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Late onset Pompe disease: Clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients

Wolfgang Müller-Felber [a,*], Rita Horvath [b], Klaus Gempel [b], Teodor Podskarbi [c], Yoon Shin [c], Dieter Pongratz [d], Maggie C. Walter [d], Martina Baethmann [e], Beate Schlotter-Weigel [d], Hanns Lochmüller [d], Benedikt Schoser [d]

[a] *Haunersche Kinderklinik, Childrens Hospital, Ludwig-Maximilians-University, Lindwurmstr. 4, 80337 Munich, Germany*
[b] *Metabolic Disease Center, Munich-Schwabing, Institute of Clinical Chemistry, Academic Hospital Munich-Schwabing, Germany*
[c] *Molecular Genetics and Metabolism Laboratory, Munich, Germany*
[d] *Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians-University, Munich, Germany*
[e] *Department of Pediatrics, Community Hospital III. Orden, Munich, Germany*

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Abstract

To describe the clinical and neurophysiological spectrum and prognosis in a large cohort of biochemically and genetically proven late onset Pompe patients. Thirty-eight diagnosed with late onset Pompe disease at our neuromuscular department during 1985 and 2006 are described in detail.

The mean delay from onset of symptoms or first medical consultation until diagnosis was 10.4 and 7.1 years, respectively. A different diagnosis was suggested in 11 of 38 patients. Ten patients underwent repeated muscle biopsies before diagnosis of Pompe disease was established. Limb girdle weakness was the most frequent presenting sign. Six patients complained of myalgia. Wolf–Parkinson–White syndrome was found in 3 of 38 patients. Respiratory failure preceded the onset of overt limb muscle weakness in three patients. The course of the patients was progressive in all, but there was a wide variety of progression, which did not correlate with the age of disease onset. In 71% of the patients, neurophysiological investigations revealed a myopathic EMG pattern, half of the patients had spontaneous activity including complex repetitive discharges. A normal EMG was found in 9% of the patients. Nerve conduction studies were normal in all.

Pompe disease should be taken into consideration in patients with unexplained limb girdle muscular weakness with respiratory failure. Cardiac manifestations may not be restricted to infantile Pompe disease.

Keywords: Acid maltase deficiency; Follow-up study; Glycogen storage disease type 2; Glycogenosis type 2; Pompe disease; Natural history; Late onset Pompe

1. Introduction

Pompe disease, also known as glycogenosis type II, glycogen storage disease type II, or acid maltase deficiency is an autosomal recessive inherited disorder, which is progressively debilitating. In a considerable number of children, death occurs by cardiac and respiratory failure. A significant number of adult patients suffer from respiratory failure, too. This rare disorder has an estimated prevalence of 1 in 40,000 [1,2]. It is a lysosomal storage disorder caused by a deficiency of the enzyme acid alpha-glucosidase (GAA), which converts glycogen to glucose in the acid environment of lysosomes (pH 4–5). GAA deficiency leads to an accumulation of glycogen within lysosomes, and rupture of lysosomes results in cellular dysfunction, abnormal autophagy and structural disorganization in different

* Corresponding author. Tel.: +49 89 51602895; fax: +49 89 51607402.
E-mail address: wolfgang.mueller-felber@med.uni-muenchen.de (W. Müller-Felber).

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tissues [3]. Glycogen depositions are mainly localized in cardiac, skeletal and smooth muscle, whereas other tissues may be affected less frequently [4].

Initially, Pompe disease was described as rapidly progressive infantile disorder, which led to death by respiratory and cardiac failure within the first two years of life. The children presented with hypertrophic cardiomyopathy and severe generalized muscle weakness. This rare form is termed now the classical infantile form of Pompe disease. In the last 30 years, a growing number of patients with a late onset type of this disease have been described [5]. As in patients with infantile onset, there is a progressive deterioration of proximal and truncal muscles with predominant involvement of the lower limbs. Respiratory function may be affected early, but the heart was reported spared in most adult patients [6,7]. Initial symptoms may be subtle with some difficulties climbing stairs or rising from a chair or an elevation of creatine kinase levels. Initial symptoms are non-specific and may mimic other neuromuscular disorders. Therefore, there is a substantial risk to miss accurate diagnosis. Nevertheless, most patients progress to a severe generalized weakness. A considerable number becomes wheelchair bound and/or may require assisted ventilation [5,8].

