Case report

Ophthalmic considerations in patients with Pfeiffer syndrome

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Abstract

Purpose: We report here a newborn male infant with striking features consistent with severe Pfeiffer syndrome type II, including cloverleaf skull deformity with pansynostosis, extreme proptosis, upper extremity contractures, broad big toes and thumbs with varus deviation and genetic mutation in the FGFR2 gene. The authors review the ophthalmic complications in Pfeiffer syndrome and discuss the unique surgical strategies used for obtaining adequate corneal coverage in these unique patients.

Observations: Ophthalmic considerations in Type 2 Pfeiffer Syndrome include vision loss secondary to increased intracranial pressure, and extreme proptosis as a result of orbitostenosis and midfacial retrusion. Our patient has undergone multiple ophthalmic/oculoplastic, neurosurgical, and midfacial surgeries as a result of corneal deterioration due to extreme exorbitism.

Conclusions and importance: It is important for ophthalmologists to be aware of the ophthalmic complications associated with patients with craniosynostosis syndromes. Our case identifies the importance of close communication between ophthalmology and plastic reconstructive surgery to help formulate the most successful plan in treating corneal decompensation and proptosis in Pfeiffer Syndrome patients.

1. Introduction

Pfeiffer Syndrome (PS) is a craniofacial syndrome originally defined by craniosynostosis, broad thumbs and great toes and partial variable soft tissue syndactyly of hands and feet [1]. Three subtypes of Pfeiffer syndrome have been identified [2]. Type 1 is classic PS with mild manifestations of brachycephaly, midface hypoplasia, and abnormalities of the digits. Type 1 PS patients have normal intelligence, a good outcome, and familial inheritance. Type 2 consists of a cloverleaf skull, extreme proptosis, digital abnormalities, ankyloses of the elbows, and developmental delay. Type 3 is similar to type 2 without cloverleaf skull deformity. Types 2 and 3 have a uniformly poor outcome with death in infancy common. In severe PS (type 2 and 3), the management of the faciostenosis and upper airway compromise provides the possibility for survival beyond infancy with the potential for unimpaired intellectual development [3]. All subtypes of PS are result of mutation in the FGFR2 and, rarely, FGFR1 genes.

Ocular manifestations play an essential role in the diagnosis and management of PS. Common ophthalmic findings in severe forms of PS include shallow orbits, severe proptosis, exyclotorsion of the orbits, strabismus, and optic nerve compression from increased intracranial pressure [2]. Less commonly, anterior segment anomalies have been described in patients with Pfeiffer syndrome, including limbal scleralization, corectopia, and iris colobomas [4].

The goal of this report is to illustrate the severe ophthalmic complications and complicated management strategies in this patient with Type 2 Pfeiffer Syndrome. The collection and evaluation of protected patient health information in our manuscript was HIPAA-compliant.

2. Case report

The patient is a Hispanic male infant born at 38 week gestational age via uncomplicated vaginal delivery. Apgar scores were 7 and 9 at 1 min and 5 min respectively. Prenatal diagnosis of craniosynostosis was made by ultrasound examination and genetics consult had already been planned. Clinical features at birth included...
cloverleaf skull deformity with pansynostosis, upper extremity contractures, broad big toes and thumbs with varus deviation (Fig. 1A), low set ears, high arched palate, and severe proptosis. A diagnosis of Pfeiffer syndrome type 2 was made. Genetic testing was obtained and a mutation in the FGFR 2 gene was found. Ophthalmologic exam at birth demonstrated bilateral proptosis with excclyptolotred globes and over elevation in adduction. Bilateral lagophthalmos of 1.0 mm with good Bell’s reflex, trace conjunctival injection and healthy corneas were noted. The rest of the anterior segment exam was normal. The Optic nerves showed no evidence of edema or pallor. Ocular management at that time consisted of aggressive lubrication for lagophthalmos.

On day 19 of life increased intracranial pressure was noted and craniectomy was performed by the neurosurgical service. The patient at month 2 of life had episodes of right globe prolapse that was manually reduced by the ophthalmology service and corneal abrasion OD that was treated with antibiotic drops. At month 4 of life, the patient benefited from a bi-frontal orbital advancement via distraction osteogenesis by the plastic surgery team. Despite the anterior vault distraction and the resulted increased intracranial volume, his proptosis and globe subluxation became increasingly more pronounced and lagophthalmos worsened (Fig. 1B). Theoretically, Monobloc frontofacial advancement with the associated midface advancement would address all of these problems. In the pediatric population, this procedure can be complex to execute and poses significant risks to the patient. In addition to facial skeletal plasticity and softer bone with low intrinsic strength, which makes it harder to make osteotomies and maintain fixation, there is also a high relapse rate. On the other hand, the three most serious complications affecting these syndromic children (i.e., raised intracranial pressure, upper airway obstruction, and cornea-threatening exorbitism) have their most deleterious effect on development when they occur in the first 3 years of life and, in the most severe cases, during their first year [5–7].

