MALIGNANT HYPERTHERMIA

▪ *History*

• Ombrédanne (1929) described postoperative hyperthermia & pallor in children, with an associated high mortality → ***Ombrédanne syndrome***
• Denborough & Lovell in 1960 first accurately described the familial nature of the syndrome
• at that time the ***mortality* ~ 70-90%**
• Briskey 1964 described pale soft exudative (PSE) pork
• the term ***malignant hyperthermia*** was first used in print by Wilson
• Hall *et al.* 1966 described porcine MH, in conjunction with rigidity, in suxamethonium-halothane anaesthetised swine, and correlated the response with human MH
• 1971 saw the first international symposium
• ***Harrison, 1975*** described the efficacy of ***dantrolene*** in treating porcine MH
• the introduction of dantrolene in prevention and management was made in **1979**
• the mortality from a full blown episode has presently decreased from ~ 80% to **~ 10%**

▪ *Incidence*

• ***autosomal dominant*** metabolic defect, with reduced penetrance and variable expression
• some families do not follow this pattern of inheritance
• therefore, ? transmitted by more than one gene & more than one allele
• estimated ***incidence*** is,

a. ***fulminant*** MH
   i. total anaesthetics ~ 1:250,000
   ii. using suxamethonium ~ 1:62,000 (↑ ~ 4x)

b. ***suspected*** MH
   i. total anaesthetics ~ 1:16,000 (↑ ~ 4x)
   ii. using suxamethonium ~ 1:4,200 (↑ ~ 4x)

c. reported incidence in ***children*** **~ 1:3,000 - 1:15,000**
   • this large difference may be due to retrospective study design, or the age at which most surgery is performed

NB: suxamethonium ~ 4x ↑ incidence
children ~ 15-80x ↑ incidence

Pathophysiology

▪ ***Skeletal Muscle***

• most of the study of the pathophysiology has been done in MHS swine
• the metabolic defect is in the transport of Ca^{++} across the ***sarcoplasmic reticulum***
• during normal contraction, muscle membrane depolarization reaches the terminal sac of the SR via the T-tubules and leads to release of Ca^{++} from the sarcolemma and the mitochondria
• the normal resting cytosolic $[Ca^{++}] \sim 10^{-7}$ M $\rightarrow$ $\uparrow \sim$ 10x during depolarization
• the main defect lies in the inability of the SR to store Ca^{++}, with the cytosolic $[Ca^{++}] \sim \uparrow$'d 3-4x
• upon triggering MH this increases up to ~ 17x (**~ 6x** normal depolarization, 5×10^{-5} M)
• the large increase in intracellular $[Ca^{++}]$ leads to,

a. ATP'ase activation with conversion of ATP $\rightarrow$ ADP
b. inhibition of ***troponin***, enabling muscle contraction
c. activates phosphorylase kinase & glycogenolysis $\rightarrow$ ATP & heat
d. increased ***mitochondrial*** $[Ca^{++}]$ & increased ***aerobic glycolysis***

$\rightarrow$ ATP depletion & increased muscle metabolism
anaerobic metabolism & lactic acidosis
high MRO_2, VCO_2, heat production
eventual cellular breakdown & rhabdomyolysis

• mitochondria effectively act as a secondary store for Ca^{++} and have deficient function in MH
• this deficiency alone does not account for MH, and earlier theories regarding uncoupling of oxidative phosporylation have been discounted

NB: the action of ***dantrolene***, inhibiting Ca^{++} release from the SR, effectively localises the abnormality between the motor end-plate and the SR Ca^{++} release mechanism

• mitochondrial deficiencies ***do not*** explain diminished aerobic responses in MH,

1. VO_2 during exercise increases $\leq$ 10x
2. VO_2 during MH consistently increases **~ 3x**,
   given the metabolic derrangements this is inappropriately ***low***
3. mitochondrial VO_2 and ATP production appear to be limited in MH,
   i. binding of Ca^{++} - reserve function to supplement the SR
   ii. intracellular acidosis
   iii. electrolyte abberations
   iv. ? genetic disorder of function

• the ***earliest*** abnormalities appear in the venous effluent from affected muscle,

1. decrease in pH & P_{O2}, and
2. increase in P_{CO2}, lactate, $[K^+]$ and temperature

NB: these occur ***prior*** to changes in HR, core temperature or circulating catecholamines

• ***lactate*** increases ***before*** there is evidence of tissue hypoxia ($\downarrow P_{vO2}$)
• the increased demand for ATP alters the ratio $\rightarrow \uparrow NAD^+/NADH$ forcing an increase in lactate production

• ***heat*** dissipation & muscle energy requirements will initially be met but later blood flow will be shunted away from the skin in order to increase muscle blood flow

$\rightarrow$ dramatic rise in core body temperature

• heat production derives from,

i. aerobic metabolism
ii. anaerobic metabolism
iii. neutralisation of acid
iv. hydrolysis of high energy phosphate compounds
v. muscle fibre contraction/relaxation

• later, muscles swell with ***rhabdomyolysis*** and efflux of Ca^{++}, K^+ and CPK
• the resulting ***hyperkalaemia*** is the major source of mortality
• early increases in K^+ are due to sympathetic stimulation & hepatic efflux

■ ***Calcium Entry Blockers***

• Ca^{++} channel blockers have contradictory effects in MH,

1. they generally affect smooth muscle more than skeletal
2. block contractures in affected human muscle *in vitro*
3. are associated with elevations of K^+ and increased ***mortality*** when used *in vivo*, especially in conjunction with ***dantrolene***
4. in conjunction with dantrolene may result in hypotension
5. they do not prevent or effectively treat MH in swine

NB: therefore, their use is ***contraindicated*** in the management of MH

▪ ***Ryanodine Receptor***

• large protein, 5032 AA, which spans the T-tubule & sarcoplasmic reticulum → **Ca^{++}** ***channel***

1. ***all*** strains of MHS swine have a defective ryanodine receptor
   → RYRI 615 $^{Arg \rightarrow Cys}$
2. molecular genetic studies on some affected families have shown a defect on the long arm of **C_{19}** (C_{19} q 13.1), which codes for thr RYRI receptor in humans
3. several studies have shown abnormal ***calcium induced calcium release CICR***, possibly related to abnormalities of the ryanodine receptor in humans

• normal release of calcium from the SR being by ***depolarisation induced calcium release DICR***

NB: CICR may represent an abnormal pathway for Ca^{++} release once MH is triggered, and is blocked by dantrolene at 37°C

• therefore the disease in swine is believed to be a ***point mutation*** in the coding of RYRI
• however, the human aetiology is more complicated

1. only 2 of over 90 human families tested have the point mutation found in swine
2. MHS is associated with other muscle disorders which are not near the RYRI gene
3. other linkage studies is humans do not map to C_{19} q 13.1
4. MHS is swine is a ***recessive trait***, cf. the autosomal dominant disease in humans

