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QUANTITATIVE EYE MOVEMENT ANALYSIS IN MACHADO-JOSEPH DISEASE PATIENTS

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TRABALHO FINAL DO 6º ANO MÉDICO TENDO EM VISTA A ATRIBUIÇÃO DO GRAU DE MESTRE NO ÂMBITO DO CICLO DE ESTUDOS DE MESTRADO INTEGRADO EM MEDICINA

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ABSTRACT

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is the most worldwide known SCA. MJD is characterized by progressive deterioration of cerebellar, pyramidal, extrapyramidal, motor neuron and ocular motor systems. Ocular motor manifestations constitute early findings in the disease process.

The main goal of this work was to describe and analyze eye movement abnormalities in a large cohort of MJD patients. We studied 38 MJD patients (24 females) and 22 controls (12 females). All participants underwent detailed video-oculographic analysis, including eccentric gaze, smooth pursuit, saccades, optokinetic response (OKR) and vestibulo-ocular reflex (VOR). Ocular motor data in MJD patients was compared with that of controls and further correlated with motor disability using Scale for the Assessment and Rating of Ataxia (SARA), disease duration and number of CAG repeats.

MJD patients showed lower smooth pursuit, OKR and VOR gain than controls. Saccade velocity was significantly higher in patients. SARA score positively correlated with intensity of eccentric nystagmus and negatively correlated with VOR and OKR gain. Number of CAG repeats negatively correlated with VOR and OKR gain. Disease duration negatively correlated with OKR gain.

We show in a large sample of MJD patients that OKR, VOR and pursuit gain, together with saccade velocity are strong markers of disease, genetic status and progression in MJD.

KEY WORDS

Machado-Joseph disease, Spinocerebellar ataxia type 3, Oculomotor movements, Video-oculography.

INTRODUCTION

Spinocerebellar ataxias (SCAs) are a group of inherited degenerative diseases, which are classified according to the clinical features and genetic locus of the mutation. Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is the most worldwide known SCA.(1–3) This disease is caused by an abnormal CAG trinucleotide expansion on the ATXN3 gene, a mutation that leads to a polyglutamine (polyQ) expansion in the gene product, conferring it a toxic gain of function. There is a well-known correlation between age at onset of gait ataxia and CAG repeat. (3) The average onset is adulthood (around 40 years)(4) and the global prevalence of SCA is 3 in 100,000. (5) Portugal population-based prevalence is similar to the global prevalence, although there are specific high prevalence regions, as in some Azorean islands. (835.2:100,000 in Flores, and 27.1:100,000 in São Miguel)(6)

MJD is characterized by progressive deterioration of cerebellar, pyramidal, extrapyramidal, motor neuron and oculomotor systems which gives rise to a large phenotypic variation. (2,7) Clinical presentation, severity and progression velocity is also directly related to the CAG expansion length, being earlier, more severe and rapidly progressive with larger repeats. (8) Although classical hallmarks are limb and gait ataxia, ocular motor manifestations are early and relevant findings. The main objective of oculomotor system is to bring new visual targets to the fovea or to maintain and stabilize images of interest. The saccadic, pursuit and vestibular systems, among others, are crucial to achieve this goal. (9) These systems are mainly controlled by neuronal subsets within the cerebellum and brainstem, which are greatly affected in MJD. (9) Oculomotor findings in MJD are diverse and include: gaze-evoked nystagmus (GEN), increased square-wave jerks (SWJ), decreased smooth pursuit, vestibulo-ocular reflex (VOR) and optokinetic response (OKR) gains, as well as dysmetric (hyper- or hypometric) and slow saccades.(10–12) Disease severity and progression in MJD and in most SCAs is usually assessed using SARA (Scale for the Assessment and Rating of Ataxia) score.(13) Some authors have suggested that oculomotor features in MJD could portrait a disease biomarker and may also correlate with disease progression severity. (2,3)

The goal of this work was to describe and analyze eye movement abnormalities in a large cohort of MJD patients, using contemporary oculomotor and vestibular assessment methods, and to correlate these findings with patient characteristics, including disease severity, number of CAG repeats, cognitive status and disease duration, in order to ascertain eye movements assessment's role as a marker of MJD.

