

# Congenital Myopathies

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**CONGENITAL MYOPATHIES** – rare\* **congenital\*\* nonprogressive\*\*\* primary myopathies**, not explained as *dystrophic* or *metabolic* abnormalities\*\*\*\*.

- \* incidences < 1 per 100,000.
- \*\* in some cases, no symptoms are not present at birth; other cases manifest in utero as reduced fetal movements, and delayed 2<sup>nd</sup> stage of labor.
- \*\*\* patients are remarkably active despite their weakness, but some congenital myopathies (e.g. nemaline myopathy, centronuclear myopathy) have progressive weakness with fatal outcome.
- \*\*\*\* statement reflects ignorance about etiology.

The commonest presentation - floppy baby with delayed motor milestones, difficulty in keeping up with peers.

- limb-girdle weakness, although distal weakness can occur in some families.
- reduced muscle bulk (no hypertrophy), reduced muscle stretch reflexes.
- muscle weakness can lead to *skeletal defects* (pectus excavatum, kyphoscoliosis, dislocated hips, pes cavus, etc); marfanoid, slender body habitus; characteristic dolichocephalic head, long thin face, high arched palate; muscles of jaw may be too weak to hold it closed.
- *respiratory weakness with CO<sub>2</sub> retention at night* causes morning headaches, daytime somnolence.



Differential diagnosis, evaluation, and management are similar.

- Main diagnostic method - morphological characteristics on **muscle biopsy**.
- CK – normal or only slight increased.
- EMG - myopathy

## MYOTUBULAR-CENTRONUCLEAR MYOPATHY

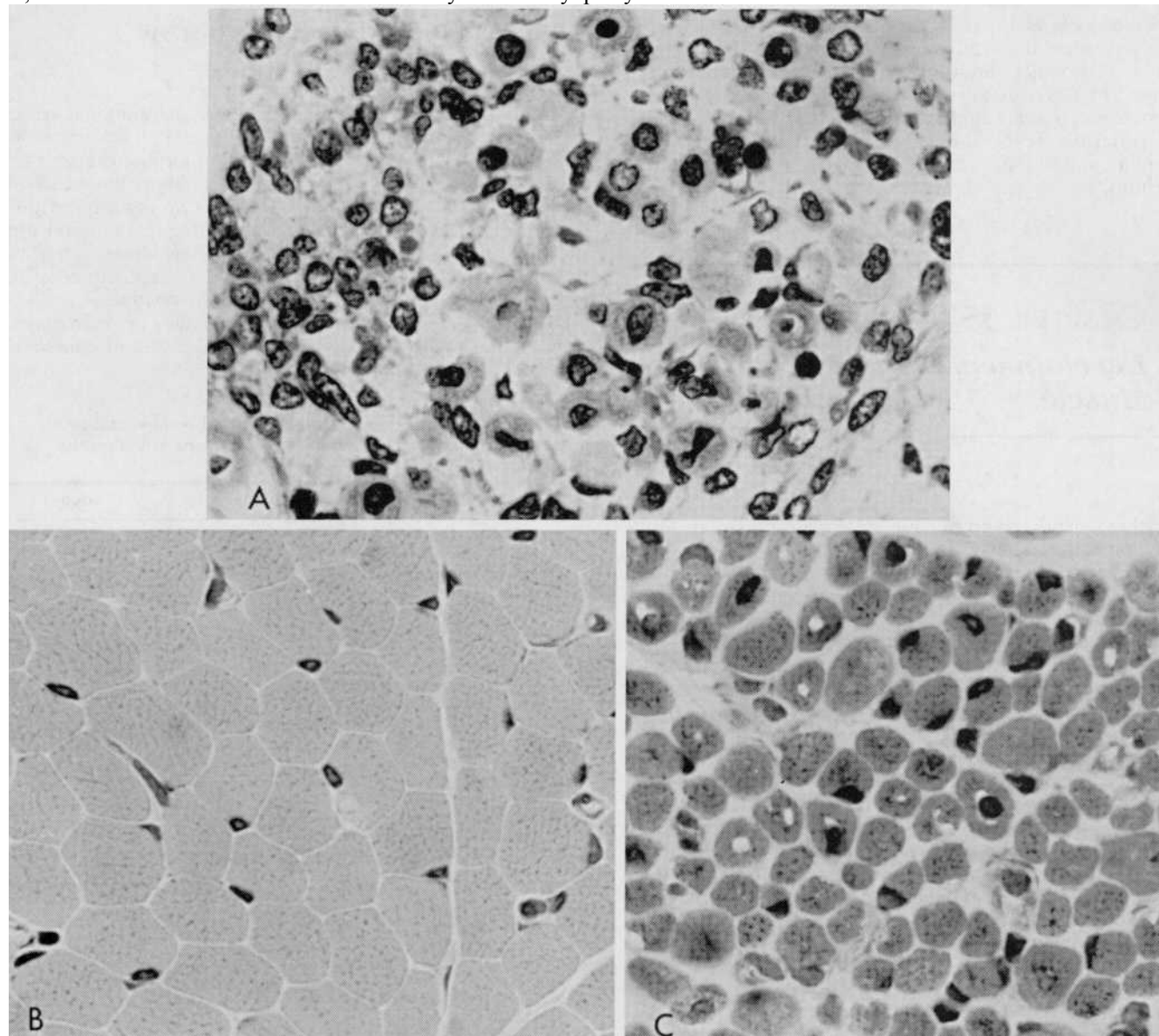
Large **CENTRAL NUCLEI** occupy 25-80% muscle fibers

