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Letter to the Editor

Eye movement changes in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

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1. Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disease due to *ECGF1* gene mutations (chromosome 22) causing multiple deletions and depletion of mitochondrial DNA in skeletal muscle. The determination of the activity of the gene-product tymidine phosphorylase (TP) in leukocytes and genetic analysis are diagnostic. External ophthalmoplegia, severe gastrointestinal dysmotility, cachexia, peripheral sensory-motor neuropathy, diffuse myopathy and leukoencephalopathy are typical findings. The severe disease progression leads to death in a few years [1]. Allogeneic hematopoietic stem cell transplantation (HSCT) may restore enzymatic levels improving the clinical outcome [2].

Extraocular muscles (EOMs), fast and fatigue resistant, are affected early in MNGIE, as in other mitochondrial diseases, and their dysfunction parallels the disease evolution. This vulnerability is due to their higher mitochondrial content and metabolic rate than limb skeletal muscles, implying a particular dependence on oxidative phosphorylation and a selective vulnerability to respiratory chain dysfunctions. Moreover, EOMs are functionally divided in the orbital and global layers, containing muscle fibers with unique structural and functional properties that may make them differently susceptible to the mitochondrial failure [3].Their recruitment appear to reflect their fatigability, being the fast but low fatigue resistant fibers of the orbital layer activated mainly during saccades [4].

These changes may be quantified by the analysis of the dynamic properties of saccades, which therefore could provide a reliable and reproducible clinical assessment and follow-up in MNGIE and other mitochondrial disorders.

2. Case report

We describe the saccadic features of two patients affected by MNGIE: patient 1 (P1, 27 years old) with juvenile onset and rapid evolution who received HSCT at 23 years [5] and patient 2 (P2, 47 years old), late onset and severe course, who was waiting for transplant. P2 presented with a typical phenotype and analysis for TP revealed a homozygous A to C transition in exon 7 (A3371C). P1 instead, carrying a homozygous c.1249dupC mutation of TP, improved clinically after transplant and restored enzyme activity to normal levels [5]. Patient's information and data acquisition were collected under the approval of the local ethical committee. Informant consent was obtained from each patient.

Horizontal visually guided saccades were recorded at 10° and 18° of eccentricity. Detailed methods of signal processing and saccade analysis have been reported elsewhere [6]. Saccadic parameters were compared separately with a control group of 25 healthy subjects (11 males, 14 females) of mean age 43.2 years (range 30–68 years) (see ref. [6] for details).

Both patients showed slow and hypometric saccades (Fig. 1A–C) as demonstrated by a significant reduction ($p < 0.001$) of peak velocity (P1, 10°:241 ± 48°/s, 18°:324 ± 69°/s; P2, 10°:165 ± 56°/s, 18°:213 ± 73°/s) and amplitude (P1, 10°:8.3 ± 1.7°, 18°:17.6 ± 2.1°; P2, 10°:6.7 ± 2.5°, 18°:9.8 ± 5.1°) compared to controls (10°:383 ± 65°/s; 18°:498 ± 85°/s and 10°:10.2 ± 1.1°; 18°:18.1 ± 1.7°, respectively). Particularly, P1 showed fragmented trend especially in saccades to far targets (18°), with greater speed and accuracy respect to P2, which often failed to reach the target and showed saccades with increased duration and low speed. These very slow saccades often showed an interruption of the velocity profile (camel-hump profile) (Fig. 1A, B).

A peculiar saccadic behavior resulted from comparing adducting and abducting saccadic parameters in our patients (Fig. 1D–E). Indeed, for larger saccades, we found faster adducting than abducting saccades in P2, with a greater loss of accuracy: peak velocity at 18° was 240 ± 84°/s adducting vs 197 ± 61°/s abducting ($p < 0.001$); error in accuracy was 10.5 ± 3.3°adducting vs 8 ± 5.5°abducting ($p < 0.001$). Conversely, P1 showed faster abducting than adducting saccades: peak velocity at 10° was 219 ± 42°/s adducting vs 255 ± 48°/s abducting ($p < 0.001$); at 18°:271 ± 45°/s adducting vs 370 ± 51°/s abducting ($p < 0.005$).