Until recently, no effective therapy for Pompe's disease was known. However, in 2006 enzyme replacement therapy with recombinant human acid alpha-glucosidase has been approved for clinical use in patients with Pompe disease in Europe and US. Clinical studies in infants have shown that enzyme replacement led to improvement in skeletal and cardiac muscle function and to increased survival in many patients [9–14]. Moreover, there is some evidence that this treatment may also be applicable in late onset patients [4]. Single late onset patients have already been successfully treated [15].

For that reason, clinical suspicion and correct diagnosis of adult Pompe patients has received additional attention. The purpose of this paper is to describe clinical, neurophysiological and radiological findings of late onset Pompe disease in a group of 38 patients diagnosed in our neuromuscular department between 1985 and 2006.

2. Patients and methods

We included 38 patients in whom Pompe disease was diagnosed at the neuromuscular department of the University of Munich (Friedrich-Baur-Institute) between 1985 and 2006. All patients were caucasians, 13 patients were male, 25 patients female. The mean age at time of diagnosis was 40.9 years (7–61). There was a family history of Pompe disease in 4 patients (11%).

Diagnosis of Pompe disease was based on muscle biopsy findings with a severely reduced acid maltase activity and an increase of total glycogen. All patients underwent open muscle biopsy for diagnostic purposes. All muscle specimens were processed using standard histological procedures. One part of the biopsy was embedded in glycol methacrylate, and another part was frozen in liquid nitrogen. Cryosections (8–10 μm) were routinely stained, including haematoxylin & eosin, reduced nicotinamide adenine dinucleotide-tetrazolium reductase (NADH), adenosine triphosphatase reactions (ATPase) at pH 4.6 and 10.4, modified Gomori trichrome, van Gieson, cytochrome *C* oxidase, succinic dehydrogenase, AMP-deaminase, phosphorylase, oil-red O, Sudan black B, acid phosphatase, non-specific esterase, and periodic acid-Schiff. For biochemical analysis, muscle specimens were immediately frozen in liquid nitrogen and stored at −80 °C. Glycogen concentration, neutral and acid maltase activity were determined by previously described methods [16].

Genomic DNA was isolated from either leukocytes or muscle tissue of 19 patients using the QIAmp Blood Kit (Qiagen, Hilden, Germany). From the remaining patients, DNA was not available for analysis. Direct sequencing of the entire coding region (20 exons) as well as flanking intronic sequences of *GAA* was performed. Nucleotides are numbered according to the GenBank Accession No. NM_000152.

All participants (or their legal guardians) gave informed written consent for the muscle biopsy and mutational analysis. All patients underwent clinical and neurophysiological examination by one of the coauthors. For the assessment of muscle weakness the MRC-scale and for the graduation of the disability the Walton scale were used. Neurophysiological examination included measurement of sensory and motor NCVs and needle electromyography of the biceps brachii, quadriceps femoris and anterior tibial muscles using standard procedures. Thirteen patients underwent MRI examination of the thigh muscles (T1-weighted images, T2-weighted images). In 6 patients, contrast enhanced scans with gadolinium were performed. ECG data at the time of diagnosis were available from 25 patients, and Holter monitoring in nine patients. Echocardiographic examination was performed in 21 patients. Eighteen patients underwent pulmonary function testing and blood gas analysis during initial diagnostic work-up. Pulmonary function testing was done in a prone position in all.

Demographic and clinical data were summarized by the use of descriptive statistics. Time-to-event outcomes, including time to first ventilator support and time to use of walking devices or wheelchair, were analyzed.

3. Results

3.1. Age at onset and time delay for making the correct diagnose

Thirty-eight patients (32 adult, 6 juvenile) have been examined. The mean age of the patients at time of diagnosis was 40.9 years (range 7.3–7 years). First symptoms were evident at age 30.7 years (range 1–52.6 years). Onset of the disease was uncertain in eight patients who reported minor symptoms such as poor performance at school sport.

