

# Late-onset myopathies: clinical features and diagnosis

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**Late-onset myopathies are not well-defined since there is no clear definition of 'late onset'. For practical reasons we decided to use the age of 40 years as a cut-off. There are diseases which only manifest as late onset myopathy (inclusion body myositis, oculopharyngeal muscular dystrophy and axial myopathy). In addition, there are diseases with a wide range of onset including 'late onset' muscle weakness. Well-known and rather frequently occurring examples are Becker muscular dystrophy, limb girdle muscular dystrophy, facioscapulohumeral dystrophy, Pompe disease, myotonic dystrophy type 2, and anoctamin-5-related distal myopathy.**

**The above-mentioned diseases will be discussed in detail including clinical presentation – which can sometimes lead someone astray – and diagnostic tools based on real cases taken from the author's practice. Where appropriate a differential diagnosis is provided. Next generation sequencing (NGS) may speed up the diagnostic process in hereditary myopathies, but still there are diseases, e.g. with expansion repeats, deletions, etc, in which NGS is as yet not very helpful.**

**Key words:** myopathies, late-onset, hereditary, acquired

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## Conflict of interest

The Author declares no conflict of interest

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## Introduction

Myopathies may be defined based on the clinical presentation (distal myopathy, limb girdle muscular dystrophy, facioscapulohumeral dystrophy, etc.) or on the onset (congenital, early-onset, childhood-onset, late onset myopathies), on histopathological findings (e.g., myofibrillar myopathies, central core disease), and in exceptional cases an eponym is used, like in Duchenne and Becker muscular dystrophy.

This paper will address myopathies with a late onset, but immediately we run into difficulties, because there is no cut-off for the age when the adjective 'late' is appropriate. The addition 'late onset' may sometimes give rise to confusion. It is common knowledge that oculopharyngeal muscular dystrophy (OPMD) is a late-onset disease, since the age at onset is always beyond 50 years, whereas late-onset Pompe disease starts at age 12 months since this subtype is distinguished from the infantile onset Pompe disease.

A pragmatic approach would be to distinguish two categories (see Table I):

1. Myopathies which only manifest with late onset muscle weakness;
2. Myopathies with a wide range of onset including late onset muscle weakness.

This overview will not be comprehensive, only the most frequent or well-known hereditary and acquired myopathies will be addressed. A case

**Table I.** Late onset myopathies.

<b>Myopathies only manifesting with late onset muscle weakness</b>		
<b>Hereditary</b>	<b>Gene</b>	<b>Salient clinical features</b>
Oculopharyngeal muscular dystrophy	<i>PAPBN1</i>	Asymmetric ptosis, dysphagia
<b>Acquired</b>		
Inclusion body myositis (IBM)	Not relevant	Asymmetric weakness of quadriceps muscles, deep finger flexors and oesophageal muscles
Isolated neck extensor weakness	Not relevant	Dropped head, no underlying disease
Slow late onset nemaline myopathy* <sup>34</sup>	Not relevant	Predominantly proximal and axial muscle weakness. Respiratory muscle involvement is common. Associated with a monoclonal protein (MP) or HIV infection. Treatable.
<b>Myopathies with a wide range of onset including late onset of muscle weakness</b>		
<b>Hereditary</b>		
Becker muscular dystrophy	<i>DMD</i>	Proximal muscle weakness, calf hypertrophy, exercise-related cramps, myalgia, rhabdomyolysis, dilated cardiomyopathy
Limb girdle muscular dystrophy, FKRP-related	<i>FKRP</i>	Proximal muscle weakness, calf hypertrophy, exercise-related cramps, myalgia, rhabdomyolysis, dilated cardiomyopathy
Facioscapulohumeral dystrophy	<i>DUX4</i>	Symmetric weakness of the facial and scapulothoracic muscles, descending to the axial and leg muscles. Rarely onset in anterior tibial or calf muscle
Late-onset Pompe disease	<i>GAA</i>	Proximal muscle weakness, diaphragm involvement at an early stage
Myotonic dystrophy type 2	<i>ZNF9</i>	Proximal muscle weakness, myalgia, cardiac involvement
Myofibrillar myopathy* <sup>35</sup> such as DES, PLEC 1, CRYAB, FLNC, MYOT, ZASP, BAG3, FHL1, and DNAJB6. Objective: To retrospectively analyze genetic mutations and demographic, clinical, and morphological aspects of PAM in a French population. Methods: Forty-eight PAM patients (29 men, 19 women)	<i>DES, FLNC, MYOT, CRYAB, ZASP, BAG3, DNAJB6</i>	Distal muscle weakness (66%) most common, followed by simultaneous distal and proximal weakness. Respiratory and cardiac involvement occur frequently
Anoctamin-5 related distal myopathy	<i>ANO5</i>	Proximal or distal muscle weakness, cardiological involvement
Mitochondrial myopathy* <sup>36</sup>	Various in mitochondrial and nuclear genomes	Various phenotypes (chronic progressive external ophthalmoplegia), proximal myopathy (most common), exercise induced muscle pain, fatigue, often associated with involvement of other systems (cardiomyopathy, epilepsy, or stroke-like episodes)
Congenital myopathy* <sup>37</sup>	<i>RYR1 (most common), ACTA1, MYH7, DNM2, SELENON, MYH2, CACNA1S</i>	Proximal muscle weakness in all, axial muscle weakness (RYR1), rhabdomyolysis (RYR1, CACNA1S), malignant hyperthermia (RYR1), skeletal abnormalities
<b>Acquired</b>		
Idiopathic inflammatory myopathies (IIM's) other than IBM* - immune mediated necrotizing myopathy, dermatomyositis (DM), non-specific myositis, antisynthetase syndrome (ASS) <sup>38</sup>	Not relevant	Subacute onset muscle weakness of the proximal muscles and dysphagia. Skin abnormalities in DM and in a proportion of ASS patients. DM and IMNM associated with cancer. Most IIM's, in particular non-specific myositis associated with connective tissue disorders. Treatable.

