The ophthalmic sequelae of Pfeiffer syndrome and the long-term visual outcomes after craniofacial surgery

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BACKGROUND Pfeiffer syndrome is a rare, genetic condition characterized by craniosynostosis and midface hypoplasia, with resultant ophthalmic sequelae. The gold standard of treatment is fronto-orbital advancement. We analyzed a large database of Pfeiffer syndrome patients to report the rate of ophthalmic sequelae and the long-term visual outcomes after craniofacial surgery and to compare Pfeiffer syndrome to other craniosynostosis syndromes.

METHODS The medical records of Pfeiffer syndrome patients examined between 1988 and 2010 were examined retrospectively. Diagnosis was based on clinical and genetic testing. Long-term data were presented as a rate of incidence per person-year to overcome variable follow-up times.

RESULTS A total of 22 patients were included. Proptosis (n = 21 [95%]), refractive error (n = 13 [59%]), and strabismus (n = 12 [55%]) were the most common primary features at presentation. Exposure keratitis (n = 9 [41%]) and amblyopia (n = 3 [14%]) were the most common secondary features. At presentation, 24 eyes [86%] with documented best-corrected visual acuity were normal; 4 [14%] were impaired; and none were blind. Fronto-orbital advancement reduced the rate of proptosis from 28%/person-year at presentation to 2%/person-year. There were no cases of active exposure disease postoperatively. At last follow-up, there was a 7%/person-year rate of impaired vision secondary to corneal scarring and amblyopia and a 3%/person-year rate of blindness—all from optic atrophy.

CONCLUSIONS In this study, the rates of proptosis and exposure keratitis were high in Pfeiffer syndrome, especially compared to Apert and Crouzon syndromes. Fronto-orbital advancement was successful in correcting orbital abnormalities. Long-term ophthalmic follow-up is essential to ensure best visual outcome. (J AAPOS 2016;20:315-319)

Pfeiffer syndrome is a craniosynostosis syndrome with an incidence of 1 in 100 000 live births, that arises from a mutation in the fibroblast-growth-factor-receptor (*FGFR*) gene.[1-3] It has a well-recognized phenotype, with its classical features including, bicoronal craniosynostosis, midface hypoplasia with shallow orbits, broad thumbs and great toes, and variable syndactyly of the hands and feet.[1-3] Associated ophthalmic sequelae have been previously described in the literature; however, because of the relative rarity of Pfeiffer syndrome, reports of the ophthalmic findings are limited to isolated case reports and small case series or found in larger, combined craniosynostosis syndrome studies. The reported ophthalmic features include proptosis, strabismus, optic nerve atrophy, refractive error, exposure keratopathy, cataracts, and iris coloboma.[4,5]

Fronto-orbital advancement is the current gold-standard of treatment for Pfeiffer syndrome patients. Its primary aim is to relieve elevated intracranial pressure by increasing the intracranial volume and to correct underlying orbital and midface structural abnormalities to prevent ophthalmic and otolaryngologic complications.[1-3] There are no data documenting long-term visual outcomes after craniofacial surgery in Pfeiffer syndrome.

The purpose of the present study was to analyze a large database of patients with Pfeiffer syndrome to report the incidence of ophthalmic sequelae, document the long-term visual outcomes after craniofacial intervention, and

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Table 1. Criteria for grading proptosis and exposure keratopathy

Grade	Criteria
Proptosis	
Mild	<22 mm exophthalmos
Moderate	22–25 mm exophthalmos
Severe	>25 mm exophthalmos
Exposure keratopathy	
Mild	Superficial punctate keratopathy only
Moderate	Corneal ulceration away from visual axis and/or ≤3 mm in diameter
Severe	Corneal ulceration within the visual axis and/or >3 mm in diameter; suppurative keratitis; corneal perforation

to compare this data with other craniosynostosis syndromes, such as Apert and Crouzon syndromes.

