5th Congress of the European Academy of Neurology

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Teaching Course 17

Congenital myasthenic syndromes and the myotonic dystrophies - diagnostics and possible treatment (Level 3)

Myotonic dystrophy 1 and 2 -diagnosis, recommendations for care and future treatment options

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Myotonic dystrophy 1 and 2 – diagnosis, recommendations for care and future treatment options

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02.07.2019

Myopathies - multisystem disorders

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- Myotonic dystrophy type 1 (DM1)
- Myotonic dystrophy type 2 (DM2, proximal myotonic myopathy PROMM, Ricker`s disease)

2 typical clinical scenarios in adult neurology with implications for a timely diagnosis

- **Case No. 1:** a young mother with a floppy neonatal just diagnosed with severe congenital DM1
  ⇒ new diagnosis of mild *adult-onset* DM1 in the mother
  more than half of the affected mothers do not carry a diagnosis of DM1
  because their condition has gone unrecognized, or has not generated any symptoms
- **Case No. 2:** a middle-aged patient with chronic pain syndrome previously diagnosed with fibromyalgia ⇒ late diagnosis of DM2

The young mother, Auguste Rodin, 1885

Myotonic dystrophy type 1

DM1 – Steinert`s disease

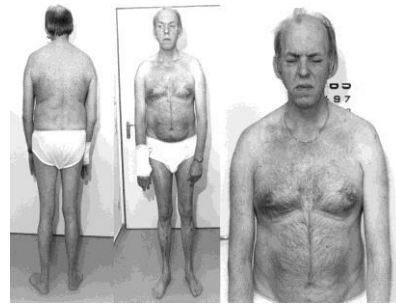
First clinical description:

1909 (Steinert), Steinert`s disease
1912 (Curschmann)

Prevalence:

5-15/100,000 (ø 13.5 in Europe)

DM1 is highly prevalent in certain founder populations, e.g. in Canada (Northeastern Quebec) 200:100,000



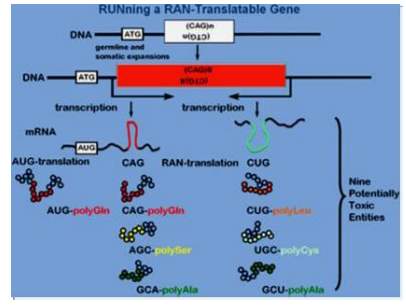
- **Most common hereditary myopathy in adulthood**
- First symptoms *in utero,* congenital, in early or late adulthood
- Repeat expansion disorder

Genetic background in DM1

Unstable CTG triplet repeat expansions (first described in 1992)
in the 3' non-coding region (UTR) of *DMPK*, the gene encoding the dystrophia myotonica protein kinase (*DMPK*)

transcribed, even translated: sense and antisense repeat-associated Non-ATG translation/**RAN translation**
→ protein pathology similar to HD, SCA8, FXTAS, *C9orf72* ALS/FTD

- Repeat size ≈ age at disease onset, disease severity (esp. with small repeat sizes)
- Repeat expansions are highly unstable in dividing and non-dividing cells, even in somatic cells of a person throughout life
- The CTG expansion increases when transmitted from one generation to the next → **anticipation** (symptoms begin at an earlier age in successive generations)
- Massive intergenerational expansions to 1,000 or more repeats are more likely to occur with maternal transmission: **congenital form of DM1**
- The jump from small expansions with minor symptoms to large expansions with classical *adult-onset* DM1 is more likely to occur with paternal transmission



Molecular pathogenesis
- RNA toxicity in DM1 and DM2 -

***Toxic gain-of-function* of RNA$^{(CUG)n}$**

Nuclear (and cytoplasmic) accumulation of expanded RNA transcripts

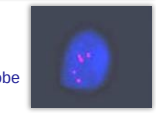
- Binding and *loss-of-function* of various RNA binding proteins (MBNL1/2, CUGBP, etc.)
- Sequestration and *loss-of-function* of MBNL1/2
- Up-regulation and *gain-of-function* of CUGBP

→ „Splicopathy“: RNA instability and aberrant alternative splicing of pre-mRNA of various genes

→ **aberrant translation of expanded repeats, haploinsufficiency of DMPK, mis-splicing with incorrect splice products and protein isoforms, disturbed protein synthesis:**

insulin receptor, CLCN1, CaV1.1 calcium channel, cardiac troponin T, RYR-1, myotubularin MTM1, SERCA, muscular bridging integrator-1 BIN1, NMDA receptor 1, APP, Tau, etc.

In situ hybridisation, CAG probe
DM1 skeletal muscle: nuclear foci



DM1: 4 clinical phenotypes

- Clinical phenotypes may be associated with CTG repeat sizes
- 38-49 repeats are usually clinically asymptomatic, “premutation”
- DM1: ~ 50-4,000 CTGs

A) Congenital phenotype with prenatal/neonatal/congenital onset, maternally inherited; 2 presentations in the further disease course (severe and milder form)
usually 1,000-4,000 repeats

B) *Childhood-onset* phenotype, disease onset ~ 1 to 10 years of age
usually 50-1,000 repeats

C) Classical *juvenile-onset* or *adult-onset* phenotype, disease onset ~ 10 to 30 years of age
usually 50-1,000 repeats

D) Patients with very mild or *late-onset* disease presentations
usually 50-80 repeats

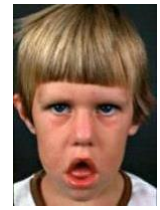
Congenital / *childhood-onset* DM1

Congenital DM1: clinical phenotype

- **Prenatal manifestations of congenital DM1**
  Reduced fetal movement, polyhydramnios, ventriculomegaly, etc.
- **Postnatal typical appearance:** Facial weakness, tented upper lip
- Feeding difficulty, failure to thrive, need for nasogastric feeding
- Neonatal hypotonia, CK levels in blood normal
- Respiratory insufficiency, need for ventilatory support

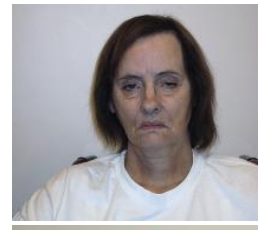
Major symptoms of congenital DM1 later in childhood or *childhood-onset* DM1:

- Mental retardation (~ 50-80%), intellectual impairment (full scale IQ in the range of 50-70), learning disabilities
- Psychomotor retardation, delayed motor milestones
- Neuropsychiatric symptoms: Autism spectrum disorders (ASD), anxiety and mood disorders, ADHS
- Few neuromuscular symptoms
- Phenotype may resemble classical DM1 in the later course of the disease



Adult-onset DM1

- Facial weakness, mild bilateral upper eyelid ptosis, frontal balding
- Juvenile cataracts
- Myotonia
- Wasting and weakness of distal > proximal limb muscles
- Fatigue, daytime sleepiness
- Endocrine disorders (diabetes, hypogonadism)
- Cardiac dysrhythmia > cardiomyopathy
- Respiratory insufficiency, diaphragmatic weakness
- Gastrointestinal symptoms
- Neuropsychological affection



Turner C, Hilton-Jones D,
J Neurol Neurosurg Psychiatry. 2010

Myotonic dystrophy type 2, DM2

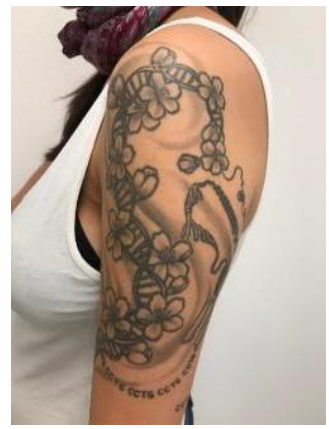
- **Symptoms usually begin in the 2nd - 6th decade (median age 48 y), no congenital form**
- Eastern European founder mutation
- Prevalence in northern Europe comparable to DM1, less frequent in the US (~ 5-fold less common than DM1), in general ~ 8-9/100,000

- **Genetic background:**
  - **CCTG repeat expansion in the first intron of *Zinc Finger Protein 9 gene* (*ZNF9*), autosomal dominant inheritance**
  - Repeat length 75-11,000 (mean ~ 5,000)
  - No clear correlation between expansion size and age at onset/disease severity
  - CCTG expansions are also unstable in somatic cells and with intergenerational transmission
  - **Less anticipation in DM2 than in DM1** (~ 0.5-1.9 decades in DM2 *vs.* ~ 2.9 decades in DM1)

DM2: clinical phenotype

- Myalgia, generalised pain, burning sensation (thigh muscles) - prior diagnosis of fibromyalgia is relatively common
- Weakness of limb girdle and trunk muscles (resembling LGMD)
- Hypertrophy of calf muscles
- Myotonia (mild)
- Mild hyperCKemia

- Tremor
- Hyperlipidemia
- Hyperhidrosis
- Cataracts
- Endocrine disorders
- Cardiac dysrhythmia > cardiomyopathy
- Fatigue, no daytime sleepiness
- Only minor neuropsychological symptoms



DM1 *vs*. DM2 – comparative features

FEATURES	DM1	DM2
GENERAL		
Epidemiology	Widespread	European
Onset age	0 to Adult	8 to 60 years
Anticipation	+	Rare
Congenital form	+	No
Life expectancy	Reduced	Normal
MUSCLE		
Weakness		
Face	+	Mild
Ptosis	+	Mild
Sternomastoid	+	Variable
Proximal legs	Late	Early
Distal	+	flex.dig. prof.
Bulbar	+	-
Muscle pain	±	++
Myotonia	+ Adult	+ Variable
Muscle size	Atrophy Face Distal limbs	Hypertrophy Calf
SYSTEMIC		
Cataracts	+	Some
Balding	+	Rare
Cardiac arrhythmias	+	Variable
Gonadal failure	+	20%
Hypersomnia	+	Variable
Hyperhidrosis	Variable	+
Cognitive disorder	Mild to Severe	Mild
LABORATORY, etc.		
Hyperglycemia	+	20%
EMG: Myotonia	+	+
Muscle Internal nuclei	Distal muscles	Type 2 fibers
Chromosome	19q13.3	3q21
Mutated gene	DMPK	ZNF9
Mutation type	CTG repeats	CCTG repeats
Repeat size	100 to 4,000	Mean ~5,000
Brain MRI	White > gray matter	White matter (> gray matter)

How to diagnose Myotonic dystrophies

- **Clinical phenotype!**
- Personal past medical history
- Family medical history
- **EMG with myotonic discharges**
  Examination of the iliopsoas muscle in DM2!

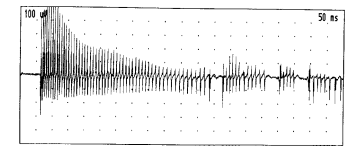
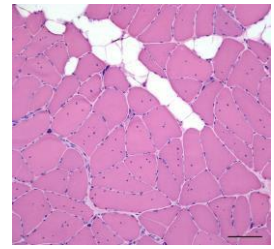


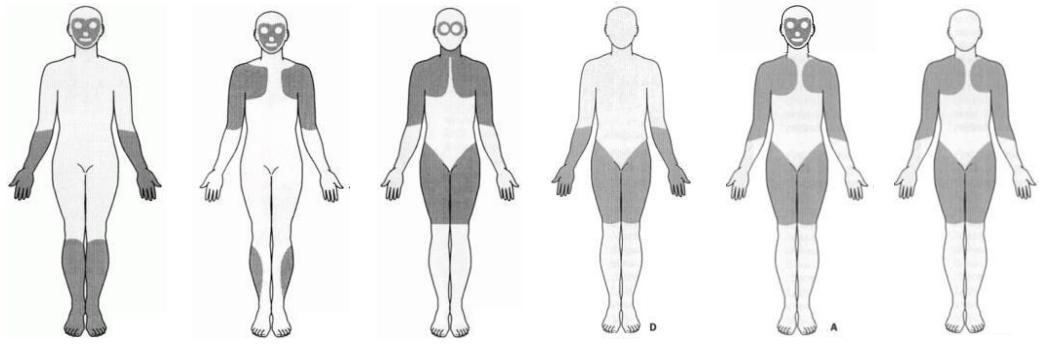
Fig. 156 ■ Salve myotonique spontanée chez un patient atteint de maladie de Steinert. Fréquence initiale de 150 Hz décroissant jusqu'à 85 Hz


DM2, vastus lateralis muscle

- **Mildly to moderately elevated CK levels and GGT in blood**
- Muscle biopsy results can be normal, unspecific, or even misleading in DM1 and DM2
  DM1: early type-1 fiber atrophy (…predominance) and type-2 fiber hypertrophy; **DM2:** predominant type-2 fiber atrophy; **DM1/2:** numerous internal nuclei, pyknotic nuclear clumps
- Neuromuscular imaging?
- **Molecular genetic testing is the gold standard in finally diagnosing DM1 and DM2**

Muscular phenotypes, DM1 and DM2

„visual diagnosis“, genetic testing first | muscle biopsy | muscle biopsy, genetic testing, biochemical analyses? *case by case decision*



DM1 ? | FSHD ? | OPMD ? | sIBM ? | DM2 ? | LGMD ?