\*These diseases will not be further discussed

vignette will be provided in selected cases, followed by general information on the disease, and where appropriate a differential diagnosis.

## Hereditary myopathies only manifesting with late onset muscle weakness

### *Oculopharyngeal muscular dystrophy*

Case 1 – A 76-year-old male was referred because of suspected ALS. He had developed gait difficulty due to weakness of the left leg after a fall. He admitted to having noticed a decrease in strength of the trunk and arm muscles. He had a hoarse voice and swallowing difficulty (later admitted to have progressive speech and swallowing difficulty since about 20 years). Previous history disclosed cataract surgery at age 74 and 75 years, respectively

Family history taking revealed that his mother may have had a ‘muscle disease’.

On clinical examination he was found to have a facies myopathica and bilateral ptosis. He had a weak cough and generalized moderate weakness and atrophy of his arm and leg muscles. There was no myotonia and no fasciculation. Reflexes were normal except for a left plantar response which was extensor.

The following ancillary tests were done, electromyography (EMG) which was consistent with a myopathy. Serum creatine kinase (CK) activity was slightly elevated (205 IU/L (upper limit of normal (ULN) 190)). Videofluoroscopy showed silent aspiration. A muscle disclosed some neurogenic features, no rimmed vacuoles, DNA analysis showed a (GCN)<sub>12</sub> repeat expansion exon 1 in the *PABPN1* gene. Based on the family history a diagnosis of OPMD was considered very likely and DNA analysis confirmed a diagnosis of autosomal dominantly inherited oculopharyngeal muscular dystrophy.

### General information

OPMD is caused by an abnormal (GCN) triplet expansion within the *PABPN1* gene

located on chromosome 14 (14q11.2-q13). While the wild-type *PABPN1* gene

contains 10 (GCN) repeats, the mutated form in OPMD is expanded to 11-18 repeats, adding

1-8 additional alanine residues at the N-terminus of the PABPN1 protein. A French study

showed that patients with OPMD with longer *PABPN1* expansion are on average diagnosed

at an earlier age than patients with a shorter expansion<sup>1</sup>.

Inheritance is usually autosomal dominant, but autosomal recessive inheritance also occurs.

The age at onset in heterozygotes is in the fourth to sixth decade.

The most salient features include often asymmetric ptosis, incomplete external ophthalmoplegia and dysphagia. Slowly progressive limb muscle weakness, usually proximal, and legs more than arms occurs in the course of the disease.

As regards ancillary investigations CK is normal or slightly elevated, EMG shows myopathic changes and sometimes features compatible with ‘denervation’. In a proportion of the muscle biopsies rimmed vacuoles can be found and at the ultrastructural level intranuclear filaments, albeit a muscle biopsy is no longer needed, since diagnosis is currently made by molecular testing.

## Acquired myopathies only manifesting with late onset muscle weakness

### *Inclusion body myositis*

Case 2 – A 57-year-old male was referred because of gradually progressive muscle weakness of the upper legs since about 5 to 6 years. He had no swallowing difficulty. Previous and family history were unremarkable.

