Diagnosis of Kearns-Sayre Syndrome Requires Comprehensive Work-up
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To the Editor: With interest, we read the article by Yu et al.\(^1\) about the clinical presentation and central nervous system (CNS) imaging in 19 patients with Kearns-Sayre syndrome (KSS), of whom 12 were genetically confirmed. We have the following comments and concerns.

The main disadvantage of the study was that the diagnosis was not genetically confirmed in all patients and mitochondrial DNA (mtDNA) deletion was detected in only 63% patients.\(^1\) What was the reason for seven KSS patients not undergoing genetic testing? Did not all patients undergo muscle biopsy? If only 12 of 19 patients underwent muscle biopsy, how can KSS be diagnosed? Among the seven patients who obviously did not undergo muscle biopsy, upon which clinical criteria were these patients diagnosed as KSS?

Among the seven patients who were not genetically confirmed, did the authors look for mtDNA point mutations in lymphocytes? It has been repeatedly reported that KSS may not only be due to mtDNA deletions but also due to mtDNA point mutations, such as m.3249G>A in the tRNA (Leu) gene, m.3255G>A in the tRNA (Leu) gene, or m.3243A>G in the tRNA (Leu) gene.

We should also be informed about the results of biochemical investigations to know about the activity of respiratory chain complexes. Complex I, complex II, complex IV, complex I and IV, complex I, III, and IV, complex I, IV, and V, and complex I, III, IV, and V deficiency or normal respiratory chain activity has been previously described in KSS.\(^2,3\)

Among the 15 patients who underwent cerebral magnetic resonance imaging, six patients showed hyperintensities on diffusion-weighted imaging in the white matter or basal ganglia.\(^1\) We should be informed about the nature and pathogenesis of these lesions. Were these lesions on the corresponding apparent diffusion coefficient map hyper-, hypo-, or iso-intense? Were these lesions interpreted as cytotoxic edema or as vasogenic edema? Can these lesions be interpreted as stroke-like lesions, the morphological correlate of a stroke-like episode?

Cognitive functions can be impaired in KSS patients.\(^4\) Did the 19 patients also undergo neuropsychological testing to assess their cognitive abilities and if they were impaired or not? Did the authors consider implantation of an implantable cardioverter defibrillator in any of their patients since four patients died from sudden cardiac death in a series of 35 KSS patients?\(^4\) Did the patients undergo long-term electrocardiogram recordings, and in particular were loop recorders implanted to see if any of the patients had a tendency to develop prolonged QT-interval, early repolarization, or ventricular arrhythmias?

It was interesting to see that only 3 of 19 had short stature.\(^1\) Short stature is one of the clinical criteria for diagnosing KSS.\(^5\)

Overall, these interesting case series should be supplemented by more detailed clinical, instrumental, and genetic data. The more information about KSS patients is collected, the more we can learn about the phenotypic and genotypic variability of these patients, and the better will be the management and outcome of KSS patients.

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**REFERENCES**

There were several articles studying the exact nature of high chain complexes in muscle tissues, which can also help provide evidence. Biochemical investigations, especially activity assay of respiratory mtDNA, mtDNA point mutations or nuclear gene mutations have been reported in other KSS patients. Apart from clinical features, muscle pathology and molecular genetic analysis can play a great role in the diagnostic workup. Muscle pathology and molecular genetic analysis can be performed in muscle tissue to do the mutation examination although RBF% cannot be measured in muscle tissue of the other four patients (patients 8, 10, 17, and 18). However, mtDNA mutation detection was available in 11 of them which showed RRF, RBF, and COX-negative fibers in all of them; single large-scale deletion in about 90% of KSS patients, which can be detected only from muscle tissues. Southern blot or long-range polymerase chain reaction can detect single large-scale deletion, but not from blood cells of KSS patients.


