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Case report

Severe distal muscle involvement and mild sensory neuropathy in a boy with infantile onset Pompe disease treated with enzyme replacement therapy for 6 years

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Abstract

Enzyme replacement therapy in infantile onset Pompe disease has led to a new phenotype with features not known in the pre-enzyme replacement therapy era. We investigated the origin of a rapidly emerging and severe weakness of the foot dorsiflexors in a 7-year-old boy after 6.5 years of enzyme replacement therapy. Electroneurography yielded normal findings except low compound muscle action potentials of the extensor digitorum brevis muscles after stimulation of the peroneal nerves. Electromyography of the tibial muscle demonstrated a myopathic pattern. Tibial muscle, sural nerve, and skin biopsy showed a myopathy with empty and glycogen containing vacuoles, a mild loss of myelinated and unmyelinated axons, and a moderately reduced intraepidermal nerve fiber density. These findings provide evidence for a severe distal muscle involvement and a mild sensory neuropathy evolving during the course of disease after long-term enzyme replacement therapy, thereby expanding the new emerging phenotype of infantile onset Pompe disease.

Keywords: IOPD; ERT; Infantile-onset Pompe disease; Pompe disease; GAA; IENFD.

1. Introduction

Infantile onset Pompe disease (IOPD) is caused by virtually complete deficiency of the lysosomal enzyme acid alpha glucosidase (GAA) and abnormal storage of glycogen, leading to hypertrophic cardiomyopathy (HCM), a myopathy with profound axial muscle weakness, and early death usually within the first year of life before enzyme replacement therapy (ERT) became available. ERT with recombinant human GAA has enabled long-term survival and achievement of motor milestones such as free walking for some of the affected. But prolonged viability has uncovered multisystemic features of IOPD not known in the pre-ERT era. However, distal muscle involvement is observed in individuals with IOPD under ERT but the underlying etiology remains unsolved [1–3]. We investigated the origin of a rapidly emerging and severe distal muscle weakness of the legs in a 7-year-old boy setting in after 6.5 years of ERT, which contributed to a substantial decline of his motor function.

2. Clinical case

The boy is the third child of healthy consanguineous Turkish parents and was born at term without complications. He was hospitalized at age 4 months due to pneumonia. Clinical examination revealed muscular hypotonia and axial muscle weakness. CK values were elevated up to 1.900 U/l (normal <200), and echocardiography disclosed severe hypertrophic cardiomyopathy (HCM) (*z*-scores for wall thickness parameters >6.2). IOPD was diagnosed by demonstrating absent GAA enzyme activity in leukocytes and confirmed by genetic testing showing the homozygous CRIM-positive mutation p.A694Gfs* in the GAA gene. ERT with 20 mg/kg recombinant human GAA every other week was started at age 5 months. HCM normalized after 7 months of treatment and the boy attained free walking at age 18

