Reviewer's report

Title: Magnetic Resonance Spectroscopy of normal appearing white matter in early relapsing-remitting MS. Disability-spectroscopy correlations.

Version: 1 Date: 16 February 2004

Reviewer: Massimo Filippi

Reviewer's report:

General
The authors used MRS to quantify NAWM damage in a group of RRMS patients and to assess the correlations between MRS metrics and clinical disability, measured using different scales. The topic of NAWM damage in MS is not novel (as also shown also by the large literature quoted by the authors). On the contrary, the different correlations found between NAWM damage and the different clinical scales used would be of more interest. Unfortunately, this aspect is underdeveloped in the manuscript.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1) From the abstract and from the text of the manuscript, it is not clear if an EDSS of 0-5.5 was an inclusion criteria or not;
2) Background: several pathological studies have shown the involvement of the NAWM in MS patients and its pathological substrates. A paragraph summarizing these papers should be added. The limitations of the clinical scales used in MS should be mentioned together with those of MRI. It is not clear how hypointense lesions load on T1-weighted images can delineate tissue damage occurring in the NAWM.
3) Objectives: the number of patients and their characteristics should be removed from this section, as they are already reported in the "Materials and methods" section.
4) Population studied:
   - "These patients had been diagnosed.. determined by an EDSS of 0 to 5.5" is meaningless. Does the EDSS determine the diagnosis of MS?
   - The scales used to assess disability should be listed.
   - As no mention in the results and in the discussion is done regarding the follow up, all the parts in the "Method" section regarding the follow up (clinical and MRI) should be removed.
   - Statistical analysis: has a comparison between NAWM areas in patients and controls been performed? The same consideration applies to MRS data from lesions and NAWM within the patient group.
5) Results:
   - Subject demographics and clinical parameters: the first sentence has already been reported in the methods. The authors should choose where to report a given data or sentence, and put it just once. If the results are written in the text, a Table with the same results is redundant. Therefore, Table 1 should remain (after removing the weight and height of the subjects) and the corresponding text should be removed from the results. Table 2 and the corresponding part in the results should be removed, unless the authors consider
particularly important (and, in this case, they should provide a reason) to present the FS scores.
Tissue metabolite concentration: was NAA/Cr ratio significantly reduced in MS lesions and in NAWM? This information would be more useful than that provided in the text.
As the correlations which resulted significant are already reported in the text, Tables 3 and 4 should be removed.
- Discussion:
The overall discussion should be shortened. The points that have been already mentioned in the introduction should be removed (in particular, the second paragraph concerning NAA). In the third paragraph, the reference to Arnold's "though" regarding Cr is not cited.
The part regarding the "Clinical outcome and 1H-MRS parameters" is really confusing. The results of previous works, as well as their similarities and differences should be summarized more concisely.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- The authors should pay more attention to the abbreviations used thought the manuscript.
- The conclusions of the abstract (EDSS is an axonal damage marker) should be deleted.
Furthermore, the MSFC is not mentioned in the abstract, however the conclusion is that it is not able to measure irreversible disability: this point should be clarified.
- The First paragraph of the background should be removed.
- The term "standard MRI" is somewhat ambiguous. Please use "conventional".
- Reference 31 is missing
- Population studied: the last sentence of the second paragraph ("This examination determined axonal damage..") should be removed.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

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

Statistical review: No

Declaration of competing interests:

None