- more often in type 1 fibers; fibers are small.
- nuclei are in single row in longitudinal section.
- *halo around central nuclei* shows increased oxidative enzyme activity, and glycogen staining (as in fetal myotubes); cylinder of myofibrils shows normal mature differentiation with ATPase stains.
- immunostains detect **vimentin** and **desmin** (normally absent after fetal period).
- original term, MYOTUBULAR MYOPATHY, was based on *morphological resemblance to myotubes*.  
 N.B. morphological similarities to myotubes are only superficial! - centronuclear myopathy is not due to arrest of myotubes!

**MYOTUBE** - muscle fiber formed by myoblast fusion during development; few myofibrils occur at periphery, and central core is occupied by nuclei and sarcoplasm - fiber has tubular appearance.

Cross-section of muscle:

- A, normal 14-wk-old fetus.
- B, normal full-term neonate.
- C, full-term neonate with X-linked recessive myotubular myopathy.



- inheritance patterns:
  - a) **autosomal recessive** - late infancy-early childhood form.
  - b) **autosomal dominant** - late childhood-adult form.
  - c) **X-linked** (Xq28 – **myotubularin\***) - neonatal form (most common).
    - \* phosphatase important in muscle cell growth and differentiation.
- prominent ptosis & ophthalmoplegia (vs. other congenital myopathies).
- neonatal form has *progressive weakness with early fatal outcome*; late forms have mild nonprogressive limb weakness without dysmorphic features.

## NEMALINE MYOPATHY

**RODS in muscle biopsy**

see p. D30 >>

- a) **autosomal dominant** - 1q21-23 ( **$\alpha$ -tropomyosin**).
  - b) **autosomal recessive** - 2q (**nebulin** is likely candidate gene).
- *mild progressive myopathy* present from birth; some individuals are more severely affected with early death.

