Bilateral Cleft Lip and Palate Accompanied by 13q- Syndrome with Deficiencies of FVII and FX: A Case Report

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The 13q deletion syndrome is a rare genetic disorder caused by structural and functional monosomy of chromosome 13. On 13q34, which is the terminal of the long arm, causative genes of coagulation factors VII and X (FVII and FX) are mapped. Patients with a combination of FVII and FX deficiencies are extremely rare and there have been few articles about perioperative coagulation support for such patients. Herein, we report on a case of bilateral cleft lip and palate accompanied by 13q deletion syndrome with deficiencies of FVII and FX.

The chromosomal investigation indicated 46, XX, del(13)(q33) by G-banding. Prothrombin time and activated partial thromboplastin time were found to be 21.0 seconds (sec) (prothrombin time–international normalized ratio 1.76) and 41.6 sec (normal range; 23.9 – 39.7 sec), respectively. The activities of coagulation FVII and FX were 22% and 36%, respectively. A two-stage cheiloplasty was performed at 4 and 7 months of age followed by a palatoplasty at 1 year and 6 months. Tranexamic acid was given intravenously three times a day for three days after each surgery. There were no adverse events such as bleeding from the oral or nasal cavities and healing of the surgical wound was good without dehiscence.

Keywords; *13q deletion syndrome, combined FVII/FX deficiency, bilateral cleft lip and palate, tranexamic acid*

INTRODUCTION

The 13q deletion syndrome is a rare genetic disorder caused by structural and functional monosomy of chromosome 13 [1]. The characteristic features of 13q deletion include growth retardation with microcephaly, facial dysmorphisms and congenital heart, brain and kidney defects [2]. On 13q34, which is the terminal of the long arm, causative genes of coagulation factors VII and X (FVII and FX) are mapped [3], and FVII and FX share many structural and functional characteristics [4]. The FX gene consists of eight exons and is located on the long arm of chromosome 13 at 13q34 and the FVII gene is located very close to it [5].

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Both FVII and FX are vitamin K-dependent serine proteases synthesized in the liver [6]. In its activated form, FVII plays a key role in the initiation of blood coagulation, while FX occupies a central position in the coagulation cascade as the first pro-enzyme of the common pathway of fibrin formation [6]. FVII deficiency and FX deficiency have an estimated worldwide prevalence of one in 500,000 and one in 1,000,000, respectively [7]. One of the main problems associated with surgery on patients with these deficiencies is the increased risk of bleeding. Severe bleeding was more likely in cases with FVII activity <0.01 iu/ml than those with FVII activity >0.01 iu/ml who typically had mild mucocutaneous bleeding or were asymptomatic [8]. For FX, bleeding was more likely to be severe in registry cases with FX activity <0.1 iu/ml than in those with FX activity >0.1 iu/ml, who typically had mild mucocutaneous or surgical bleeding or were asymptomatic [8]. Data from the United Kingdom Haemophilia Centre Doctors' Organization registry has shown that the proportion of FX-deficient patients requiring treatment is higher than other rare inherited bleeding disorders [9].

Replacement of the deficient coagulation factor and use of adjunctive therapies (antifibrinolytics, estrogen/progestogen) where appropriate are the mainstays of treatment [9]. Various therapeutic options are available for FVII deficiency, including fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC); plasma-derived FVII concentrates; and recombinant FVIIa, whereas therapy for FX-deficiency usually involves the administration of

PCC [9]. However, treatment of rare inherited bleeding disorders is still difficult as clinical management information for specific bleeding episodes is often scarce [9].

As patients with a combination of FVII and FX deficiencies are extremely rare [5], information on appropriate methods for controlling bleeding is even scarcer and treatment protocols have yet to be established. There have been at least seven published reports of combined FVII and FX deficiency because of chromosomal abnormalities yielding a total of nine patients who presented with an assortment of associated non-coagulation related abnormalities (carotid body tumors, mental retardation, microcephaly, cleft palate, atrial septal defect, ventricular septal defects and persistence of ductus Botalli) [5]. Of the nine patients, only two also presented with cleft palate [5]. Furthermore, there have been few articles about perioperative coagulation support for patients with combined FVII/FX deficiency [10, 11]. In particular, as far as we know, there have been no reports on perioperative coagulation support for patients with combined FVII/FX deficiency undergoing surgery for cleft lip and palate.