The mean time lag between onset of first symptoms and diagnosis was 10.4 years (range between 0.1 years in a presymptomatic boy with elevated liver enzymes and 31.6 years). This interval was shorter in 6 infantile and juvenile patients (median 2 years) than in adult patients (median 10.9 years). Nevertheless, in one juvenile patient who first presented with an exercise intolerance and a poor performance in school sports time between onset of symptoms and diagnosis was 31 years. The mean time lag between the first medical consultation related to symptoms and diagnosis of Pompe disease was 7.1 years (range 1 month to 21.5 years). The time which was necessary to come to a correct diagnosis was similar in the decade from 1985 to 1995 (mean 10.9 years) as compared to the decade from 1996 to 2006 (mean 10.6 years). Further details are given in Table 1.

A different diagnosis which was sustained for more than one year was given in 11 patients. Two patients were diagnosed as LGMD. In 4 patients, who showed a mixed pattern or a neurogenic pattern in the EMG a spinal muscular atrophy was diagnosed. In 1 patient, a PROMM syndrome (DM2) was assumed based on myotonic discharges in the EMG and genetic findings which later turned out to be a polymorphism in the DM2-gene. One patient who was misdiagnosed as cardiac failure suffered from deterioration of performance which did not lead to medical attention. Following cardiac arrests he had to be reanimated. One patient with a long lasting hypothyroidism and histological signs of a necrotizing myopathy was diagnosed as a hypothyroid myopathy. Myositis was diagnosed in 2 patients with Raynaud phenomenon based on a misinterpretation of histological findings.

Ten patients underwent repeated muscle biopsies until a definite diagnosis was made (two biopsies in 8 patients, three biopsies in 2 patients). In 2 of these patients, the first biopsy was done by a general pathologist without using PAS staining and histochemical examinations. In all the other patients, a complete examination including PAS-staining, acid phosphatase reaction and electron microscopic examination was done. In 2 patients, an advanced myosclerotic destruction of the biopsied muscle made a correct diagnosis impossible. In 2 patients, a neurogenic pattern with type grouping phenomen lead to the misdiagnosis of a neurogenic disorder. In 2 patients, only non-specific myopathic changes without vacuoles or an increased activity of the acid phosphatase were found. In 2 patients, vacuoles containing glycogen, lipids and mitochondria were misinterpreted as a mitochondrial disorder.

3.2. Early development and first symptom

Early development was normal in all but 3 patients. One patient, diagnosed as Pompe disease at age six, was never able to climb stairs without a banister. In 2 patients, independent walking was slightly delayed (age of 19 and 30 months). Four of the juvenile patients first presented with a limb girdle weakness, 1 with a rigid spine syndrome and 1 with a WPW syndrome and an at that time asymptomatic elevation of the CK levels.

The most common first symptom was limb girdle muscular weakness, which was found in 18 patients (Table 2). Myalgia together with a limb girdle weakness were present in 5 patients. In 2 patients exertional myalgia preceded the onset of weakness. In 1 patient who did not notice the mild proximal weakness which was seen at the neurological examination, cardiac arrhythmias due to a WPW syndrome lead to a diagnostic workup. An asymmetrical hypertrophy of the thigh brought one patient with a mild proximal weakness to medical attention. In 1 patient rigid spine syndrome was the first symptom. In 1 patient shortening of the Achilles tendon preceded proximal weakness for 20 years. Respiratory failure preceded the onset of overt muscular weakness in 3 patients. Two of these patients were brothers carrying the same mutation (patients 23 and 24; for details see Table 1).

3.3. Clinical scores and paraclinical examinations

The mean Walton score at time of diagnosis was 2.7 (range 0–7). The mean CK level at the time of diagnosis was 791 U/l (range 170–3189 U/l; normal < 180 U/l). 4 patients (pts. 2, 13, 14, 29) had a normal CK. Elevated transaminases (AST, ALT) was present in 12 patients. In all but one elevation of the transaminases was related to a rise in the CK levels.

Neurophysiological investigations showed that 71% had a myopathic EMG pattern, half of the patients had spontaneous activity including complex repetitive discharges. A normal EMG was found in 9% of the patients. Two patients had a pattern with predominant large, long duration MUAPs in proximal as well as distal muscles leading to the misdiagnosis of spinal muscular atrophy. In these 2 patients no myopathic changes were found. Nerve conduction studies were normal in all. A summary of the electromyographic examinations is given in Table 3.

