Sedation Considerations in Leigh Syndrome

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ABSTRACT

Leigh syndrome (LS) is a rare progressive neurodegenerative, mitochondrial disorder of childhood. The clinical presentation of LS is highly variable. However, in most cases, it presents as progressive neurological deterioration with motor, intellectual, and developmental regression and signs and symptoms of brainstem dysfunction with or without basal ganglia involvement. Here, we report a case of a 15-month Saudi female child with LS and encephalopathy who was discovered with a novel variant in the gene *(c.36G > A p.(Trp12*)* chr5:60241118) homozygous with a family history of a brother who died at the age of 2 years due to complications after introducing chloral hydrate for brain imaging. Herein, we report a case of LS with a novel gene variant *(c.36G > A p.(Trp12*)* chr5:60241118) homozygous and highlight the possible fatal complications of chloral hydrate in such patients.

Key Words: *Leigh Syndrome, Encephalopathy, Chloral hydrate.*

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INTRODUCTION

Leigh syndrome (LS) is a sub-acute necrotising encephalopathy, a rare progressive neurodegenerative disorder of infancy.[1,2] It is the most common mitochondrial disorder.[3,4]

Symptoms are variable due to the heterogeneous functional nature of mitochondria. Therefore, any defect in mitochondrial metabolism will affect any organ.[5] LS is also associated with acute respiratory insufficiency, especially when using sedation by chloral hydrate.[6]

The ATPase 6 (*MT ATP6*) gene is one of the most frequently mutated mitochondrial genes.[3-5] The prognosis is determined by many factors, including high cerebrospinal fluid (CSF) lactate level, lactate peak, brainstem involvement, presentation during early infancy, and failure to thrive.[5]

Herein, we report a case of LS with a novel gene variant (*c.36G >A p.(Trp12**) chr5:60241118) homozygous and highlight the possible fatal complications of chloral hydrate in such patients.

CASE REPORT

A 15-month female child presented to the Emergency Department with a decreased level of consciousness, fever, and cyanosis.

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The patient was full-term, an outcome of caesarean section due to foetal distress with no neonatal intensive care unit (NICU) admission. Her vaccination was up-to-date. She was developmentally delayed, with a developmental age of 9-month baby.

Her brother, a 2-year, was diagnosed as a case of hypoxic-ischaemic encephalopathy (HIE), who deteriorated and died after he received chloral hydrate, which was given for sedation before brain imaging which was complicated with coma and finally death.

The patient in this case report presented with a history of fever, lethargy, and focal seizures with impaired awareness. Upon admission, the patient's vital signs were as follows: blood pressure, 92/44 mmHg; temperature, 38°C; heart rate, 108 beats/min; and respiratory rate, 25 breaths/min.

Clinically, the patient was looking lethargic with a Glasgow coma scale (GCS) of 12/15 with generalised central hypotonia. Initially, the patient was admitted to the paediatric ward and investigated for hypotonia. The patient underwent a computer tomography (CT) brain and received chloral hydrate at a dose of 100 mg/kg. After the CT was performed, her GCS dropped and she became more encephalopathic, with GCS of 7/15 associated with apnoeic attacks. So, the patient was transferred to the paediatric intensive care unit (PICU).

In the PICU, the patient was connected to a high-flow nasal cannula. She continued to have apnea attacks and respiratory acidosis, so she was intubated and connected to a mechanical ventilator. On the second day of admission, magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), magnetic resonance venography (MRV), and magnetic resonance spectroscopy (MRS) of the brain were done, which showed multiple bilateral areas of abnormally high signal intensities seen symmetrically involving the basal ganglia, midbrain, periaqueductal grey matter, medulla oblongata, and inferior cere-

bellar peduncles, surrounding the fourth ventricle Figure 1. They elicited bright T2 and FLAIR signals with restricted diffusion with no evidence of significant mass effect or pathological enhancement with an impression highly suggestive of LS (mitochondrial disorder) or metabolic disorders Figure 2.