• it would therefore appear that MH is a ***heterogeneous*** group of disorders
• other potential causes include,

1. other defects on the RYRI receptor
2. IP_3 metabolism is abnormal in human MHS
3. FFA metabolism is abnormal in MHS patients
4. Na^+ channels are also defective in MHS

NB: ***all*** of these share the final common pathway of increased cytoplasmic Ca^{++}

• studies of proposed abnormal enzymes which have been ***negative*** or inconclusive includes,

1. adenylate kinase
2. adenylate cyclase
3. glutathione peroxidase

The Heart

• function is severely affected in porcine and human MH,

a. initially tachyacrdia & arrhythmias

b. later hypotension and cardiac arrest

• porcine data suggests 2° myocardial involvement
• increased myocardial MRO_2 is 2° to sympathetic stimulation, without lactate production or K^+ efflux suggestive of a 1° MH response

• human myocardial involvement was suggested due to,

1. the high incidence of ***sudden death*** in members of susceptible families
2. occurrence of non-specific ***cardiomyopathy*** & abnormal thallium scans in affected patients

NB: however, myocardial ***biopsies*** have demonstrated only artifactual changes, evidence suggests myocardial dysfunction only during acute episodes

• cardiac effects cannot be attributed to altered function of,

1. α / β receptors
2. adenosine receptors
3. cholinergic receptors

• ***cardiac arrhythmias*** are frequent and relate to sympathetic overactivity & biochemical abnormalities, cf. the CNS below

Central Nervous System

• changes appear to be 2° to,

1. hypoxia, hypercapnia and acidosis
2. hyperthermia
3. hyperkalaemia
4. autonomic hyperactivity

• the extreme picture of coma, areflexia, unresponsiveness, and fixed, dilated pupils is suggestive of acute cerebral oedema and raised ICP
• recovery is variable and related to the severity and duration of the episode
• severe hyperthermia itself, > 42.5°C, may result in a virtually flat EEG & coma
• early CNS involvement is unlikely as $CMRO_2$ & lactate production are not elevated in swine

- ***Sympathetic Nervous System***

1. stress and sympathetic overactivity can trigger MH in susceptible swine
2. signs of sympathetic overactivity occur in both human and porcine MH
3. circulating levels of adrenaline & noradrenaline are markedly elevated in MH (30^{+}x)

• however, these changes are likely to be 2°, and are not essential to MH as,

1. the catecholamine response is not required for the development of porcine MH
2. total spinal blockade & denervation, plus circulating catecholamine blockade ***do not*** affect the onset, development or charteristics of halothane induced MH

• induction of porcine MH 2° to sympathetic overactivity probably relates to an indirect effect of muscle vasoconstriction, with decreased heat-loss and local tissue hypoxia
• sympathetic hyperactivity probably produces the ***hyperglycaemia*** and a major portion of the early ***hyperkalaemia***, via hepatic efflux
• sympathetic antagonists may offer some protection by enhancing temperature loss and modifying acid-base changes, though, demonstration of this has been quite variable,

a. α-antagonists - increase heat loss by cutaneous vasodilatation
   - potentially increase muscle perfusion
b. β-antagonists - attenuate metabolism & fever
   * no improvement in survival

- ***Other Systems***

• if the patient survives the acute episode, other problems may occur,

1. consumption ***coagulopathy***
   - various causes postulated, most likely due to release of ***tissue thromboplastin*** and the gross alteration of membrane permeability throughout the body
2. ***renal failure*** occurs as a 2° phenomenon,
   i. hypotension, hypoperfusion, tissue hypoxia
   ii. haemolysis & haemoglobinuria ± ATN
   iii. myoglobinaemia & myoglobinuria ± ATN
3. ***pulmonary changes*** appear to be 2° and include,
   i. tachypnoea, hyperventilation
   ii. V/Q mismatch
   iii. increased P_{aCO2} and $ETCO_2$
   iv. decreased P_{aO2}
   v. pulmonary oedema

• a deficiency of plasma pseudocholinesterase, and an increased incidence of the fluoride resistent gene have occasionally been associated with MH
• smooth muscle ***does not*** respond abnormally in MH susceptible swine

- ***Cause of Death***

1. ***early*** - hours
   i. VF
   ii. hyperkalaemia
2. ***intermediate*** - following resuscitation
   i. pulmonary oedema
   ii. cerebral oedema
   iii. coagulopathy
   iv. acid-base/electrolyte imbalance
3. ***late*** - days
   i. MOSF
   ii. renal failure
   iii. brain damage

NB:	the height of the fever ***does not*** correlate with outcome

Signs of Malignant Hyperthermia	
Clinical	**Laboratory**
tachycardia[§]	**metabolic acidosis**[§]
tachypnoea[§]	**respiratory acidosis**[§]
hyperthermia[§]	**decreased S_{vO2}**[§]
rigidity[§]	**increased S_{vCO2}**[§]
arrhythmias	**raised $ETCO_2$**[§]
cyanosis	hyperkalaemia
skin mottling	myoglobinaemia
masseter rigidity	raised CPK
sweating	unstable BP
	coagulopathy
[§] primary signs of MH	

- ***Clinical Presentation***

• when clinical signs associated with MH are found, tachycardia, fever, muscle rigidity etc., the association with MH is ***poor*** unless more than 1 sign is present
• ie., presence of a single factor above is usually ***not MH***
• the clinical syndrome of MH may occur as a "final common pathway" in situations which are not specifically related to a susceptibility to MH, eg,

1. exaggerated heat stroke
2. neuroleptic malignant syndrome
3. muscle disorders - Duchenne

- ***Modes of Presentation***

1. masseter muscle rigidity
2. suxamethonium induced muscular rigidity
3. "full blown" syndrome - intraoperatively, or in recovery
4. intraoperative fever alone
5. neuroleptic malignant syndrome
6. heat stroke
7. episodic fever
8. SIDS

Masseter Spasm

• the occasional patient will develop trismus as the earliest sign of MH
• 2 USA retrospective studies found an incidence of trismus ~ 1% following halothane & SCh
• most often in children given a mask halothane induction, followed by SCh, therefore either,

1. MH susceptibility occurs more frequently than previously thought, or,
2. trismus may occur in normal subjects

NB: due to the comparitively low incidence of MH, the later is more likely

• tachycardia, occasional PVC's and mild metabolic acidosis usually occur
• the implication of this is uncertain, as the definition of masseter muscle spasm/rigidity varies with the investigator
• masseter muscles have an ***atypical fibre type*** which responds with slow tonic contractions

→ there is a range of response for the masseter muscles following SCh,

1. subclinical "jaw stiffness" $\equiv^{t}$ normal response
   - only demonstrable with strain devices
   - virtually none of these are MH prone
2. "jaw tightness interfering with intubation"
   ~ 1% of children
   - a small ***undetermined*** percentage are at risk of MH
3. "extreme jaw rigidity, unable to open the mouth"
   = masseter muscle rigidity, MMR
   ~ 50% are biopsy determined at risk for MH

