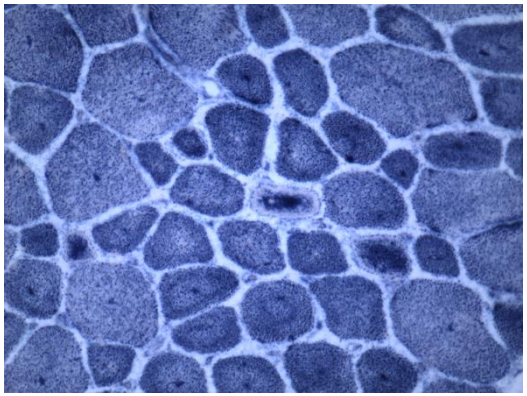
Clinical symptoms in congenital myopathies



Ulrike Schara

Dept. of Neuropediatrics

Neuromuscular Centre for children and adolescents

University of Essen

EPNS training courses, Budapest 4th to 7th April 2017

Congenital myopathies

Structure

Part 1:	Definition
	Clinical clues
	Diagnostic work-up
Part 2:	Case reports
	including therapy and clinical course
	Summary and outlook

Congenital myopathies

Definition

Congenital (structural-) myopathies comprises a group of rare and heterogeneous neuromuscular disorders with an assumed incidence of 6 : 100 000. Classification depends on histological and ultrstructural changes as well as on molecular genetic background.

First symptoms can occur in utero, usually in the first years of life; manifestation in later infancy and childhood are also reported.

Congenital myopathies

History

- fetal development, birth (often peripartal asphyxia, preterms)
- Neonatal phase:

  floppy infant, bulbar symptoms, respiratory problems
- Later manifestation:

  motor and mental development, muscle weakness, exercise tolerance, progression

Family history

- other affected family members?
- pattern of inheritance?

Congenital myopathies

hypotonia

(„floppy infant“, typical positions of arms and legs, ankle hypermobility)

muscle weakness, gait disturbances

(„floppy infant“, pos. Gowers´ sign, reduced muscle in upper limbs)

reduced or absent muscle reflexes

bulbar symptoms

(impaired swallowing and / or sucking)

respiratory problems, possibly non-invasive or invasive ventilation

muscle atrophy, often generalized

pes cavus, AMC, contractures, hip luxation, scoliosis, rigid spine,

facial hypomimia and / or dysmorphy, ptosis, ophthalmoplegia

Congenital myopathies

Leading symptoms in the neonatal period

- Arthrogryposis multiplex congenita (AMC)
- muscle hypotonia
- muscle weakness
- facial weakness
- impaired swallowing and sucking
- weak cry
- respiratory problems
- pes cavus, contractures, scoliosis, hip luxation
- MH-reaction

Congenital myopathies

Leading symptoms in later manifestation

- muscle hypotonia
- muscle weakness (proximal, often axial)
- muscle atrophy, dystrophy
- facial weakness, ptosis, ext. ophthalmoplegia
- impaired sucking and swallowing
- respiratory problems
- pes cavus, contractures, scoliosis
- rigid spine
- cardiomyopathy
- MH-reaction

Congenital myopathies

Other organs possibly affected

- İmpaired liver function, Vit-K-deficiency
- gall stones
- pyloric stenosis
- nephrocalcinosis
- slowed nerve conduction velocities
- MH-reaction

Congenital myopathies

Diagnostic work-up

- history
- symptoms and clinical clues
- laboratory measurements (**Cave!** CK often normal!!)
- muscle ultrasound, Muscle-MRI
- EKG, Echocardiography
- lung function measurements, polysomnography
- muscle biopsy (histology, EM)
- genetic analyses including next generation sequencing

  http://www.musclegenetable.fr
- **Further investigations of other organs**

  EKG, 24h-EKG, echography, lung function tests (sitting and supine position), ultrasound of abdomen and kidneys, orthopedic counseling, pediatric audiology, ophthalmology, endocrinology, gastroenterology, urology

Congenital myopathies

Differential diagnosis

- Congenital myasthenic syndromes
- Congenital muscular dystrophies
- aut.-rec. prox. spinal muscular atrophy (SMA)
- hereditary neuropathies (DSS, hypomyelin. neuropathies)
- Syndromes (e.g. Prader-Willi-Syndrome)

Case reports

Nemaline Myopathy

History
reduced fetal movements,
BW 2710g, APGAR 2/5/8

Clinic
postnatally resp. insufficiency → invasive ventilation,
tracheotomy
gen. hypotonia, muscle weakness, elongated face, hypomimia,
high arched palate, ptosis, no visual fixation,
pes cavus, AMC, impaired sucking and swallowing,
jejunale tube,
recurrent infections, maldescensus testes on both sides

