Myotonic Dystrophy (DM1), non-dystrophic Myotonia, Periodic Paralsyses

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EPNS Training Courses, Budapest 4th to 7th of April 2017

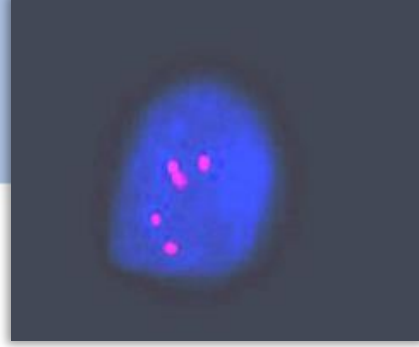
EZSE Essener Zentrum für Seltene Erkrankungen

Universitätsklinikum Essen

No conflicts of interest

Structure

- Definitions
- Genetics and pathophysiology
- Different phenotypes and clinical symptoms
- Multidisciplinary concept of care
- Outlook
- Summary



Definition DM1

- Myotonic dystrophy Typ 1 (DM1) is an autosomal-dominant inherited multisystemic disorder characterized by clinical core symptoms like myotonia, muscular dystrophy, cataracts, cardiac arrhythmia and endocrine diseases

- **1909** first description by **Steinert**
- **1912** cataracts as a core symptom was added by **Curschmann**
- **1918** description of **anticipation**
- **1936** description as **multisystemic disorder**
- **1992** Trinucleotid repeat (CTG) in the ***DMPK*** **gene**

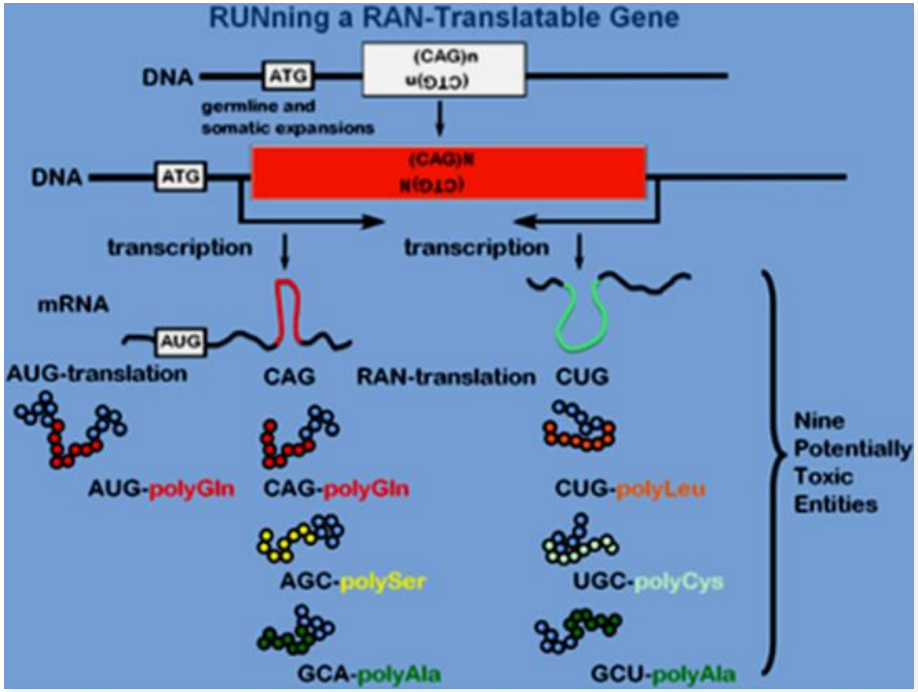
Genetics in DM1

Instabile CTG-Repeat Expansion in 3` UTR in the Dystrophia-Myotonica-Proteinkinase-gene (*DMPK*) on chromosome 19q13.3

- instability of the repeat-expansion in mitosis/meiosis
- repeat-number correlated with disease manifestation and severity

- anticipation (~ 2.9 decades)
- congenital form (maternal inherit.)

