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CASE REPORT

Russell-Silver syndrome with cleft palate: a case report

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Abstract

Background Russell-Silver syndrome (RSS) is characterized by intrauterine growth retardation, short stature without postnatal catch-up growth, and an inverted triangular face with relative macrocephaly. There have been few case reports of RSS with cleft palate, in which perioperative problems such as difficult intubation due to trismus and impossibility to wear a mouth gag due to growth failure of the mandible were described. The case of a female RSS patient with cleft palate who underwent palatoplasty is reported.

Case presentation Although her weight was particularly low (5920 g), palatoplasty was performed under general anesthesia at 3 years and 6 months of age. Despite limited mouth opening, intubation was relatively easy. Although her mandibular alveolar width was narrow, a Dingman mouth gag could be tightly fastened around her mouth. Postoperatively, the patient was transferred to the intensive care unit without extubation due to pharyngeal edema. On the following day, since the pharyngeal edema had improved, the endotracheal tube was extubated, and her respiratory status was subsequently stable.

Conclusions In RSS patients with cleft palate, there have been a few reports of pharyngeal edema. Thus, the risk of pharyngeal edema must be considered in such patients.

Keywords Russell-Silver syndrome · Cleft palate · Palatoplasty · Pharyngeal edema

Introduction

Russell-Silver syndrome (RSS: OMIM 180860) is characterized by intrauterine growth retardation, short stature without postnatal catch-up growth, and an inverted triangular face with relative macrocephaly [1]. RSS occurs in around one per 100,000 births, and there are approximately 500–1000 cases in Japan [2]. RSS is one of the conditions resulting from abnormal imprinting [3]. Maternal uniparental disomy of chromosome 7 (mUPD7) is found in 5–10% of RSS patients, and hypomethylation in imprinting control region (ICR) 1 in 11p15 is found in at least 35–65% of cases [1, 3, 4].

There have been few case reports of RSS with cleft palate [5]. Some problems have been reported with palatoplasty at the usual age. The main problems include low bodyweight and the impossibility of intubating an endotracheal tube and of putting on the Dingman mouth gag [6].

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In this report, palatoplasty performed for an RSS patient with cleft palate, which was not easily performed due to poor bodyweight gain, trismus, and so on, is described.

Case report

A female patient was brought to our Department of Oral and Maxillofacial Surgery for the treatment of cleft palate that was identified on medical examination at 6 months of age. She had been delivered by emergency cesarean section at 29 weeks' gestation. At birth, her weight was 534 g (− 4.2 SD), and her length was 29 cm (− 3.7 SD). Her 1-, 5-, and 10-min Apgar scores were 2, 6, and 9, respectively. Her postnatal heart rate exceeded 100 bpm, but she was unable to breathe spontaneously. Since she showed pink up with continuous positive airway pressure (CPAP), endotracheal intubation was performed in the operating room. Because of her extremely low birth weight and premature birth, she was cared for in the neonatal intensive care unit (NICU). She had several complications, including patent ductus arteriosus (PDA), left thumb polydactyly, and chronic lung disease. At 5 months of age, the patent ductus arteriosus was closed under general anesthesia. It was considered that the feeding disturbance was due to the

PDA and chronic lung disease. After discharge, she was found to have a cleft palate, and she was referred to our department at 6 months of age.

Her height was 49.6 cm and her weight was 3800 g at the time of the initial visit to our department, and she presented with an inverted triangular face, micrognathia, and cleft palate (Fig. 1). Oral intake was 10 ml of milk, but a further 90 ml of milk were given through a nasogastric tube, and this was administered six times a day. Using a feeding nipple for exclusive use in cleft palate cases, the quantity of feeding and weight gain were monitored in our department. At 7.5 months of age, she started baby food once-daily in conjunction with tube feeding.

She was the first born of a 37-year-old mother and a 52-year-old father who were genetically unrelated. There was no family history of congenital anomalies. Her mother became pregnant by in vitro fertilization-embryo transfer (IVF-ET), and she had a past history of cerebellar infarction and hypertension.

At 11 months of age, genetic analysis was performed by methylation analysis of the differentially methylated region (DMR) using a pyrosequencing method. The analysis showed hypomethylation of the H19-DMR in chromosome 11, but no methylation in chromosome 7. Thus, based on the results of the genetic analysis, she was diagnosed with RSS.

