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Case report

Clinical features of Pompe disease with motor neuronopathy

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Abstract

Pathological studies on rodent models and patients with Pompe disease have demonstrated the accumulation of glycogen in spinal motor neurons; however, this finding has rarely been evaluated clinically in patients with Pompe disease. In this study, we analyzed seven patients (age, 7–11 years) with Pompe disease who received long-term enzyme replacement therapy. In addition to traditional myopathy-related clinical and electrophysiological features, these patients often developed bilateral foot drop, distal predominant weakness of four limbs, and hypo- or areflexia with preserved sensory function. Electrophysiological studies showed not only reduced amplitudes of compound muscle action potential, but also absent or impersistent F waves and mixed small and large/giant polyphasic motor unit action potentials with normal sensory study. Muscle biopsy usually showed the existence of angular fingers, fiber type grouping or group atrophy. Taken together, these features support the co-existence of motor neuronopathy additionally to myopathy.

Keywords: Electromyography; Motor neuronopathy; Pompe disease.

1. Introduction

Pompe disease (glycogen storage disease type II or acid maltase deficiency) is an autosomal recessive glycogen storage disease, which results from deficiency of acid α-glucosidase, leading to impairment of glycogen degradation in lysosomes [1]. Subsequently, the glycogen accumulation in skeletal and cardiac muscles causes progressive myopathy and cardiomegaly with weakness and hypotonia of four limbs and heart failure. With the advent of enzyme replacement therapy (ERT), the life expectancy markedly increases from 1 year to more than decade in infantile-onset Pompe disease [2]. Patients who get early genetic diagnosis and receive ERT asymptomatically may thus show variable clinical manifestations at future disease onset.

Although patients with Pompe disease usually present with progressive proximal muscle weakness, which is a typical feature of myopathy, previous pathological studies of Pompe disease also demonstrated the accumulation of glycogen in spinal motor neurons of rodent models [3–5], and patients [6–9] with abnormal neuromuscular junction [10,11]. However, there is still no clinical or electrophysiological studies focusing on the features of motor neuronopathy in patients with Pompe disease. Here we analyzed seven patients with Pompe disease who received ERT since birth or infancy and showed some clinical, electrophysiological, and muscular pathological features of motor neuronopathy.

2. Case report

In the cohort of 10 patients of infantile-onset Pompe disease identified by newborn screening [12], six of them accepted to have the detailed neurological and electrophysiological assessment. They all received ERT continuously since diagnosis of Pompe disease until now.

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Table 1
Clinical neurological features of patients with Pompe disease.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Current Age/Gender	7/M	11/M	7/F	9/M	11/M	11/M	9/M
Age at diagnosis	NBS	NBS	NBS	NBS	NBS	NBS	1-year-old
Speech	dysarthria	dysarthria	dysarthria	dysarthria	dysarthria	dysarthria	dysarthria
Weakness predominance	distal	distal	generalized	proximal	distal	distal	proximal
Foot drop	+	+	+	+	–	+	–
Muscle power:							
Neck (flexion/extension)	4-/4+	4-/4	4-/4+	3/4-	4-/4+	4/4+	4/5
Upper limb (P/D)*	4+/4-	4/4-	4-/4	3/4	4+/3	4+/3	4+/5
Lower limb (P/D)*	4+/1	1/1	4-/3	3/3	4-/4-	4-/0	4/4+
Deep tendon reflex	areflexia	areflexia	hyporeflexia	hyporeflexia	hyporeflexia	areflexia	hyporeflexia
Sensory function	Normal	Normal	Normal	Normal	Normal	Normal	Normal

D indicates distal; F, female; M, male; NBS, newborn screen; P, proximal.
* Shoulder abduction for proximal upper limb, finger flexion for distal upper limb, hip flexion for proximal lower limb, and ankle dorsiflexion for distal lower limb; muscle power with the worse side was recorded.

Table 2
Electrophysiological and muscular pathological features of patients with Pompe disease.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Nerve conduction study							
CMAP Median ($N>5$)	6.1/NP	6.4/7.7	16.8/16.8	11/NP	10.9/8.5	8/7.6	9.3/9.3
Peroneal ($N>2$)	1.4/1	0.8/0.6	1.6/1.8	1.1/0.8	2.1/1.1	0.2/0.3	3.6/2.8
SAP Median ($N>10$)	37/NP	67/78	87/65	62/NP	82/83	54/52	47/39
Sural ($N>5$)	16/17	17/32	34/22	21/17	14/23	7/10	14/14
F-waves* Median	absent/ NP	absent/ absent	normal/ normal	normal/ NP	normal/ normal	Impersistent/ impersistent	normal/ normal
Peroneal	absent/ impersistent	impersistent/ absent	impersistent/ normal	absent/ absent	normal/ absent	absent/ absent	normal/ normal
Electromyography							
Spontaneous activity	–	Myotonia	–	Myotonia	Myotonia	Myotonia	–
Polyphasic waves	Mixed	Mixed	Mixed	Small, brief	Small, brief	Small, brief	Mixed
Muscle biopsy							
Angular fiber	+	+	+	–	+	+	+
Muscle type grouping or group atrophy	+	+	+	–	+	–	+

