Anesthetic considerations in Leigh disease: Case report and literature review

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ABSTRACT

Leigh disease is an extremely rare disorder, characterized by a progressive neurodegenerative course, with subacute necrotizing encephalomyelopathy. It usually presents in infancy with developmental delay, seizures, dysarthria, and ataxia. These patients may also develop episodes of lactic acidosis that usually lead to respiratory failure and death. Due to the rarity of the condition, the most appropriate anesthetic plan remains unclear. We present a patient with Leigh disease, who required general anesthesia. The pathogenesis of the disease is discussed and previous reports of perioperative care from the literature are reviewed.

Key Words: *Leigh disease, mitochondrial disorders, propofol, volatile agents*

INTRODUCTION

Leigh disease is a subacute necrotizing encephalomyelopathy that was first reported in 1951, by Denis Leigh.[1] It is one disease of the family of disorders classified as 'mitochondrial myopathies' that also include mitochondrial encephalopathy; lactic acidosis, and stroke-like episodes (MELAS) syndrome; neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP); and Kearns-Sayre syndrome. Leigh disease is extremely rare with an estimated prevalence of approximately one in 40,000 live births.[2]

We present our experience in the management of general anesthesia in a patient with Leigh disease, who underwent dental rehabilitation.

CASE REPORT

The Institutional Review Board (IRB) approval and a written informed consent were obtained from a parent for publication of the case and the accompanying images.

Access this article online	
Quick Response Code:	Website: www.saudija.org
	DOI: 10.4103/1658-354X.97037

A 15-year-old, 45 kg adolescent was scheduled for dental rehabilitation under general anesthesia. A diagnosis of Leigh disease was made at three years of age by the characteristic clinical findings, classical radiological findings [Figure 1], and muscle biopsy. He originally presented at three years of age with generalized tonic–clonic seizures, an ataxic gait, and dysarthria. He had a twin brother who died at 14 years of age from the same disease. His only medication included once daily Keppra® (levetiracetam) to control the seizures. On physical examination, he was mentally intact, but with dysarthria and an ataxic gait. His vital signs were within normal limits and his cardiovascular and respiratory examinations were unremarkable. Airway examination revealed a Mallampati score of I. His hematological workup and electrolytes were within normal limits.

On the day of surgery, the patient was held nil per os for eightr hours, and midazolam (2.5 mg) in divided doses was administered intravenously in the preoperative holding area. He was transported to the Operating Room where routine monitors were placed. Anesthesia was induced with propofol (2 mg/kg) and fentanyl (2 μg/kg). Neuromuscular blockade was achieved with cis-atracurum (0.2 mg/kg) followed by easy nasotracheal intubation with a 6.5 mm cuffed endotracheal tube. Maintenance anesthesia included propofol infusion at 120 to 170 μg / kg/minute to maintain the bispectral index (BIS) between 40 and 50. No volatile anesthetic agents were administered. An additional dose of fentanyl (1.5 μg/kg) was administered intraoperatively, to supplement the propofol infusion and maintain

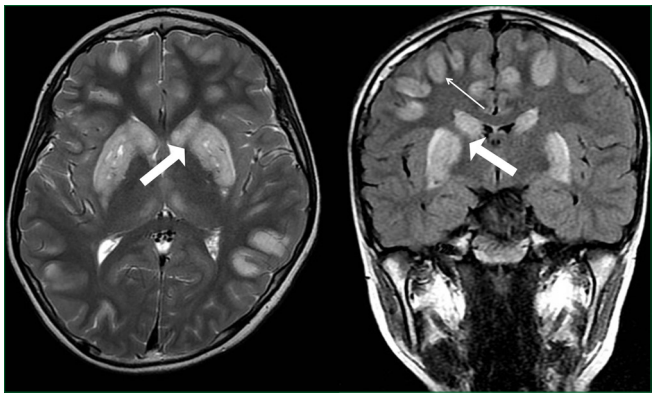

Figure 1: T2 MRI images show; (big arrows) bilateral symmetrical high signal changes in Caudate nuclei and Putamen, with high signal changes in the deep cortical gray matter (small arrow), all changes that indicate acidemic encephalopathy

hemodynamic stability during surgical manipulation. Intraoperative mechanical ventilation was provided using a volume-controlled mode and the $ETCO_2$ was maintained between 30 and 35 mmHg. External warming was used to maintain the patient's body temperature between 36 and 37°C. Postoperative analgesia was managed with paracetamol (800 mg IV) and diclofenac sodium (75 mg IV) with no additional opioids. Granisetron (1 mg) was administered pre-emptively to prevent postoperative nausea and vomiting. The procedure lasted 3.5 hours and the total fluid administration included 500 mL of normal saline. Following the procedure, the patient's trachea was extubated and he was transferred to the post anesthesia care unit (PACU) with close observation of his respiration and temperature. The postoperative course was uncomplicated. He returned to his baseline mental status, maintaining normal oxygen saturation on room air. He was transferred to the inpatient ward and was discharged on postoperative day two, in good condition.

