Child's Nervous System
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CASE REPORT

Fronto-orbital advancement in a patient with Marshall-Smith syndrome: a case report and review of the literature

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Abstract

Objective The present report aimed to document the clinical features of a case of Marshall-Smith syndrome (MSS), an extremely rare embryonic developmental disorder with associated craniosynostosis.

Patient and method We presented herein a case of a 2-year-old female patient with MSS who underwent fronto-orbital advancement for multisuture craniosynostosis.

Results The patient's proptosis improved after surgery, and no further surgical intervention was required for corneal exposure. A second FOA followed by revision tarsorrhaphy further improved eye closure.

Conclusion Surgical procedures to correct dysplastic features and limit neurological impairment are a worthwhile supportive treatment for improving the quality of life and general condition of patients with MSS.

Keywords Fronto-orbital advancement · Marshall-Smith syndrome · Craniofacial dysmorphism · Exophthalmos

Introduction

In 1971, Marshall and Smith reported the first two cases of a syndrome characterized by facial deformities, failure to thrive, and bone age advancement in early life more rapid than that seen in any other specific syndromes [5]. This condition, which came to be known as Marshall-Smith syndrome (MSS), is an extremely rare embryonic developmental disorder of which only about 40 cases to date have been reported worldwide [11].

Craniofacial dysmorphism in patients with MSS includes prominent eyes, coarse eyebrows, upturned nose [5], prominent forehead, micrognathism, and proptosis [1]. Other characteristics are motor and mental retardation, umbilical hernia, agenesis of the corpus callosum, optic atrophy [12, 15], hearing impairment [16], laryngeal hypoplasia, hypoplastic epiglottis [2], and cerebellar hypoplasia [14]. Factors strongly affecting the survival of patients with MSS are persistent respiratory difficulties leading to pneumonia, atelectasis, aspiration, and pulmonary hypertension.

All MSS cases occur sporadically and do not show parental consanguinity. The patients present with a normal karyotype. Laboratory findings deny endocrine abnormalities. A number of recent genetic studies following the discovery of de novo mutations involving the NFIX (nuclear factor I/X) gene in MSS patients have helped to elucidate the etiology of the disease [4, 6, 10].

We presented herein a patient with synostosis of the metopic, left coronal, and sagittal sutures which resulted in narrowing of the anterior fossa, leading to progressive traction on the optic nerves and cataract development secondary to exposure keratitis. Fronto-orbital advancement was performed to limit visual deterioration and improve the craniofacial contours (Fig. 1). To the best of our knowledge, the present study is the first to report fronto-orbital advancement in a patient with MSS.

Case presentation

A 2-year-and-2-month-old female patient was referred to the Neurosurgery Department of Tokyo Metropolitan Children's

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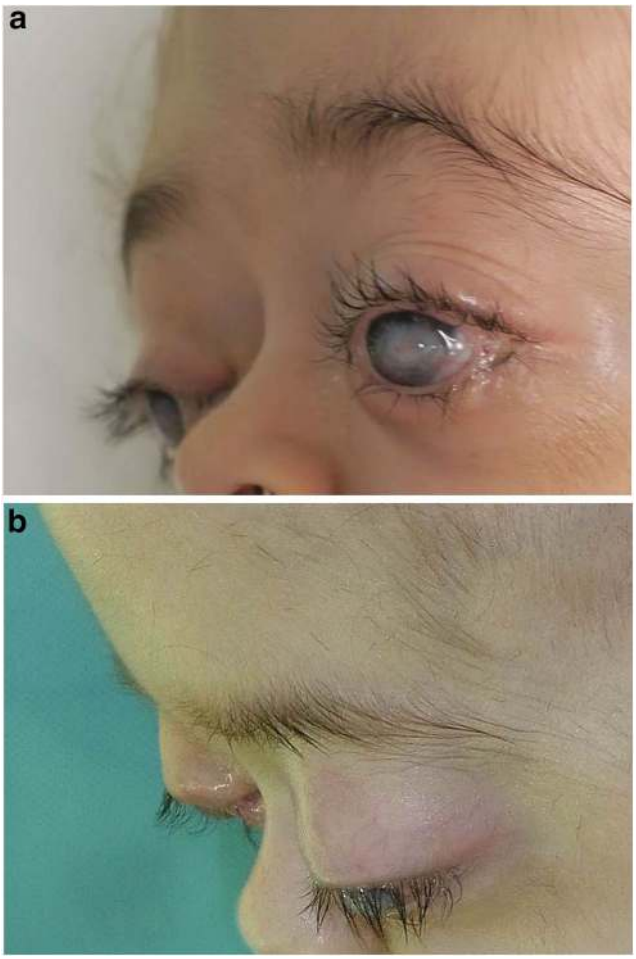