Echocardiographic examination, performed in 21 patients, did not reveal hypertrophic or dilatative cardiomyopathy in any of the investigated patients. Three patients without echocardiographic signs of cardiomyopathy suffered from arrhythmias due to a Wolf–Parkinson–White syndrome (WPW syndrome). Holter-ECG was done in 9 patients. Patients showed arrhythmias corresponding to Lown I (1 patient), Lown II (1 patient) and Lown IV (3 patients).

Pulmonary function testing was done in 18 patients at the time of diagnosis. The mean FVC was 71% of the normal (range 17–101%). Hypercapnia with a $pCO2 > 45$ was found in 4 patients.

MRI of the thigh showed a sparing of the rectus femoris in most but not in all patients. Pathological findings were pronounced in the dorsal part of the thigh. Gadolinium enhancement was found in all patients. Details concerning MRI findings are outlined in Table 3.

Results of the muscle biopsies are shown in Table 4.

Table 1
Patient characteristics

Pat. No.	Sex	Onset of symptoms (years)	Age at dx	Disability (Walton) at dx	Start of ventilation	Loss of ambulation	Special features	Mutations
1	f	3	7	0	6	amb		G638W(c.1912G > T)/ **A610V(c.1829C > T)**
2	f	38	59	3				n.a.
3	f	26	27	2		amb	Stroke (28 years)	A237V(c.710C > T)/G293R(c.877G > A)
4	f	46	52	4				n.a.
5	m	22	22	1		amb		c.−45 T > G/**Y685X(c.2055C > A)**
6	f	14	20	3	25	25		n.a.
7	f	51	60	6		amb		c.−45 T > G/2nd unidentified
8	m	27	33	3				n.a.
9	f	39	49	2				**IVS7-15G > A/IVS19-4T > G**
10	f	50	56	3				n.a.
11	m	40	71	6			Lown II	n.a.
12	m	47	49	0	49	amb		c.−45T > G/c.−45T > G
13	f	36	52	3				n.a.
14	m	30	62	3	62	amb		n.a.
15	m	15	15	0	16	amb	Rigid spine syndrome	c.−45T > G/L355P(c.1064T > C)
16	f	25	41	0				c.−45T > G/**IVS4 + 5ins7**
17	f	39	43	1				n.a.
18	m	53	53	1			Hearing impairment	n.a.
19	f	9	40	3		amb		n.a.
20	m	?	21	0		31		n.a.
21	f	46	56	2		60		c.−45T > G/2nd unidentified
22	f	42	43	1		amb	Hearing impairment, Lown IVa	c.−45T > G/c.379detTG
23*	m	18	18	1	19	37	Hearing impairment, WPW (27 years)	c.−45T > G/**c.1369delG**
24*	m	22	22	1	23	33		c.−45T > G/**c.1369delG**
25	f	42	46	0				n.a.
26	f	2	3	4	20	amb		c.−45T > G/C103G(c.307T > G)
27	m	36	50	3	64		Hearing impairment, Lown IVbWPW (60 years)	c.−45T > G/2nd unidentified
28	f	39	67	7				n.a.
29	f	38	48	3				n.a.
30	f	35	37	3				n.a.
31	f	31	50	2				c.−45T > G/G648S(c.1942G > A)
32	f	22	34	6	34	34		c.−45T > G/**P522A(c.1564C > G)**
33	f	16	24	2				c.−45T > G/2nd unidentified
34	m	14	17	1	32	32	WPW (17 years)	IVS6-22T > G/G648S(c.1942G > A)
35	f	32	55	2	61	60	Lown IVa	n.a.
36	m	31	55	0				n.a.
37	f	49	55	3				c.−45T > G/**G359R (c.1075 G > A)**
38	f	30	45	2				n.a.

*, brothers; ?, cannot be determined.

3.4. Follow-up examinations

Eighteen patients underwent repeated neurological examination at our department by one of the coauthors. The mean observation period was 14.8 years (range 3–21 years). During this follow-up period, 6 patients lost ambulation. The time from first symptoms until loss of ambulation was 17.8 years (range 11–27), from diagnosis to loss of ambulation 9.6 years (range 4–16).