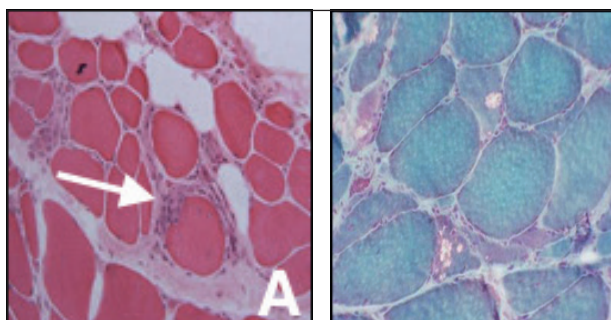
On clinical examination he was found to have severe wasting and weakness of the quadriceps muscles. In addition, we noticed slight weakness of the facial muscles, a positive Gowers’ phenomenon, slight weakness of the iliopsoas muscles and of the m. extensor hallucis longus weak (MRC grade 4). Vibration sense of the big toes was absent and there was areflexia.

Ancillary testing: CK was slightly elevated (2 x ULN). Anti-cN1A autoantibodies were positive. EMG showed spontaneous muscle activity in the quadriceps and gastrocnemius muscles. An MRI disclosed fatty replacement and atrophy of the quadriceps muscles. A muscle biopsy showed mononuclear cell infiltrates invading non-necrotic muscle fibres and rimmed vacuoles (Fig. 1).

He was diagnosed with inclusion body myositis based on the clinical findings and the ancillary tests. During follow-up proximal muscle weakness further deteriorated and he became wheelchair bound. He also developed dysphagia.

### General information

Inclusion body myositis (IBM) is both an inflammatory and myodegenerative condition. The presence of inflammatory cells mostly cytotoxic CD8+Tcells sur-



**Figure 1.** A) (pt 2): H&E stain showing a mononuclear cell infiltrate surrounding and invading a non-necrotic muscle fibre (arrow); B): Modified Gomori stain showing two muscle fibres with rimmed vacuoles (arrows).

rounding and focally invading non-necrotic muscle fibers indicate an immune attack<sup>2</sup>. The evidence of rimmed vacuoles with abnormal protein aggregation and deposition of congophilic inclusions within the muscle fibers, in association with mitochondrial dysfunction, supports the presence of a degenerative component<sup>2</sup>.

IBM is the most common late onset acquired myopathy. The age at onset is later than 45 years and the duration of symptoms should be more than 12 months according to a consensus workshop<sup>3</sup>. In 35% of the patients falls and difficulty standing are the first manifestations. Decreased dexterity and swallowing difficulty may also be presenting symptoms. Muscle weakness is often asymmetrical and slowly progressive.

There is a characteristic distribution of muscle weakness including the thigh muscles (quadriceps), deep finger flexors, oesophageal muscles and facial muscles. Sometimes weakness in other distal muscles (foot extensors or the calf muscles) may also be early manifestations. Usually there is no muscle pain.

There has been a heated debate about the minimum requirements for a diagnosis. The 'Griggs criteria' were initially considered to be mandatory<sup>4</sup>. However, gradually we and others found that rimmed vacuoles were not always present in the muscle biopsies of patients who otherwise fulfilled the clinical criteria for IBM<sup>5,6</sup>. Based on an evaluation by Lloyd et al. on the specificity and sensitivity of published diagnostic criteria the following diagnostic criteria for IBM were established: weakness in the quadriceps muscles more than hip flexors, as well as in finger flexors more than shoulder abductors. In addition, patients are required to have at least one of the following pathological features: endomysial inflammation, rimmed vacuoles, increased MHC-I, 15 to 18 nm filaments, or accumulation of amyloid or other proteins<sup>7</sup>.

Serum CK activity can be normal and moderately elevated to a maximum of 15 times the upper limit of

normal<sup>8</sup>. EMG is consistent with a myopathy showing increased spontaneous activity and fibrillation potentials, associated with short duration, low-amplitude, motor unit potentials often mixed with long duration, high-amplitude motor unit potentials. These findings are also present in non-IBM myositis<sup>9</sup>. Elevated cN-1A antibodies are reported to be 33 to 76% sensitive and 92 to 96% specific for IBM. They were reported in various autoimmune disorders, including Sjögren's syndrome, systemic lupus erythematosus and dermatomyositis<sup>2</sup>.