Diagnosis
muscle biopsy with Nemaline rods (EM)
genetic analysis without mutations detected so far

Symptomatic Therapy

X-chrom.-rec. myotubular myopathy

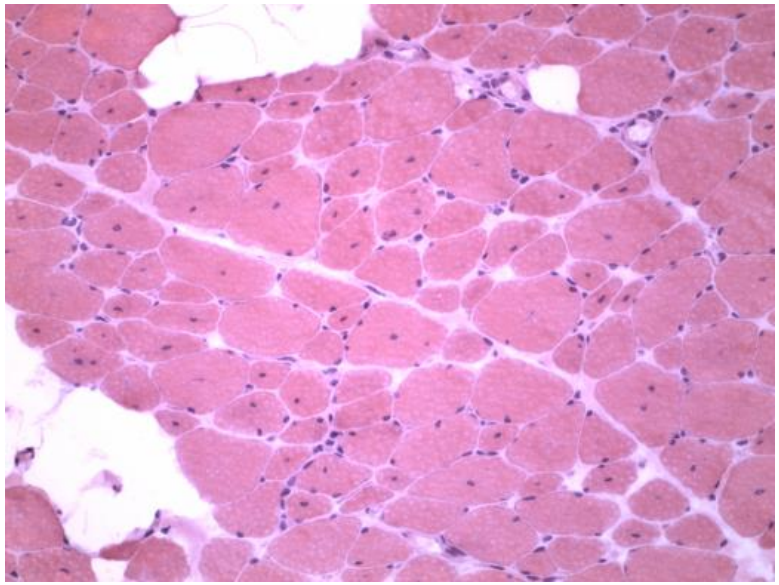
Clinical clues:

floppy infant with areflexia,
bulbar symptoms and
often primäry resp. Insufficiency,

but also facial hypomimia and
ptosis on both sides

Clinical examination of the mother, usually healthy!

Does muscle biopsy help for diagnosis?
Genetic analysis in *Myotubularin*-Gene .



X-chrom.-rec. MTM / aut. ZNM

- X-chromosomal (*MTM1*), aut.-dom. (*DNM2*), aut. rec. inheritance (*BIN1)*
- **Diagnostic work-up:**
  history, symptoms, CK often normal
  → muscle biopsy: histology, (EM)
- **Clinical course:**
  scoliosis, contractures (rigid spine), bulbar symptoms, opthalmoplegia, cardiological and pneumological complications, reduced life expectancy in neonatal manifestation
- **Therapy:**
  symptomatic, no cure so far *!*

Pyridostigmine bromid in MTM / ZNM

- impaired neuromuscular transmission in an animal model reported in the literature (e.g. zebrafish)
- reports about positive effects of pyridostigmine bromid in patients with Myotubular Myopathy (*MTM1*), zentronuclear myopathy (ZNM) with mutations in *Dynamin2*-gene and myopathies caused by *RYR1*-mutations

Own experiences:

- MTM: better development of motor functions and improved respiratory situation (reduced ventilation time / day and night)
- ZNM with *DNM2 and RYR1*-mutations: improvement of muscle function and exercise tolerance

Prospective, longitudinal Study of the Natural History and Functional Status of Patients with Myotubular Myopathy (MTM)

Poster: WMS Congress 4.-8.10.2016: Baseline data from patients with myotubular myopathy enrolled in a European prospective and longitudinal natural history study, Neuromuscul Disord 2016; 26 Suppl: 116-117

RyR1-associated myopathy

History

intrauterine reduced fetal movements, postnatally
hypotonia, impaired swallowing and sucking,
tube feeding for 6 months, no ventilation, delayed motor development
normal mental development

Clinical symptoms

gen. muscle atrophy, gen. hypotonia, muscle weakness,
facial hypomimia, ptosis, external ophthalmoplegia, high arched palate,
good exercise tolerance, restrictive lung function, no cardiological problem

Diagnosis

initial cong. myopathy suspected, e.g. *SEPN1, RyR1*, DD CMS with *COLQ mutation,* muscle biopsy rejected by parents,
depending on clinical symptoms *RyR1* gene analysis

