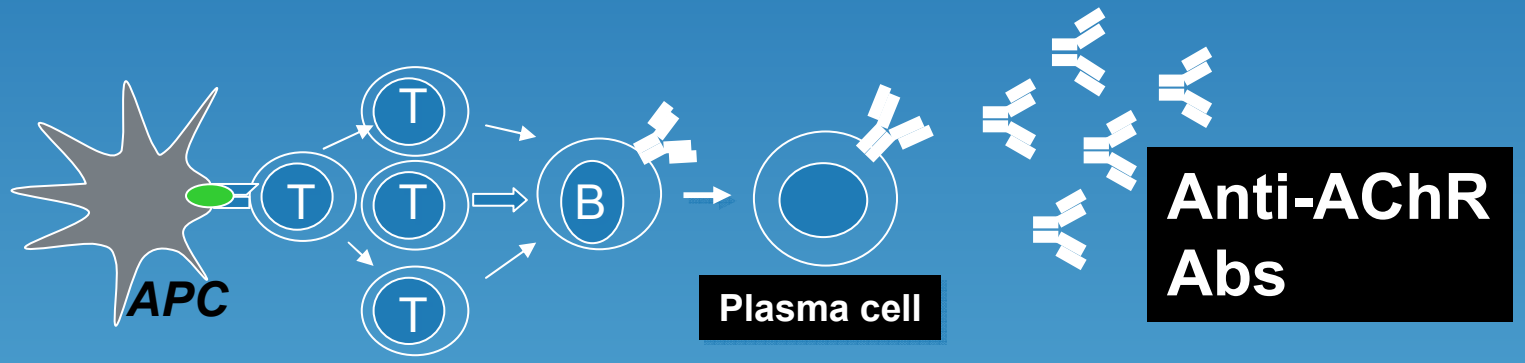
- T-cell mediated immunity ha
- asia and thyr

