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CLINICAL INFORMATION

Anesthetic management of a patient with 15q tetrasomy for dental treatment

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KEYWORDS
Chromosome 15q tetrasomy;
General anesthesia;
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Abstract
Background and objectives: 15q tetrasomy is a chromosomal abnormality that is a part of the heterogeneous group of extra structurally abnormal chromosomes. This syndrome is characterized by epilepsy, central hypotonia, developmental delay and intellectual disability, and autistic behavior. This is the first report of the anesthetic management of a patient with this syndrome.
Case report: We administered general anesthesia for dental treatment in a patient with 15q tetrasomy.
Conclusions: Appropriate planning for the prevention of complications such as seizures and hypotonia, and for delayed emergence from anesthesia, is required. Specifically, choosing short-acting drugs that do not induce seizures, together with suitable monitoring, resulted in successful anesthetic management of the patient with 15q tetrasomy.
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PALAVRAS-CHAVE
Tetrassomia do cromossomo 15q;
Anestesia geral;
Tratamento odontológico

Manejo anestésico de paciente com tetrassomia 15q para tratamento odontológico

Resumo
Justificativa e objetivos: Tetrassomia 15q é uma anomalia cromossômica que faz parte do grupo heterogêneo de cromossomos extras, estruturalmente anormais. Essa síndrome é caracterizada por epilepsia, hipotonia central, atraso no desenvolvimento e deficiência intelectual e comportamento autista. Este é o primeiro relato do manejo anestésico de um paciente com essa síndrome.
Relato de caso: Administramos anestesia geral para tratamento odontológico em um paciente com tetrassomia 15q.

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Conclusões: Um planejamento adequado para prevenir complicações como convulsões e hipotonia e para emergência tardia da anestesia é necessário. O manejo anestésico bem-sucedido do paciente com tetrassomia 15q foi o resultado específico da escolha de fármacos de curta duração que não induzem convulsões e monitorização adequada.
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Introduction

Chromosome 15q tetrasomy is a constituent of the heterogeneous group of extra structurally abnormal chromosomes.[1] This syndrome displays distinctive clinical features, such as epilepsy, central hypotonia, developmental delay and intellectual disability, and autistic behavior.[1] Incidence at birth is estimated at 1 in 30,000; but no previous reports have described the anesthetic management of a patient with this syndrome.

Case report

The patient was a 25 year-old man (height, 153 cm; weight, 51 kg) who was scheduled for extraction of four impacted wisdom teeth and scaling under general anesthesia. He had a history of difficulty in sucking and feeding from birth and had started walking at the age of 2.5 years, because of developmental delay and hypotonia. He had no medical history of aspiration pneumonitis. He was diagnosed with 15q partial tetrasomy syndrome at the age of 8 years. He had experienced frequent generalized seizures since he was 7 years old, and had been treated with clobazam and carbamazepine. He showed autistic or autistic-like features. Although he had severe intellectual disability, he could speak one-word sentences and follow simple instructions. Blood examinations and ECG were unremarkable, except for slight liver dysfunction. He had a history of delayed emergence from general anesthesia 5 years earlier at our department.

On the day of the dental procedure, the patient entered the operating room and did not offer resistance to the monitors being worn. Slow induction was performed with 5% sevoflurane and 100% oxygen (6 $L.min^{-1}$), following which an intravenous catheter was inserted and left in place, and fentanyl, thiamylal and rocuronium were administered. After uneventful mask ventilation, nasal intubation was performed with a 6.5 mm cuffed Nasal RAE™ endotracheal tube under direct visualization of the glottis. General anesthesia was maintained with air, oxygen, desflurane (fraction of inspired oxygen = 0.4) and remifentanil under controlled ventilation. Immediately after the induction of anesthesia, the Train Of Four Ratio (TOFR) was 0, increasing to 0.6 after 10 min. By the start of the surgery, it had reached 0.9. The Bispectral Index (BIS) value during the surgery was maintained between 50 and 65, without any unexpected large variations in the value. His vital signs remained stable with a blood pressure of 80–90/40–50 mmHg, heart rate of 60 bpm, SpO_2 of 99%–100%. Sugammadex was administered after the surgery and extubation was performed after confirming that muscle function was fully restored, as indicated by a TOFR of 1.0. The operative time was 74 min and anesthesia time was 146 min. The patient was discharged on the following day without any problems such as perioperative respiratory complications and seizures.

