16 Clinical scales and vestibulo-ocular reflex show changes in time since pre-clinical stages in Machado-Joseph disease/spinocerebellar ataxia type 3 (BIGPRO Study)

Camila Maria de Oliveira[1], Gabriela Bolzan [1], Gabriela Ecco[1], Amanda Henz[1], Anastacia G. Rocha[1], Nathalia Kersting[1], Mariana Rieck[2], Ana Carolina Martins[1], Vanessa B. Leotti[1,2], Maria-Luiza Saraiva-Pereira[1,2], Laura B. Jardim [1,2].

[1] *Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;* [2] *Hospital de Clínicas de Porto Alegre, Brazil.*

Acknowledgements: CAPES, CNPq, FAPERGS, FIPE-HCPA.

Presenting author: Camila Maria de Oliveira

Contact: camila.maria1602@gmail.com

Aims: Reliable biomarkers for pre-clinical stages are needed for spinocerebellar ataxia type 3/Machado-Joseph Disease (SCA3/MJD), a disease due to a CAG repeat expansion (CAGexp). BIGPRO study aims to validate biomarkers for disease progression since pre-clinical periods (bigpro.webnode.com). We report baseline findings obtained from clinical scales and vestibulo-ocular reflex (VOR).

Methods: data was collected from ataxic and at 50% risk subjects between 2017 and 2018. Age at onset (AO) was the age at which the subject and relatives first noticed gait ataxia. Time after onset was the time elapsed since the AO. Genetic tests performed in at risk subjects were double-blind.The CAGexp was used to estimate "time to onset" at birth and corrected for current age (doi: 10.1111/ene.13779) for pre-ataxic carriers (SARA < 3), which were divided in pre-ataxic carriers far from age of ataxia onset (PAFF) – when prediction at birth of ataxia onset was more than 4 years – or near (PAN) age of onset. Time to/time after onset (TimeToAfterOnset) was the dimension of time versus start of gait ataxia estimated for all SCA3/MJD carriers, calculated for current age in pre-ataxic carriers. Primary outcomes for this report were the clinical scales NESSCA, ICARS, INAScount, CCFS and SCAFI and the vestibulo-ocular reflex gain (VOR), measured by video-oculography (EyeSeeCam - doi: 10.3233/VES-160579). VOR was studied using the regression analysis of eye and head velocities between 10ms before to 100ms after the onset of the impulse – average of both sides (VORr). Results are presented as mean (SD) or median (IQR) according to distribution and were considered statistically significant when $p<0.05$ after adjustment. Correction for multiple comparisons was performed with Benjamini–Hochberg method and separately for each research question.

Results: 35 ataxic carriers – TimeToAfterOnset of 5.86 (4.1) years –, 24 PAFF – TimeToAfterOnset of -14.46 (6.63) years –, 14 PAN – TimeToOnset of -5.0 (0.96) years – and 22 controls were included. Parameters under study that showed significant differences between controls and PAN were: NESSCA – 2.0 (1.0) versus 8.0 (5.0) –, INAScount – 1.0 (2.0) versus 3.5 (4.0) –, SCAFI – 0.69 (0.34) versus -0.83 (0.74) – and VORr – 1.06 (0.05) versus 0.89 (0.18) ($p <0.001$, post-hoc Tukey/Dunn). TimeToAfterOnset from all 73 CAGexp carriers correlated with all clinical scales and VORr ($p<0.001$). When considering only pre-ataxic carriers, time to onset correlated with NESSCA, ICARS, INAScount and VORr (rho=0.615, 0.625, 0.424 and -0.521, respectively, $p<0.05$). VORr correlated with SARA in ataxic carriers (rho=-0.454, $p=0.024$).

Discussion: VORr, NESSCA, ICARS, INAScount and SCAFI distinguished pre-clinical carriers near the predicted age of onset from controls. VORr, NESSCA, ICARS and INAScount correlated with time to onset when considering only pre-ataxic carriers. In addition, VORr showed external validity with SARA. These results suggest these could be possible candidate biomarkers for the pre-ataxic period in SCA3/MJD. Longitudinal evaluations are under progress to support these findings.