Pediatric Anesthesia and Critical Care Journal 2022;10(1):37-43
doi:10.14587/paccj.2022.6

PACCJ

Perioperative care of a child with Zellweger syndrome

A. Gibbs[1], J. D. Tobias[2,3]

[1]The Ohio State University, College of Medicine, Columbus, Ohio, USA
[2]Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital and the Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, Ohio, USA

Corresponding author: J. D. Tobias, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital and the Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, Ohio, USA. Email: Joseph.Tobias@Nationwidechildrens.org

Keypoints

1. Zellweger syndrome (cerebro-hepato-renal syndrome) is characterized by defects in the structure, function, or number of peroxisomes, which are essential for the β-oxidation of very-long-chain fatty acids.
2. The primary clinical features of Zellweger syndrome include renal, hepatic, and adrenal dysfunction along with neurological abnormalities including seizures, developmental delay, visual, and hearing impairment.
3. CNS involvement with hypotonia and the residual effects of anesthetic agents may impact perioperative respiratory function and upper airway control leading to postoperative respiratory insufficiency or failure.
4. Preoperative evaluation should include an evaluation of renal, hepatic and coagulation function. As the majority of patients may have adrenal insufficiency, an ACTH stimulation test is recommended to evaluate adrenocortical function.

Abstract

Zellweger syndrome (ZS) is an autosomal recessive disorder characterized by defects in the structure, function, or number of peroxisomes, which are essential for the β-oxidation of very-long-chain fatty acids. Disordered peroxisome function leads to a wide range of metabolic abnormalities and end-organ involvement including renal, hepatic, neurologic, and adrenal dysfunction. We report an 18-month-old girl with ZS requiring general anesthesia during placement of bilateral cochlear implants. The potential perioperative concerns of ZS are discussed, previous reports of anesthetic care reviewed, and options for anesthetic care presented.

Keywords

Zellweger syndrome; peroxisomes; fatty acid metabolism; β-oxidation

Introduction

Zellweger syndrome (ZS) is a congenital disorder characterized by defects in the structure, function, or number of peroxisomes, which are essential for the β-oxidation of very-long-chain fatty acids. It is inherited as an autosomal recessive trait with an estimated incidence of 1,50,000-70,000. Original reports of the constellation of its clinical signs and symptoms were first reported in the 1960's. Bowen et al. described a syndrome that included failure to thrive, congenital glaucoma, dysmorphic craniofacial features, and early death (before 2 years of age).[1] Smith et al. described two siblings with similar multiple congenital malformations in addition to polycystic kidneys and intrahepatic biliary dysgenesis.[2,3] In 1967, Passarge and McAdams were the first to use the term cerebro-hepato-renal syndrome to describe the organ system involvement of the disoder.[4] The syndrome bears the name of the Swiss American pediatrician, Hans Zellweger, who contributed two of the originally described patients. However, it was not until 1973 that the causal link between ZS and peroxisomes was made, when

Goldfischer et al. described the absence of peroxisomes in hepatocytes and renal proximal tubules.[5,6]

Due to the essential role peroxisomes play in fatty acid oxidation, their reduced function leads to a wide range of metabolic abnormalities and end-organ involved that is characteristic of ZS.[6] The primary phenotypic features of ZS include renal, hepatic, and adrenal dysfunction along with neurological abnormalities, development delay, and visual and hearing impairment. When clinical signs and symptoms manifest during infancy, death frequently occurs before the first year of life.[7,8] Anesthetic care may be required during various diagnostic imaging modalities or surgical procedures aimed at treating the end-organ involvement of the disease process. We report an 18-month-old girl with ZS requiring general anesthesia care during ear, nose, and throat surgery (bilateral cochlear implants). The perioperative concerns of ZS are discussed, previous reports of anesthetic care reviewed, and options for anesthetic care presented.

