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Extraocular muscle function in adult-onset Pompe disease tested by saccadic eye movements

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Abstract

Glycogen storage disease type II (Pompe disease) affects mainly proximal skeletal muscles. Despite older histological evidence of extraocular muscle involvement, ocular motor palsies or other eye movement abnormalities are not considered part of the clinical picture.

We investigated the dynamics of saccadic eye movements of five patients suffering from late-onset Pompe disease and compared their performance to that of age matched healthy controls. Horizontal rightward and leftward saccades were recorded binocularly, while subjects looked at LED targets placed at ±5°, 10° and 15° eccentricities.

No differences in saccade amplitudes, peak velocities or durations were observed between controls and patients. More specifically, for 5° saccades, patients had a mean peak velocity of 146°/s with duration of 76 ms. For 10° and 15° saccades these values were 258°/s, 86 ms and 324°/s, 101 ms respectively, thereby lying well within one standard deviation of the mean of normal data. Moreover, saccadic amplitude accuracy was also unimpaired.

These results indicate that patients with late onset Pompe disease perform fast and accurate horizontal saccades without evidence of muscle paresis or other ocular motor abnormalities. Reported histological abnormalities of extraocular muscles do not appear to have a phenotypic impact.

Keywords: Pompe disease; Eye movements; Saccades; Extraocular muscles; Neuroophthalmology

1. Introduction

Pompe disease (PD), also known as glycogen storage disease type II or acid maltase deficiency is a progressive muscle disease caused by a deficiency of acid alpha-glucosidase. The underlying mutation on chromosome 17q25 is inherited in an autosomal recessive manner. Although it is considered a rare disease, it is of particular interest recently due to new and emerging treatment possibilities mainly through enzyme replacement therapy [1,2].

Patients present with a broad clinical phenotype exhibiting marked variations in age of onset, organ involvement and prognosis [3,4]. Severe deficiency or complete loss of alpha-glucosidase activity results in the infantile form of PD, which is characterized by marked generalized weakness, hypertrophic cardiomyopathy, respiratory insufficiency and death by 1 year of age. The more benign, late-onset (or adult-onset) form shows a variable age of onset that ranges from early childhood into adulthood. Typically, these patients present with a slowly progressive myopathy affecting the proximal muscles of the pelvic girdle and the torso and, to a lesser

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degree, the shoulder girdle. Respiratory symptoms are the main complication, while the cardiac muscle is usually spared. Although ptosis may occasionally occur, extraocular muscle (EOM) involvement in the sense of a gaze palsy is not considered part of the clinical picture [5,6].

Nonetheless, there are few older and more recent histological findings that argue for the existence of myopathic changes in EOMs in PD. The first report appeared in 1964, presenting light microscopic images of vacuolization and excess glycogen in EOM of an infantile onset patient [7]. A transmission electron microscopy study of a second infantile-onset case was reported in 1972 [8]. This patient showed abundant glycogen in myocytes of the inferior oblique muscle, as well is in endothelial capillary cells and in the adjacent connective tissue. Van Der Walt et al. [9] reported the first autopsy EOM findings of an adult-onset case. Light microscopy of the extraocular muscles showed extensive vacuolization; electron microscopy showed replacement of myofibrils by numerous membrane-bound vacuoles containing glycogen and other structureless material. Most recently, Yanovitch et al. [10] presented histological findings from both an infantile- and an adult-onset patient, making similar observations (e.g., vacuolar myopathy and glycogen accumulation) to the previous reports in the infantile case. The adult-onset Pompe patient, however, had no histological changes in the EOM [10].

Here, we aimed to determine whether there are subclinical ocular motor abnormalities in late-onset PD subjects by analyzing the metrics of horizontal saccadic eye movements to eccentric targets.

2. Methods

Nineteen healthy subjects (12 women, 7 men, age range 29–66 year) without any known neurological or ocular motor abnormalities as well as five patients (3 women, 2 men, age range 33–52 year) with late onset PD were recruited after informed consent. All patients were on enzyme replacement therapy for at least 2.5 years. On examination, they showed a predominately limb-girdle paresis and were categorized as having moderate disease severity on the Walton Scale of Muscle Function (WMF, range 0–7) (Table 1) [11,12]. None of the patients had lid ptosis. Two patients (female 50 and male 45 year-old) were using nocturnal non-invasive ventilation. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Department of Neurology of the University of Athens.

Subjects were seated in a chair in a dimly illuminated room with their head restrained by a forehead-chin headrest. Visual targets were red LEDs mounted on a horizontal bar located 140 cm away from the subject's head. In order to test rightward and leftward horizontal saccades of different amplitudes, one target, the starting position, was always straight ahead (0°), while the other target appeared at ±5°, ±10° or ±15°. Both the straight ahead and the eccentric target were continuously present while subjects were instructed to make saccades between the two LEDs. Subjects were given auditory instructions to execute five saccades for each distance at ~2 s intervals, resulting in 30 saccades (5 saccades × 3 amplitudes × 2 directions). At the beginning of the session, a calibration was performed using targets at 0°, +15° and −15°.

Horizontal eye movements were recorded using an infrared corneal reflection device (IRIS system, Skalar Delft) [13], A/D converted at 500 Hz with 14-bit resolution and a passband extending from dc to 70 Hz. Eye position records were smoothed offline using a 2nd degree, 8 samples, Savitzky–Golay filter and instantaneous velocity was derived thereafter by digitally differentiating the displacement signal. Saccades were detected using a $30°s^{-1}$ criterion and were verified visually by the examiner. Amplitude, duration and peak velocity were determined using a custom-made interactive program (Fig. 1), that extracted peak velocity and saccade duration from the velocity trace and saccade amplitude from the displacement trace. Endpoint accuracy for each target was calculated as the standard deviation of five consecutive saccade amplitudes.

Besides WMF, clinical disease severity was also recorded by means of manual muscle strength testing according to the MRC (Medical Council) scale. A sumscore ranging from 0 to 40 was calculated for each patient by bilateral examination of shoulder abductors, elbow flexors, hip flexors and knee extensors [12].

After testing for normal distribution, *t*-tests were employed for parameter comparisons between patients and controls. Repeated measures ANOVA was applied for within group comparison of saccadic accuracy at different amplitudes. Associations of clinical characteristics (disease severity, muscle strength) and

Table 1
PD patients' demographics and clinical scales. ERT: Enzyme Replacement Therapy, WMF: Walton Scale of Muscle Function, MRC: Medical Research Council scale of muscle strength (sumscore for 8 muscles).

Gender	Age	Disease onset (age in years)	ERT (in years)	WSMF	MRC
M	33	23	4	3.00	26
F	48	43	3	2.50	36
M	45	35	3	3.00	34
F	52	20	5	3.50	22
F	50	15	2.5	3.50	30