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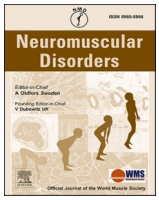

Research paper

Management of presymptomatic juvenile patients with late-onset Pompe disease (LOPD)

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ABSTRACT

Late-onset Pompe disease (LOPD) includes patients from 1 year of age to adulthood. The vast heterogeneity in clinical manifestations and disease progression is not fully explained; however, a short disease duration and a young age seem to be good predictors of a better response to treatment. For this purpose, we investigated and followed up a cohort of 13 juvenile patients with LOPD from the clinical and therapeutic point of view, mainly pointing out the transition from presymptomatic to symptomatic status.

We retrospectively collected clinical, morphological, biochemical and molecular data from 13 juvenile LOPD patients. Motor and respiratory functional data, obtained during annual follow-up visits, were analyzed. The data included serial evaluations of the Medical Research Council (MRC) scale, the 6-Minute Walking Test (6MWT), the Gait, Stairs, Gower, and Chair (GSGC) score, and seated and supine Forced Vital Capacity (FVC). Muscle Magnetic Resonance Imaging (MRI) was also included, although it was not performed in all cases.

Currently, patients mean age is 18 years. All patients but one were diagnosed because of an isolated hyperCKemia: the mean age at diagnosis was 6.8 years (range 1–18). The onset of symptoms occurred from 6 months to 12 years after the diagnosis. The mean clinical follow-up duration was 9 years (range 2–18). From the genetic point of view, the most shared mutation was c.32–13T>*G*, found in twelve patients as compound heterozygosis. Seven patients underwent muscle biopsy, which showed vacuolar myopathy with glycogen accumulation in four of them with unspecific changes in the other three cases. Five patients developed proximal muscle weakness during the follow-up with a mild waddling gait and a positive Gowers manoeuver. Muscle MRI revealed mild hypotrophy of the thighs at the development of symptoms in four out of five cases. Four patients started alglucosidase alfa, and one avalglucosidase alfa. These five patients on Enzyme Replacement Therapy (ERT) showed motor and respiratory stability in the following years.

Timely identification of emerging clinical manifestations in presymptomatic LOPD patients, as a result of careful follow-up, is essential to start prompt treatment to modify the disease natural course.

1. Introduction

Late-onset Pompe disease (LOPD) is a rare inherited metabolic myopathy with autosomal recessive trait. It is characterized by a deficiency of the acid alpha-glucosidase (GAA) due to a mutation in the *GAA* gene. This enzyme is involved in the lysosomal degradation of glycogen, and its genetically determined deficiency leads to a multisystemic accumulation of glycogen [1].

LOPD manifests after the first year of life and can present with significant clinical heterogeneity in childhood, adolescence, or adulthood. It is characterized by a slow and progressive decrease of skeletal muscle function, with weakness predominantly at axial and proximal limb muscles, more pronounced at the pelvic girdle than at the shoulders. The respiratory involvement is quite recurrent, mainly because of a diaphragm weakness leading to the development of progressive respiratory insufficiency, which is usually the primary cause of death in these

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patients [2].

Clinical manifestations can vary significantly depending on the age of onset, the affected muscle groups, and the degree and rate of progression of myopathic changes, which are usually slowly disabling [3]. Muscle weakness is very often preceded by a long history of intolerance to physical exercise, fatigue, and muscle pain. These symptoms, along with an elevation in serum creatine kinase (CK) levels can be considered as a preclinical phase of LOPD [4].

Considering the mild and unspecific symptomatology by which the disease can present over a long period, a mean diagnostic delay of about six years has been reported since symptoms onset [5]. However, implementing newborn screening programs and developing more sensitive diagnostic algorithms [6], have significantly reduced the delay and provided a rapid diagnosis, even in presymptomatic patients. Management of this kind of patient is still poorly described in the literature, and the best time for starting treatment remains highly debated.

Indeed, Enzyme Replacement Therapy (ERT) was authorized in 2006 for Infantile Onset Pompe Disease (IOPD) and LOPD. European Pompe Consortium (EPOC) guidelines for starting and stopping treatment have been suggested since 2017 [7] and recently reviewed [8], also considering the opportunity of switching from one to another type of ERT. The main criteria for starting ERT included a patient with confirmed diagnosis and symptomatic because of muscle weakness and/or respiratory insufficiency. However, the management of presymptomatic patients, so far, is not particularly detailed, leaving the treatment choice to the competence of muscle disease experts, usually according to the current recommendations [9]. We herein report on our experience with 13 young patients who were diagnosed with LOPD at a presymptomatic disease stage.