CMAP indicates compound muscle action potential at distal stimulation; N, normal cutoff point; NP, not performed; SAP, sensory action potential.
Data were results from right/left limbs in mV.
* The cut-off values of F-impersistence are 50% and 40% for median and peroneal nerves, respectively.

The other one patient (patient 7) developed postnatal generalized hypotonia, got diagnosis of Pompe disease at the age of 1 year, and received ERT after then. The mean age of seven patients (6 male) was 9.3 ± 1.8 years (7–11 years old). The clinical, electrophysiological, and muscular pathological features were summarized in Tables 1 and 2, respectively.

All patients had dysarthria with nasal speech and weakness of neck and four limbs symmetrically. Five (71%) of seven patients showed bilateral foot drop. Using the Medical Research Council (MRC) scale, muscle power of neck flexion was 3 to 4. Notably, four (57%) patients revealed distal predominant weakness of four limbs, with two of them showing marked discrepancy of muscle power between proximal (4- to 4+) and distal (0–1) lower limbs (patients 1 and 6). The deep tendon reflex (DTR) in four limbs was absent in three patients and decreased in four. Otherwise, the examinations on sensory or cerebellar function were unremarkable.

The nerve conduction study showed reduced amplitudes of compound muscle action potential (CMAP) in peroneal nerves of six patients (86%) with preservation of CMAP in median nerves. The motor nerve conduction velocity and distal motor latency were all normal. The sensory studies on median, ulnar, and sural nerves were within normal limits. However, F-waves were absent or impersistent in median or peroneal nerves of six patients (86%) with normal minimal F-latency. The electromyography showed needle-induced myotonia in four patients (57%) at rest. All patients showed small brief polyphasic waves, indicating existence of myopathy; however, four of them (57%) also had large polyphasic waves or giant waves with amplitudes of motor unit action potential (MUAP) of 5 to 10 mV.

All of them have received muscle biopsy of the quadriceps at the age from 1 month to 7 years and we retrospectively reviewed the muscle pathology. In addition to muscular intracytoplasmic glycogen accumulation, the existence of

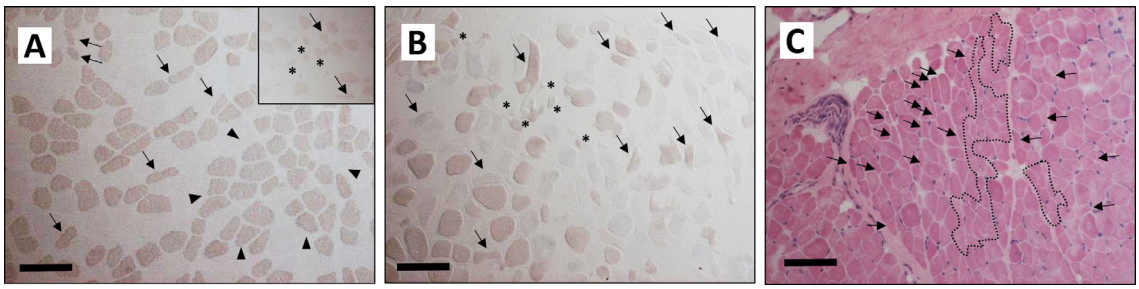

Fig. 1. Muscle pathology in patients with Pompe disease. (A) ATPase stain (pH 9.4) of quadriceps tissue section from patient 7 at the age of 3 years shows focal grouping of the same muscle fiber type (triangle) and existence of angular fiber (arrow). Panel shows presence of angular fiber and group atrophy of muscle fibers (asterisk) by ATPase stain (pH 4.3). (B) ATPase stain (pH 4.3) of quadriceps tissue section from patient 3 at the age of 6 months shows group atrophy of muscle fibers and existence of angular fibers of both type I and type II fibers. (C) H&E stain of quadriceps tissue section from patient 5 at the age of 6 months shows group atrophy of muscle fibers (dotted line) and existence of angular fibers. Scale bar = 50 μm.

angular fibers, muscle fiber type grouping or group atrophy can be detected in six (86%) patients using H&E and ATPase stains (Fig. 1). One patient had severe glycogen accumulation with only few scatter myocytes, impeding further analysis.

