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Perioperative care of a patient with neuronal ceroid lipofuscinoses

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Abstract

The neuronal ceroid lipofuscinoses (NCL) are a group of inherited, autosomal recessive, and progressive neurodegenerative diseases, which result from an enzymatic defect or the deficiency of a transmembrane protein, leading to the accumulation of lipopigments (lipofuscin) in various tissues. NCL results in the impairment of function in several end-organs including the central nervous system with loss of cognitive and motor function, myoclonus, and intractable seizures. Additional involvement includes the cardiovascular system with arrhythmias and bradycardia as well as impairment of thermoregulation leading to perioperative hypothermia. Given the complexity of the end-organ involvement and the progressive nature of the disorder, the anesthetic care of such patients can be challenging. Till date, there are a limited number of reports regarding the anesthetic management of patients with NCL. We present an 18-year-old patient with NCL who required anesthetic care during replacement of a vagal nerve stimulator. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement of NCL discussed, and options for anesthetic care presented.

Keywords: *Batten disease, Jansky-Bielschowsky disease, neuronal ceroid lipofuscinoses*

INTRODUCTION

The neuronal ceroid lipofuscinoses (NCL) are a group of inherited (autosomal recessive), progressive degenerative disorders of the central nervous system (CNS). These disorders, broadly classified as a lysosomal storage disorder, result either from an enzymatic defect or the deficiency of a transmembrane protein, leading to the accumulation of lipopigments (lipofuscin) in various tissues including the CNS.[1] The lipopigments are composed of fats and proteins and appear as a greenish – yellow color when viewed under an ultraviolet light microscope.

The variants of NCL are generally classified by their age of onset and the composition of the storage material. The four variants include: (1) infantile (INCL, Santavuori-Haltia disease), (2) late infantile (LINCL, Jansky-Bielschowsky disease), (3) juvenile (JNCL, Batten disease, Spielmeyer-Vogt disease), and (4) adult (ANCL, Kufs disease).[2] Despite differences in the age of onset and the exact enzymatic process involved, the NCL share similar phenotypic expression including rapidly progressive changes in visual acuity with eventual visual loss, the onset of seizures, loss of cognitive and motor function, and premature death.[2] The diagnosis is based on the characteristic clinical features with confirmation by an assay of enzyme activity, molecular genetic testing, and electron microscopy of biopsied tissues. Molecular genetic testing for the eight genes (PPT1, TPP1, CLN3, CLN5, CLN6, MFSD8, CLN8, and CTSD) known to be associated with NCL is clinically available. Three lysosomal enzymes: Palmitoyl-protein thioesterase 1 (PPT1) encoded by the gene PPT1, tripeptidyl-peptidase 1 (TPP-1) encoded by the gene TPP1, and cathepsin D (CTSD) encoded by the gene CTSD have been identified as being deficient in NCL. Assays of the enzymatic activity of PPT-1 and TPP-1 are clinically available.[3]

Due to the progressive and debilitating nature of the disorder, anesthetic care may be required during supportive or palliative procedures. Given the complexity of the end-organ involvement and the progressive nature of the disorder with respiratory and cardiac involvement, the anesthetic care of such patients can be challenging. Till date, there are a limited number of publications reporting the anesthetic management in patients with NCL. We present an 18-year-old male with NCL who required anesthetic care during replacement of a vagal nerve stimulator (VNS). Previous reports of anesthetic care for these patients is reviewed, the end-organ involvement discussed, and options for anesthetic care presented.

CASE REPORT

Institutional Review Board approval is not required at Nationwide Children's Hospital (Columbus, Ohio) for the presentation of single case report. The patient was an 18-year-old, 63.1 kilogram male who presented for replacement of aVNS. His past history was significant for macular vision loss starting at 5 months of age and tonic-clonic seizures which started 6 months later. Because of a family history of "Batten disease" in his maternal great cousins, the clinical diagnosis of NCL was investigated immediately and was subsequently diagnosed using genetic testing with mutations of the CLN6 gene identified. His mother carries the same mutation. The patient was diagnosed as having a variant of late-infantile NCL with the CNL6 gene mutation. He subsequently developed worsening intractable epilepsy with generalized tonic-clonic seizures more than once a day with limited response to anticonvulsant therapy. Additionally, there was cognitive developmental impairment, language delay, ataxia, and spasticity of all four extremities. A vagal nerve generator had been implanted 7 years earlier to help in controlling his seizure disorder. The generator was nearing the end of its battery life, and therefore it was elected to replace the vagal nerve generator. Current home medications included lamotrigine (50 mg twice a day), baclofen (10 mg three times a day), levetiracetam (900 mg twice a day), clonazepam (1.5 mg twice a day), and valproic acid (625 mg twice a day). A preoperative electrocardiogram (ECG) and laboratory data (hemoglobin, coagulation function, electrolytes, blood urea nitrogen, creatinine, and liver functions tests) were within normal limits.