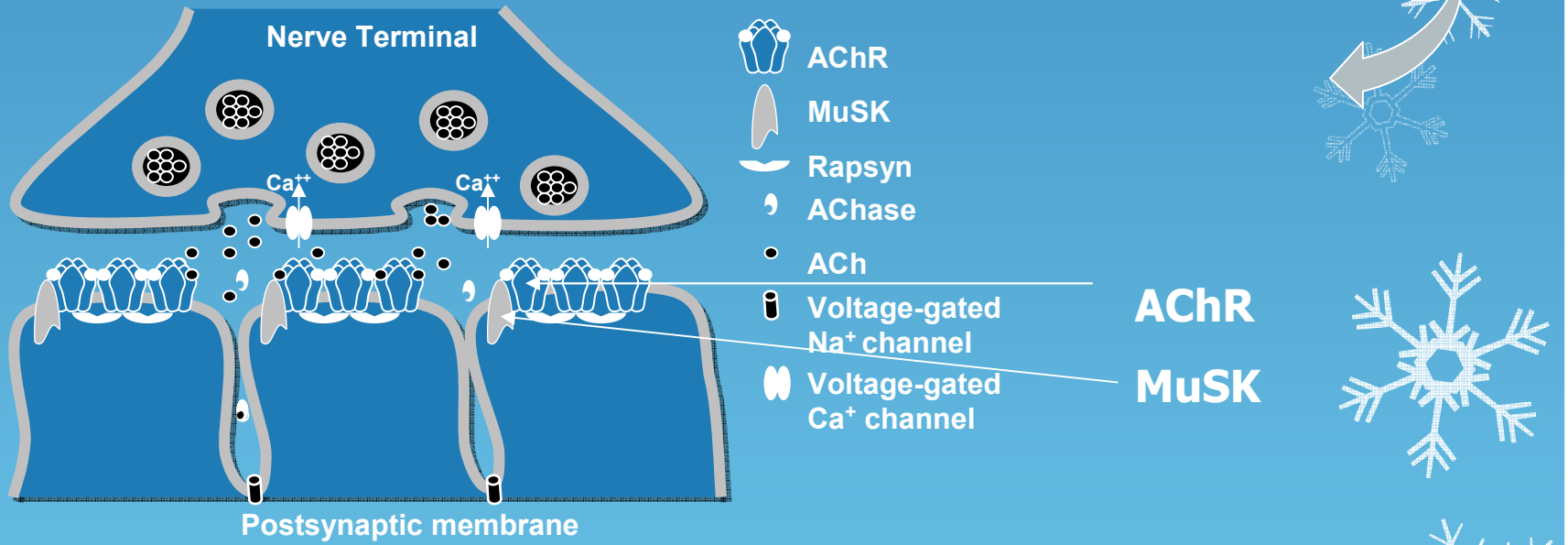






What is happening in the immune system in people with MG?





Thymus in Myasthenia gravis

- 10 % of pts with MG have Thymic tumour
  - Mostly in MG patients > 30 years
  - AChRAb 95% to 100%
- 70 % have hyperplastic changes in thymus
  - Younger age groups
  - Female
  - HLA: B8 & DR3
- Atrophy: 20%
  - Usually > 50 years

MG: Initial presentation and progression

- Initial symptoms
  - Eye muscle weakness 75%
  - Head/neck weakness 15%
  - Limb weakness 10%

- Within first year
  - ~75% develop head/neck +/- limb weakness
  - ~67% reach maximum MG severity
  - ~20% experience severe exacerbation/MG crisis

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 pattern - MG

- Ocular
  - Ptosis & ophthalmoplegia
  - Usually asymmetric & bilateral
- Bulbar
  - Dysarthria, dysphagia, weak mastication
  - Complicated with aspiration pneumonia
  - Facial: > 95%
- **Respiratory failure**
  - Life-threatening
  - Etiology
    - diaphragmatic & intercostal muscle weakness
    - vocal cord paralysis
- **Systemic**
  - Typical: symmetric
    - Proximal > distal
    - Arms > legs
  - Selective weakness
    - Posterior neck
    - Occasional distal

Severity classification of MG

	Osserman/71	Drachman/82
Grade 1	Ocular	Focal
Grade 2	a: Mild generalized b: Severe generalized	Mild generalized
Grade 3	Acute fulminating	Severe generalized
Grade 4	Late severe	Crisis

Investigation of MG

Ice pack Test

- Ice pack test
  - Application of ice to the eyes for 2–5 minutes, ensuring that the ice is covered to prevent ice burns
  - raise of 2 mm of the palpebral fissure following the removal of the ice pack
  - physiological theory behind
    - cooling the tissues, and more specifically the skeletal muscle fibres, the activity of the acetylcholinesterases are inhibited (laboratory data suggest below 28°C)

Fig 2. Before the ice pack test (left) and immediately after the ice pack test (right).

Advantage of ice pack test

- cheap, safe, and very quick to perform as it can be carried out at the bedside in approximately 3–5 minutes
- Particularly in patients with contraindication to Tenilon test
- The sensitivity of this test was 76.9% for the 5-minute application and the specificity was 98.3% with no false-positives reported

Chatzistefanou KI, Kouris T, Iliakis E, et al. The ice pack test in the differential diagnosis of myasthenic diplopia. Ophthalmology 2009;116:2236–43

Disadvantage of ice pack test

- Can only evalute patients presenting with ptosis as symptom, not for patients complaining of diplopia

Workup
Pharmacological testing

- Edrophonium (Tensilon test)
  - Evaluate weakness (i.e. ptosis and opthalmoplegia) before and after administration
- Underlying theropy
  - Patients with MG have low numbers of AChR at the NMJ
  - Ach released from the motor nerve terminal is metabolized by Acetylcholine esterase
  - Edrophonium is a short acting Acetylcholine Esterase **Inhibitor** that improves muscle weakness
  -

