Congenital myasthenic syndromes (CMS)

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EZSE Essener Zentrum für Seltene Erkrankungen

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CMS

Structure

Part I:	Definition
	Pathophysiology and Genetics
	Diagnostic work-up
	Therapeutic options
Part II:	Case reports illustrating therapeutic options and clinical courses

CMS

Definition

Congenital myasthenic syndromes are a group of rare clinically and genetically heterogeneous disorders of the neuromuscular junction.

Usually, symptoms occur during the first and second year of life, but, later manifestation in adolescence and adulthood are also reported.

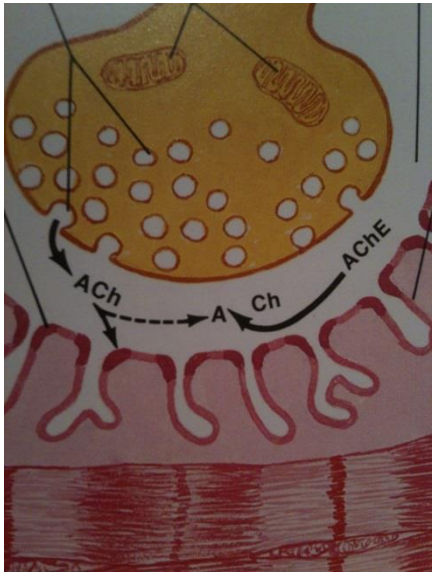
CMS – Diagnostic work-up

- **History** (clinical clues, other affected family members?)
- **Clinical examination** (hallmarks: exercise intolerance, fluctuating weakness)
- **Repetitive 3 Hz stimulation test** (at rest, after exercise)
- Single fibre-EMG ?
- Intraveneous Edrophonium chloride-test ?
- **Genetic analysis** (direct gene analysis, next generation sequencing)
- **Morphological** / neurophysiological **investigations of muscle specimen**
- Antibodies (AChR-, MuSK-, Titin-, LRP4-antibodies)

- Pathology of the thymus gland? (chest X-ray, CT, MRI)
- EEG, cranial MRI

CMS – Therapy

- Pyridostigmine
- 3,4 – Diaminopyridine
- Ephedrine
- Salbutamol, Albuterol
- Fluoxetine
- Quinidine
- Acetazolamide



CMS Genes

presynaptic:

- ***CHAT***
- ***Myo9A***
- ***SNAP25B***
- ***Synaptotagmin 2***

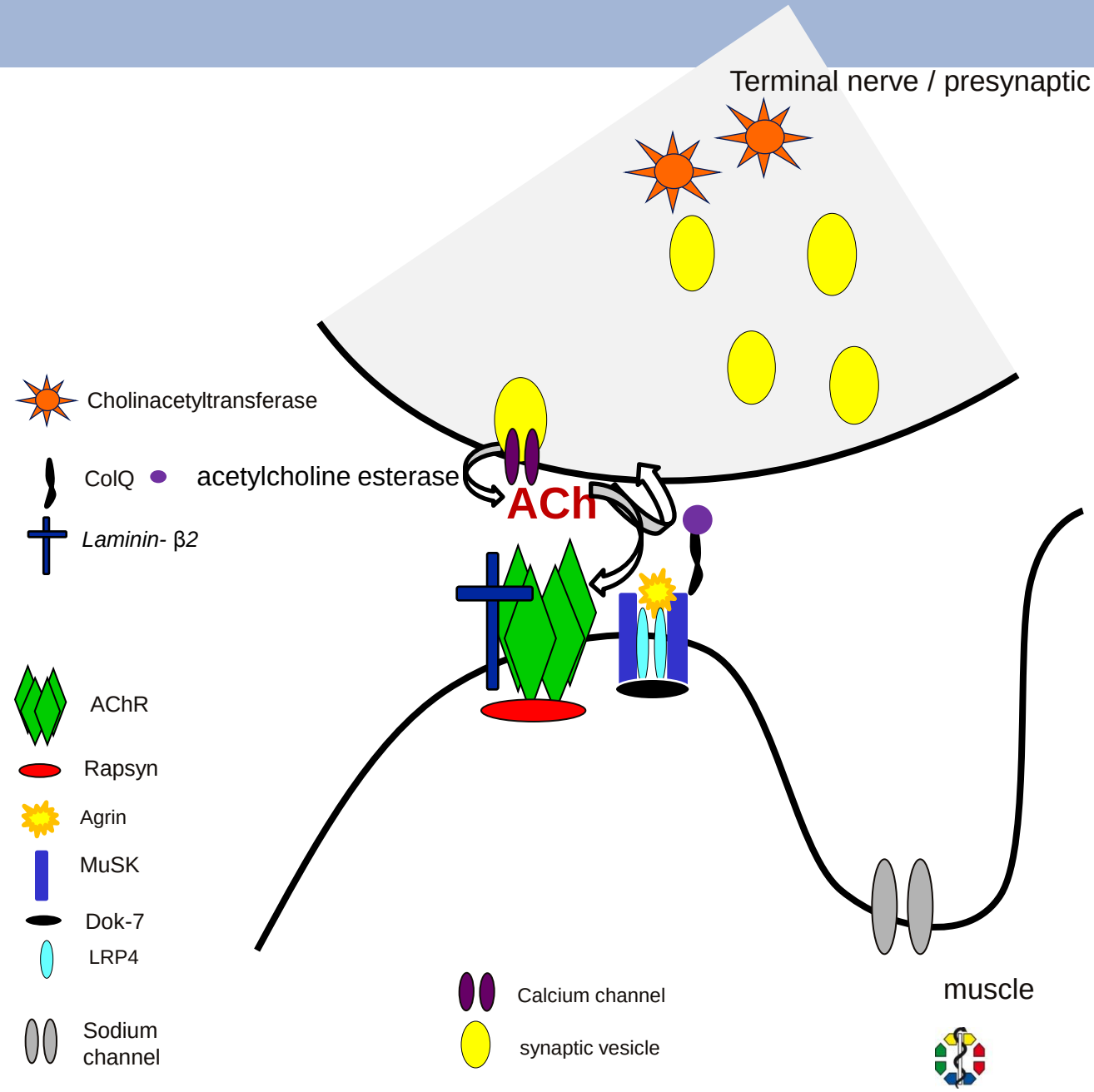
synaptic / basal lamina:

- ***COLQ***
- ***Laminin- β2***

postsynaptic:

- ***CHRNA1***
- ***CHRNB1***
- ***CHRND***
- ***CHRNE***
- ***RAPSN***
- ***AGRN***
- ***MUSK***
- ***DOK-7***
- ***LRP4***
- ***PREPL***
- ***SCN4A***
- ***Plectin***
- ***Col13A1***
- ***GFPT1***
- ***DPAGT1***
- ***ALG14, ALG2***
- ***GMPPB***

- ***SLC25A1***



Modified: McConville and Vincent, 2002, Abicht 2012, Wibbeler 2015

Congenital myasthenic Syndrome

Mutation in *CHAT*

- reduced fetal movements
- recurrent apnoea
- respiratory insufficiency and ventilation

- path. décrement

- positive effects
  of AChE-inhibitors and 3,4Diaminopyridin
- improved muscle power but an ongoing psychomotor developmental delay

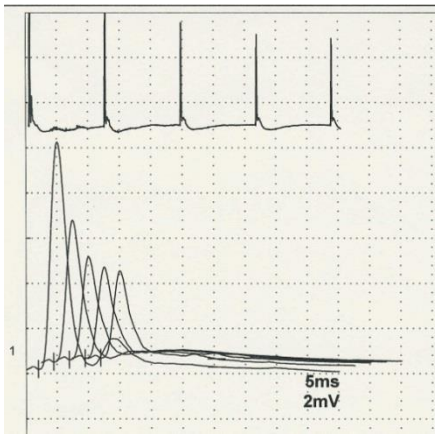
- one younger more severly affected brother

- homozygote mutation in *ChAT* (G417R) on both alleles

Congenital myasthenic Syndrome

Mutations in *COLQ*

- neonatal manifestation
- ptosis, external ophthalmoplegia, recurrent apnoea, respiratory insufficiency
- reduced pupillary light response



- repetitive muscle action potential

- worsening of symptoms with AChE-inhibitors
- tracheotomy, wheelchair dependency,
- psychomotor delay

- two mutations in *COLQ (W148X + C386S)*

Congenital myasthenic Syndrome

Mutation in *CHRNE*

- 3 cousins of a consanguineous family
- manifestation in the first year of life
- co-incidence of Phenylketonuria
- path. Décrement
- positive effect of AChE-inhibitors
- in the elder patient addition of 3, 4-Diaminopyridin
- constant proximal muscle weakness
- and exercise intolerance
- in the younger sister also neonatal start
- homozygote mutation ε392del3 in Gen *CHRNE*

Congenital myasthenic Syndrome

Mutation in *CHRND*

- manifestation in the first year of life,
- motor developmental delay, exercise intolerance
- crises with deterioration
- path. repetitive 3Hz Stimulation test
- homozygote mutation in *CHRND*
- AChE-inhibitor therapy
- complete recovery
- development of contractures
- missense mutation in exon 10, microdeletion Exon 8/Intron 9

Congenital myasthenic Syndrome

Mutation in *RAPSN*

- manifestation prenatal / neonatal
- AMC, crises with deterioration
- no path. décrement
- positive effect of AChE-inhibitors
- complete recovery

- two mutations in *RAPSN*

  (N88K+chrom. 4.5 kB Del.)

