

CASE REPORT

Undiscovered phenotype of KARS1-related mitochondrial leukoencephalopathy

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ABSTRACT

Background: Infantile onset progressive leukoencephalopathy with or without deafness is an autosomal recessive neurodegenerative disorder with variable clinical presentation, manifesting in infancy or early childhood. This disorder results from a homozygous or compound heterozygous mutation in the *KARS1* gene, resulting in a dysfunctional mitochondrial enzyme.

Case Presentation: We report a 4-year-old Saudi boy of non-consanguineous parents, with a compound heterozygous mutation in the *KARS1* gene presenting with speech delay, bilateral sensorineural hearing loss, unilateral progressive hemiparesis, iron deficiency anemia, and lytic bone lesions.

Conclusion: *KARS1* mutation has a heterogeneous phenotypic presentation and variable clinical severity. We report a new clinical feature of lytic bone lesions which could potentially expand the phenotype of this genetic disorder spectrum. Early recognition of the clinical presentation is warranted to facilitate diagnosis, prognosis, and appropriate family counseling.

Keywords: *KARS1*, leukoencephalopathy, developmental delay, hemiplegia, deafness, lytic bone lesions.

Background

KARS1 gene is located on chromosome 16q23.1 and contains 15 exons of which the alternative splicing of the first 3 exons results in the encoding of the cytoplasmic and mitochondrial isoforms of lysyl-tRNA synthetase (1); which is responsible for catalyzing the conjugation of amino acids to cognate tRNAs for protein synthesis. Homozygous variants in the *KARS1* gene have been linked to different phenotypes involving various organ systems, including Charcot-Marie-Tooth disease, infantile-onset progressive leukoencephalopathy with or without deafness, congenital deafness and adult-onset progressive leukoencephalopathy, cardiomyopathies, immune-hematological disorders, among others (2-6). Most reported cases presented with developmental delay, microcephaly, seizures, and oculomotor abnormalities. Various reports show evidence of mitochondrial dysfunction as seen in magnetic resonance spectroscopy (MRS) and mitochondrial oxygen consumption (7).

Case Report

A 4-year-old Saudi boy presented with progressive walking difficulty due to weakness of the left lower limb along with left-sided upper limb weakness over a period of 3 weeks. His neurological symptoms were preceded by a febrile illness requiring antibiotics. There was no associated dysarthria, facial weakness, bulbar symptoms,

or seizures. No headaches, change in sensorium, or behavioral changes. No visual symptoms were reported. He was investigated at a local hospital and managed as a case of suspected perinatal stroke and thus commenced on Aspirin.

The child was born full-term following an unremarkable pregnancy via spontaneous vaginal delivery without any neonatal complications. He continued to develop and gain his milestones appropriately on time except for receptive and expressive speech delay. Hearing assessment at the age of 3 years revealed bilateral moderately severe sensorineural hearing loss. He was fitted with a hearing aid and provided speech therapy with modest improvement of his language skills.

His parents are non-consanguineous, and his three older siblings are all healthy. The mother had a history

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of unknown-cause early abortion. Family history was unremarkable for neurodevelopmental or neurogenetic disorders apart from mild hearing difficulty in his father that was never evaluated and thus unknown if it is due to genetic or non-genetic causes.

His neurological examination was remarkable for left-sided weakness, where his left upper and lower limbs were moving against gravity but not against resistance. He had left-sided hypertonicity and hyperreflexia in upper and lower limbs with left foot clonus. The power in his right upper and lower limbs was normal, yet with mild hypertonia in both. His cranial nerve examination was normal apart from poor hearing. His gait was notable for unsteadiness and left-sided circumduction. There were no cerebellar signs. No contractures or deformities. The child had poor speech but was fairly interactive and following commands. There were no distinctive features or any neurocutaneous stigmata. His systemic examination was unremarkable without any organomegaly.