Edrophonium (Tensilon test)

- False positive test
  - Consider that Edrophonium can improve weakness in diseases other than MG such as ALS, poliomyelitis, and some peripheral neuropathies
- Contraindications
  - mechanical intestinal or urinary obstruction.
  - 2/3 degree heart block
  - Sinus bradycardia

Work-up

- Lab studies
  - Anti-acetylcholine receptor antibody
    - 80-90% in generalized myasthenia
    - 50% of patients with pure ocular myasthenia
  - Anti-striated muscle
    - Present in 84% of patients with thymoma who are younger than 40 years

AChR antibody test

- Antibody level does NOT correlate with disease severity between patients
- In an individual patient, changes in antibody levels do correlate

AchRAb Positive

- Adults with generalized MG: 85 to 90%
- Childhood MG: 50%
- Ocular MG: 50% to 70%
- MG with thymoma: nearly 100%
- Some patients taking penicillamine +/- MG

AchRAb False +

- Thymoma without MG
- Immune liver disorders
- Lambert-Eaton syndrome (13%)
- Primary lung cancer: 3%
- Older patients (> 70 years): 1% to 3%
- Neuromyotonia

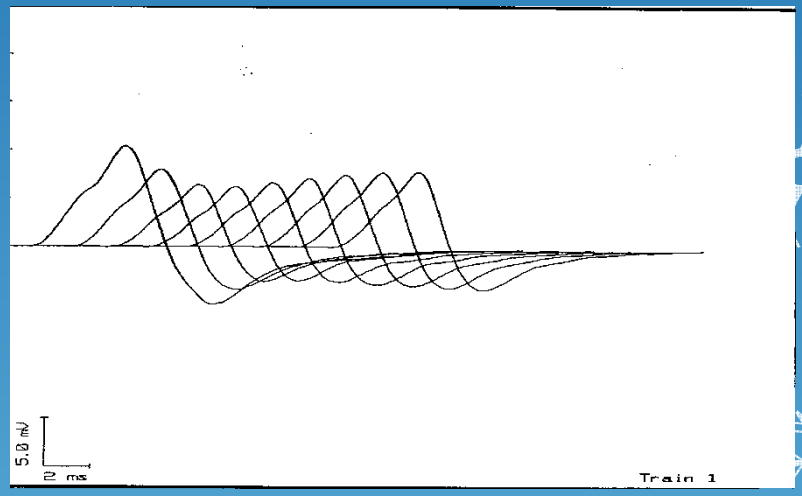
“Antibody negative” MG

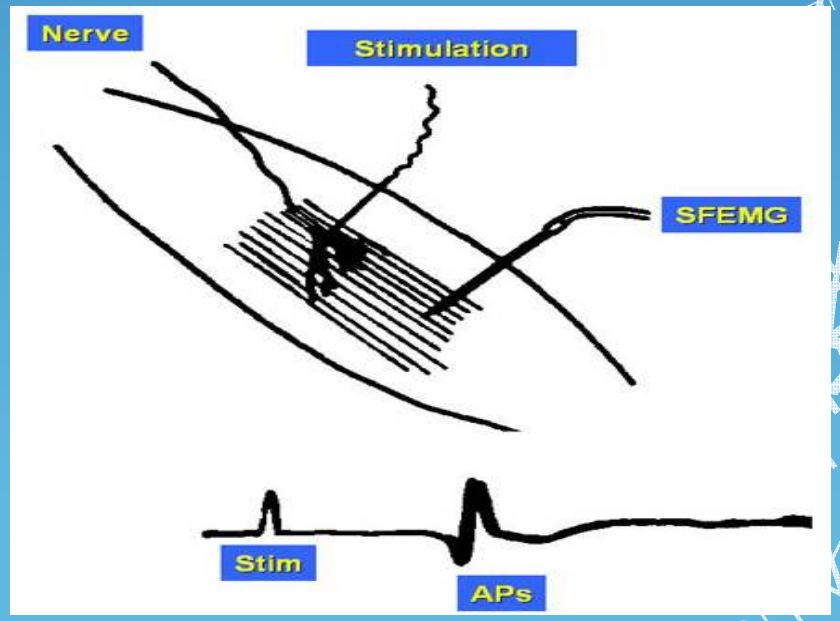
- 40-50% of patients with ocular MG
- MuSK antibodies in 40% of AChR negative, generalized MG