#### *Isolated neck extensor weakness ('dropped head')*

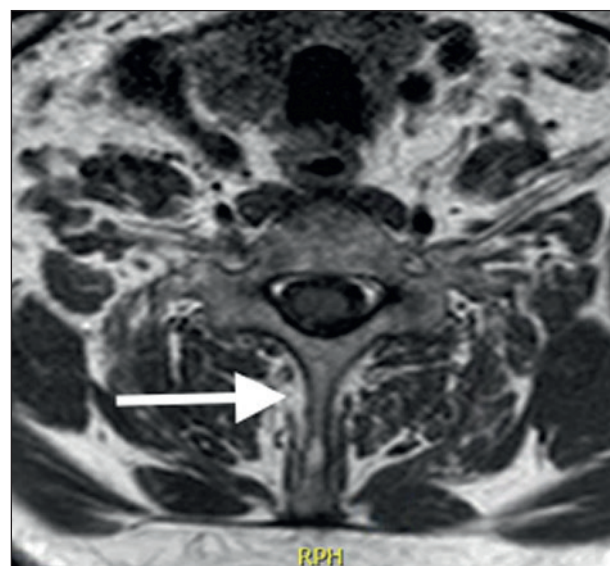
Case 3 – A 74-yr-old male experienced a painful neck (VAS score 42 out of a maximum of 100. Fourteen days later he developed a dropped head which hampered him in his activities (walking, biking, social activities).

On examination there was anteroposition of the head, which was not redressible. Hypertrophy and increased tone of the bilateral m. trapezius descendens were found. Range of motion was limited in all directions. No fasciculations, normal reflexes.

Ancillary tests: MRI showed fatty replacement of the multifidus muscles (Fig. 2).

Based on the history, clinical examination, and additional investigations amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA), myositis, and myasthenia gravis were ruled out and he was diagnosed with isolated neck extensor weakness.

He received a collar for a couple of months and physiotherapy was given. There was a follow-up for more than 4 years and the patient had less pain (VAS 10), did not



**Figure 2** (Pt 3). MRI of the neck muscles showing fatty replacement of the multifidus muscles (arrow).

develop weakness in other muscles and had been able to restart his activities.

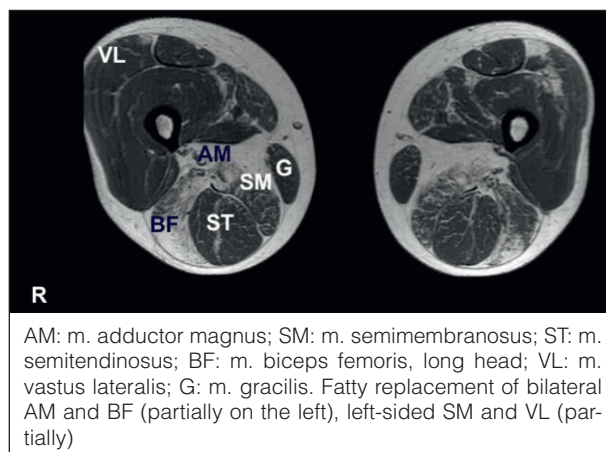
### General information

Dropped head is defined by weakness of the cervical paraspinal muscles resulting in flexion of the head and cervical spine that is typically passively correctable. Patients typically present with neck pain. Dropped head as first or prominent manifestation of neuromuscular disease can be found in several non-myopathy diseases, including ALS/PMA, myasthenia gravis, in particular associated with anti-muscle-specific kinase antibody (MuSK) antibodies, and Lambert-Eaton syndrome. It has also been described as presenting symptom in IBM, other myositis subtypes, Pompe's disease, facioscapulohumeral dystrophy, myofibrillar myopathy, mitochondrial myopathy, sporadic late onset nemaline myopathy (SLONM), but usually on clinical examination other muscles appeared to be affected as well<sup>10</sup>. The term isolated neck extensor weakness was coined by Katz and should be reserved for patients with only severe extensor muscle weakness showing a benign course in whom the muscle biopsy findings were non-specific<sup>11</sup>. A systematic review showed that the mean age of patients was 63.6 (95% CI 60.9-66.2 y) and the majority were female<sup>12</sup>. In a large cohort of 92 patients diagnostic work up was conclusive in 57 patients (53%)<sup>10</sup>. Among these patients, inflammatory myopathy (often associated with a connective tissue disorder, in particular scleroderma) and SLONM were the most frequent ones. The authors recommend perform a comprehensive work up in patients presenting with dropped head<sup>10</sup>.