• the last group is that often quoted as showing ~ 50% positive for MH with a contracture test
• this association is frequently quoted for the second group, which would lead to an expected MH susceptibility frequency of ~ 0.5% !!
• the actual incidence of true MMR is uncertain and Miller suggests the incidence of MMR is actually less than the quoted 1%, and there is a need for formal prospective studies
• the problem is then of how to manage the child who displays MMR,

1. Rosenburg (1988)
   - stop anaesthesia
   - administer dantrolene
   - monitor for rhabdomyolysis (CPK, myoglobinuria)
   * muscle biopsy
2. Gronert (1988)
   - continue with safe agents
   - monitor for rhabdomyolysis
   - monitor $ETCO_2$, temp., etc.
   * muscle biopsy
3. Littleford (1991)
   - continue (triggering) anaesthesia
   - look for other rigidity
   - monitor $ETCO_2$, temp., etc.
   * muscle biopsy

NB: the later is clearly the most controversial and it would seem unwise to continue when equally effective, safe alternatives are available

• recommendations by ***Kaplan***, ASA 1992,

1. jaw stiffness
   - able to be opened with firm manual pressure
   - normal response and usual anaesthetic may be continued
2. diminished mouth opening ~ 1:100 children
   - mouth cannot be fully opened, despite firm manual pressure
   - interfers with intubation
   - more suggestive of MH ? incidence unknown
   - switch to non-triggering agents, monitor carefully & continue anaesthetic
3. masseter muscle rigidity
   - jaw cannot be budged, "jaw of steel"
   - may well be the beginning of MH episode ~ 50% children
     ~ 25% adults
   - stop anaesthetic & monitor carefully

NB: #2/3 → monitor temperature, HR, BP in recovery for 4 hours
obtain postoperative serum CK's q6h x 4
urine for myoglobin
monitor in hospital for 24 hours
if CK > 20,000 then assume MHS positive
counsel with family regarding ***muscle biopsy***

■ ***Triggering***

1. a genetic predisposition
2. the absence of inhibiting factors
3. the presence of triggering factors

• ***depolarisation*** may be a significant factor, either "awake" or anaesthesia induced,

a. mechanical threshold is lower cf. "normal", therefore predisposed to contractures
b. SCh & carbachol trigger MH susceptible muscle
c. electrical stimulation triggers MH susceptible muscle
d. non-depolarising muscle relaxants delay the appearance of MH

NB: however, 4-aminopyridine does not trigger MHS swine ? why

• ***volatile*** induced MH may be triggered by,

a. perturbation of the surface membrane
   - halothane → surface or internal membranes of the fibril
   - SCh → end-plate effects
b. ? effects on the SR or mitochondira *in vivo*
   - effects on isolated preparations imply these are too small to trigger MH

• ***succinylcholine*** has a number of variant responses which may occur in isolation or combination,

a. muscle contracture

b. altered membrane permeability without contracture
   - resulting in release of myoglobin, CPK, and K^+
   - this occurs to a small extent in "normal" individuals
   - enhanced by the presence of halothane and reduced by curare

c. an increase in metabolism
   - as for MH, is usually associated with altered permeability and contracture

• ***nitrous oxide*** has been proposed as a weak trigger, however there is minimal evidence for this

• ***amide*** local anaesthetics were previously thought to trigger MH, but have since been exonerated
• animal data showing Ca^{++} release from the SR require mM concentrations not achieved clinically

• ***muscle relaxants*** block the effects of SCh in triggering MH and delay or attenuate the effects of the volatile agents
• dTC has been associated with greater lactate production in porcine MH & does produce contracture in denervated muscle, indicating it may have some depolarising action not normally clinically evident
• however, it has not been shown to trigger porcine MH
• ***reversal*** of NMJ blockade with antiacetylcholinesterase agents could theoretically trigger MH
• however, 4-aminopyridine which increases ACh does not, and reversal has been performed in susceptible patients without untoward effects

• the youngest reported episode was *in utero*, immediately prior to birth, at LUSCS under GA
• the father was known MH susceptible
• delayed onset of MH may represent depressed MH responses, 2° to drugs, or to proloned anaesthetic stresses

• ***awake triggering*** occurs readily in the porcine model 2° to heat stress, exercise, anoxia, apprehension and excitement
• these relate to muscle activity or increase temperature, as suggested by,

1. MHS swine increase MRO_2 & lactate production in response to,
   i. heat > 41°C or carbacholine, but
   ii. ***not*** α/β sympathetic agonists
2. these abnormal responses are blocked or delayed by neuromuscular blockers

• factors which suggest non-anaesthetic triggering in humans include,

1. increased incidence of unexplained ***sudden death*** in affected families
2. these families develop a non-specific ***cardiomyopathy***
3. there are a series of case reports relating heat stroke, unusual stress & fatigue, and myalgias to possible awake MH episodes

- ***Differential Diagnosis Raised $ETCO_2$***

a. increased CO_2 production
- fever
- sepsis, sepsis syndrome
- light anaesthesia
- pregnancy
- thyrotoxicosis
- obesity
- drugs

b. decreased ventilation

i. increased anaesthetic depth - SV

ii. machine related - ↓ FGF, disconnect, leak

iii. ventilator related
- setting, malfunction
- decreased driving pressure
- decreased patient compliance (pressure cycled)

iv. breathing circuit
- Mapleson - ↓ FGF, disconnect, obstruction
- circle
  - valve malfunction
  - absorbant (depletion, channeling or bypass)
  - obstruction, leak, disconnect

v. pulmonary
- upper airway obstruction
- mainstem intubation
- secretions, blood, aspiration
- asthma, ARDS
- CCF
- pneumothorax, haemothorax

vi. extrathoracic
- ↑ abdominal muscle tone
- retractors with ↓ pulmonary compliance
- ascites
- pregnancy
- morbid obesity

c. monitor error
- calibration drift
- moisture in measuring chamber

d. multifactorial - pregnancy, obesity, children, etc.

