Anesthetic considerations in Smith-Lemli-Opitz syndrome

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Purpose: Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive syndrome characterized by congenital anomalies affecting the airway, cardiorespiratory, gastrointestinal, genitourinary, and central nervous systems. The presence of these anomalies as well as the potential for muscle rigidity with or without hyperthermia present challenges to anesthesia. This report describes our institution's experience with SLOS patients undergoing anesthesia in Canada.

Clinical features: Three patients diagnosed with SLOS at McMaster University underwent a total of five anesthetics for diagnostic imaging and surgical procedures. The age of the patients ranged from two months to four years. Four intravenous anesthetics and one balanced general anesthetic were administered. One patient was noted to have a diminished laryngoscopic view but no difficult intubations were encountered. One patient required re-intubation due to upper airway obstruction related to the surgical procedure in the postoperative period. No cardiovascular, respiratory, or temperature complications were experienced.

Conclusion: This report describes the anesthetic management in three patients with SLOS. Although the syndrome raises a number of potential anesthetic concerns, few complications were seen. This is consistent with other cases reported in the literature, which is reviewed in this report.

Objectif : Le syndrome de Smith, Lemli et Opitz (SSLO) est un syndrome autosomique récessif rare caractérisé par des anomalies congénitales qui touchent les voies aériennes, les systèmes cardiorespiratoire, gastro-intestinal, génito-urinaire et nerveux central. La présence de ces anomalies de même qu'une possible rigidité musculaire avec ou sans hyperthermie compliquent l'anesthésie. Le présent article décrit l'expérience vécue dans notre institution avec des patients atteints du SSLO qui sont soumis à une anesthésie.

Éléments cliniques : Trois patients chez qui le SSLO a été diagnostiqué à l'université McMaster ont subi cinq anesthésies lors d'interventions en imagerie diagnostique et en chirurgie. Les patients étaient âgés de deux mois à quatre ans. Quatre anesthésies totalement intraveineuses et une anesthésie générale équilibrée ont été administrées. On a noté, chez un patient, une vue laryngoscopique limitée, mais sans difficultés d'intubation. Un patient a eu besoin d'une deuxième intubation après l'opération, à cause d'une obstruction des voies aériennes supérieures liée à la technique chirurgicale. Aucune complication cardiovasculaire, respiratoire ou liée à la température ne s'est présentée.

Conclusion : L'article décrit la gestion anesthésique de trois patients qui présentaient le SSLO. Même si le syndrome soulève de nombreuses questions anesthésiques potentielles, peu de complications ont été observées. Cette situation cadre bien avec d'autres cas mentionnés dans la documentation, laquelle est revue dans cette présentation.

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THE Smith-Lemli-Opitz syndrome is an autosomal recessive syndrome characterized by variable developmental delay, dysmorphic facial features, cleft palate, and a spectrum of congenital anomalies affecting the central nervous, cardiac, respiratory, gastrointestinal, and genitourinary systems.¹⁻³ First described in 1964,¹ the minimum incidence is estimated to be 1 in 60,000 with a carrier frequency of 1 in 122,² but it is more likely to be as common as 1 in 20,000 to 1 in 30,000.⁴ Until 1994, diagnosis of SLOS was based on the recognition of clinical features. Since then, SLOS has been demonstrated to result from an enzymatic defect in 7-dehydrocholesterol- Δ^7 -reductase, which leads to an accumulation of 7-dehydrocholesterol (7-DHC) and generalized cholesterol deficiency.^{5,6} To confirm the diagnosis of SLOS, it is necessary to demonstrate the elevated plasma levels of 7-DHC. The gene for SLOS has been mapped to chromosome 11q12-13 and mutations in the 7-DHC reductase gene have been demonstrated in patients with SLOS since 1998.^{6,7}

Given the plethora of congenital anomalies, SLOS patients are likely to undergo anesthesia for diagnostic procedures and corrective surgery. In this paper, we report our departments' clinical experience with SLOS patients undergoing anesthesia and review the anesthetic considerations of this syndrome.