General and specific care in DM1 and DM2

- **No curative treatments are currently available**
- Management of DM is based on **genetic counseling**, preserving function and independence, **preventing cardiopulmonary complications**, and providing **symptomatic treatment** for e.g. myotonia, pain, etc.

- Cardiological, pulmonary, endocrinological examinations; neurological sleep laboratory (polysomnography)
- Neuropsychological support
- Physical therapy, speech therapy, occupational therapy, socio-medical support, rehabiliation services

MYOTONIC DYSTROPHY FOUNDATION
Care and a Cure

Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 1

2018

Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2

2019

Neurology, Clinical Practice

Anesthetic management in DM1 and DM2

Although a **higher incidence of adverse reactions to medications** has been reported for DM1 (~ 8%), it is yet not clear whether similar risks occur also in DM2 patients. However, the advice is to adopt anesthesia guidelines similar to DM2 as suggested for DM1.

Risks of anesthesia are most significant in the post-anesthesia period → appropriate management

Possible post-anesthesia complications reflect heightened sensitivity/prolonged interaction of sedatives and analgesics

Resultant clinical effects of sedation and analgesia include:

- Reduced level of consciousness, impaired ventilatory function, heightened pharyngeal dysfunction and aspiration, increased gastrointestinal dysmotility

During anesthesia, risks stem from the multisystemic features:

- **DM1/2 do not increase risk of true malignant hyperthermia reaction, though avoidance of succinylcholine is warranted**
  → **difficult intubation** secondary to exaggerated contracture, masseter spasm, and laryngospasm; hyperkalemia
  → if a muscle relaxant is needed, then **use a non-depolarizing agent** with a short recovery index
- Cardiac rhythm and conduction defects need to be closely monitored
- Ventilatory failure and poor airway protection require monitoring and support
- Gastrointestinal dysmotility requires monitoring

Pregnancy and obstretic management

DM2 > DM1 may worsen during pregnancy (temporarily)

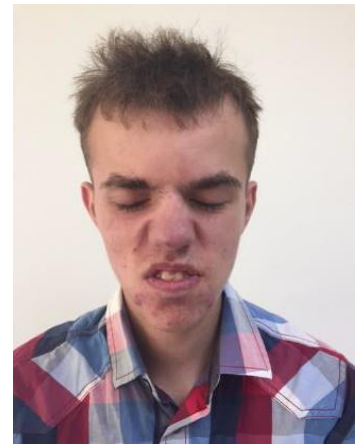
Mothers with DM1 (>> DM2) are more likely than the general population to experience the following:

- Ectopic pregnancy
- Premature delivery
- Prolonged labor and delivery related to both uterine muscle dysfunction and skeletal muscle weakness
- Postpartum hemorrhage due to inadequate uterine contractions or retained placenta
- Untoward reactions to analgesia or anesthesia during labor and delivery

Treat with:

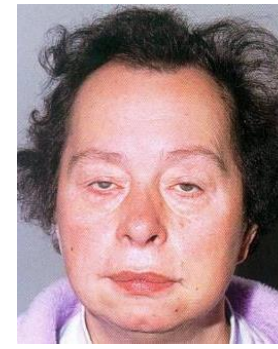
- High-risk obstetrician (maternal-fetal medicine specialist) for prenatal care and delivery
- Analgesics or sedating anesthetic drugs should be used carefully, particularly during pregnancy, esp. during the third trimester and during delivery
- Pediatric or neonatal specialist at delivery if the mother is affected with DM1, due to risk of congenital onset when maternally inherited
- Availability of a neonatal intensive care unit

Cranial manifestations: *juvenile-onset* DM1



Cranial manifestations: *adult-onset* DM1

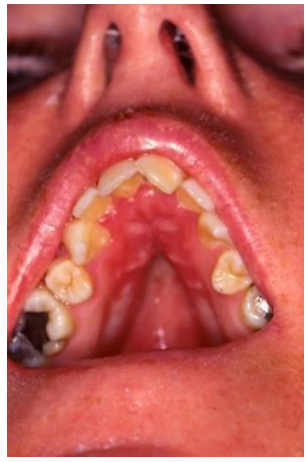
- Frontal balding
- Ptosis
- Facial weakness
- Wasting of temporalis and masseter muscles
- Mild dysphagia
- Dysarthria

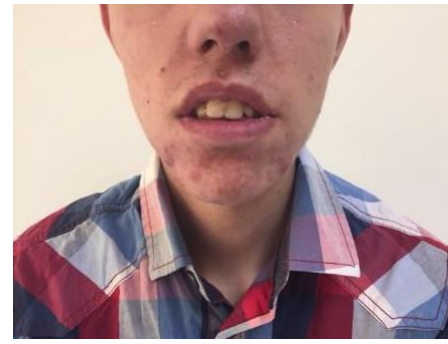


Treat with:

- Speech and swallowing therapy

High-arched palate in DM1





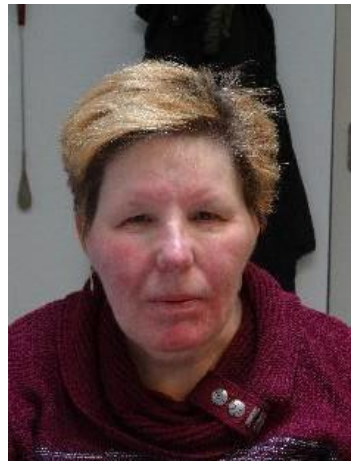
Caries, plaque and gingivitis; enamel defects?

