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MEGDEL Syndrome in a Child From Palestine: Report of a Novel Mutation in *SERAC1* Gene

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Abstract

We report the first Palestinian child manifesting with 3-methylglutaconic aciduria psychomotor delay, muscle hypotonia, sensorineural deafness, and Leigh-like lesions on brain magnetic resonance imaging (MRI), a clinical phenotype that is characteristic of MEGDEL syndrome. MEGDEL syndrome was recently found to be caused by mutations in *SERAC1*, encoding a protein essential for mitochondrial function, phospholipid remodeling, and intracellular cholesterol trafficking. We identified a novel homozygous mutation in *SERAC1* gene (c.1018delT) that generates frame shift and premature termination of protein translation. Plasma and cerebrospinal fluid lactate, plasma alanine, and respiratory chain complexes in fresh muscle were normal. This report further expands the genetic spectrum of MEGDEL syndrome and adds to the evidence that it is associated with variable patterns of respiratory chain abnormalities.

Keywords

MEGDEL, Leigh-like syndrome, sensorineural deafness

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3-Methylglutaconic aciduria constitutes a heterogeneous group of rare, inherited diseases that share a common metabolic finding: increased excretion in the urine of 3-methylglutaconic acid.[1] Five distinct types have been recognized: 3-methylglutaconic aciduria type I is an inborn error of leucine metabolism; the additional 4 types all affect mitochondrial function through different pathomechanisms.[2] The heterogeneous group of 3-methylglutaconic aciduria type IV consists of patients with various organ involvement and mostly progressive neurologic impairment in combination with 3-methylglutaconic aciduria and biochemical feature of dysfunctional oxidative phosphorylation.[2,3] Patients with MEGDEL syndrome present during early childhood with the unique combination of 3-methylglutaconic aciduria, deafness, progressive spasticity and dystonia, psychomotor retardation, and Leigh-like syndrome on brain magnetic resonance imaging (MRI).[2-4] Variable patterns of respiratory chain activities were reported from normal to multiple defects.[3-5]

Before this report, 15 different mutations in *SERAC1* were identified as the genetic cause of MEGDEL syndrome in 16 patients.[4,5]

We report a patient with 3-methylglutaconic aciduria, sensorineural deafness, and bilateral basal ganglia lesions resembling Leigh syndrome. Blood and cerebrospinal fluid lactic acid were normal and the activity of mitochondrial complexes I-V measured in fresh muscle biopsy sample were normal. This clinical phenotype was associated with the identification of a novel homozygous deletion mutation in exon 10 of *SERAC1* gene.

Case Summary

This 21-month-old boy was born at term from consanguineous Palestinian parents after uneventful pregnancy. Intrauterine growth was retarded and birth weight was 2200 g (–2.5 standard deviation). The length and head circumference at birth were not available. At age 2 days, he was hospitalized at a neonatal unit for evaluation of lethargy and poor sucking. He was found to have hypoglycemia that improved after treatment with intravenous fluids and glucose infusion and the results of sepsis workup were negative. At age 9 months, he was unable to sit and at age 1 year, he showed significant motor and speech

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delay. There was no history of seizure or abnormal behavior. At age 18 months, brainstem auditory evoked potential showed moderate bilateral sensorineural hearing loss requiring the application of hearing devices.

He was hospitalized at our unit at age 21 months for evaluation of psychomotor delay and deafness. His growth parameters were as follows: weight 9400 g (–3 standard deviation), length 78 cm (–2 standard deviation), and occipitofrontal circumference 45 cm (<–2.5 standard deviation). Neurologic examination showed mild generalized hypotonia. He had normal eye contact and ophthalmic examination. There were no dystonia, dysmorphic features, or skeletal abnormalities.

Investigations included the following: serum ammonia 44 μmol/L (controls 10-50 μmol/L), blood lactic acid 1.4 mmol/L (controls 1.1-2.4 mmol/L), cerebrospinal fluid lactic acid 2.1 mmol/L (controls 1.1-2.4 mmol/L), plasma alanine 195 μmol/L (controls 152-547 μmol/L), free T4 0.92 ng/L (controls 0.8-2 ng/L), aspartate aminotransferase 55 U/L (controls 15-46 U/L), alanine aminotransferase 43 U/L (controls 8-45 U/L). Serum calcium, phosphorous, and venous blood gas were normal. Serum amino acid chromatography was also normal.

Echocardiogram showed left diastolic dysfunction but no evidence of cardiomyopathy. Urine organic acid analysis showed moderate but persistent excretion of 3-methylglutaconic acid and 3-methylglutaric acids without 3-hydroxyisovaleric aciduria. MRI of the brain showed T2 high signal intensity in the basal ganglia symmetrically affecting both lenticular nuclei (Figure 1). Coronal and sagittal T2-weighted images at the level of the cerebellum showed abnormal fourth ventricle and hypoplasia of the inferior cerebellar vermis (Figure 2A, B). Blood cardiolipin levels and OPA3 genetic testing were normal. Muscle biopsy showed normal enzymatic activities of the mitochondrial respiratory chain complexes I-V.