Report of case series

All patients with suspected SLOS were identified through the Biochemical and Clinical Genetics Clinic at McMaster University. Diagnoses were confirmed by demonstration of elevated 7-DHC plasma levels. Five

patients were identified. A total of five anesthetics were given to three of the identified patients. Details of the physical and biochemical findings associated with SLOS have been reported previously^{3,4} for the three patients. The details surrounding the anesthetics have not been reported previously.

Patient A

The first patient was a four year old, 15.5 kg boy who underwent an elective magnetic resonance imaging (MRI) scan of his head. He had no other health problems aside from SLOS. Prior to induction of anesthesia, his vital signs were SpO₂ 98%, HR 98 bpm, BP 70/30 mmHg, and temperature 35.8°C. Induction of anesthesia was achieved with 70 mg propofol. Total intravenous anesthesia (TIVA) with a 200 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ propofol infusion was used for maintenance. The child breathed spontaneously with nasal prongs. The vital signs remained within 90% of the pre-induction values during the uneventful procedure and recovery period.

Patient B

The second patient was the two year old, 11 kg brother of patient A. He too underwent elective MRI scan of his head. Aside from SLOS, he also had gastroesophageal reflux, mild supravalvular aortic stenosis and coarctation, and an aberrant right subclavian artery. His pre-induction vital signs were SpO₂ 100%, HR 130 bpm, BP 90/40 mmHg, and temperature 36.7°C. Induction of anesthesia and tracheal intubation was achieved with 30 mg propofol and a 4.5 mm oral endotracheal tube (ETT). Anesthesia was maintained with TIVA using a 200 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ propofol infusion and

FIGURE 1 Frontal and profile views of a patient with severe physical manifestations of SLOS. Used with permission from the parents.

FIGURE 2 Frontal and profile views of Patient B at three and a half years of age with minimal physical manifestations of SLOS. Used with permission from the parents.

spontaneous ventilation. Vital signs remained within 90% of pre-induction values throughout the anesthetic and recovery period.

Patient C

The third patient underwent three procedures within her first year of life. The diagnosis of SLOS was made shortly after birth. She also had a cleft palate and recurrent aspirations. At two months of age, when she weighed 2.7 kg, the patient underwent endoscopic percutaneous insertion of a gastrostomy tube. Preoperative vital signs were SpO₂ 100%, HR 140 bpm, BP 90/60 mmHg, and temperature 36.5°C. An inhalational induction was performed with halothane 5% and oxygen 100% along with cricoid pressure. Upon laryngoscopy, the posterior arytenoids were visualized and the trachea was intubated with a 3.5 mm oral ETT. Balanced general anesthesia was maintained with 1 to 2 MAC isoflurane, 2 L·min⁻¹ N₂O, 2 L·min⁻¹ O₂, and boluses of rocuronium along with intermittent positive pressure ventilation (IPPV). Analgesia was obtained by infiltration of the gastrostomy site with local anesthetic. Vital signs were SpO₂ 95%, HR 150 to 190 bpm, BP 120/60 mmHg, and temperature 36.9°C during the one hour procedure and returned to pre-induction values during recovery.

Two months later, the patient underwent a MRI scan of her head. Her weight was 2.8 kg. Pre-induction vital signs were similar to her first procedure. Induction of anesthesia was accomplished with 10 mg propofol. Laryngoscopic view remained unchanged and the trachea was intubated with a 3.5 mm oral ETT. Maintenance of anesthesia was with 2 L·min⁻¹ N₂O and 2 L·min⁻¹ O₂ along with 10 mg propofol boluses every 15 min. Pressure controlled ventilation with 15 cmH₂O ventilating pressure and 5 cmH₂O positive end-expiratory pressure at 30 breaths·min⁻¹ were used. Vital signs remained within 90% of pre-induction values during the procedure and recovery period.