Thirteen patients underwent cardiological follow-up examinations. During a mean period of 13.9 years (range 4–21) no overt cardiomyopathy developed.

In 10 patients, initiation of mechanical ventilation became necessary. The mean time between onset of symptoms and start of assisted ventilation was 15.1 years (range 1–35 years). The mean time between diagnosis and start of ventilation was 4.6 years (range 0.1–15.2 years). Ventilatory support was necessary prior to loss of ambulation in six patients. In 2 patients, onset of mechanical ventilation preceded diagnosis by one month, in another 2 patients ventilation was required at the time of diagnosis. In 5 patients, mechanical ventilation was started between years 1 and 15 after diagnosis (mean 8.3 years).

4. Discussion

This report describes clinical and diagnostic findings in a cohort of 38 patients with late onset Pompe disease who

Table 2
Initial symptoms

Symptom	(*n*) Patients
Limb girdle weakness	18
Trunk weakness	4
Exercise intolerance	2
Myalgia	7
Rigid spine syndrome	1
WPW syndrome	1
Respiratory failure	3
Asymptomatic CK elevation	4
Pes equines	1
Hearing loss	1
Asymmetrical hypertrophy of the thigh	1

were diagnosed at our neuromuscular department during a period of 21 years.

4.1. Delay in diagnosis

In our large cohort of late onset Pompe disease, the delay from onset of symptoms to diagnosis was around 10 years. Other groups reported a similar delay [5] Part of the delay in diagnosis may be attributed to the slow progression of the disease at least during the early phase. The annual incidence of Pompe disease in Southern Germany was slightly lower than estimated by the epidemiological data of the Netherlands and Taiwan. Assuming that around 5 million people live in the region of our neuromuscular centre, there was an annual incidence of adult onset Pompe disease of 0.036/100,000. The estimated incidence in the Netherlands is about 2/100,000 [17,18]. There may be several reasons for this discrepancy: (i) a considerable number of Pompe patients may be missed. Even in our specialized centre, Pompe disease was assumed based on clinical examination in nine patients only; (ii) the clinical presentation is non-specific limb girdle weakness as seen in half of our patients. Specific features such as weakness of paraspinal or respiratory muscles were found at the time of diagnosis in four patients, only, (iii) even if muscle biopsy is performed, there is a considerable risk to miss the diagnosis [19]. In 10 patients, only repeated biopsies led to a suspicion of Pompe disease and finally biochemical workup of the muscle samples. This indicates that in nonclassified limb girdle myopathies Pompe disease has to be taken into consideration. These shortcomings indicate that awareness and investigational skills for the disease has to be further improved in different medical fields. Enzyme measurement in white blood cells or in a dry blood spot test should be performed when seeing a patient with undiagnosed LGMD.

4.2. Additions to the phenotypic spectrum of late onset Pompe disease

While most of the clinical findings are in line with previous reports of patients with late onset Pompe disease, there are some remarkable clinical features that have not been reported, yet. Cardiac problems occurred frequently in our population of late onset patients. Three patients suffered from symptomatic Wolf–Parkinson–White syndrome (WPW syndrome). A short PR-time has been reported in the infantile form of Pompe disease more frequently, and WPW syndrome has been detected in a few children with Pompe disease [20,21]. To our knowledge, patients with WPW syndrome have not been reported in late onset Pompe disease. WPW syndrome seems to be more common in patients with Danons disease, which is a lysosomal storage disease with normal acid maltase activity in the tissue. The most common form is late onset Danon disease, which is characterized by severe cardiomyopathy and mild myopathy starting in the second or third decade, covering prominent arrhythmia with WPW syndrome, and sometimes mental retardation [22]. It is tempting to speculate that there might be a selective accumulation of glycogen in the conduction system of the heart even in the absence of hypertrophic cardiomyopathy. Cardiac glycogen accumulation was observed in autopsies of adult Pompe disease [23]. In mice after completed development of the cardiac conduction system, a glycogen deposition leads to a remodelling of the atrioventricular system [24]. In addition, 3 patients without echocardiographic signs of cardiomyopathy and without a history of ischemic heart disease showed Lown IV on Holter-ECG. This clearly indicates that cardiac monitoring is necessary in adult Pompe patients.