METHODS

Participants

For our observational study, we recruited genetically-proven MJD patients above 18 years old from the Neurogenetics Clinic of Coimbra University Hospital Centre, Portugal, using the following exclusion criteria: a structural lesion in the cerebellum or brainstem on imaging; history of previous ocular motor and/or vestibular disorder unrelated to MJD; unable to perform ocular motor assessment. Thirty-eight patients (63% (n=24) females; mean age±SD, 49.8±12.2 years) were included. Additionally, twenty-two age- and sex-matched healthy controls (54.5% (n=12) females; mean age±SD, 50.7±12.5 years) were recruited from our hospital service.

Study protocol was submitted and approved by our Ethics Hospital Committee (CHUC-132-16). Before the examination a written informed consent was obtain from all participants in accordance to the Declaration of Helsinki.

Clinical Assessment

All patients were interviewed and examined by experienced movement disorders neurologists, following a pre-established protocol. Demographic data such as gender, age, first symptom, disease duration (i.e., time passed between the age at first symptom and the clinical assessment) and number of CAG repeats were collected. Scale for the Assessment and Rating of Ataxia (SARA) was used to measure the severity of ataxia(4) and the Montreal Cognitive Assessment (MoCA) (14) was used to evaluate cognitive performance in suitable patients. Although three patients were preclinical asymptomatic carriers (SARA score = 0), they were included, since oculomotor deficits might be present at this stage. (4)

After this initial evaluation, all participants underwent Video-Oculography.

Video-Oculography

Participants were seated on a chair facing the center of a wall-projected screen, at a viewing distance of 1.5 meters, with their head manually restrained. Eye movements were recorded using a binocular video-oculography (Interacoustics VO425, Assen, Denmark; 105Hz), with every session starting with a 5-point calibration procedure.

The oculomotor exam included smooth pursuit (participants needed to follow a target moving sinusoidally 60° at 10°/s for 60 seconds), eccentric gaze (30s fixation of a target located ±30° horizontally for each side), OKR (participants looked straight ahead at vertical black stripes spaced at 15° intervals and rotating at 20°/sec to each side for 30 sec) and saccades evaluation (rapid fixation of a randomly target appearing between 5° and 30° for 120 seconds). Monocular video-oculography, using EyeSeeCam, Munich, Germany (250Hz), was used for

evaluating VOR during high acceleration head rotations maneuver (participant's head was briskly moved in the maximally-excitatory direction for each horizontal semicircular canal plane by the examiner while fixating a 1.5- meter distance target, twenty valid trials were performed for each side).

Statistical analysis

Oculomotor variables, calculated by built-in software, included GEN slow phase velocity (SPV); pursuit gain (i.e., eye/target mean velocity∗100%); OKR SPV; saccade latency (i.e., time [ms] between onset of the target and the start of the saccade), gain (i.e., saccade/target amplitude∗100%) and average velocity (i.e., eye velocity between saccade onset [velocity increase above 10% of the peak velocity] and offset [velocity decrease below 10% of the peak velocity]), and VOR gain (eye velocity divided by head velocity at 60 milliseconds).

The Shapiro-Wilk test was used to test normality. Non-parametric tests were chosen to avoid type I error. To compare between-groups, Mann-Whitney and Chi-square were used. Spearman univariate regression analysis was used to evaluate the relationship between oculomotor variables and MoCA, SARA score, CAG repeat number, and disease duration, controlling for age. The Bonferroni method for correcting multiple comparisons was used to calculate the p value, which was set at 0.007 for between-groups analysis and 0.001 for correlation analysis.

RESULTS

Baseline characteristics

Table 1 summarizes the demographic data on our participants. The most frequent presenting symptom was imbalance (n=30; 78,9%) and the second most frequent was diplopia (n=3; 7.9%), and then there were other less common presenting symptoms including dysphagia and dysarthria.

Table 1. Demographic data.

