

Myotubular / Centronuclear Myopathy

Clinical Spectrum and Management

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Background

- Large Dutch family with X-linked inheritance described by Van Wijngaarden et al. in 1969
- Affected males showed muscle fibres resembling fetal muscle fibres = myotubes
- Argument about nomenclature: myotubular or centronuclear?

Initiative by Professors Peter S. Harper
and Alan E.H. Emery

The ENMC International Consortium on Myotubular Myopathy

- Initiated in 1993, members in nine countries
- Gene identified in 1996
- Correlations studied: mutation – clinical picture
- Basic mechanisms now being elucidated
- Current Co-ordinators: Drs. Enrico Bertini and Jocelyn Laporte

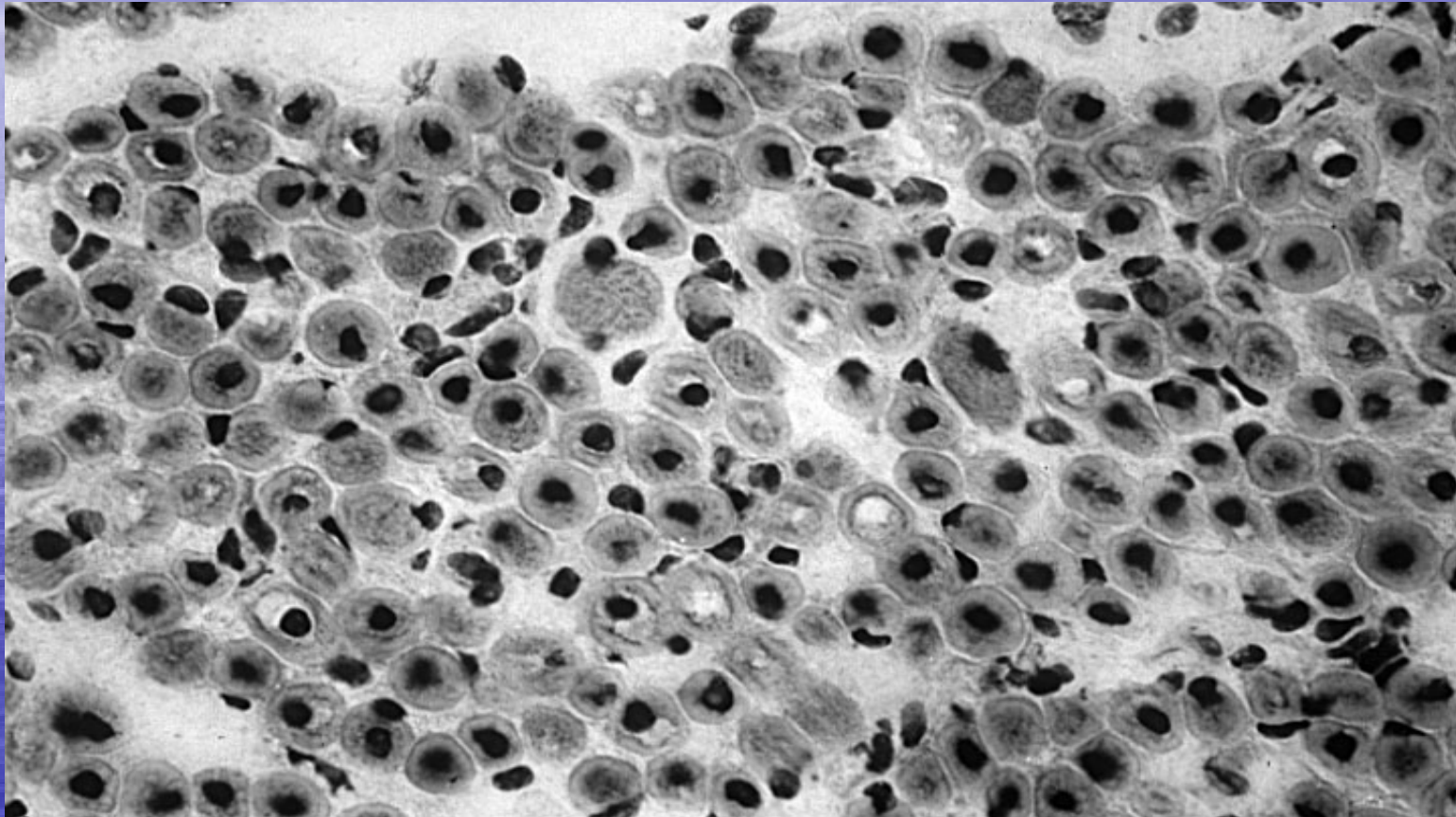
Group of congenital myopathies

- Inborn muscle disorders
- Names based on structural abnormalities in muscle fibres

Definition of myotubular myopathy

- Clinically: generalised muscle weakness and floppiness
- Histologically: presence of small rounded muscle fibres, with centrally located nuclei, resembling fetal myotubes