In 1 patient hearing loss with loss of cochlear function preceded the onset of neuromuscular symptoms by two years. This may suggest that there is an early accumulation of glycogen in neural cells even in adult patients. In 1 patient, a rigid spine phenotype was the initial presentation. A similar case has been published recently [25]. This indicates that in juvenile patients Pompe disease has to be included in the differential diagnosis of rigid spine syndrome.

4.3. Differential diagnostic aspects

Most of our patients suffered from a proximal weakness as the first muscular symptom as reported by others [5]. Nevertheless, there are a considerable number of patients who complain about muscle pain as a prominent muscular symptom. Hagemanns reported similar findings in late onset Pompe patients using a questionnaire [26]. Therefore, adult Pompe disease seems to be an important differential diagnosis of myotonic dystrophy type 2 which frequently presents with myalgia and proximal weakness in adulthood [27].

Respiratory problems can precede loss of ambulation in a considerable number of patients [28]. Therefore, early respiratory problems in a patient with a neuromuscular disorder should raise the suspicion of Pompe disease.

Table 3
EMG and MRI findings

Pat. No.	Electromyographic findings							MRI						
	FIB, PSW	HFD	Myotonia	Myopathic pattern	Neurogenic pattern	Mixed pattern	Normal	Rectus fem.	Vast. lat.	Vastus interm.	Vastus medialis	Ischio-crural	Bic. fem.	Contrast enhanc.
1	–	–	–	–	–	–	–							
2	–	–	–	–	–	–	–	+	+	+	+	+++	+++	n.d.
3	+++ (ta, q, bi)	0	++ (q)	+++ (ta, q, bi)										
4	++	0	0	++ (q, t)	0	0								
5	0	0	0	0	0	0	ta, q, bi, de		++	++	++	++	++	++
6	n.d.		0											
7	0	+ (q)	0	+ (q)			ta, bi, de							
8	0	0	0	Bi ++		++ ta,q			++	++	++			n.d.
9	0	0	0	+					+	+		+++	+++	n.d.
10	++	++	0	Trap +	+ ta, q, fe									
11	0	0	0	Bi++		+ ta, q								
12	+	++	0	++										
13	++	++	0	+++					+	+	+	++	++	n.d.
14	0	0	0		++ ta, q, bi									
15	++	0	0	++										
16	++	++	0	++										
17	0	0	0	++										
18	0			++										
19	++			++				+	++	++	++	+++	+++	n.d.
20	0	0		++										
21	0					++								
22										+	+	++	++	n.d.
23				++										
24	n.d.													
25														
26	0			++										
27		++		++								++	++	n.d.
28	0			++										
29	0			++										
30								+	++	++	++	+++	+++	++
31														
32	0	0	0	+++			ta, re, bi, iod		++		+++	+	+	+
33	0	0	0	++										
34														
35	0	0	0	0	++ ta, q, bi									
36	0	0	0	0	0	0	ta, q, bi							
37	0	0	0	0	0	0	ta, q, bi		+	+	+	++	++	+
38		++	++	++										

HFD, high frequency discharges; PSW, positive sharp waves; FIB, fibrillations; ta, tibialis anterior; bi, biceps brachii; q, quadriceps femoris; iod, interosseus dorsalis I; de, deltoideus; fe, finger extensors; +, slight changes; ++, moderate changes; +++, severe changes.