	SCA3 (n=38)	Controls (n=22)
Age (mean±SD)	49.9±12.3	50.8±12.5
Sex (female [%])	24 (63%)	12 (54.5%)
Disease duration (mean±SD)	7.5±5.7	NA
CAG repeats (mean±SD)	70.6±4.6	NA
Sara Score (mean±SD)	9.4±7.1	NA
Presenting symptom		
Imbalance n(%)	30(78.9%)	NA
Diplopia n(%)	3(7.9%)	NA
Dysarthria n(%)	1(2.6%)	NA
Dysphagia n(%)	1(2.6%)	NA

No., Number; SD, Standard deviation; SCA3, Spinocerebellar ataxia type 3; NA, Not applicable

Ocular motor data

The majority of patients presented GEN (n=30, 78.9%) and this was absent in all controls (mean SPV 3.8±4.2 *vs* 0, $p<0.001$). Patients showed significantly lower smooth pursuit gain and lower OKR SPV than controls, (mean gain 78.9±11.5 *vs* 90.3±4.2, $p<0.001$; mean SPV 10.9±4.9 *vs* 17.0±2.4, $p<0.001$, respectively). Saccade velocity was significantly higher in patients (mean velocity 474.5±81.3 *vs* 417.9±45.2, $p=0.004$). There was a tendency for lower saccade gain in patients (mean gain 89.1±13.1 *vs* 93.2±3.8, $p=0.08$). No difference was found in saccade latency between groups (mean latency 230.6±44.2 *vs* 213.1±32.7, $p=0.158$). VOR gain was significantly decreased in patients when compared to controls (mean gain 0.7±0.3 *vs* 1.0±0.1, $p<0.001$).

Correlation analysis

In correlation analysis, SARA score positively correlated with disease duration (R= 0.600, p<0.001). SARA score also positively correlated with mean GEN SPV and negatively correlated mean VOR gain and mean OKN SPV (R=0.728, p<0.001; R=-0.648, p<0.001; R=-0.643, p<0.001, respectively). Number of CAG repeats also negatively correlated with VOR gain and OKN SPV (R=-0.577, p<0.001; R=-0.576, p<0.001, respectively), while disease

duration negatively correlated with OKN SPV (R=-0.542, p=0.001). Figure 1 shows all the significant correlations. We also found a few near-significant correlations between: VOR gain and disease duration (R=-0.461, p=0.004); GEN and number of CAG repeats (R=0.447, p=0.006) and pursuit gain and disease duration (R= -0.437, p=0.007). Saccades' latency, velocity and gain did not show any correlations with SARA score, disease duration nor number of CAG repeats. MoCA scale did not correlate with any of the oculomotor parameters.

Table 2. Oculomotor data.

	SCA3 (n=38)	Controls (n=22)	*p-value* (Patients vs Controls)
GEN (mean± SD)	3.8 ± 4.2	-	<0.001
OKN SPV (mean± SD)	10.9 ± 4.9	17.0 ± 2.4	<0.001
Pursuit gain (mean± SD)	78.9 ± 11.5	90.3 ± 4.2	<0.001
Saccade latency (mean± SD)	230.5 ± 44.2	213.1 ± 32.7	0.158
Saccade velocity (mean± SD)	474.5 ± 81.3	417.9 ± 45.2	0.004
Saccade gain (mean± SD)	89.1 ± 13.0	93.2 ± 3.8	0.08
VOR gain (mean± SD)	0.7 ± 0.3	1.0 ± 0.1	<0.001

SCA 3, Spinocerebellar ataxia type 3; SD, Standard deviation; OKN SPV, Optokinetic nystagmus slow phase velocity; GEN, Gaze evoked nystagmus; VOR, Vestibulo-ocular reflex

