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Diagnosing Mitochondrial Encephalomyopathy With Lactic Acidosis and Stroke-Like Episodes (MELAS) Requires Not Only Phenotypic But Also Genotypic Verification

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TO THE EDITOR

We read with interest the article by Henry et al about a 28-year-old black female with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), diagnosed upon the clinical presentation and the cerebral magnetic resonance imaging (MRI) findings.[1] We have the following comments and concerns.

We do not agree with the statement that cerebral MRI is the gold standard for diagnosing and monitoring MELAS.[1] The gold standard for diagnosing MELAS is the genetic confirmation that a patient with a clinical presentation suggestive of MELAS also carries a pathogenic mtDNA or nDNA variant explaining the phenotype.[2] To strengthen the suspicion of MELAS, biochemical investigations of the muscle homogenate or of fibroblasts could be helpful. Further support for diagnosing MELAS could come from histologic and immune histologic investigations of the muscle.

The initial cerebral computed tomography (CT) typically shows a stroke-like lesion (Figure 1 in the paper).[1] Nonetheless, the patient was diagnosed with herpes meningoencephalitis and treated with acyclovir. Unfortunately, no results of cerebrospinal fluid (CSF) investigations were presented. Was there pleocytosis, lactate elevation, or polymerase chain reaction positivity for herpes virus in the CSF? Was the stroke-like lesion on cerebral CT confirmed by MRI? The standard treatment of stroke-like episodes (the clinical equivalent of a stroke-like lesion) is L-arginine or L-citrulline.[3]

MELAS is usually a multisystem disease affecting not only the central nervous system but also the ears, eyes, endocrine organs, myocardium, gastrointestinal tract, kidney, bone marrow, and skin.[2] Were organs other than the cerebrum affected in the index case? Was the patient prospectively investigated for clinical or subclinical involvement of organs other than the brain? Recognizing multisystem involvement is crucial because it may strongly determine the outcome of these patients.[4]

Because the family history was positive for mitochondrial disorder (MID) in the brother and child, it would be interesting to know if the index patient's mother or father also presented with phenotypic features of MID and if they were tested for any of the known MELAS mutations. Did the pattern of inheritance follow a maternal or an autosomal trait? Was there phenotypic heterogeneity between the parents, brother, child, and the index case?

The patient was initially treated with topiramate.[1] Why was the patient switched to levetiracetam? Did she experience side effects from topiramate? Because patients with MID frequently develop tiredness and easy fatigability, we should be informed if these manifestations deteriorated upon administration of levetiracetam.

Overall, this interesting case requires genetic confirmation of the diagnosis, extensive family investigations, and prospective workup for multisystem involvement.

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AUTHORS' REPLY

We appreciate the points raised regarding our article along with the constructive comments. We would like to clarify that the term *gold standard* was intended to be used in the context of imaging, underscoring the classic spectrum of imaging findings seen with MELAS. We concur that imaging alone is not the gold standard for diagnosis and that a thorough clinical and genetic workup is warranted for the diagnosis of MELAS.

Regarding other points raised, the herpes simplex virus polymerase chain reaction test was negative, and the patient had no CSF leukocytosis. The CT-MRI correlation for the left temporal lesion is described and illustrated in the report. Muscle spasms were mentioned, but no

information about other organ dysfunction was reported. We are unable to answer the other specific questions in regard to this patient's clinical course because much of the inquired detail occurred prior to referral to our institution or is not specified in the available records. Further, some of the specific issues raised are outside the focus on imaging intended in the article.

Sincerely,

Caitlin Henry, MS, Neema Patel, MD, William Shaffer, MD, Lillian Murphy, MD, Joe Park, MD, Bradley Spieler, MD