Since it was deemed that the patient was too young to have Monobloc frontofacial advancement with distraction osteogenesis, a treatment alternative was needed. Oculoplastics performed a bilateral upper and lower lid retraction repair with full thickness skin grafting to the left upper lid and bilateral lateral internal tarsorrhaphies (Fig. 1C). Although, exposure was still noted it was improved without corneal decompensation. The patient returned for outpatient clinic appointment at month 6 of life. His previous tarsorrhaphy sites were dehisced and both globes demonstrated severe proptosis and chemosis. The left eye had a central necrotic corneal ulcer with granulomatous debris on the cornea and purulent discharge with surrounding erythematous conjunctiva and pronounced lagophthalmos (Fig. 1D). He was sent for inpatient treatment with fortified antibiotics. B scan ultrasound of the left eye did not show elements of vitreous haze that would support endophthalmitis. Multiple ophthalmic subspecialties concurred that the best chance of saving the patient’s left eye was to perform a Gunderson flap. The Gunderson flap unfortunately failed during the post-operative period and the corneal ulcer persisted. After a long discussion with the family it was decided that early frontofacial advancement was the only chance for globe salvage. Monobloc frontofacial advancement with distraction osteogenesis was performed with concurrent placement of bilateral suture tarsorrhaphies (Fig. 1E). Six weeks after midface advancement suture tarsorrhaphies were removed and showed marked improvement in his chemosis with resolution of his corneal ulcer and complete globe coverage without exposure.

Consent for use of patient information and identifying photography was obtained in writing by the legal guardian of the patient.

3. Discussion

Pfeiffer syndrome was first described in 1964 as a clinical presentation of craniosynostosis, broad thumbs and great toes, and partial variable soft tissue syndactyly of hands and feet [1]. It is also called acrocephalosyndactyly type 5. PS affects about 1 in 100,000 individuals [8]. Mild variants tend to be familial and carry a relatively good prognosis. More severe presentations of Pfeiffer syndrome have subsequently been described which may include severe craniostenosis, extreme proptosis, and upper airway

![Fig. 1. Clinical photographs of Patient: (A) note broad big toe with varus deviation and (B) severe proptosis with exposure. (C) After bilateral upper and lower eyelid retraction repair with full thickness skin grafting to the left upper eyelid. He also had internal tarsorrhaphies placed. (D) Unfortunately, at next presentation he had a corneal ulcer with infection on the left side as well as inferior corneal exposure on the right. (E) He ultimately had midface advancement with repeated suture tarsorrhaphies to both eyes.]
obstruction. These severe forms carry a poor prognosis and tend to be sporadic rather than familial [9].

Ocular manifestations play an essential role in the diagnosis and management of Pfeiffer syndrome. Clinical review in one of the largest cohorts with PS to date showed that orbitostenosis, marked by extreme proptosis, was evident in all the type 2 and type 3 patients. Midfacial retrusion was coincident in these cases and this deficiency of inferior support contributes significantly to the exorbitism [10]. The shallow orbits create proptosis and may lead to exposure keratopathy and corneal ulceration/infection as in our case. The entire orbits tend to excyclotorted, creating anomalous insertions of the extraocular muscles. Strabismus is common, particularly exotropia and over elevation in adduction. Increased intracranial pressure can occasionally lead to optic nerve compression and optic nerve hypoplasia has also been reported [4,9,11,12].

The short anterior cranial base, with consequent extreme anteroposterior shortening of the orbit and midfacial retrusion, means that support and protection of the globe can only be anticipated after advancement of the midface [10]. Tarsorrhaphy, canthal ligament release, and levator lengthening provide only short-term solutions to the coverage of the proptotic globe. In our case, midface advancement was chosen at an earlier age that would be optimal because of the deterioration of the left globe.

In extreme cases of PS, the cranio-orbito-faciostenosis demands aggressive early suture release, hydrocephalus management, orbital expansion, and airway management to permit survival to childhood and beyond instead of uniform early demise. Our case demonstrates the dramatic nature of proptosis seen in PS type 2. Appropriate globe coverage can only be achieved permanently with craniofacial reconstruction and eyelid or ocular surgical techniques should only be viewed as temporizing.

Author contribution

Each of the authors has contributed to, read and approved this manuscript.

Conflict of interest

None of the authors has any conflict of interest, financial or otherwise.

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