3. Discussion

Both patients showed hypometric and low speed saccades compared to controls, particularly for larger movements, reflecting a global EOMs muscle weakness due to severe mitochondrial myopathy.

Moreover, the saccadic profile of the transplanted patient was greater than that of the untreated patient. Indeed P1, despite slow and hypometric saccades (multi-step pattern), satisfied the mean sequence relationship between speed and amplitude (Fig. 1A and C). Moreover, as reported in normal subjects [6], her abducting saccades were faster than adducting.

P2, instead, showed extremely slow and hypometric saccades not fulfilling the mean sequence, and abducting saccades were severely compromised so adducting saccades were faster. Differences in residual enzymatic activity and disease severity may explain the different velocity and amplitude profiles of saccades between the two patients. However, it does not completely clarify the diverse adducting and abducting saccadic behavior.

A possible explanation of this difference may be the uneven dissemination of the mutated mitochondria in lateral vs medial recti fibers based on their random duplication or a diverse genetic expression [4].

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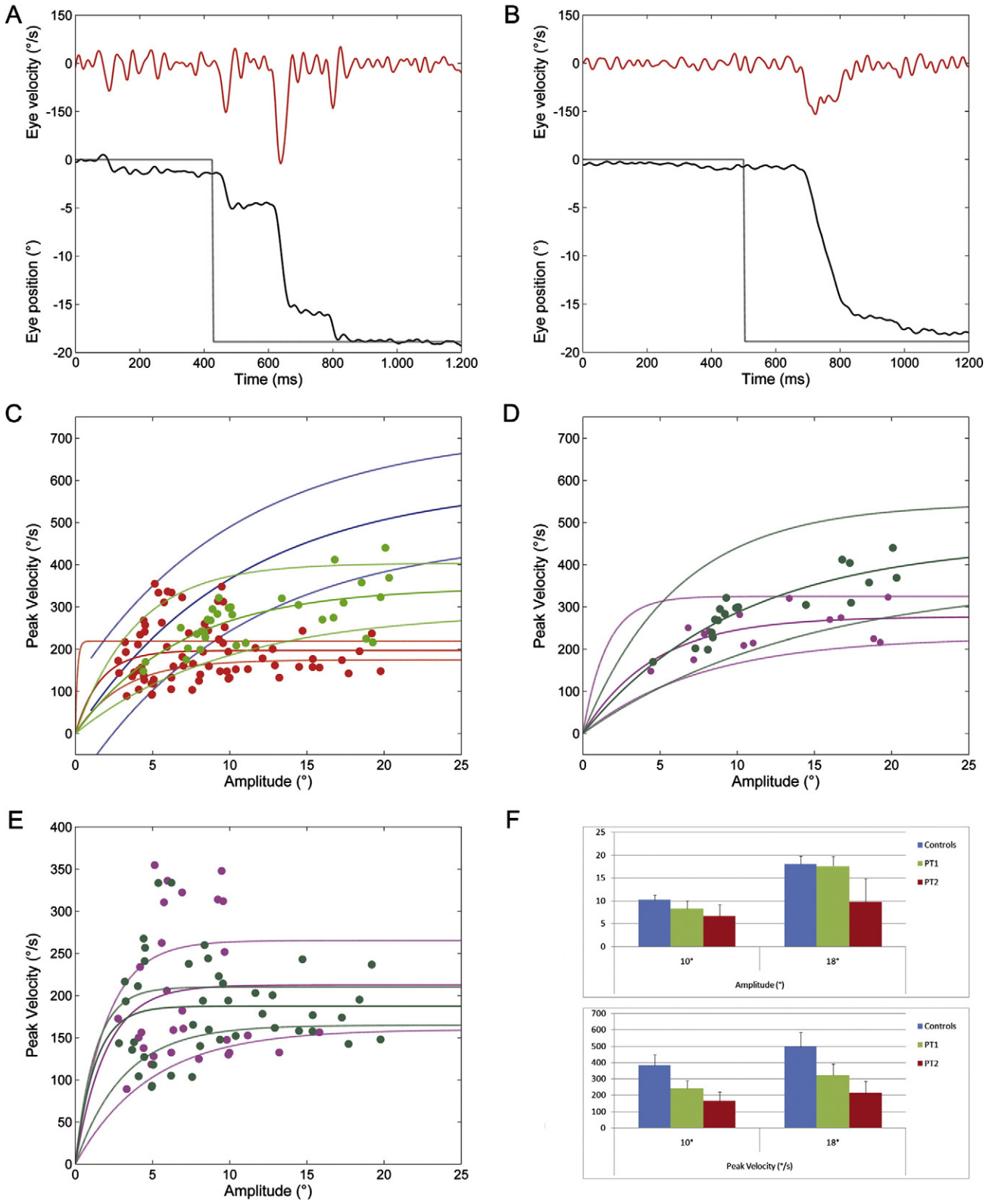