- prevalence for the adult type in Europe: 5-15 / 100 000
- no data for other subtypes



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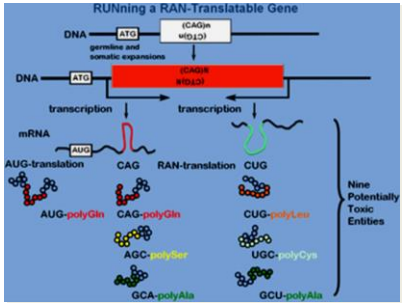
Molecular Pathogenesis in DM1



- pathology on RNA-level:
  toxic effects of incorrect RNA-transcripts
  by nuclear (and cytoplasmic) accumulation

- bindung and functional disorder of RNA-binding proteins
- „spleißopathy“

- impaired cellular protein biosynthesis

Phenotypes of DM1

- disease severity partially depends on number of **CTG-repeats (50 – 2000 repeats)**
- manifestation pre-/postnatal **congenital DM1 (CDM1)**
- manifestation 1-10 years **infantile DM1 (ChDM1)**
- manifestation after the age of 10 years **juvenile DM1 (JDM)**
- **despite different phenotypes think of overlaps!**

Congenital DM1

1. Symptoms pre- / postnatal

- reduced fetal movements
- hydrops fetalis
- hydramnios
- hypotonia and muscle weakness, facial weakness
- impaired sucking and swallowing
- failure to thrive
- respiratory problems, often resp. insufficiency and ventilation
- pes cavus
- other contractures

Congenital DM1

2. Symptoms during clinical course

- typical facial stigmata
- delayed motor development
- delayed speech development
- cognitive disorders
- ADHD, ADD
- cardiovascular problems
- other psychological aspects
- clinical myotonia, myotonic discharges in EMG
- **reduced life expectancy!**

Infantile DM1

1. **Symptoms**

- **often no muscle weakness!**
- in case of weakness distal distribution
- in some patients slight motor developmental delay
- facial weakness, but not typical as in CDM1
- cardiological problems, **cardiac arrhythmias!**
- **cognitive disorder** as the leading symptom
- speech disturbance
- learning difficulties
- behavioural syndromes (autism, ADHD, ADD)

Infantile DM1

1. Clinical course

- problems in school, learning difficulties
- no school graduation
- difficulties on the labour market
- educational problems
- behaviour disorders, communication problems
- social problems, often no independent life possible
- **sudden cardiac death caused by malignant cardiac arrhythmia**!!!
- psychiatric disorders
- usually life expectancy not reduced

Juvenile DM1

Symptoms as in the adult type

Multisystemic disorder!

- muscle weakness and atrophy
- myotonia
- cataracts
- endocrine disorders
- daily fatigue
- malignant cardiac arrhythmia
- gastrointestinal problems
- respiratory problems
- psychiatric comorbidities

Definition non-dystrophic Myotonia

- **Non-dystrophic myotonia** are autosomal inherited disorders caused by chloride and sodium channel defects characterized by the clinical core symptom myotonia, which is defined as failure of muscle relaxation after activation. Patients report this as muscle stiffness of varying degree.

- Inheritance in **Myotonia congenita Becker** is autosomal-recessive with early manifestation and more severe clinical course
- Inheritance in **Myotonia congenita Thomsen** is autosomal-dominant and usually milder

Genetics and Pathophysiology in non-dystrophic Myotonia

Mutations in the *CLCN1* gene coding for the skeletal muscle chloride channel CLC-1 on chromosome 7q35

- mutations cause reduction or absence of chloride channels at the skeletal muscle membrane leading to a decreased muscle action potential and an increase of membrane excitability as the underlying pathophysiology of clinical myotonia

- **autosomal-recessive mutations** are the reason for a shortened protein
- **autosomal-dominant mutations** lead to a dominant negative effect of the mutated protein on other CLC-1 subunits

- **Cave! Mutations in *SCNA4*** can also cause **phenotypes of „chloride channel myotonia“**

Non-dystrophic Myotonia

Symptoms

- in newborns impaired opening of the eyes after crying
- muscle hypertrophy although muscle weakness
- muscle stiffness
- myotonia, percussion myotonia
- aggravation by cold, emotional stress or after activity
- lid lag
- cardial arrhythmia possible
- in **Becker myotonia** male > female
- in **Thomsen myotonia** milder phenotypes in 90%, 10% without clinical symptoms

Paramyotonia congenita

- autosomal-dominant
- mutations in the ***SCNA4*** gene (alpha subunit) on Chr 17q23.1-q25.3

Symptoms

- worsening with activity, **no warm up!**
- worsening by cold (hypomimia, no eye opening)
- recurrent attacks lasting seconds till one day
- no progression, no muscle weakness
- usually no therapy necessary

Kalium-aggravated myotonia

- autosomal-dominant
- mutations in the ***SCNA4*** gene (alpha subunit)
  on Chr 17q23.1-q25.3