Laboratory analysis showed slightly increased lactic acid at 3.3 mmol/L and borderline hemoglobin of 11.5 g/dL with indices suggestive of iron deficiency anemia. Immunoglobulins IgG and IgA levels were normal, but IgM level was low. His stroke and vasculitis work-up was unremarkable. He had a normal echocardiography

and Holter monitoring. His nerve conduction study (NCS) was normal; however, Electromyography could not be done given the nature of the exam and sub-optimal cooperation of the child.

Computerized tomography (CT) of the brain showed bilateral asymmetric hypodensities involving the posterior limbs of the internal capsule and extending superiorly through the corona radiata to the centrum semiovale, more pronounced on the right side, with mild associated swelling. CT Angiogram and CT Venogram were normal.

His brain magnetic resonance imaging (MRI) showed abnormally high T2 signal intensity within the corticospinal tract and the splenium of the corpus callosum (Figure 1A and B) with expansion and restricted diffusion (Figure 1C and D). Numerous variable-sized ill-defined T2/T1 hypointense lesions were seen throughout the axial skeleton involving the skull, the whole spine, ribs, and pelvic girdle (Figure 1E and F). No associated fractures or soft tissue components were seen. MRS was remarkable for a significant decrease in NAA peak with prominent choline and creatine peaks (Figure 2).

Whole exome sequencing revealed compound heterozygous mutations in *KARS1* gene c.306+1G>T P.? (NM_001130089.1) splicing mutation with uncertain

