Author’s response to reviews

Title: Pediatric Multiple Sclerosis: A review

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Response to review and editorial comments.

We thank the reviewers and the editorial office for their valuable comments and suggestions which have certainly improved the scientific quality of the manuscript. Below, we responded to the comments by a point-to-point approach and the changes were either highlighted in yellow in the manuscript.

Kumaran Deiva (Reviewer 1):

Q*How many articles did the authors collected and what criteria they used to select specific articles? Who are the experts who participated in the PARADIGMS study group.?

Response-We have added all the experts who participated in the PARADIGMS group. The experts selected articles that had either studied or included paediatric patients using the PubMed, EMBASE Cochrane reviewer. Reviews and publications in peer-reviewed journals published in the last 20 years or any article that has a substantial impact or results that was published beyond 20 years were included. Given the rarity of the disease, we had to include studies that were conducted in specialised centres or extracted from national registries.
Q*Authors precise in the abstract that the revised IPMSSG criteria improved the accuracy of diagnosis, but no paper no studies have been cited in the results section.

Response-In the diagnostic criteria section, we cited two papers (ref 29, and 30) which are related to the IPMSSG diagnostic criteria.

Q*There were many clinical trial for the dimethyl fumarate in children, FOCUS is mainly looking on DMF effect on MRI in children with RRMS while CONNECT is an open label study on comparing AVONEX against DMF in children with RRMS.

Response-We have included the FOCUS and CONNECT trials of DMF in children.

Banu Anlar (Reviewer 2):

Q*In order to add to existing knowledge, it would have been much more interesting to compare local and regional series and present a list of areas where data are needed.

Response-We have added some regional data and the lack thereof.

Q*The MS course in cases with onset at < 16 years of age is very similar in different populations.(Line 78)" Which populations? Please add references to support this. How different are these populations? For instance, some group of patients, mostly from Italy, showed early cognitive deterioration. This has not been reproduced in all series.

Likewise;

1-early MS being more inflammatory and more aggressive in North America, Italy, it would be useful to underline the need for data from elsewhere. Environmental, infectious, vitamin D, sun exposure conditions vary.

2-Relapses are more frequent in patients with POMS compared with adult-onset MS. (only in some areas of the world)
3- Cognitive impairment is frequent in POMS.

These are supported by only one reference (#3) or references from the same center (#11 and 13).

4- Axonal damage: Ref. #10 is the only study referred to, whilst more than one imaging studies can and should be added to this assessment especially since biopsied tissues (or patients) are unlikely to represent early ped-MS in current patients.

Response-The term "different populations" is referring to different cohorts included in studies conducted in different countries (Italy, Russia, France, USA, and Kuwait) (references 1-3, 14-16, 19-20). We added this.

1/2/3- We will emphasize the need for regional data.

4- We had added one case study on axonal damage (Anderson RC et al 2005 neurosurgery)

Q*The Conclusion contradicts what the manuscript repeated several times: "little evidence (specified as class I in the Introduction), for the effect of DMT in children" There is little data in favor of early DMT slowing disability even for adults (most recent Cochrane review Filippino et al); let alone in children. Line 405 (it is important to start DMT early) is therefore an overstatement, perhaps under the effect of industry's decades-long work.

Response--The rationale of starting DMTs early is to limit the axonal damage secondary to extensive inflammatory changes seen earlier in the disease process. As mentioned before, children with MS have highly active disease with frequent relapses and extensive demyelinating plaques on MRI with predominance of having brainstem/cerebellar relapses which are usually disabling. So, it is evident that delaying (or halting) the accumulation of disabilities at earlier stage would improve the overall neurological status.
In short, the language has further been improved, the methods explained and the scarcity of regional data emphasized, and the conclusion elaborated. Hopefully we've answered your comments satisfactory.