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Reply:

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REPLY:

We thank Dr Padilha and colleagues for the letter written in response to our recently published article, "MR Imaging Features of the Cerebellum in Adult-Onset Neuronal Intranuclear Inclusion Disease: 8 Cases." The authors stated that 3 patients with genetically confirmed fragile X-associated tremor/ataxia syndrome (FXTAS) presented with imaging findings similar to those in the patients described in our report. In addition, they actually show MR images of 2 cases, one presenting with both the paravermal signal changes on FLAIR images and abnormal high-intensity signal along the cortico-medullary junction on DWI and the other presenting with abnormal high-intensity signals both in the middle cerebellar peduncle on FLAIR and along the cortico-medullary junction on DWI.

Considering the cases described by the authors, we agree with their statement that the MR imaging features of adult-onset neuronal intranuclear inclusion disease (NIID) may be indistinguishable from FXTAS. Indeed, because the finding of an abnormal high intensity signal along the corticomedullary junction on DWI has been considered unique to NIID and useful for discriminating NIID from FXTAS,[1] we consider the cases described by the authors to be very important.

As the authors pointed out, *FMR1* permutation was not analyzed in our patients; thus, we cannot rule out the possibility that some patients with FXTAS were included in our subject group. Crucially, however, in 2 previous reports, the paravermal abnormal signal and abnormal signal in the middle cerebellar peduncle were observed in patients with NIID in whom a diagnosis of FXTAS was excluded by genetic testing of the *FMR1* gene.[2,3] Moreover, an abnormal high-intensity signal along the corticomedullary junction on DWI was also observed in a study in which a diagnosis of FXTAS was excluded in most subjects by genetic analysis.[4] Therefore, MR imaging features such as paravermal abnormal signals, abnormal signals in the middle cerebellar peduncle, and abnormal high-intensity signals along the corticomedullary junction on DWI are considered common findings that can be observed in both NIID and FXTAS. This point is very interesting. As the authors also noted, the histopathologic features of NIID resemble those of FXTAS and some cases of FXTAS present with dementia and peripheral neuropathy, which are common clinical manifestations of adult-onset NIID.[4] Because of their similar symptoms, pathology, and imaging findings, NIID and FXTAS are presumed to have a considerable degree of overlap in their pathophysiologies.

Finally, although the authors state that FXTAS seems to be more common than NIID, we note that this remains speculative. Since the usefulness of skin biopsy for the diagnosis of NIID was first described, the number of NIID diagnoses has increased, and reports describing cases with NIID have also increased, especially in Japan. It thus seems that adult-onset NIID is not as rare as previously thought.[5] On the other hand, the first case of FXTAS diagnosed in a living patient in Japan was reported in 2010,[6] and FXTAS continues to be considered a rare disease entity in Japan. There may be racial differences in the prevalence of these entities, with FXTAS being more common in whites and NIID more common in Japanese. In addition, patients with FXTAS may be mixed with those diagnosed with NIID by MR imaging findings and skin biopsy, and patients with NIID may be mixed with those clinically suspected of FXTAS without genetic confirmation. To clarify the accurate prevalences and racial differences of these entities, genetic analysis of the *FMR1* permutation in the diagnosis of NIID is a crucial first step, and such analysis was included in the diagnostic algorithm of NIID described by Sone et al.[4]

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