Herein, we report on perioperative coagulation support for patients with bilateral cleft lip and palate accompanied by 13q deletion syndrome with deficiencies of FVII and FX who underwent cheiloplasty and palatoplasty.

Case report

A female baby was born by normal vaginal delivery at 40-weeks-and-1-day gestation. She had a weight of 2,768 grams, a height of 48 centimeters (cm), a head circumference of 32 cm and a chest circumference of 31.5 cm at birth. Her 1- and 5-minute Apgar scores were 8 and 9, respectively. This scoring system provides a standardized assessment for infants after delivery. The Apgar score comprises 5 components: (1) color; (2) heart rate; (3) reflexes; (4) muscle tone; and (5) respiration [12]. Each of these components is given a score of 0, 1, or 2 [12]. An infant with an Apgar score of seven or above is generally considered to be normal and not suffering from birth asphyxia [12]. The pregnancy was without reported complications. There was no history of drug ingestion or X-ray examination during pregnancy. She had a complete bilateral cleft lip and palate (Fig. 1) and perineal canal. The chromosomal investigation indicated 46, XX, del(13)(q33) by G-banding. As a result of the pre-surgical screening examination at 3 months of age, prothrombin time (PT) and activated partial thromboplastin time (APTT) were found to be 21.0 seconds (sec) (prothrombin time–international normalized ratio: PT-INR 1.76) and 41.6 sec (normal range; 23.9–39.7 sec), respectively, both of which were slightly prolonged (Table 1). The activities of the coagulation FVII and FX were 22% and 36%, respectively. She did not experience any abnormal bleeding or hematoma formation from which a tendency to bleeding was suspected.

She was the third born of a 32 year-old mother and a 32 year-old father, who were genetically unrelated. There was no family history of congenital anomalies and her mother had no notable medical history.

A two-stage cheiloplasty was performed under general anesthesia at 4 and 7 months of age according to the Millard technique [13], i.e. a rotation-advancement method, with a small triangular flap. First, the left side cleft lip was repaired, and a neonatal tooth which had erupted at the anterior edge of the left lateral segment was extracted. Three months later, the right side cleft lip was repaired. A palatoplasty was subsequently performed according to the Wardill-Kilner push back technique [14, 15], i.e. a two-flap palatoplasty with elevation of the mucoperiosteal flaps, under general anesthesia at 1 year and 6 months (Fig. 2). Tranexamic acid (50mg) was given intravenously three times a day for three days after each surgery. 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 postoperative course was good, she was discharged on the 8th day after each surgery.

Subsequently, we examined her course as an outpatient. At two years of age, the upper lip shape was good, and the surgical scar was not outstanding (Fig. 3). On the other hand, her speech development was delayed, and meaningful words were not produced. However, she has been able to swallow using a straw, and the nasal emission during feeding has ceased. We are continuing speech therapy.

Figure 1: Preoperative facial appearance at 2 months of age. She presented with complete bilateral cleft lip and palate. In particular, this problem is characterized by a protruding premaxillary and a small prolabium.