Symptoms

- fluctuating symptoms from day to day with variable severity
- no muscle weakness
- aggravation by muscle activity, kalium intake (nutrition!) and other depolarizing agents
- therapeutic options reduction of kalium intake, Mexiletin (not long-term) and Carbamazepin

Definition and Pathophysiology of periodic Paralyses

- **primary periodic paralyses** are autosomal inherited disorders caused by mutations in the calcium, sodium and kalium channel or **secondary symptoms** in syndromes or endocrine disorders
- for intact signal transmission from nerve to muscle membrane to the t-tubular system and endoplasmatic reticulum different cation channels play an important role
- in case of impaired channel function membranes can be hyperexcitable and cause myotonia or can be hypoexcitable and therefore cause muscle weakness and paresis
- clinical clues are fluctuating symptoms during attacks, in between muscle function and strength usually normalized

Hypokalemic periodic paralysis

- genetically heterogeneous, mutations in genes encoding sodium, calcium and kalium channels, aut.-dom., male/female 3:1

Symptoms

- manifestation from infancy to young adulthood
- no myotonia
- severe attacks with quadriplegia, often starting during nighttime
- provocation by decreased kalium, stress, after exercise, Glc/insulin

Therapy

- kaliumchloride during attacks, long-term Acetazolamid, diuretics with kalium retention, dichlorphenamide

Cave! Thyrotoxicosis, Anderson-Tawil syndrome (kalium-channel)
congenital myopathy (calcium channel)

Hyperkalemic periodic paralysis

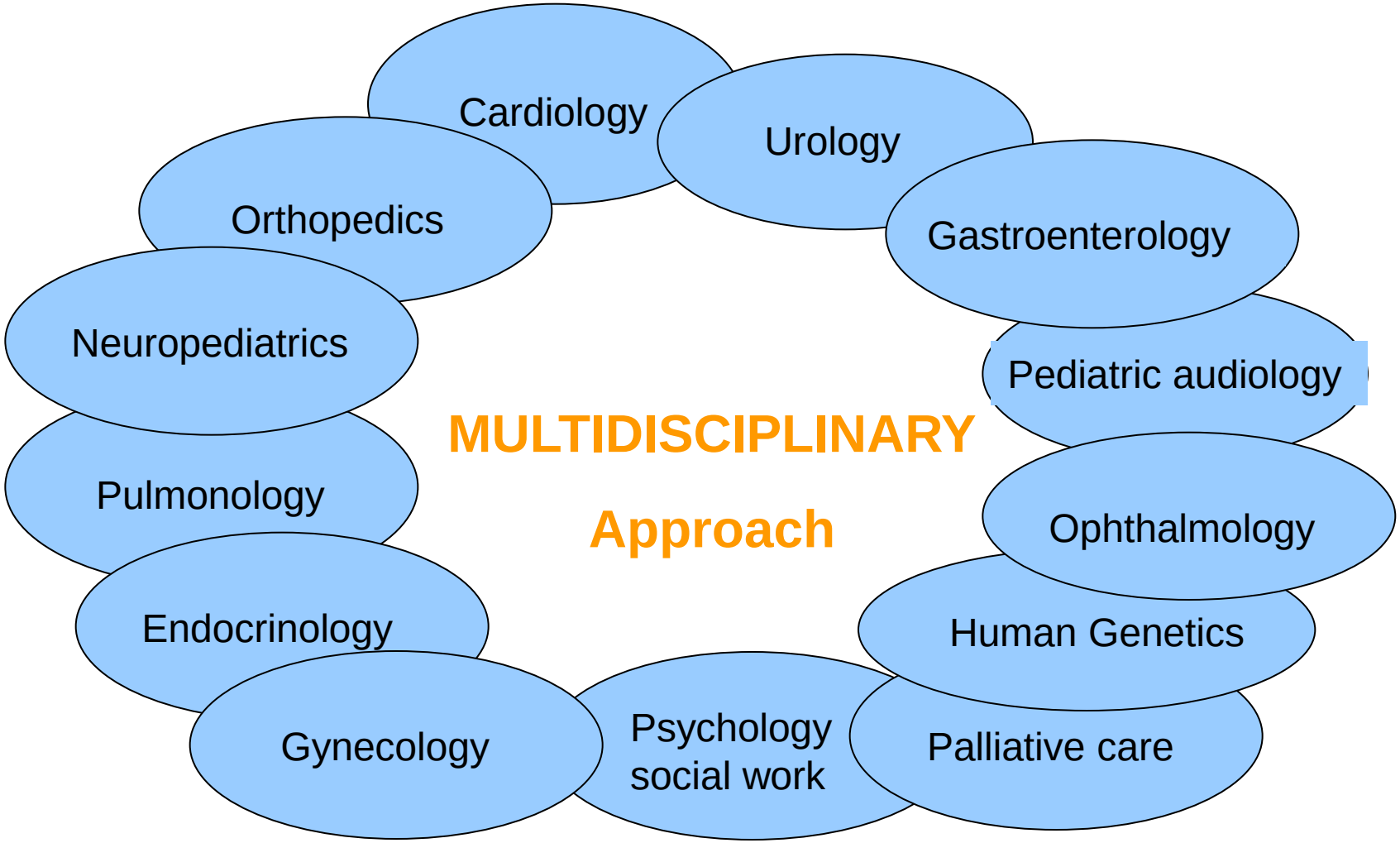
- genetically aut.-dom. mutations in gene encoding sodium channel

