General Anesthesia for a Patient With Pelizaeus-Merzbacher Disease

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We report the successful management of general anesthesia for a patient with Pelizaeus-Merzbacher disease (PMD). PMD is one of a group of progressive, degenerative disorders of the cerebral white matter. The typical clinical manifestations of PMD include psychomotor retardation, nystagmus, abnormal muscle tone, seizures, and cognitive impairment. General anesthesia for a patient with PMD may be difficult mainly because of seizures and airway complications related to poor pharyngeal muscle control. In addition, the possibility of exacerbation of spasticity should be considered. A 20-year-old man with PMD required removal of impacted wisdom teeth under general anesthesia. General anesthesia was induced with thiamylal, fentanyl, and desflurane. Anesthesia was maintained with desflurane and continuous intravenous remifentanyl under bispectral index and train-of-4 monitoring. Anesthesia lasted 1 hour 20 minutes and was completed uneventfully. Airway complications, seizures, and exacerbation of spasticity did not occur postoperatively. Preoperatively, our patient had no history of epilepsy attacks or aspiration pneumonia, and no clinical symptoms of gastroesophageal reflux disease. Therefore, exacerbation of spasticity was one of the most likely potential complications. Identification of these associated conditions and evaluation of risk factors during preoperative examination is important for performing safe anesthesia in these patients.

Key Words: General anesthesia; Pelizaeus-Merzbacher disease; BIS; Body temperature; Desflurane.

Pelizaeus-Merzbacher disease (PMD) is an inherited leukodystrophy caused by hypomyelination of the central nervous system (CNS) due to mutations of the proteolipid protein 1 (PLP1) gene. The PLP1 gene is located on the X chromosome (Xq22.2). Thus, PMD follows an X-linked recessive pattern of inheritance.^{1,2} Disorders of CNS myelin formation cause various neurologic symptoms.

Clinical manifestations of PMD are psychomotor retardation, nystagmus, abnormal muscle tone (hypoto-

nia in the first few months, which turns into spasticity later), and ataxia. In some cases, there may be dystonic posturing, athetotic movements, stridor, feeding difficulty, seizures, and cognitive impairment.³ The life span of patients with PMD depends on the severity of symptoms. Patients with severe congenital PMD often die of respiratory complications during infancy or early childhood. If they get through this early period of life, they can live into their third decade of life. Patients with classic PMD may survive to the sixth decade of life or longer.⁴

When administering general anesthesia to patients with PMD, seizures and airway complications related to pharyngeal weakness should be considered.^{4,5}

In the US, the prevalence of PMD in the population is estimated at 1 : 200,000 to 1 : 500,000. In Japan, the

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incidence was reported to be 1.45 per 100,000 male live births.^{2,4} Because of its low incidence, there are few reports on the anesthetic management of patients with PMD. We report here the conduct of general anesthesia in a patient with PMD. Anesthesia and surgery were initially postponed because of hyperthermia, but were later completed successfully.

CASE REPORT

A 20-year-old man required general anesthesia for extraction of impacted wisdom teeth because he had mental retardation and was uncooperative for the dental treatment. His developmental milestones were delayed from birth and he exhibited nystagmus, abnormal muscle tone, and ataxia. He was diagnosed with PMD by brain magnetic resonance imaging studies and genetic testing at the age of 3 years and 6 months. He underwent 2 surgeries for cross-leg deformity due to spasticity under general anesthesia at the age of 12 and 13 years, both procedures being uneventful. Because of an allergy to fresh cream, he had been on bepotastine, an antihistamine, since the age of 12 years. At the age of 15 years, he received clonazepam for approximately 1 year because of fever of unknown origin and exacerbation of involuntary movements.

He was usually homebound and sometimes received rehabilitation at a hospital or carried out light work in a day-stay institution for people with disabilities. On preoperative examination, he was 139 cm (55 inches) tall and weighed 34 kg. He had a blood pressure of 95/72 mm Hg, heart rate of 95 bpm, percutaneous oxygen saturation of 97%, and body temperature of 37.4°C. His blood tests, urinalysis, chest X-ray, and electrocardiogram were unremarkable. His airway examination revealed no respiratory distress, and his lungs sounded clear. Cardiac examination revealed regular rate and rhythm and no murmurs. His habitual medications included clonazepam, which he had begun to take again 3 years earlier, and bepotastine. He could follow easy directions, but could not express meaningful words because of cognitive impairment. He could swallow normal meals without aspiration and did not require any food modification. However, he needed total assistance in eating because of involuntary movements of the upper limbs. He was not able to take tablets, but was able to take powdered medicine. Physical examination revealed nystagmus; ataxia with spasticity, especially in the lower limbs; and frequent movements of the upper limbs and upper body. He could not stand straight and walk, but he could operate a wheelchair by himself. As he had no past history of epilepsy, aspiration pneumonia, or swallowing

difficulties, it was decided to perform general anesthesia, and an appointment for the treatment was made.

