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CASE REPORT

Can stapedius reflex testing objectively measure muscle function in Pompe patients?

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Key Clinical Message

We assessed the value of stapedius reflex testing as an objective measurement of striated muscle function in four patients with Pompe disease. Common tests of disease severity and efficacy of enzyme replacement therapy (ERT) yield highly variable results that depend on patient cooperation and day-to-day performance, whereas stapedius reflex thresholds improved in seven of eight ears after 2 years of ERT.

Keywords

Enzyme replacement therapy, muscle function, Pompe disease, stapedius reflex testing.

Introduction

Pompe disease is a rare autosomal recessive glycogen storage disorder with an estimated incidence of 1:40,000; the current worldwide prevalence may be 5000–10,000 people [1, 2]. Pompe disease is caused by acid alpha glucosidase (GAA) deficiency which leads to lysosomal glycogen accumulation in multiple tissues [1, 2], but primarily compromises limb girdle and cardiac muscle fibers [1, 2].

Pompe disease is an inherited disorder caused by a mutation of the acid alpha glucosidase (GAA) gene, which is mapped to the long arm of chromosome 17 (location 17q25.2-q25.3); up to date, almost 300 distinct GAA mutations have been identified [3].

Enzyme replacement therapy (ERT) is available for Pompe disease patients [1]. However, high costs triggered considerations to limit ERT if functional assessments fail to show benefits [4–6].

Evaluation of ERT benefits in adult onset Pompe patients is based on tests such as the 6-min walking test (6MWT), test of muscle strength by the Medical Research Council (MRC) sum score [4, 7, 8], and pulmonary function by parameters such as forced vital capacity (FVC) [4]. Yet, test results vary with patient cooperation, day-to-day performance, and inter-rater variability [1, 9]. Moreover, the 6MWT and FVC reflect interactions of several systems including cardiac, circulatory, pulmonary, and muscular capacity but do not specifically measure muscle strength [9], while MRC sum scores of large muscles might miss subtle changes in muscle strength.

Monitoring of muscle function might be more precise with the examination of small muscles that consist of only few fibers and contract independently from patient cooperation.

The smallest striated muscle is the stapedius muscle. It contracts independently from patient cooperation in response to stapedius reflex activation which occurs to protect the inner ear when the sound pressure insonating the ear exceeds a specific threshold [10]. Contraction of the stapedius muscle pulls the stapes head away from the oval window, toward the cavum tympani, and thus reduces sound wave transmission toward the cochlea [10]. This muscle contraction causes a sudden step-like increase in sound pressure rejection toward the outer ear

canal. The sound pressure threshold at which the increase occurs reflects the stapedius reflex threshold (SRT) [10]. Increases in SRT objectify, for example, early stages of neural dysfunction or stapedius muscle weakness [10].

Hanisch et al. [11] reported increased SRT in adult onset Pompe patients which is due to glycogen storage in the conductive middle ear apparatus of early- and late-onset Pompe disease patients [2, 11–14]. We assume that recovery of only a few muscle fibers will improve stapedius muscle contraction and thus lower SRTs [10]. Consequently, we hypothesize that stapedius reflex testing identifies subtle changes in muscle function, independently from patient or examiner contributions, and might thus refine standard tests used to evaluate ERT benefits [1].

Therefore, this study evaluated stapedius reflex responses in four adult-onset Pompe patients before as well as 1 and 2 years after ERT onset and compared results to those of standard clinical tests.

Materials and Methods

In four adult Pompe patients (three women, 58.3 ± 9.2 years), we prospectively assessed disease progression and ERT effects. The University of Erlangen Nuremberg Ethics Committee had approved the study. All participants had given written informed consent.

All patients underwent detailed neurological evaluations before ERT onset (biweekly 20 mg/kg alglucosidase alfa®, intravenously), and every 6 months.

We tested strength of 30 muscles using the MRC grading scale and calculating a sum score as described elsewhere [8]. We monitored whole body functional activity using the Walton–Gardner-Medwin Scale (WGMS) [7]. Before and every 8 weeks after ERT onset, we measured functional capacity using the 6MWT [1]. Every 12 months, we monitored pulmonary function as percent predicted FVC in upright position. Patients measured their peak expiratory flow velocity (PEF) weekly and before each ERT session using a hand-held peak flow meter (Vitalograph GmbH, Hamburg, Germany) [15].