Electrical tests

- Repetitive nerve stimulation (RNS)
- Single fiber EMG

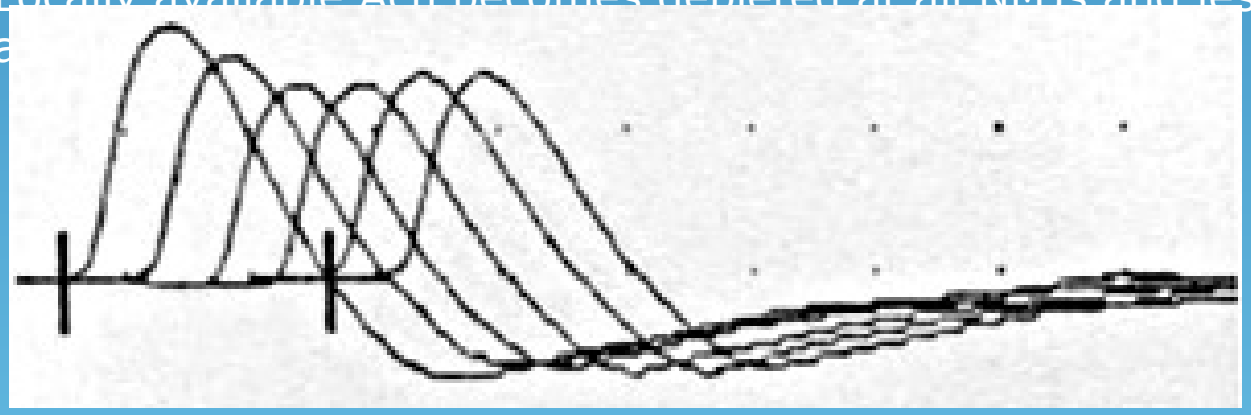
SFEMG is more sensitive than RNS in MG





Electrodiagnostic studies: Repetitive Nerve Stimulation

- Low frequency RNS (1-5Hz)
  - Locally available Ach becomes depleted at all NMJs and less a



Work-up

- Imaging studies
  - Chest x-ray
    - Plain anteroposterior and lateral views may identify a thymoma as an anterior mediastinal mass
  - Chest CT scan is mandatory to identify thymoma
  - MRI of the brain and orbits may help to rule out other causes of cranial nerve deficits but should not be used routinely

Treatment in MG

Overview--Treatments

- Short Term
  - Symptomatic: (Anticholinesterases agents) Mestinon
  - Immune-mediating: IVIG, Plasma Exchange
- Medium Term
  - Immune-Mediating: Steroids
- Long Term
  - Immune-Mediating: Several
- Longer Term
  - Thymectomy

MYASTHENIC CRISIS

- Severe generalized weakness and respiratory failure
- Seen after stress (URI, infection, medication change, surgery, obstetrical delivery, high environmental temperature)
- Patient needs ventilatory support
- Patient will need help with all ADL
- Suctioning, chest PT

Precipitants (n=20)

Yeh et al; Acta Neurol Scand 2001; in press

Pneumonia/pneumonitis
Bronchitis
URI
Sepsis
Surgery
No obvious precipitant

Drugs interfere NM transmission

Variety	Drug
Antibiotic	*Aminoglycoside*, *Fluoroquinolone*, Tetracycline, Sulfonamide, Penicillin, Macrolide, Lincomycin, Colistin, Polymyxin, Quinocrine, Chloroquine
CNS	*Transquillizer*, *Barbiturate*, Anticonvulsant, Lithium, Mg salt, TCA, Haloperidol
Anesthesic	Halothane, Ether, Trichloroethylene
CV	*B-blocker*, *Verapamil*, Quinidine, Procainamide
Others	*Narcotic*, Penicillamine, Iodinated contrast