Fig. 1 Photo of the orbital part of the patient's face (the patient's permission was obtained to publish the photo). The purpose of the surgery was to limit visual deterioration and improve the cranio-facial contours. **a** Before surgery **b.** 1 year after the first surgery

Medical Center (TMCMC) by the ophthalmology department of a university hospital. The patient had symptoms of increased bone age, delayed psychomotor development, respiratory failure, scoliosis, and short stature. No intracranial anomalies besides mild ventriculomegaly were present. She had a history of tracheostomy at age 51 days at the hospital where her MSS was diagnosed. The diagnosis was confirmed by the Department of Clinical Genetics at TMCMC. Although no *NFIX* gene mutation was detected by a chromosomal microarray analysis, accelerated osseous maturation, the course of respiratory difficulty, and facial features led to a definitive diagnosis of MSS.

Due to the orbital deformation, the patient had difficulty closing her eyes (Fig. 2). To treat the corneal perforation, corneal transplantation was performed at ages 15 months, 17 months, and 22 months at the referring hospital. Furthermore, a partial permanent tarsorrhaphy was performed simultaneously with the first corneal transplantation at age 15 months but was not fully effective due to the severe protrusion of the eyeballs.

Computed tomography (CT) revealed metopic, sagittal, and left coronal synostosis (Fig. 3). To prevent further deterioration of the cornea, craniofacial surgery was performed to improve the fronto-orbital contours and protect the bilateral corneas.

Surgery

The abovementioned multisuture craniosynostosis imparted a dolichotrigonocephalic shape to the head. However, orbital advancement was required to advance the upper-lateral orbital rim to improve eyelid closure. Considering the patient's age and advanced bone maturation in MSS, distraction osteogenesis was thought to be appropriate to reduce the resultant bony defect. Therefore, the decision was made to modify the fronto-orbital advancement by distraction osteogenesis, which was carried out as follows (Fig. 3).

The patient was placed in a supine position, and a zig-zag skin incision was made on the scalp. A frontal craniotomy was performed, and the bone flap was removed. The supra-orbital bar was osteotomized and removed and then a midline osteotomy of the supra-orbital bar was performed. The divided supra-orbital bar was fixed with a resorbable plate to act as a hinge during distraction (Fig. 4). This modification was done to enable the advancement of the lateral orbital rim with minimal advancement of the central forehead as a means of improving the trigonocephaly. Morcellation craniotomy was performed behind the removed frontal bone to avoid irregularity

Fig. 2 Preoperative photo of the orbital area showing severe proptosis due to orbital deformation. The eyelids were unable to be fully closed (the patient's permission was obtained to publish the photo)

