Anesthetic Management of a Patient with Type II Alexander Disease: A Case Report
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Patients with type II Alexander disease have white matter dysplasia, which may cause various symptoms due to nerve conduction impairment. When providing anesthesia to a patient with Alexander disease, careful and patient-specific individualized risk evaluation must be preceded by planning the method of anesthesia and anesthetic drugs. This is the first case report of a patient with type II Alexander disease who underwent general anesthesia. We performed general anesthesia on a 45-year-old male with type II Alexander disease for laparoscopic cholecystectomy, using remimazolam, remifentanil, and rocuronium. Despite the use of reversal agents including flumazenil, naloxone, and sugammadex, the patient manifested a delay in emergence but successfully recovered from anesthesia without postoperative complications. In consideration of the possibility that leukodystrophy may have altered responses to anesthetics, the action of an anesthetic agent may be prolonged or delayed in patients with type II Alexander disease. We recommend using drugs with a short duration of action and which can be reversed immediately by a reversal agent.

Keywords: Alexander disease; Leukoencephalopathies; Demyelinating diseases; Remimazolam; Delayed emergence from anesthesia; General anesthesia; Case report

INTRODUCTION

Patients with type II Alexander disease have white matter dysplasia, which may cause mental change, seizures, and decreased motor function due to abnormal nerve impulse conduction. As in other leukodystrophies, there may be a high risk of airway complications especially during perioperative periods, due to common gastrointestinal symptoms such as reflux or vomiting, abundant oral secretion, high probability of seizure, pharyngeal muscle weakness, and along with prolonged bedridden state [1,2].

Also, Alexander disease has various types and may show numerous clinical manifestations differing from patient to patient. Therefore, the anesthetic concerns of these patients should include a careful and prudent evaluation of risks regarding individual symptoms. Furthermore, a patient-specific evaluation must be preceded by selecting the type of anesthesia and anesthetic drugs.

We performed general anesthesia on a type II Alexander disease patient for laparoscopic cholecystectomy, using remimazolam, remifentanil, and rocuronium. These drugs have a short duration of action and possess agents that can directly reverse their effect. We present a successful anesthetic management experience in type II Alexander disease patients accompanied by a delay in recovery but no complication, along with a review of related literature about the anesthetic and neurologic considerations.

CASE REPORT

A 45-year-old male patient (height 172 cm; weight 68 kg) was admitted to the emergency room due to abdominal pain in the right upper quadrant. The patient was diagnosed with acute cholecystitis and it was decided that he would undergo laparoscopic cholecystectomy.

The patient had type II Alexander disease with neurological symptoms including decreased motor function, which was diagnosed at another hospital in 2018. There were no other underlying diseases. At the time of admission, the patient was alert and had...
General anesthesia was scheduled after fasting for more than 8 hours, and no premedication was administered before surgery. Immediately after the patient arrived at the operating room, the electrocardiogram and pulse oxygen saturation were continuously monitored. Blood pressure was checked at 5-minute intervals. Before induction of general anesthesia, blood pressure was 113/73 mm Hg, heart rate was 86 beats/min, and pulse oxygen saturation was 99%. The first patient state index (PSI) was measured as 95.

After preoxygenation with 100% oxygen, remimazolam (6 mg/kg/hr) and remifentanil (range, 0.2–0.3 mcg/kg/min) was continuously administered intravenously, and 1% lidocaine 70 mg was administered intravenously to induce anesthesia while observing PSI. The patient’s consciousness was lost, neuromuscular monitoring with train of four (TOF) was started using Twitchview (Blink Device Company, Seattle, WA, USA). And 50 mg of rocuronium was administered intravenously while manual ventilation with a face mask, and when there was no response to stimulation (TOF 0/4), an endotracheal tube with an inner diameter of 7.5 mm was intubated. A relatively high dose of rocuronium was given for rapid sequence induction since Alexander disease patients have a high risk of aspiration and was given in expectation of prolonged surgery.

For maintenance of anesthesia, remimazolam (range, 0.6–1 mg/kg/hr) and remifentanil (range, 0.2–0.4 mcg/kg/min) were continuously infused and titrated to maintain PSI between 30–60. No additional doses except the initial dose of rocuronium were administered for muscle relaxation during the operation. During the surgery, blood pressure fluctuation occurred due to posture change, but it was temporary. Blood pressure and heart rate were well controlled within an acceptable range.

The TOF ratio at the end of surgery was measured as 14%, and at the same time, 0.4 mg of glycopyrrolate and 15 mg of pyridostigmine were administered to reverse residual muscle relaxant action. After 10 minutes of reverse agent administration, the TOF ratio was 31%, and after 15 minutes, it was 63%. We considered that sufficient time has passed for the peak effect of the reversal agent, so 100 mg of sugammadex was additionally administered. After 5 minutes, the TOF ratio was found to be 75%, and sugammadex 100 mg was additionally administered, after another 5 minutes TOF ratio was measured 100% at last. In summary, for the TOF ratio to reach from 14% to 100%, we required 0.4 mg of glycopyrrolate and 15 mg of pyridostigmine, and an additional 200 mg of sugammadex with a time of 25 minutes.

The onset time of remimazolam is 1 to 3 minutes, and the duration is 10 minutes [3,4]. In this case, considering the possibility of delayed recovery, we discontinued remimazolam infusion in advance, approximately 15 minutes before the end of the operation. At 30 minutes after discontinuation of remimazolam, the patient’s level of consciousness was between 45 to 60 or less PSI, and arousal was not achieved. Then 0.25 mg of flumazenil was given twice within 5 minutes each for reversal of remimazolam. At 35 minutes after discontinuation of remimazolam, the PSI level rose to 74, but arousal and spontaneous respiration still did not happen.