Case report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). The patient was an 18-month-old girl who presented for anesthetic care during bilateral cochlear implantation. Past medical history included an uncomplicated pregnancy and delivery at full term. The child did not pass her newborn hearing test and during her first few months of life was not meeting developmental milestones. Her earliest symptoms were hypotonia in her lower extremities that was noted at the 1-month postnatal visit. At that time, ultrasound examination of the lumbar spine and hips was unremarkable. Nystagmus first noticed at 7 months of age and decreased eye contact noted at 8 months of age prompted an ophthalmology evaluation. The ophthalmology evaluation revealed vertical and horizontal nystagmus along with delayed visual maturation. These findings were concerning for an intracranial malignancy or tumor which prompted magnetic resonance imaging (MRI) of the brain. A T2 weighted brain MRI did not reveal an intracranial malignancy/tumor; however, there were multiple areas with patchy white matter hyperintensities, primarily involving the bilateral parietal lobes. These abnormal findings lead to a neurology evaluation. The neurology assessment was concerning for a possible genetic leukodystrophy due to the abnormal MRI in combination with the progressive nature of her visual symptoms, gross motor delay, and long standing hypotonia. Subsequent genetic testing included a leukodystrophy gene panel and biochemical laboratory work-up with a comprehensive metabolic panel, complete blood count, lysosomal enzyme screen, as well as long chain and very long chain fatty acids. The results of the laboratory evaluation of very long chain fatty acids and elevated liver transaminases indicated a peroxisome biogenesis disorder. Genetic testing then identified two pathologic mutations in the PEX1 gene and confirmed the diagnosis of ZS at 11 months of age. Following the diagnosis, the hepatology service was consulted due to persistent elevation of hepatic enzymes (alanine aminotransferase 200 U/L, normal range ≤ 40 U/L and aspartate aminotransferase 500 u/L, normal range 20-60 U/L), and a mild elevation in the total bilirubin to 1.4 mg/dL. Hepatology work-up identified abnormal coagulation studies with a prolonged partial thromboplastin time (PTT) of 80-100 seconds, normal range 24-36 seconds and a mild prolonged of the prothrombin time (PT) to 15-17 seconds, normal range 12.7-14.7 seconds. The PTT and PT did not correct with vitamin K supplementation; however, the PT did correct with mixing studies using normal plasma indicating primarily a factor VII deficiency. Endocrinology evaluation revealed decreased cortisol levels, elevated adrenocorticotropic hormone (ACTH) levels, and a deficient ACTH stimulation test which led to a diagnosis of primary adrenal insufficiency. At 12 months of age, the patient was noted to have decreased responsiveness to sounds. An otolaryngology evaluation identified bilateral sensorineural hearing loss that continued to progress over the following months. At 18-months of age, the child presented for bilateral cochlear implantation under

general anesthesia. The patient's medical conditions, past medical history, current medications, and allergies were reviewed during the preoperative evaluation. The family history was negative. Previous anesthetic care for MR imaging at 9 months of age and bilateral ear tube insertion at 15 months of age were unremarkable. These were performed with sevoflurane using a laryngeal mask airway. SARS-CoV-2 (COVID) nucleic acid amplification test was negative. On physical examination, the patient appeared in no acute distress with a body weight of 8.85 kg. She was normocephalic with moist mucous membranes and thick mucoid nasal secretions. Generalized hypotonia was noted. Cardiovascular and respiratory examination was normal. Neck range of motion was within normal limits with a Mallamaptai II airway examination. Current medications included hydrocortisone 1.2 mg every 8 hours, vitamin K 0.5 mg every day, and vitamin B complex. The patient was classified as an American Society of Anesthesiologists' physical classification 3. In preparation for surgery, the patient was held nil per os for 6 hours. The patient was transported to the operating room and routine American Society of Anesthesiologists' monitors were placed. Anesthesia was induced by inhalation of sevoflurane in nitrous oxide and oxygen. After the induction of anesthesia, a peripheral intravenous catheter was placed. Bag-valve-mask ventilation was uncomplicated. Following the administration of propofol, direct laryngoscopy was performed with a Macintosh laryngoscope and the patient's trachea was intubated with a 4.0 mm cuffed endotracheal tube. Maintenance anesthesia included sevoflurane (expired concentration 2-2.5%) in air and oxygen and morphine (0.8 mg). Surgical site infection prophylaxis was provided by the administration of ceftriaxone (50 mg/kg). Stress dose prophylaxis for adrenal insufficiency included hydrocortisone (20 mg). Given the patients history of factor VII deficiency, epsilon aminocaproic acid (100 mg/kg) was administered thirty minutes prior to incision in consultation with the hematology service. Intraoperative hypotension (blood pressure 60-70/25-35 mmHg) was treated first by the administration of fluid and then with intermittent bolus doses of phenylephrine (2-4 µg/kg) and then a phenylephrine infusion at 0.5-1 µg/kg/min. During the 5-hour surgical procedure, fluid intake included lactated Ringers (550 mL) and 5% albumin (80 mL). Ondansetron (0.15 mg/kg) was administered for prophylaxis against postoperative nausea and vomiting. Following completion of the surgical procedure, the patient's trachea was extubated and she was transferred to the post-anesthesia care unit. Incremental doses of morphine and fentanyl were administered for postoperative analgesia. The postoperative course was unremarkable and she was discharged home the same day.

