Reviewer’s report

Title: Late-onset Spinal Form Xanthomatosis without Brain Lesion: a Case Report

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Reviewer: Janbernd Kirschner

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The authors present an interesting case of an 77-year old Japanese man with enlargement of Achilles and patellar tendon enlargement progressive gait disturbance. Clinical examination showed hyperactive reflexes of the lower extremities and positive Babinski sign. MRI imaging revealed increased T2 intensity of the dorsal column of the spinal cord and no abnormalities in the brain. The authors identified genetic abnormalities in the CYP27A1 gene and conclude that this case represents a spinal manifestation of cerebrotendinous xanthomatosis.

This is a very atypical presentation as the patient has no history of infantile-onset diarrhea, childhood-onset cataract, and no abnormalities on cerebral imaging. Therefore some more information would be needed before attributing the clinical manifestation to a spinal form of Cerebrotendinous xanthomatosis:

1) Laboratory findings: Normal ranges for cholestanol should be provided. Bile alcohols should be measured in urine and plasma. Cholestanol and apolipoprotein B should be measured in CSF if possible. Plasma lactate level should also be reported. Vit B12 deficiency should be excluded as a potential differential diagnosis.

2) More clinical data should be provided relating to dorsal column function, e.g. vibration and joint position sensation.

3) Genetic results: More evidence of the pathogenicity of the two mutations should be provided. Both parents should be tested for heterozygosity. The argument that they have not been tested because they were asymptomatic is not valid. Multiple sequence alignments and missense prediction tools should be used to underline the causal relation.

In line 140 the authors state: We have performed mutational analysis of all 9 exons of the CYP27A1 gene in Japanese patients with late-onset xanthomatosis with long spinal lesions. Does this mean that more patients with spinal lesion have been analysed? This should be clarified.

Discussion: The authors should discuss in more detail the available evidence and literature on spinal involvement in xanthomatosis. This should also include the recent publications by Abe R et al. (Spinal form cerebrotendinous xanthomatosis patient with long spinal cord lesion. J Spinal Cord Med. 2015 May 5, PubMed PMID: 25941960) and Nicholls Z et al. (Diagnosis of spinal...

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

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Unable to assess

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No

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