- ***Differential Diagnosis Fever / Tachycardia***

a.	equipment misuse / malfunction	- inaccurate temperature probes - blanket > 40°C - humidfier > 43°C - radiant warmer too close to patient
b.	decreased heat loss	- raised ambient temperature - excessive coverings - drug induced vasoconstriction
c.	increased heat production	- thyrotoxicosis - phaeochromocytoma - osteogenesis imperfecta - sepsis - transfusion reaction - familial fever
d.	central deregulation	- hypothalamic injury (anoxia, oedema, trauma) - prostaglandin E_1 - serotonin
e.	drug reactions	- neuroleptic malignant syndrome - atropine, glycopyrrolate, tricyclics (ACh-Synd.) - droperidol, metoclopramide - monoamine oxidase inhibitors - amphetamines, cocaine, ketamine - aspirin (overdosage)
f.	***malignant hyperpyrexia***	

Evaluation of Susceptibility

- ***Diagnosis***

1. unequivocal clinical episode of MH
2. first degree relative with unequivocal MH, plus raised CPK
3. positive muscle biopsy

- ***Muscle Testing***

• excised muscle is placed on stretch in a bath at 37°C
• optimal length-tension is established, then caffeine ± halothane are added
• the muscle is then stimulated supramaximally and the contracture amplitude measured,

a. halothane → increased
   caffeine → reduced ***MH susceptible***

b. caffeine + halothane → broad spectrum of response
   • ?? this represents an,
   i. inherent lack of precision of the test, or
   ii. a spectrium of susceptibilty to MH

• the responses to caffeine 2 mmol/l and halothane ≤ 2% are the only tests that ***unequivocally discriminate*** between MH survivors and controls
• the problem is the patient who is muscle biopsy negative but clinically positive
• a wide range of expression of the disorder has been observed in both pigs and humans
• thus, most laboratories trend toward false positive results as the consequences of a false (+)'ve are less than a false (-)'ve

NB: as yet, ***no false negative*** results have been reported

- ***Associated Diseases***

• the majority of cases are unsuspected, however, there are a number of conditions associated with an increased risk of MH,

a. diseases almost certainly related → ***central core disease***

b. diseases possibly related
   i. Deuchenne muscular dystrophy
   ii. King-Denborough syndrome ? RDM says certainly related
      • short stature, musculoskeletal deformities and mental retardation
   iii. other myopathies
      - Schwartz-Jampel syndrome
      - Fukuyama muscular dystrophy
      - Becker muscular dystrophy
      - familial periodic paralysis
      - myotonia congenita
      - SR-ATP deficiency synd. & mitochondrial myopathy

c. diseases coincidentally related
   i. SIDS
   ii. neuroleptic malignant syndrome
   iii. others
      - lymphomas
      - osteogenesis imperfecta
      - glycogen storage disease

• other tests are non-conclusive but helpful in assessment
• elevated serum ***CPK*** **~ 60-70%** of MH patients even at rest
• the usefulness of this in assessment lies in the absence of ***other causes*** of elevation and on the ***degree*** of elevation
• in the absence of other explanations, a ³ **10x *rise*** in the clinical setting of hypermetabolism is diagnostic of MH until proven otherwise
• other proposed investigations include,

1. post-ischaemic tetanic stimulation = "torniquet test"
2. lowered CvO_2 in the ischaemic arm
3. halothane induced platelet ATP depletion

NB: results from these have ***not*** been consistently reproducible

- ***Malignant Neuroleptic Syndrome***

1. the picture may be similar to MH but there is associated drug administration and the onset is over days to weeks
2. impairment of ***motor function*** with rigidity, akinaesia, & extrapyramidal disturbance
   ∝ central ***dopaminergic*** derangement
3. deterioration in mental status, with stupor, delerium & coma
4. ***hyperpyrexia*** develops, with deterioration of other "vegetative" functions
   → diaphoresis, labile BP & HR, and tachypnoea

Management - Acute

1. stop all ***triggering agents*** immediately
   * continue with safe agents if surgery cannot be immediately ceased
2. ***hyperventilate*** with **100% O_2**
   * use new soda-lime & change to "clean MH-machine", when available
3. administer ***dantrolene*** **2-3 mg/kg** immediately
   - 20 mg vials with - NaOH to a pH ~ 9-10
     - mannitol to maintain isotonicity
   - a **7**0 kg adult will require **7** vials initially, and may need up to 35 vials in total

   i. repeat dose every **5 minutes** until vital signs normalise

   ii. total dose up to 10-20 mg/kg

   iii. continue with 1 mg/kg q6h ó/IV postoperatively for 48-72 hrs
   - RDM states 15 hourly as this is the approximate half-life
4. ***bicarbonate*** **1-2 mmol/kg** stat, then follow AGA's
5. initiate cooling
   - iced saline, cooling blanket, body cavity lavage
   - extracorporeal circulation
   * cease at ~ 38-39°C to prevent hypothermia
6. manage hyperkalaemia
   - control MH by giving dantrolene
   - $NaHCO_3$
   - insulin & dextrose
   * CaCl for life-threatening arrhythmias
   * hypokalaemia frequently follows treatment
7. manage arrhythmias
   - procainamide 3 mg/kg if persistent
   - to maximum of 15 mg/kg
8. manage DIC
   - maintain tissue perfusion, IVT
   - decrease temperature
   - 1° treatment of MH
9. monitoring
   - AGA's, $ETCO_2$, SpO_2, ECG, core T°
   - U&E's, Ca^{++}, CK, myoglobin
   - APTT/PT, platelets, FDP's
10. maintain urine output - IVT ± mannitol/frusemide
11. transfer to ICU - observe for 24-48 hours
12. counsel family ± investigate

NB: no anaesthetic should be given without access to 36 vials of dantrolene & a clean anaesthetic machine (Kaplan)

- Gronert (Miller) states it is no longer necessary to provide a non-contaminated anaesthesia machine by flushing with O_2 for several hours
- removal of the vaporisers, replacement of the fresh gas outlet hose, use of a disposable circle with a flush of O_2 for 6 minutes is sufficient

- ***Protocol For Management Royal Hobart***

1. ***recognition***
   i. masseter spasm following SCh
   ii. unexplained tachycardia
   iii. tachypnoea in unparalysed
   iv. rising $ETCO_2$
   v. rising temperature
   vi. cyanosis / arterial desaturation
2. immediate ***action*** following recognition of acute MH
   i. announce life-threatening emergency & conclude surgery ASAP
   ii. send for skilled anaesthetic/ICU assistance
   iii. enlist the ***immediate*** assistance of at least 4 ***experienced*** nurses
   iv. anaesthetist in charge ***simultaneously*** coordinates 5 tasks,
      - reconstitution & administration of dantrolene
      - removal of precipitating causes
      - monitoring
      - resuscitation
      - active cooling

- ***Dantrolene***

i. 20 mg vials + 60 ml sterile water
ii. final pH ~ 9.5, ∴ large bore central line preferable
iii. poor solubility & difficult to prepare, may occupy several nurses
iv. 2-3 mg/kg bolus, then 1 mg/kg 5 minutely prn, to maximum 20 mg/kg
v. dantrolene takes ~ 6 minutes to have any effect

- the actions of dantrolene include,

a. decreases ***release*** of Ca^{++} from the SR, without affecting re-uptake
b. ? antagonises the effects of Ca^{++} at the actin/myosin - troponin/tropomyosin level
c. muscular weakness, which may potentiate NMJ blockade
   ~ 5-15 mg/kg produces significant muscular relaxation
d. there is ***no*** effect on NMJ transmission
e. up to 15 mg/kg there is ***no*** significant effect on the CVS
f. up to 30 mg/kg there is ***no*** significant effect on respiration