Myotube-like muscle fibres in MTM



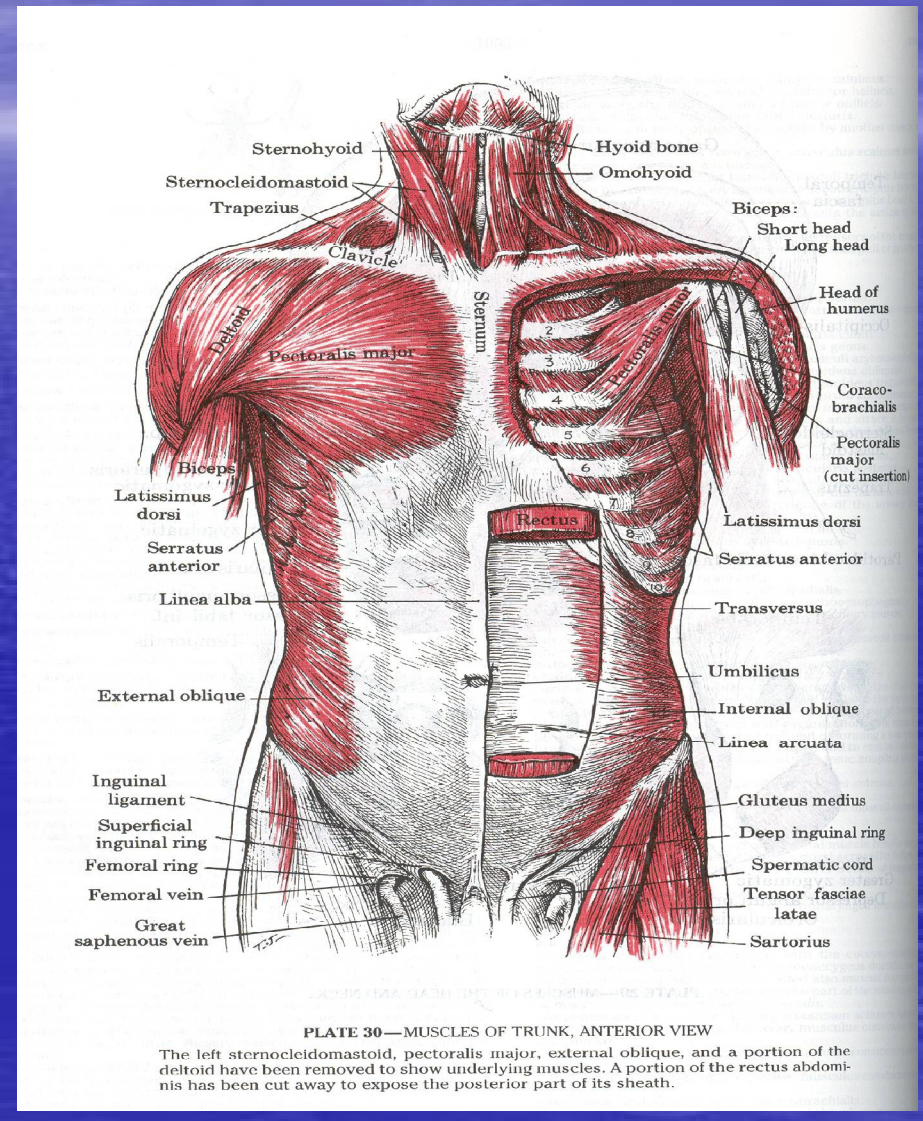
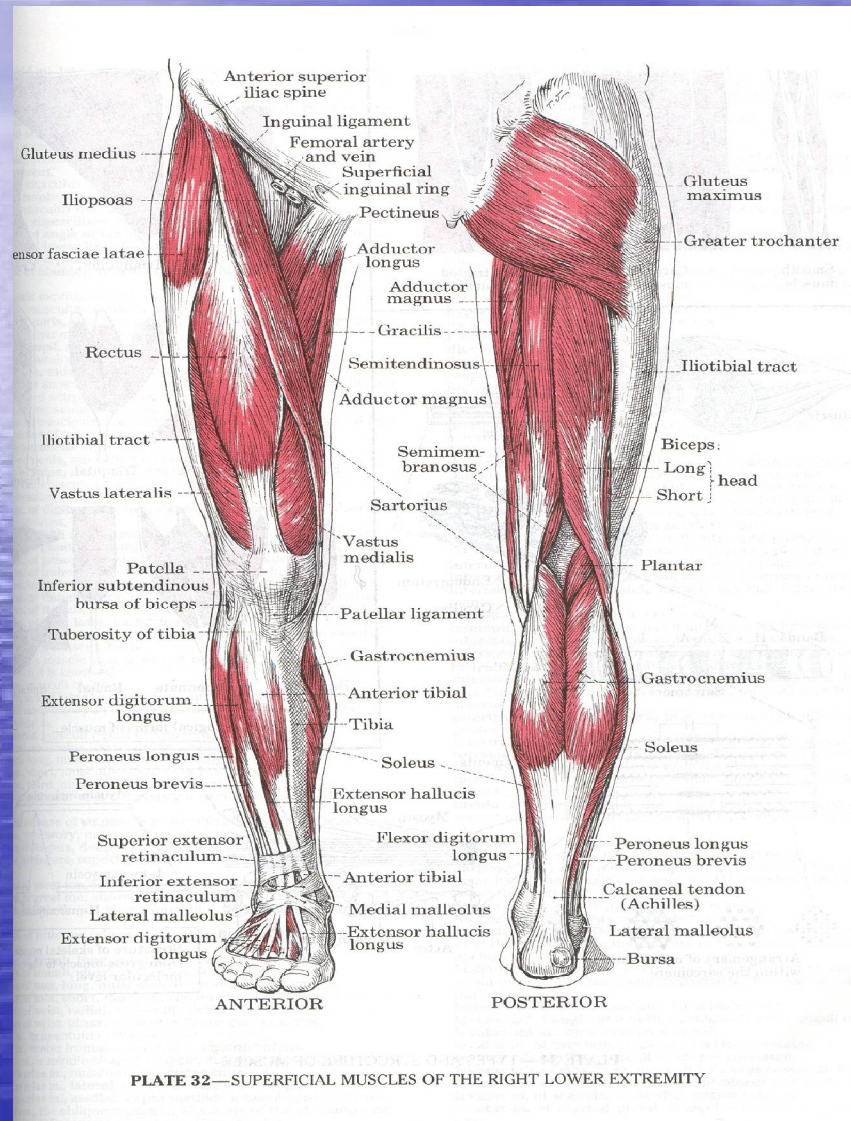
Clinical picture