Genomic amplification of whole *SERAC1* gene exons and direct sequencing was performed from the DNA extracted from peripheral blood sample showed that the patient is homozygous for the mutation c.1018delT in exon 10. It is a deletion mutation of T at codon 340 that generates frame shift and premature termination of protein translation after 9 codons (W340GfsX9). Genetic analysis of *SERAC1* gene of both parents showed that they are heterozygous for the same mutation and confirms that they are obligate carriers.

The clinical course was characterized by progressive hypotonia and psychomotor retardation. At age 2 years, the patient succumbed to death after an acute episode of severe pneumonia that led to cardiorespiratory arrest.

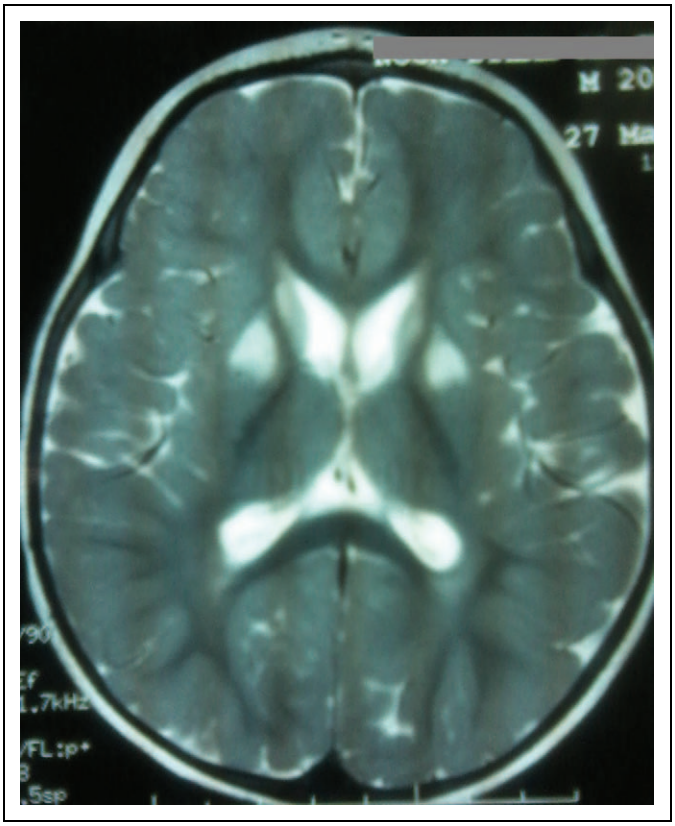

Figure 1. Magnetic resonance image (MRI) of the brain of the index patient. T2-weighted image showing high signal intensity in the basal ganglia symmetrically affecting both lenticular nuclei.

Discussion

The 3-methylglutaconic aciduria type IV is definitely the most intriguing type of the 3-methylglutaconic aciduria with a rapidly broadening spectrum.[2] In contrast to the well-defined distinct types I, II, III, and V, 3-methylglutaconic aciduria type IV is most frequently associated with progressive neurologic impairment, variable organ dysfunction, and biochemical features of a dysfunctional oxidative phosphorylation.[1,2]

Association of 3-methylglutaconic aciduria type IV with Leigh syndrome is rare. Two siblings with 3-methylglutaconic aciduria type IV fulfilled the diagnostic criteria of Leigh syndrome; They had progressive neurologic disease, increased blood and cerebrospinal fluid lactate, and hyperintense lesions on T2 MRI symmetrically affecting both caudate, lenticular nuclei, and the middle portion of both thalami but both had normal enzyme activities of respiratory chain complexes assayed in muscle biopsy homogenates.[1]

MEGDEL syndrome had originally been described in 4 patients with a distinct clinical phenotype characterized by 3-methylglutaconic aciduria, sensorineural deafness, neuroradiologic evidence of Leigh disease, recurrent lactic acidemia, severe neonatal infections, and hypoglycemia.[3] Biochemical evaluation confirmed a deficient oxidative phosphorylation in muscle biopsy and/or in fibroblast of the 4 children. In addition, all had recurrent lactic acidemia from the first weeks of life.[3] Additional 11 patients with MEGDEL syndrome were reported, showing almost similar phenotype with psychomotor retardation, spasticity or dystonia, sensorineural deafness, Leigh-like lesions on brain MRI, and brain atrophy.[2,4] Using exome sequencing, mutations are found in *SERAC1*, encoding an enzyme involved in phosphatidylglycerol remodeling.[4] The enzyme is essential for both mitochondrial function and intracellular cholesterol trafficking.[4]

