Reviewer’s report

Title: Observational cohort study of the natural history of Niemann-Pick disease type C in the UK: a 5-year update from the UK clinical database

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Reviewer: Alberto Benussi

Reviewer's report:

This is an observational cohort study from the UK clinical database on the natural history of Niemann-Pick type C, comprising more than 140 patients. The authors perhaps fall a bit short in reporting only the prevalence of signs and symptoms, without inferring on statistical correlations between age groups, but probably this was not the objective of this work. The article is well written and clear in most points. I have few comments to address below:

- Abstract, page 2, line 36: the phrase "(mean [SD] age at last follow up 2.5 [1.8] years; n=11/death 20.8 [15.9] years; n=3)" is difficult to interpret, please clarify.

- Background, page 3, line 29: authors should also briefly discuss the measurement of plasmatic oxysterols as a diagnostic or screening aid, which have been recently described and many groups are beginning to use.

- Results, page 6, line 30: the authors report that having a sibling with NP-C leads to a more rapid diagnosis in younger siblings; perhaps this was not only the case with "younger" but also "older" patients, considering the extreme heterogeneity of this disease. Authors should also include the time elapsed from disease onset to diagnosis (both data are already reported but not the elapsed time), and the difference between this time and the time elapsed if one had an affected sibling.

- Results, page 7, line 5: authors could briefly report which type of psychiatric disturbances were recorded, if available.

- Results, page 12, line 16: what do the authors mean by "no identifiable NP-C mutations were recorded in three sibling pairs"? Please clarify.
- Discussion, page 14, line 13: authors should cite the source when referring to "neonatal jaundice can herald a more aggressive clinical course of NP-C, particularly if neurological abnormalities appear during the first 4 years of life".

- Discussion, page 15, line 36: authors correctly underline the high degree of phenotypic heterogeneity in patients with NP-C. Perhaps authors should also include that this extreme variability has also been observed in monozygotic twins carrying the same disease mutation (see Benussi et al, Journal of Neurology, 2015).

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

Yes

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

Yes

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

Yes

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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Please indicate the quality of language in the manuscript:

Acceptable

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