1.1. Patients and methods

We retrospectively collected clinical, morphological, biochemical, and molecular data from a cohort of 13 young patients affected by LOPD. The patients involved in the study are followed at the Neurology and Neuromuscular Diseases Unit of Messina, Italy, and the Department of Neurology of Ludwig-Maximilians-University of Munich, Germany. In these subjects, the diagnosis of LOPD was suggested by residual GAA enzyme activity through dried blood spot (DBS) or skeletal muscle analysis and confirmed by *GAA* genetic testing. Motor and respiratory functional data, obtained annually, were retrospectively collected. These evaluations were performed according to EPOC guidelines [10]. Motor function was tested using the Medical Research Council scale (MRC), 6 Min Walking Test (6MWT), and Gait, Stairs, Gower, Chair (GSGC) score, which measures the four functional items that usually correlate with the severity of the disease [11]. Respiratory function was assessed through spirometry measuring seated, and supine Forced Vital Capacity (FVC). The clinical profile of each subject was further investigated using electromyography, muscle biopsy, echocardiography, and muscle Magnetic Resonance Imaging (MRI) (T1 and STIR sequences for quantification of fat fraction). We examined this cohort mainly as regard as disease progression and treatment response, also evaluating the best time for starting ERT in presymptomatic patients.

2. Results

We studied a cohort of 13 patients that included two couples of siblings (see Table 1). At the time of diagnosis, the mean age of patients was 6.8 years, ranging from 1 to 18 years. Mean clinical follow-up lasted 9 years, ranging from 2 to 18 years. The current age ranges from 6 to 34 years, with an average of 18 years. Ten out of thirteen patients were referred to a neurologist because of unexplained and persistent CK elevation, two were siblings of affected individuals, also carrying hyperCKemia, and the last one was incidentally diagnosed by DBS during a routine preoperative evaluation for minor surgery. Isolated hyperCKemia (ranging from 374 to 2935 U/L) was the most significant clinical feature before the onset of muscle weakness.

Interestingly, patient 2, apart from CK elevation, complained of fatigue and intolerance to prolonged physical exercise during the preclinical phase of the disease. No other patients reported muscle pain or muscle-related symptoms at first evaluation. The echocardiographic study was normal in all patients, except for a mild mitral and aortic insufficiency detected in patient 8, and a clinically and hemodynamically not significant Patent Foramen Ovale (PFO) in patient 10.

Electromyography study was performed in all patients with a predefined sequence of muscle examinations, including the right biceps brachii, the first dorsal interosseous muscle of the right hand, the right vastus lateralis, the right tibialis anterior, and the right paravertebral muscles. The EMG findings appeared normal in all cases except for patient 1, who exhibited myotonic discharges at paravertebral muscles, and patient 6, who displayed increased polyphasic motor unit potentials in all explored muscles. Although no muscle weakness was present, we performed muscle MRI to look for possible subclinical damage. However, when first examined, only normal findings were found. Therefore, muscle biopsy site was selected according to the most usually investigated muscle as quadriceps femoris.

GAA activity was performed in eleven out of thirteen patients: in seven patients on muscle biopsy samples and in four on DBS. The remaining two patients, a couple of brothers (patients 3, 4), displayed hyperCKemia and have been enrolled in a protocol with a direct genetic analysis. However, the diagnosis of all patients was confirmed through *GAA* genetic testing (patients genotypes listed in Table 1). The most common mutation was c.32–13T>*G*, found in compound heterozygosis in twelve patients, whereas, interestingly, patient 7 showed a compound heterozygosis with two different changes as c.1655T>C/IVS1–3C>A, associated in the past with a more severe disease course [12,13]. Seven patients underwent muscle biopsy, revealing four cases of vacuolar myopathy with glycogen accumulation. Unspecific changes were detected in the remaining three cases. Biochemical results showed a residual GAA activity ranging from 0.8 % to 25 %.

During the clinical follow up, all the patients performed annually a complete clinical evaluation but patient 2 voluntarily missed the controls for ten years. Later, five patients developed muscle symptoms (eight remained presymptomatic) which occurred from 6 months to 12 years after the diagnosis. The most common phenotype observed was characterized by proximal and axial weakness. Proximal muscle weakness was more pronounced at the pelvic girdle than at the shoulder girdle. Indeed, neurological examinations revealed strength reduction in the gluteal, iliopsoas, quadriceps, and femoral biceps muscles, with an MRC score ranging from 4+ to 3+ for each muscle group. Pelvic girdle muscles weakness led to a mild waddling gait and positive Gowers manoeuver in all five patients. Two patients (patients 7, 11) exhibited scapular winging (see Fig. 1) whereas axial and lower girdle weakness with mild hyperlordosis characterized the other three patients (patients 1, 2, 5).