Respiratory muscles

- Forced vital capacity
  - Consider ICU admission/mechanical ventilation if FVC<15-20ml/kg
  - Repeat testing of respiratory parameters to see the worsening trend
- Arterial blood gas measurements
  - Insensitive measure of respiratory decompensation in HG
    - Hyperventilation picture in the intial finding
    - CO2 retention decompensate of the respiratory muscles

Management of an suspected MG crisis

- Monitor FVC regularly
  - Initiate mechanical ventilation if FVC <15-20ml/kg
  - Stop anticholinesterase
  - Check blood Ig pattern ach receptor Ab before IVIG
  - Avoid drug that can worse NM junction
    - AMINOGLYCOSIDES, QUININE B-BLOCKER MUSCLE RELAXANTS, PENICILLAMINE
  - Supportive measure
  - IVIG/plasma exchange

IVIG

- 2g/kg IVIG over course of 3-5 days
- Common adverse events of IVIG
  - fever, headache, nausea
- Uncommon side effects
  - severe anaphylactic reaction might occur in patients with IgA deficiency.
  - Volume overload may occur in cardiomyopathy
  - Solute-induced renal failure may occur in patients with pre-existing renal impairment.
  - Thrombosis and stroke,

Plasma exchange in MG crisis

- Remove large molecular weight particles from plasma
- Removal circulating antibodies, immune complexes, cytokines and other inflammatory mediators
  - Ach receptor level fall with PE

Clinical response: plasmapheresis

Author-year	no	Method	Response
Dau-81	60	PE	74%
Fornasari-85	33	PE	61%
Mantegazza-87	37	PE	87%
Antozzi-91	70	PE	70%
Kornfeld-92	43	PE	91%
Shibuya-94	20	IAP	55%
Yeh-99	45	DFP	84%

Plasma exchange

- Open or retrospective studies
- Class I evidence of equal effectiveness as IVIG in MG crisis

Plasma Exchange - MG

- Dose: 5 exchanges (around 50ml/kg) per exchange performed over 9 to 10 days

- Indications:
  - MG crisis
  - Pre-thymectomy (respiratory/bulbar involvement)
  - Urgent/semi-urgent operation is needed in an unstable MG patients

Plasmapheresis

- Advantages
  - Very short onset of action (3 to 10 days)
- Disadvantages
  - Requires specialized equipment & personnel
  - Complications more frequent in elderly
    - Vascular access: thrombosis, infection
    - Pneumothorax
    - Air embolism
    - Hypotension/fluid overload, congestive heart failure
    - Acid base homeostasis and hypocalcaemia related to citrate infusion for anticoagulation
  - High cost with short-term effects (weeks)

IVIG

Table 1: Major randomised controlled trials comparing different types of treatment in generalised myasthenia gravis

