

Single Case – General Neurology

Late-Onset Pompe Disease Presenting with Isolated Tongue Involvement

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Keywords

Pompe disease · Glycogen storage disease type II · Acid maltase deficiency · Late-onset Pompe disease · Tongue weakness

Abstract

Late-onset Pompe disease (LOPD) is a rare autosomal recessive metabolic disorder that is caused by deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA), which is responsible for glycogen breakdown. It has a wide clinical spectrum but usually presents with limb girdle and respiratory muscles weakness. Tongue involvement has been rarely reported as the sole initial symptom of LOPD. A 65-year-old male presented with difficulty in speech and eating for a 4-year duration. He started to notice speech difficulty with production of particular speech sounds such as /l/, /d/, and /t/. Within 1 year, he developed difficulties in manipulating food with the tongue and oral residue in lateral sulci requiring digital manipulation, which was suggestive of tongue muscles weakness. Clinical examination showed tongue fasciculations, mild atrophic changes, and mild tongue weakness. Investigations showed mildly elevated creatine kinase levels, and electromyography of the tongue muscles revealed moderate spontaneous activity, denervation, chronic reinnervation with high-amplitude motor unit potentials, and positive sharp waves, with preserved recruitment. Given the diagnostic uncertainty, a screening for LOPD was performed using a dried blood spot, and GAA enzyme activity levels were found to be low; 1.06 $\mu\text{mol/L/h}$ (reference values in adults: 2.10–29.00 $\mu\text{mol/L/h}$). Next-generation sequencing showed pathogenic variant in *GAA* gene, confirming the diagnosis of LOPD. This rare report of LOPD presenting with isolated tongue involvement adds to the expanding phenotypic variability of this disease. Tongue involvement is an important and early clinical sign of LOPD that needs careful evaluation and can aid in early diagnosis of this rare and treatable disease.

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Introduction

Pompe disease, also referred to as acid maltase deficiency or glycogen storage disease type II, is a rare autosomal recessive metabolic disorder. It is caused by deficiency of the glycogen-degrading lysosomal enzyme acid alpha-glucosidase (GAA), resulting in excessive accumulation of glycogen in the lysosomes and cytoplasm of all tissues, most notably in skeletal muscles [1]. Its incidence is variable, depending on the different screening programs. It is estimated to affect 1 in 40,000 in Caucasians [2] and 1 in 283,000 in patients from Europe [3], while a higher incidence (1/14,000) was found in African-American patients [4].

It is caused by mutations in the *GAA* gene, located on chromosome 17q25.2-q25.3. *GAA* gene is highly pleomorphic, and more than 300 different mutations have been reported, with c.-32-13T>G mutation being the most common. Depending on the residual GAA enzyme activity, time of the onset (below 1 year or after 1 year of age), and disease progression, Pompe disease is classified into infantile-onset (IOPD) and late-onset Pompe disease (LOPD) [5].

Initially, cases of IOPD had been described as a rapidly progressive infantile disorder that leads to respiratory and cardiac failure and ultimately death, within the first 2 years of life. Meanwhile, LOPD typically presents with a slowly progressive weakness of proximal, trunk, and respiratory muscles, and it has been increasingly recognized that its clinical presentation is heterogeneous with a multisystemic nature [5, 6]. The diagnosis of LOPD is challenging and is usually delayed. This is attributed to several factors including its rarity, variability in the clinical presentation, and overlap with signs and symptoms encountered in other neuromuscular disorders (NMDs). Other conditions to consider in the differential diagnosis of LOPD include, but are not limited to, amyotrophic lateral sclerosis, limb-girdle muscular dystrophy, Duchenne/Becker muscular dystrophy, spinal muscular atrophy, and other glycogen storage diseases [6, 7]. The approval of recombinant GAA as enzyme replacement therapy for LOPD has changed the course of the disease and increased attention to the wide spectrum of LOPD clinical phenotypes [8]. Recent data suggest the involvement of the orofacial striated muscles, including the tongue, in LOPD [9]. Herein, we present a rare case of a 65-year-old male who presented with isolated involvement of the tongue muscles, as the only initial presentation of LOPD.