The patient was able to sit up at 18 months of age. She could produce babbling at 18 months and pronounce single words at 21 months. She could take all of her food orally at 2 years and 1 month. At that time, she underwent surgery for left thumb polydactyly under general anesthesia. Because the width of her mouth opening was approximately the breadth of one finger, difficulties with palatoplasty were anticipated, but the procedure was nevertheless scheduled at the age of 2 years and 6 months because of favorable speech development. Unfortunately, the surgery had to be postponed because of emergency hospitalization for hypoglycemia and acute upper respiratory tract inflammation. Shoe-shaped orthoses were fitted at 2 years and 7 months, and she was able to walk 4 months later. At 3 years, she could produce two-word phrases, so the palatoplasty was again scheduled at 3 years and 5 months. However, the surgery had to again be postponed due to emergency hospitalization for pneumonia. At this time, she could open her mouth to approximately the breadth of two fingers. Although her weight was particularly low, at 5920 g, the palatoplasty was finally performed under general anesthesia at 3 years and 6 months.

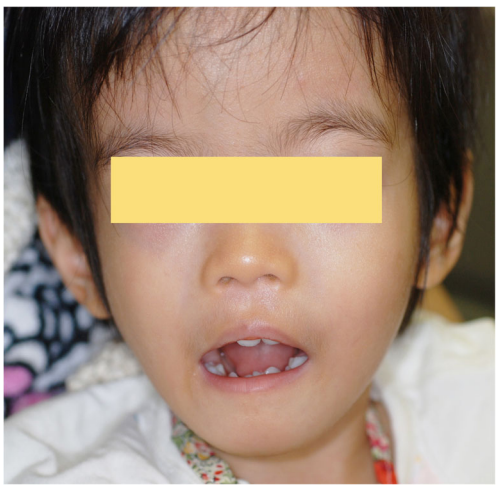

Fig. 1 The patient has an inverted triangular face and micrognathia

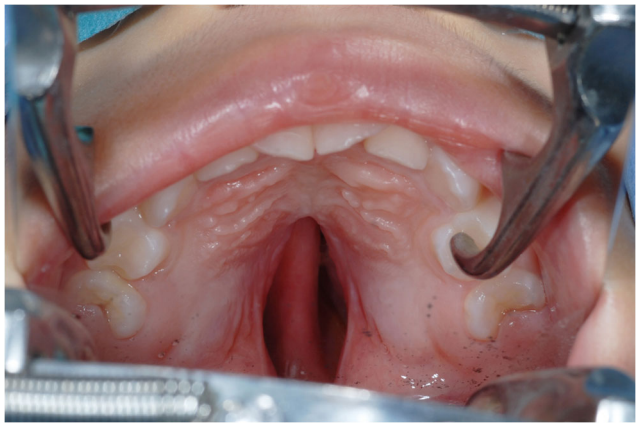

Fig. 2 A V-shaped, hard, and soft cleft palate is seen. (preoperative state)

Her mouth opening was limited, but intubation was relatively easy. She had a V-shaped hard and soft cleft palate preoperatively (Fig. 2). Although her mandibular alveolar width was narrow, a Dingman mouth gag was wearable tightly. The Wardill-Kilner push back technique is a palatal retrodisplacement technique by elevation of the mucoperiosteal flaps [7]. The following modifications were made to the original technique: release of lateral tension by cutting off continuity of the palatal aponeurosis and tensor palatine muscle, Z-plasty to the nasal mucosa at the soft palate, and a muscle sling was then formed for cleft muscle.

The patient was cared for postoperatively in the ICU without extubation because of pharyngeal edema. A maintenance infusion with 7.5% glucose was given at 20 ml/h to prevent postoperative hypoglycemia. On the following day, the endotracheal tube was extubated due to improvement of the pharyngeal edema, and her respiratory status was subsequently stable. Two days after the operation, she ingested rice gruel soup, and her oral intake progressed smoothly. The pre-breakfast blood glucose level was 60–80 mg/dl, and no hypoglycemic episodes occurred. Five days after the operation, she could eat sufficient rice gruel, and the infusion was terminated. There were no adverse events such as bleeding from the oral or nasal cavities, and healing of the surgical wound was good, without dehiscence. Because the patient's postoperative course was good, she was discharged on the 8th day after surgery.

At 6 months after surgery, elevation of the soft palate was poor, and she displayed hypernasality and glottal stop. In addition, blowing was impossible, and she was then diagnosed

as having velopharyngeal insufficiency. She wore a palatal lift prosthesis (PLP) at 7 months after surgery (age 4 years), and trained in blowing and so forth, but the velopharyngeal insufficiency was not improved. At 1 year 5 months after surgery (age 4 years, 11 months), the device was changed to a bulb type PLP (bulb-PLP) (Figs. 3 and 4), and nasal emission was reduced dramatically. Blowing was enabled, and the acuity of the vowel sounds rose. To date, she continues speech training wearing the device.