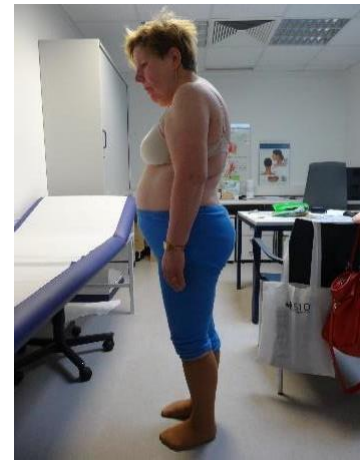
Tented upper lip in congenital DM1

Treat with:

- Regular dental care, patient education

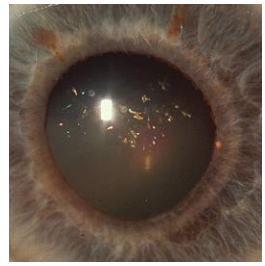
DM2: clinical phenotype

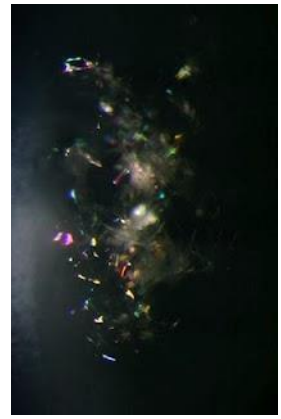




Cataracts in DM1 and DM2

- First manifestation in adolescence or early adulthood (premature/juvenile cataracts)
- Multicolored iridescent appearance, located in the posterior lens capsule (polychromatic cataract by slit lamp examination)
- „Christmas tree cataract“

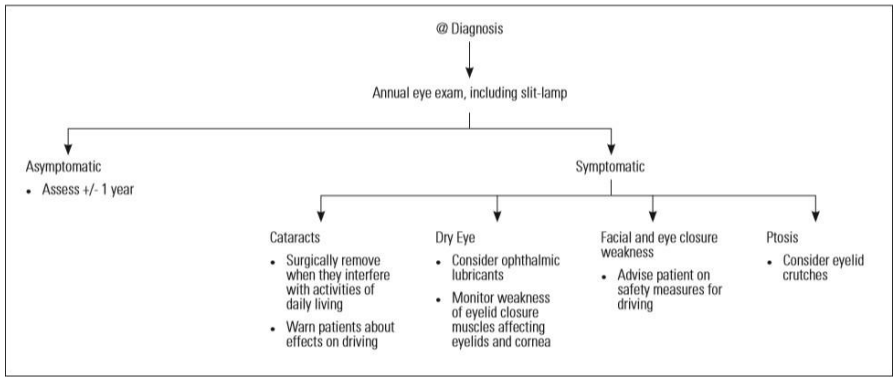




BMJ 2010; 341: c6644
„A christmas tree cataract“

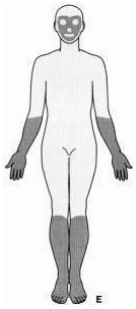
Care recommendations: Ocular management

Fig. 3 DM Ocular Recommendations Flowchart



DM1: Neuromuscular phenotype

- Muscle wasting and weakness with **preferential involvement of cranial and distal limb muscles,** esp. neck flexors, long finger flexors, ankle dorsiflexors > plantar flexors → **marked instability of gait**
- Muscle atrophy and weakness of elbow extensors and limb girdle muscles over time
- **Validated scale to score the severity of muscle involvement: MIRS**



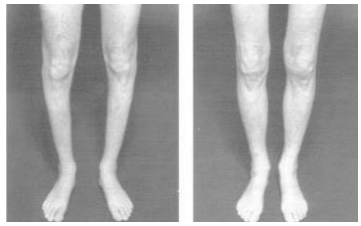


***Table 1** Muscular Impairment Rating Scale (MIRS)*

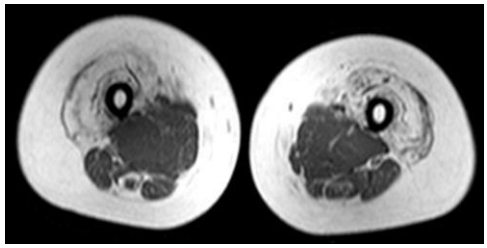
Grade	Description
1	No muscular impairment
2	Minimal signs Myotonia, jaw and temporal wasting, facial weakness, neck flexor weakness, ptosis, nasal speech, no distal weakness except isolated digit flexor weakness
3	Distal weakness No proximal weakness except isolated elbow extensor weakness
4	Mild to moderate proximal weakness
5	Severe (MRC scale ≤−3/5) proximal weakness

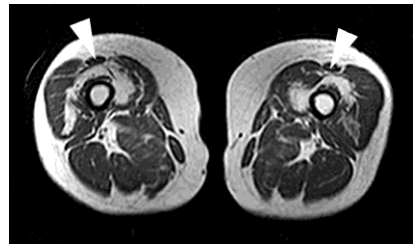
MRC = Modified Medical Research Council Scale.

Mathieu *et al.*, Neurology 2001

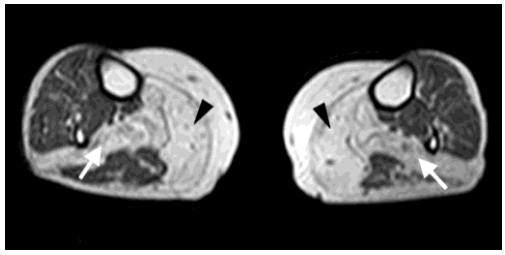
Neuromuscular imaging in DM1

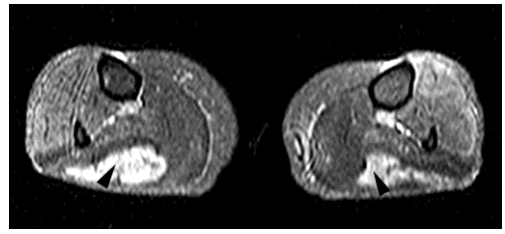
- Fatty degeneration and edema-like changes in skeletal muscle
- Predominant affection:
  Anterior compartments of thigh muscles, calf muscles (medial > lateral head of gastrocnemius muscles, soleus muscle)
- The following muscles are usually spared:
  Posterior compartment of thighs, rectus femoris, gracilis, tibialis posterior muscles





