Author's response to reviews

Title: Nystagmus as an early ocular alteration in Machado-Joseph disease (MJD/SCA3)

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Author's response to reviews: see over
Dear Prof. Beom S. Jeon

Thank you for your answer concerning our manuscript “Nystagmus as an early ocular alteration in Machado-Joseph disease (MJD/SCA3)” (MS:5087949611129600).

We have carefully read the comments of the reviewers and made the corresponding revisions in our manuscript (main changes in the text are highlighted in yellow). A list of point-by-point replies is provided below. We believe that the modifications made have indeed improved the manuscript and we look forward to have it published in “BMC Neurology”. We have also made the modifications in accordance with the editorial requirements.

Sincerely,

Mafalda Raposo

Reviewer Ludger Schöls

1
Raposo and colleagues report on gaze evoked nystagmus in patients with manifest spinocerebellar ataxia type 3 (SCA3) and in individuals at risk to develop SCA3 (first degree relatives of patients). In accordance with the literature they find gaze evoked nystagmus to be a frequent sign in SCA3. More important, they found 17% of 48 asymptomatic mutation carriers but none of the 42 non-carriers to present with nystagmus.

This study confirms gaze-evoked nystagmus as an early sign of SCA3 that may present before onset of gait ataxia as it had been shown recently (Jacobi, et al. Lancet Neurol 2013;12:650-658). This article is of major importance in respect to the present paper and needs to be included in the discussion. It further proves the statement wrong that nystagmus has not been studied in early stages of SCA3 before (lines 67/68).

We have carefully read the paper indicated and modified the text, as suggested (lines 64-66). Also, the results reported in the paper referred were included in the discussion (lines 174-175). Although in fact this cannot be considered the first study of nystagmus in early stages of SCA3, it’s important to note that the number of asymptomatic carriers evaluated in our study (48) is 2 fold higher than the paper by Jacobi et al. (2013), and therefore it should allow a more in-depth analysis of the role of nystagmus in the early stages of Machado-Joseph disease (Jacobi, et al. Lancet Neurol 2013;12:650-658).

2
The authors should specify which of the mutation carriers developed nystagmus. For the presymptomatic group they should calculate the time from estimated onset of disease for each individual using the correlation of (CAG)n repeat length and age at onset in symptomatic individuals. Were the mutation carriers with nystagmus those who were closest to estimated disease onset?
I got the impression that most of the risk individuals with nystagmus converted to manifest disease during the observation period. This should be stated more clearly (lines 138 – 140).

As the reviewer suggested, we calculated the time from onset (Jacobi et al., 2013); for this calculation, however, we did not use the estimated onset, but the reported age at onset which was available to us. The time from onset definition was included in methods section, lines 107-108. From 48 asymptomatic carriers, 19 (40%) developed gait ataxia during the follow-up period of the study. Also, 5 of the 8 that presented nystagmus at PT evaluation also developed ataxia. This information was included in the manuscript (lines 138-144) and in figure 2.

ICARS and SARA, both semiquantitative ataxia scales, were validated in several Spinocerebellar Ataxias (SCAs), including MJD. Both scales show similar reliability and responsiveness. Although ICARS presents some interdependency or redundancy of some of its items, SARA also presents some drawbacks, its variability is high and a large sample size is required for small differences. Both scales were used in studies of the natural history of MJD as well as in clinical trials. The responsiveness of SARA on disease duration was similar to that of ICARS. ICARS scores for MJD patient’s correlated with both disease duration and the number of CAGs in the expanded allele (reviewed in Saute et al, 2012. Cerebellum. 2012; 11(2):488-504).

The idea we were trying to convey in lines 175-178 was that it is important to enrich the clinical evaluation of nystagmus; our goal, therefore, was not to suggest that these would be the best scales to clinically evaluate MJD patients, but to suggest that their complementary use is of importance (line 176) and we fully understand the reviewer comments on this matter. In a pleomorphic disease, such as MJD, ataxia and non-ataxia scores should provide a better view of overall disability and allow a better assessment of disease impact. As an example, NESSCA, although being a specific scale for MJD, is a semiquantitative ataxia and non-ataxia scale and was validated and used to measure disease progression (reviewed in Saute et al, 2012. Cerebellum. 2012; 11(2):488-504).

The manuscript tends to be lengthy. Lines 51 – 57 are not relevant to the manuscript and can be skipped. Conclusions are redundant and can be omitted from the rather short discussion.

In accordance with this comment, lines 51-57 were removed from the manuscript. Conclusions were trimmed (lines 189-191).
Reviewer Hee Tae Kim

1

Author found that nystagmus in SCA3 with presymptomatic patients should be considered as early ocular manifestation. However they didn't show additional ocular findings in cerebellar disease (such as ocular dysmetria, poor pursuit etc). In addition to nystagmus other ocular findings should be investigated in this study.

We agree with the reviewer that other ocular features should be studied (please see discussion section, lines 181-186). However, our focus in this particular paper was to evaluate nystagmus, since this clinical sign is highly frequent in MJD patient’s and is the ocular abnormality most consistently reported for this disease. For example, saccadic dysmetria studies in MJD reported conflicting results. Has been reported that 86% of the patients had hypermetric saccades, while in another study was observed a predominance of hypometric (56%) over hypermetric saccades (18%) (reviewed in Rodriguez-Labrada R and Pérez-Velázquez L, 2012. In Spinocerebellar Ataxia. Edited by Gazulia J. Intech; 2012:1–198.).

2

Author should describe full demographic data.

Demographic data was described in lines 124-128, and is also supported by information presented in Table 1.

3

Regarding the nystagmus, author should fully describe other signs (cerebellar signs, gait ataxia, other oculomotor signs etc), but author used only ICARS subscore for description of nystagmus.

All subjects clinical evaluated during this study performed a complete neurological exam; in accordance with this comment the main results were included in the manuscript (lines 147-150). Moreover, other clinical features were described (such as age at onset and disease duration). We have also complemented this information by adding a new figure to illustrate the main clinical findings.

4

Not sufficient explanation of limitation in this study was defined.

A clarification of the limitations of this study was performed (lines 181-186).