Discussion

First described by Baudhuin and DeDuve, peroxisomes are single-membrane-bound, typically spherical, organelles ranging in size from 0.1–1 microns in diameter and numbering from a few hundred to a few thousand in mammalian cells.[7,8] The peroxisome matrix contains 50 or more enzymes that participate in various metabolic pathways including β-oxidation of straight and long (C14–22) chain fatty acids, very long (≥ C24) chain fatty acids, and leukotrienes; synthesis of cholesterol and ether-lipids (plasmalogens); and oxidation of d-amino acids and polyamines. The assembly and function of mammalian peroxisomes involves the protein products of 16 different genes termed PEXs. The PEX genes encode peroxins and the peroxisome biogenesis factors required for the proper assembly of peroxisomes. Defects in 14 of these PEX genes have been identify to cause peroxisome biogenesis disorders (PBD). These PBDs are a heterogeneous group of autosomal recessive disorders in which peroxisome assembly are impaired or their function is impacted. Given the distribution of peroxisomes in multiple tissues types, these disorders result in end organ involvement of several organ systems.[6] Based on their phenotypic expression, various peroxisomal disorders have been described including ZS, neonatal adrenoleukodystrophy, infantile Refsum disease, and rhizomelic chondrodysplasia punctata type 1 (RCDP1).[9,10] These

disorders are considered a spectrum of diseases, all related to peroxisome function. The incidence varies from 1/17,000 births for the more common disorder, neonatal adrenoleukodystrophy, to 1/50,000-70,000 for ZS.[1,11]

The description of the phenotypic clinical picture of ZS was described prior to its identification as a disorder of peroxisome function. It was first observed among siblings by a Swiss-American pediatrician Dr. Hans Zellweger in the mid 1960s. The initial description included many of the classical phenotypic features including hypotonia, facial dysmorphism, and developmental delay. However, the underlying pathology of the syndrome was not identified until 1973, when it was linked to a decreased number of peroxisomes, specifically in renal tubular epithelial cells and hepatocytes. This deficiency was subsequently linked to the PEX genes.[12] Defective peroxisome function results in the accumulatio of very long-chain fatty acids and bile acid precursors in the eyes, brain, liver, and kidneys thereby leading to the metabolic abnormalities and phenotypic characteristics that have come to be recognized as ZS. These core features include liver dysfunction, adrenocortical dysfunction, hearing and vision impairment, and developmental delay.[12]

As with all surgical care, the plan for the provision of anesthesia starts with a thorough preoperative history and physical examination. In patients with ZS, the preoperative evaluation is focused to identify end-organ involvement of the disorder. Significant CNS involvement is a hallmark of the disorder. Although the disorder includes dysmorphic craniofacial features, the anecdotal reports from the literature and the experience from our patient have demonstrated that airway management and endotracheal intubation have not been problematic.

As noted in our patient whose initial presentation was hearing loss identified during newborn hearing screening, the accumulation of very long chain fatty acids leads to demyelination with sensory impairments including hearing and vision deficits.[13] Our patient's hearing impairment progressively worsened with profound bilateral sensorineural hearing loss at 18 months of age.[14] These concerns along with impairment of general cognitive function can impact communication during the perioperative period. Additional CNS manifestation of ZS include seizures and hypotonia.[15] Significant impairment of CNS cognitive function with associated hypotonia and poor pharyngeal control may lead to chronic aspiration and chronic lung disease. Depending on the preoperative history, rapid sequence induction with endotracheal intubation may be indicated to prevent gastric aspiration during anesthetic care.

Preoperative management to limit perioperative seizures includes monitoring and optimizing anticonvulsant medications prior to the surgical procedure. Additionally, routine anticonvulsant medications should be administered prior to surgery despite preoperative nil per os regulations.[16] Ongoing intraoperative and postoperative dosing of anticonvulsant medications is suggested with alternative routes of delivery or alternative medications if enteral administration is not feasible during the perioperative period. Previous reviews have outlined specific perioperative concerns in patients with seizure disorders.[17,18]

When selecting specific agents for the induction and maintenance of anesthesia in patients with an underlying seizure disorder, there is generally limited evidence-based medicine to guide optimal agent selection. Likewise, there are limited data to absolutely contraindicate the use of any of the commonly used inhalational or intravenous anesthetic agents. In general, the inhalational and intravenous anesthetic agents including the barbiturates, benzodiazepines, propofol, ketamine, and the inhalational anesthetic agents are anticonvulsants.