## Hereditary myopathies with a wide range of onset including late onset muscle weakness

### Becker muscular dystrophy

Case 4 – A 44-year-old man was referred because of an elevated CK (1300-2200 IU/L (normal < 171)). On history he did not complain about muscle weakness. Previous history disclosed diabetes mellitus type II. On examination he was found to have hypertrophic calves and focal atrophy of the left thigh, but no muscle weakness. MRI showed replacement of the adductor magnus and the long head of the biceps femoris muscle by fat (Fig. 3), a muscle biopsy revealed reduction of dystrophin, and a subsequently performed DNA analysis of the dystrophin gene disclosed an in-frame deletion of exons 2-7 compatible with a diagnosis of Becker muscular dystrophy. Cardiological examination did not reveal any abnormalities but the patient was scheduled to undergo cardiological screening on a regular basis.



**Figure 3** (Pt 4): MRI of the upper legs.

### General information

Becker muscular dystrophy (BMD) is an X-linked recessive disease caused by a mutation in the *DMD* (dystrophin) gene, which is the largest human gene, consisting of 79 exons. Approximately 60% of the patients have a deletion of one or more exons, and in 5-10% of the BMD/DMD patients, duplications are found. Approximately 10% of the patients have a point mutation. The mutations in BMD are usually in-frame, leading to an altered but still functioning dystrophin. Symptoms typically begin between ages 3 and 21, with a mean age of onset of 11 years. However, onset at a much later age and even in the seventh decade has also been reported<sup>13</sup>.

In BMD muscle symptoms and signs are more heterogeneous than in DMD, ranging from very mild, such as exercise-induced myalgia or cramps, to severe progressive muscle weakness in thigh muscles. Weakness and wasting of the quadriceps femoris muscles can be the only symptom for a long time. Usually in due course the upper limbs become affected as well. Cardiac involvement is similar to that in DMD – degeneration of cardiac muscle fibres leading to rhythm disturbances and dilated cardiomyopathy - and ultimately present in all BMD patients. Severe dilated cardiomyopathy requiring heart transplantation may be the presenting symptom in BMD<sup>14</sup>.

CK is usually more than five times elevated. BMD may present with hyperCKemia without clinical symptoms as in our patient. Electromyography usually does not contribute to the diagnosis, especially not if CK is more than 10 times elevated. Muscle imaging of the thigh muscles may be helpful showing fatty replacement of the adductor magnus muscle, semimembranosus muscle and long head of the biceps femoris muscle as the first manifestations which are specific findings<sup>15,16</sup>. Pathological changes include an abnormal variation in muscle fiber size due to atrophic and

hypertrophic fibers, focal necrosis, and regeneration, and extensive endomysial fat and connective tissue. For diagnostic confirmation immunohistochemistry with antibodies raised against different parts of dystrophin are used as a qualitative measure for dystrophin in muscle tissue. In BMD muscle immunohistochemistry may show that dystrophin is distributed normally but globally reduced or that the staining is discontinuous with either a normal or reduced intensity. However, often this test is not sufficient to confirm the diagnosis of BMD. Western blot analysis, which is a semi-quantitative measurement of dystrophin, can detect abnormal amounts of dystrophin and/or dystrophin with a different molecular weight. For accurate genetic classification there is a variety of sequencing and genetic diagnosis methodologies ranging from Sanger sequencing which is a low throughput, conventional strategy with lower cost than more advanced sequencing and allowing for sequencing the dystrophin gene to next generation sequencing<sup>17</sup>.

Differential diagnosis may include limb girdle muscular dystrophy, spinal muscular atrophy type 3 and Pompe disease which all manifest with a limb girdle distribution of weakness and may be associated with a markedly elevated CK and calf hypertrophy.

#### *Limb-girdle muscular dystrophy*

Case 5 - A 41-year-old male was referred because of back ache. On history taking he admitted that had not been able to keep up with his peers at sport. He experienced exercise-related myalgia from early childhood onwards and had once had myoglobinuria. Since the neurologist from elsewhere had noticed firm calves and wasted thighs, he was referred.

On examination there was calf hypertrophy and atrophy of the thigh muscles. He was found to have weakness of the m. iliopsoas and adductors and a positive Gowers' phenomenon indicating muscle weakness of the gluteal and quadriceps muscles.

An immunostained muscle biopsy showed reduced alpha-dystroglycan and subsequently a homozygous missense mutation c.826C > A; p.Leu276Ile was found in the fukutin-related protein gene. Thereupon the patient was diagnosed with LGMDR9 FKRP-related, formerly known as LGMD2I (see below).

