Case Presentation

Primary mitochondrial myopathy or mito mimick?

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Sektion für Neuromuskuläre Erkrankungen

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Past medical history and clinical features

♂ *1968

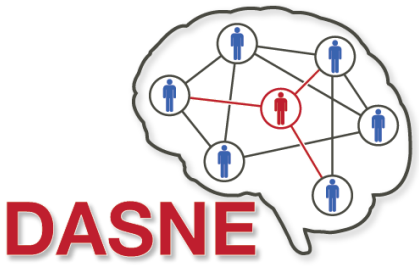
First presentation at the age of 43 years at the neuromuscular outpatient department with following symptoms:

- HyperCKemia of 8055 U/l
- Known persistent CK elevation in blood > 1000 U/l for years
- Horizontal gaze nystagmus, rotatory spontaneous nystagmus, **tunnel vision**, oromandibular dyskinesia, dysarthria, **proximal muscle weakness** MRC 4 and muscle atrophy (shoulder > hip girdle), **cerebellar ataxia**, atactic gait, postural and intention tremor of upper limbs

Family History:

- Brother with similar symptoms (retinitis pigmentosa, muscle weakness, cerebellar ataxia: exclusion of SCA 1, 2, 3, 6, 7, 17)

Past medical history and clinical features



prenatal	early postnatal period	age 2	age 3
development and birth unremarkable	feeding problems	recurrent febrile episodes, pneumonia and otitis media	suspected encephalitis, unexplained seizures, severe regression of motor development

early childhood - adulthood

- **continued febrile episodes attributed to respiratory tract infections**, exclusion of inborn or acquired immune deficiency
- **gastrointestinal complaints**
- **retinitis pigmentosa** with tunnel vision
- **delayed motor and cognitive development:**
  - independent walk at age 7
  - attendance of school for physically handicapped children, sheltered workshop
- "stable disease" since age 25 years

Muscle Biopsy (M. vastus lateralis)

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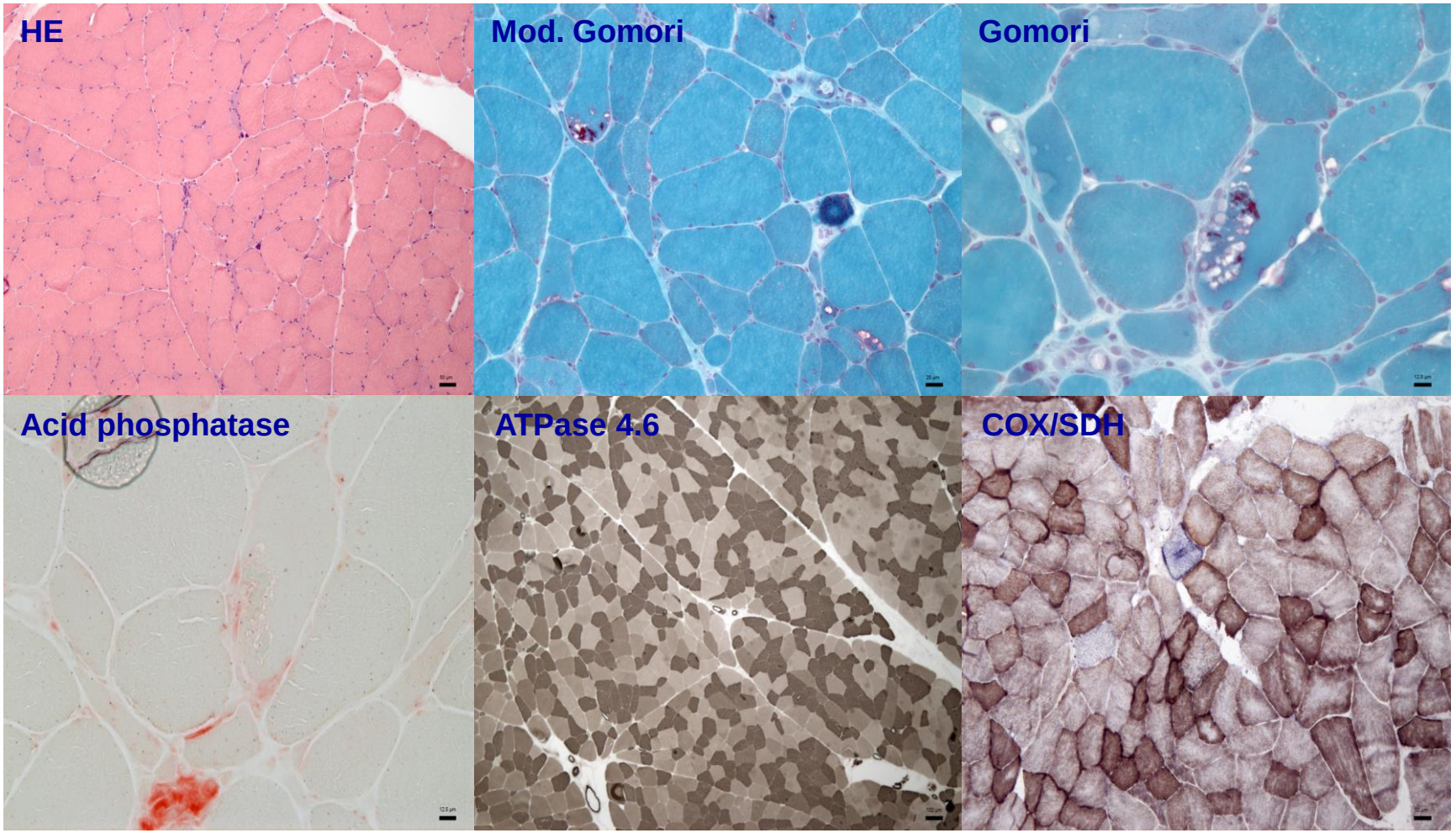