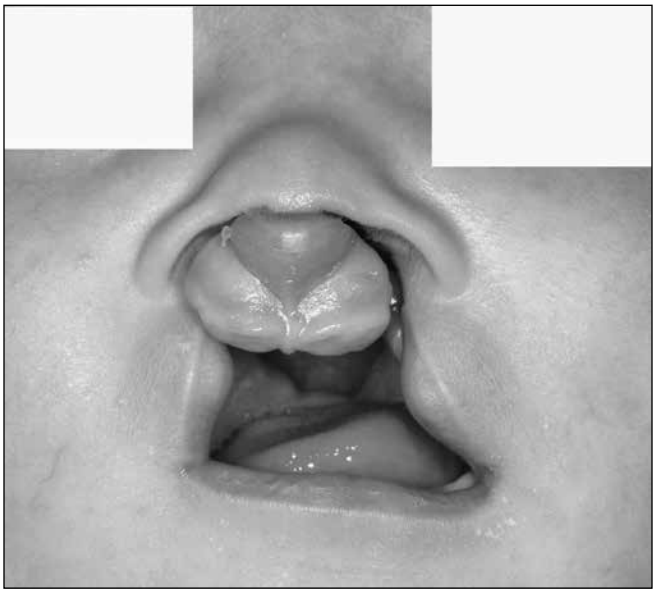


Table 1. Blood coagulation data

	3 months of age	8 months of age	1 year & 2 months of age	1 year & 4 months of age
PT(sec.)	21	18.4	26.6	21.2
PT-INR	1.76	1.56	2.17	1.88
APTT(sec.)	41.6	37.6	36.3	32
FVII(%)	22	-	15	-
FX(%)	36	-	48	-

normal range of APTT; 23.9–39.7 sec.

Figure 2: Preoperative intraoral view at palatoplasty performed at 1 year and 6 months of age. She had complete cleft of the hard and soft palate.

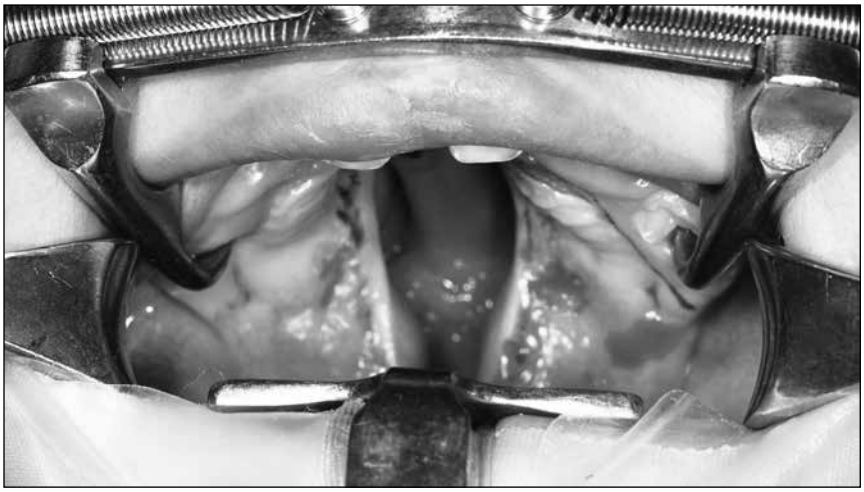
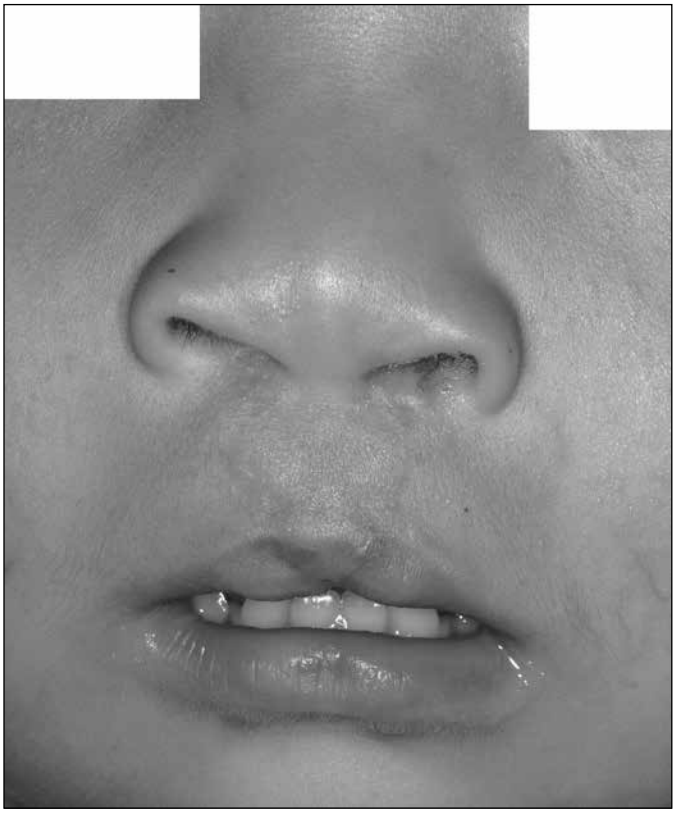


Figure 3: Postoperative facial appearance at 2 years of age. Her lip healed without an outstanding scar. She had a moderately short columella, but the shape of the vermilion was good without a whistling lip deformity.