In addition, we assessed SRTs of the right and left ear, before, 1 and 2 years after ERT onset in patients 1 (female, 46 years) and 2 (male, 65 years), and 1 and 2 years after ERT onset in patients 3 (female, 69 years) and 4 (female, 53 years). Prior to SRT measurements, patients underwent otological examination and standard pure tone audiometry for air- and bone conduction to rule out otologic abnormalities or hearing impairment.

Stapedius muscle tension was determined indirectly by measuring the associated change in acoustic impedance at the tympanic membrane. The impedance change is directly proportional to the muscle tension, and was measured with an acoustic bridge that compensated for the air volume of the ear canal interposed between the input end of the bridge tube and the tympanic membrane using a standard clinical impedance meter (AT1000 impedance module, Auritec, Hamburg, Germany). Probe frequency was 226 Hz.

Stapedius muscle reflex contractions were produced by single bursts of 0.5, 1, 2, and 4 kHz tones. Tone bursts lasted for 300 msec and were delivered at sound pressure levels from 70 to 100 dB HL in steps of 5 dB. Bursts were turned on and off with transients of 5 msec effective duration. Muscle tension in response to tone bursts was measured in the ipsilateral ear [16].

We calculated mean ipsilateral SRT values from reflex contractions in response to the four presented single bursts (0.5, 1, 2, and 4 kHz) for each patient's left and right ear.

Reflex thresholds between 70 and 90 dB HL are considered normal and reflex thresholds above 90 dB HL are considered elevated [10].

If thresholds in response to less than 4 of the four presented single bursts were above detectable limits of the impedance meter, we defined threshold values as 110 dB. If thresholds in response to all four presented single bursts were above detectable limits of the impedance meter, we defined thresholds as "not detectable."

Otologic examination prior to SRT assessments showed normal findings and no hearing impairment in all patients.

Results

Standard monitoring and clinical neurological examination showed no relevant changes after 1 and 2 years of ERT (Table 1): MRC sum scores remained almost stable and values fluctuated or deteriorated by 0.7 and in one patient by 2 points within the 2 years of ERT. WGMS remained stable in patients 1 and 2 and slightly deteriorated in patients 3 and 4 from 5 before ERT onset to 6 after 1 and 2 years of ERT.

The 6MWT could not be performed by the wheelchair bound patient 2, showed no change in patient 3, but an increase in patient 1 by 3.3%, and a decrease in patient 4 by 3.5%.

The 6MWT average distance did not change significantly in the three patients from values before ERT onset (353.3 ± 92.9 m) to values after 2 years of ERT (355.0 ± 105.0 m).

FVC slightly deteriorated in patients 1 and 2, was almost unchanged in patient 3, and slightly improved in patient 4 after 2 years of ERT.

Similarly, maximum PEF velocities did not change significantly in our four patients from values before ERT

Table 1. Age at time of diagnosis, Walton–Gardner-Medwin scores, MRC sum scores, 6-min walking test results, forced vital capacities in upright position, peak expiratory flow velocities, and ipsilateral stapedius reflex thresholds of the left and right ear in four late-onset Pompe patients before and 1 and 2 years after onset of enzyme replacement therapy (biweekly 20 mg/kg alglucosidase alfa®, intravenously), as well as percent changes between values at baseline and values after 1 year of enzyme replacement therapy and between values after 1 year and after 2 years of enzyme replacement therapy.