DISCUSSION

Given the rarity of this disorder, there are only a handful of previous reports of anesthetic care in such patients and limited evidence-based medicine on which to determine the most appropriate anesthetic management for such patients [Table 1].

Given the dependency of several end-organ systems on mitochondrial function, disorders that disrupt mitochondrial function may significantly impact normal physiological functions. This involvement is generally most pronounced in those tissues with the highest metabolic rate, and therefore, those that are most dependent on normal mitochondrial function include the central nervous system, the cardiovascular system, and the skeletal muscle. During the preoperative examination, an evaluation focused on these organ systems may help to identify the comorbid conditions that will impact anesthetic care. Of primary concern to the anesthesia provider is the potential for myocardial involvement. Although our patient did not manifest signs of myocardial dysfunction, the mitochondrial defects involving aerobic metabolism have been linked with cardiac involvement, typically hypertrophic cardiomyopathy. The incidence of cardiac involvement varies depending on the specific defect, being most common in patients with the Kearnes-Sayer syndrome.[3] To date, there are no reports in the literature describing cardiac-related anesthetic events in patients with Leigh disease. However, in their series of 35 patients with Leigh disease, Rahman *et al.* reported two patients with cardiac manifestations (the exact involvement was not specified).[4]

One of the primary intraoperative considerations in patients with Leigh disease is the choice of the agents to be used to provide general anesthesia. Although there are anecdotal reports of their successful use in patients with Leigh disease, the two concerns that have been expressed regarding the use of volatile agents include their potential effects on mitochondrial function and the risk of malignant hyperthermia (MH) in patients with mitochondrial disorders. Morgan *et al.* reported that were no complications in a cohort of 16 children with mitochondrial defects, one of them with Leigh disease, who received general anesthesia with sevoflurane in 100% oxygen, supplemented with fentanyl, during brief surgical procedures, mostly muscle biopsy.[5] However, Bains *et al* have postulated that the volatile anesthetic agents may inhibit the mitochondrial electron transport chain, thereby suggesting that these agents are contraindicated in patients with mitochondrial disorders.[6] An anecdotal report has also demonstrated a marked regression of developmental milestone regression after general anesthesia, with halothane, in a child with Leigh disease.[7] Although there was a previously voiced concern regarding the association of malignant hyperthermia (MH) with mitochondrial disorders, this issue has been dismissed in the most recent literature.[8] In our case, we chose to use propofol for the induction and maintenance of anesthesia for its known antiepileptic effects, rapid recovery profile, and safety in patients at risk for MH, on the off-chance that there had been a misdiagnosis of Leigh disease and some other myopathic condition was present, which could predispose to MH. However, concern has also been raised regarding the use of propofol in patients with mitochondrial disorders.[9] Given the concerns with both the volatile agents and with propofol, other options that have been suggested for patients with mitochondrial disorders include a regional anesthetic technique or potentially the α_2-adrenergic agonist, dexmedetomidine.[10,11] Regardless of the anesthetic agents that are chosen, we suggest the

Table 1: Surgical procedures, anesthetic modalities, and complications

Author / year	Age / gender	Surgical procedure	Induction of anesthesia	Maintenance of anesthesia and intraoperative fluids	Perioperative outcome and issues
Ward[7], 1981	14.5 month old / F	Surgical correction of strabismus and myringotomy tube		Halothane	Marked development milestone regression
Greenberg *et al.*,[14] 1990	10 month old / M 5.5 year old / F	Lumbar puncture evoked potential examination CT scan	Sedation with oral chloral hydrate (100 mg / kg)		Respiratory failure (both patients)
Grattan-Smith *et al.*,[15] 1990	M	Pneumo-encephalogram	Thiopental sodium, suxamethonium	Halothane and nitrous oxide	All three patients developed respiratory failure. All had preoperative respiratory manifestations
	M	Muscle biopsy	Thiopental	Thiopental	
	F	Bronchoscopy		Halothane	
Shenkman *et al.*,[16] 1997	5 month old / F	Extracorporeal shockwave lithotripsy	Ketamine, midazolam	Propofol and N2O 70% D5 ½ NS	None
Cooper *et al.*,[17] 2003	21 years / F	Scoliosis surgery	Midazolam, propofol , fentanyl, vecuronium	Maintenance anesthesia no specified. Ringer's lactate	Acute lung injury, sepsis, respiratory failure, reactivation of her brain disease, then died
Shear *et al.*[10], 2004	19 month old / F	Muscle biopsy	Glycopyrrolate, ketamine	Spinal anesthesia with tetracaine	None
Jacobs *et al.*,[18] 2004	17 years / F	Scoliosis surgery	Sevoflurane (8%) in O2 / N2O (70% / 30%)	Propofol (150-200 μg / kg / minute), remifentanil , cisatracurium propacetamol, tramadol, morphine. Crystalloids included Plasmalyte and tetrastarch	None
Ellis *et al.*,[19] 2005	16 years / F	Molar extraction	Midazolam and propofol	Propofol infusion	Intraoperative seizures
Gozal *et al*,[20] 2006	6 year / F 2 year / F 1.5 year / M 0.5 year / M 3 year / F	Percutaneous endoscopic gastrostomy	Propofol	Propofol infusion (50–100 μg / kg / min)	None
Sasaki *et al*,[21] 2008	17 years / F	Laryngotracheal separation and open fundo-plication	Vecuronium	Propofol (75–100 μg / kg / minute) and fentanyl infusions	None. Mechanical ventilation and propofol sedation continued for seven days postoperatively to prevent the surgical stress response
Our case	15 years / M	Dental rehabilitation	Propofol, fentanyl	Propofol infusion, cisatracurum, fentanyl, paracetamol, and diclofenac. Normal saline 9%	None

