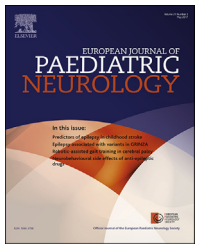
Official Journal of the European Paediatric Neurology Society



Original article

Longitudinal follow-up to evaluate speech disorders in early-treated patients with infantile-onset Pompe disease

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ARTICLE INFO

Article history:
Received 22 March 2016
Received in revised form
14 November 2016
Accepted 6 December 2016

Keywords:
Infantile-onset Pompe disease
Speech disorder
Articulation disorder
Hypernasality
Speech intelligibility
Enzyme replacement therapy

ABSTRACT

Background: Patients with infantile-onset Pompe disease (IOPD) can be treated by recombinant human acid alpha glucosidase (rhGAA) replacement beginning at birth with excellent survival rates, but they still commonly present with speech disorders. This study investigated the progress of speech disorders in these early-treated patients and ascertained the relationship with treatments.

Methods: Speech disorders, including hypernasal resonance, articulation disorders, and speech intelligibility, were scored by speech-language pathologists using auditory perception in seven early-treated patients over a period of 6 years. Statistical analysis of the first and last evaluations of the patients was performed with the Wilcoxon signed-rank test.

Results: A total of 29 speech samples were analyzed. All the patients suffered from hypernasality, articulation disorder, and impairment in speech intelligibility at the age of 3 years. The conditions were stable, and 2 patients developed normal or near normal speech during follow-up. Speech therapy and a high dose of rhGAA appeared to improve articulation in 6 of the 7 patients (86%, $p = 0.028$) by decreasing the omission of consonants, which consequently increased speech intelligibility ($p = 0.041$). Severity of hypernasality greatly reduced only in 2 patients (29%, $p = 0.131$).

Abbreviations: AROM, active range of motion; CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; FEES, fiber-optic endoscopic examination of swallowing; IOPD, infantile-onset Pompe disease; NBS, newborn screening; NMES, Neuromuscular electrical stimulation; PCC, Percentage of Consonants Correct; rhGAA, recombinant human acid α-glucosidase; SLP, speech-language pathologist; ST, speech therapy.

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http://dx.doi.org/10.1016/j.ejpn.2016.12.004

Conclusion: Speech disorders were common even in early and successfully treated patients with IOPD; however, aggressive speech therapy and high-dose rhGAA could improve their speech disorders.

1. Introduction

Pompe disease is a lysosomal disorder in which a deficiency of acid α-glucosidase (GAA, EC 3.2.1.20) causes the intralysosomal accumulation of glycogen in all tissues, most notably in cardiac, skeletal, and smooth muscle cells.[1] Clinically, patients with Pompe disease present with a wide spectrum of symptoms, ranging from the classic infantile-onset Pompe disease (IOPD), which is severe, progresses rapidly, and usually presents with hypertrophic cardiomyopathy, to the more slowly progressing, later-onset forms. In classic IOPD patients, symptoms begin very early in life (median age of 2 months), and death may occur shortly thereafter if the patient remains untreated (median age of 8.7 months).[2,3] The initial experiences of enzyme replacement therapy (ERT) with recombinant human GAA reduced the risk of invasive ventilation of IOPD to 66.7% at 24 months of age and to 49.4% at 36 months of age.[4,5] Survivors present with respiratory failure, inability to walk,[6] arrhythmia,[7] gastroesophageal reflux,[6] ptosis,[6,8] hearing loss,[6,9] hypernasal speech with a flaccid dysarthria, and oropharyngeal dysphagia.[8,10]

In Taiwan, we initiated newborn screening (NBS) of Pompe disease to achieve early diagnosis and early treatment in 2005,[11] and we demonstrated a greater effect on survival rates than for late treatment initiation.[12] The long-term outcomes for 10 patients with classic IOPD who were diagnosed by NBS[13] and were cross-reactive immunologic material (CRIM)-positive revealed that none of the patients required mechanical ventilation, all could walk independently, and all had motor capabilities sufficient for participating in daily activities, including school. However, muscle weakness remained a problem for these patients, and speech disorders were common after a median treatment time of 63 months (range 28–90 months).

Speech disorders are not uncommon in late-treated infantile-onset Pompe survivors who were symptomatic at the time of ERT initiation.[14] Previous studies have revealed that the speech disorders in Pompe disease feature consonant substitutions; consonant omissions and cluster reductions; mild to moderate hypernasal resonance; hoarseness; and wet voice, which involves flaccid dysarthria and velopharyngeal incompetence.[8,14] Flaccid dysarthria results from a disruption of muscular control and may reflect involvement of a single muscle or a group of muscles of the speech systems (e.g., phonatory, articulatory, or a combination).[15,16] Velopharyngeal incompetence can result from facial or bulbar muscle weakness. All the aforementioned muscles can be damaged by glycogen storage in late-treated Pompe disease. However, these speech muscles in the early-treated patients should logically exhibit less damage, since these patients have better motor functions in the other muscle groups. In this study, we aimed to analyze the speech characteristics of early-treated patients by a pre-designed assessment to understand the progress of speech disorders in these patients, and to determine whether early ERT can be beneficial to speech disorders.

2. Materials and methods

2.1. Patients

This study comprised 7 patients with classic IOPD who received speech evaluations and therapy at the National Taiwan University Hospital. The patients had been treated with recombinant human α-glucosidase (rhGAA) beginning between 14 and 89 days after birth (Table 1), starting with the labeled dose of rhGAA (20 mg/kg/every other week) and adjusting to high-dose rhGAA treatment (20 mg/kg/week or 40 mg/kg/every other week) according to their clinical responses.[12,13,17] All the patients in this study were CRIM-positive, and no side effects were observed because of this higher and/or more frequent dosing regimen. None of the patients had a sustained high titer of anti-rhGAA IgG antibodies, and all of them were ambulatory. Five of the 7 patients were identified through NBS for Pompe disease; one through prenatal diagnosis; and one through a health checkup at 2 months of age, which revealed an asymptomatic heart murmur. None of the patients presented any of the following conditions affecting their speech: (1) congenital structural abnormalities of the velar-pharynx, such as cleft palate or submucous cleft palate diagnosed by otolaryngologists and (2) brain injury during delivery. Except for Patient 7, all patients received hearing tests beginning at the age of 3 years with pure-tone audiogram and tympanogram. None of the patients were using hearing aids as of the end of this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The Institutional Review Board approved this study (NTUH-200703045R), and written informed consent was obtained from the parents of all patients included in the study.

2.2. Speech evaluation

Speech evaluations were performed for each patient yearly after 3 years of age using the Mandarin articulation test. The Mandarin articulation test instructs subjects to name 45