	Before ERT (0)	After 1 year of ERT (1)	After 2 years of ERT (2)	% Change 0 versus 1	% Change 1 versus 2
Patient 1: 46 years, female, age at time of diagnosis = 40 years					
Walton–Gardner-Medwin score	3	3	3	0	0
MRC sum score	46.0	45.3	46.0	−1.5	+1.5
6-min walking test	460 m	462 m	475 m	+0.4	+2.8
Forced vital capacity (predicted value 3.53 l)	1.29 l	1.16 l	0.95 l	−10.1	−18.1
Peak expiratory flow velocity	400 L/min	390 L/min	400 L/min	−2.5	+2.6
Stapedius reflex threshold left/right [dB]	n.d./n.d.	98.8/87.5	91.3/87.5	–/–	−7.6/0
Patient 2: 65 years male, wheelchair bound, age at time of diagnosis = 44 years					
Walton–Gardner-Medwin score	7	7	7	0	0
MRC sum score	38.0	38.0	37.3	0	−1.8
6-min walking test	–	–	–	–	–
Forced vital capacity (predicted value 4.20 l)	2.96 l	2.67 l	2.72 l	−9.8	+1.9
Peak expiratory flow velocity	170 L/min	200 L/min	180 L/min	+17.6	−10.0
Stapedius reflex threshold left/right [dB]	98.8/93.8	86.3/91.3	90.0/91.3	−12.7/−2.7	+4.3/0
Patient 3: 69 years, female, age at time of diagnosis = 53 years					
Walton–Gardner-Medwin score	5	6	6	+20.0	0
MRC sum score	45.3	43.3	43.3	−4.4	0
6-min walking test	310 m	290 m	310 m	−6.5	+6.9
Forced vital capacity (predicted value 2.98 l)	3.07 l	3.25 l	3.04 l	+5.9	−6.5
Peak expiratory flow velocity	290 L/min	270 L/min	300 L/min	−6.9	+11.1
Stapedius reflex threshold left/right [dB]	Not assessed	85.0/85.0	80.0/81.3	–/–	−5.9/−4.4
Patient 4: 53 years, female, age at time of diagnosis = 40 years					
Walton–Gardner-Medwin score	5	6	6	+20.0	0
MRC sum score	40.0	39.3	39.3	−1.8	0
6-min walking test	290 m	270 m	280 m	−6.9	+3.7
Forced vital capacity (predicted value 3.25 l)	3.29 l	2.95 l	3.35 l	−10.3	+13.6
Peak expiratory flow velocity	370 L/min	350 L/min	390 L/min	−5.4	+10.3
Stapedius reflex threshold left/right [dB]	Not assessed	93.8/n.d.	96.3/98.8	–/–	+2.7/–

n.d., not detectable.

onset (307.5 ± 102.8 L/min) to values after 2 years of ERT (317.5 ± 102.1 L/min). Yet, PEF velocities fluctuated in all patients from one biweekly assessment to the next, 2 weeks later (Fig. 1).

In contrast SRTs changed with ERT

SRTs were above detectable limits in patient 1 prior to ERT onset, but were measurable after 1 year at 98.8/87.5 dB (left ear/right ear) and further improved after 2 years of ERT to 91.3/87.5 dB. In patient 2, SRTs improved from 98.8/93.8 dB before ERT to 90.0/91.3 dB after 2 years of ERT. In patients 3 and 4, SRTs improved in three of four ears from SRTs assessed after 1 year of ERT to measurements after 2 years of ERT.

Overall, stapedius reflex testing showed improved thresholds in seven of eight ears after 2 years of ERT, while thresholds deteriorated in one of eight ears (patient 4; Fig. 2).

Discussion

In contrast to clinical parameters, stapedius reflex thresholds improved after 2 years of ERT in seven of eight ears. Only one threshold slightly deteriorated from the first to the second year after ERT onset.

SRT changes do not reflect changes in quality of life [9], but indicate objective changes in stapedius muscle function, independently from day-to-day variability in patient cooperation which was particularly prominent with PEF measurements [9].

In contrast, all standard tests showed contradictory changes that were below relative changes needed for patients to perceive their performance as "a little bit better" (or "worse") than their previous results, that is, below so-called minimal clinically important differences (MCIDs) [9]. Lachmann and Schoser emphasized that adult-onset Pompe patients do not perceive 6MWT changes below 5–11% as "better" or "worse" than their

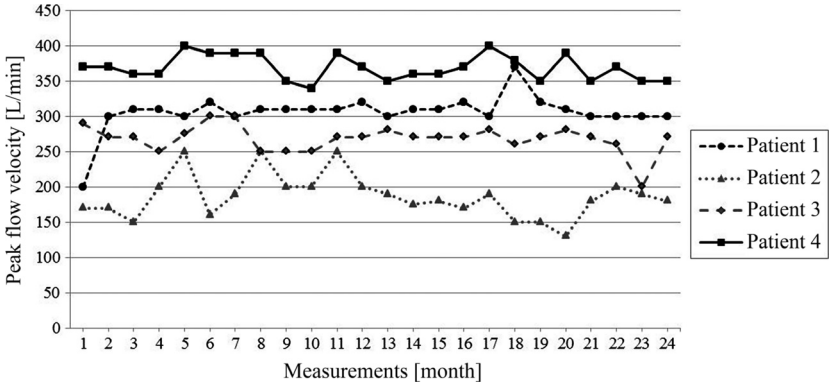

Figure 1. Significant fluctuations of monthly maximal peak expiratory flow velocities of four late-onset Pompe patients assessed during 24 months of ERT.