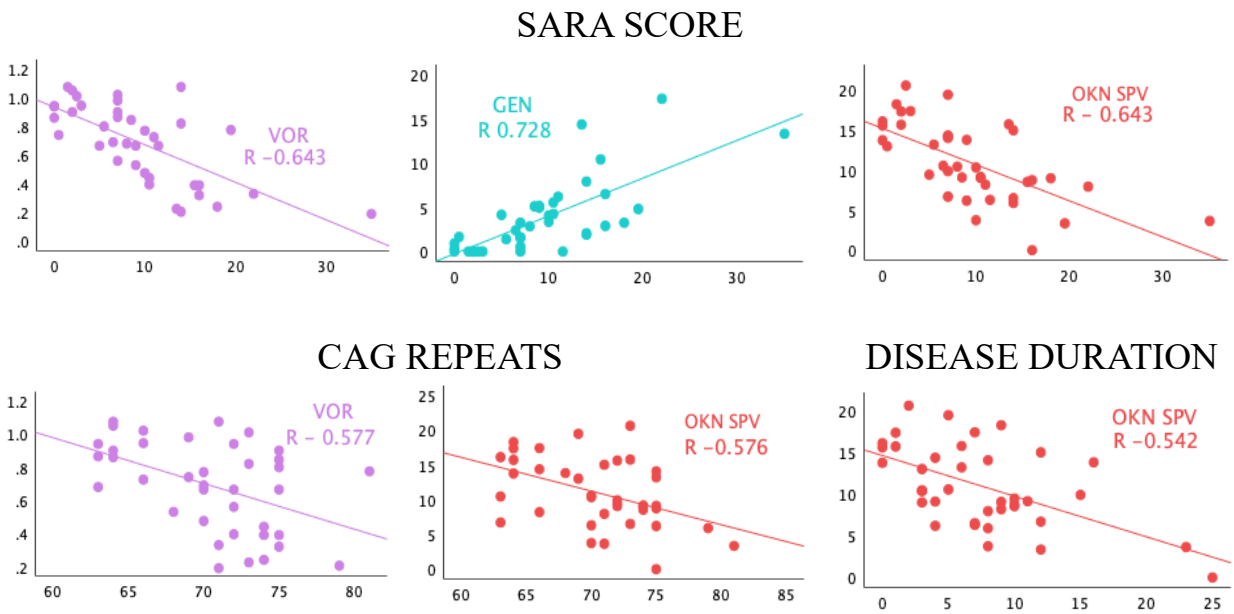

Figure 1. Correlation analysis.

OKN SPV, Optokinetic nystagmus slow phase velocity; GEN, Gaze evoked nystagmus; VOR, Vestibulo-ocular reflex

DISCUSSION

In this work, we reported detailed ocular motor features of a large cohort of Portuguese MJD patients, which significantly differed from a healthy control group. We could also establish significant correlations between these oculomotor characteristics and clinical and genetic status.

Diplopia was the presenting symptom in around 10% of our patients, only surpassed by ataxia, which is similar with previous reports. (15)

Previously, detailed ocular motor analysis has been reported only in small samples of MJD patients, (n=7 in (16) and n=3 in (17), while we reported data in a group of 38 MJD patients. Moreover, our MJD group spans a wide spectrum of disease duration (0 up to 25 years), motor status (accessed by SARA score, 0 up to 35), making our sample data more representative of MJD spectrum. Importantly, ocular motor assessment was still possible to perform in patients with severe and longstanding disease in our series, given its non-invasiveness and easiness to apply, emphasizing the potential use of eye movement analysis as a biomarker in patients with neurodegenerative diseases.

Gaze evoked nystagmus was almost universally present in our patients' sample. The presence of GEN reflects dysfunction in the integrator system, suggesting the involvement of cerebellar flocculus/paraflocculus (cFL/PFL) in MJD, a key structure that improves the neural integrator function by providing a feedback loop that converts the velocity signal of an eye movement to

a position command.(9,18) Previous studies, reported GEN in 81.8% (19) and 98% (20) of the MJD patientes, supporting cFL/PFL degeneration in MJD. While prevalent in MJD, and therefore a biomarker of the disease when differentiating from normal controls, GEN is also highly prevalent in several other SCAs (11,16,20) making it a less specific biomarker among SCAs.

