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Ophthalmic manifestations in patients with syndromic craniosynostosis

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Abstract

Context: Congenital craniofacial anomalies are a rare group of disease. Ophthalmological involvement in craniofacial synostosis ranges from mild aesthetic abnormality to sight threatening damage to optic nerve.

Aim: Study the ophthalmic manifestations in patients with syndromic craniosynostosis.

Materials and Methods: Patients diagnosed to have syndromic craniosynostosis underwent complete ophthalmic evaluation including visual acuity by age appropriate method, cycloplegic refraction, strabismus evaluation, anterior segment and fundus evaluation. Measurement of proptosis, inter pupillary, inter inner canthal and inter outer canthal distances were also done.

Results: 22 patients were studied. 12(54.5%) were male and 10(45.5%) were female. 9(40.9%) had Crouzon syndrome, 8(36.4%) had Apert syndrome, 2(9.1%) each had Frontonasal dysplasia and Pfeiffer syndrome and 1(4.5%) had Antley-Bixler syndrome. All of them had some ophthalmic involvement. Hypertelorism was seen in 54.5%, telecanthus in 27.3%, proptosis was seen in 63.6%, 64.3% of which was non-axial; extra-ocular muscle abnormalities was seen in 72.7%, strabismus in straight gaze in 54.5%, ametropia was seen in 40.9%, visual impairment was seen in 18.2%, anterior segment and optic disc abnormalities were seen in 64.6% each.

Conclusion: Ophthalmic involvement among the syndromes was more common with Crouzon syndrome. Ophthalmic evaluation should be an integral part of evaluation of the craniosynostosis patient.

Keywords: Craniosynostosis, Apert syndrome, Crouzon syndrome.

Introduction

Craniosynostosis is a premature closure of one or more cranial sutures. Virchow in 1851 demonstrated that following closure of a suture the growth proceeded parallel to it while it was arrested in the direction perpendicular to it. The prevalence of the disease has been estimated to be about 1 in 2000 to 5000 live births.(1) The diagnosis and treatment of this condition is important as the patients develop a series of complications affecting their neurological, visual and social development.

The cause and presentation of Craniosynostosis is varied and heterogenous and has been mapped to several genes coding for the fibroblast growth factor receptors (FGFR) 1, 2 and 3. Craniosynostosis can either be syndromic or non-syndromic. Non-syndromic usually involves a single suture although complex multi sutural synostosis can also occur without any recognizable syndromes. Syndromic craniosynostosis usually involves multiple sutures – with a recognizable pattern for each syndrome.(1)

Ophthalmological evaluation in a patient with craniofacial anomalies is mandatory due to the incidence of ophthalmic abnormalities in these disorders, and also because it serves as a reliable indicator for timing of surgery and follow-up. Ocular problems in craniofacial synostosis may either be primary due to the developmental disturbances or secondary as a result of the altered anatomy; they may be structural or functional. Structural manifestations include proptosis, hypertelorism or telecanthus, down-slanting palperal fissures, ptosis, lacrimal system abnormalities, keratoconus, extra-ocular muscle abnormalities and optic nerve abnormalities. Functional abnormalities are refractive errors, amblyopia and strabismus.

Abnormal protrusion of the eyeball is called proptosis. It can be axial or non-axial depending on the position of the globe. In Indian population a value >19mm or a difference of more than 2mm between the two eyes is considered abnormal.(2) It is mainly a result of mid face hypoplasia and Shallow orbits.

Increased interorbital distance is called hypertelorism. Its measurement is based on the inter pupillary and inter canthal (outer and inner) distances for which normal values are available.(3,4) Telecanthus or the lateral displacement of the medial canthi without bony hypertelorism may occur. Epicanthal folds and ptosis of various degrees may also occur. Down-slanting palpebral fissure, caused by the asymmetry between the growth of the frontal and maxillary portion of the face is seen in most syndromes.(5) Lacrimal duct abnormalities with nasolacrimal duct blockage are also found.

Extra ocular muscle abnormalities are reported in close to 90% of syndromic cases. It can be structural or functional. FGFR are present on the extra-ocular muscles, which account for the structural abnormalities.(5,6) Complete absence, anomalous insertion, bifid medial rectus, micro anatomical anomalies have all been reported. Abnormal movement of the eyes can also be present when there is no structural abnormality. The most common are an apparent Superior Oblique underaction, Inferior Oblique(IO) overaction

and Lateral rectus (LR) underaction. Pattern strabismus, especially V pattern is the rule rather than the exception in most syndromicsynostosis.[5,6]

Anterior segment abnormalities reported include keratoconus, exposure keratopathy, eccentric pupil, iris coloboma, anterior chamber abnormalities including Peter's anomaly, thick irides and ciliary bodies and shallow anterior chamber with occluded angles.