At the progression of symptoms, MRI revealed muscle abnormalities in 4 out of 5 patients. A mild hypotrophy was present in three cases (patients 5, 7, 11) and a moderate hypotrophy, involving posterior and medial compartments of the thighs, was present in patient 2, with a more pronounced muscle bulk reduction at the adductor muscles and bilateral biceps femoris. It is noted that patient 1, although symptomatic, showed normal muscle imaging.

Regarding ERT start, four patients initiated therapy with alglucosidase alfa, while one was treated with avalglucosidase alfa (patient 5). The mean follow-up duration under treatment was 8 years, ranging from 1 to 16 years. Four patients undergoing ERT showed sustained stability in motor or respiratory functions over time, demonstrated through 6MWT, GSGC and seated and supine FVC (see Fig. 2). In addition to these clinical aspects, muscle MRI did not reveal any sign of disease progression after a mean follow-up of 8 years. Interestingly, patient 7, whose genotype has been associated in the literature with a severe

Table 1
Demographics and clinical features Demographics and clinical features.

	Sex	Current age	Age at diagnosis	CK at diagnosis	Mutation allele 1	Mutation allele 2	Muscle biopsy at diagnosis	GAA activity (%)	Age at symptoms onset	Neurological examination	Muscle MR at diagnosis	Muscle MR at symptoms onset	ERT
Patient 1	M	26	16	2935	c.−32–13T>*G*	c.2481+102_2646+31del	Not performed	4.6	16	Proximal muscle weakness	Normal	Normal	Yes
Patient 2	M	34	18	558	c.−32–13T>*G*	c.525del.T	Vacuolar myopathy. Ultrastructural features characterized by the presence of lysosomal autophagic material and glycogen accumulations.	1,1	30	Proximal muscle weakness	Not performed	Hypotrophic thighs	Yes
Patient 3	F	15	9	458	c.−32–13T>*G*	c.784G>*A*	Normal glycogen content. Sparse punctate positivity for acid phosphatase in rare fibers. Minimal muscle damage without specific features.	*	/	Normal	Normal	Normal	No
Patient 4	M	6	1	374	c.−32–13T>*G*	c.784G>*A*	Not performed	*	/	Normal	Not performed	Normal	No
Patient 5	F	27	10	700	c.−32–13T>*G*	c.1802C>G	Not performed	3.3	20	Mild proximal muscle weakness	Normal	Mild adipose substitution (thighs)	Yes[#]
Patient 6	M	20	6	889	c.−32–13T>*G*	c.2481+102_2646+31del	Not performed	2.5	/	Normal	Normal	Normal	No
Patient 7	M	24	1	460	c.1665T>C	IVS1–3C>A	Vacuolar myopathy with glycogen accumulation.	20	3	Proximal muscle weakness	Normal	Mild atrophic psoas/thighs	Yes
Patient 8	M	24	6	800	c.−32–13T>*G*	c.1082C>G	Nonspecific signs of muscle pathology	4.2	/	Normal	Normal	Normal	No
Patient 9	M	10	1	1095	c.−32–13T>*G*	c.2481+102_2646+31del	Muscle damage with vacuolar accumulation features.	9	/	Normal	Normal	Normal	No
Patient 10	M	6	1	610	c.−32–13T>*G*	c.118C>T	Not performed	0.8	/	Normal	Not performed	Normal	No
Patient 11	F	14	2	519	c.−32–13T>*G*	c.118C>T	Vacuolar myopathy with glycogen accumulation.	24	7	Proximal muscle weakness	Normal	Mild adipose substitution (thighs)	Yes
Patient 12	F	22	4	737	c.−32–13T>*G*	c.2481+102_2646+31del	Caliber variability of fibers with atrophic fibers in the perifascicular area, no glycogen accumulation.	4.3	/	Normal	Normal	Normal	No
Patient 13	F	15	14	123	c.−32–13T>*G*	c.2055 C > A	Not performed	25	/	Normal	Normal	Normal	No

[*] Biochemical data not available for the patient because they were included in an hyperCKemia protocol and directly performed GAA genetic analysis.
[#] Avalglucosidase alfa.