The surgery was postponed, however, because his body temperature rose to 38.5°C on the night before the treatment. On questioning, it was revealed that his temperature often rose to nearly 40°C on the night before such events as vaccination or stays at a day-stay institution for people with disabilities. He once underwent a medical examination by a family physician and had a fever on that day as well. There were no abnormal physical findings and his chest X-rays and blood test indicated no abnormality. As stress was thought to be responsible for the hyperthermia and he had a past history of fever of unknown origin that was treated by clonazepam, 5 mg of diazepam was prescribed as the preanesthetic medication and the treatment was rescheduled.

Five milligrams of diazepam was taken on the night before the treatment. On the morning of the operation, his body temperature was 37.8°C with no symptoms of respiratory tract infections. General anesthesia was performed on schedule.

On admission to the operating room, his blood pressure was 140/71 mm Hg and his heart rate was 120 bpm. In addition to standard electrocardiogram, pulse oximetry, noninvasive blood pressure, and end-tidal CO₂, bispectral index (BIS) and train-of-4 (TOF) monitoring were performed.

General anesthesia was induced with thiamylal (150 mg), fentanyl (0.1 mg), and desflurane (1.2 minimum alveolar concentration [MAC]) in air and oxygen. After these drugs were administered, his blood pressure decreased to 108/66 mm Hg and his heart rate to 103 bpm. Rocuronium (20 mg) was administered to facilitate nasal tracheal intubation. Anesthesia was maintained with desflurane (0.67 MAC) in air and oxygen and continuous intravenous remifentanyl (0.1 µg/kg/min). A BIS level was maintained around 60 during operation. The TOF ratio decreased to zero soon after administration of rocuronium and it became 1.0 approximately 40 minutes later. Before extubation, sugammadex was administered.

Anesthesia lasted 1 hour 20 minutes and was completed uneventfully. Neither significant changes in hemodynamics nor delayed emergence from anesthesia was noted. At the end of anesthesia, his rectal temperature was 36.9°C.

DISCUSSION

PMD is defined as a CNS dysmyelinating disorder in which myelin is not formed properly. Early manifestations include hypotonia, nystagmus, and delay in motor

development, which can be noted within the first year of life. Spasticity, ataxia, and choreoathetotic movements develop later. In severe cases, patients show congenital psychomotor developmental arrest and severe neurological symptoms. Feeding problems, stridor, progressive contractures, and seizures may be present.⁶

Many patients with PMD are prone to aspiration. Fatalities in children with severe PMD are usually due to aspiration.⁴ Therefore, the anesthesiologist should pay particular attention to respiratory complications. In such patients, rapid emergence from anesthesia and postoperative monitoring are essential. BIS monitoring as a guide to administration of adequate doses of anesthetics and narcotics and TOF monitoring for confirmation of recovery of neuromuscular function are extremely important. Although it is controversial whether or not they are effective in severe cases, preoperative administration of gastrointestinal stimulants, gastric secretion inhibitors, antacids, antiemetics, and anticholinergics and rapid sequence induction may be considered.^{7,8} For a patient with an extremely high risk of aspiration, Nissen fundoplication may be performed.

Seizures may occur in severe cases.³ To detect their occurrence early and to treat them appropriately, it is important to evaluate the type of epilepsy during the preoperative examination. The side effects of anticonvulsant drugs and possible interactions with drugs used for anesthesia should also be considered. General anesthetics have both proconvulsant and anticonvulsant properties.⁹ Attention to the occurrence of seizures is necessary for any general anesthetic agent. Among isoflurane, sevoflurane, and desflurane, particular care is necessary during use of sevoflurane, especially when used in high concentrations, because of reports that deep anesthesia with sevoflurane is a risk factor for excitation of the CNS. Also, hypocapnia is associated with electroencephalogram (EEG) changes.^{10,11} When administering inhalation agents, it may be necessary to pay attention to hyperventilation and high concentrations of the agents. Although propofol should theoretically have strong anticonvulsant properties, as it exhibits both GABAergic effects and persistent sodium current and calcium current blockade, some report that propofol can cause abnormal movements. However, most of these events are classified as seizure-like phenomena of nonepileptic origin.¹² There is clinical evidence that propofol has anticonvulsant effects and is therefore considered a safe drug for general anesthesia.¹⁰

One of the most common symptoms of PMD is spasticity, which may increase in certain situations. During the emergence period, attention should be paid to exacerbation of spasticity.¹³ TOF monitoring is useful for the early detection of spasticity, and benzodiazepine should be available for its management.