use of depth of anesthesia monitoring, as both the amount and the duration of the agent used may be important factors affecting mitochondrial function.

Another important issue regarding intraoperative care is the choice of a neuromuscular blocking agent. Although there are a few reports regarding the use of succinylcholine in patients with Leigh disease, we would suggest that succinylcholine be avoided because of the potential risks of rhabdomyolysis and hyperkalemia in patients with myopathic conditions.[12] Furthermore, patients with myopathic conditions can have a prolonged recovery time after non-depolarizing neuromuscular blocking agents, even when intermediate acting agents such as rocuronium and atracurium are used.[13] Given its non-organ dependent elimination and stable recovery profile even in myopathic conditions, we chose to use cis-atracurium in our patient. However, as prolonged recovery has been reported

in patients with Leigh disease, monitoring of the neuromuscular function is suggested, especially when repeated doses are indicated. We chose a multi-modality approach for postoperative analgesia by using the non-opioid agents (paracetamol and diclofenac), in addition to the short-acting opioid, fentanyl. Table 2 summarizes the potential perioperative complications and suggestions for their prevention and management.

In conclusion, a thorough preoperative assessment of the respiratory, cardiovascular, and renal functions is necessary, for the proper preparation of the patient with Leigh disease, prior to anesthetic care. Normocapnia, normothermia, and avoidance of lactate containing solutions are necessary. Although MH has not been reported with Leigh disease, it may be best to avoid triggering agents as other myopathic conditions with a propensity for MH may be misdiagnosed as Leigh disease, especially with diagnostic procedures.

Table 2: Suggested anesthetic approach for patients with Leigh disease: Possible adverse effect and related anesthetic considerations

Possible cardiac and respiratory involvement
Careful preoperative cardiac and respiratory evaluation
Pre-existing respiratory abnormalities increase the risk of postoperative respiratory failure, thus preoperative optimization of pulmonary function is suggested
Intraoperative seizures
Effective preoperative control with antiepileptic therapy
Documentation of therapeutic anticonvulsant levels
Ongoing intraoperative administration of anticonvulsants whenever feasible
Normalize serum electrolytes and glucose
Propofol and midazolam both have antiepileptic effects
Lactic acidosis
Use fluids that contain dextrose during the period of preoperative fasting, to provide basal glucose requirements
Check preoperative lactate level
Frequent intraoperative serum lactate, pH, and glucose monitoring
Avoid barbiturates (e.g., thiopental) and sodium valproate
Avoid lactate containing fluids (e.g., Ringer's lactate)
Controversy regarding volatile anesthetic agents vs. propofol
Monitor the depth of anesthesia
Avoid opioids with long duration of action, especially for short procedures
Use regional anesthesia and adjunctive agents (NSAIDs and acetaminophen) to limit opioid needs
Postoperative respiratory monitoring for major procedures.
Maintain normothermia
Maintain normocapnia and avoid any hypoxia
Minimize risks of infection
Use sodium bicarbonate or sodium citrate for acute exacerbations of acidosis[22]
Muscle relaxant considerations
Mitochondrial myopathies may be associated with prolonged neuromuscular blockade, although there are no reported cases of prolonged neuromuscular blockade in Leigh disease
Use intermediate-acting agents such as cis-atracurium
Monitor neuromuscular function if repeated doses are used
Avoid succinylcholine as an exaggerated hyperkalemic response may occur in myopathic conditions
Malignant hyperthermia
Although there is no reported case with use of volatile agents, we suggest the use of total intravenous anesthesia
Future studies are ongoing for evaluating the feasibility of using dexmedetomidine in these patients

ACKNOWLEDGMENTS

We would like to thank Dr. Insha Al-Rahman, Dr. Sven Larsson, and Mr. Gabriel Camalig, for their kind assistance.

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How to cite this article: Terkawi AS, Wani TM, Al-Shuaibi KM, Tobias JD. Anesthetic considerations in Leigh disease: Case report and literature review. Saudi J Anaesth 2012;6:181-5.
Source of Support: Nil, **Conflict of Interest:** None declared.