The patient was held *nil per os* for 6 hours except for his usual morning doses of lamotrigine, baclofen, levetiracetam, clonazepam, and valproic acid. In the preoperative surgical unit, his blood pressure was 105/65 mm Hg, heart rate was 74 beats per minute, SpO_2 was 96% while breathing room air, and his body temperature was 36.1°C. After he was transported to the operating room, routine American Society of Anesthesiologists' monitors were placed. Anesthesia was induced with propofol (250 mg or 4 mg/kg), fentanyl 100 μg (1.6 μg/kg), and hydromorphone 0.4 mg (6.3 μg/kg) which were administered intravenously through an existing peripheral intravenous line. Bag-valve-mask ventilation was provided with oxygen and sevoflurane. At an end-tidal sevoflurane concentration of 5.5-6%, direct laryngoscopy was performed, and a 7.0 mm cuffed endotracheal tube was easily placed on the first attempt without the use of neuromuscular agents. Throughout the induction of anesthesia, room temperature was at 26.7°C and active warming provided using a forced air warming device. Immediately after anesthetic induction, the patient's body temperature was 35.5°C. Anesthesia was maintained with oxygen, air, sevoflurane (end-tidal concentration 1 to 3%) without neuromuscular blockade. During surgery, vital signs were maintained at their baseline range by adjustment of the inspired sevoflurane concentration. Heart rates varied from 65 to 80 beats per minute with a normal sinus rhythm. No bradycardia or arrhythmias were noted. Despite forced-air warmer and the administration of fluid *via* a warmer throughout the surgery, his body temperature decreased to a low of 34.9°C intraoperatively, but had increased to 35.3°C at the completion of the procedure. Following completion of the surgical procedure, the patient was transferred to the post-anesthesia care unit (PACU) in stable condition. He emerged from anesthesia smoothly and his trachea was extubated within 30 min of transportation to PACU. After an uneventful recovery, he was discharged home on the same day of surgery. The remainder of his postoperative course was unremarkable.

DISCUSSION

As with the anesthetic care of all patients, the focus of effective perioperative care of patients with NCL begins with the preoperative examination and the identification of end-organ involvement by the primary disease process. Till date, there are a limited number of anesthetic reports regarding the perioperative care of such patients [Table 1]. As noted in our patient and most patients with NCL, given the progressive

deterioration of CNS function, seizures are a frequent presenting sign and accompanying problem in these patients. In the care of such patients, simple maneuvers to limit the potential for perioperative seizures includes a documentation of therapeutic anticonvulsant levels prior to the surgical procedure with optimization of therapy by the pediatric neurology service as well as the administration of routine anticonvulsant medications the day or the procedure. These should be administered despite concerns of the patient's *nil per os* status. When enteral administration is not feasible, alternative routes of delivery including intravenous administration is feasible for many of these agents. Consultation with the neurology or pharmacology service is suggested when questions arise concerning dosing conversion from enteral to intravenous administration. Additionally, specific anticonvulsant medications can be administered per rectum.[9] In addition to their administration the morning or the surgery, for prolonged procedures, the continued redosing of anticonvulsants intraoperatively is suggested to maintain therapeutic levels during prolonged surgical procedures. As noted in our patient, despite maximal anticonvulsant therapy, many patients with NCL will continue to have seizure episodes on a daily basis. Although our patient was presenting to have the battery changed on his VNS, given potential problems with electrocautery interference with the VNS, these devices should be turned off prior to surgical procedures and then reactivated in the recovery room.[10] Additional invariable CNS consequences of NCL include dementia, cognitive impairment, and visual loss. These conditions increase the difficulty of providing effective communication with the patient. In specific circumstances, premedication or parental presence in the operating room may be needed to alleviate anxiety.