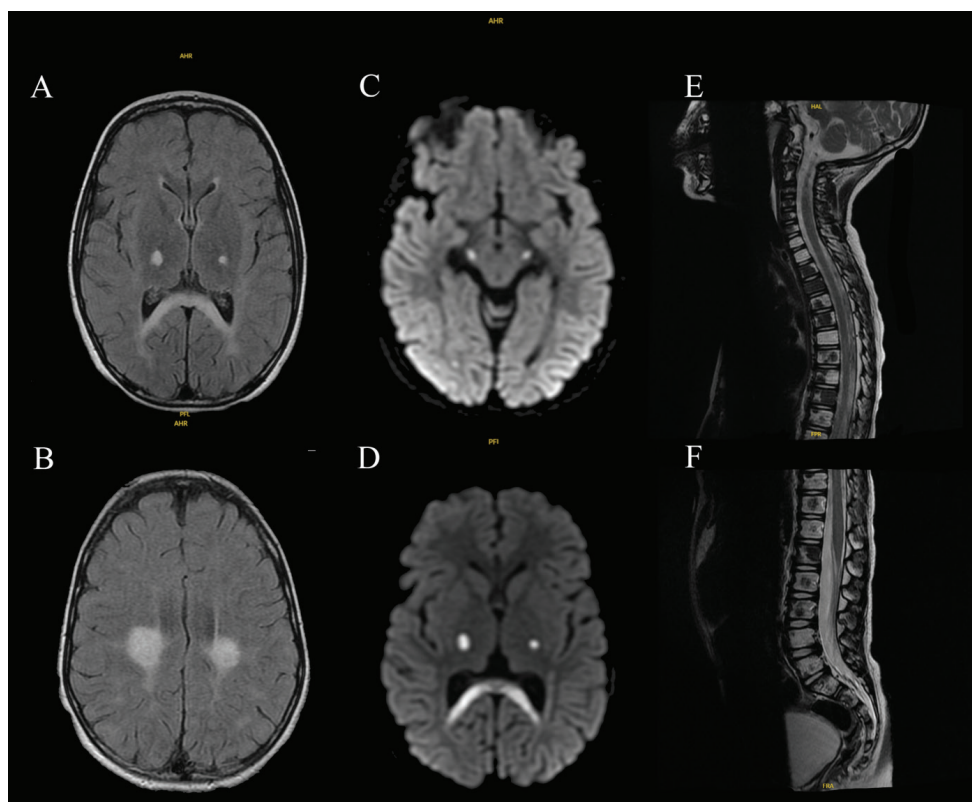


Figure 1. (A, B) MRI brain, axial view, T2 FLAIR, showing relatively symmetrical T2 hyperintensities in the corticospinal tract bilaterally, extending from the perirolandic cortex across the corona radiata, posterior limb of the internal capsules till the cerebral peduncles and the splenium of the corpus callosum. (C, D) MRI brain, axial view, DWI, showing restricted diffusion bilaterally along the corticospinal tract and the splenium of the corpus callosum. (E, F) MRI spine, sagittal view, T2 FRFSE revealing the numerous variable-sized ill-defined T2/T1 hypointense lesions are seen throughout the axial skeleton involving the skull, the whole spine, ribs, and the pelvic girdle. No associated osseous fracture or soft tissue component is seen.

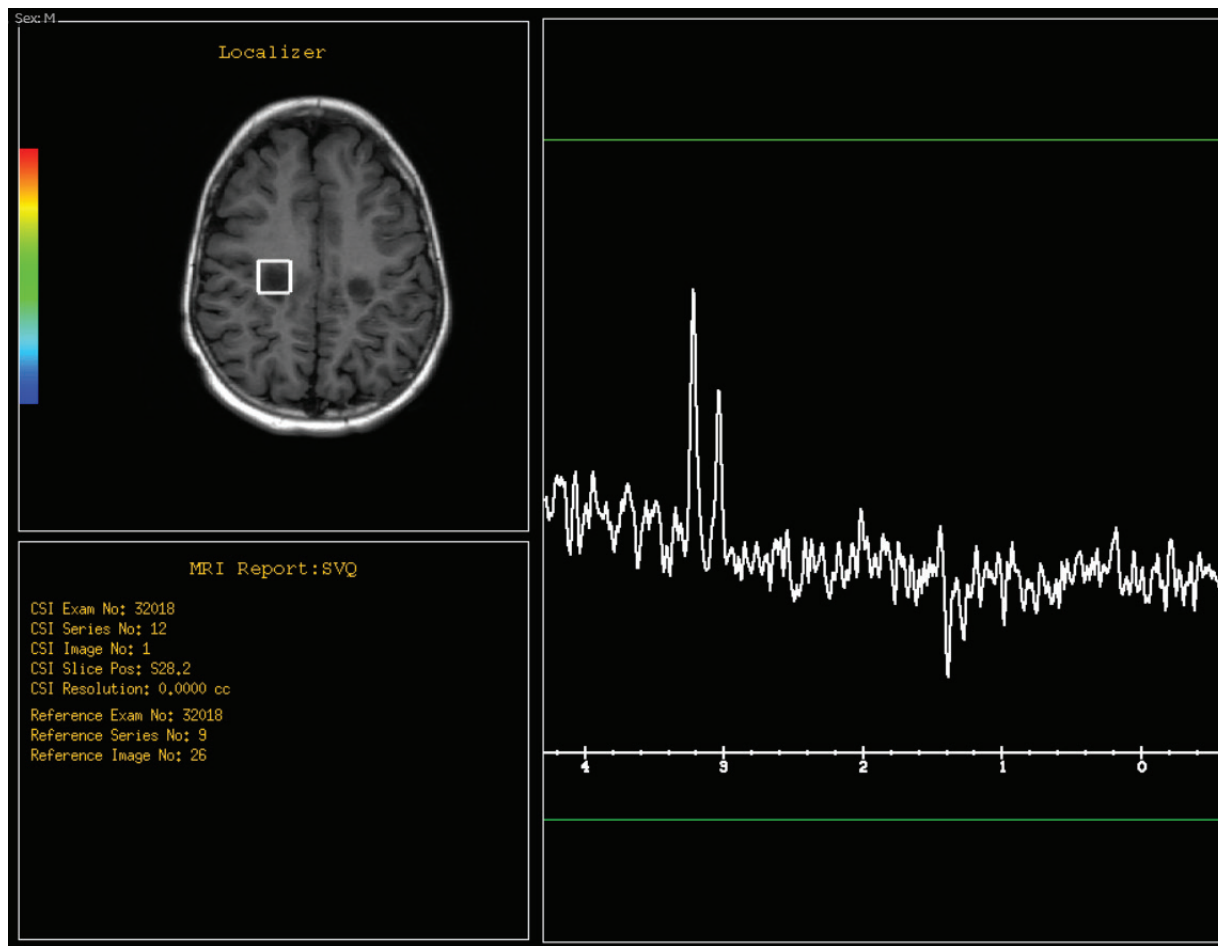


Figure 2. MRS brain: significant decrease in NAA peak is noted with prominent choline and creatine peaks.