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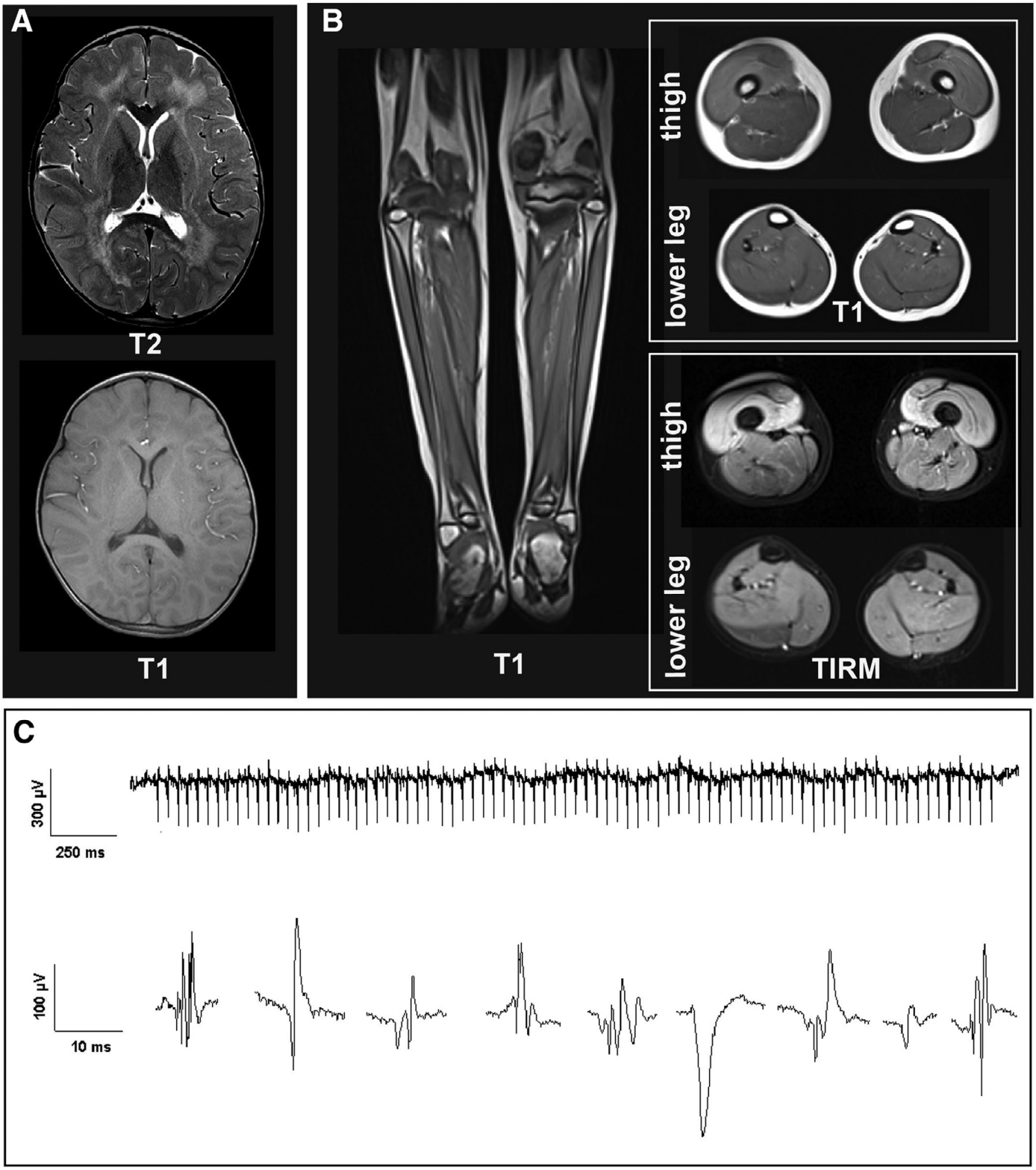

Fig. 1. T1 and T2 weighted cranial MR image show a symmetrical and bilateral leukencephalopathy with signal hyperintensities in T2 of the periventricular and deep white matter with apparent sparing of the U-fibers and involvement of the internal capsules (A). T1 weighted skeletal muscle MR images show preserved muscle bulks and no fatty degeneration, while Turbo-Inversion Recovery-Magnitude (TIRM) sequences disclose edematous alterations predominantly of the quadriceps muscles at the level of the thigh and of the lower leg muscles (B). Electromyography of the left anterior tibial muscle demonstrates marked complex-repetitive discharges lasting 5–25 s (upper line), as well as polyphasic motor unit potentials with short duration and low amplitude (lower line) (C).