Anecdotal reports suggest increased sensitivity to anesthetic agents in patients with CNS impairment related to ZS, providing support for the use of short acting agents (volatile anesthetic agents, intravenous agents, and opioids) to allow for rapid awakening and limited impact on postoperative upper airway and respiratory function.[19] Preoperative sedative medications should only be administered with continuous monitoring of respiratory function. The potential for perioperative respiratory failure

may be increased by pre-existing respiratory dysfunction from hypotonia, poor cough effort, chronic aspiration or recurrent pneumonia. Given the potential for postoperative events related to airway patency and respiratory function, continuous postoperative monitoring of respiratory function is suggested following prolonged surgical procedures.

Hypotonia can significantly impact the choice of neuromuscular blocking agents (NMBAs). Patients with pre-existing motor weakness and hypotonia may be sensitive to the effects of non-depolarizing NMBAs. The novel reversal agent, sugammadex, offers the potential to reverse significant residual neuromuscular blockade in patients with neuromyopathic conditions.[20] Given the limited data available, no definitive conclusions can be drawn regarding the safety of succinylcholine in this patient population. In the presence of hypotonia, we would suggest that succinylcholine is relatively contraindicated given the potential for an exaggerated hyperkalemic response.[21] In our patient, endotracheal intubation was accomplished following the administration of propofol without the use of a NMBA.

Another common end-organ effect of ZS is hepatic dysfunction caused by the defective metabolism and the subsequent accumulation of very long chain fatty acids. Common manifestations of hepatic dysfunction associated with ZS noted in our patient included hepatomegaly, elevated liver function tests, and coagulation abnormalities.[22] Hepatic dysfunction and chronic hypoalbuminemia can impact drug metabolism and pharmacokinetics.[23] Hepatic dysfunction may progress to fibrosis, cirrhosis, and hepatic insufficiency or failure. Given the invariable presence of hepatic involvement, preoperative assessment of hepatic function, serum albumin, and coagulation function is suggested. In our patient, coagulation dysfunction was attributed primarily to factor deficiency. Given the limited extent of the surgical dissection, hematology and hepatology consultation in our patient recommended the perioperative administration of epsilon amino caproic acid. For more invasive procedures, based on the preoperative coagulation profile, treatment of the coagulation disturbances may include the administration of vitamin K, fresh frozen plasma, cryoprecipitate, recombinant factor VIIa or prothrombin complex concentrates.[24]

Patients with ZS should be screened for adrenal insufficiency.[25] The diagnosis of adrenal insufficiency is generally based on an ACTH stimulation test with an inadequate increase in serum cortisol levels. Treatment includes daily supplementation of corticosteroids with an increased dose during times of acute illness or surgical stress.[26] Our patient was diagnosed with adrenal insufficiency shortly after her initial diagnosis at 11 months of age. Perioperative care in our patient included intraoperative administration of intravenous hydrocortisone with a return to daily supplementation once oral intake was resumed postoperatively.

Renal involvement with ZS includes the development of renal cortical cysts and renal stones, specifically calcium oxalate stones.[2,7,27] Although a single cortical cyst generally remains asymptomatic, patients with ZS can develop several of these fluid-filled cysts that can cause enlargement of the kidneys leading to complications such as hypertension or altered renal function. Additionally, the formation of renal stones may lead to renal insufficiency secondary to hydronephrosis. Our patient was evaluated with a renal ultrasound and was found to have normal appearing kidneys.

In summary, ZS is a multi-system disorder resulting from defects in the structure, function, or number of peroxisomes, which are essential for the β-oxidation of very-long-chain fatty acids. In general, the disorder is progressive as there is no definitive treatment. Surgical interventions may be aimed at ameliorating the end-organ effects of the disorder. To date, there are a paucity of reports regarding the anesthetic management of patients with ZS.[19,22] Anesthetic care may be impacted by CNS involvement with seizures, hypotonia, visual/hearing impairment, and cognitive dysfunction. Hepatic involvement may include progressive hepatic cirrhosis and

hepatic insufficiency with altered drug metabolism or impaired coagulation function. Additional end-organ involvement includes the invariable presence of adrenal insufficiency and the potential for alterations in renal function related to renal stone formation or multiple cysts.