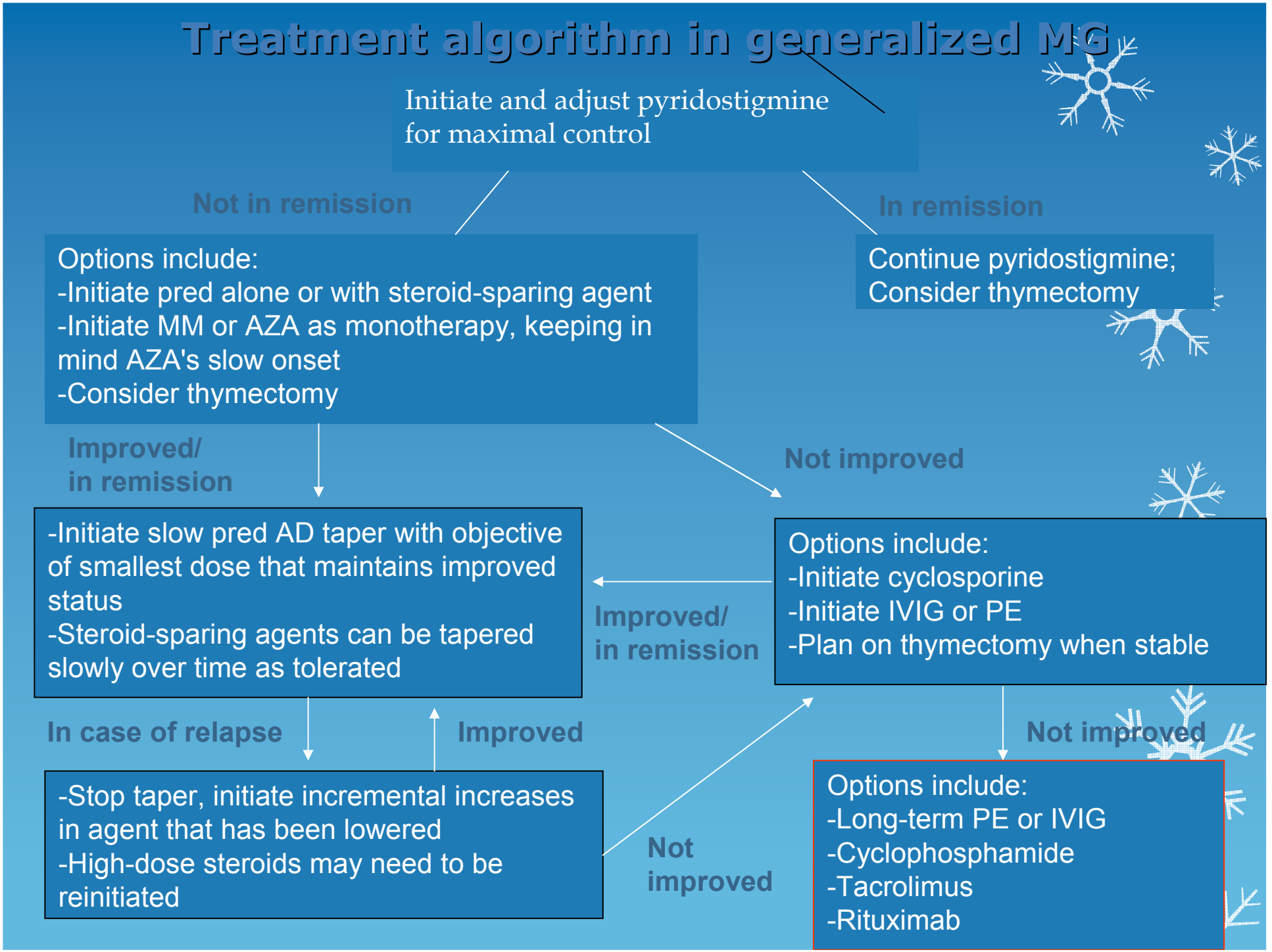
Trial	Patients	Intervention	Outcome
Wolfe GI 2002[23]	15 with stable mild or moderate MG	IVIG v placebo	No significant difference
Zinman 2007[25]	51 with acute exacerbation of MG	IVIG v placebo	Significant improvement in muscle strength in group with severe disease
Gajdos 1997[26]	87 with acute exacerbation of MG	IVIG v PE	No significant difference
Rønager 2001[27]	12 with stable moderate or severe MG	IVIG v PE	No significant difference
Cochrane group[22] (personal communication)	33 with acute exacerbation of MG	IVIG v oral methylprednisolone	No significant difference