At ten months of age, the patient underwent tonsillectomy and cleft palate repair. She was now 4.1 kg with vital signs of SpO₂ 98%, HR 160 bpm, BP 80/50 mmHg, and temperature 36.5°C. After premedication with 0.1 mg atropine, induction of anesthesia and tracheal intubation was with 30 mg propofol and a 4.0 mm oral ETT. This time, only the epiglottis could be seen with laryngoscopy but intubation was successful on the first attempt. Anesthesia was maintained with 700 mL·min⁻¹ N₂O, 300 mL·min⁻¹ O₂, 150 to 200 µg·kg⁻¹·min⁻¹ propofol infusion, and intermittent 1 µg·kg⁻¹ fentanyl boluses along with IPPV with a tidal volume of 100 mL at 15 breaths·min⁻¹. Again, vital

TABLE Details of SLOS cases published in the anesthesia literature

<i>Year (Ref)</i>	<i>Number of patients</i>	<i>Biochemical confirmation?</i>	<i>Description of anesthetic</i>	<i>Complications reported</i>
1987 (9)	1 (11 yr male)	N	1 anesthetic: Halothane-N ₂ O-O ₂	Severe hypotension, ST segment depression, hyperthermia (38.9°C)
1988 (10)	1 (7 yr male)	N	2 anesthetics: Halothane-N ₂ O-O ₂ / succinylcholine / caudal	Muscle rigidity, hypothermia (34.9°C)
1995 (11)	1 (4 yr male)	Y	Enflurane-N ₂ O-O ₂ / vecuronium 3 anesthetics: Halothane-N ₂ O-O ₂ / vecuronium / caudal	Hypothermia (35.1°C) Muscle rigidity, hyperthermia (38.0°C)
1996 (12)	5	Y	Isoflurane-air-O ₂ / pancuronium Halothane-N ₂ O-O ₂ / atracurium 38 anesthetics (37 with halothane)	Hyperthermia (39.0°C) Muscle rigidity Difficult intubation (1 anesthetic)

signs were maintained within 90% of the preoperative values during the procedure. During the recovery period, the patient required O₂ 70% to maintain her SpO₂ > 90%. Five hours after surgery, the patient required re-intubation due to upper airway obstruction from localized tissue edema and she was admitted to the intensive care unit, where she made an eventual uneventful recovery.

Discussion

Smith-Lemli-Opitz syndrome is a rare inherited biochemical disorder with a number of congenital anomalies. The spectrum of physical findings ranges from isolated cleft palate, cataracts, or minimal 2-3 toe syndactyly associated with developmental delay and behavior abnormalities (SLOS type I) to severely affected newborns with ambiguous genitalia and multiple congenital defects that may be incompatible with life (SLOS type II).⁸ The external genitalia are normal in females; in males the anomalies range from normal to completely unvirilized or ambiguous genitalia.¹⁻⁴ Internal anomalies affect the cardiorespiratory (see below), gastrointestinal (see below), genitourinary (renal cystic dysplasia, hydronephrosis, renal agenesis), and central nervous (holoprosencephaly, agenesis of corpus callosum) systems. In many cases of SLOS type I the behavioural and developmental features overshadow the minimal physical findings leading to the diagnosis of idiopathic mental retardation, attention deficit disorder, or pervasive developmental disorder.^{3,8} Figures 1 and 2 illustrate the wide phenotypic spectrum seen in SLOS.

Given the clinical features associated with SLOS, patients are likely to undergo diagnostic procedures such as cranial MRI and corrective surgery for anom-

alies such as cleft palate. Little information is available on the anesthetic considerations of SLOS. A MEDLINE search and review of references found only four citations.⁹⁻¹² Of these, two had a clinical diagnosis of SLOS before the biochemical defect was discovered.^{9,10} The Table summarizes the cases from the literature. Our case series is the first to be reported in Canada. With the inclusion of our three patients, eleven patients undergoing 49 general anesthetics and two caudal anesthetics have been reported. However, the two cases reported before 1994^{9,10} must be considered with caution, as at that time the biochemical defect was not known and these patients may represent disease entities other than 7-DHC reductase deficiency.^{2,8}