significance (class 3), that was never reported in the literature before, and a missense likely pathogenic (class 2) mutation in *KARSI* gene c.379T>C p.Phe127Leu (NM_001130089.1), which was previously reported by Ardisson et al (8) in two Italian patients with leukoencephalopathy with spinal cord calcification. This mutation suggests the diagnosis of mitochondrial disorder with progressive leukoencephalopathy, infantile-onset, with or without deafness with compound heterozygosity. No other variants or mutations were reported in his WES results to explain the whole or part of his phenotype. Sanger sequencing was offered to the family but was not done due to paternal preferences, compromising crucial information about the inheritance pattern of the mutation.

The child was started on L-carnitine, biotin, thiamine, and cholecalciferol and commenced on regular, intensive physiotherapy and occupational therapy. On follow up, the child had progression of his symptoms with regression in his language skills and increasing spasticity of the limbs making the child immobile and completely dependent on a caregiver for activities of daily living.

Discussion

The reported child has a compound heterozygous mutation in the *KARSI* gene with a phenotype consistent with infantile-onset progressive leukoencephalopathy with deafness.

To the extent of our knowledge, *KARSI*-related disorders are being more recognized with the help of molecular genetics; however, the majority of studies are case reports from different populations irrespective of ethnicity, with the majority of cases reporting a compound heterozygous mutation in *KARSI* gene rather than homozygous mutations (2,3,5,6).

Clinical presentations in these cases varied with some patients having onset since birth presenting with developmental delay and microcephaly, whereas others showing a regressive course (6). Seizure is a common presentation or association with developmental delay. Hearing loss is commonly diagnosed. Our patient's presentation is unique as he presented with stroke-like symptoms with asymmetrical weakness and spasticity. The weakness of his limbs was progressive over a period of a few weeks which was probably triggered by the inter-current illness. Interestingly, our patient showed full-length T2/T1 hypointense lesions throughout the axial skeleton involving the skull, the whole spine, ribs, and pelvic girdle lytic lesions, which was not reported before, and although such association is not yet confirmed, it suggests an expanded phenotype of *KARSI* related disorders. Leukoencephalomyelopathy, deafness, seizures, and spinal cord calcification have been reported previously in three children (4,5), two of which are Japanese siblings with *KARSI* mutation who were also

reported to have anemia (4). Our reported patient did not have any cord calcification but he had a long-standing iron-deficiency anemia despite iron supplementation. Importantly, the lack of segregation analysis prevents us from exploring whether the patient's father's hearing loss was due to a splice mutation and recognizing the inheritance pattern of the patient's mutation.

Conclusion

In summary, this is a confirmed case of regressive leukoencephalopathy, infantile-onset, with deafness with compound heterozygous mutations in the *KARS1* gene in a Saudi patient. He had a matching phenotype of leukoencephalopathy, progressive infantile-onset, with deafness and anemia. The lytic lesion in the axial skeleton is a feature not described in earlier reports, which could be an additional feature of this disorder.

This condition is one of the mitochondrial disorders spectrum where early intervention with supportive management should be advocated.

We highlight the genetic and phenotypic heterogeneity of *KARS1* mutations and the possibility of associated skeletal lesions, contributing to the genetic diagnosis and family counseling of the parents of patients with such mutations.

Declaration of conflicting interests

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Consent for publication

Not necessary for this manuscript.

Ethical approval

Consent was waived for all participants in this study by the research center at King Fahad Medical City, Riyadh, Saudi Arabia; given the observational design of the study.

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