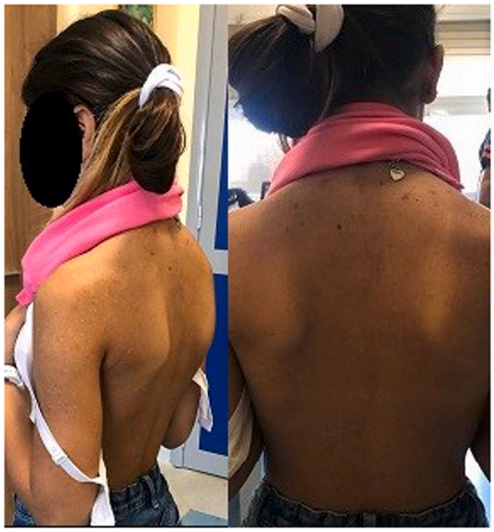

Fig. 1. Scapular winging of patient 11.

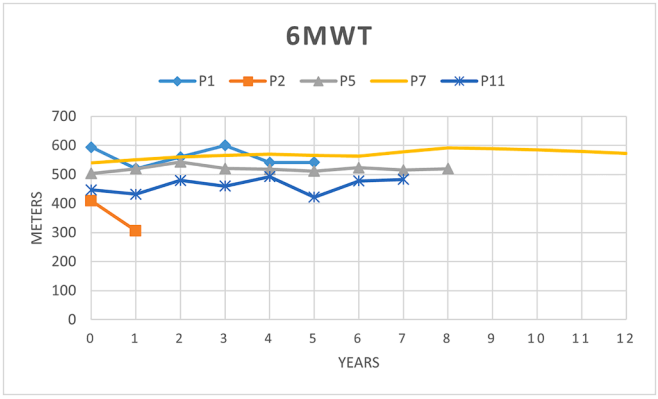

Fig. 2. 6MWT outcome under ERT.

disease course, demonstrated stability in motor function, even after 16 years of treatment: 6MWT at ERT start was 540 m, and at the last follow-up visit 573 m.

On the other hand, patient 2 was diagnosed at 18 years of age, but he did not follow the usual clinical recommendations, mainly not attending follow-up visits for ten years. At 30 years of age, he decided to return under clinical control showing an evident progressive muscle degeneration and ERT was started. Although this, a year later, pelvic girdle muscle weakness worsened. In fact, at ERT start, he achieved 409 m in 6MWT, but one year later the distance covered decreased to 306 m. In contrast, respiratory function remained relatively stable: FVC 3.2 liters at start and 3.18 liters one year later. Similar to the motor function progression, muscle MRI showed muscle deterioration. After a year, muscle MRI showed severe atrophy with total or subtotal fatty replacement of the adductor muscles, semimembranosus, and biceps femoris, along with partial atrophy of the vastus intermedius muscle, advanced hypotrophy with irregular muscle residues in the gluteal muscles, and nearly complete atrophy of the psoas and anterior abdominal wall muscles (see Fig. 3).

Regarding respiratory function, three out of five patients demonstrated slight improvement or stability of FVC %. Notably, patient 5, treated with avalglucosidase alfa, achieved a sustained positive outcome, starting with an FVC % of 77 % and reaching 81 % after 8 years of treatment. The remaining two patients (patient 1, 7) initially showed stabilization (FVC respectively 91 % and 75 %) followed by a secondary decline (respectively after 7 years, 78 % and after 16 years, 41 %).

About the two pairs of brothers, the two younger siblings (patients 4, 10) of patients 3 and 11, respectively, remained presymptomatic until age of six with normal psychomotor development. The older sibling (patient 11) developed mild proximal weakness at 8 years of age and started treatment with alglucosidase alfa. This patient demonstrated clinical improvement, as evidenced by the 6MWT, which increased from 458 to 503 m. GSGC score remained stable; spirometry showed a predicted percentage of FVC from 115 % to 100 % after 7 years.

3. Discussion

LOPD includes patients ranging from one year of age to adulthood. The extensive heterogeneity in clinical manifestations and disease progression is not fully explained. When the first symptoms appear, a timely ERT start seems to predict a favorable treatment response [14,15]. Since patients of younger age and with less severe myopathic damage may benefit more from ERT, it is necessary to consider the precise timing to initiate treatment in these patients and develop specific protocols [16]. In this cohort, the preclinical stage has been mainly characterized by elevated hyperCKemia that preceded the onset of muscle symptoms by a mean time of 10 years before muscle degeneration and disease progression.

Eight patients remained presymptomatic throughout the follow-up with no significant variation in 6MWT and FVC % and muscle strength. The current age of this subgroup ranges from 6 to 24 years old.