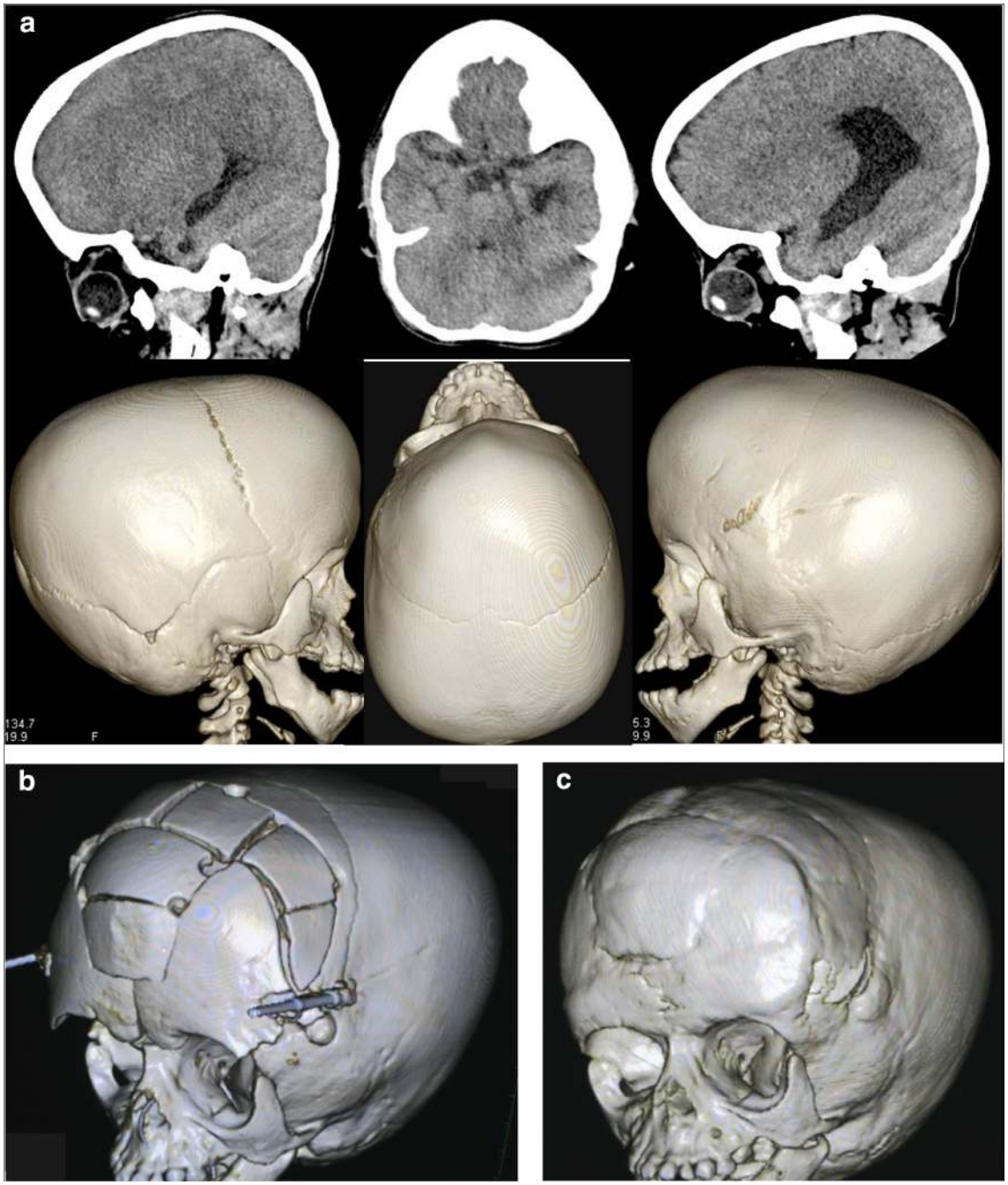

Fig. 3 3D CT image reconstruction. **a** Preoperative CT image showing metopic, sagittal, and left coronal synostosis. **b** CT during distraction showing osteotomization and removal of the supra-orbital bar followed by a midline osteotomy of the bar. The distraction device was placed on both sides of the fronto-orbital bar. **c** At postoperative year 1, the total distraction was 14.5 mm at the lateral orbital rim. Distraction of the central part of the supra-orbital bar was minimal, resulting in a flatter frontal shape than before surgery

of the frontoparietal contours. A distraction device was placed on both sides of the fronto-orbital bar, and the wound was closed in layers.