Neuromuscular imaging in DM1

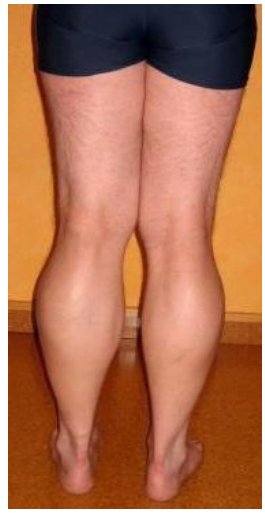


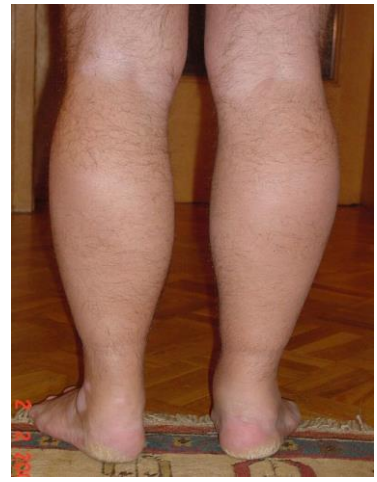


DM2: Clinical neuromuscular phenotype

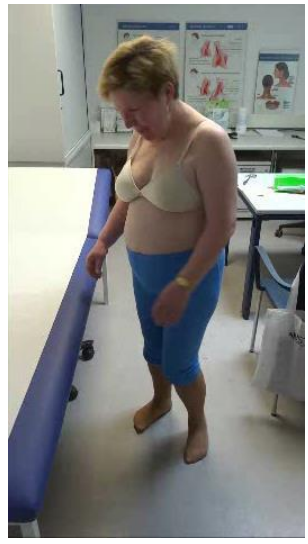
- **Pain is a common feature**
- **A prior diagnosis of fibromyalgia is relatively common**
- **Common initial symptoms are difficulty standing up from a chair, rising from a squatting position, or climbing stairs. Working with the arms overhead may be difficult, too.**
- **Although progression is slow, in some patients it seems to accelerate after ~ age 50 y**
- DM2 predominantly affects the **limb girdle, trunk muscles** and neck flexors > extensors
- Distal limb muscles are usually spared until later in the course
- There is much less cranial and respiratory muscle weakness compared to DM1
- Muscle wasting is less pronounced than in DM1
- Some patients show hypertrophy of calf muscles

DM2: Neuromuscular phenotype



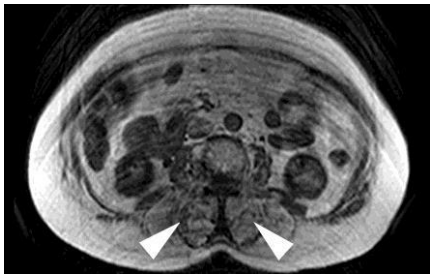


DM2: Neuromuscular phenotype

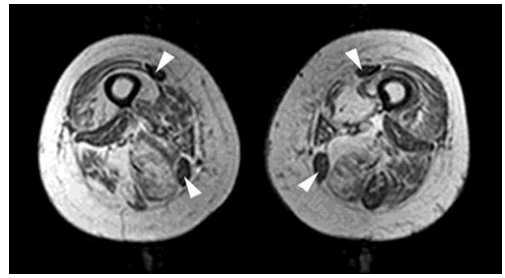


Neuromuscular imaging in DM2

- No highly specific pattern of muscle involvement in contrast to DM1
- However, rectus femoris and gracilis muscles are usually also spared
- A more proximal focus of muscle degeneration in contrast to DM1
- Involvement of distal limb and trunk muscles in clinically advanced disease stages



Erector spinae muscles are frequently fatty degenerated



Fatty degeneration of thigh muscles sparing rectus femoris and gracilis muscles

Care recommendations: Neuromuscular symptoms in DM1 and DM2

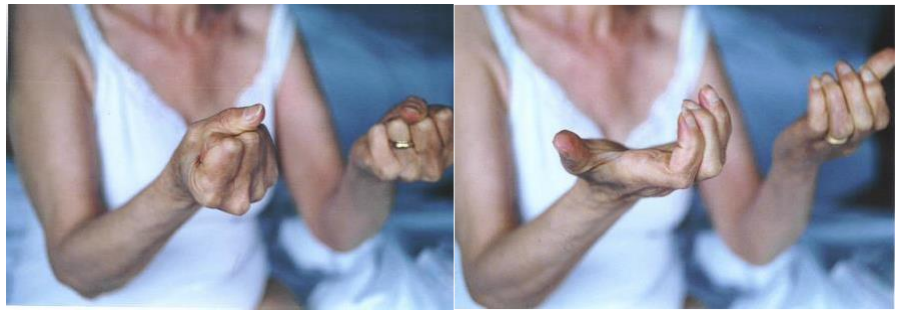
- Physical and occupational therapy
- Speech and swallowing therapy
- Moderate- or low-intensity aerobic and resistance exercise
- Assistive and adaptive devices such as orthoses, braces, canes, walkers, hand-splints, etc.
- Home and environmental modifications as necessary
- Appropriate rehab specialist for individual recommendations, reference to specialized rehab centers

Chronic pain in DM2 >> DM1:

- Treat with conventional pain medications (Ibuprofen, etc.)
- Try antidepressant drugs or anti-convulsive medication (e.g. gabapentin, pregabaline, duloxetine, citalopram)
- Other remedies, such as massage, nerve blocks, heat/ice, or chiropractic may provide benefit
- Anecdotally, some patients have reported that cannabis helps ease pain, however more research needs to be conducted

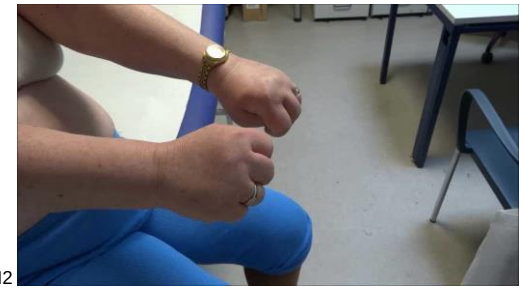
Myotonia

- The action myotonia in DM1 preferentially involves specific muscle groups of the forearm, hand, tongue, and jaw
- Myotonia may improve over time (whereas dystrophic changes worsen)