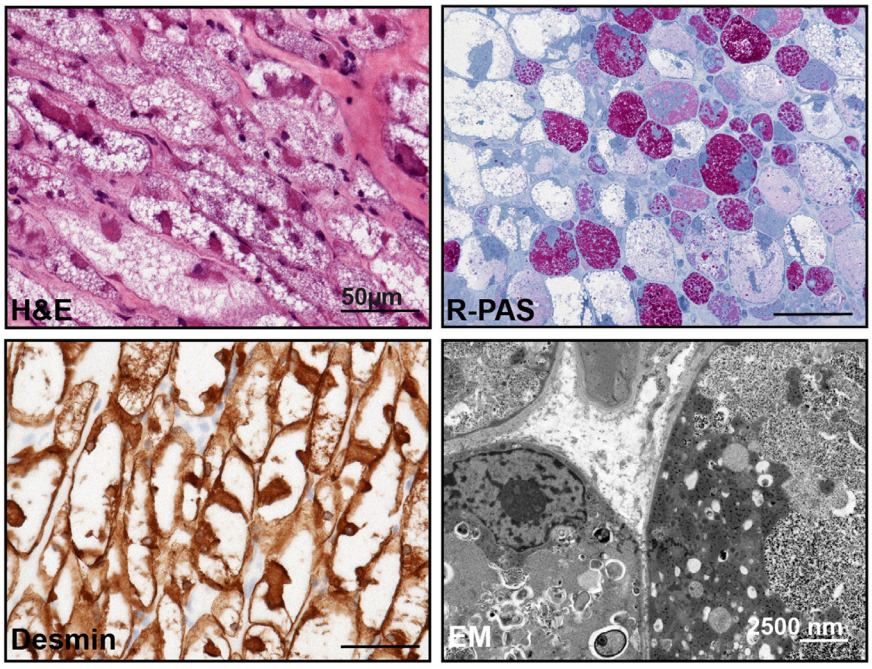

Fig. 2. A muscle biopsy from the tibial muscle depicts a severe myopathy (H&E) with glycogen containing and empty vacuoles in PAS stained semithin resin sections (R-PAS). Immunohistochemistry with antibodies against the cytoskeletal protein desmin and electron microscopy show only a few remaining myofibrils.

months despite some residual proximal muscle weakness (hip flexors: MRC muscle scale grade 4; foot dorsiflexors: MRC muscle scale grade 5). Marked oro-facial muscle weakness not ameliorating during ERT makes the patient's speech difficult to understand, and moderate to profound bilateral hearing loss prompted hearing aid fitting at age 2 years. Cerebral magnetic resonance imaging (MRI) at age 7 years demonstrated symmetric white matter lesions (Fig. 1A), while the boy's cognitive performance, assessed by the non-verbal Snijders-Oomen Test (SON-E 2½-7), was substantially reduced to 48 (normal >85).

The patient's motor function remained quite stable until pre-school age, when his walking distance in the 6-minute-walk test (6MWT) declined significantly from 370 m at age 6 years to 250 m 6 months later, and to 210 m at age 7 years. This was associated with a change of his gait pattern with reduced step length and higher lifting of the leg than normal when walking due to weak dorsiflexion of the feet (MRC muscle scale declined from 5 to grade 2 in six month), (supplementary video). No joint rage of motility, orthoses or physical activity as a potential damage were present in this patient. In an attempt to clarify the cause of this new dorsiflexor weakness, MRI of the legs was performed, showing preserved muscle bulks and no fatty degeneration of the leg muscles, but edematous alterations predominantly of the quadriceps muscles at the level of the thigh and of the lower leg muscles (Fig. 1B).

Electrophysiology yielded normal nerve conduction velocities and amplitudes of the right and left motor and sensory median nerves, and of the right and left sural nerves. By contrast low compound muscle action potentials despite normal conduction velocities were recorded from both extensor digitorum brevis muscles after stimulation of the peroneal nerves. F-wave latencies of the median and peroneal nerve were within the normal range. Median and tibial somatosensory evoked potentials were normal, and motor evoked potentials recorded from the abductor digiti minimi and extensor digitorum brevis muscles revealed no gross abnormalities. Electromyography of the left vastus and anterior tibial muscles disclosed neither fasciculations nor positive sharp waves at rest, but demonstrated marked complex-repetitive discharges lasting 5–25 s. These bursts could be elicited by inserting and displacing the needle, but not by percussion. In addition, polyphasic motor unit potentials with short duration and low amplitude were recorded (Fig. 1C).

A combined biopsy of the right anterior tibial muscle, right sural nerve, and skin was performed during general anesthesia necessary to change the patient's port catheter at age 7 ½ years, in order to investigate whether this distal muscle weakness was of myopathic or neuropathic origin, and to clarify whether an increase of the enzyme dose could be meaningful. Muscle biopsy evaluation showed a myopathy with empty and glycogen containing vacuoles, and few remaining myofibrils, consistent with a severe pathology, suggesting that increasing enzyme dosage would not be meaningful (Fig. 2) [4]. Sural nerve biopsy analysis displayed a discrete loss of myelinated axons and a few collagen pockets at the ultrastructural level, indicating some additional loss of unmyelinated fibers (Fig. 3B). Only a few glycogen deposits in artery vessel walls and Schwann cells were present, but no unequivocal myelin abnormalities