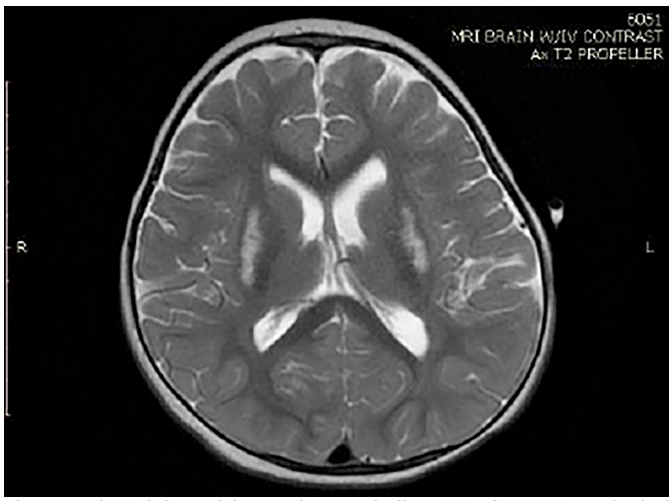

Figure 1: The axial cut of the cranioencephalic magnetic resonance (T2) of the patient with Leigh syndrome shows focal, bilateral, and symmetric hyperintensities.

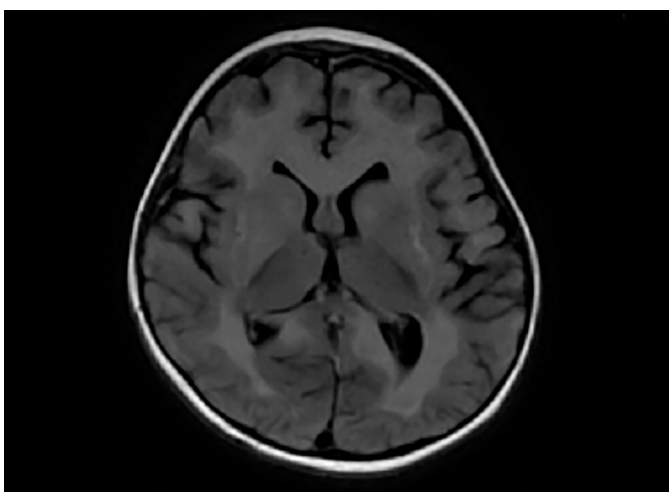

Figure 2: MRI (FLAIR) of the brain showing basal ganglia and periventricular area high signals.

The patient developed acute respiratory distress syndrome (ARDS) with bilateral pleural effusion. She required the insertion of bilateral chest tube drains complicated by pulmonary hypertension, which was treated with sildenafil and nitric oxide. Since admission, the patient had been in an encephalopathic state. Follow-up MRI was done approximately one month later and showed severe progression of the disease with a recently seen extensive area of diffusion restriction of the white matter in the supratentorial region as well as in cerebellar peduncles with involvement of basal ganglia, corpus callosum, midbrain, pons, medulla and proximal aspect of the spinal cord with unremarkable MRA and MRV.

Routine laboratory findings were normal. COVID-19 swab was negative. Upon admission, blood ammonia was 43 µmol/L, and plasma lactate was 3.6 mmol/L. CSF analysis showed protein, 98 mg/dl, glucose, 4.1 mg/dL, WBCs 1, and lactate, 7.5 mmol/L. The blood culture showed *Candida parapsilosis* and *Streptococcus epidermidis*. Endotracheal tube (ETT) culture showed *Pseudomonas*. So, the patient received good coverage of antibiotics and anti-fungals according to culture and sensitivity.

The whole exome sequencing (WES) result showed pathological variant *c.36G >A p.(Trp12*)* chr5:60241118 in the ND4FA2 gene (OMIM:609653) causative for autosomal recessive nuclear type 10 mitochondrial complex I deficiency (Leigh disease).

Fifteen days later, the patient started to be hypotensive, bradycardic, and started desaturating and was declared dead after full resuscitation. The cause of death was nuclear type 10 mitochondrial complex I deficiency (Leigh disease) and septic shock.

DISCUSSION

LS is a sub-acute necrotising encephalopathy, a rare progressive neurodegenerative disorder of infancy that typically presents between 3 and 12 months of age.[1,2] It was described by the British neuropathologist and psychiatrist Denis Leigh in 1951 AD.[1-3] LS has a grave prognosis and represents one of the most common mitochondrial disorders.[3,4]

Symptoms are variable due to the heterogeneous functional nature of mitochondria.[5] Most cellular ATP is produced from oxidative phosphorylation which is part of mitochondrial metabolism and depletion of ATP leads to lactic acidosis, vascular congestion, hypoxia, and ultimately necrosis.[1]

Therefore, any defect in mitochondrial metabolism will affect any organ.[5] Neurological, cardiac, and musculoskeletal systems are most affected due to their high oxygen requirements.[5] However, most of the symptoms are neurological such as developmental delay, regression, progressive cognitive decline, dystonia, ataxia, brain stem dysfunction, seizures, respiratory dysfunction, weakness, fatigue, hypotonia, tremors, poor sucking, poor feeding, ptosis, nystagmus, and failure to thrive. Some patients may present with non-neurological manifestations, including dysmorphisms, cardiac (such as dilated cardiomyopathy and hypertrophic cardiomyopathy), endocrinological (short stature, hypertrichosis, and diabetes), or diarrhoea and vomiting as gastroenterological symptoms.[5]