Case Report

A 65-year-old Kuwaiti male, father of 5 children with a past medical history of hyperlipidemia, presented with a gradual onset and slowly progressive 4-year history of speech and swallowing difficulties. He first noted speech difficulty with production of particular speech sounds such as /l/, /d/, and /t/. Within 1 year, he noticed difficulties in manipulating food with the tongue while chewing and oral residue in lateral sulci requiring digital manipulation, which suggests impairment in oral phase of swallowing. In the following year, he started to have difficulty in swallowing solid food, followed by semi-solid food, which required him to change his oral diet to a softer form. He attributed this initially to pharyngitis that he developed at that time and was evaluated by otolaryngologist several times. His clinical nasal and laryngeal endoscopic examinations were normal. He was then referred to a gastroenterologist for upper gastrointestinal endoscopic examination, and a diagnosis of gastroesophageal reflux disease was made, and the patient was started on a proton pump inhibitor.

The patient then noticed difficulties in smooth tongue movement, so he was referred to a neurologist for further evaluation. His initial clinical examination was reported as normal, apart from tongue fasciculations. He underwent magnetic resonance imaging (MRI) of the

brain and whole spine, which were normal. Nerve conduction study (NCS) and needle electromyography (EMG) including the tongue were performed and showed normal results. His speech and swallowing difficulties slowly progressed, and the patient sought a second medical opinion. A second needle EMG was performed which showed denervation in the form of fibrillation potentials and positive sharp waves. Despite not fulfilling the clinical or neurophysiological diagnostic criteria, the patient was given the diagnosis of motor neuron disease and was asked to start riluzole. The patient was resistant to accept the diagnosis, and he was referred to our tertiary center for further management.

His clinical examination showed an alert and conscious male with normal higher mental functions and normal gait. Speech assessment suggested dysarthria with speech-sound distortions, noted with the production of /l/, for example. Language function was normal. Cranial nerve examination was unremarkable, except for the presence of tongue abnormalities including fasciculations, mild atrophy, and mild weakness, with no deviation. Muscle power was of Medical Research Council (MRC) grade 5/5 all over. Deep tendon reflexes were 1 + all over. He had normal sensory and cerebellar examination with bilateral down-going plantar response.

A follow-up needle EMG showed moderate spontaneous activity and positive sharp waves, denoting denervation in the tongue muscles. The voluntary record revealed chronic reinnervation changes. No myotonic discharges were detected. High-amplitude motor unit potentials were observed, with relatively preserved recruitment. In the thoracic region and both thighs, there was evidence of increased polyphasia, fasciculations, and higher amplitude of motor unit potentials, with mildly decreased recruitment. In both upper limbs and the calf, there was no fasciculations, mild to moderate polyphasia, and some higher motor potentials, with adequate recruitment. Nerve conduction study was normal. The picture was nonconclusive, favoring a neurogenic rather than myopathic pattern and did not fulfill the diagnostic criteria for motor neuron disease, so further investigations were warranted.

An extensive laboratory workup was performed which showed normal complete blood count; renal and liver functions; serum electrolytes; inflammatory markers (erythrocyte sedimentation rate and C-reactive protein); serum vitamins B1, B6, B12, and folate; protein electrophoresis; immunoglobulin assay; thyroid function; and antithyroid autoantibodies. A panel for vasculitis and autoimmune antibodies yielded negative results. Anti-acetylcholine receptor and anti-muscle-specific kinase antibodies were negative. However, serum creatine kinase levels were mildly elevated; 284 U/L (22–198 U/L). MRI study of the brain and cervical spine was normal.

Given the diagnostic uncertainty of the condition, a screening for LOPD was performed using a dried blood spot on a filter paper. GAA enzyme activity was found to be low; 1.06 $\mu\text{mol/L/h}$ (reference values in adults: 2.10–29.00 $\mu\text{mol/L/h}$). Next-generation sequencing was conclusive of a pathogenic variant in *GAA*, 17q25.2-q25.3, confirming the diagnosis of LOPD. This variant is related to cytosine-to-thymine nucleotide change that lead to amino acid substitution of alanine for valine in residue 242 of the protein coded by *GAA*.

The patient was started on enzyme replacement therapy with alglucosidase alfa (Myozyme[®]), with a dose of 20 mg/kg body weight (1,700 mg) administered every 2 weeks as an intravenous infusion over approximately 4 hours. He underwent physical, occupational, and speech therapy, which included 4 sessions/week of lingual resistance training. Outcome measures included maximum anterior isometric tongue pressure, maximum endurance hold time, speech intelligibility, airway safety, and patient-reported outcomes.