The choice of anesthetic agents in patients with seizure disorders remains somewhat controversial. Although it has been postulated that specific agents may activate the electroencephalogram (EEG) and hence augment seizure activity; in general, the inhalational and intravenous anesthetic agents are anticonvulsants. Many of these agents including the barbiturates, propofol, and the volatile agents have been used successfully to treat status epilepticus that is refractory to conventional therapy.[11,12] Although seizure-like activity and even occasional spike and wave activity on the EEG have been reported with the use of sevoflurane, these effects are rather and generally occur only when the inspired concentration is rapidly increased during anesthetic induction.[13,14,15] As such, its use even in patients with seizure disorders is acceptable.[16] Additional agents whose use remains controversial in patient with seizure disorders include ketamine, etomidate, and the synthetic opioids including remifentanil.[16] While it has been generally recommended that ketamine is contraindicated in patients at risk for seizure activity, the most recent literature has demonstrated the anticonvulsant effect of this agent and even used it to treat status epilepticus thereby further confounding this issue.[17,18] Given these concerns, we chose to use a combination of sevoflurane, propofol, and the opioids, fentanyl, and hydromorphone for maintenance of anesthesia in our patient.

Another important factor in providing anesthetic care in such patients is the choice of neuromuscular blocking agent especially with regards to the safety of using succinylcholine. Given the associated involvement of the CNS, it has been suggested that succinylcholine be avoided because of possible hyperkalemia.[4,19,20] However, the anecdotal safe use of succinylcholine in patients with NCL has been reported.[6,7] Issues of airway management may be further magnified by the presence of lower esophageal sphincter dysfunction, and aspiration risk in patients with CNS involvement. Yamada *et al.* recommended the preoperative administration of agents to decrease gastric acidity and augment motility.[4] In patients with a true aspiration risk, rapid sequence intubation with cricoid pressure may be considered. In this scenario, a rapidly acting neuromuscular blocking agent may be required. Alternatively, rapid sequence intubation can also be accomplished using a combination of propofol and remifentanil without a neuromuscular blocking agent.[21,22] In our patient, as the surgical procedure did not require neuromuscular blockade, we chose to accomplish endotracheal intubation using a deep plane of sevoflurane anesthesia supplemented with intravenous propofol.[23] Although neuromuscular blockade was not required in our patient, specific concerns may be existing with the use of such agents in patients with CNS disorders with hypotonia including an exaggerated and prolonged response. Prior to their withdrawal, rapacuronium and mivacurium, two short-acting neuromuscular blocking agents, offered the ability to achieve complete neuromuscular blockade to allow for endotracheal intubation with an acceptable recovery time even for briefer procedures.[24,25] If available, rocuronium in combination with sugammadex is another option.

In addition to the perioperative aspiration risk, poor airway tone may predispose these patients to developing upper airway obstruction or respiratory failure in postoperative period. These issues may be compounded by pre-existing respiratory dysfunction from hypotonia, poor cough effort, chronic aspiration, or recurrent pneumonia. Preoperative assessment regarding usual respiratory pattern, history of recurrent pneumonia, or swallowing problems may identify at risk patients. As the residual effects of anesthetic agents may impact upper airway control and postoperative respiratory function, whenever feasible, short acting agents whose effects dissipate rapidly should be considered. Regardless of the agents used, postoperative monitoring of respiratory function is suggested. As appropriate based on the surgical procedure, regional anesthesia may be used instead of general anesthesia or as an adjunct to provide postoperative analgesia and thereby minimize the perioperative effects of opioids. Preoperative preparation should include aggressive treatment of respiratory infections and as cognitive function permits, instruction regarding the use of techniques such as incentive spirometry. Postoperatively, non-invasive techniques of respiratory support such as bilevel positive airway pressure support (BiPAP) may facilitate postoperative tracheal extubation and prevent atelectasis in patients with altered respiratory function.[26,27]

