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Reply:

S.D. Roosendaal and M.S. van der Knaap

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REPLY:

We thank Dr Finsterer for his comments on our article. We agree that brain imaging patterns in mitochondrial disease are highly variable. Most important, the subject of our study was not MR imaging abnormalities in mitochondrial disease in general. We did not focus on patients with a diagnosis of a mitochondrial defect to assess the spectrum of related abnormalities on brain MR imaging. The focus of our study was on MRIs of leukoencephalopathies that were found to be caused by a mitochondrial defect. We aimed at identifying MR imaging features suggesting a mitochondrial leukodystrophy in general and at distinguishing MR imaging patterns related to particular gene defects. We, therefore, did not specify up front which mitochondrial defects would be included in our study; we included the defects that were found. A consequence of this approach is that diseases dominated by gray matter abnormalities or stroke-like lesions, such as caused by *POLG1* or *TWINK* pathogenic variants or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, were not part of the study.

Most mitochondrial leukodystrophies are caused by pathogenic variants in a nuclear gene, while most defects in mitochondrial DNA do not lead to extensive brain white matter abnormalities. As a consequence, only 6 of the 132 leukodystrophy cases in our study had a defect in mitochondrial DNA, all

with a large deletion and a diagnosis of Kearns-Sayre syndrome. That Kearns-Sayre syndrome may have causes other than a large deletion in the mitochondrial DNA and that for defects in the mitochondrial DNA, the heteroplasmy percentage matters are subjects outside the scope of our study. The MR imaging features mentioned in the article suggestive of a mitochondrial basis of a leukodystrophy are a result of the study, not a preconceived idea. The same applies to the finding that some MR imaging patterns are suggestive of specific underlying mitochondrial defects.

We acknowledge that the timing of the MR imaging acquisition influences the imaging features. This is not unique for mitochondrial disease. The aim of our study was to facilitate a radiologic diagnosis; therefore, when multiple MRIs were available in our patient group, we always used the first one for our analysis, often performed shortly after symptom onset. For most patients, follow-up was not available. Thus, we have not investigated follow-up images. We agree this is a limitation of the study.

Thus, in our study we identified MR imaging features commonly shared by patients with a mitochondrial leukodystrophy at presentation. These findings may facilitate a rapid genetic confirmation of their disease.

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