Monitoring disease progression was done using manual muscle testing (MMT), 6-min walk test (6MWT), and pulmonary function test (PFT) at the initial phase of treatment and during follow-up. After 6 months of treatment, the clinical condition was stable with no further progression, and there was no need for gastrostomy tube feeding or significant weight

loss. He had mild improvement of maximum endurance hold time, speech intelligibility, and overall quality of life despite no significant improvement of maximum anterior isometric tongue pressure.

Discussion

Clinical presentation of LOPD is largely variable, ranging from asymptomatic hyperCKemia, severe proximal skeletal muscle weakness, to weakness of the respiratory muscles, requiring mechanical ventilation. Tongue involvement in IOPD has been traditionally described with the classic phenotype [10]. However, in LOPD, tongue involvement has rarely been reported as the sole initial symptom of the disease despite being observed as an early axial sign [9]. This finding further adds to the expanding phenotypic variability of LOPD.

Involvement of the orofacial muscles in LOPD had been addressed in the literature, with several pathological studies documenting the involvement of every striated muscle examined, including the tongue muscles, in the form of vacuolar myopathy [11]. Dubrovsky and colleagues [12], reported tongue weakness in 100% of 19 consecutive LOPD patients, over a period of 3 years. Weakness was of mild to moderate severity in 95% of them, and associated dysarthria and/or dysphagia was present in 37% of patients. However, none of those patients had tongue weakness as a presenting symptom in their cohort. Moreover, Jones and colleagues [13], quantitatively assessed lingual weakness in 24 patients, where 80% of their sample showed weakness of the tongue. Severity was mild in 29%, moderate in 29%, and severe in 42%. In our patient, decreased tongue strength and dysarthria heralded bulbar involvement for about 2 years before dysphagia developed. He did not progress to proximal muscle weakness of respiratory affection, 4 years into the disease course. In the literature, dysphagia in particular and dysarthria were rarely reported in LOPD, and this case provides additional evidence regarding their involvement [9, 13]. Maggi and colleagues [14], reported a 47-year-old male who developed difficulty in moving his tongue and lips and in swallowing, 4 years before being diagnosed with LOPD. In contrast to our case, their patient developed mild limb muscle wasting and weakness, with waddling gait and marked spine lordosis.

The EMG findings in LOPD are characterized by vivacious spontaneous activity and a high rate of different EMG patterns. Beside the myopathic patterns reported in 70% of patients, neurogenic patterns and spontaneous activities such as myotonic and pseudomyotonic discharges, fibrillations, and positive sharp waves have been seen [15]. In our case, a neurogenic pattern was seen in the tongue muscles, in the form of denervation, and chronic reinnervation changes.

Tongue abnormalities on MRI were found to be more common in LOPD compared to other NMD. LOPD patients showed severe and consistent tongue and axial muscles involvement, with less marked involvement of peripheral musculature, in several MRI studies [16]. A bright tongue sign is a well-described finding in patients with NMD, in the form of bright hyperintense signal in T1-weighted images in brain MRI. Karam and colleagues [17], found “bright tongue sign” in 4/6 patients with LOPD, compared to 4/28 patients with other NMD, in addition to tongue atrophy in 3/6 patients with LOPD, compared to 6/28 patients with other NMD. Moreover, in a radiological study by Carlier and colleagues, using whole-body MRI in 20 patients with LOPD, all facial muscles were not affected except for the tongue muscles, in which fatty infiltration was intense and precocious [18].

Furthermore, a 2021 observational study [19] showed greater tongue involvement in LOPD compared to those with other acquired/hereditary myopathies, in the form of a statistically

significant decrease in quantitative tongue strength, sonographic muscle thickness, and echointensity, secondary to more fibrofatty replacement and atrophy in LOPD. They suggested that quantitative tongue weakness and atrophy can differentiate LOPD from other myopathies. This report has a limitation of not performing instrumental swallowing assessment such as a video fluoroscopic study.

Conclusion

This rare report of isolated tongue weakness as the only initial manifestation of LOPD adds to the expanding phenotypic variability of this rare disease. Involvement of the tongue is an important early clinical sign of LOPD that is usually overlooked and needs careful evaluation to be appreciated. Clinical assessment of tongue strength can be useful in early diagnosis of this rare and treatable disease.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this report. Ethical approval was not necessary for the preparation of this article as this is a case report study and does not include experimenting on animal and human subjects.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jasem Al-Hashel was the patient's primary neurologist and was involved in collection of clinical data. Ismail Ismail wrote the initial draft of the manuscript and performed literature search. Jasem Al-Hashel and Ismail Ismail reviewed, edited, and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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