Discussion

Chromosome 15q tetrasomy is also known as inverted duplication 15 (inv dup[15]) or isodicentric chromosome 15 (idic[15]).[2] It is caused by an extra inv dup(15) marker chromosome, cytogenetically defined as inv dup(15) (pter → q12-13: q12-13 → pter) by FISH analysis.[1] Our patient's karyotype was 47, XY, + idic(15)(q12), i.e. tetrasomy with the extra derived chromosome at 15q11-q12. 15q tetrasomy is clinically associated with seizures, hypotonia, developmental delays, intellectual disability, congenital heart defects, brain abnormalities, and dysmorphic facial features, such as downslanting palpebral fissures, low set ears, micrognathia, prominent mandible, and cleft palate.[1,2] 15q11-q13 is considered a prime candidate region for the mapping of epilepsy genes and the relationship with autism.[2,3] Gene tetrasomy may alter GABA receptor activity upon which the major CNS inhibitory mechanisms rely.[1] 15q tetrasomy affects encoding of $GABA_A$ receptor subunits (GABRB3, GABRA5, GABRG3), which is related to the seizures and autism associated with this syndrome.[3] Some reports show high complication rates of seizures in 15q tetrasomy patients (63%–75%).[1,3] Therefore, the challenges for anesthesiologists managing such patients are attacks of seizures, perioperative respiratory complication and prolonged muscle relaxation related to hypotonia, and difficult airways.

The following five points were considered when we planned the anesthetic management for the present patient. First, for the prevention of seizures, the patient took his regular antiepileptic medicines on the day of surgery, and thiamylal, which has anticonvulsant effects, was injected at the induction of anesthesia. We also had to examine the medicines which were substituted for the regular ones in case the patient could not ingest orally perioperatively. Desflurane is a suitable drug for use in patients with epilepsy since it does not have epileptiform activity[4] while there have been several reports of epileptoid EEG patterns observed under sevoflurane anesthesia.[5] It is quite difficult to observe a seizure during general anesthesia. However, previous reports have shown that abnormal fluctuations or decreases in BIS values under anesthesia resulted from occurrences of epileptiform EEG activity, and that BIS monitoring might not only give useful information on the sedative-hypnotic state,

but also on the development of abnormal epileptiform EEG activity.[5] Therefore, we monitored the depth of anesthesia during surgery and observed for fluctuations in BIS values.

Second, hypotonia, which might lead to serious anesthetic complications, should be considered in these patients. Generally, hypotonia is associated with a prolonged effect of non-depolarizing muscle relaxants. In this case, rocuronium was administered only at the time of anesthesia induction and neuromuscular monitoring was continuously performed during anesthesia. At the previous anesthetic management of this patient, vecuronium, which has a longer duration of action as compared with rocuronium, and an anti-cholinesterase agent for which the reversal effect is incomplete compared with sugammadex, were used for this patient, which was considered the cause of the residual muscle relaxation effect. Muscle hypotonia with joint hyperextensibility and drooling is observed in almost all individuals with 15q tetrasomy,[1] which can result in aspiration. For this reason, we anticipated the risk of postoperative aspiration, although the patient had no history of aspiration. Fortunately, no worsening of the hypotonia or respiratory deterioration was seen perioperatively in this patient.