Five of the thirteen patients developed muscle weakness and started treatment during follow-up. Four of them began ERT early at the onset of symptoms. They showed stability in motor outcome measures, including patient 7, whose genotype has been previously associated with a worse prognosis. Conversely, a poor treatment response was evident in patient 2, likely due to an already degenerated muscle functionality at ERT start. In line with motor outcome measures, respiratory function remained stable in 3 patients after 2-to-8 years of treatment. In the other two cases, we assisted in an initial stabilization, followed by a secondary decline. However, in these two patients, it seems that the secondary decline occurred later than reported in the literature [15]. These findings support the good practice of starting treatment at the disease onset, looking for a longstanding benefit.

One can suppose that an early diagnosis could optimize a therapeutic response. In that case, DBS screening focusing on selected populations, such as patients with isolated hyperCKemia or limb-girdle weakness, are increasingly helpful in identifying patients with GAA deficiency [17], even in consideration that DBS has demonstrated a quite high sensitivity (93 %) [18,19]. Nowadays, a more extensive application of newborn screening could help in the very early identification of affected patients, allowing physicians to undertake a clinical longitudinal follow-up of LOPD patients and monitor the rate of progression of muscle degeneration.

Myopathic damage in Pompe disease is characterized by the formation of abnormal autophagolysosomal complexes, which disrupt vesicular trafficking. These phenomena may lead to reduced enzyme efficacy, accounting for the varying clearance of glycogen stores and the resultant differences in therapy effectiveness [20,21]. It is conceivable that these pathological hallmarks of the disease (including glycogen accumulation, vacuolar degeneration, autophagic buildup, and alterations in vesicular trafficking) [22] manifest subtly in these patients before clinical symptoms.

While a consistent biomarker of disease progression for identifying these pathological processes is still needed for LOPD, some imaging techniques have taken an emergent role in the early detection and monitoring of muscle morphological alterations.

Muscle MRI is increasingly used to detect and monitor muscle damage. Moreover, it has been reported that T1 sequences can reveal muscle involvement, even in presymptomatic individuals, suggesting an earlier timing for starting therapy [23–25]. In our cohort, muscle MRI revealed muscle hypotrophy at the development of symptoms in four