Subjects and Methods

In this longitudinal study, the medical records of patients with Pfeiffer syndrome presenting to the Australian Craniofacial Unit (ACFU) between 1988 and 2010 were reviewed retrospectively. Ethics approval and waiver of consent was obtained the South Australian Health Human Research Ethics Committee. ACFU records were searched for the following terms: *Pfeiffer syndrome*, *craniosynostosis*, *fronto-orbital advancement*, and *FGFR* mutation. Diagnosis of Pfeiffer syndrome was based on clinical findings and genetic testing. Case notes were reviewed for all patients, and data were recorded in a standardized database according to the following parameters: age at presentation; sex; nationality and ethnicity; uncorrected and best-corrected visual acuity (BCVA) at presentation; refraction; the presence of proptosis, strabismus, and/or amblyopia at initial and subsequent examinations; anterior segment and fundus findings at initial and subsequent examinations; surgical procedures performed by the ACFU; postoperative complications; most recent best-corrected visual acuity; and duration of follow-up. Exclusion criteria were as follows: history of craniofacial surgery prior to presentation to the ACFU, no pre- or postoperative ophthalmic assessment, and 3 or more variables missing from the patient's dataset.

All ocular examinations were carried out by one of two experienced ophthalmologists (MH, JB), who subjectively graded the severity of proptosis and corneal disease according to the criteria outlined in Table 1. BCVA was either assessed using age-appropriate clinical examinations or measured through sweep visual evoked potentials (VEPs). Normal vision was defined as "fixes and follows," best-correct visual acuity better than 6/12,[6] or normal sweep VEP measurements (>15-30 cycles/degree).[7] Impaired vision was divided into mild (BCVA of 6/12 to better than 6/18 or sweep VEP of 15 to >10 cycles/degree), moderate (BCVA of 6/18 to better than 6/60 or sweep VEP of 10 to >3 cycles/degree), and severe (BCVA of 6/60 to better than 3/60 or sweep VEP of 3 to >2 cycles/degree) categories.[6,7] Blindness was defined as BCVA no better than 3/60 or grossly impaired VEP (≤2 cycles/degree).[6,7]

Due to the variable lengths of follow-up for each of our patients, we chose to measure final outcomes as a rate, measured as incidence per person-years. The term person-years signifies the sum of each patient's follow-up time.[8]

Table 2. Prevalence of ophthalmic sequelae at presentation in our cohort of Pfeiffer syndrome patients

Ophthalmic finding	No. patients as percentage of recorded data (%)	No. patients as percentage of total cohort (%)
Proptosis	21/22 (95)	21/22 (95)
Exposure disease	9/21 (43)	9/22 (41)
Papilloedema	1/16 (6)	1/22 (5)
Refractive errors	12/13 (92)	13/22 (59)
Hypermetropia	6/13 (46)	6/22 (27)
Astigmatism	4/13 (31)	4/22 (18)
Myopia	2/13 (15)	2/22 (9)
Emmetropia	1/13 (8)	1/22 (5)
Strabismus	12/12 (100)	12/22 (55)
Divergent	7/12 (58)	7/22 (32)
Convergent	3/12 (25)	3/22 (14)
Mixed	2/12 (17)	2/22 (9)
Ambylopia	3/12 (25)[a]	3/22 (14)

[a]1 bilateral, 2 unilateral.

Results

A total of 22 patients (11 males) met inclusion criteria. Six patients were Australian residents (5 white, 1 Asian). The remaining 16 were from Indonesia (6 [Austronesian]), Singapore (5 [Austronesian]), the Middle East (3), and the South Pacific (2 [Melanesian]). The mean age at presentation was 2.8 months (range, 4 weeks to 23 years). Patients were followed for a mean of 8.7 years (range, 3 months to 22 years), which is equivalent to 149 person-years.[8]

Ophthalmic Features of Pfeiffer Syndrome at Presentation

Proptosis affected 21 patients (20 bilateral; 1 unilateral) at presentation (n = 21 [95%]). Of the 41 affected eyes, 24 (59%) were classified as severe, with 4 experiencing at least 1 episode of globe luxation prior to craniofacial intervention. Nine patients (41%) had bilateral active exposure keratitis at presentation. Refractive error was always bilateral and found in 13 patients (59%), with hypermetropia (n = 6 [46%]) most common. Strabismus was recorded in 12 patients (55%), with a preponderance toward exodeviations (n = 7 [58%]). Papilledema without optic nerve atrophy was noted in 1 patient at presentation, an asymptomatic 6-month-old. Other ophthalmic findings, each found in 1 patient, included unilateral iris coloboma, bilateral anterior polar cataracts (not visually significant), and unilateral lower lid entropion. Table 2 outlines the findings at presentation in more detail.

Visual Acuity at Presentation

Visual acuity was recorded for 28 eyes (64%) of 14 patients at presentation. Normal BCVA was recorded in 24 eyes (86%) of 13 patients (11 bilateral, 2 unilateral); there