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Educational Corner – Case Report

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Not All Neonatal Encephalopathies Are due to Perinatal Hypoxia

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DARS2 mutation · Genetic disorders · Leukoencephalopathy · Neonatal encephalopathy · Hypoxic Ischemic encephalopathy

Abstract
A late preterm female neonate, born to a consanguineously married couple by normal vaginal delivery and unremarkable family history, was admitted to our NICU soon after birth for management of respiratory distress secondary to meconium aspiration syndrome and persistent pulmonary hypertension of newborn. She required intensive ventilatory and hemodynamic support and was encephalopathic since birth but did not fulfill the criteria for therapeutic hypothermia. Extensive metabolic workup revealed no diagnosis, but neuroimaging showed characteristic findings consistent with the diagnosis of leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation. This was supported by the result of whole exome sequence that identified a novel homozygous mutation, c.1191 + 11A>C, for DARS2 gene confirming the diagnosis.

Introduction

Neonatal encephalopathy (NE) defines neonates with abnormalities in sensorium, neuromotor status, and seizures. Moderate/severe NE affects 0.5–3/1,000 live births in developed countries and carries high risk of mortality and/or morbidity [1]. Hypoxic ischemic encephalopathy (HIE) is a specific diagnosis attributed to those NE secondary to reduced blood flow and/or oxygenation around the time of birth. Criteria such as low Apgar scores, acidemia, multiorgan dysfunction point toward HIE [2]. Therapeutic hypothermia (TH) in HIE reduces the risk of death and disability [3]. NE due to infection, malformations, strokes, metabolic and genetic disorders act as differentials of HIE. At such a time, an assumption that NE is due to HIE acts as a distractor to other etiologic possibilities [2].

Genetics and genomics are considered a major contributor to NE diagnostic algorithm [1]. Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), a rare genetic disorder, can also present as "HIE mimic." We present a case of a late preterm girl with an ultimate diagnosis of LBSL who posed a diagnostic dilemma since birth, forcing a look beyond the "HIE conundrum."

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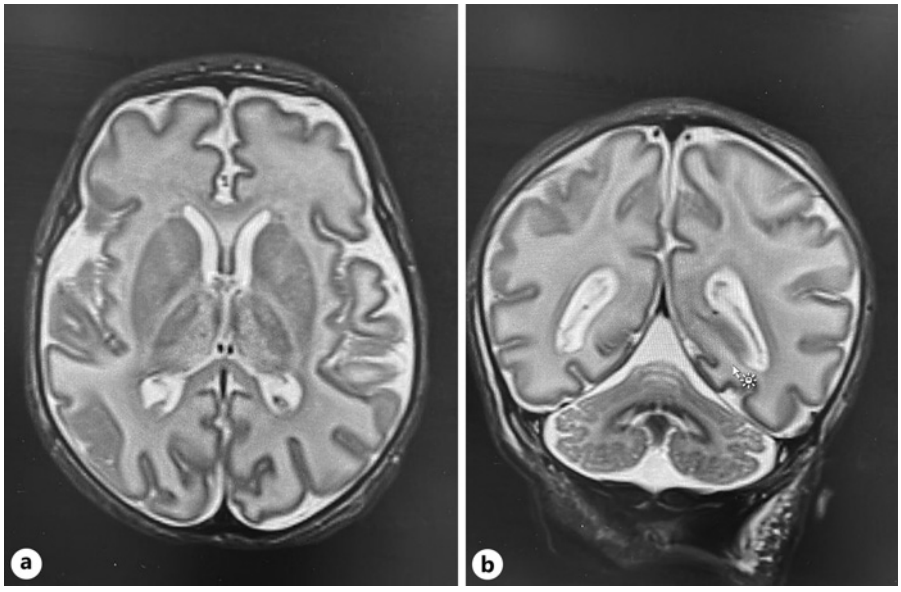

Fig. 1. a, **b** MRI brain (day 7) showing abnormalities in periventricular white matter, internal capsule, and brain stem.

Case Report

A female neonate born at 36 3/7 weeks to first cousins after a relatively uncomplicated pregnancy was admitted soon after birth for ventilatory support. Family history (including siblings) remained unremarkable. Born via normal vaginal delivery through meconium-stained liquor weighing 2,350 g (51st centile), her length and head circumference were 49 cm (96th centile) and 30.5 cm (7th centile), respectively (intergrowth 21st chart). No antecedents of fetal compromise were noted. Poor respiratory efforts at birth required positive-pressure breaths followed by endotracheal intubation due to respiratory distress. APGAR scores were assigned as 2 and 7 at 1 and 5 min, respectively. She was ventilated and brought to the NICU.

On examination, she was noted as non-dysmorphic with minimal spontaneous movements, limited limb extension, hip abduction, and hypotonia followed by hypertonia and brisk reflexes. Fundi were normal.