The surgical procedure was completed without event, but due to the extreme thickness of the bone, bleeding was more copious than usual during the fronto-orbital advancement surgery, and the osteotomy was more time-consuming.

Postoperative course

The patient's postoperative recovery was uneventful. No problems with anesthesia, including postoperative ventilator weaning, were observed. Distraction osteogenesis was begun on postoperative day 6 at 1 mm/day, then reduced to 0.5 mm/day from postoperative day 17 to evaluate the resultant shape more carefully, and completed on postoperative day 23. The

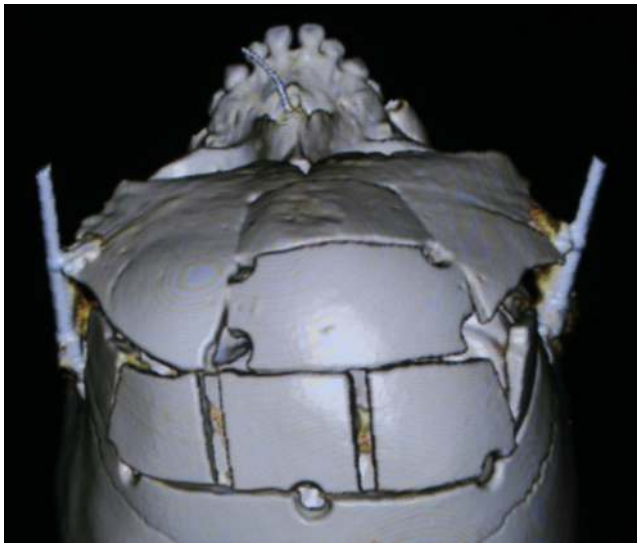

Fig. 4 The "hinge" procedure. Because the midline of the frontal bone piece was osteotomized, the distracted bone flap was gradually bent

total distraction was 14.5 mm at the lateral orbital rim. Distraction of the central part of the supra-orbital bar was minimal; hence, the resultant frontal shape was flatter than the preoperative shape (Fig. 5).

Although some difficulties using the device (such as detaching the distraction rod from the base of the device) were encountered during the observation period in the outpatient clinic, re-attachment was performed manually without anesthesia or sedation. The patient was re-admitted after osteogenesis bridged the bone defect 4 months following the completion of distraction. Removal of the distraction device was performed under general anesthesia without event.

Following surgery, the proptosis improved, and no further surgical treatment for corneal exposure was required. However, a mild recurrence of proptosis was observed 3 years after surgery. For the treatment of the recurrent proptosis, a redo FOA followed by revision tarsorrhaphy was carried out at age 6 years. An additional 16-mm advancement was achieved with the redo FOA distraction, which further improved eye closure (Fig. 6).

Discussion

MSS and its clinical course

Morbidity and mortality in patients with MSS are mainly due to respiratory complications and to a lesser extent to failure to thrive. In most of the reported cases, the patients died in infancy or early childhood. Life expectancy can be prolonged by aggressive management of the respiratory and feeding difficulties. Intensive dietary management, including nasogastric feeding and gastrostomy, as well as management of respiratory difficulties, including a tonsillectomy and adenoidectomy, can improve the prognosis. Continuous, overnight nasogastric feeding, rather than bolus feeding, is likely to decrease the frequency of respiratory complications by reducing aspiration [16].