Patients with craniosynostosis are susceptible to raised intra-cranial tension which can lead to optic atrophy and visual failure. Screening for papilledema is one of the earliest and most reliable methods for detecting raised intracranial tension.

Apart from the structural abnormalities the visual function in these patients is also compromised. The visual loss in these patients can be ascribed to amblyopia, optic neuropathy or exposure keratitis. Amblyopia could be secondary to uncorrected refractive errors, stimulus deprivation or strabismic.[7]

Khan SH et al[7] retrospectively reviewed a series of 141 diagnosed cases of Crouzon, Apert, Pfeiffer and Saethre-Chotzen syndromes. The mean age at presentation was 23.3 months. 40.3% of patients had astigmatism ≥1D, 64% of which was oblique and was more common in Apert's syndrome (52.4%). Anisometropia of more than 1D was found in 18% patients. Horizontal strabismus was found in 70% - 38% exotropia and 32% esotropia. 44% had alphabet pattern, 95% of which was a V pattern. 39.8% had visual acuity 6/12 or less in their better eye.

Aims and Objectives

- Ophthalmic manifestations in patients with syndromic craniosynostosis.
- To establish the role of ophthalmic evaluation for craniosynostosis patients.

Materials and Methods

The study was conducted at the Department of Ophthalmology, Amrita Institute of Medical Sciences, Kochi, Kerala on an outpatient basis on patients diagnosed to have Craniofacial synostosis based on clinical examination along with Computerized tomography or Gene mutation study.

Each patient underwent a complete ophthalmic evaluation that included age, sex, diagnosis based on the suture with synostosis and associated syndromes, craniofacial Procedures done, visual Acuity, cycloplegic refraction, extraocular movements, strabismus measurement, anterior segment abnormalities by slit lamp examination, fundus examination by Indirect Ophthalmoscopy.

Visual acuity was tested for central, steady and maintained if age ≤1 year; with Cradiff chart for age 1-3 years, Lea symbol chart for age 3-6 years; Snellen's chart for age>6 years. Visual impairment defined as unsteady or unmaintained fixation in age ≤1year or best corrected visual acuity (BCVA) ≤ 6/12 of Snellen equivalent (LogMAR 0.3) in at least one eye. Amblyopia was defined as a difference of 2 or more lines between the 2 eyes or visual acuity ≤6/12 with no structural abnormalities to explain the same.

All patients underwent retinoscopy after attaining cycloplegia with Homatropine 2% eye drops instilled twice 20 minutes apart. Spherical equivalent was derived from the retinoscopy value and was considered for diagnosing refractive errors. Ametropia - hyperopia if spherical equivalent was ≥+2D for age more than 5 years and ≥ +3D for age less than 5 years, myopia if the spherical equivalent was ≥-1.5D, astigmatism if the cylindrical value was ≥ 1.5D and anisometropia if the difference was > 1.5 D between the two eyes. Ductions and versions were checked in all 9 gazes. Strabismus when present was measured with Hirschberg and alternate prism bar cover test. Anterior segment was examined under slit lamp and fundus using indirect ophthalmoscopy.

Interpupillary distance, inter innercanthal and inter outercanthal distance were measured with a transparent millimeter scale. Bony inter orbital distance was measured from the axial cut in Computerised Tomography (CT) (Siemen's 64 slice multi-detected computerized tomography scanner – 1mm axial and coronal cuts)passing through the recti and lens. The distance between a point on each lacrimal bone representing the anterior end of the medial orbital wall is taken as the anterior inter-orbital distance.[4] Orbital orientation was checked in the coronal section of CT. If the angle between two lines drawn through the superior and inferior recti of each eye respectively was beyond 170 to 10 degrees, it was defined as excyclorotation.[10]

Values published by Lakshminarayana P[3] and Waitzmann A[4] were taken as normal and compared with that of study groups. Normal values based on age is given in the Table 1.

Hypertelorism was defined as an increased interpupillary distance (IPD) compared to age matched normal. Telecanthus is an increased inter innercanthal distance (IICD) with normal IPD. A value beyond the higher end of normal range for age matched normal was considered as hypertelorism and below the lower end was considered as hypotelorism.