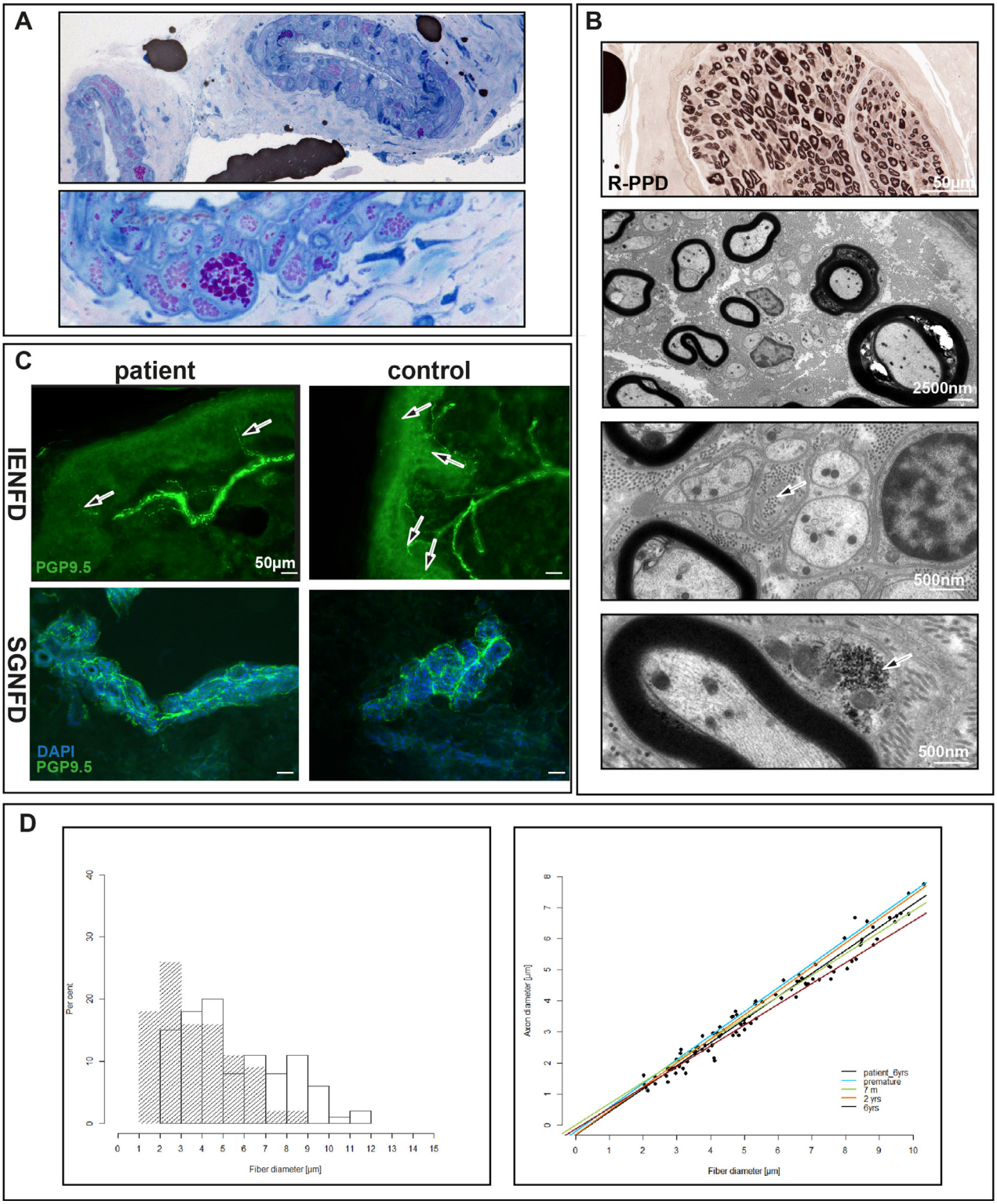

Fig. 3. Sural nerve biopsy analysis reveals some glycogen deposits in arterial vessel walls (R-PAS) (A). PPD stained semithin resin sections (R-PPD) and electron microscopy display mild loss of myelinated axons and a few collagen pockets (arrow), indicating some loss of unmyelinated axons, while only minimal glycogen accumulations in Schwann cells (arrow) are visible (B). Immunofluorescence staining with an antibody against PGP9.5 in a skin biopsy specimen from the distal leg depicts reduced intraepidermal nerve fiber density (IENFD) (arrows) and sweat gland nerve fiber density (SGNFD) when compared to an age matched healthy control (C). Morphometric analysis of the sural nerve demonstrates a bimodal pattern of axon (hatched) and fiber diameters in the histogram with mild loss of small sized fibers (2–4 µm). Correlating fiber with axon diameters discloses normal myelin thickness. Both parameters are compared to controls from the literature (D).

