SACCADIC EYE MOVEMENTS IN A TYPE 3 GAUCHER'S DISEASE CHILD DURING ENZYME REPLACEMENT THERAPY

A. Accardo*, S. Pensiero**, M.G. Pittis***, G. Ciana***, B. Bembi***, P. Perissutti**

*Department of Electronics (DEEI), University of Trieste, Italy
** Department of Ophthalmology, IRCCS "Burlo Garofolo" of Trieste, Italy
*** Metabolic Diseases Unit, IRCCS "Burlo Garofolo" of Trieste, Italy

accardo@deei.units.it

Abstract: The metabolic Gaucher disease (GD) is sometimes associated with neurological manifestations that involve ocular motor systems. Less severe type of GD (type 1) is treatable with enzyme replacement therapy (ERT) while in neuronopathic forms the efficacy of this therapy is less clear. In order to study the possible effect of ERT on neurological symptoms, we annually recorded the saccadic eye movements in a boy affected by GD3. After a saccadic test was carry out and eye movements were acquired, the saccadic movements were identified and classical parameters, like latencies, amplitude/duration (A/D) and amplitude/peak velocity (A/Vp) relationships, were evaluated. The results show that in this GD3 patient, a high ERT dose at the first neurological symptoms resolved the brain stem manifestations, even if two years of therapy needed. Since the limited success of ERT in reversing the neurological symptoms of GD reflects the poor permeability of the blood-brain barrier or the rapid CNS turnover of this enzyme, a continuous replacement of glucocerebrosidase in the CNS seems necessary for the treatment of neuronopathic GD. Further studies are necessary to evaluate higher ERT dosages and new methods of administration to bypass the brain barrier.

Introduction

Gaucher disease (GD) is an inborn error of metabolism, due to a deficiency of glucocerebrosidase, characterised by parenchymal disease of the liver, spleen, and bone marrow with concomitant anaemia and thrombocytopenia (GD1), sometimes additionally associated with neurological manifestations in the less common GD2 and GD3 forms: the acute neuronopathic GD2 with infantile onset and relentless neurological degeneration leading to death usually by age 2 years, and the subacute GD3 in which neurological involvement has a later onset and a more variable course than GD2.

Detection of ocular motor signs in GD is diagnostic of neuronopathic disease, and in GD3 they may precede the emergence of overt neurological signs by many years. The main sign is severe difficulty (in GD3) or virtually a total inability (in GD2) in generating saccades (saccadic initiation failure, SIF). When saccades can be made, they are usually slow. Therefore, objective ocular motor assessment can improve the detection of GD3 [1].

GD1 is treatable with enzyme replacement therapy (ERT). For neuronopathic GD, the efficacy of ERT is less clear. It may relieve the systemic component of GD2, but does not reverse neurological symptoms [2]. In GD3, reports are inconsistent, with some patients showing some neurological remission and others progression [3, 4].

As already detected in the bone involvement (skeletal responses to treatment develop much more slowly than haematological or visceral responses), ERT could need more time to act also in the nervous cells, so that an improvement could be seen only in GD3, disease more slow than GD2. Moreover, because the effect on the neurological symptoms could be slight and therefore not proved by their regression, objective evaluations should be used. For this purpose we annually recorded the saccadic eye movements in a boy affected by GD3, from the age of 6 to 11 years.

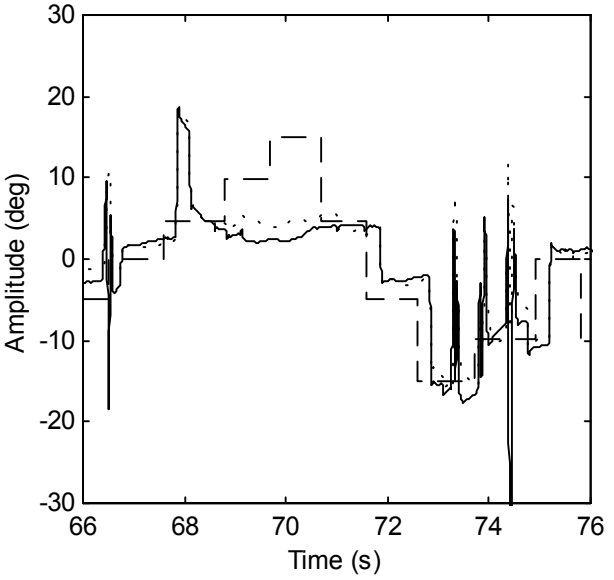

Figure 1: Example of the first eye movement recording showing blinks and SIF in the eye position. Solid line: right eye, dotted line: left eye