Genetics: mutations in *RyR1*

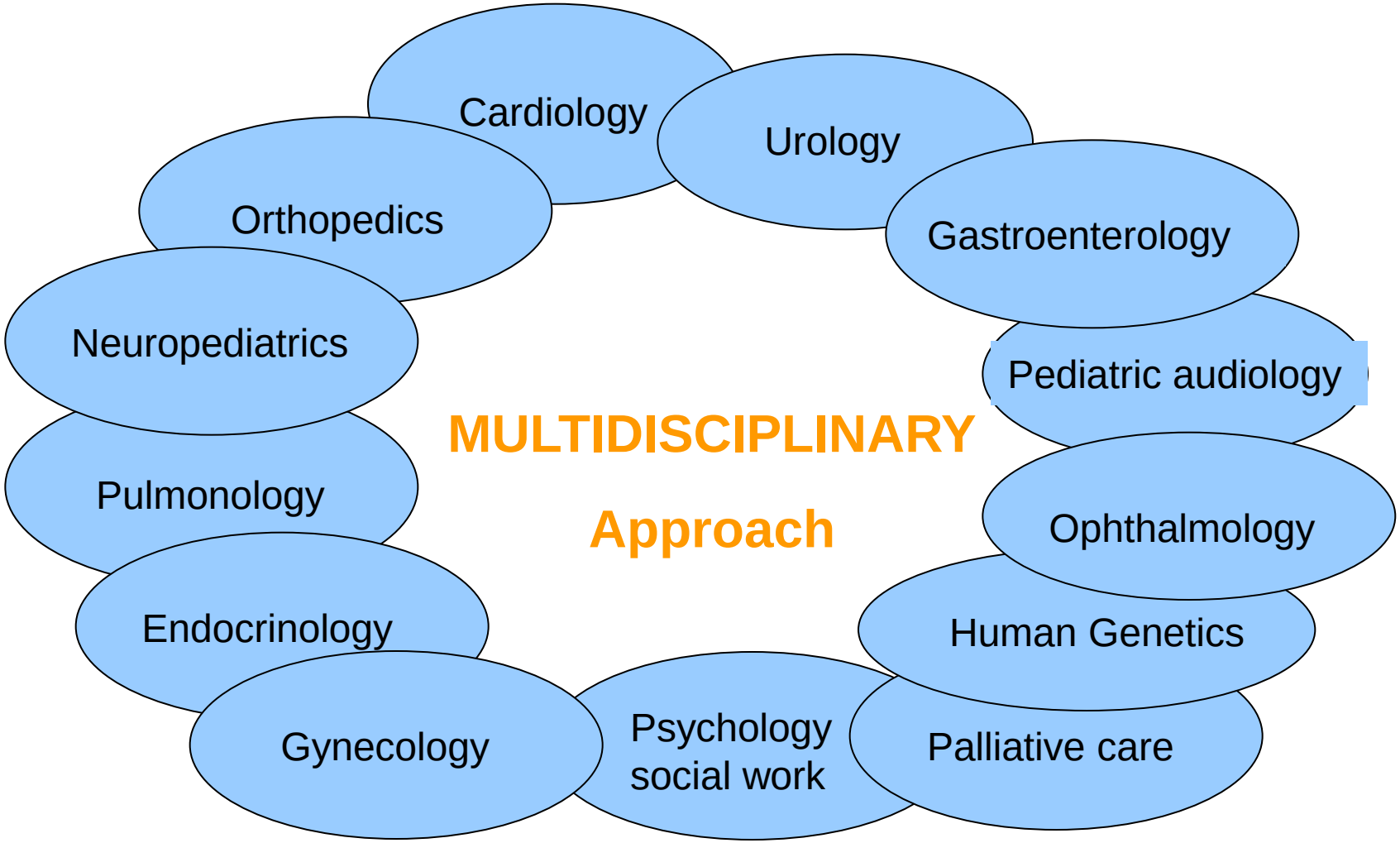
SEPN1-associated myopathy

History
intrauterine and postnatally normal,
unstable gait, recurrent falls,
positive Gowers` phenomenon, dystrophy since
6. months of life, normal mental developement,
Impaired headcontrol

Clinic
gen. hypotonia and muscle atrophy, axial and prox.
muscle weakness, mild facial hypomimia,
large ears, hyperlordosis, MER normal,
mentally alert

Clinical course
exercise intolerance, non-invasive ventilation,
wheelchair for longer distances, percutane gastric tube necessary

Genetics: two *missense* mutations in *SEPN1*



EZSE Essener Zentrum für Seltene Erkrankungen

Summary

- **obvious variability of clinical symptoms and muscle biopsies**, results are typical but not specific
- think of **other affected organs!!**
- **Muscle MRI** can add important facts.
- **Genetic analyses** should be initiated depending on clinical, MRI and biopsy data. In every single patient appropriate genetic methods have to be discussed.
- **http://www.musclegenetable.fr**
- **A therapeutic trial with AChE-inhibitors** can be helpful because of possible positive effects.

Outlook

New classification depending on new pathophysiological insights:

defects of sarcolemmal and intracellular membrane re-modelling and of excitation-contraction-connections

defects of the neuromuscular transmission, first positive experiences with pyridostigmine bromide therapy (MTM, TPM 2 and 3, RyR1)

impaired mitochondrial distribution and function

impaired myofibriliar strength development

atrophy and autophagy

Aim: Development of more directed therapeutic strategies