Reviewer's report

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

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Reviewer: Ludger Schöls

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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).

The authors should specify which of the mutation carriers developed nystagmus. For the pre-symptomatic 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).

Lines 170-172: The authors consider nystagmus as an important part of an ataxia rating scale as it depicts an early sign. I can only partly agree with that. If an ataxia scale is meant to measure severity of disease it should not focus on clinical signs but on measures correlating with handicap. This is clearly shown for the Scale for the Assessment and Rating of Ataxia (SARA, Schmitz-Hubsch et al. Neurology 2006) but not for ICARS that is preferred by the authors but includes several inter-related items.

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.

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
No competing interests