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CLINICAL SCALES AND VESTIBULO-OCULAR REFLEX AS BIOMARKERS OF PRE-CLINICAL STAGES IN MACHADO-JOSEPH DISEASE/SPINOCEREBELLAR ATAXIA TYPE 3 (BIGPRO STUDY)

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BACKGROUND

Spinocerebellar Ataxia Type 3/Machado-Joseph Disease (SCA3/MJD) is an autosomal dominant disorder caused by a CAG repeat expansion (CAGexp) at the ATXN3. Causal treatment is not available yet. During the recent years, promising progress has been made in the understanding the pathogenesis. Since a causal therapy will be more efficient if starting early in life, reliable biomarkers for pre-clinical phases are needed. BIGPRO (Biomarkers and genetic modifiers in a study of presymptomatic and symptomatic SCA3/MJD carriers) is a longitudinal study aiming to validate biomarkers for disease progression in SCA3/MJD since pre-clinical periods (bigpro.webnode.com). Vestibulo-ocular reflex (VOR) alterations is one of them. VOR stabilizes images on the retinas (when gaze is held steady on a location) during head movement by producing eye movements in the direction opposite to head movement, thus preserving the image on the center of the visual field(s)

AIM: to report baseline findings obtained from clinical scales and VOR parameters registered by video-oculography.

METHODS

Baseline data were collected from 30 symptomatic and 59 at 50% risk SCA3/MJD subjects. Genetic tests performed in at risk subjects were double-blind. For presymptomatic carriers, time left until the onset of gait ataxia was estimated by their CAGexp and was called “time to onset”; they were classified as far from (AFF) or near (AN) (4 years or less) the predicted age at onset (AO). Time to/time after onset (TtoAfterOnset) was the dimension of time to all SCA3/MJD carriers. SARA, SCAFI, NESSCA and INAScount were obtained.

VOR was measured by video-oculography (EyeSeeCam): the average gain observed at 60ms from the start of the head impulse (VOR60) was considered. Bonferroni corrections was used; different letters mean pairwise significances.

RESULTS

Table 1 describes the present cohort. CAGexp and TtoAfterOnset of 30 symptomatic, 13 AN and 24 AFF were respectively 75.40 (3.06), 77.00 (3.19) and 74.21 (2.38) repeats (ns); 4.5 (0 to 8), -4.85 (-6 to -4) and -14.46 (-29 to -7) years.

Table 1 – Overall characteristics of BIGPRO cohort

	Symptomatic carriers	AN	AFF	Related controls	p
Males/total (%)	19/36 (52.8%)	6/13 (46.2%)	10/24 (41.7%)	8/22 (36.4%)	0.647†
Age at evaluation (years)	41.08 (9.71)[a]	33.31 (9.25)[b]	27.17 (5.54)[b]	31.32 (9.44)[b]	<0.001††
CAG repeat larger allele	75.22 (3.00)[ab]	77.00 (3.19)[a]	74.21 (2.38)[b]		0.021††
CAG repeat larger allele	75.22 (3.00)	75.19 (2.97)			0.962†††
TtoAfterOnset (Time versus start of gait ataxia, in years)	5.69 (4.15)[a]	-4.85 (0.80)[b]	-14.46 (6.63)[c]		<0,001††

†Chi-square test; †† Anova; †††t test. Tukey tests: different letters mean significant differences.

Clinical scales and VOR of symptomatics, AN, AFF and controls were all significantly different between groups (p<0.05) (**Table 2**).

	Symptomatic carriers	AN	AFF	Related controls	p
NESSCA	14.15 (5.00)[a]	6.85 (3.34)[b]	2.75 (2.31)[c]	1.77 (1.38)[c]	<0.001
SARA	8.25 (6.00-11.88)[a]	1.00 (0.50-2.50)[b]	0.50 (0.00-1.38)[b]	0.50 (0.00-1.00)[b]	<0.001
ICARS	22.50 (15.00-34.00)[a]	6.00 (3.00-8.00)[b]	2.00 (0.25-4.75)[b]	1.00 (2.25-0.00)[b]	<0.001
INAScount	5.79 (2.21)[a]	3.54 (2.37)[b]	1.63 (1.56)[c]	1.14 (1.21)[c]	<0.001
SCAFI	-0.02 (0.87)[a]	-0.81 (0.83)[b]	0.41 (0.40)[bc]	0.72 (0.38)[c]	<0.001
CCFS	1.05 (0.09)[a]	0.95 (0.06)[b]	0.92 (0.03)[b]	0.91 (0.05)[b]	<0.001
VORr	0.66 (0.25)[a]	0.86 (0.19)[b]	1.02 (0.06)[bc]	1.06 (0.05)[c]	<0.001

Tukey and Dunn tests: different letters mean significant differences.

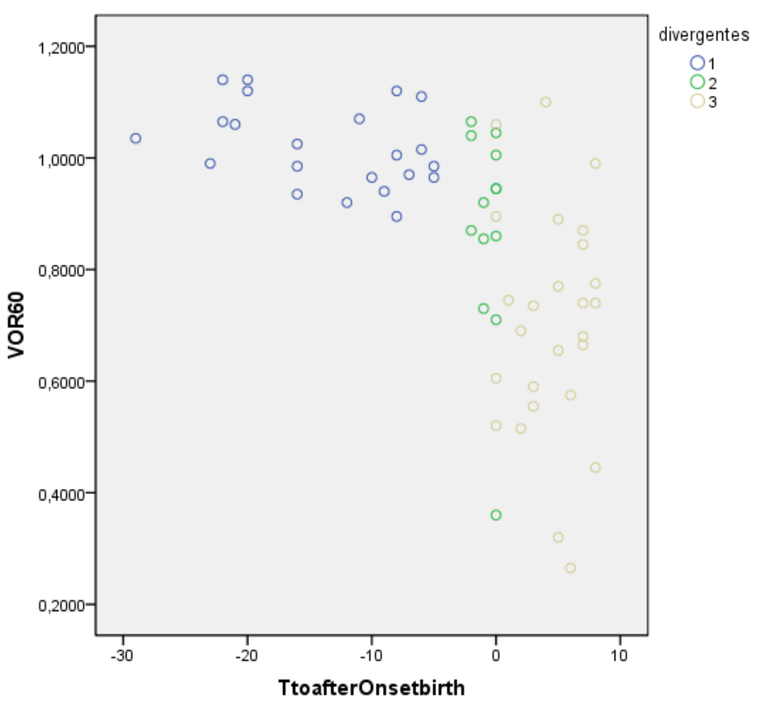

Figure 2. Correlation between TtoAfterOnset and VOR

TtoAfterOnset of the 37 presymptomatic carriers correlated (r=0.443 to 0.627) with ICARS, NESSCA, VOR and INAScount. **Figure 2** exemplifies this association.

CONCLUSION

VOR60 and NESSCA were the biomarkers that distinguished presymptomatic AN from controls and correlated with TtofterOnset. Due to that, they seemed to be the best candidate biomarkers for the presymptomatic period in SCA3/MJD. Our longitudinal observation will try to confirm these findings.