NB: there is ***no*** evidence of ***toxicity*** when administered acutely

• reducted muscle rigidity results in rapid normalisation of serum biochemistry, especially hyperkalaemia, and cardiac function
• cardiac arrhythmias & arrest are almost always 2° to hyperkalaemia/acidosis, the myocardium is not directly involved in MH pathology
• these can usually be managed by treating the 1° disturbance
• $CaCl_2$ can be used as a last resort for hyperkalaemia
• Ca^{++}-channel blocking agents should ***not*** be used as they may result in cardiovascular collapse in the presence of dantrolene

- ***Precipitating Causes***

1. high priority
   i. remove all inhalational agents & known trigger agents,
      • remove vapourisers from Boyle's machine
   ii. hyperventilate with O_2 > 10 l/min FGF
2. lower priority
   i. soda lime ***is not*** a significant reservoir for volatile, but will require replenishing due to rapid exhaustion
   ii. replace rubber hoses
      • 1 minute at 10 l/min O_2 → [halothane] < 100 ppm
        ~ 100 x less than expired gas

- ***Monitoring / Tests***

1. S_pO_2 / $ETCO_2$ / BP / ECG
2. temperature probes - rectal & oespohageal
3. IABP - for serial AGA's initially
   - pressure monitoring is lower priority
4. baseline biochemistry - ECU & AGA's initially
5. IV access
   i. large peripheral line - fluids
      - initial administration of dantrolene
   ii. CVC line - EJV / IJV preferable due to risk of ***coagulopathy***
      - administration of dantrolene
      - pressure monitoring
6. urinary catheter **> 2 ml/kg/hr** target urine output
   - sample for ***myoglobinuria***
7. repeat tests
   i. AGA's ~ 10 minutely
   ii. ECU ~ hourly
   iii. Coag's ~ hourly

- ***Resuscitation***

1. paralyse with ***pancuronium***
2. intubate & hyperventilate with 100% O_2 > 2-3x MV
   - as guided by $ETCO_2$ / AGA's
3. administer HCO_3^- as per AGA's ? initial bolus per RDM
4. management of ***arrhythmias***
   i. treat MH with dantrolene
   ii. propranolol - 1 mg boluses prn
   iii. procainamide ~ 3-5 mg/kg slowly
   ≤ 20 mg/kg maximum dose
   iv. calcium channel blockers are ***contraindicated***
5. management of ***hyperkalaemia***
   i. treat MH with dantrolene
   ii. correction of acidosis with HCO_3^-
   iii. Actrapid 10^U / Dextrose 50% 50 ml
   iv. RHH states do not use $CaCl_2$, cf. ASA lectures say OK if hyperkalaemia severe
   v. avoid resonium - action too slow
   - hypokalaemia common in recovery phase of MH
6. ***renal protection***
   i. saline diuresis
   ii. mannitol ± frusemide
   iii. maintain urine output > 2 ml/kg/hr
7. management of ***coagulopathy***
   i. treat MH with dantrolene
   ii. maintain tissue perfusion - CVP/MAP
   - IVT fluids ± inotropes
   iii. decrease temperature
   iv. FFP/platelets if clinical bleeding

- ***Active Cooling***

1. commence immediately
   i. fanning, cool sponges
   ii. ice packs to groins, axillae, neck, popliteal & cubital fossae & abdomen
   iii. gastric, peritoneal, bladder, rectal or pleural lavage with cool saline
2. reduce theatre temperature if possible
3. cease active cooling at core temperature < 38.5°C

- ***Follow-Up Immediate***

1. admit to ICU
2. intensive monitoring for 24-48 hours
   i. temperature- core & peripheral
   ii. ECG, IABP, CVP ± PAOP
   iii. biochemistry - ECU, CK's, myoglobinuria
   - AGA's
   - Coag's
   iv. urine output
   v. neuromuscular status *rigidity
3. ***dantrolene***
   - ~ 1mg/kg q6h for 24 hours
   - higher doses prn - ↑ rigidity / temperature
   - ↓ pH, P_{aO2} / ↑ P_{aCO2}
   - may be given enterally if GIT functioning (price ~ 1000x less)

- ***Follow-Up Late***

1. this is ***essential***
2. counsel patient & family
3. screening CK's on all family members
4. suggest muscle biopsies if CK normal
5. medi-alert bracelets, letters etc.

Management - Elective

- ***Assessment***

1. history from patient or relatives, previous anaesthetic records, etc.
2. detailed informed consent from patient / guardian
3. bias for regional anaesthesia if practicable
4. schedule operation during "working hours" when staff available

- ***Conduct of General Anaesthesia***

a. preparation of theatre personnel

b. prepare a "clean" anaesthetic machine
   - Miller, Kaplan and others state separate machine no longer required
   - remove vaporisers from machine & flush for > 10 minutes with 10 l/min O_2
   - replace all rubber hoses with new rubber or ***plastic hoses***
   - fit new ***rubber belows*** to the ventilator

c. ***MH cart***

i.	drugs	- dantrolene 36 vials + 2000 ml sterile H_2O
		- $NaHCO_3$
		- dextrose 50%
		- mannitol 25%, frusemide
		- procainamide
		- chlorpromazine
ii.	equipment	- T° probes
		- NG tubes
		- urinary catheters
		- disposable breathing circuit
		- soda lime for circle
		- blood collection tubes
		- syringes/needles, AGA syringes
		- CVC cannulation equipment

d. use of safe anaesthetic agents

e. monitoring - $ETCO_2$, SpO_2, ECG, NIBP, FiO_2
   - T° core & peripheral
   ± urinary catheter

f. adequate recovery ≥ 4 hrs duration → ward or ***home***

g. alert back-up support - anaesthetic staff
   - local ICU

Anaesthetic Agents for MH	
Unsafe	Safe
ALL modern ***volatile agents*** • halothane = worst • enflurane • isoflurane • desflurane & sevoflurane	barbiturates propofol ketamine etomidate N_2O
suxamethonium	non-depolarizing relaxants anticholinesterases anticholinergics
	opioids droperidol benzodiazepines
	local anaesthetics[1]
	catecholamines digoxin Ca^{++}

[1] amides raise $[Ca^{++}]_{ICF}$ but do not trigger MH, therefore, they may theoretically worsen an ongoing episode

MH - Prophylaxis

- though prophylaxis would seem prudent in all patients, dantrolene may be associated with,
    i. nausea & vomiting
    ii. phlebitis
    iii. lethargy
    iv. severe muscle weakness in some disease states
    v. potentiation of neuromuscular blockade
    vi. uterine atony postpartum
    vii. placental transfer and neonatal hypotonia