Since this type of LGMD is associated with cardiac involvement he was referred for cardiological screening albeit he was asymptomatic. A dilated cardiomyopathy was found and unfortunately, he died from heart failure, as a result of decompensation of the cardiomyopathy waiting for heart transplantation.

#### **General information**

Limb girdle muscular dystrophy (LGMD) is named after the distribution of muscle weakness. The term 'limb

girdle muscular dystrophy' was coined by Walton and Nattrass in 1954 who identified LGMD as a separate clinical entity from X-linked recessive Duchenne muscular dystrophy, autosomal dominant facioscapulohumeral muscular dystrophy and autosomal dominant myotonic dystrophy<sup>18</sup>. After the first molecular genetic characterisation of a number of LGMDs, a European Neuromuscular Centre (ENMC) consortium reached a consensus on the classification of LGMD subtypes in 1995<sup>19</sup>. An alphanumeric system was introduced, in which the number 'one' or 'two' was assigned to a dominant or recessive mode of inheritance, respectively. A letter was assigned based on the order of discovery of linkage assignment to a certain genetic locus or of a new disease gene. Since the letter of the alphabet had been reached as far as the autosomal recessive LGMDs are concerned, but even more importantly disease entities were included which did not predominantly manifest with limb-girdle distribution of muscle weakness (e.g., laminopathy or myofibrillar myopathy) or were already known as a separate disease entity (e.g., Pompe disease, also known as LGMD2V) another ENMC workshop was organized in 2017<sup>20</sup>. The participants formulated a definition of LGMD: "[...] a genetically inherited condition that primarily affects skeletal muscle leading to progressive, predominantly proximal muscle weakness at presentation caused by a loss of muscle fibres. [...] the condition [...] must have an elevated serum creatine kinase activity, must demonstrate degenerative changes on muscle imaging over the course of the disease, and have dystrophic changes on muscle histology, [...]".

Subsequently the definition was applied to the existing classification and ten conditions did no longer fulfill the criteria of LGMD. Four novel conditions which did were added. The formula for the new classification was as follows: "*LGMD, inheritance (R or D), order of discovery (number), affected protein*". In our case the diagnosis is LGMDR9 FKRP-related.

FKRP mutations cause a number of rare, autosomal recessive muscular dystrophies, the most common of which is LGMDR9, FKRP – related and muscular dystrophy – dystroglycanopathy type C, 5 (MDDGC5), and even rarer congenital conditions. Even within LGMDR9 there is a wide variation as regards age at onset and disease severity. Recently the data of a large cohort assembled in a registry (Global FKRP Registry) was analyzed<sup>21</sup>. The mean age of diagnosis for LGMDR9 was 30.1 ± 17.3 years. The presenting symptoms were muscle weakness of the lower limbs and hyperCKemia. Respiratory insufficiency requiring (non)invasive ventilation was found in a fair proportion of patients (18.2%) and 23.3% reported a heart condition, i.e. dilated cardiomyopathy.

Exercise-related rhabdomyolysis and myalgia can

occur and may be the sole manifestation for a number of years<sup>22</sup>.

Diagnosis is most reliably made by molecular analysis. Since LGMDR9 has much in common with other LGMDs and Becker muscular dystrophy (limb girdle distribution of muscle weakness, calf hypertrophy, high CK, dystrophic pattern on the muscle biopsy) usually NGS with a targeted gene panel is done. Immunostaining of a muscle biopsy may reveal a reduced alpha-dystroglycan but can be normal in less severely affected patients.

Pulmonary and cardiological screening should be carried out after the diagnosis has been established.

### *Facioscapulohumeral dystrophy*

Case 6 – A 50-year-old male patient was referred because of calf muscle weakness noticed since age 45 years. The patient was previously described<sup>23</sup>. He did not complain about back ache, sciatic pain, or paresthesia.

On examination there was atrophy of both calves, left more than right and he was not able to walk on tiptoes. Achilles tendon jerks were absent. He was also found to have axillar folding, no facial weakness, no scapulae alatae.

Based upon the presence of axillar folding a diagnosis of FSHD was considered and indeed a short (20) EcoRI fragment on chromosome 4q was found confirming the diagnosis.

### **General information**

Facioscapulohumeral dystrophy (FSHD) type 1 is a slowly progressive, autosomal dominantly inherited myopathy defined by a contraction of the D4Z4 repeat array on chromosome 4q35, with a residual EcoRI fragment of 10–38 kb.