DISCUSSION

Depending on the size and location of the deletion, the 13q deletion syndrome can be divided into three groups; Group 1: deletion of the chromosome region proximal to band 13q32; Group 2: deletion of chromosome band 13q32; Group 3: distal deletion of bands 13q33-34. Group 1 and Group 2 deletions always result in congenital malformations, severe intellectual disabilities and growth retardation, while most of the patients with Group 3 deletion present with intellectual disabilities alone and are rarely afflicted by other major malformations [1, 16].

Pavlova *et al* [4] have reported that the following two forms of associations in combined FVII/FX deficiency are recognized. The first form results from genetic defects occurring by chance as a single, co-inherited, individual clotting factor deficiency. It can be assigned as a digenic disorder that requires autosomal inheritance of deleterious variants in both F7 and F10. The second form is recognized in individuals with partial deletions within the chromosome 13q34 region containing both F7 and F10. The deletion of F7 and F10 may be accompanied by the abovementioned additional clinical features. The present patient had the second form.

Monitoring of two reported patients showed that, in one case, decreased levels of FVII and FX did not change over time. In the other, however, the level of FX increased with time while the level of FVII did not change [17]. In our patient, the level of FX had increased one year later, while the level of FVII had decreased slightly (Table 1). Because there is a possibility of measurement errors and there are no past reports to refer to, we can make no further comment on the temporal change of coagulation factor levels.

As 13q34 deletion syndromes are rare cytogenetic disorders, there have been few reports on the associated coagulopathy that allow for prediction of surgical bleeding risk, and there has also been no previous description of therapeutic interventions to prevent abnormal surgical bleeding [11]. Chilcott *et al* [11] have described the successful use of FFP and recombinant factor VIIa (rFVIIa) for complex ventricular septal defect (VSD) repair and spinal surgery in patients with combined deficiency of FVII and FX, respectively. In patients with FVII deficiency alone, a baseline plasma FVII activity in the range 10-20 iu/dl has been suggested as a threshold above which the risk of surgical bleeding is low [10]. However, Chilcott *et al* [11] have asserted that aggressive coagulation support is justified because of the additional reduction of FX activity and because of the nature and extent of the proposed surgery. They considered that the residual FX activity in their patient would be sufficient to enable hemostasis even though FX was not specifically replaced [11]. They administered rFVIIa as follows; after the preoperative bolus of 20 μg/kg rFVIIa, a similar bolus at 3-hour intervals was administered during surgery, and at 4-hour intervals for a further 3 days postoperatively [11]. As a result, there was minimal postoperative wound oozing and no further red cell transfusion was required [11].

In contrast, in cleft palate surgery, the raw tissue remains exposed on the surface of the palatal bone, on which slight bleeding continues for several hours, but transfusion is not usually required. However, a risk of post-operative hemorrhage is a concern in patients undergoing coagulopathy. The recommended levels of FVII and FX necessary for hemostasis are 10-15% and 10-20%, respectively [9]. When minor surgeries are performed on patients with coagulation activities under these recommended levels, administration of tranexamic acid should

be considered according to the recommendations of Mumford *et al*[8]. However, it is still unknown whether these recommendations can be applied to patients with combined FVII and FX deficiencies. Because the activities of FVII and FX in our patient were 22% and 36%, respectively, and rFVIIa is not available under the Japanese medical insurance system, we planned prophylaxis with tranexamic acid and administration of FFP if we could not control bleeding, as a result of discussions with the pediatrician in charge. By following these procedures, intra- and post-operative bleeding were well controlled.

CONCLUSION

A case of bilateral cleft lip and palate accompanied by 13q deletion syndrome with deficiencies of FVII and FX was reported. The activities of coagulation FVII and FX were 22% and 36%, respectively. A two-stage cheiloplasty was performed at 4 and 7 months of age followed by a palatoplasty at 1 year and 6 months. Tranexamic acid was given intravenously three times a day for three days after each surgery. There were no adverse events such as bleeding from the oral or nasal cavities and healing of the surgical wound was good without dehiscence.

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