- therefore, prophylaxis may be recommended for,
    1. prolonged procedures ≥ 2 hours
    2. physiologically stressful procedures
    3. in the presence of underlying disease states which are intolerant of a hypermetabolic state or myoglobinuria

    NB: dantrolene 2.5 mg/kg IV 30 mins to 2 hrs pre-anaesthesia
    dantrolene 5 mg/kg ó 24 hours postoperatively

Management - Family

- most important is adequate information and support
- biopsy of the patient is reasonable after an appropriate interval (> 6 weeks)
- biopsy of the remaining family members is ***not essential***, as most anaesthetists will treat them as susceptible irrespective of the biopsy result
- biopsy at the time of incidental surgery is therefore logical
- prior to biopsy dantrolene & droperidol should be avoided as they "normalise" the abnormal responses of MH susceptible individuals
- those refusing biopsy should have their plasma CPK checked, if elevated this may be taken as evidence of MH susceptibility in a close relative

MYOPATHIES

Classification

1. ***hereditary***
   - i. muscular dystrophies
   - ii. myotonias
   - iii. congenital myopathies
   - iv. glycogen storage diseases
   - v. glycolytic defects
   - vi. lipid metabolism disorders
   - vii. familial periodic paralysis
2. ***acquired***
   - i. neuromuscular junction
   - ii. autoimmune
   - iii. endocrine & metabolic
   - iv. toxic myopathies
   - v. alcohol
   - vi. infective
   - vii. infiltrative
   - viii. disuse atrophy
   - ix. rhabdomyolysis

- ***Hereditary Myopathies***

a.	muscular dystrophies	- Duchene - Becker's - limb girdle, F-S-H, etc.
b.	myotonias	- dystrophica myotonica - myotonia congenita - paramyotonia
c.	congenital myopathies	- central core - nemaline - microtubular - congenital fibre disproportion
d.	glycogen storage diseases	- types II, III, IV, V
e.	glycolytic defects	- types VII, IX, X, XI
f.	lipid metabolism disorders	- carnitine deficiency - carnitine palmityltransferase deficiency
g.	familial periodic paralysis	

- ***Acquired***

a. **neuromuscular junction**
- myasthenia gravis
- Eaton-Lambert
- organophosphates

b. **autoimmune**
- SLE, RA
- polymyositis / dermatomyositis
- polymyalgia rheumatica

c. **endocrine**
- diabetes
- thyrotoxic (apathetic), hypothyroidism
- hypo / hyperparathyroid
- hypopituitarism
- Cushings, ? Addison's

d. **metabolic**

i.	hypo	- glycaemia / K^+ / Ca^{++} / $HPO_4^=$
ii.	hyper	- Mg^{++} / K^+
iii.	nutritional	- vitamin E & D deficiency
iv.	systemic disorders	- renal & hepatic failure - malignancy

e. **toxic myopathies**

i.	focal (IMI)	- pentazocine, pethidine
ii.	generalised	- chloroquine, clofibrate, colchicine - steroids, D-penicillamine - propranolol, perhexiline, labetalol
iii.	rhabdomyolysis	- alcohol, heroin, amphetamines, PCP, cocaine
iv.	malignant hyperthermia	* see table

f. **alcohol** * multifactorial

g. **infective**

i.	viral	- influenza A & B, adenovirus, EBV, herpes - Coxsackie B_5 - dengue, measles
ii.	bacterial	- brucella - legionella - Staphlococcal - leptospirosis
iii.	fungal	
iv.	protozoal	- toxoplasmosis, trichinosis, worms

h. **infiltrative** - amyloid, tumour, fibrositis

i. disuse atrophy

j. rhabdomyolysis - traumatic, toxic, MH

MYASTHENIA GRAVIS

Def'n: a neuromuscular disorder resulting in weakness and fatiguability of skeletal muscle, due to an ***autoimmune*** mediated decrease in the ***number***, and ***functional integrity*** of ACh receptors at the neuromuscular junction;
"the prototype of antibody mediated autoimmune disease"

i. ***degradation*** of AChR's at an accelerated rate due to cross-linking
ii. effective ***junctional blockade*** due to receptor occupancy by antibodies
iii. damage to the postsynaptic membrane due to ***complement activation***

- ***Essential Features***

a. muscular weakness
   - external ophthalmoplegia ≥ 90%
   - facial weakness
   - bulbar muscle involvement * risk of aspiration
   - respiratory failure

b. easy fatigability

c. recovery with rest or anticholinesterases

Myasthenia Grades[§]	
I	• extraocular muscle involvement only • good response to anticholinesterases
IIA	• generalised mild muscle weakness • no respiratory involvement • good response to anticholinesterases and steroids
IIB	• generalised moderate muscle weakness, and/or bulbar dysfunction • more severe, rapidly progressive • may involve respiratory muscles
III	• acute, fulminating presentation, and/or respiratory dysfunction • rapid deterioration over ≤ 6 months • high mortality
IV	• late, severe, generalised myasthenia gravis • incidence: 1:20,000 • females > males • 80% > 20 yrs • progression from types I & II

[§] Osserman and Genkins (1971)

- ***Presentation***

a. ***transient neonatal myasthenia***
- ~ 15-20% of neonates born to myasthenic mothers
- pregnancy may result in remission or exaccerbation of maternal myasthenia
- *no correlation* between the severity of maternal disease and neonatal occurrence
- *no correlation* between the level of maternal AChR-Ab and neonatal occurrence
- spontaneous remission usually in 2-4 weeks

b. ***congenital or infantile myasthenia***
- ***not*** autoimmune, possibly autosomal recessive inheritance
- rare in the absence of maternal myasthenia
- comprises a number of genetically determined abnormalities of the AChR or the post-synaptic membrane

c. ***juvenile myasthenia***
- ~ 4% onset before 10 years and ~ 24% before age 20 years
- marked female predominance ~ 4:1
- pathologically identical to the adult disease, though, thymoma *is not* a feature

d. ***adult myasthenia***
- prevalence ~ 1:20,000 * F:M ~ 3:2 overall
  - F:M ~ 2:1 < 50 years
  - F:M ~ 1:1 > 50 years
- males tend to have more severe & rapidly progressing disease
- hyperplasia of the thymus in > 70%, ***thymoma*** in 10-15%
- distribution, severity & outcome are determined by the course within the first 2-3 years following onset, suggesting most ACh receptor damage occurs early
- ~ 14% remain localised to the extraocular muscles, 86% becoming generalised

- ***Anti-ACh-Receptor Ab's***

NB: * virtually diagnostic if present

i. all grades ~ 85-90% (+)'ve
ii. grade I ~ 50% (+)'ve
iii. AChR-Ab (-)'ve patients have mild or localised myasthenia
iv. IgG predominantly against the a***-subunit*** of the endplate receptors
v. individual patients have heterogenous populations of AChR antibodies
vi. there is limited sharing of idiotypes between patients
vii. T-cells become sensitised against ***thymic myoid cell*** AChR's during maturation
viii. ***T-cell dependent*** B-cell antibody production results in circulating Ab's

