SERAC1 variants may manifest as MEGDEL plus

Abstract:

Keywords: mutation, MEGDEL, mitochondrial, genetics, Leigh-like syndrome.

LETTER TO THE EDITOR

With interest we read the article by Snanoudj et al. about an infant male with MEGDEL syndrome due to a novel, compound heterozygous splice site variant in SERAC1 [1]. The patient manifested clinically with psychomotor regression, failure to thrive, spasticity, mild dystonia, deafness, epilepsy, optic atrophy microcephaly, lactic acidosis, neonatal hepatopathy, Leigh-like features on cerebral MRI, and 3-methylglutaconic acid urea [1]. We have the following comments and concerns.

The phenotypic spectrum of MEGDEL syndrome is broader than so far anticipated [2]. In addition to the brain, ears, muscle, and the gastrointestinal tract, the eyes, endocrine organs, the heart, and the peripheral nerves may be affected [2]. Thus, we should know if the index case was prospectively investigated for mild or subclinical involvement of systems not apparently clinically affected. Additionally, we should know if in addition to developmental delay, failure to thrive, optic atrophy, seizures, the basal ganglia lesions, microcephaly, dystonia, axial hypotonia, and diffuse cortical and subcortical atrophy, ataxia, tremor, chorea, dyskinesias, cognitive decline, dysphagia, dysarthria, or spinal cord lesions had developed [3]. Since MRI showed marked involvement of the brainstem [1], explaining failure to thrive, it is conceivable that dystarthis, dysphagia, and even respiratory dysfunction were also a feature of the phenotype. We should be informed if there were any indications for brainstem dysfunction in the index case.

The patient was reported to have manifested, in addition to failure to thrive, with epilepsy [1]. Thus, we should be informed about the EEG findings and the antiepileptic drug (AED) treatment applied. Since some of the AEDs are known to be mitochondrion-toxic [4], we should know if in addition to developmental delay, failure to thrive, optic atrophy, seizures, the basal ganglia lesions, microcephaly, dystonia, axial hypotonia, and diffuse cortical and subcortical atrophy, ataxia, tremor, chorea, dyskinesias, cognitive decline, dysphagia, dysarthria, or spinal cord lesions had developed. Since MRI showed marked involvement of the brainstem, we should know if in addition to developmental delay, failure to thrive, optic atrophy, seizures, the basal ganglia lesions, microcephaly, dystonia, axial hypotonia, and diffuse cortical and subcortical atrophy, ataxia, tremor, chorea, dyskinesias, cognitive decline, dysphagia, dysarthria, or spinal cord lesions had developed.

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Muscle biopsy was carried out at age 1y revealing only non-specific findings [1]. Since MEGDEL patients may manifest with myopathy, we should be informed about the ultrastructural findings on electron-microscopy and the results of biochemical investigations. Ultrastructural findings previously reported include frequent subsarcolemmal tubular aggregates composed of parallel collections of concentric double-walled tubules [5]. Biochemical findings previously reported include reduced complex-II, complex-III, and complex-IV activity [5].

It is surprising to see in table 1 that there was no oxidative phosphorylation defect, neither in the muscle nor in fibroblasts [1], but that there was lactic acidosis, suggesting respiratory chain dysfunction. We would be interested in an explanation of this discrepancy and if lactate was accidentally measured after a seizure, thus representing a false positive result.

Since the patient experienced respiratory distress after general anaesthesia for dental surgery at age 8y [1], we should be informed about the potential triggers of this adverse reaction. Was the reaction attributable to the aesthetics, analgesics, or muscle relaxants applied or a reaction to the premedication?
Overall, this interesting case could be more meaningful if the inconsistencies mentioned above were solved and if additional information as requested above was provided. As long as the full phenotypic spectrum of MEGDEL syndrome has not yet been encountered, it is crucial to describe even minor findings and to prospectively investigate these rare patients for subclinical or mildly manifesting involvement.

REFERENCES