End-organ involvement may also include the cardiovascular system with a propensity of these patients to develop intra-operative bradycardia. Miao *et al*. reported that patients with INCL had a significantly more frequent incidence of intra-operative sinus bradycardia than a control group.[28] The study cohort included eight patients with INCL, ranging in age from 10 to 32 months and 25 control patients, ranging in age from 18 to 92 months. The patients were anesthetized with propofol or sevoflurane for 62 nonsurgical procedures. Patients with INCL had significantly more sinus bradycardia when compared with controls (10 *versus* 1, $P < 0.001$). All episodes of sinus bradycardia were successfully treated with atropine or glycopyrrolate. Additionally, despite active warming techniques, hypothermia was also more common. In approximately 80% of these cases, the bradycardia was associated with hypothermia. Autonomic nerve dysfunction including impaired thermoregulation is Autonomic nerve dysfunction including impaired thermoregulation results in a propensity in a propensity for these patients to develop perioperative hypothermia and bradycardia. Although bradycardia has been reported most frequently, additional involvement of the conduction system has included intraventricular conduction delays, repolarization disturbances, supraventricular tachyarrhythmias, as well as ectopic atrial and ventricular foci.[29] An autopsy study of three patients with NCL provides additional insight into the cardiac involvement of these patients.[30] Histologic examination of the myocardium in these three patients demonstrated significant infiltration of the myocardium and valvular structures with the storage material. Additionally, in two of the patients the storage was associated with hypertrophy and dilatation of both ventricles as well as extensive degenerative myocardial changes with interstitial fibrosis and fatty infiltration. Given these findings, the authors cautioned that the myocardial changes could result in clinical manifestations of a restrictive-type of cardiomyopathy. The authors suggested that the lack of clinical symptomatology related to these findings relates to the limited activity of these patients. Given these concerns, it appears that a preoperative electrocardiogram and echocardiogram should be obtained. Ready access to treatment for arrhythmia and bradycardia including transcutaneous pacing are suggested. Given the association of bradycardia and hypothermia, active warming is suggested with some combination of warming the environment, use of overhead warming lights, intraoperative forced air, and warming of intravenous fluids.

In summary, we present the patient with a LINCL. As is noted in our patient and from anecdotal reports in the literature, several challenging problems including severe CNS involvement with loss of developmental milestones, myoclonus, and intractable seizures; cardiac involvement with intra-operative arrhythmias including bradycardia; and a propensity for perioperative hypothermia. Preoperative examination, the assessment of end-organ impairment by the primary disease process, and close postoperative monitoring are mandatory for the effective perioperative care of patients with NCL.

Footnotes

Source of Support: Nil

Conflict of Interest: None declared

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Figures and Tables

Table 1

Authors and reference	Patient demographics	Anesthetic technique	Intraoperative problems and management
Yamada *et al.*[4]	14-year-old, 28.7 kg girl with JBD undergoing resection of a gingival tumor and an infected sinus in the sacral area	Induction with atropine 0.25 mg, thiamylal 100 mg, and sevoflurane. Maintenance of anesthesia included 66% nitrous oxide and 1-3% sevoflurane in oxygen without a NMBA	Intraoperative hypothermia of 34.5°C treated by use of a humidifier, fluid warmer, circulating-water-mattress, and forced-air warming device. Required active warming for 2 hours following the 5.5 h surgical procedure. Also developed postoperative myoclonus which was treated with diazepam
Hiramori *et al.*[5]	Siblings. 31-year-old and 29-year-old women for gastrostomy tube placement	Induced and maintenance with propofol and opioids. Non-depolarizing NMBA's were administered	No problems except for mild perioperative hypothermia. The bispectral index fluctuated widely during the case in both patients
Gopalakrishnan *et al.*[6]	17-month-old, 10.5 kg girl, diagnosed with batten disease undergoing an eye examination, electroretinogram, and biopsy of the conjunctiva	Induction with sevoflurane, nitrous oxide and oxygen followed by the administration of glycopyrrolate and propofol once IV access was obtained. No NMBA's were administered	The authors stated that they avoided potentially epileptogenic agents including fentanyl, ketamine, and etomidate
Defalque.[7]	38-year-old, 64.5 kg man with Kufs disease who underwent exploratory laparotomy	Premedication with intravenous midazolam (2 mg). RSI with succinylcholine and etomidate. Maintenance anesthesia with 0.5-1% isoflurane in nitrous oxide and oxygen. Neuromuscular blockade with intravenous vecuronium	Slow emergence despite limited residual isoflurane in end-tidal gas. Awoke 90 minutes following conclusion of the case. Authors caution against use of medications that may block dopamine receptors due to Parkinsonian like symptoms in these patients
Pereira *et al.*[8]	Two patients 14-year-old boy with NCL6, weighing 43 kg undergoing a PEG tube replacement 20-year-old girl with NCL3 (Batten disease), weighing 42 kg undergoing a PEG tube insertion	Premedication with intravenous midazolam (1 mg). Intravenous atropine administered. Induction and maintenance of anesthesia with sevoflurane and nitrous oxide in oxygen. No NMBA's were administered	Difficulty in intubation in the second case because of poor mouth opening

JBD – Jansky-Bielschowsky disease; NMBA – Neuromuscular blocking agent; INCL – Infantile neuronal ceroid lipofuscinoses; PEG – Percutaneous endoscopic gastrostomy; RSI – Rapid sequence intubation

Previous reports of anesthesia for patients with neuronal ceroid lipofuscinoses