ISSN: 1727-1983

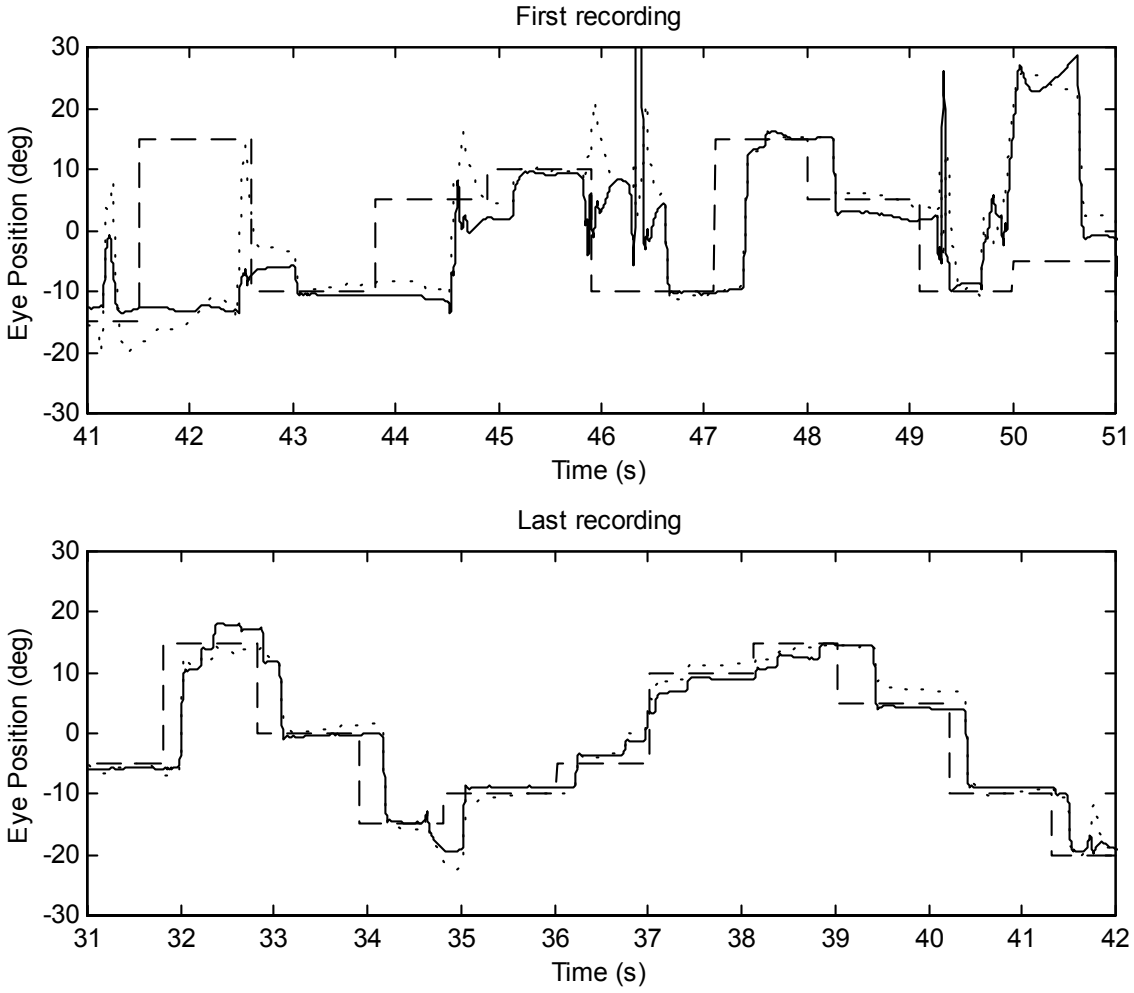

Figure 2: Tracts of the first eye movement recording (A) compared to the last recording, after enzyme replacement therapy (B). Blinks and profile alterations disappeared in the last case. Solid line: right eye, dotted line: left eye, dashed line: target.

Materials and Methods

The patient was a male who presented, at the age of 5 years, splenomegalia and a slight speech lag. A diagnosis of GD was performed (based on measurement of beta-glucocerebrosidase activity in the circulating leukocytes) and an ERT was begun (Cerezyme, 30 U/kg every two weeks). Patient's genotype was P159T/recombinant allele.

A year later he showed some alterations of the saccadic eye movements (see results). Therefore the ERT dose was elevated to 60 U/kg. Eye movements were recorded annually on the occasion of his clinical and laboratory examinations. ERT was maintained at the same dosage.