Genetic findings

Heterozygous mutations in the *NFIX* (nuclear factor I/X) gene which uniformly escape nonsense-mediated mRNA decay (NMD) are reportedly responsible for MSS [4]. In 2014, Schanze et al. [10] demonstrated that deletions of either exon 6 or exons 6 and 7 were responsible for a quarter of the MSS phenotype. The recurrent deletions of exons 6 and 7 in the

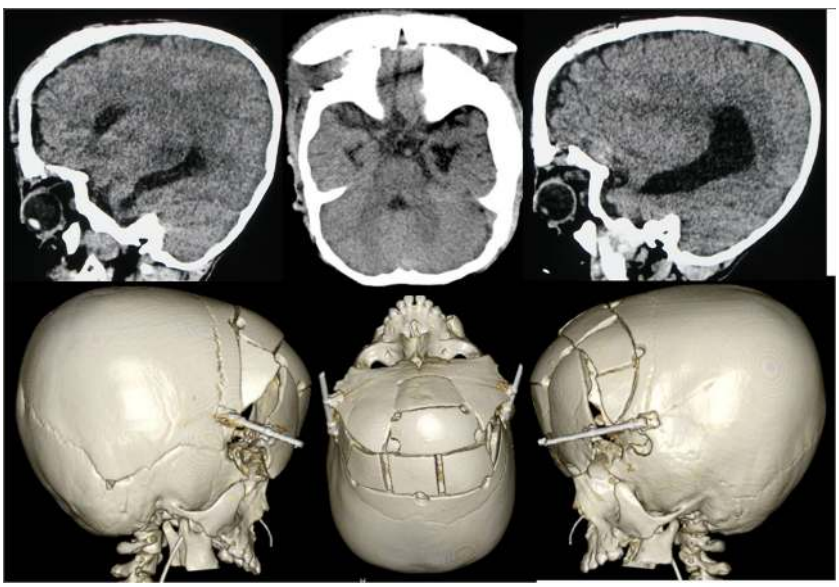

Fig. 5 Sagittal and axial CT image and 3D CT reconstruction after FOA. Compared with Fig. 3a, which demonstrates the preoperative state, improvement of the exophthalmos can be seen here after skull expansion