were seen (Fig. 3A and B). Morphometric analysis of the sural nerve was performed at a transmission electron microscope and the findings were compared to published normal controls. This revealed a bimodal axon and fiber diameter distribution with some reduction of small fibers (2–4 μm) [5]. Relating fiber to axon diameter displayed a normal myelin sheet thickness [6] (Fig. 3D). Skin biopsy analysis showed a moderately reduced intraepidermal nerve fiber density (IENFD) of 7.3 (normal value at age 20 years >10.9 fibers/mm), and a modestly diminished sweat gland nerve fiber density (SGNFD) of 32% (normal value at age 20 years >40%), suggesting some involvement of small fibers and autonomic nerves (Fig. 3C) [7–9].

3. Discussion

Our patient with IOPD treated with ERT since early age shows proximal and marked oro-facial muscle weakness, hearing loss, and language disorder. These features are in line with other reports analyzing long-term outcome and are characteristics of the new phenotype associated with IOPD in the ERT-era [1–3]. CNS abnormalities such as enlargement of the inner and outer cerebrospinal fluid spaces are common in IOPD [10]. As in our patient, a leukencephalopathy, rarely involving the pyramidal tracts [11], as well as a cognitive impairment of variable degree are also frequent in IOPD [12]. This can be attributed to the fact that the recombinant enzyme cannot cross the blood-brain barrier, and the evidence of some cases of progressive leukoencephalopathy also adds to the growing evidence that the CNS accumulation of glycogen in classical onset IOPD cases may not be as benign as previously considered [11,12].

Secondary worsening of motor function despite initially positive effects of ERT is more and more recognized in older IOPD subjects [1,2]. Prominent weakness of the dorsiflexors as in our patient has been observed in other individuals with IOPD with foot drop as a common observation [1,3], and has also been recognized as a rare symptom in subjects with late onset Pompe disease (LOPD) [13]. Principally, this distal weakness could be due either to glycogen deposition in the central nervous system and the peripheral nerves, or to involvement of additional muscles by the myopathic process. The muscle MRI findings in our patient such as preserved muscle bulks, largely absent fatty degeneration, and edema-like changes of the lower limb muscles are completely in line with the findings recently reported in a cohort of 9 IOPD patients [14]. The electrophysiological and histopathologic findings in our patient suggest that the feature of distal muscle weakness is due to progression of the myopathy, and that it is not caused by peripheral nerve damage or central nervous system involvement. Interestingly, motor nerve involvement was not clinically relevant. However, autopsy studies in IOPD patients have described glycogen deposits in Schwann cells [15], and GAA-/- Pompe mice develop a demyelinating neuropathy [16]. Skin biopsy analysis is an objective and sensitive tool to assess intraepidermal nerve fiber density (IENFD), and a reduced IENFD reflects small fiber neuropathy (SFN), indicating involvement of the peripheral nervous system [17]. In Pompe disease, reduced IENFD has been described in 2 LOPD patients so far [18]. In line with these observations, our findings demonstrate involvement of the peripheral nervous system with reduction of small and autonomic dermal nerve fibers as well as mild loss of myelinated and unmyelinated sensory fibers in an IOPD patient under ERT too. Lack of major glycogen deposits in Schwann cells and normal myelination of the axons in our patient are compatible with an axonal degeneration due to glycogen accumulation in dorsal root ganglia, as it has been described in mouse models of Pompe disease [19,20].

In conclusion, we provide evidence for a rapid progression of distal muscle involvement and a mild sensory neuropathy evolving during the course of disease after long-term ERT, and thereby expand the emerging new phenotype of IOPD. Additional affection of distal muscles by the myopathic process and stable cardiac status during follow-up also exemplify the divergent response of heart and skeletal muscle to ERT. The underlying etiology is not fully understood and other potential causes as an involvement of neuromuscular junction or vascular pathology should be discussed and investigated in more detail.

Acknowledgments

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Ethic statement

The parents provided written informed consent. The study was approved by the ethic review board of the JL University Giessen.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.03.004.

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