Although remifentanil was discontinued immediately after surgery, in consideration of the residual effect of opioid analgesics, 0.2 mg of naloxone was given intravenously at the moment of TOF 95%, PSI around 70 (20 minutes after the surgery ended, 35 minutes after stopping remimazolam). Shortly after, the patient finally recovered consciousness and spontaneous respiration. Extubation was done after confirming the patient’s ability to obey and command. Additionally, to reduce the residual side effects of opioid analgesics and with a concern of the drug interaction with remimazolam, although the prolonged effect of remifentanil has not been previously reported, 0.6 mg of naloxone was injected intramuscularly and the anesthesia was terminated. Fig. 1 summarizes the timeline of the series of events.

The total anesthesia time was 2 hours 40 minutes, and the time taken from the completion of the operation to the completion of
the anesthesia was 25 minutes. The patient was transferred to the intensive care unit in the ward after going through the post-anesthesia care unit. The patient was discharged without complications 3 days after the surgery.

**DISCUSSION**

Myelin is a major component of the cerebral white matter, that is composed of lipid membranes wrapping around axonal processes to increase the rate and efficiency of neuronal action potential conduction. Myelin formation and degradation may be affected by several hereditary or acquired degenerative disorders which may be divided into leukodystrophies. Leukodystrophies are a group of progressive, degenerative disorders that include metachromatic leukodystrophy (MLD), adrenoleukodystrophy, Krabbe’s disease, Canavan’s disease, Pelizaeus-Merzbacher disease, and Alexander disease.

Alexander disease, first described in 1949 by W. Stewart Alexander, is unique from the leukodystrophies that the majority of cases are sporadic, and are not inherited. The age of onset varies from prenatal to adult. Patients are currently classified into two distinct disease categories, with type I disease being early-onset and type II disease which is mostly adult-onset [5]. Type II Alexander disease is a rare autosomal-dominant leukodystrophy characterized by slowly progressive dysarthria, dysphagia, palatal tremor, cerebellar ataxia, and pyramidal signs [6]. Alexander disease is mostly a result of a de novo mutation in the gene coding for the astrocyte-specific cytoskeletal intermediate filament protein, glial fibrillary acidic protein, and gives the astrocytes their characteristic pathological appearance as Rosenthal fibers [7,8].

As like in other neural conduction disorders with white matter dysplasia, Alexander disease patients may present altered mental status or frequent convulsions. In addition, during induction or emergence from anesthesia, it may be difficult to secure the airway of patients due to seizures, and these patients have a greater risk of respiratory complications due to gastroesophageal reflux, muscle weakness, and prolonged bed rest.

Because Alexander disease is a rare disease and the adult-onset type is rarer among them, there were no reports or publications related to anesthetic management as far as we know. We decided to refer to anesthetic management of other leukodystrophy patients, however, publications describing anesthesia or anesthesia-related complications in leukodystrophy patients are also scarce and limited to case reports with a few numbers of retrospective studies, most of which were for magnetic resonance imaging examinations [1,2,9]. Those reports typically describe complications including hypoxia, nausea, vomiting, bradycardia, convulsions, aspiration, and arrhythmias [1,2,9].
Similarly, in another retrospective study about the safety of anesthetic in patients with Krabbe disease and MLD, complications were reported in 11 of 287 anesthesia cases (3.8%), six of 185 Krabbe patients (3.2%), and five patients (4.9%) in 102 MLD cases. This study retrospectively analyzed the incidence of complications between the general population and the disease group, and it was found that the disease group had a higher incidence of complications (0.246% vs. 3.8%) [9].

With regard to Alexander disease, there are reports of anesthesia for pediatric type patients; however, there are no reports for the rarer type II Alexander disease. Therefore, we considered the possibility of altered response to anesthetic agents and various situations that may occur due to nerve conduction disorder. Preceding anesthesia, we planned to use drugs that have a short duration of action and that have a reversal agent. For sedation, a novel benzodiazepine class drug remimazolam, which has a short duration and can be reversed by flumazenil immediately, was used. Remifentanil is also a short-acting drug and can be reversed by naloxone. Lastly, rocuronium was used as a muscle relaxant, as sugammadex was in place for immediate detoxification.

As a limitation of our study, the drug interaction between remimazolam and remifentanil may have been involved in delayed emergence which makes it difficult to discern what might have caused it. In an animal study using monkeys about the drug interaction of remifentanil with remimazolam revealed that the sedative effects of remimazolam were synergistically enhanced with remifentanil, in detail, mean sedative doses were reduced by 94% [10]. However, as remimazolam is a novel drug and lacks study in humans, there was no such evidence of the drug interaction with remifentanil in human beings.

In practice, as we expected, the patient in our case presented delayed recovery from anesthesia including both neuromuscular blockade and sedation, furthermore, additional time was necessary for recovery even after the use of each reversal agent. In summary, to the best of our knowledge, this is the first case report of a patient with type II Alexander disease who underwent general anesthesia. Since type II Alexander disease patients may present various clinical manifestations, careful and patient-specific individualized consideration of these risks based on the disease progression must be preceded prior to planning the method of anesthesia and anesthetic drugs when providing regional or general anesthesia. Considering the high risk of complications, close monitoring is necessary during the perioperative period. Lastly, as we experienced in this case, in consideration of the possibility that Alexander disease may have altered responses to anesthetics due to leukodystrophy, the action of an anesthetic agent may be prolonged or delayed in patients with Alexander disease. Therefore, we would like to recommend using drugs with a short duration of action which could be reversed immediately by reversal agents.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**