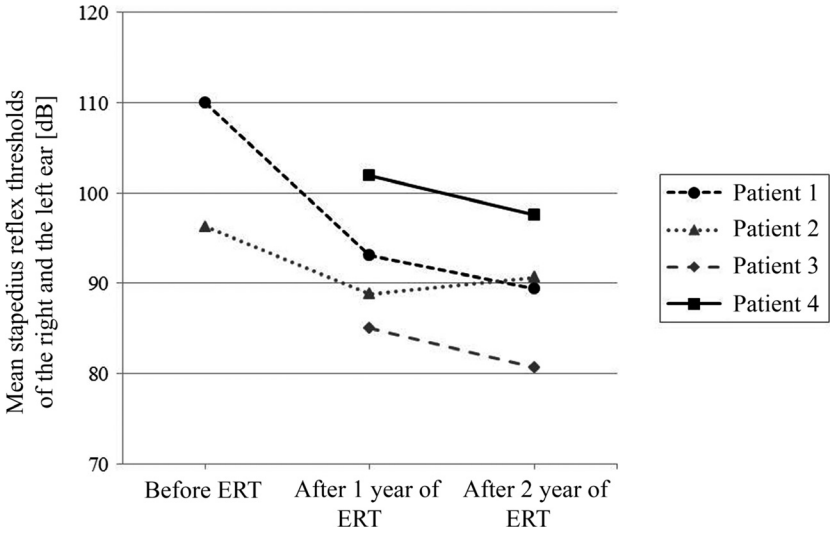

Figure 2. Mean values of ipsilateral left and right ear stapedius reflex thresholds (dB HL), in two late-onset Pompe patients before and 1 and 2 years after onset of biweekly enzyme replacement therapy (ERT) with alglucosidase alfa® (Myozyme™, 20 mg/kg KG, intravenously), and in two patients after 1 and 2 years of biweekly ERT.

previous performance [9]. For FVC, MCID requires 3–9% FCV changes [9]. In our patients, 6MWT and PEF changes after 2 years ERT were below MCID criteria.

Moreover, PEF values varied significantly from one measurement to the next and increased only by 5.9%, 3.5%, and 5.4% after 2 years of ERT, that is, within the intraindividual retest variability.

Furthermore, the results of our "standard" tests were contradictory. In patient 1, PEF values suggested unchanged respiratory function while FVC suggested 26.4% deterioration and 6MWT results suggested 3.3% improvement.

In patient 2, PEF indicated 5.9% respiratory improvement, while FVC values suggested 8.1% deterioration, and MRC sum scores remained almost unchanged after 2 years of ERT. In contrast, SRTs improved after 1 and 2 years of ERT from pretreatment values by almost 9%.

In patient 3, MRC sum scores and FVC suggested slight deterioration, 6MWT results remained unchanged, and PEF values improved after 2 years of ERT.

In patient 4, PEF and FVC values suggested slight improvement, while 6MWT results deteriorated slightly after 2 years of ERT.

Limitations of the 6MWT were evident in our wheelchair bound patient [9].

Conclusions

Our discrepant "standard" test results support concerns regarding the relevance of these tests to determining

Pompe disease progression [9]. Stapedius reflex thresholds more precisely monitored striated muscle improvement after 2 years of ERT, probably because SRTs depend on only a few striated muscle fibers [10].

The Swiss Pompe guideline suggests ERT discontinuation after 12 months if two of three rather subjective tests, 6MWT, cumulative MRC sum scores, and FVC values, deteriorate by more than 10% from pretreatment values [4]. Stapedius reflex testing might add an objective parameter to current standard tests and might thus improve therapeutic decisions of vital relevance.

Although stapedius reflex thresholds do not reflect changes in quality of life, they may provide a more objective measure of ERT efficacy and might thus protect patients against cessation of an expensive though probably still efficient treatment.

In conclusion, our preliminary data suggest that large scale multicenter studies are needed to determine whether the stapedius reflex measurement adds valuable information to existing parameters and thus provides a more objective decision regarding ERT.

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Conflict of Interest

Dr. Hilz receives personal compensation for speaking activities and consulting services and receives research support from Genzyme, a Sanofi Company. Dr. Hoppe, Dr. Moeller, Mr. Wang, and Dr. Koehn report no disclosures.

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