Early Infantile Leigh-like *SLC19A3* Gene Defects Have a Poor Prognosis: Report and Review

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ABSTRACT: Solute carrier family 19 (thiamine transporter), member 3 (*SCL19A3*) gene defect produces an autosomal recessive neurodegenerative disorder associated with different phenotypes and acronyms. One of the common presentations is early infantile lethal Leigh-like syndrome. We report a case of early infantile Leigh-like *SLC19A3* gene defects of patients who died at 4 months of age with no response to a high dose of biotin and thiamine. In addition, we report a novel mutation that was not reported previously. Finally, we review the literature regarding early infantile Leigh-like SLC19A3 gene defects and compare the literature with our patient.

KEYWORDS: *SCL19A3* gene defect, *SLC19A3* gene, Leigh syndrome, Leigh-like, biotin, thiamine

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Introduction

Solute carrier family 19 (thiamine transporter), member 3 (*SCL19A3*) gene defect produces an autosomal recessive neurodegenerative disorder associated with different phenotypes and acronyms. The known phenotypes include early infantile Leigh-like, classical childhood, and Wernicke-like encephalopathy. In early infantile lethal Leigh-like syndrome, the probands usually present in the first 3 months of life with Leigh-like syndrome: poor feeding, vomiting, acute encephalopathy, and lactic acidosis. Magnetic resonance imaging (MRI) of patients' brains usually shows high T2 signals involving the perirolandic area, bilateral putamen, and medial thalamic nuclei, with the spectroscopy showing lactate peaks.[1] The second phenotype is the classical childhood onset biotin-thiamine responsive basal ganglia disease. In this disorder, the symptoms usually start between 3 and 7 years of age with subacute encephalopathy and confusion, dysarthria, and dysphagia, with occasional central facial palsy or external ophthalmoplegia that progresses to severe cogwheel rigidity, dystonia, seizure, quadriparesis, and even death if left untreated with biotin and thiamine.[2–4] The third phenotype is the adult Wernicke-like encephalopathy-*SLC19A3* gene defect, which was reported in 2 Japanese men, both of whom presented in their second decade of life with status epilepticus, diplopia, nystagmus, ptosis, ophthalmoplegia, and ataxia. Brain MRI showed high-intensity signals in the bilateral medial thalamus and periaqueductal gray region. The patients showed a dramatic response to a high dose of thiamine.[5] The disease is caused by a defect in thiamine transporter 2 (hTHTR2), which is encoded by the *SLC19A3* gene. Diagnosis is usually made after molecular testing for the *SLC19A3* gene defect, and measurement of the free thiamine level could be a potential biomarker for monitoring and diagnosis of this disorder.[6] The treatment consists of thiamine alone or in combination with biotin for life.[2,3,7] In this report, we describe a case of early infantile Leigh-like-*SLC19A3* gene defects who died at 4 months of age with no response to a high dose of biotin and thiamine. In addition, we report a novel mutation that was not reported previously. Finally, we review the literature regarding early infantile Leigh-like-*SLC19A3* gene defects and compare it with our patient.

Case Report

A 2-month-old infant, full-term, through a normal vaginal delivery, was born to healthy Saudi consanguineous parents with appropriate growth parameters and no significant antenatal history. This first child of this couple was discharged on the second day of life with no complications. He presented to our center with a 3-day history of low-grade fever, poor feeding, decreased activity, and complex partial seizures in the form of turning the head to the right with eye staring; then, the patient was admitted to the pediatric intensive care unit, where he was started on parenteral phenobarbital and antibiotics after performing all necessary investigations, including a septic workup. Then, the patient's condition deteriorated as he became encephalopathic and required mechanical ventilation. On examination, his length was 56 cm (5th percentile), weight was 4 kg (5th percentile), and head circumference was 38.5 cm (25th percentile).

He had poor eye contact, horizontal nystagmus, axial hypotonia with appendicular hypertonia, hyperreflexia, and clonus in both upper and lower limbs. Other system examinations were unremarkable. Investigations showed the following results. Brain MRI showed cystic changes in both cerebral hemispheres and signal abnormality in the brain stem and cerebellum. There were abnormalities in the bilateral basal ganglia

