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Reply:

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Reply:

We thank Dr Aboul-Enein for his comments. As Dr Aboul-Enein pointed out, the heterogeneity of the multiple sclerosis (MS) disease course in individual patients makes it an interesting problem that is, at the same time, also very difficult to study. This is due primarily to its decades-long course, especially because other MR imaging markers have so far yielded mixed results in their long-range predictions.[1-3] Our study was, therefore, predicated on the notion that neuronal damage has long been implicated as the main cause of MS damage (see Kornek and Lassmann for a review[4]) and that it may occur even before a confirmed clinical diagnosis of the disease.[5,6]

We were surprised, therefore, that our cohort of patients with MS, all of whom fulfilled the Barkhof criteria,[7] have retained "clinical silence," (ie, little to no decline during a long [≥15 years] disease duration) but have whole-brain *N*-acetylaspartate (WBNAA) indistinguishable from that projected from individuals with MS of a much shorter disease duration. The choice of a clinically benign cohort came to circumvent, in part, the need for a difficult long serial study by applying instead the argument that patients with MS who are "benign" after 15–35 years have always been so. Most surprising, the expectation that their WBNAA would also be benign (ie, analogous to that of controls) was refuted; this result indicates that global neuronal sparing is, in fact, not a feature of this phenotype.

While we agree that there is no substitute for a lengthy follow-up, the observation that the cross-sectional amount of NAA loss depends on the disease duration supports (though does not prove) the notion that the decline in this marker in the benign population is indistinguishable from cross-sectional rates of patients with MS of much shorter disease duration and is substantially lower than that in healthy contemporaries. This finding suggests that fortuitous lesion location and efficient brain plasticity may be the 2 likely mechanisms that distinguish benign from nonbenign phenotypes. The implication of this likely conjecture is that this overall decrease in healthy neurons may eventually sap compensatory ability and/or that one or a few lesions in the spine or in eloquent regions may have precipitous consequences. This outcome is increasingly likely, specifically in light of the new research, mentioned in the original letter.[8]

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