Third, at the time of the patient's anesthetic management 5 years earlier, the total anesthesia time was 100 min, including approximately 30 min for emergence. Prolonged emergence at that time might have been caused by the following: (1) Enhanced anesthetic effect due to a synergistic effect with the anticonvulsant. (2) Sevoflurane, which has a higher partition coefficient than desflurane, was used during the maintenance of anesthesia. Therefore, during the current anesthesia, we used desflurane and remifentanil for maintenance under BIS monitoring. As a result, delayed emergence did not occur. Extubation was performed only 10 min after the end of surgery without residual effects of narcotics. On the other hand, anticonvulsants act on drug metabolizing enzymes and consequently increase the requirement of opioids and muscle relaxants. Therefore, careful attention has to be paid to the dose of drugs related to anesthesia, maintaining a balance between preventing convulsions due to light anesthesia, and avoiding prolonged emergence and prolonged effects of muscle relaxants due to increased anesthetic effects.

Fourth, anticipating the patient's lack of cooperation at the time of anesthesia induction, due to his autistic-like behavior, he practiced with the visual material of the TEACCH method[6] used for autistic patients at the preoperative anesthesia consultation, to familiarize him with the anesthesia induction period and facilitate a smooth induction. This resulted in a successful induction.

Finally, preoperative evaluation of the patient for a difficult airway is important, since patients with this syndrome sometimes display maxillofacial abnormalities. The patient did not have any features that suggested the likelihood of a difficult airway.

We administered sugammadex at the end of the anesthesia though TOFR had reached 1.0 for more safety of the patient. It is necessary to control neuromuscular block exactly especially in this patient with hypotonia as mentioned previously and the reaction to muscle relaxants was not predictable because there was no report of the anesthetic management of a patient with 15q tetrasomy in the past. Even at a TOFR > 0.9 or 1.0 measured at the adductor pollicis muscle, some subjects still have impaired pharyngeal or respiratory function.[7] Although TOF monitoring is important, the evaluation of the clinical signs is also necessary.[8] However, we could not observe the correct and reliable response or signs to our instructions because this patient had severe intellectual disability. We needed both the reversal of muscle relaxant to make up for clinical signs and TOF as an objective monitoring.

As this is the first report of the anesthetic management of a patient with 15q tetrasomy, the problems that may occur at the time of anesthetic management due to the clinical features associated with the chromosome abnormality are not well known. Hence, we reviewed the previous anesthetic reports of patients with genetically similar diseases. Chromosome region 15q11-q13 is known for its instability, and the genetically damaged segment in 15q tetrasomy is almost the same as in Prader-Willi Syndrome (PWS) and Angelman Syndrome (AS). 15q tetrasomy is derived from overexpression of the chromosome 15q11-q13 region that is maternal in origin, while PWS is mainly caused by deletion of paternally expressed gene, and AS is caused by deletion of maternally expressed UBE3A gene of derived 15q11-q13 region.[3] Due to hypotonia, prolonged muscle relaxant effects during general anesthesia have been previously reported in patients with PWS and AS.[9,10] Moreover, the deletion of $GABA_A$ receptor in AS[11] may cause resistance to GABA-stimulating anesthetics, such as propofol. In fact, an animal experiment of AS showed more reduction in drug sensitivity to propofol than inhalation anesthetics.[12] However, although it is not clear whether the same reaction to anesthetics as in AS are observed in patients with 15q tetrasomy as well, we carefully monitored BIS during anesthesia in the present patient. More studies on the relationship between 15q tetrasomy and various anesthetic agents, by collecting more case reports and by conducting genetic research, would be useful.

Conclusion

We administered general anesthesia to a patient with 15q tetrasomy. In such patients, it is important to make efforts for the prevention of complications such as seizures and hypotonia, and to avoid prolonged emergence. In conclusion, the use of short-acting drugs that do not induce seizure and suitable monitoring resulted in successful anesthetic management of 15q tetrasomy.

Conflicts of interest

The authors declare no conflicts of interest.

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