Fig. 1. The Fig. 1 shows an example of 18° horizontal saccade of patient 1(A) and patient 2 (B). Panels C–E illustrate the main sequence relationships of peak velocity versus amplitude. The data point (C) are saccades of patient 1 (light green circle) and patient 2 (red circle). Saccades of patient 1, in abduction, are represented by dark green circle and those in adduction by fuchsia circle (D). The saccades of patient 2 in abduction are depicted by circle dark green and adduction by fuchsia circle (E). The graph-bar shows the peak velocity and amplitude values of the MNGIE patients in respect to controls (F).

Another possibility is the different distribution and susceptibility to fatigue of fiber subgroups in lateral versus medial recti. EOMs contain about 90% of fast-twitch single-innervation fibers (SIFs) with high mitochondrial content and resistance to fatigue. However, while orbital layer contains only fatigue resistant SIFs, the global layer contains fast-twitch fibers with different degrees of fatigue resistance, and very fast but rapidly fatigable pale fibers recruited during saccades [7–9]. Both layers are activated during saccades; the orbital, more fatigue resistant,

ensures a more sustained contraction in larger movements [9,10]. The medial recti, responsible of adduction, are thicker and have a higher percentage of orbital fast-twitch fibers than the lateral recti, responsible of abduction [9,10]. These structural differences may possibly have a dynamic counterpart as observed in our patients [3,7,8]. Data from a larger number of patients could confirm and better elucidate this specific behavior.

In conclusion, the saccadic profile may provide a reliable measure of muscle dysfunction. Low-speed and short saccades, particularly in abduction, reflect a clinically severe mitochondrial involvement, while multistep, normal speed saccades with well-preserved abduction indicate a more efficient aerobic muscle activity. In this respect, analysis of adducting and abducting saccades may have a clinical relevance in the differential diagnosis with other ophthalmoparesis or myasthenia usually affecting adduction more than abduction and adding further insight into pathophysiology of EOMs susceptibility to energy deprivation due to muscle damage.

Eye movements recorded through an eye-tracking technique is an easily repeatable and noninvasive tool that can help in diagnosis, follow-up and evaluation of the response to treatment in various mitochondrial myopathies, such as MNGIE.

Conflict of interest

All authors declare no conflict of interest.

Acknowledgments

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Claudia Vinciguerra
Eye-tracking and Visual Application Lab (EVALab), University of Siena, Italy
Neurometabolic Unit Department of Medicine, Surgery and Neurosciences, University of Siena, Italy

Pamela Federighi
Eye-tracking and Visual Application Lab (EVALab), University of Siena, Italy

Francesca Rosini
Elena Pretegiani
Eye-tracking and Visual Application Lab (EVALab), University of Siena, Italy
Neurometabolic Unit Department of Medicine, Surgery and Neurosciences, University of Siena, Italy

Elena Cardaioli
Maria T. Dotti
Francesco Sicurelli
Antonio Federico
Neurometabolic Unit Department of Medicine, Surgery and Neurosciences, University of Siena, Italy

Alessandra Rufa
Eye-tracking and Visual Application Lab (EVALab), University of Siena, Italy
Neurometabolic Unit Department of Medicine, Surgery and Neurosciences, University of Siena, Italy
Corresponding author at: University of Siena, viale Bracci 2, Policlinico Santa Maria alle Scotte, Siena, Italy.
Tel.: +39 0577233136; fax: +39 057740327.
E-mail address: rufa@unisi.it.

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