Several concerns have been raised regarding anesthesia in SLOS. The most serious complication has been muscle rigidity with or without hyperthermia in the presence of volatile anesthetic agents. Ten patients have received volatile agents (halothane, isoflurane, enflurane) for induction or maintenance of anesthesia. Two experienced generalized muscle rigidity: the first case was associated with perioperative hypothermia¹⁰ and the second case was associated with postoperative hyperthermia.¹¹ A third patient had severe hypotension and intraoperative hyperthermia without muscle rigidity but no further information was provided to determine likelihood of malignant hyperthermia (MH).⁹ In the first two cases,^{10,11} muscle rigidity was associated with elevations of creatinine kinase of less than 10,000 IU·L⁻¹. Respiratory acidosis (pH 7.05) and hypercarbia (P_aCO₂ 105 mmHg) were observed in one case.¹¹ Additional signs of MH (myoglobinemia, myoglobinuria, hyperkalemia, cardiac dysrhythmias) were absent in both cases. In all three instances, MH was not considered to be the diagnosis, dantrolene was not admin-

istered, and muscle biopsy was not performed after the adverse event. Based on the information available, two cases^{9,10} would be considered to have a "somewhat less than likely" likelihood of MH and one case¹¹ would have a "very likely" likelihood of MH according to the Larach MH Clinical Grading Scale.¹³ These three cases did not have biochemical confirmation of SLOS. Neither Haji-Michael *et al.*¹² nor we noticed any episodes of muscle rigidity or hyperthermia.

Concerns also exist regarding difficult intubation in patients with SLOS. Prominent incisors, micrognathia (67 to 100 %), and tongue abnormalities (12 to 63 %) have been observed.^{2,8} In addition, palatal abnormalities are common (78 %).² Cleft palate (37 to 68 %) and high arched palate are frequently seen.^{2,8} These anatomic features may increase the difficulty of laryngoscopy and tracheal intubation. In our series, one patient had an abnormal laryngoscopic view, which worsened with age; however, intubation was not difficult. Haji-Michael *et al.*¹² also reported one difficult intubation but no further detail was provided.

In addition to a potentially difficult airway, cardiorespiratory problems further complicate anesthesia in patients with SLOS. The majority of respiratory complications seen in SLOS are the result of aspiration due to gastroesophageal reflux, pyloric stenosis, or Hirschsprung's disease.² Congenital pulmonary anomalies such as hypoplastic or incomplete lobulation of the lungs (25 to 56 percent)^{2,14} result in diminished lung volumes and can further complicate anesthesia. Congenital heart disease affects 37 to 84 % of patients.^{2,14,15} The commonest cardiac lesions in SLOS are those with abnormal intracardiac blood flow (secundum type atrial septal defects, ventricular septal defects, the hypoplastic left heart syndrome spectrum, and patent ductus arteriosus).¹⁴

Apart from the anatomical and physiological considerations of SLOS, anesthesia can also be difficult as patients with SLOS may display uncooperative behaviour.⁴ In one case series, 53 % of patients exhibited aggressive behaviour.²

Given the concerns outlined above, patients with SLOS who undergo anesthesia should be assessed by an anesthesiologist and a clinical geneticist before surgery. Detailed airway and cardiorespiratory examinations are necessary to delineate the extent of abnormality in these systems. Although there have been no reports of failed intubation, a high index of suspicion for difficult intubation should be maintained. Aspiration and endocarditis prophylaxis may be required depending on the clinical findings and on the surgical procedure. The decision regarding the avoidance of MH triggering agents during anesthesia is

controversial since there is insufficient evidence to support or refute an association between SLOS and MH. Perioperative temperature monitoring should be utilized. Malignant hyperthermia should be considered if a patient develops rigidity, respiratory acidosis, temperature increase, or cardiac dysrhythmias in the presence of triggering agents.

In summary, we report three patients with SLOS undergoing anesthesia. This rare genetic syndrome raises a number of anesthetic concerns including possible MH susceptibility, difficult airway, aspiration risk, and hemodynamic complications from congenital cardiac disease. Although careful assessment is necessary, the current literature reports few serious complications in patients with SLOS.

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