## CENTRAL CORE DISEASE

**CENTRAL / ECCENTRIC CORES**

see p. D30 >>

- **autosomal dominant** point mutations of **ryanodine receptor** on 19q13.1 (allelic to malignant hyperthermia!).
- consistently associated with **malignant hyperthermia!** (use dantrolene before anesthesia)

## CONGENITAL FIBER-TYPE DISPROPORTION

**increased number of small type I muscle fibers**

- **type 1 fibers** are at least 12% smaller than **type 2 fibers** (**type 2 fibers** are of normal / increased size).
- **autosomal recessive** inheritance with no genetic marker.
- no specific pathophysiological explanation (most poorly understood and characterized congenital myopathy).
  - association with *cerebellar hypoplasia* suggests that pathogenesis may be abnormal suprasegmental influence on developing motor unit during stage of histochemical muscle differentiation (at 20-28 wk of gestation).
- not severe, nonprogressive, generalized hypotonia and weakness present at birth.
  - atrophy & hypotonia > weakness (child may be stronger than expected during examination).
  - mild **congenital contractures** are often present.

## OTHER CONGENITAL MYOPATHIES

**NONSPECIFIC CONGENITAL MYOPATHY** - biopsy shows only minor nonspecific myopathic features.

**CYTOPLASMIC BODY (s. DESMIN-RELATED) MYOPATHY** - accumulations of desmin.

**MULTICORE/MINICORE MYOPATHY**

**FINGERPRINT BODY MYOPATHY**

**SARCOTUBULAR MYOPATHY**

**REDUCING BODY MYOPATHY**

**TRILAMINAR MYOPATHY**

**HYALINE MYOPATHY WITH FOCAL LYSIS OF MYOFIBRILS**

**MYOFIBRILLAR MYOPATHY**

## *Congenital Muscle Anomalies*

### BRAIN MALFORMATIONS and MUSCLE DEVELOPMENT

Abnormal descending impulses along **bulbospinal pathways** alter LMN discharge patterns that determine histochemical differentiation of muscle.

**CEREBELLAR HYPOPLASIA** - infants are hypotonic and developmentally delayed; muscle biopsy - delayed muscle maturation, fiber-type predominance.

**Corticospinal tract** does not participate because it is not yet functional during this fetal period - supratentorial lesions are less likely to alter muscle development.

## AMYOPLASIA

- congenital absence of individual muscles; common and often asymmetric.
- most common - **palmaris longus** muscle - absent in 1/3 **normal** subjects.
- unilateral absence of **sternocleidomastoid** muscle → **congenital torticollis**.
- absence of one **pectoralis major** muscle - part of **Poland anomalad**.

Causes

- a) **defective myogenic regulatory genes** → **GENERALIZED AMYOPLASIA** (documented in *mice* and theoretical in *humans* - would result in *spontaneous fetal loss*).
- b) **defective mesodermal plate** (e.g. *sacral agenesis*) → abnormal somites → failure to form bony vertebrae and muscles (**SEGMENTAL AMYOPLASIA**).
- c) **absence of long bone** → aplasia / hypoplasia of associated muscles (e.g. radius absence → aplasia of *flexor carpi radialis*).
- d) **undeveloped innervation** (e.g. in lower limbs in severe *myelomeningocele*).

## PROTEUS SYNDROME (s. Muscular Dysgenesis, Elephant Man's Disease)

- disturbance of cellular growth, involving ECTODERMAL and MESODERMAL tissues.

PROTEUS - Greek god who appeared in different forms

- possible genetic (not mendelian) origin.
- histology - *muscular dysgenesis*; abnormal zones adjacent to zones of normal muscle formation and do not follow anatomic boundaries (disorder of abnormal paracrine growth factors?).

Variable and changing phenotype:

- 1) **hemihypertrophy** - asymmetric overgrowth of extremities - thickening of bones, excessive muscle growth without weakness, grossly enlarged hands (macroductyly) and feet (large flat feet - "moccasin feet"), bony defects, hypocalcemia
- 2) **hemimegalencephaly** (distorted head gigantism), mental deficiency, seizures
- 3) **skin** - thickened, hyperpigmented areas, verrucous lesions, hemangiomas and lipomas (subcutaneous and abdominal) (often confused with neurofibromatosis type I)

BIBLIOGRAPHY for ch. "Neuromuscular, Muscular Disorders" → follow this [LINK >>](#)