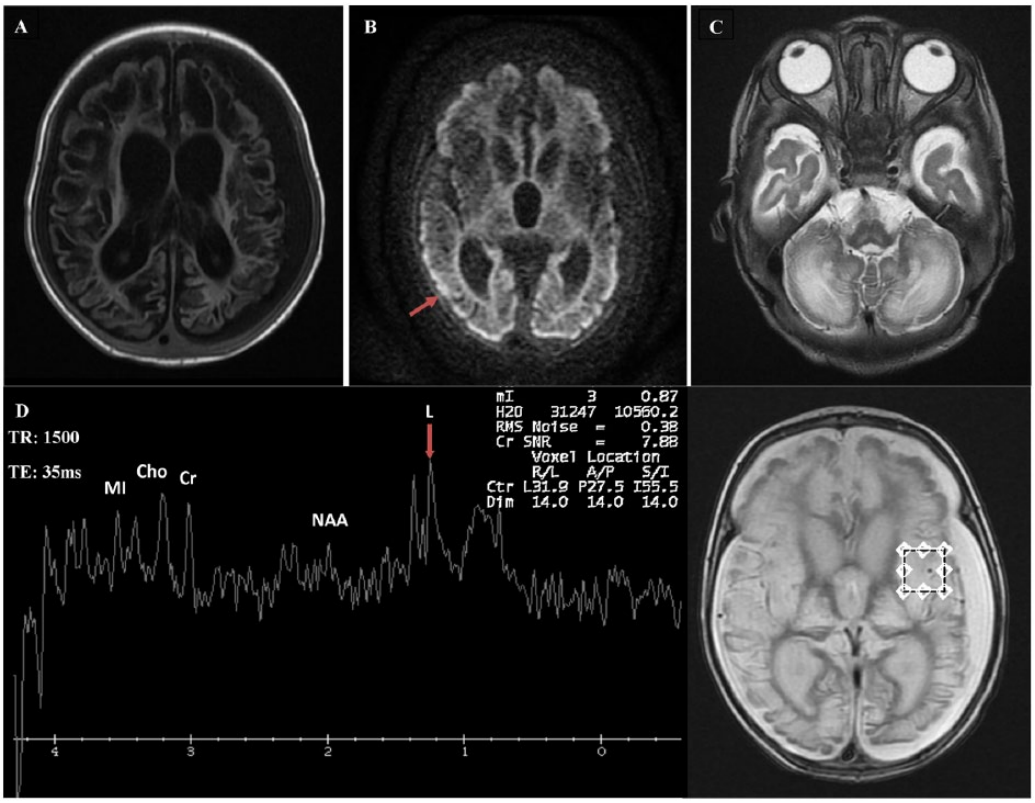

Figure 1. Brain MRI and MRS. (A)-T1 weighted axial section showing extensive brain damage with cystic encephalomalacia, bilateral subdural effusion, and ex vacuo enlargement of the ventricles. (B) Diffusion-weighted image, axial section, showing restricted diffusion in the margin of the cerebral cortices bilaterally (arrow). (C) T2-weighted axial section showing abnormal signaling in the cerebellum and volume loss in brain stem. (D) MRS showing mild lactate peak at 1.3 ppm (arrow). TE: 35 ms. Ch indicates choline; Cr, creatine; L, lactate; MI, myoinositol; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; TE, echo time.

and thalamus, with volume loss. There was diffuse volume loss of both cerebral hemispheres with ex vacuo enlargement of the ventricles. There were bilateral moderate subdural effusions (Figure 1). Magnetic resonance spectroscopy confirmed a mild lactate peak at 1.3 ppm (Figure 1). Electroencephalogram demonstrated a slow diffuse background indicating nonspecific encephalopathy. There was low voltage activity with periods of suppression, followed by a burst of low-voltage multifocal epileptic discharges. The epileptic discharge was greater over the right temporal head region. The auditory brain stem response, echocardiogram, and ophthalmology evaluation were normal.

Lab investigations showed mildly elevated lactic acid in the blood, ranging from 2.6 to 3.0 mmol/L (normal values are 1.2-2.2 mmol/L). Blood gas showed mild metabolic acidosis as follows (venous pH: 7.30, P_{CO2}: 52 mm Hg, base excess: −1.7). Plasma amino acids showed mildly elevated alanine levels. All other biochemical investigations in the serum, urine, and cerebrospinal fluid were unremarkable.

Whole exome sequencing revealed a novel homozygous frameshift duplication in the *SLC19A3* gene (NM_025243.3; c. 91dupT, p. Val65Glyfs*160). The parents were tested, and they are heterozygous for this mutation. The patient was started on high doses of biotin 20 mg twice a day (10 mg/kg/d) and thiamine 75 mg twice a day (37.5 mg/kg/d). Despite maximal support, the patient's condition deteriorated, and he succumbed at 4 months of life.