- ***Complications***

a. myasthenic crisis - severe life-threatening relapse
b. cholinergic crisis
c. respiratory failure - aspiration, infection, weakness
d. "Mary Walker phenomenon"
→ acute muscle weakness following exercise due to ***lactic acidosis***
e. ***cardiomyopathy***
f. associated diseases making weakness worse - hyper / hypothyroidism
- SLE, RA, polymyositis

- ***Differential Diagnosis***

i. myasthenic syndrome - Eaton-Lambert
ii. neurasthenia
iii. hyperthyroidism
iv. botulinism
v. intracranial mass lesions

- ***Eaton-Lambert Syndrome***

i. acquired disorder of ***quantal release*** of ACh from motor nerve terminal
ii. usually males, aged 50-70 years
iii. disease predominantly of the ***limb girdle*** muscles
iv. high association with ***small cell carcinoma*** of the lung
v. ? IgG-Ab to the presynaptic voltage-dependent Ca^{++} channels
vi. ACh content and acetyltransferase activity are normal
vii. decreased quantal release decreases MEPP frequency
viii. ***dysautonomia*** may occur, with dry mouth, impaired accomodation, urinary hesitancy and constipation
ix. EMG → "characteristic"
  - incremental response
  - improvement with exercise / tetanic stimulation
  - marked deficit with "normal" clinical strength[§]
x. weakness is not reliable reversed with anti-AChE agents, however, 3,4-diaminopyridine increases ACh release
xi. patients are sensitive to ***both*** deplarising and non-depolarising relaxants

NB: [§] this is in contrast to myasthenia, where the EMG abnormality is ***mild*** in the presence of marked clinical weakness

Myasthenic Crisis

Def'n: sudden, severe life-threatening relapse

a. may last weeks-months

b. risk factors
- introduction of steroids
- age
- pregnancy
- infection
- surgery, trauma

c. drugs
- aminoglycosides, tetracyclines
- class Ia antiarrhythmics
- narcotics, volatile anaesthetics
- muscle relaxants

- ***Clinical Features***

a. rapid deterioration

b. positive tensilon test

c. NM stimulation
- tetanic fade
- post-tetanic facilitation

Cholinergic Crisis

a. excessive doses of anticholinesterases

b. risk factors
- recovery phase from any "stress"
- following response to steroids
- thymectomy
- plasmapheresis
- immunosuppressives

c. differentiation from ***myasthenic crisis***

- ***Clinical Features***

a. negative Tensilon test

b. NM stimulation

i. depressed single twitch

ii. ***absent*** fade & absent post-tetanic facilitation

Tensilon Test

• ***edrophonium*** is commonly used due to rapid onset (< 30s) and short duration of action (~ 5m), resulting from freely ***reversible*** binding with ACh-E
• objective assessment of one of the unequivocally weak groups of muscles,

a. initial dose 2-3 mg IV
b. improvement (+)'ve - test is terminated
c. no improvement (-)'ve - further dose of 8 mg
d. small initial dose due to unpleasant side-effects
   - nausea, diarrhoea, salivation, fasciculations and rarely syncope
   - atropine (0.6 mg) should be available for administration
e. false positives - amyotrophic lateral sclerosis
   - placebo-reactors

• some cases may be better assessed with a long acting anticholinesterase agents, such as neostigmine

Treatment

a. ***anticholinesterases***
   - little benefit in severe cases with respiratory muscle involvement
   - animal studies show long term administration results in changes in the AChR similar to those seen in myasthenia
   - patient education regarding overdose (cholinergic) vs. underdose (myasthenic)

   i. neostigmine 15 mg qid ~ 0.5 mg IV
      ~ 1.5 mg IM
   ii. pyridostigmine 60 mg 6-8 hrly

b. ***immunosupression***
   i. prednisolone 50-100 mg/day → increases muscle strength
   ii. cyclophosphamide, azathioprine

c. ***plasmapheresis***
   - every 2-3 days for 2 wks → ~ 45% show marked improvement or remission
   - however, this only lasts 4 days to 12 weeks
   - indications

   i. myasthenic crisis, especially with respiratory failure
   ii. respiratory failure
   iii. preoperative (for thymectomy)
   iv. refractory to drug therapy (steroids & anticholinesterases)

- ***Thymectomy***

NB: should be performed on ***all*** adult patients with ***generalised*** disease, especially between puberty & 55 years;
there is also unanimity regarding resection of thymomas, although, disease remission is less frequent

a. removal of thymoma ~ 10% of cases, most are benign
- resection to prevent local spread

b. therapeutic thymectomy ≤ 85% of patients improve
~ 35% achieve drug-free remission

- thymus is abnormal in ~ 75% (65% hyperplasia + 10% thymoma)
- improvement may begin up to 1-10 years post-surgery !!
- there is ***no evidence*** that removal in ***childhood*** results in immunodeficiency
- operation is usually recommended for patients with only extraocular disease
- the anterior, ***trans-sternal approach*** is superior, as even small remnants left during the transcervical approach will limit success

Anaesthetic Management

- use regional or local anaesthesia whenever possible

a. **preoperative evaluation**
- age, sex, onset & duration of disease
- presence or absence of thymoma
- bulbar involvement, aspiration risk
- CAL

b. **optimisation of condition**
- steroids ± azathioprine (age > 15)
- plasmapheresis
? anticholinesterases

- the use of anticholinesterases is debated
- they potentiate vagal responses & require the use of atropine
- decrease the metabolism of suxamethonium and ester local anaesthetics

c. **premedication**
- avoid respiratory depressants
? atropine IM ± benzodiazepines

d. **induction / maintenance**
- deep inhalational anaesthesia
- balanced anaesthesia with muscle relaxants

- abnormal response to both depolarizing (↓) & non-depolarizing (↑) relaxants
- these responses are seen during remission & with localised extraocular disease
- the ED_{95} for SCh in myasthenia may be 2-2.5 x normal, however ***type II blockade*** is readily produced
- conversely, the ED_{95} for the non-depolarising agents may be 10% of normal
- atracurium & vecuronium have short enough half-lives to allow titration to effect

e. **postoperative management**
- neuromuscular monitoring should be continued into the postoperative phase
- few studies correlate tests of NMJ function with adequacy of ventilation

NB: the differential responses seen between peripheral versus bulbar muscles is further exaggerated in the myasthenic patient !