To carry out the ocular test an infrared bichannel probe based on the "limbus tracking" technique was used. A visual dot stimulus was randomly moved in time and position in a visual range of +/- 15deg with amplitudes of 5, 10 and 15 deg producing a sequence of displacements pursued in binocular vision. From the identified saccadic movements, the amplitude/duration (A/D) and amplitude/peak velocity (A/Vp) characteristics as well as the latencies were evaluated.

Furthermore, alterations in the eye movement velocity profiles such as the presence of intermittent SIF with blinking were investigated.

Results

The analysis of the first eye movement recording (figure 2A) showed a large number of blinks, typical of neuronopathic GD, and some short tracts of SIF (figure 1). Many saccades presented velocity profile irregularities, such as slowing down and oscillations (figure 3). The A/D characteristic showed the highest values among all registrations; also the A/Vp relation presented the lowest peak velocities (figure 4) and the latencies were the largest (257 ± 75 ms).

After the increase of ERT dose, an improvement of saccades was detected in the two successive exams

ISSN: 1727-1983

(figure 2B), then situation appeared constant. SIF was not present any more, blinks were rare, latencies were shorter (202±52 ms), duration decreased and peak velocities were higher (figure 4) than in the first examination. Only some velocity profile irregularities persisted.

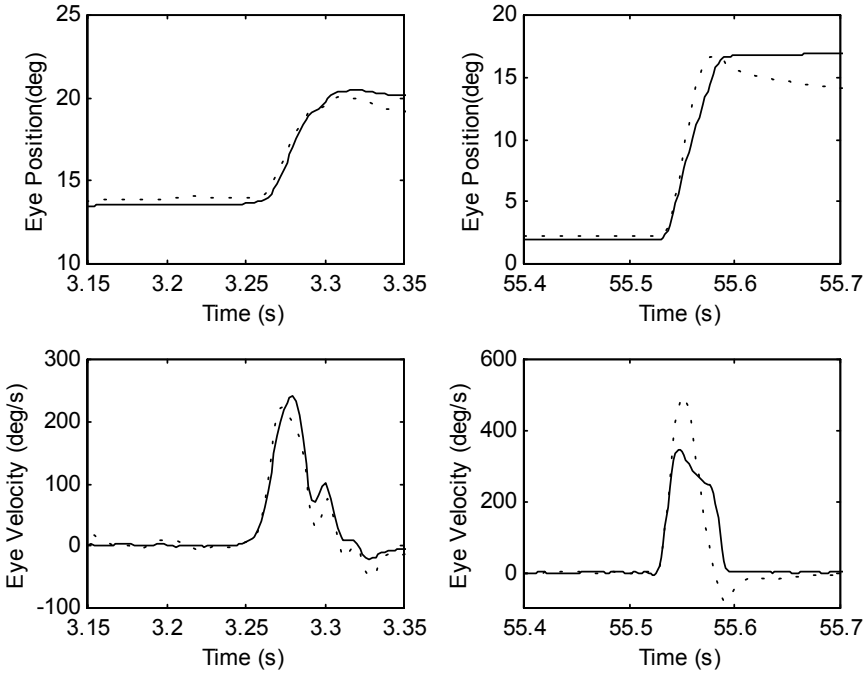

Figure 3: Examples of velocity profile alterations during the first recording. Right eye: solid line, left eye: dashed line.