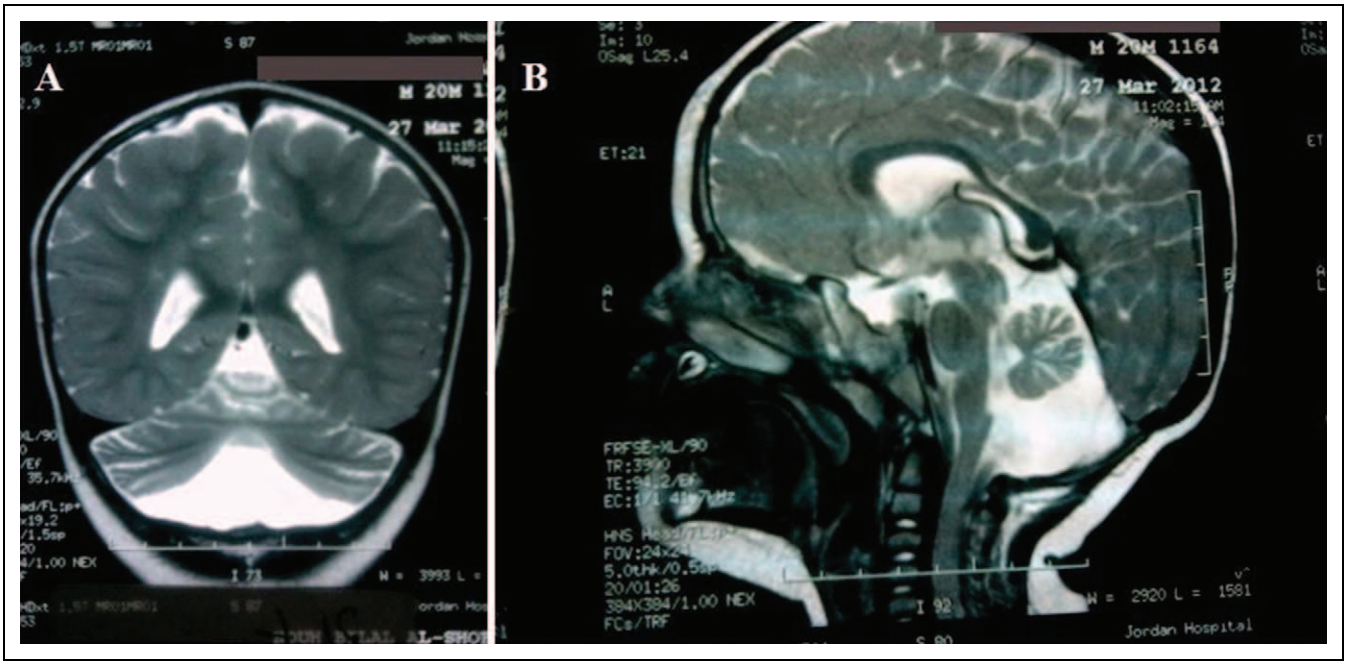

Figure 2. (A) Coronal T2-weighted image of the index patient at the level of the cerebellum showing hypoplasia of the inferior cerebellar vermis. (B) Sagittal T2-weighted image passing through the midline showing abnormal fourth ventricle with inferior vermis hypoplasia.

The identification of *SERAC1* as the genetic cause of MEGDEL syndrome lead to the description of 15 different mutations in 16 patients.[4,5] Psychomotor delay, sensorineural deafness, dystonia, and Leigh-like brain imaging were the characteristic findings in all of them. One patient additionally developed microcephaly and optic atrophy and his biochemical investigations showed normal plasma lactate and alanine.[5] The authors attributed these biochemical findings to the normal respiratory chain complexes in muscle biopsy homogenate. This phenotype was caused by a novel homozygous mutation in *SERAC1* (c.202C>T;pArg68), a nonsense substitution that generates a premature stop codon at position 68 of SERAC1 protein.

A clinical picture simulating a primary mitochondrial hepatic disorder consistent with the MEGDEL syndrome including 3-methylglutaconic aciduria, sensorineural deafness, encephalopathy, and a brain MRI with signs of Leigh disease has been reported in 4 patients caused by novel mutations in *SERAC1* indicating that infantile hepatopathy is a cardinal feature of MEGDEL syndrome. The authors proposed to name the disease "MEGHDEL syndrome."[6]

In the cardiomyopathic subgroup of 3-methylglutaconic aciduria type IV, most patients had complex V deficiency and an overlapping phenotype with that previously described in isolated complex V deficiency.[7-12] To our knowledge, no mutations in *SERAC1* were identified in this subgroup.

In our patient, the clinical phenotype is consistent with MEGDEL syndrome. This phenotype correlated with the identification of a novel homozygous deletion mutation in *SERAC1* gene. Biochemical findings included an increased excretion of 3-methylglutaconic acid and 3-methylglutaric acid without 3-hydroxyisovaleric aciduria compatible with a diagnosis of 3-methylglutaconic aciduria type IV. Similar to the patient described by Tort et al, plasma alanine and lactate were normal in addition to normal respiratory chain complexes in muscle biopsy.

Although the finding of the neuroradiological evidence of Leigh(-like) disease is rather specific for oxidative phosphorylation disorders,[2] we did not find this correlation in our patient.

In summary, this report further expands the genetic spectrum of MEGDEL syndrome and adds to the increasingly recognized evidence that it is associated with variable patterns of respiratory chain abnormalities from normal to multiple defects.

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Author Contributions

The study was devised by IMD. Genetic analysis was performed by SuA. SaA and TJ contributed equally to the preparation of case summary.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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