IVIG = intravenous immunoglobulin, MG = myasthenia gravis, PE = plasma exchange

Medical management for MG crisis

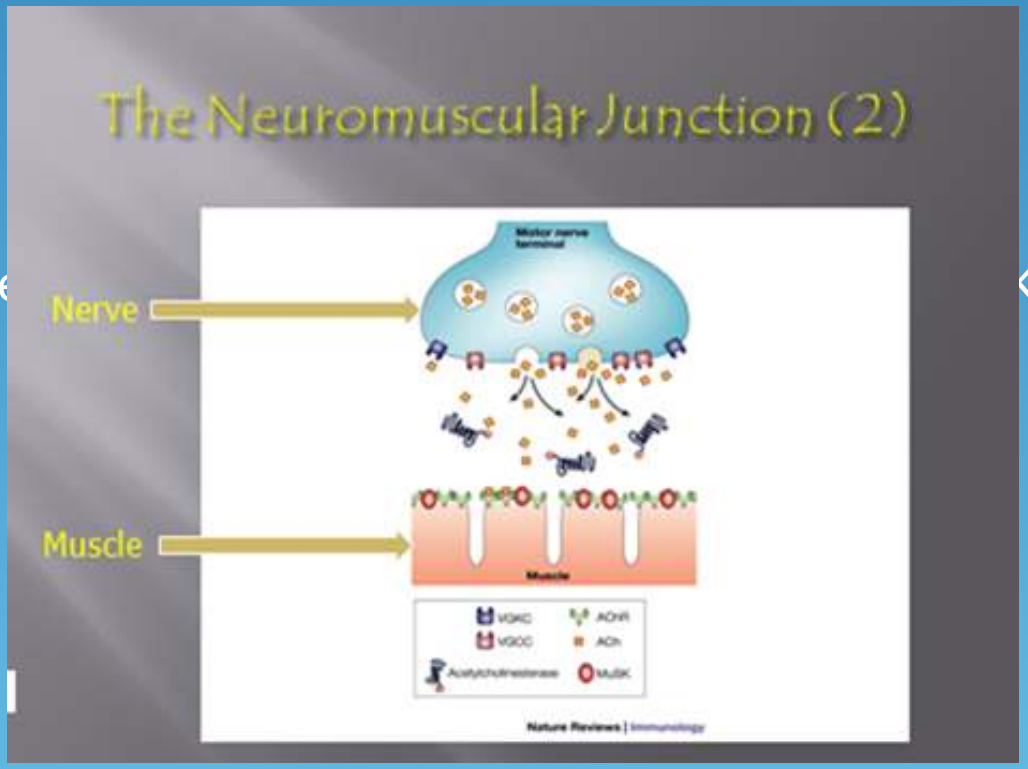
- Transient improvement with plasma exchange/IVIG only
- need long term immunosuppression with either **corticosteroid** or other agent such as **azathioprine**

