Reviewer's report

Title: Parkinsonian Phenotype in Machado-Joseph Disease (MJD/SCA3): a Two-Case Report

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Reviewer: carlo ferrarese

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Review of the manuscript “Parkinsonian Phenotype in Machado-Joseph Disease (MJD/1 SCA3): a Two-Case Report” by C. Bettencourt and colleagues submitted to BMC Neurology.

In this manuscript the Authors describe parkinsonian phenocopies in two young patients carrying 72 CAG triplets within the ATXN3 gene, known to cause Machado-Joseph disease (MJD). They excluded concomitant Parkinson’s disease (PD) -related mutations, and subsequently assessed different polymorphisms previously associated to PD, hypothesizing they might act as epistatic factors on the triplet expansion MJD mutation. DJ-1 and APOE alleles previously associated to an increased risk of sporadic PD were present in both patients, and the authors conclude suggesting that future studies might focus on the genetic background surrounding MJD mutations and possibly modulating its phenotypic expression including the early occurrence of extrapyramidal signs.

The cases are well documented and at least one of the two pedigrees seems to support their conclusions. However, the results of their analysis may be considered only as preliminary findings in just two cases, since the association between the g.168_185del DJ-1 polymorphism and PD is not yet completely clear, and the associations with the APOE genotype might be coincidental due to their relative high frequency.

In conclusion, I feel that the starting point for this work is sound but the results need to be confirmed in other patients, before they may be considered significant and not merely coincidental.

Major compulsory revision:
DJ-1 g.168_185del polymorphisms (and APOE as well) should be assessed in a wider population of MJD patients not expressing extrapyramidal signs, in order to further speculate on the significance of this finding.

Discretionary revision:
It might be interesting to include the assessment of TBP alleles as well. In fact, SCA17 mildly expanded alleles might be a risk factor for parkinsonian disorders. For example, Kim and colleagues screening more than 1,000 parkinsonisms, found 10 patients with an expanded number of repeats, using 42 as the upper normal limit. Among 400 healthy controls the same authors identified four individuals carrying 42/44 repeats: these subjects showed a concomitant
decreased striatal DAT binding [Neurology 2009; 2:1385-9]. Analogously, Chen and colleagues hypothesized that mildly expanded TBP alleles might tend to express with a parkinsonian phenotype [Clin Chim Acta 2010; 411:375-80].

Minor essential revisions:
1. line 79: delete “a” before more
2. line 99: slowness rather than “lentification”
3. line 114: rephrase “with slowly progressive gait ataxia”

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**
'I declare that I have no competing interests'