FSHD generally starts during adolescence, but with a wide range of onset (4–60 years). The presenting symptoms are typically variable degrees of muscle weakness, involving the facial and shoulder girdle muscles, leading to the characteristic scapulae alatae, often in an asymmetrical manner. Rarely, an onset in the anterior tibial muscle or calf muscle was reported and sometimes without apparent facial involvement<sup>23,24</sup>. In due course other muscles are involved as well, i.e. the quadriceps muscles, hamstrings, abdominal muscles, upper arm muscles, pelvic girdle, and distal leg muscles. In a proportion of the patients swallowing difficulty and respiratory involvement occur. On the other end of the spectrum are patients who are asymptomatic and show some subtle symptoms on clinical examination. This variability may also occur within families.

CK may be elevated but is usually normal, EMG is not helpful and the same holds true for the muscle biopsy which often shows non-specific features, albeit inflammation may occur. MRI can be useful showing (asymmetri-

cal) replacement of the hamstring muscles, adductor muscles, rectus femoris, and gastrocnemius medialis muscles, also in early stage disease and in patients without leg muscle weakness<sup>25</sup>.

Diagnosis is established by genetic analysis. The smallest remaining fragments may be correlated with the most severe phenotype, i.e. infantile FSHD manifesting with paralysis of the facial muscles.

There is also another FSHD subtype (2) caused by mutation in the structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1) gene with a similar phenotype to FSHD type 1.

### *Pompe's disease*

Case 7 – A 51-yr-old female was referred because of difficulty getting up the stairs and mounting a horse since about 2 years. In retrospect, symptoms may have been present since age 40 years. She had always been good at sports as an adolescent and young adult.

Family history disclosed that there were 9 sibs of whom the eldest sister may have the same problems.

On examination there was a positive Gowers' phenomenon caused by weakness of the pelvic girdle and thigh muscles. Otherwise no abnormalities.

Ancillary investigations showed that CK was elevated (5 x ULN). A muscle biopsy revealed accumulation of glycogen in vacuoles. There was deficiency of acid maltase in leukocytes: 21 (N 60–250) nmol/hr/mg.

All these ancillary investigations suggested the diagnosis of Pompe's disease and this was confirmed by DNA analysis showing that she was a compound heterozygote for c.IVS1-13T > G and C.379-380delTG (p.Cys127fs) mutations in the *GAA* gene.

After the diagnosis the lung function was assessed, and she was referred for enzyme replacement therapy.

### **General information**

Glycogen storage disease type II or Pompe disease, also referred to as acid maltase deficiency, is a rare lysosomal storage disease characterized by the accumulation of glycogen primarily in muscle tissue. It is an autosomal recessive inherited disease in which there is a deficiency in the activity of the lysosomal enzyme acid  $\alpha$ -glucosidase. The  $\alpha$ -glucosidase gene is located on the long arm of chromosome 17 and myriad mutations have been identified.

The disease presents as a spectrum of phenotypes, ranging from a rapidly fatal phenotype in infants to slower progressive phenotypes in older children and adults. We will confine ourselves to the late onset Pompe disease (LOPD). The disease can start at any age after the age of 12 months. In addition to limb-girdle muscle weakness, the diaphragm is often involved irrespective of the

severity of the limb muscle weakness. Other features include ptosis, bulbar dysfunction, and scapular winging. Since the early symptoms of late-onset Pompe disease are non-specific, it often takes several years to reach the correct diagnosis. It is of utmost importance to diagnose the patients as early as possible since they can be treated with  $\alpha$ -glucosidase alfa enzyme replacement therapy.

CK is usually moderately elevated. EMG may show a myopathic pattern and signs of membrane irritability with myotonic discharges. A muscle biopsy may show vacuoles filled with glycogen as in our patient but is often non-specific. Measurement of  $\alpha$ -glucosidase activity in dried blood spots (or in leukocytes) is essential for the diagnosis of late-onset Pompe disease. Given its high specificity and sensitivity, mutation analysis of the  $\alpha$ -glucosidase gene may be performed as a confirmatory test. Currently, next generation sequencing with a targeted gene panel including the *GAA* gene is applied on patients with a clinical picture that may fit with Pompe disease. In a large cohort of unselected adult patients with hyperCKemia and/or limb girdle muscular weakness, a prevalence of late-onset Pompe disease of 2.4% was found by target gene panel screening <sup>26</sup>.

### *Myotonic dystrophy type 2*

Case 8 – A 60-year-old female was referred because of a 10-year history of progressive weakness. In particular, she had difficulty with climbing stairs and exercise-induced myalgia. She underwent cataract surgery at age 58 years. Family history disclosed that her brother had died but was known to have a pacemaker installed. Her father and two paternal uncles were known with ‘heart conditions’ and cataract surgery or walking difficulty.

