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Pattern Recognition in Mitochondrial Leukodystrophies is Hampered by the Peculiarities of Mitochondrial Genetics

We read with interest the article by Roosendaal et al[1] about the imaging findings in 132 patients with mitochondrial leukodystrophy. It was concluded that in many of these patients, general MR imaging features suggestive of a mitochondrial disorder (MID) can be identified and that several MR imaging patterns correlate with specific genotypes.[1] The study is appealing but raises concerns.

Not addressed were the influences of mitochondrial genetics, particularly of heteroplasmy and mitochondrial DNA (mtDNA) copy number, on cerebral imaging in MIDs. Phenotypic expression in the brain strongly depends on these highly variable factors and makes pattern recognition on imaging almost impossible because each individual patient can present with a variable combination of cerebral manifestations within a single family and between unrelated families. A patient with mtDNA-related MID with a low heteroplasmy rate may have normal MR imaging findings, whereas a patient with high heteroplasmy rates may manifest various degrees and extensions of white matter lesions. Furthermore, mutations in various nuclear DNA–related genes (eg, *POLG1, TWNK*) secondarily damage mtDNA molecules in an incidental manner, resulting in highly individual genetic constellations and highly variable phenotypes.

Not addressed was the progression of MIDs across time.[2] What can be found on cerebral MR imaging is always a snapshot of the current brain pathologies. Because MIDs have a strong tendency to progress with time, the time point at which imaging is performed strongly determines what can be found. Thus, a putative pattern may considerably change with time and may not be recognizable at a distant time. We should know whether follow-up images were available and were compared with previous studies.

Also, Kearns-Sayre syndrome (KSS) is genetically heterogeneous. KSS may be due not only to single mtDNA deletions but also to mtDNA point mutations.[3] Furthermore, single mtDNA deletions differ considerably in size and location among patients. This is why KSS cannot be regarded as a single entity but rather constitutes a group of highly variable phenotypes.

Likewise, attributing an imaging pattern to a particular respiratory chain complex defect can be misleading, because the residual activity of these multiprotein complexes varies considerably, depending on the affected subunit and the effectiveness of compensatory mechanisms and antioxidative capacities.

Missing is the discussion of stroke-like lesions (SLLs), which are pathognomonic for mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome but occur in other MIDs as well.[4] SLLs are dynamic conditions, changing their expansion and morphology depending on their evolutionary stage.[4] Although SLLs frequently originate from the cortex, subcortical structures are usually involved.

Cerebral imaging patterns in MIDs can be highly variable and inconsistent.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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