MJD patients also showed decomposed ocular smooth pursuit. Schöls et al. described the same finding in 94% of the MJD patients. (20) Similarly to GEN, it points to a cFL/PFL dysfunction. Still, additional pontine degeneration involving nucleus reticularis tegmentum pontis (NRTP) might also partially explain pursuit deficits, since lesions of NRTP can impair not only the accuracy of horizontal saccades but also of horizontal smooth pursuit. (21,22) Moreover, lesions in NRTP seem to equally explain decreased optokinetic response in MJD patients (20,23) as reported in this study. Optokinetic nystagmus is a physiological oculomotor reflex that contributes to the stabilization of retina images(24). There is however a general lack on the pathophysiology of decreased OKR in MJD.

We also studied the velocity, latency, and gain of horizontal saccades. Information on literature regarding abnormalities of saccades' velocity in MJD is controversial, and indeed there are reports showing non-significant changes between MJD patients and healthy individuals (16), while others found saccade abnormalities in MJD. Burk et al. reported mild reduction of velocity in near one third of the studied patients. (7) Rosini et al. found that saccade velocity, although unusual, could be decreased, but it could also be normal or even increased. (11,17) Caspi et al. tried to explain this discrepancy by suggesting that a single oculomotor deficit can explain two apparently contrasting abnormalities, i.e.., slow saccades and the presence of dynamic overshooting. It was proposed that saccades' system uses velocity feedback and no matter the abnormality, all the MJD patients have a common damage in the dorsal oculomotor vermis (OMV, lobules V-VII), which leads to velocity feedback impairment. (25) In accordance with previous reports, in our study saccade velocity was higher in patients, which nevertheless also suggests a velocity feedback impairment. Regarding saccade gain, dysmetric saccades, mostly hypermetric saccades, have been widely described in MJD patients, favoring fastigial nucleus involvement. (16,19) We did not observe such finding in the current series. In contrast, there was a tendency for saccades to be hypometric, supporting OMV involvement instead (see above). There are no significant abnormalities reported in saccade latency, supporting relative sparing of cortical and subcortical structures, at least during initial stages of the disease. (16,22) Cerebellum has a pivotal role in keeping ocular motor responses calibrated correctly. OMV and fastigial nuclei are important in the control of saccade amplitude and direction, debated above. (11,18,25) Already cerebellar dentate nuclei seem to be responsible for further controlling saccades' latency (11), which also seems to be spared, according to our findings. (21)

VOR gain was significantly decreased in MJD patients, in accordance to previous reports which found early vestibular involvement in this disease. (2,22) Unlike GEN, poor VOR gains are less common in other SCAs , which make this feature more specific of MJD. (16)
GEN, VOR and OKR correlated with SARA score. SARA score is a tool for assessing ataxia, it is made up of 8 items related to motor disfunction and its score can range from 0 to 40, being 40 the most severe ataxia. (3) Specifically, the more severe the ataxia is the more intense will the eccentric nystagmus be, and the lower will VOR and OKR gains be. VOR and OKR also correlated negatively with the number of CAG repeats, meaning that a larger number of CAG repeats is associated with a worse response of both VOR and OKR. Disease duration correlated negatively with OKR, meaning that a longer course of the disease is associated with a poor optokinetic response. We also had a series of near significant correlations that should be further addressed in future studies. Overall, these findings prove that ocular motor abnormalities are highly prevalent in MJD and these should be considered as potential monitoring agents of the progression of the disease in future clinical trials, which so far is accomplished by using SARA. There are other scales including ICARS (International Co-Operative Ataxia Rating Scale), which has a subscale that measures ocular motor dysfunction (ICARS-OD) based on severity of nystagmus, ocular pursuit, and saccades, but it has limited use due to its many assessment items. (26) Finally, Seshagiri et al. suggests that OKR and saccades are the parameters which better quantify oculomotor dysfunction in SCAs. (23) In the present work OKR was indeed the only parameter correlating with disease duration.

CONCLUSION

Several eye movement abnormalities seem to constitute potential clinical, genetic and progression markers in MJD. Their inclusion as a secondary outcome in future therapeutic trials in MJD should be considered.

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