Airway complications and seizures increase the risk of general anesthesia in patients with PMD. Our patient had no history of aspiration pneumonia and no clinical symptoms of gastroesophageal reflux disease. Hence, we judged that the perioperative risk of respiratory complications was low. Additionally, the patient had no medical history of epileptic seizures. We were concerned about exacerbation of spasticity during the emergence period, but this did not occur. If exacerbation of spasticity was noted, we would have immediately administered diazepam suppositories. Alternatively, intravenous administration of diazepam might also be effective.

The planned surgery was postponed once because the patient's body temperature rose to 38.5°C on the night before the procedure. His temperature had risen to nearly 40°C on the night before some events, such as a vaccination or stays at the day-stay institution. Medical examination by his family physician revealed no respiratory infections or abnormal findings other than PMD. The cause of hyperthermia was unclear, although he had a history of exacerbation of involuntary movements and fever of unknown origin at the age of 15 years. His pediatrician supposed that the spasticity was exacerbated because of stress, which resulted in the development of hyperthermia. He also had cognitive disturbances and verbal communication was impossible. When he needed to express something, the spasticity sometimes worsened. We recognized that hyperthermia on the eve of the surgery might have occurred by the same mechanism.

Exacerbation of spasticity may lead to muscle contractures, and in some cases, patients may develop status dystonicus. It is defined as increasingly frequent and severe episodes of generalized dystonia, which necessitate urgent hospital admission and often interfere with respiration and causes metabolic disturbances such as hyperpyrexia, dehydration, respiratory insufficiency, and acute renal failure secondary to rhabdomyolysis.^{14,15} In our patient, stress reduction and prevention of spasticity exacerbation in the preoperative period were extremely important. When providing general anesthesia for patients with spasticity and cognitive disturbances, such as with PMD, and a past history of fever of unknown origin, drugs such as midazolam, clonazepam, haloperidol, propofol, pimozide, and/or dantrolene should be available for the treatment of status dystonicus.

It is reported that all anesthetic drugs usually used for induction and maintenance can be used in patients with PMD.⁵ We administered thiамylal, fentanyl, desflurane, and rocuronium. No untoward effects of use of these drugs were observed. We used desflurane for maintenance of anesthesia, whereas Tobias⁵ used isoflurane. Emergence and recovery from anesthesia performed with desflurane is faster as compared with other inhalation agents, and there is no evidence that desflurane has

epileptiform activity. Therefore, desflurane would appear to be a suitable drug for use in patients with PMD.

We used TOF monitoring. We were able to confirm the full recovery from muscle relaxation because the TOF ratio was 1.0. We administered sugammadex before extubation to ensure disappearance of the effect of rocuronium.

Spasticity does not appear with adequate neuromuscular blockade. If spasticity appears, this would occur after the effect of the muscle relaxant has disappeared. We are able to predict the time point when spasticity might appear by monitoring neuromuscular function. We recommend that TOF monitoring should be used in all patients with PMD for early detection of spasticity and prevention of postoperative respiratory complications due to residual neuromuscular blockade with muscle relaxants.

BIS monitoring was used in this case. This also facilitates maintenance of appropriate depth of anesthesia and prevention of delayed emergence. As the patient's previous EEG 1 year earlier showed no significant abnormality, BIS values were considered reliable in this case. Wang et al reported that EEG abnormalities might appear late in PMD, and EEGs performed several years after the onset of symptoms might show slowing of alpha rhythms and appearance of theta and delta waves.¹⁶ In severe cases of PMD, reliability of BIS values may decrease. To confirm the accuracy of BIS values, it may be necessary to evaluate for EEG abnormalities before anesthesia.

Lastly, although it does not appear that PMD contributes to an increased risk of malignant hyperthermia (MH), should spasticity and hyperthermia occur under anesthesia along with other common malignant hyperthermia signs and symptoms, such as increased end-tidal CO₂ and tachycardia, malignant hyperthermia treatment would need to be strongly considered.

In conclusion, we provided safe anesthesia management to a patient with PMD. In such patients, seizure disorders and the presence of gastroesophageal reflux disease and altered airway muscle tone with the risk of aspiration might lead to serious anesthetic complications. Prevention of exacerbation of spasticity should also be considered. Appropriate evaluation of these associated conditions during the preoperative examination, intraoperative appropriate monitoring, reduction in stress, and choice of anesthetic drugs that have no proconvulsant properties should allow the safe provision of anesthesia to patients with PMD.

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