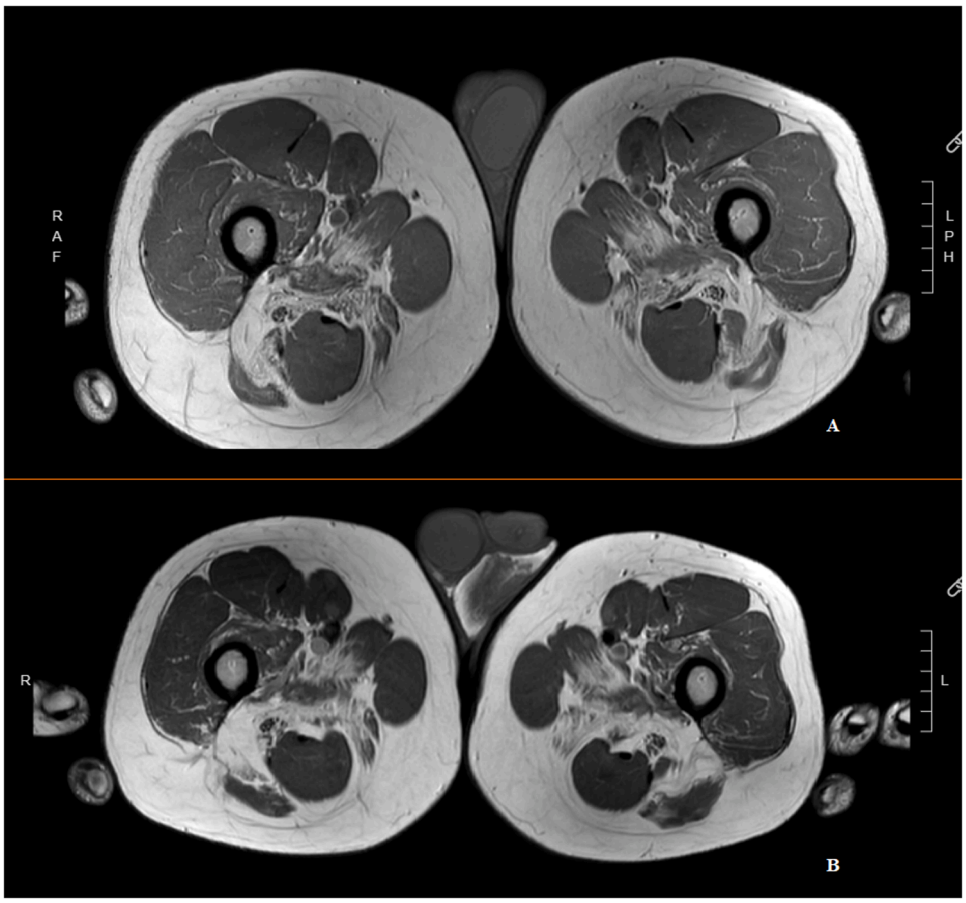

Fig. 3. Muscle MRI T1 sequence of patient 2: A) before ERT start showing moderate-severe hypotrophy involving posterior and medial compartments of the thighs, with a more pronounced muscle bulk reduction at the adductor muscles and bilateral biceps femoris, and B) after 1 year of treatment, showing atrophy with total or subtotal fatty replacement of the adductor muscles, semimembranosus, and biceps femoris.

cases, while in patient 1 it remained normal despite proximal muscle weakness.

Diaphragm ultrasound has also been used to monitor respiratory involvement in LOPD and correlate with seated and supine FVC. In a case-control cohort study, including four presymptomatic patients, diaphragm thickness and mobility were less involved than in patients with an established respiratory insufficiency. When comparing presymptomatic patients with healthy controls, diaphragm thickness showed a reduction, serving as a valuable tool in anticipating the diagnosis of subclinical dysfunction of the diaphragm [26,27].

More recently, an investigation on glycogen imaging in muscle tissues of 10 LOPD patients, compared it with some usual outcome measures such as muscle MRI, ultrasound, spirometry, functional muscle tests, and QoL scales. Multispectral optoacoustic tomography (MSOT) uses near-infrared lasers to induce localized tissue heating and expansion, generating acoustic pressure waves. Glycogen serves as an effective optoacoustic imaging target due to its high water-binding capacity. MSOT appeared promising for detecting subcellular pathologies by identifying glycogen/water increases with high sensitivity [28].

In this cohort, it was not possible to identify specific genetic, clinical or prognostic factors to evaluate the likelihood of disease progression to a symptomatic form. However, early MRI features promoted an early ERT start as the recent EPOC recommendations suggested [8].

4. Conclusions

Presymptomatic patient management represents an informative opportunity for identifying prognostic factors and monitoring the disease progression under ERT. Our experience suggests that programs aimed to increase awareness about LOPD among clinicians have been effective for earlier recognition of unspecific symptoms and rare diseases and for addressing patients to the expert neuromuscular Centers. Diagnostic techniques, including DBS screening in selected populations and muscle MRI, allow timely intervention and a proper evaluation of progressive muscle degeneration. A comprehensive follow-up strategy is crucial in presymptomatic patients: regular annual clinical evaluations combined with every other year muscle MRI assessments form the cornerstone of this approach. Emphasizing the identification of emerging muscle symptoms allows optimization of treatment outcomes, as stated in this cohort of 13 young patients.

Ethical consideration

This case report followed ethical standards to ensure respect for the patients' dignity and rights. Written informed consent was obtained from the patients to collect and publish clinical data and images. The patients were informed about the nature of the study, its purposes, and the use of personal information. Measures were taken to ensure the patients' anonymity.

CRediT authorship contribution statement

M. Porcino: Writing – original draft, Investigation, Data curation, Conceptualization. **O. Musumeci:** Writing – review & editing, Writing – original draft. **C. Usbergo:** Investigation. **A. Pugliese:** Investigation. **I. G. Arena:** Investigation. **C. Rodolico:** Writing – review & editing. **B. Schoser:** Writing – review & editing, Data curation. **A. Toscano:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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References

[1] Labella B, Cotti Piccinelli S, Risi B, Caria F, Damioli S, Bertella E, et al. A comprehensive update on late-onset pompe disease. Biomolecules 2023;13(9):1279. https://doi.org/10.3390/biom13091279. Aug 22PMID37759679PMCIDPMC10526932.

[2] Toscano A, Rodolico C, Musumeci O. Multisystem late onset Pompe disease (LOPD): an update on clinical aspects. Ann Transl Med 2019;7(13):284. https://doi.org/10.21037/atm.2019.07.24. JulPMID31392196PMCIDPMC6642938.

[3] Müller-Felber W, Horvath R, Gempel K, Podskarbi T, Shin Y, Pongratz D, et al. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord 2007;17(9–10):698–706. https://doi.org/10.1016/j.nmd.2007.06.002. OctEpub 2007 Jul 23PMID17643989.