Care recommendations: Myotonia

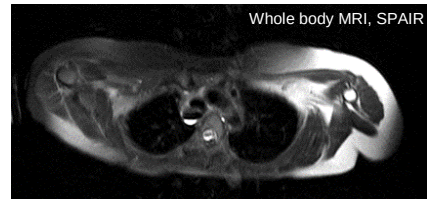
- Mexiletine is an effective treatment for myotonia in patients without cardiac abnormalities
- Serial monitoring by a cardiologist is warranted
- Alternatively, other anti-arrhythmic drugs can be applied to provide relief for myotonia (propafenone, etc.)
- All drugs are *off-label use* for the application in DM1 and DM2
  (even though mexiletine has recently been approved in the EU for the use in non-dystrophic myotonia)



Grip myotonia in DM2

Gastrointestinal symptoms in DM1 > DM2

- Involvement of smooth muscles
- Abdominal pain and bloating
- Dysphagia
- Slow gastric emptying, gastric paresis
- Insufficiency of the cardia of the stomach, gastroesophageal reflux
- Intestinal dysmotility
- Dilated colon, fecal impaction, megacolon
- Diarrhea, often alternating with constipation
- Cholelithiasis
- Anal incontinence



Gastroesophageal reflux

Care recommendations: Gastrointestinal symptoms in DM1 and DM2

Treat with:

Non-pharmacologic treatments for gastrointestinal symptoms:

- High-fiber diet for patients with diarrhea or constipation, nutrition consultation
- Dysphagia therapy
- Tube feeding may be required in patients with severe dysphagia (DM1, not DM2)
- Regular check for colorectal cancer!

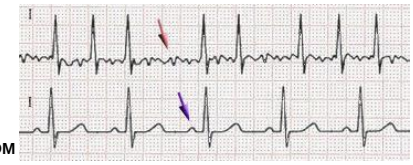
Potential pharmacologic treatment for gastrointestinal symptoms:

- Loperamide, with care, for **diarrhea**; gentle laxatives for **constipation** (e.g. lactulose, bisacodyl, pantothenic acid/vitamin B5, etc.)
- Metoclopramide or domperidon to reduce the symptoms of gastroparesis, pseudo-obstruction and gastric reflux (potential side-effects: severe cardiac complications, dyskinesia!)
- Probiotic regimens may be tried

Cardiac involvement in DM1 > DM2

- **Cardiac pathophysiology preferentially targets the cardiac conduction system**
- **Sudden cardiac death is a common cause of death in adults with DM1, second only to respiratory failure**
- **Dilated, non-ischemic cardiomyopathy is an infrequent but recognized occurrence in adults with DM1**
- Clinical presentations include pre-syncope, syncope, palpitations, dyspnea, chest pain or cardiac arrest
  - Bradyarrhythmias and tachyarrhythmias (most frequently atrial fibrillation, atrial flutter)
  - Increased risk of ventricular tachyarrhythmias, a mechanism responsible for cardiac arrest

There are defined criteria on a standard 12-lead ECG that indicate cardiac involvement in DM



Care recommendations: Cardiac symptoms

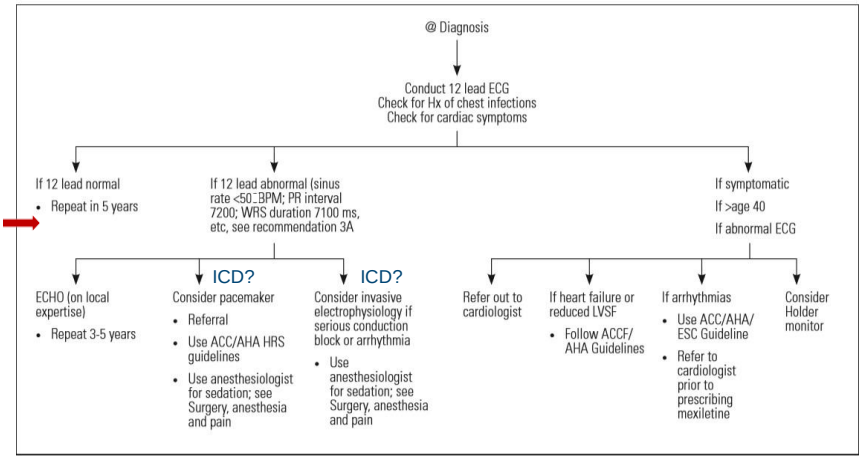
- **Serial periodic clinical cardiology evaluations**
- **Refer patients with cardiac symptoms, abnormal ECG, & patients over the age of 40 y without previous cardiac evaluation to a center experienced in DM1 care**
- Cardiac imaging modalities other than ECHO (echocardiography) may be reasonable alternatives (e.g. cardiac MRI)
- Consider **a primary (prophylactic) or secondary (symptomatic) prevention pacemaker or Implantable Cardioverter Defibrillator (ICD)** in a DM patient found to be at **high risk** of cardiac arrest or sudden cardiac death from abnormalities detected via noninvasive or invasive cardiac testing, **even in the absence of a guideline-based indication**

ACC (American College of Cardiology)/AHA (American Heart Association)/HRS (Heart Rhythm Society) Guidelines for Device-based Therapy of Cardiac Rhythm Abnormalities (see http://www.ncbi.nlm.nih.gov/pubmed/18498951), 2008/update 2017

ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities

Care recommendations: Cardiac symptoms

Fig. 2 Cardiac Care Recommendations Flowchart



annually,
& annual ECHO

Respiratory symptoms in DM1 > DM2

- **Chronic respiratory impairment and pulmonary complications are the primary cause of mortality and morbidity in DM1**
- Breathing problems result from muscle weakness of the diaphragm, abdominal and intercostal muscles, and myotonia; also weakness of the swallowing muscles
- → poor ventilatory force, low blood oxygen, elevated blood carbon dioxide levels
- → increased risk of pulmonary infections and aspiration
- Insufficient air flow during sleep may contribute to disrupted sleep and excessive daytime fatigue, and central nervous system factors may contribute to the breathing difficulties
  → **obstructive and/or central sleep apnea syndrome**

Care recommendations: Respiratory symptoms

Test for:

- Forced vital capacity (**FVC**) and forced expiratory volume in one second (**FEV1**), maximum inspiratory pressure (**MIP**) and maximum expiratory pressure (**MEP**), nocturnal oximetry and a cough peak expiratory flow
- Prominent snoring, nightly interrupted sleep, an MIP value of less than 60 or an FVC of less than 50% of predicted: **sleep study**

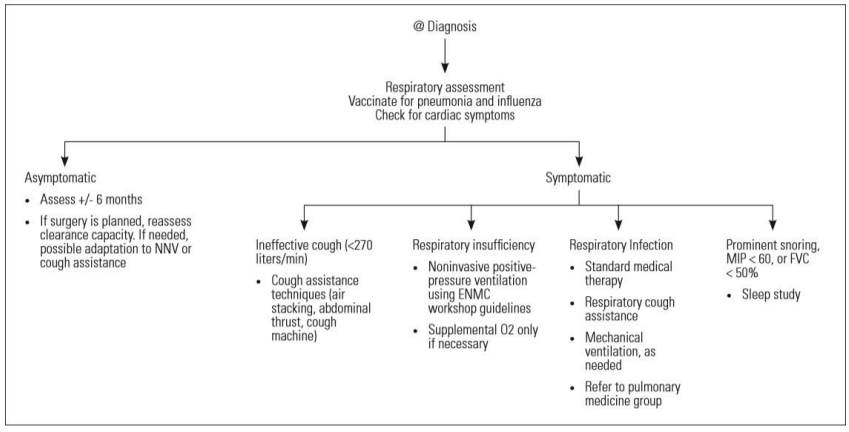
Treat with:

- **Vaccinations for influenza and pneumonia**
- **Respiratory infections should be treated as soon as possible**, as well as respiratory cough assistance and mechanical ventilation (as needed)
- Airway clearance and lung volume recruitment techniques for patients with ineffective cough, and during chest infections and perioperative periods
- Noninvasive positive-pressure ventilation (NIV) for respiratory insufficiency and sleep-related breathing disorders
- **Supplemental oxygen with great caution – even in conjunction with noninvasive ventilation**

Care recommendations: Respiratory symptoms

Clinicians must monitor issues such as recurrent pneumonia at baseline & serially with pulmonary function tests, at least forced vital capacity (FVC)

Fig. 1 Respiratory Care Recommendations Flowchart



Further multisystemic features in DM1/DM2

Endocrine and metabolic abnormalities

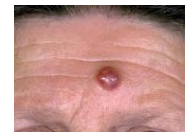
- **Hyperinsulinemia** following glucose ingestion, glucose and HbA1c values typical of prediabetes or impaired glucose tolerance, **tissue-specific insulin resistance** → however, the frequency of type 1 or type 2 diabetes in patients with DM1 and DM2 is probably comparable to that seen in the general population
- Increased incidence of thyroid, parathyroid and gonadal dysfunction in patients with DM1 > DM2, **abnormalities in the regulation of the hypothalamic-pituitary axis**
- **Hyperlipidemia in DM2 >> DM1**

Gonadal insufficiency in DM1 > DM2:

- Problems of erectile dysfunction, infertility with oligo- and azoospermia in males
- Diminished ovarian reserve in females, reduced fertility, spontaneous abortion and stillbirth, higher rate of irregular menstruations

Dermatological symptoms

- **Multiple pilomatrixomas**, frontal balding, alopecia



Laboratory tests

- CK levels in blood mildly/moderately elevated, liver enzymes/GGT ↑, IgG↓, testosterone ↓, IGF-1 ↓, FSH ↑, hyperlipidemia

Care recommendations: Endocrine and metabolic symptoms in DM1/DM2

Test for:

- Liver enzymes at baseline and then annually, chronic liver enzyme/GGT elevation is usually seen and does not necessarily indicate the need for liver biopsy
- TSH and free T4 levels at baseline and every three years, more frequent monitoring is necessary if thyroid dysfunction is suspected
- Oral glucose tolerance testing, HbA1c and fasting plasma glucose annually
- Levels of serum lipids at baseline and then every three years (DM2 > DM1), with more frequent testing if hyperlipidemia develops
- As the impact of statins on DM is uncertain, patients should be monitored carefully for muscle-related impacts if statins are needed

Treat with:

- Statins if needed because of an increased cardiovascular risk (DM2 >> DM1)
- Minoxidil (Rogaine) for DM-associated hair loss
- Lifestyle changes and appropriate medications to normalize blood glucose and insulin levels for treatment of insulin resistance
- Diabetes care according to national treatment guidelines

Brain affection in DM1 and DM2

- **Fatigue in DM1 and DM2**
- **Excessive daytime sleepiness in DM1**
- **Neuropsychological deficits in DM1 > DM2**

Treat with:

- NIV/assisted ventilation if symptoms are related to a sleep-related breathing disorder or to respiratory affection
- Cognitive behavioural therapy
- Stimulant therapy with modafinil can be considered in central hypersomnia or fatigue (*off-label* use!) – check cardiological involvement first!

Neuropsychological findings in *adult-onset* DM

- **Neuropsychological deficits, cognitive dysfunction; DM1 > DM2**
  executive dysfunctioning, cognitive slowing, attention deficit disorders, visual spatial deficits
- Behavioural abnormalities, avoidant and passive behaviour; DM1 > DM2
- Specific personality traits (apathy, indifference, lack of motivation); DM1 >> DM2
- „Lack of self-awareness“; DM1
- „Theory of mind“ dysfunction ⇒ social behavioural abnormalities; DM1
- Depression, esp. in early disease stages in DM1 (and in more advanced disease stages in DM2)

Brain disconnection disorder?