Symptoms

- manifestation before 20 years of age
- milder attacks with focal plegia, often starting early morning
- provocation by fasting, hunger, cold, after exercise
- seldom myotonia, paramyotonia possible, muscle weakness
- Cave **cardiac arrhythmia!**

Therapy

- sugar enriched and kalium reduced meals in the morning, dextrose during attacks
- long-term Acetazolamid, Salbutamol, thiazid diuretics, calcium gluconate, Mexiletin, dichlorphenamide


Cardiology
Urology
Orthopedics
Gastroenterology
Neuropediatrics
Pediatric audiology
MULTIDISCIPLINARY
Approach
Pulmonology
Ophthalmology
Endocrinology
Human Genetics
Gynecology
Psychology
social work
Palliative care

Concept of Care

Ideally

in a neuromuscular centre with experiences

Neuromuscular Problems

muscle weakness, myotonia, myalgia, periodic paresis,
contractures, scoliosis
physiotherapy
“warm-up“ in case of myotonia
devices
early cooperation with orthopedics, surgery?
bone denth measurements
e.g. Mexilitene in case of severe myotonia, no long-term therapy!
Phenytoin, Carbamazepin
in case of pain therapy with Gabapentin
in periodic paralyses therapy during attacks and long-term treatment

Diagnosis and Genetics

Clinic

Explanation of symptoms and suspected diagnosis

Genetics

mutations
autosomal recessive and dominant inheritance
maternal inheritance in CDM1
anticipation
somatic mosaic
risk of recurrence
prenatal diagnostic

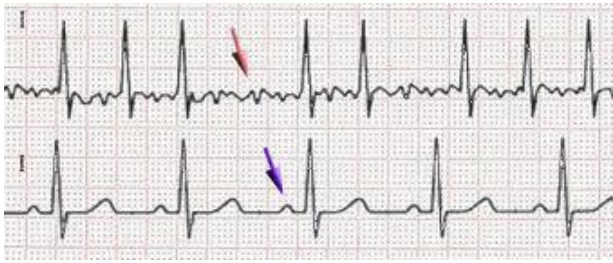
Concept of Care

Pneumological problems

hypoventilation, apnoea, aspiration, resp. insufficiency, daily fatigue

early initiation of lung function and / or polysomnography
assistent cough
non-invasive mask ventilation
Influenza and Pneumococci vaccination
Ritalin or Modafinil in case of excessive daily fatigue

Concept of Care

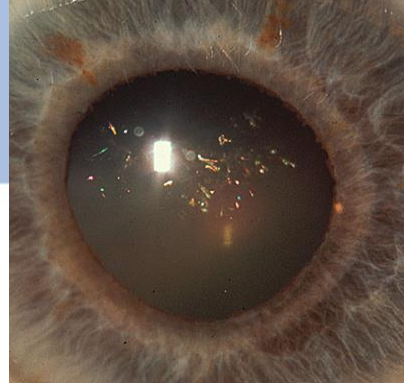


Cardiological problems

cardiac arrhythmia, seldom cardiomyopathies
long-QT syndrome, Brughada syndrome

EKG – control during follow-up 1 / year
24h-EKG 1 / year
echocardiography
cardio-MRI (every 2 - 5 years)
longer monitoring in case of clinical symptoms but normal results
pacemaker
defibrillator

