Reviewer’s report

Title: Case report: An unexpected link between partial deletion of the SHANK3 gene and Heller's dementia infantilis, a rare subtype of autism spectrum disorder

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Reviewer: Hannelore Ehrenreich

Reviewer's report:

In their manuscript "Case report: An unexpected link between partial deletion of the SHANK3 gene and Heller's dementia infantilis, a rare subtype of autism spectrum disorder", the authors provide a detailed clinical description of a 10-year-old girl carrying an interstitial 22q13.3 deletion encompassing the first 17 exons of SHANK3. According to her mother, the girl developed normally until 4 years of age. At school, her language was very poor, she had attention problems and became more and more agitated. This was followed by social withdrawal. The clinical assessment including ADI-R and CARS at age 7 by the authors of the current manuscript showed her poor developmental and adaptive skills consistent with childhood disintegrative disorder.

This is an interesting case where a 22q13.3 microdeletion leading to haploinsufficiency of SHANK3 seems associated with severe regression. It is worth reporting. However, there are some important issues which should be addressed by the authors.

Most importantly, it should become very clear in the manuscript, that the authors cannot exclude other genetic causes for the regression phenotype since no deep genotyping was performed. For example, genes like MECP2 or fragile X genes, known to be associated with regression, were not sequenced for mutations. And there are more candidates. This problem has at least to be mentioned as a severe limitation!

Other points:

1. How does the genetic diagnosis of SHANK3 haploinsufficiency facilitate clinical care monitoring? There is still a lot of clinical heterogeneity between individual SHANK3 haploinsufficiency patients complicating the treatment and prognosis.

2. Pages 5 and 6, clinical assessment: How was the behavioral observation conducted? Did you perform the ADOS? If not, did you still prompt certain behaviors to create the opportunity to observe them or is the clinical assessment of the current behavior based on spontaneous observations? Did she show any descriptive or conventional gestures? Did she respond to the calling of her name? What about sensory processing abnormalities?
3. In the ADI-R your case does not fulfill the criteria for abnormalities in the domain of stereotyped, restricted patterns of behavior. Why did you still come to the conclusion that there is a qualitative impairment in restricted, repetitive behavior?

4. Please note that the gene names should be written in Italics along the manuscript (SHANK3 and MECP2).

5. Page 3, paragraph 2: Please add references relating to the clinical profile of patients with SHANK3 haploinsufficiency.


7. Page 3, line 41: What do you mean by 'natural history'?

8. Page 4, line 2: What do you mean by 'confrontation with precise phenotypical descriptions'? Is 'confrontations' the right word in this context?

9. Page 4, line 44: When you mention 'use of objects', you might want to add 'functional'.

10. Page 4, case presentation: Was there abnormal posturing in the first months of life? What about self-regulation? Was negative affect increased?

11. Page 6, line 21 and Table 2: Please check the total Child Autism Rating Scale score (CARS) that L. presents. Should it be 44.5 instead of 47?

12. You might want to think about structuring the clinical assessment part according to the different symptom domains.

13. Please make sure that your spelling is consistent. Sometimes you use the American and sometimes the British English spelling.

14. Page 9, line 33: 'instinctual' may not be the right term as you also refer to behaviors that are learned (e.g. toilet-training). You may want to use 'automated'.

15. Page 10, line 27: You state that the case presented could lead to 'several' differential diagnoses. You then only mention autistic disorder and Rett syndrome. The latter can be ruled out due to the lack of MECP2 mutations. Please mention further alternative diagnoses besides Dementia infantilis.

16. Page 10, line 46: You discuss anti-NMDA-receptor encephalitis or B12 deficiency as a potential mechanism explaining the clinical picture. Did you test your case for anti-NMDAR1 seropositivity or B12 deficiency?

17. Page 10, line 58: You mention that other cases with SHANK3 deletions display sensory processing abnormalities. Did your case present sensory processing abnormalities?
18. Was pain perception altered?

19. Given the non-availability of home video recording of the case, it would be interesting to include the health book filled by the paediatricians as a figure or a box.

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

Unable to assess

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Not suitable for publication unless extensively edited

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