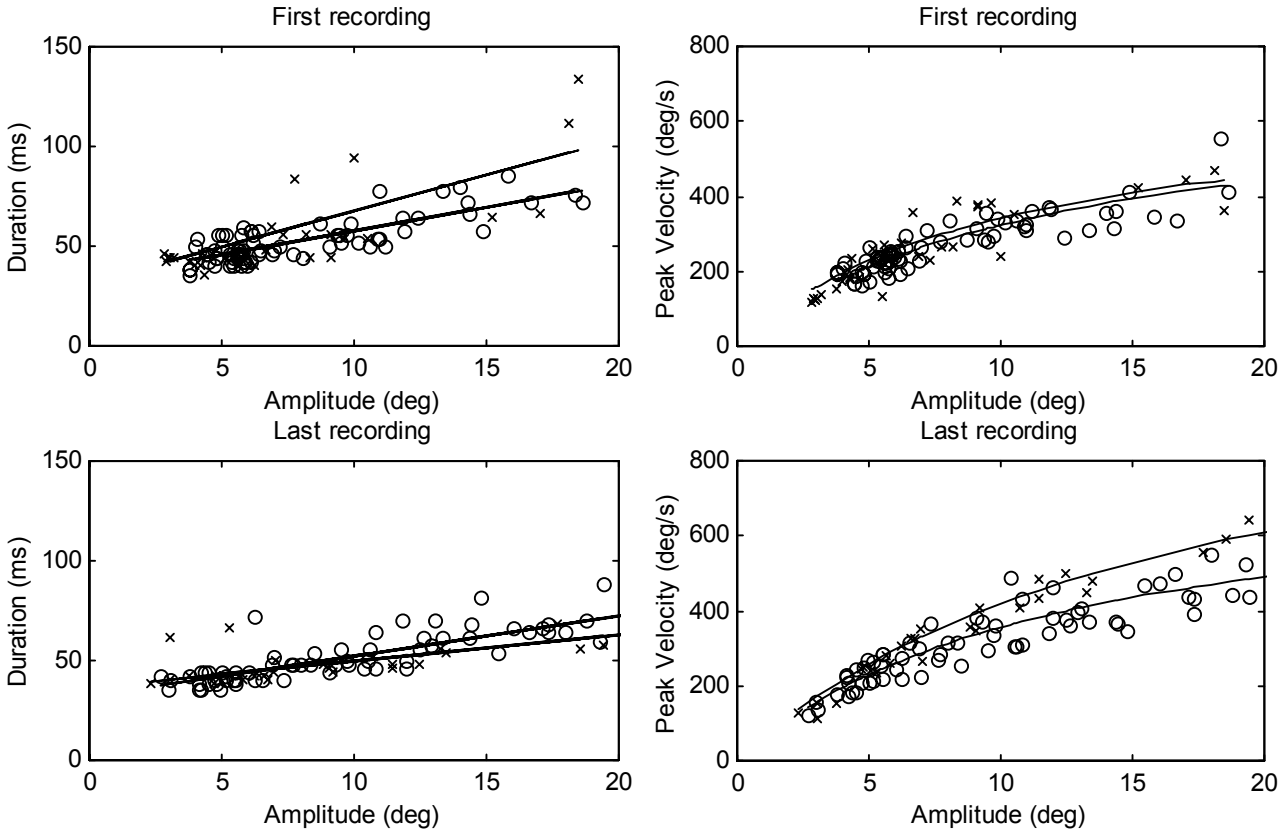

Figure 4: Amplitude/Duration (left) and Amplitude/Peak Velocity (right) relationships at the first (top) and the last (bottom) recording. Circle=right eye, cross=left eye.

ISSN: 1727-1983

Conclusions

The limited effectiveness of ERT in overcoming the neurological symptoms in neuronopathic GD is probably due to a number of factors, among them the lack of permeability of the blood-brain barrier, the relatively rapid turnover of glucocerebrosidase (supplied with ERT) in the CNS [5], and the possible accumulation of other toxic substances, such as glucosylsphingosine [6].

On the contrary, in this GD3 case, where a high dose therapy was carried out at the first neurological symptoms, ERT was able to reduce the manifestations consequent to brain stem involvement, but this effect was not immediate but needed of two years of therapy.

Therefore, continuous replacement of glucocerebrosidase in the CNS is necessary for the treatment of neuronopathic GD. Further studies are necessary to evaluate higher ERT dosages and new methods of administration to by-pass the brain barrier.

References

[1] HARRIS CM, TAYLOR DS, VELLODI A., (1999): 'Ocular motor abnormalities in Gaucher disease. '*Neuropediatrics*. 1999; 30: pp. 289-293

[2] GERMAIN DP., (2004): 'Gaucher disease: clinical, genetic and therapeutic aspects.' *Pathol Biol (Paris)*. 2004; 52(6): pp. 343-350

[3] ALTARESCU G, HILL S, WIGGS E, JEFFRIES N, KREPS C, PARKER CC, BRADY RO, BARTON NW, SCHIFFMANN R., (2001): 'The efficacy of enzyme replacement therapy in patients with chronic neuronophatic Gaucher's disease.' *J Pediatrics*. 2001; 138: pp. 539-547

[4] CAMPBELL PE, HARRIS CM, VELLODI A., (2004): 'Deterioration of the auditory brainstem response in children with type 3 Gaucher disease.' *Neurology*. 2004; 63(2): pp. 385-387

[5] MIGITA M, SHIMADA T, HAYAKAWA J et al., (2003): 'Home treatment with enzyme replacement therapy in a 5-yearold girl with type 2 Gaucher disease.' *Pediatr Int* 2003; 45: pp. 363-365

[6] ORVISKY E, SIDRANSKY E, MCKINNEY CE, LAMARCA ME, SAMIMI R, KRASNEWICH D, MARTIN BM, GINNS EI., (2000): 'Glucosylsphingosine accumulation in mice and patients with type 2 Gaucher disease begins early in gestation.' *Pediatr Res*. 2000; 48: pp. 233-237

ISSN: 1727-1983