Muscle Biopsy (M. vastus lateralis)

Entfernt: Abbildungen aus Publikation.

Mitochondrial Disease ?

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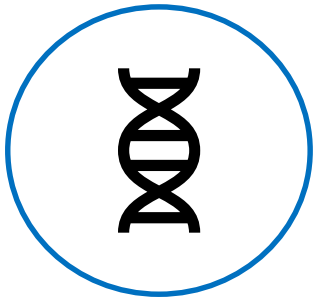
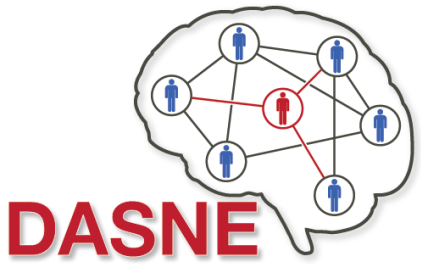
Analysis of respiratory chain enzyme activities, skeletal muscle homogenate

(Activities in U/g FG)	Controls N = 43 : 25m, 18f, 3-77 years	
Citratesynthase (CS)	13,9 ± 4,5	10,26
NADH:CoQ1 Reductase	2,42 ± 0,82	1,4
Complex I / CS	0,13 ± 0,045	0,137
Cytochrome c Oxidase	9,41 ± 2,87	1,03
Complex IV / CS	0,68 ±0,15	0,1



Genetic Testing

- long range PCR of mitochondrial (mt) DNA in skeletal muscle: no mtDNA deletions/rearrangements
- no pathogenic sequence variants in *POLG1* (RFLP analysis)
- exclusion of NARP syndrome and pathogenic mtDNA point mutations by mtDNA sequencing (muscle tissue)
- no pathogenic sequence variants in *CAPN3* (LGMD2A)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Neuromuscular revisitation 2018

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- progression of motor limitations, recurrent falls, uses walking frame
- reports detection of **compound-heterozygous pathogenic mutations in the *MVK* gene** through the attending ophthalmologist
  - MVK (NM_000431.3), c.59A>C, p.His20Pro
  - MVK (NM_000431.3), c.1000G>A, p.Ala334Thr

→ **Mevalonate kinase deficiency**

metabolic disorder that disrupts the biosynthesis of cholesterol and isoprenoids

Entfernt: Abbildung aus Publikation.
DOI:10.2147/TACG.S93933

Source: Mevalonate kinase deficiency: Current perspectives - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Overview-of-the-mevalonate-pathway-Notes-The-pathway-starts-with-conversation-of_fig1_305487591 [accessed10 Jul, 2019]

Mevalonate kinase deficiency (MKD)

Spektren der Erkrankung

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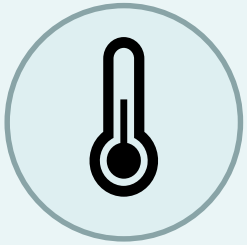
Hyperimmuno-globulinemia D
+
periodic fever syndrome

(Hyper-IgD syndrome, HIDS)



residual enzyme activity

mevalonic aciduria (MVA)

Mevalonate kinase deficiency (MKD)

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= autoinflammatory disease with attacks of hyperinflammation

Entfernt: Abbildung aus Publikation.

Mitochondrial pathology:

Disturbed mitophagy? Autophagic vacuoles…

Accumulation of mtDNA mutations?

Increased ROS?

Coenzyme Q10 deficiency?

Vitamin deficiencies A, D, E, K?

Mevalonate kinase deficiency (MKD)

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Review of Literature

- neuromuscular phenotype and histopathological characteristics of MKD-associated myopathy poorly described to date
- heterogeneous phenotypes
- ultrarare: ~ 200 cases described worldwide (mostly HIDS)

Conclusions

- consider MKD in patients with suspected mitochondrial disorder/myopathy
- ask about recurrent febrile episodes!

Treatment: Canakinumab (humanized monoclonal antibody against Interleukin 1 beta)
Anakinra (interleukin 1 receptor antagonist)?
Simvastatin? Coenzyme Q10?