Discussion

RSS was reported independently by Silver et al. [8] and Russell [9]. Silver et al. [8] described congenital hemihypertrophy, low birth weight, and short stature. Russell [9] described intrauterine growth retardation and characteristic facial features, including a triangular shaped face with a broad forehead and a pointed, small chin with a wide, thin mouth. Although both reports emphasized different phenotypic features, a single disease entity was later identified and classified as RSS [1]. RSS occurs in around one per 100,000 births, and there are approximately 500–1000 cases in Japan [2]. The main complications include gastrointestinal disorders, feeding difficulties, genitourinary anomalies, café au lait spots, developmental delay, hypoglycemia, and cardiac disease [1]. There has been a report that some individuals with RSS have Pierre Robin sequence and cleft palate, but severe craniofacial anomalies are uncommon. In the present case, the patient had intrauterine growth retardation, short stature without postnatal catch-up growth, and an inverted triangular face with relative macrocephaly. She also had a patent ductus arteriosus, feeding difficulties, and hypoglycemia.

RSS is one of the conditions resulting from abnormal imprinting [3]. The manifestations of the imprinting abnormality occur due to genetic and epigenetic changes, and the onset

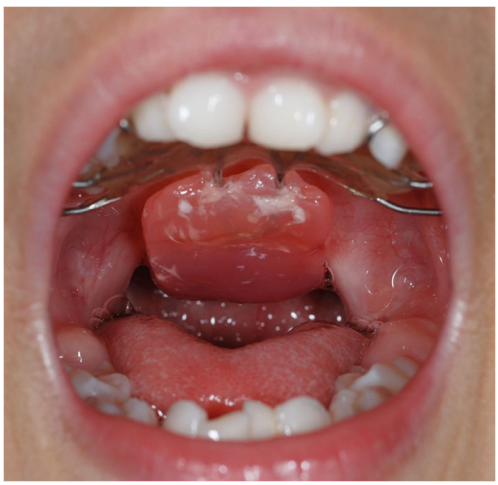

Fig. 3 A bulb type palatal lift prosthesis (bulb-PLP) put on in her mouth is shown

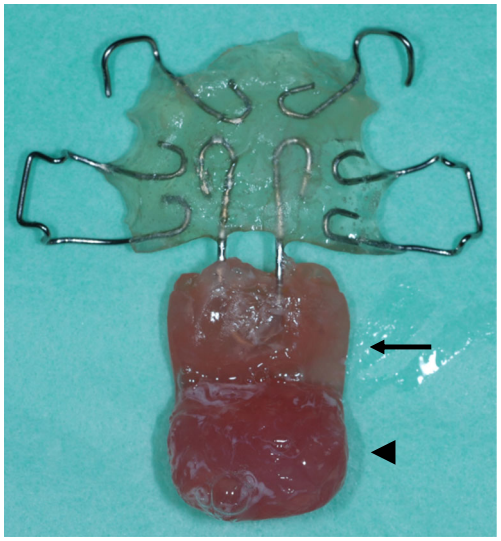

Fig. 4 The bulb-PLP consists of a palatomaxillary section and a palatovelar section. The palatovelar section (arrow) activates the velar muscles by lifting the velum. The bulb portion (arrow-head) of the tip blocks the velopharyngeal gap

causes are uniparental disomy, epimutations, chromosomal structural abnormalities, and point mutations [3]. As for the causes in RSS patients, mUPD7 was found in 10%, and hypomethylation of ICR1 in 11p15 was found in 35–65% [1, 3, 4]. A gene within chromosome 7 that might be responsible has attracted attention. Although it has been found that this region is involved, the extent of its involvement is as yet unclear [3]. The domain to imprint, including multiple imprinting genes, is present in 11p15. Within this domain, two sub-domains exist, one of which is H19-DMR, which contains the imprinting control regions (ICRs) [2]. Furthermore, there are two different ICRs, ICR1 and ICR2, as well as the telomeric ICR1, which controls expression of H19 and IGF2 [9]. H19-DMR is a differentially methylated region. It is in a methylated state when it is of paternal origin, and it is non-methylated when it is of maternal origin [4]. Because CTCF protein cannot bind to methylated H19-DMR, the enhancer acts on IGF2, and because CTCF protein is connected to non-methylated H19-DMR, the enhancer acts on H19 [4]. As mentioned above, when paternally derived H19-DMR, which is originally in a state of methylation, becomes hypomethylated, decreased expression of IGF2 and surplus expression of H19 occur. The enhancer derived from the father then acts in the same way as that derived from the mother. RSS subsequently develops as a result of the suppression of placental and fetal development [4].

In the present case, genetic analysis was performed by methylation analysis of the differentially methylated region (DMR) using a pyrosequencing method. The analysis showed hypomethylation of H19-DMR in chromosome 11, but no methylation in chromosome 7. To the best of our knowledge, including the present report, there have been five reported surgical cases of RSS with cleft palate in Japan [2]. It has been

reported that cleft palate or bifid uvula occurs in 7% of patients with hypomethylation of ICR1 and in no patients with maternal UPD7 [10]. Three cases of RSS with cleft palate have been reported overseas [5], and, as in the present case, they were all caused by hypomethylation of ICR1.