References

1. Bowen P, Lee CS, Zellweger H, Lindenberg R. A familial syndrome of multiple congenital defects. Bull Johns Hopkins Hosp. 1964;114:402-14.
2. Smith DW, Opitz JM, Inhorn SL. A syndrome of multiple developmental defects including polycystic kidneys and intrahepatic biliary dysgenesis in 2 siblings. J Pediatr. 1965;67:617-24.
3. Opitz JM, Zu Rhein GM, Vitale L, et al. The Zellweger syndrome (cerebro-hepato-renal syndrome) Birth Defects Orig Art Set. 1969;2:144-58.
4. Passarge E, McAdams AJ. Cerebro-hepato-renal syndrome. A newly recognized hereditary disorder of multiple congenital defects, including sudanophilic leukodystrophy, cirrhosis of the liver, and polycystic kidneys. J Pediatr. 1967;71:691-702.
5. Goldfischer S, Moore CL, Johnson AB, et al. Peroxisomal and mitochondrial defects in the cerebro-hepato-renal syndrome. Science. 1973;182:62-4.
6. Weller S, Gould SJ, Valle D. Peroxisome biogenesis disorders. Annu Rev Genomics Hum Genet. 2003;4:165-211.
7. Berendse K, Engelen M, Ferdinandusse S, et al. Zellweger spectrum disorders: clinical manifestations in patients surviving into adulthood. J Inherit Metab Dis. 2016;39:93-106.
8. Braverman NE, D'Agostino MD, MacLean GE. Peroxisome biogenesis disorders: Biological, clinical and pathophysiological perspectives. Dev Disabil Res Rev. 2013;17:187-96.
9. Powers JM, Tummons RC, Caviness VS, Moser AB, Moser HW. Structural and chemical alterations in the cerebral maldevelopment of fetal cerebro-hepato-renal (Zellweger) syndrome. J Neuropathol Exp Neurol. 1989;48:270-89.
10. Rafique M, Zia S, Rana MN, Mostafa OA. Zellweger syndrome - a lethal peroxisome biogenesis disorder. J Pediatr Endocrinol Metab. 2013;26:377-9.
11. Berger J, Gärtner J. X-linked adrenoleukodystrophy: clinical, biochemical and pathogenetic aspects. Biochim Biophys Acta. 2006;1763:1721-32
12. Zellweger H, Maertens P, Superneau D, Wertelecki W. History of the cerebrohepatorenal syndrome of Zellweger and other peroxisomal disorders. South Med J. 1988;81:357-64.
13. Lee PR, Raymond GV. Zellweger syndrome. Neurology. 2013;80:e207-10.
14. Grayer J. Recognition of Zellweger syndrome in infancy. Adv Neonatal Care. 2005;5:5-13.
15. Kheir AEM. Zellweger syndrome: A cause of neonatal hypotonia and seizures. Sudan J Paediatr. 2011;11:54-8.
16. Jones CT, Raman VT, DeVries S, Cole JW, Kelleher KJ, Tobias JD. Optimizing anticonvulsant administration for children before anesthesia: a quality improvement project. Pediatr Neurol. 2014;51:632-40.
17. Kofke WA. Anesthetic management of the patient with epilepsy or prior seizures. Curr Opin Anaesthesiol. 2010;23:391-9.
18. Perks A, Cheema S, Mohanraj R. Anaesthesia and epilepsy. Br J Anaesth. 2012;108:562-71.
19. Kılınç G. Anesthesia management in a patient with Zellweger syndrome. Med Sci Disc. 2019;6:82-3.
20. Tobias JD. Current evidence for the use of sugammadex in children. Paediatr Anaesth. 2017;27:118-25.
21. Martyn JAJ, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms. Anesthesiology. 2006;104:158-69.
22. Platis CM, Kachko L, Peled E, Katz J. Anesthesia for the child with Zellweger syndrome: a case report. Paediatr Anaesth. 2006;16:361-2.
23. Poppers PJ. Hepatic drug metabolism and anesthesia. Anaesthesist. 1980;29:55-8.

24. Amitrano L, Guardascione MA, Brancaccio V, Balzano A. Coagulation disorders in liver disease. Semin Liver Dis. 2002;22:83-96.
25. Schwartz RE, Stayer SA, Pasquariello CA, Lowe DA, Foster CJ. Anaesthesia for the patient with neonatal adrenoleukodystrophy. Can J Anaesth. 1994;41:56-8.
26. Woodcock T, Barker P, Daniel S, et al. Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency: Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK. Anaesthesia. 2020;75:654-63.
27. van Woerden CS, Groothoff JW, Wijburg FA, et al. High incidence of hyperoxaluria in generalized peroxisomal disorders. Mol Genet Metab. 2006;88:346-50.