Treatment algorithm in generalized MG



Musk-antibody related myasthenia gravis

- Muscle

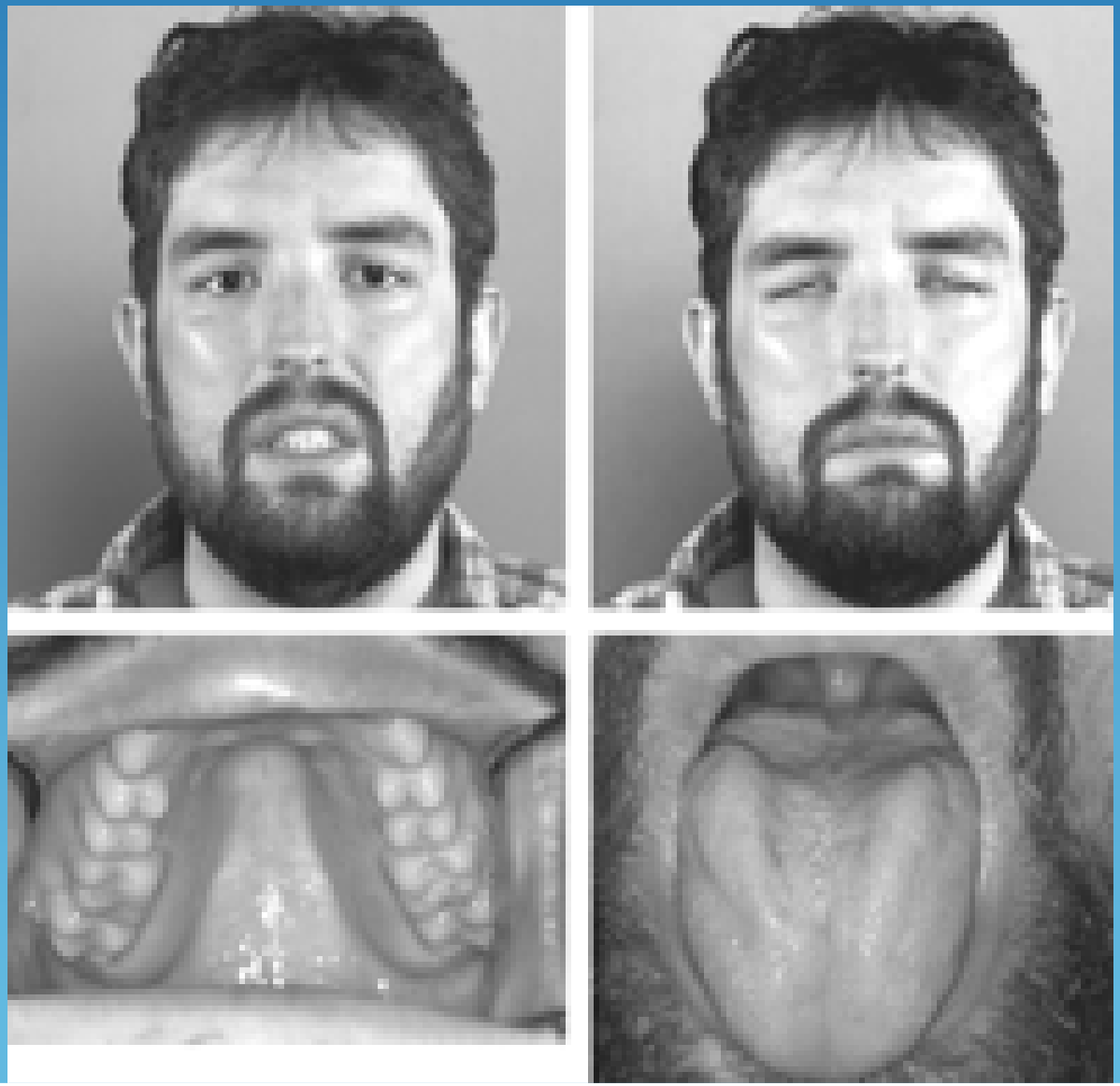


Musk-antibody related myasthenia gravis

- Present in 40-50% of Ach receptor negative generalized myasthenia gravis patients
- Around 80-90% of MUSK MG patients are women
- Highest reported prevalence being closer to the equator and the lowest closer to the poles

	Ach-receptor Ab-MG	MUSK Ab-MG
Clinical features	Ocular, axial, limb muscles	Fasio-pharyngeal muscle weakness and atrophy Predominent neck and respiratory weakness Mild limb weakness/ocular
Clinical course	Variable	Usually acute and progressive ---crisis
Treatment	Acute: IVIG/PE Immunotherapy	Acute: PE>>IVIG (dramatic and rapid response) Vary response to Mestinon (Anticholinesterase responses) Hypersensitivity-sx worsen

Musk-antibody related myasthenia gravis clinical features



Problems in diagnosis of MUSK-Ab related MG

Expensive in testing of MUSK Antibody

~HKD 7300