Elective Postoperative Ventilation		
Factor		Points
long history of myasthenia	> 6 yrs	12
moderate to severe CAL	- not 2° to MG	10
high pyridostigmine dose	> 750mg/day	8
diminished vital capacity	< 2.9 l < 40 ml/kg	4

NB: total score > 10 points = post-operative ventilation for > 3 hours

- following transcervical thymectomy ~ 7.4% of patients require prolonged (> 3 hrs) ventilation

- ***Outcome***

a. ***thymectomy*** benefits ~ 96% of patients, irrespective of preoperative status
   i. ~ 46% develop complete remission
   ii. ~ 50% are asymptomatic or improve on therapy
   iii. ~ 4% remain the same

b. thymectomy ***does not*** always result in a decrease the anti-AChR-Ab titre

NB: the anti-AChR sensitised T-cells survive long after thymectomy

MUSCULAR DYSTROPHIES

Duchenne Muscular Dystrophy

a. ***X-linked recessive*** disorder, affecting almost exclusively ***males***

b. incidence ~ 13-33:100,000
~ 1:3,000-8,000

c. progressive, ***symmetrical*** weakness of the pelvic & shoulder girdles,
   i. onset by age 5 years
   ii. leg braces by 8-10
   iii. non-ambulatory by 12 years
   iv. survival beyond 25 years rare

d. associated problems
   - tendon and muscle contractures
   - progressive ***kyphoscoliosis***
   - impaired pulmonary function
   - ***cardiomyopathy***
   - intellectual impairment (~ 33%)

e. palpable enlargement of some muscles, resulting initially from ***hypertrophy*** and later from replacement with fat and connective tissue

f. laboratory findings
   i. CK, aldolase
      - massive & early elevations
      - MM & MB bands
      - not BB (cancer, heart trauma, CPB, CT disorders)
   ii. EMG
      - myopathic pattern
   iii. ECG
      - tall R in V_1, deep Q in precordial leads
   iv. biopsy
      - necrotic fibres, phagocytosis, fatty replacement

g. carrier detection
   i. CK
      ~ 50% of female carriers show elevation
   ii. DNA probes
      - abnormal gene coding for ***dystrophin***
      - restriction fragment length polymorphisms (RFLP's)

h. complications
   i. respiratory
      - respiratory failure
      - recurrent infections
   ii. CVS
      - ***cardiomyopathy*** in almost ***all*** patients
      - CCF occurs rarely, only with major stress
      - arrhythmias occur but also uncommon
      * cardiac death is ***rare***
   iii. GIT
      - acute gastric dilatation (may be fatal)
      - aspiration syndromes

Myotonic Dystrophy *Dystrophica Myotonica*

a. ***autosomal dominant*** ~ 1:10,000

b. onset - typically 2nd or 3rd decade
- affected individuals may remain asymptomatic

c. *congenital myotonic dystrophy*
- occurs in infants of affected mothers with severe facial and bulbar palsy
- neonatal respiratory insufficiency may occur but is usually self-limiting

d. clinical features
- manifests as an inability to relax muscles following strong contraction
- initially muscles of face, neck and distal extremities
- characteristic "hatchet" face
  - ptosis, temporal wasting, drooping of the lower lip and sagging of the jaw
- cardiac involvement usually affects conducting tissue
  - 1st degree ***heart block*** is present in the majority
  - CHB may dictate pacemaker insertion
  - ***sudden death*** may occur, tachyarrhythmias & CCF are less frequent
- respiratory muscle weakness may be severe with minimal limb involvement
- impaired ventilatory drive & extreme sensitivity to opioids etc.
- central & peripheral ***sleep apnoea*** with chronic hypoxia may lead to ***cor pulmonale*** and this is the usual cause of CCF in these patients

e. characteristic facial features
   i. ptosis
   ii. posterior subcapsular cataracts
   iii. atrophy of facial muscles and sternomastoid
   iv. frontal baldness
   v. hyperostosis frontalis

f. laboratory studies
   i. CK - normal or mildly elevated
   ii. EMG - characteristic myotonia & myopathic features
   iii. ECG - 1st degree HB ± CHB
   iv. biopsy - distinctive ***type I fibre atrophy***
   v. genetics - mutant gene long arm of C_{19}
   * antenatal diagnosis possible

g. general management
- condition is seldom so disabling as to require treatment
- ***phenytoin*** is drug of choice
- antimyotonia agents, quinidine & procainamide, may ***worsen*** cardiac conduction

h. treatment of myotonic contractures - hydrocortisone
- procainamide
- dantrolene

- ***Myotonic Contracture Triggers***

  i. cold, shivering, stress
  ii. trauma, exercise, mechanical stimulation
  iii. tourniquets, hyperkalaemia
  iv. ***drugs*** - suxamethonium
  - halothane
  - anticholinesterases

- ***Other Complications***

i.	respiratory muscle weakness	- respiratory failure
ii.	myotonic contracture	- chest wall rigidity - difficult to ventilate
iii.	cardiomyopathy	± cor pulmonale
iv.	endocrinopathy	- hypothyroidism - diabetes mellitus
v.	gastrointestinal disease	- pharyngeal weakness - aspiration risk
vi.	gonadal atrophy	
vii.	intellectual impairment	
viii.	hypersomnia / sleep apnoea syndrome	
ix.	possible association with MH	* abnormality on C_{19}
x.	drugs	- contractures - respiratory depression

Myotonia Congenita

a. occurs as autosomal dominant and autosomal recessive forms
b. those with the ***recessive*** form may develop slight weakness, those with the dominant form do not
c. there is no other significant organ involvement
d. respond well to antimyotonia agents - quinine, procainamide, tocainide
   - phenytoin
   - acetazolamide

Miscellaneous Muscular Dystrophies

1. oculopharyngeal dystrophy
2. congenital muscular dystrophy
3. distal muscular dystrophy
4. scapuloperoneal dystrophy

Congenital Myopathies

NB: 1. these are rare disorders, distinguished from the *muscular dystrophies* by the presence of ***specific histochemical*** & ***structural*** abnormalities in muscle
2. a non-progressive course is common but not invariable
3. pectus excavatum, kyphoscoliosis, hip dislocation & pes cavum are common

▪ ***Central Core Disease***

- the first congenital myopathy described, by Shy & Magee in 1956
- ***autosomal dominant*** inheritance but sporadic cases occur
- weakness of muscles of the face & legs is usually mild
- serum CK and EMG may be normal
- diagnostic biopsy with "central cores" in fibres, devoid of oxidative enzymes
- almost ***definite*** association with ***malignant hyperpyrexia***

▪ ***Nemaline Myopathy***

- usually autosomal dominant, may be recessive or sporadic
- infantile hypotonia is present & striking leading to respiratory failure
- serum CK may be normal, EMG usually shows myopathy

▪ ***Myotubular Myopathy***

- multiple patterns of inheritance plus sporadic cases
- similar to above but distinguished by external ophthalmoplegia
- CK is normal or slightly elevated, the EMG abnormal

▪ ***Congenital Fibre Disproportion***

- hypotonia, weakness, delayed motor milestones, skeletal deformities as above
- biopsy shows increased number of small type I fibres, with normal or hypertrophied type II fibres