- Excess amniotic fluid, weak fetal movements
- Floppiness and muscle weakness at birth
- Contractures, limited eye movements
- Breathing problems
- Great variability, even within families

Floppiness can be marked



Patterns of weakness



Muscle weakness may cause other features

- High-arched palate
- Joint deformities
- Flat or deformed chest
- Breathing difficulties
- Scoliosis

Myotubular myopathy is not thought to influence

- Brain
- Heart
- Smooth muscle
- Lungs (at least not to begin with)
- Nerves (at least not to begin with)

Modes of inheritance

- X-linked – affected boys have inherited faulty gene from usually unaffected Mother
- Recessive – faulty gene from both unaffected parents
- Dominant – faulty gene from one affected parent

- In real life, many patients are the only affected person in their family, and it may be difficult to be certain about the mode of inheritance, unless the causative mutation has been identified
- Genetic counselling should be offered

Genetic counselling in X-linked MTM

- Most mothers of affected boys are carriers
- Carrier status can be examined by mutation detection
- Mutation-based prenatal diagnosis offered also where carrier status is not verified (mosaicism)
- Variability even within families

Female carriers of the X-linked form

- Recurrent miscarriages, male stillbirths
- Most carriers are symptom-free
- Some have minor weakness
- A minority show overt muscle disease

No-one to blame for carrying
faulty gene

Autosomal (non-X-linked) forms (dominant or recessive)

- Genes being identified
- Clinically usually milder, variability being defined

Dynamin-2-related form

- Dominant inheritance, more than 10 families known
- Onset in adolescence or early adulthood
- Pain on exercise may be first symptom
- Drooping eyelids. Eye movements may be normal
- Distal (peripheral) weakness and contractures
- Special feature of muscle biopsy: radial strands

Bitoun et al 2005, Fischer et al 2006, Schessl et al 2007

Amphiphysin 2 (BIN 1)-related form

- Recessive inheritance, 3 families
- Inborn or childhood onset
- Proximal weakness
- Very variable severity

Nicot et al, in press

Care of persons with myotubular/centronuclear myopathy

Multidisciplinary team work

All require physiotherapy

- Maintain muscle strength
- Maintain ranges of movement
- Maintain mobility
- Prevent scoliosis and back pain
- Maintain breathing, assist coughing
- Maintain independence in activities of daily living



Main issue

Breathing

Breathing: preventing problems

- Treatment for swallowing difficulties
- Chest physiotherapy, assisted coughing
- No smoking
- Vigorous treatment of infections

Breathing: Assessment!

- Regular assessment needed (vitalography)
- More detailed assessment if lung volume smaller than 60 % of normal (polysomnography)

Look out for symptoms of too shallow breathing

- Headache
- Nausea
- Drowsiness
- Difficulty getting going
- Don't want breakfast
- Drop in energy levels and concentration
- Bad mood
- Frequent night-time awakenings
- Nightmares
- Night sweating

Use of mechanical aids

- To maintain quality of life
- To maintain independence

Mechanical aids

- Some may need mechanical ventilation, usually by mask
- Some may require a wheelchair

Surgery

- To prevent severe scoliosis damaging breathing
- Other surgery only if really necessary
- Anaesthesia carefully administered
- Immediate postoperative mobilisation with the help of a physiotherapist

Occupation

- Free from physical strain
- Free from tobacco smoke and other toxic agents
- Free from high risk of infection

Pregnancy and delivery

- Careful management and planning
- Neurologist, obstetrician and anesthesiologist working together

Thank you!