3. Discussion

Pathological studies on rodent models and patients with Pompe disease have demonstrated the accumulation of glycogen in spinal motor neurons [3–9]. However, this finding has rarely been evaluated clinically in patients with Pompe disease. Since ERT was not able to target central nerve system (CNS) because of the existence of blood brain barrier [13,14], the motor neuronopathy may persist despite ERT treatment. In this study, we found that patients with Pompe disease receiving long-term ERT often developed bilateral foot drop, distal predominant weakness of four limbs, and hypo- or areflexia with preserved sensory function. Electrophysiological studies showed not only reduced CMAP amplitudes, but also absent or impersistent F waves and mixed small and large/giant polyphasic waves with normal sensory study. Muscle biopsy usually showed the existence of angular fingers, muscle fiber type grouping or group atrophy. Taken together, these features support the co-existence of motor neuronopathy in addition to myopathy.

The typical neurological manifestations of Pompe disease include general weakness/hypotonia of neck and four limbs and dysarthria with preservation of sensory and cerebellar function [1], which are compatible with a pathological result of myopathy. In our patients, additionally to above clinical features, we also found that about 70%, 60%, and 100% of them showed foot drop, distal predominant weakness of four limbs, and hypo- or areflexia of DTR, respectively. Patients with myopathy usually developed proximal-predominant weakness, while distal-predominant weakness more likely caused from motor neuronopathy or polyneuropathy [15]. Foot drop indicates predominant weakness of tibialis anterior muscles, which is an unusual finding for myopathy but a common presentation of motor neuronopathy or polyneuropathy [15]. In addition, hyporeflexia or areflexia is a typical feature of motor neuronopathy or polyneuropathy [15]. Although severe myopathy may also show reduction of DTR, the relatively preserved muscle power (3–4+) with hyporeflexia or areflexia in upper limbs of our patients may suggest that the abnormal DTR in Pompe disease is resulted mainly from motor neuronopathy or polyneuropathy. Considering of normal sensory function, the existence of motor neuronopathy is likely.

The electrophysiological findings of Pompe disease include reduction of CMAP amplitudes with preserved sensory results in nerve conduction study and existence of needle-induced myotonia and small brief MUAPs in electromyography study [16]. The above features are characteristics of myopathy, which could be detected in most of our patients. Here, we demonstrated that patients with Pompe disease may also show absent or impersistent F-waves (86%) and large or giant MUAPs (57%). The F-wave abnormality along with relatively preserved CMAP amplitude indicates problems in motor neurons or proximal motor nerves [17]. None of our patients experienced root pain and the X-ray of whole spine in all of our patients only disclosed mild scoliosis, which made a diagnosis of radiculopathy less likely. The median CMAP amplitudes were quite well along with low peroneal CMAP amplitudes in general, which may indicate mild severity of motor neuronopathy and presence of a length-dependent problem in Pompe disease. Previous pathological study has also shown the accumulation of glycogen in spinal motor neuron, but not peripheral nerve [18]. Although glycogen can deposit in schwann cells [18,19], which play a role on nerve conduction, the motor and sensory nerve conduction velocity and F-latency were both within normal limits in all of our patients. The mixed small and large MUAPs can be seen in patients with chronic myopathy [17]; however, the existence of giant waves (5–10 mV in amplitude) is unusual for myopathy but common for motor neuronopathy. Therefore, the electrophysiological study also support that the coexisting motor neuronopathy is possible in Pompe disease.

All of our patients had typical muscle pathology for Pompe disease featuring muscular intracytoplasmic glycogen accumulation [1]. In addition, most of them showed the existence of angular fingers, muscle fiber type grouping or group atrophy, which indicated muscular denervating

changes followed by collateral reinnervation [6]. Although the above abnormalities were not severe, the coexisting motor neuronopathy in Pompe disease is still likely.

In summary, this study provides the clinical, electrophysiological and muscular pathological evidences of neuropathic changes in patients with Pompe disease. Considering of previous pathological findings of glycogen accumulation in spinal motor neuron [3–9], our findings thus support a diagnosis of motor neuronopathy in Pomp disease. Since ERT limits to target CNS because of the existence of blood brain barrier [13,14], further studies should also focus on CNS-specific therapy, eg. gene therapy; future clinical trials should also evaluate the treatment effects on non-muscular phenotypes, such as motor neuronopathy, assessing by DTR, F-wave study, MUNE, and electromyography. In the post-ERT era of Pompe disease, patients may present as variable atypical clinical manifestations. Carefully identifying these presentations, including motor neuronopathy, with regular follow-up will be helpful for optimization of clinical care and setup of future clinical trials in Pompe disease.

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