Concept of Care



Ophthalmological problems

cataracts, ptosis

think of ophthalmological investigations!
regulary slit lamp investigations during follow-up
cataract-surgery, if necessary, seldom in patients younger than 18 years
critical discussion of ptosis surgery

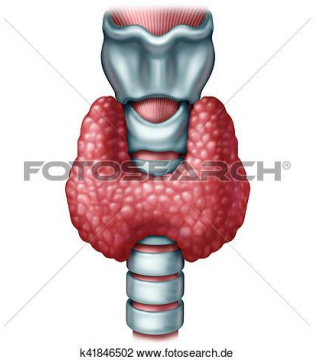
Concept of Care

Gastrointestinal problems

dysphagia, bulbar symptoms, gastrointestinal motility disturbances

documentation of weight and length
nutrition counseling
diets if necessary
discuss percutane gastric tube early!
procinetic drugs
laxans

Concept of Care



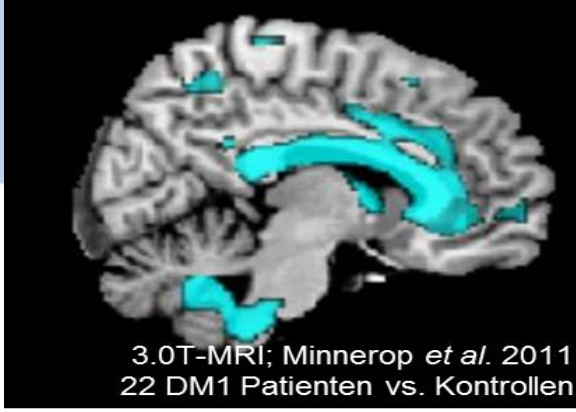
Endocrinological Problems

thyroid, impaired insuline sensibility, dyslipidemia, infertility, dysmenorrhoea

control of thyreoid function
control of serume lipids
control of glucose metabolism
perhaps, medication in case of increased glucose and cholesterin

diet
movement
think of gynekological and urological counseling early!

Concept of Care



Cognitive disturbances and behavioural disorders

cognitive disturbances, intelligence reduction, behavioural disorders, ADD, ADHD, autism

standardized age related psychological and cognitive tests
neuropsychological tests
psychiatric counseling
define and initiate adequate support
medication if necessary (e.g. ADHD)
psychosocial support for patients and families

Current situation

- no causal therapy, no cure, yet
- **main therapeutic options**: nutrition and orthopedic care incl. orthotics and other devices, orthopedic surgery (contractures, scoliosis), non-invasive ventilation, early adequate cardioprotective medication and/or devices, endocrinological therapy, therapy during attacks
- **hypothesis:** multidisciplinary care leads to a longer life expectancy and improved quality of life
- **cardiological and pneumological dysfunctions may be life limiting factors**

Outlook

- patient registry

- therapeutic concepts / studies

  Tideglusib: Glycogensynthase-kinase-3-Beta (Seronin/Threonin-Kinase, GSK3b)-Inhibitor

  corrects activity of RNA-binding proteines like CUGBP1 in DM1- animal models;

  preclinical efficacy in transgenic models and DM1 *ex vivo* muscle specimen

  ongoing clinical studies:

  OPTIMISTIC: cognitive behavioural therapy and exercise, www.optimistic-dm.eu, study closed

  IONIS-DMPK$_{Rx}$, *Biogen/Ionis*, generation 2.5 chimeric AON design
  "phase 1/2a blinded, placebo-controlled study to assess the safety, tolerability, and dose-range finding of multiple ascending doses of ISIS 598769 administered s.c. to adult patients with Myotonic Dystrophy Type 1",

  n=48, 12/14-11/16

  AMO 2, Tideglusib,, *AMO Pharma Limited*
  A single-blind, phase 2 study to evaluate the safety and efficacy of Tideglusib 400mg or 1000mg for the treatment of adolescent and adult congenital and juvenile-onset Myotonic Dystrophy Type 1", **08/16-10/17**

- gene therapy, aim: correction of pathogenic RNA-foci

Summary

- DM1 and channelopathies are rare disorders
- manifestation and clinical course are different from the adult classical type in DM1, Cave anticipation!
- symptoms in channelopathies may vary, **important is to think of them!**
- no causal therapy, no cure ,yet
- multidiciplinary care is important!
- usually, studies and therapeutic options for adults

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