In our department, palatoplasty is usually performed at 1 year and 3 or 6 months of age at a desired bodyweight of 10 kg. However, in cleft palate with RSS, the timing of palatoplasty tends to be delayed because weight gain is insufficient. There have been reports of palatoplasty performed at 3 years and 1 month of age at a bodyweight of 6365 g [6], 3 years and 3 months of age at a bodyweight of 8700 g [2], and 4 years and 1 month of age at a bodyweight of 13,000 g [11]. In the last case, palatoplasty could not be performed at 2 years and 6 months of age at a bodyweight of 9800 g because it was impossible to intubate an endotracheal tube [11]. Thus, it was a concern as to whether palatoplasty could be successfully performed in the present case because of the patient's extremely low bodyweight. However, because her speech development was progressing smoothly, we wanted to perform the palatoplasty as soon as possible. Unfortunately, the surgery had to be postponed several times due to the onset of pneumonia and hypoglycemia. In the present case, palatoplasty was performed when the patient was 3 years and 5 months, at a weight of 5920 g.

Problems with induction of anesthesia have been reported. As mentioned above, there was a report that palatoplasty could not be performed because it was impossible to intubate an endotracheal tube [11]. Furthermore, maxillofacial growth failure and facial asymmetry affect mask ventilation and tracheal intubation during general anesthesia [11]. In that case, mask ventilation was not difficult, but the mouth could be opened only about one finger width even after administration of 1 mg of vecuronium, and a Macintosh size 1 laryngoscope could not be inserted [11]. In the present case, the width of the mouth opening was the breadth of one finger at 2 years and 1 month, but the width of the mouth opening was the breadth of two fingers at 3 years and 5 months. Her mouth opening was limited, but intubation was relatively easy. There was also no problem with mask ventilation.

There has been a report of difficulty using a mouth gag at palatoplasty. Use of the Dingman mouth gag was possible, and the width of the mouth opening was 2 cm when a patient with a bodyweight of 8700 g was operated on at 3 years and 3 months of age [2]. In another report, it was not possible to put on the Dingman mouth gag for trismus at operation at 3 years and 1 month with a bodyweight of 6365 g; mouth opening was obtained by forced opening with a utility mouth gag and tongue pulling during operation, and palatoplasty was performed by opening the cavity using a universal mouth gag and pulling the tongue [6]. We considered that it was possible to put on the Dingman mouth gag because the width of the mouth opening had increased to approximately the breadth of two fingers at 3 years and 5 months, as opposed to the breadth of only one finger at 2 years and 1 month. In the present case, the use of the Dingman mouth gag was possible, but the width of the tongue blade was tight because of the narrow dental arch of the mandible. Preparation of an alternative mouth gag for the surgery is necessary, because patients with RSS often have micrognathia, a constricted arch, and trismus.

There has been a report that a dextrose infusion is needed to prevent hypoglycemia, one of the complications of RSS [11]. In the present case, hypoglycemia did not occur because a dextrose infusion was provided prophylactically after the operation due to the previous history of hypoglycemic attacks.

Since the patient was diagnosed with velopharyngeal insufficiency, she wore the PLP at 7 months postoperatively, and the device was changed to the bulb-PLP at 1 year and 5 months postoperatively. Whether to apply a speech-aid (PLP/bulb-PLP) or create a pharyngeal flap for patients with velopharyngeal insufficiency remains controversial. Both have an advantage and a disadvantage [12, 13]. With both, velopharyngeal closure can be achieved in around 90% of cases [14]. There has been a report of good results by performing a pharyngeal flap after obtaining normal articulation by wearing of the PLP and strengthening velopharyngeal closure [12]. On the other hand, there is a risk of relapse of the velopharyngeal insufficiency by regression of adenoid tissues at about 10–12 years of age if the pharyngeal flap was performed early [13]. Therefore, the treatment strategy for velopharyngeal insufficiency at our department is as follows. The necessity for pharyngeal flap surgery is judged after regression of the adenoid tissues and, until then, articulatory acquisition is aimed at in the state without nasal emission using the PLP. PLP rather than a pharyngeal flap was chosen in the present case because the patient was young (4 years old). It was concluded that perioperative care, including the potential of unidentified pharyngeal edema at palatoplasty and hypoglycemic attacks as complications of the RSS, would be difficult.

In the present case, it was not possible to extubate the patient after the palatoplasty because of immediate postoperative pharyngeal edema, but there have been no other reports of this problem to date. The cause of the pharyngeal edema was unclear, but we strongly believe that postoperative management of the airway is of the utmost importance.

Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written, informed consent was obtained from the parent of the patient.

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