Besides the symptomatology variability of LS, there is genetic and biochemical variability with more than 75 genes identified so far. Most are inherited in an autosomal recessive pattern but less commonly autosomal dominant and X-linked patterns are observed.[1,2] The ATPase 6 (*MT ATP6*) gene is one of the most frequently mutated mitochondrial genes that encode a subunit of transversion.[3-5] However, its prevalence is unknown. Also, high plasma lactate levels and high CSF lactate levels are some of LS's diagnostic tools along with increased lactate to pyruvate ratio. Hypocitrulinaemia (≤12 mmol/L) is an occasional finding in mitochondrial disease associated with (8993T > G) mutation.[1-5]

Radiological imaging is essential in diagnosing LS whenever clinical and laboratory findings are suspicious.[5] The most common signs in T2-weighted imaging of brain MRI are focal bilateral and symmetric hyperintensities which are typically located in the

basal ganglia (especially putamen) with or without brainstem, thalamus, cerebellum, cerebral white matter, and spinal cord.[5]

The clinical, genetic, and biochemical variability of LS makes the diagnosis challenging as in this patient.[1,2] An early clinical detection, laboratory investigation, radiological images, and gene study can enable early diagnosis and improve the quality of life.

Chloral hydrate is most commonly used in children for sedation for a long time. It is extensively used for non-painful diagnostic procedures in infants and children with good corroboration of efficacy and safety. It is given *via* the oral or the rectal route, to achieve an optimal sedative effect for non-painful procedures in a high percentage of patients, without the need for an intravenous-line. It is worth emphasising that LS is complicated by acute respiratory insufficiency, especially when using sedation by chloral hydrate.[6]

To date, very few reports in the literature describe chloral hydrate-related complications in LS. Greenberg and Faerber described two cases of respiratory depression following oral chloral hydrate sedation in patients with LS. However, because of the side effects on respiration in their cases, chloral hydrate was stopped for sedation in such patients with this disorder at their institute.[3]

Dexmedetomidine is another sedating drug that induces a natural state of non-rapid eye movement (REM) sleep. It acts on alpha-2 receptors. In comparison to other sedative agents, Dexmedetomidine has minimal impact on the respiratory centre and airway muscles and their tone. Dexmedetomidine can be introduced *via* the intravenous, intramuscular, or intranasal route.[4]

Due to the rarity of this disorder, there are only a few reports of anaesthetic or sedation care in such patients and limited evidence-based literature to determine the most appropriate anaesthetic or sedative drugs for the management of such disorders. During the pre-procedure examination, evaluation should be focused on identifying the co-morbid condition to avoid complications leading to organ failure.[4]

The diagnosis of LS in this case was suspected on the second day of PICU admission. The MRI brain findings plus the encephalopathic state of the patient in addition to a positive family history of her brother's death after chloral hydrate, increased the suspicion of mitochondrial disease diagnosis.[5,6]

The genetic aetiology of LS is confirmed in about 50% of cases in nuclear mitochondrial DNA, which is responsible for about 10 to 30% of cases, and the most observed mutation is the ATPase 6 (*MT ATP6*) gene, with the most frequently described mutation being the 8993T > G transversion.[3-5] So, we considered this case mutation variant *c.36G >A p.(Trp12*)* chr5:60241118 as a new variant for LS based on the clinical course of the disease with positive laboratory and MRI brain findings.

The prognosis is determined by many factors, including high CSF lactate level, lactate peak, brainstem involvement, presentation during early infancy, failure to thrive, and requirement of intensive care unit.[5] The overall prognosis of LS is guarded with no specific treatment apart from palliative care and multidisciplinary team care.[5]

In conclusion, this case highlights the potential of chloral hydrate to cause respiratory failure in patients with LS. So, based on previous reports and our case observation, we advise sleep deprivation preferably or Dexmedetomidine for procedures like, neuroimaging to avoid respiratory complications. Also, we emphasise the importance of early and accurate diagnosis of the condition and the potential risks of chloral hydrate in this disease.

PATIENT'S CONSENT:
Informed consent was obtained from the patient's parents to publish this case.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AA, SE, MAS, MS: Substantial contribution to the conception or design of the work, acquisition, analysis, interpretation of data, drafting, and revising it critically for important intellectual content.
All authors approved the final version of the manuscript to be published.

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