[4] Montagnese F, Barca E, Musumeci O, Mondello S, Migliorato A, Ciranni A, et al. Clinical and molecular aspects of 30 patients with late-onset Pompe disease (LOPD): unusual features and response to treatment. J Neurol 2015;262(4):968–78. https://doi.org/10.1007/s00415-015-7664-0. Epub 2015 Feb 12PMID25673129.

[5] Kishnani PS, Amartino HM, Lindberg C, Miller TM, Wilson A, Keutzer J. Pompe Registry boards of advisors. Timing of diagnosis of patients with Pompe disease: data from the Pompe registry. Am J Med Genet A 2013;161A(10):2431–43. https://doi.org/10.1002/ajmg.a.36110. OctEpub 2013 Aug 30PMID23997011.

[6] American Association of Neuromuscular & Electrodiagnostic Medicine. Diagnostic criteria for late-onset (childhood and adult) Pompe disease. Muscle Nerve 2009;40(1):149–60. https://doi.org/10.1002/mus.21393. JulPMID19533647.

[7] van der Ploeg AT, Kruijshaar ME, Toscano A, Laforêt P, Angelini C, Lachmann RH, European Pompe Consortium. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. Eur J Neurol 2017;24(6):768. https://doi.org/10.1111/ene.13285. Jun-e31Epub 2017 May 6PMID28477382.

[8] Schoser B, van der Beek NAME, Broomfield A, Brusse E, Diaz-Manera J, Hahn A, et al. Start, switch and stop (triple-S) criteria for enzyme replacement therapy of late-onset Pompe disease: european Pompe Consortium recommendation update 2024. Eur J Neurol 2024:e16383. https://doi.org/10.1111/ene.16383. Jun 14Epub ahead of printPMID38873957.

[9] Chien YH, Lee NC, Hwu WL, Fang JY. Disease progression in a pre-symptomatically treated patient with juvenile-onset Pompe disease - need for an earlier treatment? Eur J Neurol 2018;25(10):e111. https://doi.org/10.1111/ene.13730. OctPMID30192061.

[10] Schoser B, Laforêt P, Kruijshaar ME, Toscano A, van Doorn PA, van der Ploeg AT, European Pompe Consortium (EPOC). 208th ENMC International Workshop: formation of a European Network to develop a European data sharing model and treatment guidelines for Pompe disease Naarden, The Netherlands, 26-28 September 2014. Neuromuscul Disord 2015;25(8):674–8. https://doi.org/10.1016/j.nmd.2015.04.006. AugEpub 2015 Apr 21PMID25998612.

[11] Angelini C, Semplicini C, Ravaglia S, Moggio M, Comi GP, Musumeci O, et al. New motor outcome function measures in evaluation of late-onset Pompe disease before and after enzyme replacement therapy. Muscle Nerve 2012;45(6):831–4. https://doi.org/10.1002/mus.23340. JunPMID22581536.

[12] Niño MY, In 't Groen SLM, Bergsma AJ, van der Beek NAME, Kroos M, Hoogeveen-Westerveld M, et al. Extension of the Pompe mutation database by linking disease-associated variants to clinical severity. Hum Mutat 2019;40(11):1954–67. https://doi.org/10.1002/humu.23854. NovEpub 2019 Jul 29PMID31254424PMCIDPMC6851659.

[13] de Faria DOS, 't Groen SLMI, Hoogeveen-Westerveld M, Nino MY, van der Ploeg AT, Bergsma AJ, et al. Update of the Pompe variant database for the prediction of clinical phenotypes: novel disease-associated variants, common sequence variants, and results from newborn screening. Hum Mutat 2021;42(2):119–34. https://doi.org/10.1002/humu.24148. FebEpub 2020 Dec 21PMID33560568PMCIDPMC789881712.

[14] van der Ploeg AT, Barohn R, Carlson L, Charrow J, Clemens PR, Hopkin RJ, et al. Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa. Mol Genet Metab 2012;107(3):456–61. https://doi.org/10.1016/j.ymgme.2012.09.015. NovEpub 2012 Sep 17PMID23031366.

[15] Schoser B, Stewart A, Kanters S, Hamed A, Jansen J, Chan K, et al. Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis. J Neurol 2017;264(4):621–30. https://doi.org/10.1007/s00415-016-8219-8. AprEpub 2016 Jul 2PMID27372449.

[16] de Vries JM, van der Beek NA, Hop WC, Karstens FP, Wokke JH, de Visser M, et al. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study. Orphanet J Rare Dis 2012;7:73. https://doi.org/10.1186/1750-1172-7-73. Sep 26PMID23013746PMCIDPMC3519647.

