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 2nd 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 CO2 retention at night*** causes morning headaches, daytime somnolence.
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Differential diagnosis, evaluation, and management are similar.

Main diagnostic method - morphological characteristics on **muscle biopsy**.

CK – normal or only slight increased.

EMG - myopathy

Nemaline Myopathy

 **rods** in muscle biopsy [see p. D30 >>](http://www.neurosurgeryresident.net/D.%20Diagnostics%5CD30-39.%20Biopsy%20%28brain%2C%20nerve%2C%20muscle%29%5CD30.%20Muscle%20Biopsy%20and%20Serum%20Markers.pdf)

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

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:
	1. **autosomal recessive** - late infancy-early childhood form.
	2. **autosomal dominant** - late childhood-adult form.
	3. **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.

Central Core Disease

 **Central / eccentric cores**  [see p. D30 >>](http://www.neurosurgeryresident.net/D.%20Diagnostics%5CD30-39.%20Biopsy%20%28brain%2C%20nerve%2C%20muscle%29%5CD30.%20Muscle%20Biopsy%20and%20Serum%20Markers.pdf)

* **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

* 1. ***defective myogenic regulatory genes*** → **generalized amyoplasia** (documented in *mice* and theoretical in *humans* - would result in *spontaneous fetal loss*).
	2. ***defective mesodermal plate*** (e.g. *sacral agenesis*) → abnormal somites → failure to form bony vertebrae and muscles (**segmental amyoplasia**).
	3. ***absence of long bone*** → aplasia / hypoplasia of associated muscles (e.g. radius absence → aplasia of *flexor carpi radialis*).
	4. ***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 (macrodactyly) 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, hemangiomata and lipomata (subcutaneous and abdominal) (often confused with neurofibromatosis type I)

Bibliography for ch. “Neuromuscular, Muscular Disorders” → follow this [link >>](http://www.neurosurgeryresident.net/Mus.%20Muscular%2C%20Neuromuscular%20disorders%5CMus.%20Bibliography.pdf)

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