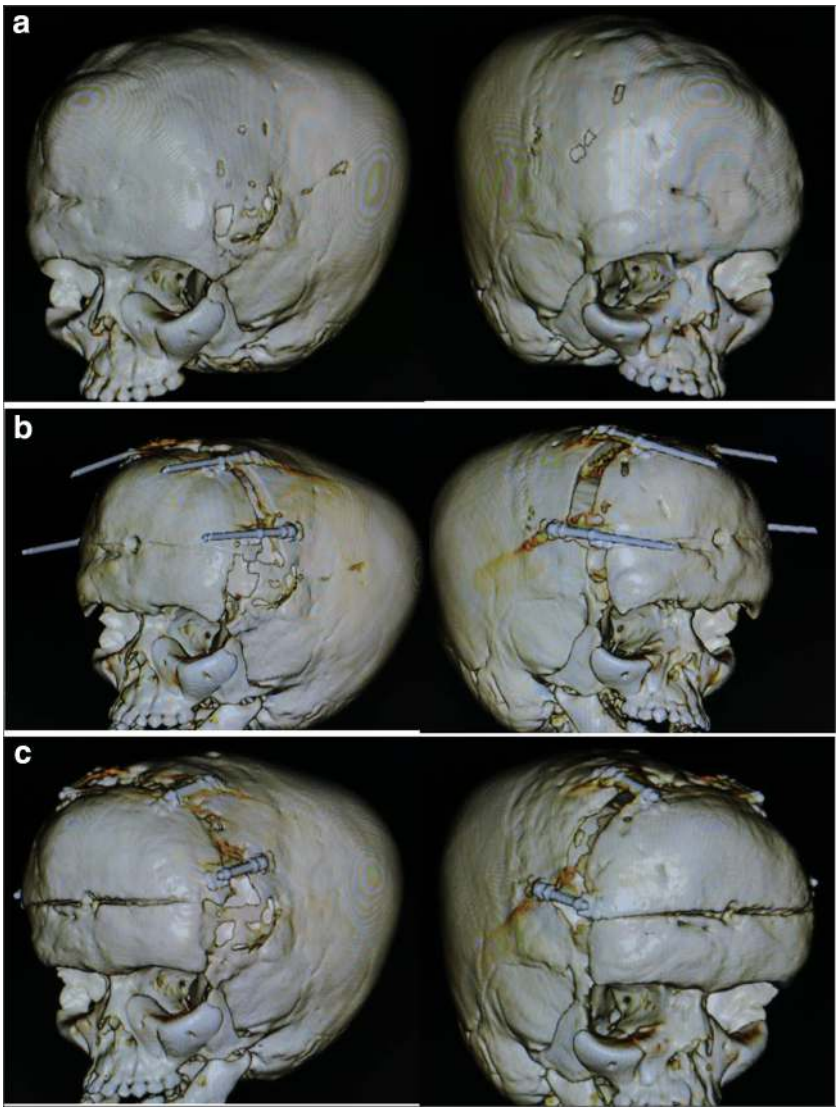

Fig. 6 Redo FOA carried out at age 6 years achieved an additional, 16-mm advancement and improved eye closure. **a** At 6 years and 1 month, immediately prior to the second FOA distraction. Artificial bone was implanted in the lower orbital rim. **b** During the second FOA distraction. **c** At 6 years and 7 months, immediately prior to device removal

NFIX gene also escape NMD, supporting the hypothesis that MSS-associated mutations do not inactivate (causing haploinsufficiency) but encode dysfunctional proteins that act in a dominant negative manner. Furthermore, genotyping has demonstrated that the deletions of exons 6 and 7 in the *NFIX* gene occur on the paternally inherited allele [10].

Abnormal ossification

Accelerated osseous maturation in MSS leads to skeletal dysplasia and skull deformities causing central nervous system compression leading to neurological deficits. In 1991, Pappas et al. [9] reported a child with MSS who was surgically treated for lower cranial nerve dysfunction and long-tract signs by decompression of the cranio-cervical junction. The first case of plastic surgery in a patient with MSS was described in 2010 by Mitsukawa and Satoh [7], who performed maxillomandibular distraction osteogenesis to improve the patient's facial deformities.

Patients with MSS usually die at an early age due to respiratory disease, which is believed to increase the probability of early death. However, Sumiya et al. [13] described a 7-year-old female patient with MSS with extremely uncommon, long-term survival attributed to successfully securing and maintaining the airway. The development of skeletal dysplasia and skull deformities due to accelerated bone maturation in MSS patients also has an impact on respiratory as well as neurological functions.

Management of craniofacial abnormalities

As mentioned previously, Mitsukawa and Satoh were the first to report using plastic surgery to treat a 4-year-old male patient with MSS. They performed maxillomandibular distraction osteogenesis to improve the patient's facial features with good

results; the proptosis and midface retrusion were corrected, the oral volume was enlarged, and the protrusion of the tongue and drooling decreased. Thus, they advocated surgery for the sake of the patient's quality of life whenever long-term survival is a possibility.

Visual loss in craniosynostosis is multifactorial (obstructive sleep apnea and anomalous intracranial venous sinuses leading to increased intracranial pressure, chronic disc edema, and optic neuropathy), and midfacial distraction is often the best way to reduce the proptosis due to shallow orbits and midfacial hypoplasia [8].

Treatment of multisuture synostosis should improve the frontal occipital and temporal dimensions. Regarding the parietal expansion, the skull shape of our patient was not typical of scaphocephaly, and the cephalic index was within the normal range. The patient never developed elevated intracranial pressure, and surgery was indicated for cosmetic reasons and treatment of the proptosis. Therefore, the lateral orbital wall was advanced sufficiently for both cosmetic reasons and functional correction. An open, remodeling approach with expansion and repositioning of the fronto-orbital bar was required to protect the orbital globe and periorbital tissues. The resulting, enlarged, lateral orbital wall architecture normalized the path of extraocular muscle excursion, thus ameliorating the functional deficits [3].

Conclusion

We reported herein a very rare case of craniofacial surgery for MSS. Surgical procedures to correct dysplastic features and limit neurological impairment are a worthwhile supportive treatment for improving the quality of life and general condition of patients with MSS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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