On examination there was moderately severe limb-girdle muscle weakness. She had firm calves and myotonia was absent.

Ancillary tests showed a slightly elevated CK, myopathic changes on EMG but no myotonic discharges. In light of the family history a diagnosis of myotonic dystrophy type 2 was considered, and genetic analysis showed a repeat expansion in intron 1 of the *ZNF9* gene.

A cardiac monitor was implanted because of two syncopes.

### **General information**

Myotonic dystrophy type 2 (DM2), also known as proximal myotonic myopathy, is a rare, multi-systemic disease. DM2 has a later onset and a usually milder phenotype as compared to DM1. DM2 lacks the severe congenital form seen in DM1. The gene defect is an unstable CCTG repeat expansion in the cellular nucleic acid-binding protein gene, formerly known as the zinc finger protein (*ZNF*) 9 gene. Like DM1, DM2 has an autosomal

dominant inheritance pattern and expansion lengths of 75 repeats or longer are considered pathogenic. There is no clear correlation between the length of the CCTG expansion and clinical severity.

Symptoms in DM2 patients usually begin in the third to fifth decades of life. Muscle weakness (proximal and axial, not facial, not distal) and/or myalgia are the most common symptoms at onset. As the duration of DM2 increases many organs and systems may be affected and therefore the patient’s management should include amongst others screening for heart diseases (cardiomyopathy, arrhythmias), diabetes mellitus/insulin resistance, thyroid dysfunctions, cataract, and gastrointestinal disturbances <sup>27</sup>. Symptom severity widely varies among patients, even within members of the same family.

There are no specific ancillary tests. Clinical myotonia or myotonic discharges on EMG are only found in a proportion of the patients <sup>28</sup>.

### *Anoctamin-5 related distal myopathy*

Case 9 – A 55-year-old man was referred because of a 5-year history of difficulty getting up the stairs. Family history was negative. On examination atrophy of the thighs and calves was found. He was not able to walk on tiptoes.

CK was markedly elevated (30x times the ULN). We established a diagnosis of a Miyoshi-like distal myopathy. Muscle imaging showed fatty replacement of the medial head of the gastrocnemius and of the gluteus minimal muscles on both sides.

A muscle biopsy revealed a dystrophic pattern and a normal dysferlin stain. DNA analysis: showed compound heterozygous mutations in the *ANO5* gene: c.191dupA (exon 5) and c.1898+1G>A (intron 17).

We followed the patients for more than 20 years and muscle weakness remained restricted to the lower extremities.

### **General information**

Mutations in the *anoctamin5*-gene which encodes a putative calcium-activated chloride channel causes LGMDR12 formerly known as LGMD 2L, Miyoshi-like distal myopathy (MMD3) and asymptomatic hyperCKemia. Historically LGMD and distal myopathy caused by *ANO5* mutation (MMD3) - and this also holds for MMD1 caused by dysferlin mutation – were considered two separate disease entities. However, natural history studies including muscle strength assessment and MRI showed that there is a spectrum in which distal-onset phenotypes already show proximal involvement in early stages and vice versa as regards proximal-onset phenotypes <sup>29</sup>. There are subtle differences between MRI findings in dysferlin and *ANO5*-related LGMD/distal myopathy <sup>30</sup>.





**Figure 4.** Meeting of the Executive Committee of the World Muscle Society in Naples, 2002.

The median of age at onset in ANO5-related myopathy is 38 years, ranging from 4 to 67 years with a male preponderance<sup>31</sup>. Exercise-related myalgia and rhabdomyolysis have been described in several papers<sup>31,32</sup>. Cardiac involvement does occur and therefore cardiological screening should be carried out after the diagnosis has been established<sup>31,33</sup>.

Ancillary tests are non-specific showing a markedly elevated CK, myopathic EMG sometimes also associated with positive sharp waves and fibrillations, and a dystrophic pattern on muscle biopsy. Attempts to detect ANO5 on immunohistochemistry were not successful.

## Conclusions

There is a variety of myopathies with may manifest with late onset muscle weakness, both hereditary and acquired conditions. Even a so-called congenital myopathy may present as late-onset muscle weakness.

I am indebted to Giovanni Nigro, with whom I shared the fascination of cardiological involvement in myopathies. The picture (Fig. 4) shows a meeting of the Executive Committee of the World Muscle Society in Naples in 2002.

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