[17] Musumeci O, la Marca G, Spada M, Mondello S, Danesino C, Comi GP, et al. LOPED study: looking for an early diagnosis in a late-onset Pompe disease high-risk population. J Neurol Neurosurg Psychiatry 2016;87(1):5–11. https://doi.org/10.1136/jnnp-2014-310164. JanEpub 2015 Mar 17PMID25783438.

[18] Toscano A, Montagnese F, Musumeci O. Early is better? A new algorithm for early diagnosis in late onset Pompe disease (LOPD). Acta Myol 2013;32(2):78–81. OctPMID24399862PMCIDPMC3866896.

[19] Lukacs Z, Nieves Cobos P, Wenninger S, Willis TA, Guglieri M, Roberts M, et al. Prevalence of Pompe disease in 3,076 patients with hyperCKemia and limb-girdle muscular weakness. Neurology 2016;87(3):295–8. https://doi.org/10.1212/WNL.0000000000002758. Jul 19Epub 2016 May 11PMID27170567PMCIDPMC4955273.

[20] Raben N, Danon M, Gilbert AL, Dwivedi S, Collins B, Thurberg BL, et al. Enzyme replacement therapy in the mouse model of Pompe disease. Mol Genet Metab 2003;80(1–2):159–69. https://doi.org/10.1016/j.ymgme.2003.08.022. Sep-OctPMID14567965.

[21] Thurberg BL, Lynch Maloney C, Vaccaro C, Afonso K, Tsai AC, Bossen E, et al. Characterization of pre- and post-treatment pathology after enzyme replacement therapy for Pompe disease. Lab Invest 2006;86(12):1208–20. https://doi.org/10.1038/labinvest.3700484. DecEpub 2006 Oct 30PMID17075580.

[22] Fukuda T, Ahearn M, Roberts A, Mattaliano RJ, Zaal K, Ralston E, et al. Autophagy and mistargeting of therapeutic enzyme in skeletal muscle in Pompe disease. Mol Ther 2006;14(6):831–9. https://doi.org/10.1016/j.ymthe.2006.08.009. DecEpub 2006 Sep 27PMID17008131PMCIDPMC2693339.

[23] Figueroa-Bonaparte S, Segovia S, Llauger J, Belmonte I, Pedrosa I, Alejaldre A, et al. Muscle MRI findings in childhood/adult onset pompe disease correlate with muscle function. PLoS One 2016;11(10):e0163493. https://doi.org/10.1371/journal.pone.0163493. Oct 6PMID27711114PMCIDPMC5053479.

[24] Díaz-Manera J, Walter G, Straub V. Skeletal muscle magnetic resonance imaging in Pompe disease. Muscle Nerve 2021;63(5):640–50. https://doi.org/10.1002/mus.27099. MayEpub 2020 Nov 6PMID33155691.

[25] Gruhn KM, Heyer CM, Güttsches AK, Rehmann R, Nicolas V, Schmidt-Wilcke T, et al. Muscle imaging data in late-onset Pompe disease reveal a correlation between the pre-existing degree of lipomatous muscle alterations and the efficacy of long-term enzyme replacement therapy. Mol Genet Metab Rep 2015;3:58–64. https://doi.org/10.1016/j.ymgmr.2015.03.010. Apr 21PMID26937398PMCIDPMC4750633.

[26] Ruggeri P, Lo Monaco L, Musumeci O, Tavilla G, Gaeta M, Caramori G, et al. Ultrasound assessment of diaphragm function in patients with late-onset Pompe disease. Neurol Sci. 2020;41(8):2175–84. https://doi.org/10.1007/s10072-020-04316-6. AugEpub 2020 Mar 11PMID32162165.

[27] Gaeta M, Musumeci O, Mondello S, Ruggeri P, Montagnese F, Cucinotta M, et al. Clinical and pathophysiological clues of respiratory dysfunction in late-onset Pompe disease: new insights from a comparative study by MRI and respiratory function assessment. Neuromuscul Disord. 2015;25(11):852. https://doi.org/10.1016/j.nmd.2015.09.003. Nov-8Epub 2015 Sep 7PMID26410244.

[28] Tan L, Zschüntzsch J, Meyer S, Stobbe A, Bruex H, Regensburger AP, et al. Non-invasive optoacoustic imaging of glycogen-storage and muscle degeneration in late-onset Pompe disease. Nat Commun 2024;15(1):7843. https://doi.org/10.1038/s41467-024-52143-6.