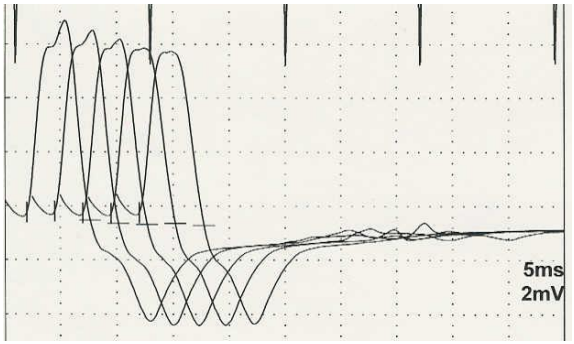
Congenital myasthenic Syndrome

Mutation in *DOK7*

- manifestation in infancy, limb-girdle weakness
- waddling and lordotic gait with internally rotated legs
- fluctuating symptoms for weeks
- path. décrement only once

- Ephedrine therapy with positive results
- longer than 8 years (4 x 25mg/day)

- homozygot mutation 1124_1127 dup TGCC
- important DD: congenital myopathies



CMS

Clinical symptoms appropriate

Genetic analyses initiated

and what is the next step

Clinical Clues I

Ethnic origin

- Mutation e1267delG *(CHRNE)* often in South East European patients and Roma
- Mutation N88K *(RAPSN)* often in CMS patients from Mid Europe
- "founder mutation" ins1293G homozygote *(CHRNE)* in patients from Maghreb

Episodic apnoea

- Pre-synaptic CMS *(CHAT mutations),* synaptic CMS *(COLQ m*utations*)*
- Post-synaptic CMS *(RAPSN mutations,* in rare cases *CHRNE m*utations)
- Sodium channel Myasthenia

Reduced pupillary light response

- AChE-deficiency *(COLQ mutations)*

Selective affection of neck-, hand- and finger-extensors

- "Slow-channel" syndrome *(subunits of the AChR)*
  and elder patients with AChE-deficiency

Clinical Clues II

AMC

- CMS caused by mutations in *RAPSN* , *CHRNA1 , CHRND* and *CHAT*
  fetal akinesia-syndrome also caused by mutations in *CHRNG* und *DOK-7*

Stridor and vocal cord paralysis in neonates or infants

- CMS with mutations in *DOK7*

Limb-girdle and axial weakness

- CMS with mutations in *DOK7*, *GFPT1, DPAGT1, ALG2, ALG14*, occasionally in *RAPSN* and *COLQ*

Association with seizures or intellectual disability

- CMS with mutations in *DPAGT1, GMPPB, PREPL, COL13A1*

Fluctuation of symptoms over days to weeks

- CMS caused by mutations in *DOK-7*

Clinical Clues III

Autosomal dominant inheritance

- SCCMS with mutations in AChR subtypes

Repetitive muscle action potential

- AChE-deficiency *(COLQ mutations)* and “Slow-channel” syndrome *(subunits of the AChR)*

Tubular aggregates in muscle biopsy

- CMS with mutations in *GFPT1, DPAGT1, ALG2*

Autophagic myopathy

- CMS with mutations in *GFPT1, DPAGT1*

AChE-inhibitors

- No effect (only initial effect under low doses or even worsening of symptoms!) in patients with AChE-deficiency *(COLQ mutations)* or “Slow-channel” syndrome *(subunits of the AChR)*
- No effect or only short time improvement (days to few weeks) in patients with *DOK-7* , *MusK*-, *Agrin* mutations

Think of...

- variability of phenotype and therapeutic effects
- neurophysiological results
- a therapeutic trial with AChE-inhibitors, but be careful in case of suspective AChE-deficiency or SCCMS
- a muscle biopsy for further diagnostic work-up:
  - if a congenital myopathy may be a differential diagnosis
  - in limb-girdle CMS: tubular aggregates in *GFPT1* and *DPAGT1*

Thanks!

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ESNEK
Erhebung seltener neurologischer Erkrankungen im Kindesalter

EZSE Essener Zentrum für Seltene Erkrankungen