The highest serum lactate was 5.8 mmol/L within the first hour and returned to normal (1.2 mmol/L) within the first 6 h. She did not satisfy criteria of TH. Her Meconium Aspiration Syndrome was complicated by persistent pulmonary hypertension and systemic hypotension, requiring intensive ventilatory and hemodynamic support that could be weaned over 5 days. Her blood and cerebrospinal fluid remained sterile.

Presence of very early-onset encephalopathy, pseudobulbar palsy, early spasticity, lack of seizures, and both cerebral function monitor and formal electroencephalogram showing burst suppression pattern prompted neuroimaging. Magnetic resonance imaging (MRI)/magnetic resonance spectroscopy of the brain (shown in Fig. 1) on day 7 demonstrated abnormalities in periventricular white matter, internal capsule, and brain stem with elevated choline and depressed N-acetyl aspartate levels, but no lactate peaks, being non-characteristic of HIE. Antenatal origins of encephalopathy were suggested. Extensive metabolic workup including cerebrospinal fluid neurotransmitters also did not reveal any cause for NE.

Whole exome sequencing on the family revealed a novel homozygous variant, c.1191 + 11A>C (both parents heterozygous), in the DARS2 gene associated with autosomal recessive LBSL (MIM: 611105). Uniformly poor prognosis was explained to the family, and genetic counseling was provided. Sibling screening was offered. She was discharged home after a stay of 3 months with gastric tube feeding and continuous oropharyngeal suction. Other than a brief readmission for respiratory illness, she remains at home thriving but with microcephaly and remains dependent on tube feeding and continuous oropharyngeal suction. Baclofen, clobazam, and scopolamine patch were started.

Discussion

LBSL is a genetic cause of NE which was identified in 2003 as distinct leukodystrophy based on highly characteristic MRI pattern [4]. Characterized by slowly progressive cerebellar ataxia and spasticity with dorsal column dysfunction [5], the age of onset is variable, typically from childhood to adulthood. Very few infantile cases and even fewer neonatal cases are reported. Neonatal presentation is very severe with death occurring in early years [5–9].

It is caused by a recessive mutation in the *DARS2* gene, which encodes the mitochondrial aspartyl-tRNA synthetase [7]. LBSL can start antenatally and can present as severe NE similar to present case [4, 7–9]. Absence of typical lactate peaks in the brain, optic atrophy, and elevated creatine kinase, as noticed in current case, are also described as part of varied presentation [6, 7].

MRI, with its strict diagnostic criteria, often helps suspect LBSL in cases of NE. In the absence of typical involvement, the diagnosis is often delayed beyond the neonatal period [5, 6].

Present case showed features of NE but without any predisposing factors of HIE secondary to perinatal hypoxia [1]. Moreover, presence of atypical features like early spasticity, absence of seizures, small head, possibility of fetal encephalopathy, consanguinity, burst suppression pattern, and MRI prompted a look elsewhere [2]. Following a structured process [10], genetic origin of her NE was identified. To the best of knowledge, this novel DARS2 mutation responsible for rapidly progressive course in infancy is one of the first reported case to be linked to NE from the Middle East. Hence, a point to remember is – not all neonatal encephalopathies are "HIE." The role of genomic studies (whole exome sequencing [WES] and whole genome sequencing [WGS]) in identifying genetic causes of NE cannot be underestimated [2], especially in Middle Eastern region. In a study done by Wei et al. [11], 36% of cerebral palsies without antecedent risk factors tested positive for genetic etiology. Although WES/WGS have increasingly identified genetic origins of "so-called HIE" neonates [2], their diagnostic yield is around 10–40% [12]. Several NE remain genetically undiagnosed [1]. Clinically targeted WES/WGS will have more answers in the future.

Another important question was – should this baby have undergone cooling? This case began as an undiagnosed NE that did not satisfy the cooling criteria and later on could be recognized as genetic NE by timely genomic studies. It is known that TH criteria are purposefully kept broad because the benefits of cooling the "likely HIE" who are actually "HIE mimics" outweigh the risks ([13] cited in Sandoval Karamian p 2 [2]). Using TH does not confirm HIE/perinatal hypoxia [2]. Genomic studies, like in present case, would have the potential not only to demystify the "atypical NE" puzzle but also to address recurring murky medicolegal issues associated with NE/HIE [1]. Systematic clinical and judicious investigative approach as described above can help identify genetic causes of NE such as LBSL among differential diagnosis of either unexplained NE or atypical HIE.

Statement of Ethics

Written informed consent to publish was obtained from the parents of the patient while maintaining strict privacy and confidentiality. Institutional Ethics Committee permission (as a policy) has been obtained prior to publication. Communications with the Ethics Committee can be shared on request. Authors indicate compliance with ethical standards in clinical research and data sharing as laid down by the Institutional Ethics Committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tushar Kulkarni and Lma Dsougi Hussein Mohamed conceived the article, performed review of the literature, and drafted the article. Mahmoud El Halik and Fatma Abdulla Mohammad Bastaki critically reviewed the article. All authors approved the final manuscript.

Data Availability Statement

Data generated or analyzed during this case are included in this article. Further inquiries can be directed to the corresponding author.

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