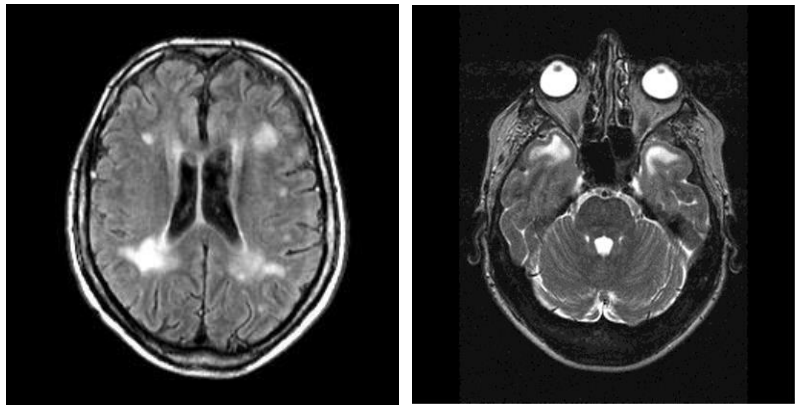
Neuroimaging in DM1 and DM2

- **Morphological and functional brain affection is evident in DM1 > DM2**
- **Degradation of white matter fiber tracts is widespread and present throughout the whole brain in DM1 > DM2**
- **Findings on gray matter are more controversial, gray matter atrophy does not seem to be regionally specific**

White matter findings in *adult-onset* DM1:

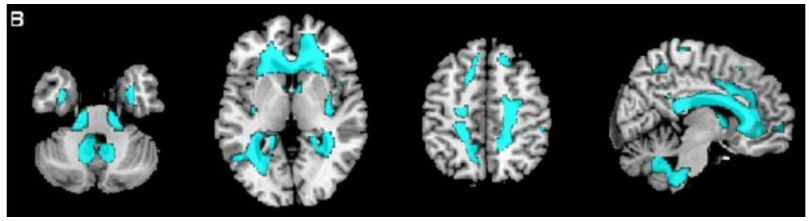
- White matter loss in all cerebral lobes, fornix, cingulum, callosal body, brainstem, cerebellum in DM1 > DM2
- Fiber tracts throughout the whole brain in DM1 > DM2
  Association (limbic system)/commissural (callosal body)/projection fibers (internal/external capsules, brainstem)
- Atrophy or hypoplasia of the callosal body
- Patchy white matter lesions (WML) in DM1 > DM2
- Anterior temporal WML (ATWML) characteristic and specific for DM1 - not present in DM2

White matter in DM1

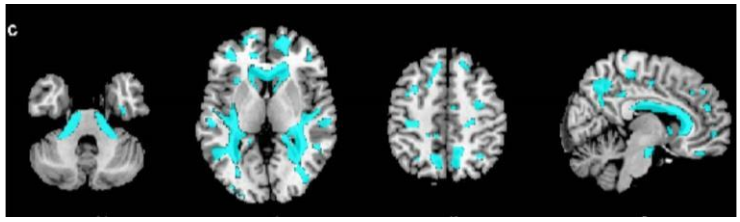


Patchy WML, ATWML, skull hyperostosis

White matter findings in DM1 and DM2
- VBM -



DM1



DM2

3.0T MRI; Minnerop *et al.* 2011
22 DM1 and 22 DM2 patients *vs.* 22 healthy controls

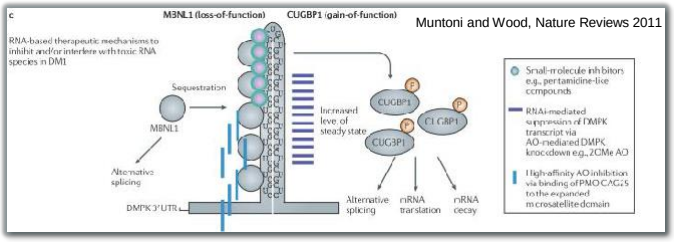
Care recommendations:
Neuropsychiatric management in DM1/DM2

Treat with:

- Refer to local support groups and local and international **patient advocacy organizations**
- Refer to a **mental health care professional** in case of psychiatric or behavioural abnormalities
- Possible treatment such as **medication** (psychostimulants, antidepressive medication), couple or family support
- **Cognitive behavioural therapy**

DGM
Deutsche Gesellschaft
für Muskelkranke e.V.

Future specific treatment options?



Muntoni and Wood, Nature Reviews 2011

RNA-based therapeutic concepts:

Therapeutic target: pathogenic expanded RNA foci (*upstream*)

- **AON that bind to toxic RNA expansions**:
  to inhibit the sequestration of splicing factors, to release splicing factors; ⇒ degradation of mutant mRNA
- RNA silencing (RNA interference) techniques (DMPK *knockdown*)

Tideglusib: glycogen synthase kinase (GSK-3b) inhibitor

Corrects the activity of RNA binding proteins like CUGBP1

- Has shown to be effective in preclinical studies of transgene DM1 models and *ex vivo* human skeletal muscle tissue
- First positive result of a phase 2 study in adolescent and adult congenital and *juvenile-onset* DM1 (fatigue, cognition, skeletal muscle)

Clinical trials in DM1

Clinical trials:

OPTIMISTIC: Cognitive behavioural therapy and physical training, www.optimistic-dm.eu
n = 255, **positive results** in patients with fatigue (capacity for activity and social participation; *Lancet Neurology* 2018)

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 (study completed)

  01/2017: "…although results from the trial showed encouraging trends in biomarker and splicing changes, the drug did not achieve concentration levels in muscle needed for it to have an effect in treating the disease. Following these results, Ionis has decided **not to advance its IONIS-DMPK-2.5Rx program"**.

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", **2016-2017**
- "Efficacy and Safety of Tideglusib in Children and Adolescents with Congenital Myotonic Dystrophy", **Phase 2/3**, **2018-2019, not yet recruiting**

ERX-963 (small molecule targeting RNA), *Expansion Therapeutics*

- "Safety, Tolerability and Pharmacokinetics of ERX-963 in Adults With Myotonic Dystrophy Type 1", **Phase 1, 2019, not yet recruiting**
  - to investigate the safety and tolerability of ERX-963 in participants diagnosed with DM1
  - to evaluate the potential of ERX-963 treatment to reduce excessive daytime sleepiness / hypersomnia and improve cognitive function in DM1 compared to placebo

DM1 and DM2 patient registries

Germany, Austria, Switzerland

UK

Myotonic Dystrophy Type 1 and 2
Treat-NMD Registries

…important for trial readiness!

France

DM Scope

Thank you for your attention!

ZENTRUM FÜR SELTENE ERKRANKUNGEN BONN

life&brain

European Reference Network
for rare or low prevalence complex diseases
Network
Neuromuscular Diseases (ERN EURO-NMD)
Member
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