Discussion

Table 1 summarizes the clinical characteristics of the early infantile form of *SLC19A3* gene defects and compares it with our patient. Interestingly, before 2013, Leigh-like *SLC19A3* gene defects were not yet a known phenotype. However, during that year, 19 infants were described from different origins but were mainly Moroccans (Table 1).[1,8,9] The clinical pictures were almost the same, with an acute devastating course between the first and third months of life. The reported patients started to have poor feeding and vomiting that progressed to seizure and acute encephalopathy after a period of febrile illness. The MRI findings showed a picture of Leigh syndrome with extensive signaling abnormalities in the brain stem and cerebellum. There were abnormalities in the bilateral basal ganglia and thalamus with brain atrophy. Magnetic resonance spectroscopy demonstrated a lactate peak in most of these patients. Subsequently, different probands from Mexico, Turkey, Sweden, and Poland were reported.[10–13] The current report is the first from Saudi Arabia with Leigh-like *SLC19A3* gene defect.

Strikingly, Yamada et al[14] reported different phenotypes of early infantile SLC19A3 gene defects that are infantile spasm.

Table 1. Summary of all published cases of the early infantile *SLC19A3* gene defect.

S. NO.	REFERENCES	NO. OF CASES	ORIGIN	M:F	AGE OF ONSET	*SLC19A3* GENE MUTATION	TREATMENT WITH BIOTIN	TREATMENT WITH THIAMINE	PROGNOSIS
1	Kevelam et al[8]	7	Canada Europe Lebanon Morocco	NA	Mean: 2.7 mo	Canadian: [c.68G>T(p.Gly23Val); r.1173_1314del(p.Gln393*)] European: [c.541T>C(p.Ser181Pro); c.1154T>G(p.Leu385Arg)] European: [c.507C>G(p.Tyr169*); c.527C>A(p.Ser176Tyr)] Lebanese: c.895_925del(p.Val299fs) Moroccan: c.1332C>G(p.Ser444Arg)	Yes	No	All died
2	Gerards et al[9]	11	Morocco	8:3	1 mo	c.20C>A(p. p.Ser7*)	Yes	Yes	All died
3	Pérez-Dueñas et al[1]	1	Morocco	M	4 wk	c.68G>T(p.Gly23Val)	10 mg/d	20 mg/kg/d	Excellent response to biotin and thiamine
4	Sremba et al[10]	1	Mexico (mixed ancestry)	F	6 wk	c.74dupT(p. Ser26LeufsX19) c.81_82dup(p.Met28fs)	No	10 mg/kg/d	Died at 12 y
5	Haack et al[11]	2	Turkey	M	18 d	c. 982del(p. Ala328Leufs*10)	10 mg/kg/d	15 mg/kg/d	Improved dramatically
6	Ygberg et al[12]	2	Sweden	M	5 wk	c.74dupT/p. Ser26LeufsX19 c.1403delA	10 mg/kg/d	60 mg/kg/d	First patient died, whereas second survived with dystonic symptoms
7	Pronicka et al[13]	1	Poland	M	Birth	c.74dupT(p.Ser26LeufsX19)	Yes	Yes	Died
8	Alfadhel[3]	1	Saudi	M	2 mo	c. 91dupT, p. Val65Glyfs*160	Yes	Yes	Died
Total		26		13:4	1-3 mo				

Abbreviations: F, female; M, male; NA, not available.

They reported 4 male Japanese patients with poor response to biotin and thiamine.

Unlike the juvenile form of the *SLC19A3* gene defect, the prognosis of early infantile Leigh-like *SLC19A3* gene defect seems to be poor despite treatment with biotin and thiamine. Indeed, 22/26 (85%) of the reported children died; 1 survived with dystonic symptoms, and only 3 patients had good response to treatment with biotin and thiamine.[1,8,9,11,12]

In addition, the early infantile Leigh-like *SLC19A3* gene defect is associated with some biochemical abnormalities, which include high lactate and alanine, increased leucine and isoleucine, and increased excretion of α-ketoglutarate, whereas the juvenile form has normal biochemical profiles.[1] This result could be explained by a deficiency of the thiamine active form (thiamine pyrophosphate), which is an important cofactor for 3 mitochondrial enzymes (pyruvate dehydrogenase complex, branched chain α-ketoacid dehydrogenase complex, and α-ketoglutarate dehydrogenase).[8]

The poor response to treatment in this phenotype supports the conclusion from functional studies that the effectiveness of treatment mainly depends on whether the transport capacity is reduced at physiological levels, whereas it seems unlikely to be beneficial in cases where the transporter function is completely abolished when there is a null mutation in the early-onset form.[15]

Conclusions

We reported the first early infantile Leigh-like *SLC19A3* gene defect from Saudi Arabia, with a novel mutation not described previously. We confirmed the poor prognosis of this a phenotype despite maximizing treatment with biotin and thiamine. We also alert clinicians to consider the SLC19A3 gene defect in any infant presenting early in life with Leigh-like syndrome. The poor response to treatment and outcome warrants thorough genetic counseling for the families and proper planning for future pregnancies.

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Author Contributions

MA performed all the work associated with preparing, writing, and submitting the manuscript and contributed to the clinical diagnosis and management of the patients.

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