Table 4
Results of the muscle biopsy

Pat. No.	Biopsy age	Muscle	Light microscopy			Electron microscopy		
			Vacuolated fibers (LM)	AP (LM)	Special feature	Lysosomal glycogen (EM)	Extra-lysosomal glycogen (EM)	Endo-vascular glycogen (EM)
1	7	a.t.	+++	+++		+++	+++	+
2	59	q.f.	++	++		+++	+++	+
3	27	b.b.	0	(+)		++	++	+
4	52	q.f.	++	++		++	0	0
5	22	b.f.	++	++		++	++	0
5	20	q.f.	++	n.d.		++		
6	21	a.t.	+++	+++		+++	+++	+
7	59	q.f.	+	++		+	++	0
8	36	q.f.	(+)	(+)		+	0	0
9	49	b.f.	(+)	(+)		+++	+++	+
10	45	q.f.	+	+	Ringbinden, terminal atrophic fibers	++	++	
11	68	q.f.	+++	+++	Ringbinden	n.d.	n.d.	
12	49	q.f.	0	0		+	+	0
12	49	Pect.			Lipomatosis and myosclerosis			
13	53	q.f.	(+)	(+)		+	+	+
14	62	delt.	(+)	0		0	(+)	0
15	14	a.t.	+++	+++		+++	+++	+
16	41	a.t.	+	+		++	++	+
17	44	q.f.	++	++		+++	+++	
18	53	a.t.	++	++	Small group atrophy	+++	+++	+
	53	q.f.	++	++		+++	+++	+
19	40	q.f.	+++	+++		+++	+++	+
20	21	a.t.	+++	+++		+++	++	++
21	66	q.f.	++	++		++	+++	0
22	42	q.f.	+	+		++	+	0
23*	19	b.b.	+	+		++	++	+
24*	18	b.b.	+	+		++	++	+
25	47	q.f.	+	+		++	++	0
26	3	q.f.	+++	+++		++	++	+
27	50	q.f.	+	+		+	+	0
28	31	q.f.	+	+		+++	++	+
29	47	a.t.	(+)	(+)		++	+	0
29	48	q.f.	(+)	(+)		+	+	0
30	47	q.f.	+	+		+	+	0
31	50	q.f.	++	++		++	+	+
32	34	a.t.	+++	+++		+++	+++	
32	24	q.f.		++			n.d.	n.d.
33	24	q.f.	+++	++		++	++	+
34	17	q.f.	+++	++		+++	++	
35	55	q.f.	++	++	Neurogenic atrophy	++	++	
36	55		0	0		+	+	
37	55	s.m.	(+)	(+)		+	0	0
38		n.d.						

AP, acid phosphatase; n.d., not done; a.t., anterior tibial; b.b., biceps brachii; q.f., quadriceps femoris; b.f., biceps femoris; s.m., semimembranosus; +, slight changes; ++, moderate changes; +++, severe changes; *, brothers.

4.4. Paraclinical examinations

Our study shows that there is a wide range of electromyographic findings in patients with Pompe disease. Most of the patients show pathological spontaneous activity at rest and a myopathic pattern during voluntary activation. Nevertheless, in some patients there is a predominant neurogenic pattern leading to a misdiagnosis of spinal muscular atrophy [29]. Some patients show myotonic discharges suggesting disorders like DM2.

MRI examination of the muscle showed that the dorsal muscles of the thigh are predominantly affected and that the rectus femoris was spared in most but not all patients. Similar findings have been shown by Pichiecchio [30]. There was contrast enhancement in all patients in whom gadolinium was applied similar to the findings in acute neuromuscular diseases like inflammatory myopathies [31]. Our findings indicate that gadolinium enhanced MRI is not useful for the distinction between myositis and Pompe disease.

4.5. Geno-phenotypic correlations

There was no correlation between the clinical phenotype and the genetic findings. Most patients (15/19) carried the c.−45T > G transversion on at least one allele, therefore, genetic testing for this mutation in juvenile and adult onset Pompe disease is recommended. Additional mutations were distributed throughout the *GAA* gene as shown by others [32,33].

4.6. Long-term follow-up

Our long-term follow-up data support that Pompe disease is a progressive disorder. However, there is a wide variability in the progression of the disease. The loss of motor function per year did not correlate with the age of onset of the disease. Therefore, age of onset is not useful as a prognostic parameter in adult late onset patients. This may not be true in those patients who get to medical attention early in childhood and adolescence. All three patients who were diagnosed before age 18 had a severe course of the disease. Nevertheless, there were patients who report some minor neuromuscular symptoms such as exercise intolerance and fatigue since early childhood. There is no correlation between age of onset of the disease and age of respiratory failure.

In summary, our data reveal the wide phenotypic spectrum of adult Pompe disease and the still insufficient assessment at disease onset preventing early diagnosis that may be warranted with the arrival of new therapeutic options.

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