Proptosis was defined as an exophthalmometry value >17 mm for age <3 years, >19 mm for Age >3 years or a difference of >2 mm between the two eyes. In children less than 2 years of age, globe protrusion was measured from CT scan. Measurement was taken in axial cut in a slice in the orbital region, transecting the lens of the globe, the optic nerve, the ethmoid air cells, the medial and lateral rectus muscle. Globe protrusion was measured as the perpendicular distance between the anterior tips of the lateral orbital wall and the most anterior point on the globe.[4]

Results

A total of 22 patients with syndromic

craniosynostosis were studied. There were 12(54.5%) male and 10 female (45.5%) patients. Age of the patients ranged from 2 months to 24 years with a mean of 5 years. 8(36.4%) were operated and 14 (63.6%) were un-operated. Distribution of the syndromes was as in Table 2. Crouzon and Apert were the most commonly encountered syndromes. The diagnosis and measurements are given in Table 3.

Some ophthalmic abnormality was seen in all the patients. Extra-ocular muscle abnormalities, optic disc changes and anterior segment abnormalities were more common. The frequency is given in Table 4.

Of the 14 patients with proptosis, 5 were axial and 9 were non-axial of which 7 were patients with Crouzon syndrome. Extraocular abnormalities seen were mostly inferior oblique overaction with or without associated superior oblique underaction and nystagmus. Strabismus was mostly V exotropia with excyclorotation of the orbit seen in 10 patients.

Myopia was the most frequent refractive error followed by with the rule astigmatism. Anisometropia was seen in 3 patients. Abnormal pupils were seen in 3(13.6%) patients, lagophthalmos in 4(19.2%), corneal exposure or opacity in 7(31.8%). 4 patients had globe luxation of which 2 had undergone tarsorrhaphy.

Partial or complete optic atrophy was seen in 7(31.8%) patients, most of which were Crouzon patients. Unilateral or bilateral disc edema was seen in 3(13.6%) patients. Other abnormalities seen were dilatation and tortuosity of vessels, myopic changes and optic disc hypoplasia.

Visual impairment was bilateral in 3(13.6%) and unilateral in 1 (4.5%). Optic atrophy was the most common cause of impairment accounting for 3 of the patients, followed by ametropia.

Distribution of ophthalmic manifestations in the syndromic patients

Apert syndrome: Of the 8 patients with Apert syndrome, genetic studies were available for 5 patients. 3 had C934G mutation and 2 had C937G mutation. The ophthalmic manifestations in the 3 patients with C934G were more, while the 2 patients with C937G had minimal involvement of the eye. Distribution of ophthalmic manifestations in Apert syndrome is given in Table 5.

Crouzon syndrome: Distribution of ophthalmic findings were described in Table 6. All 9 (100%) had proptosis of which, 2(22.2%) had axial proptosis and 7(77.8%) had non-axial proptosis. Extra-ocular muscle abnormalities were also seen in all 9 patients (100%). Strabismus in primary gaze was seen in 6 (66.7%) and all 6 with exotropia, V pattern was seen in all 9 patients. Excyclorotation was seen in 5 (55.6%) patients. Refractive errors were seen in 4 (44.4%) patients, anterior segment abnormalities and optic disc changes in 7(77.8%) patients.

Of the anterior segment abnormalities, Pupillary abnormalities were seen in 3 patients(33.3%), Corneal exposure in 2 patients (22.2%), Corneal opacity in 3 patients(33.3%), lateral tarsorrhaphy was done in 2 patients(22.2%), trichiasis was seen in 1 patient and chemosis was seen in 1 patient(11.1%). Keratoconus was seen in 1 (11.1%) patient. Papilledema was seen in 1 (11.1%) patients, optic atrophy was seen in 6 (66.7%) patients, partial in 3 (33.3%) and total optic atrophy in 3 (33.3%). Crowded disc without raised intra-cranial tension was seen in 2 (22.2%) patients.

Table 1: Normal values for reference based on age

Age	Interpupillary distance(cm)	Interorbital distance (cm)	inter innercanthal distance(cm)	inter outercanthal distance(cm)
<1	4.1 - 5.8	1.6 - 2	2.1 - 2.7	6.8 - 8
1 - 3	5 - 6.2	1.8 - 2.1	2.3 - 3	7.6 - 9.2
>3	5.6 - 6.8	2.1 - 2.5	2.6 - 3.1	8.4 - 10

Table 2: Distribution of Diagnosis of craniosynostosis patients

Diagnosis	Number of Patients	Percentage (%)
Crouzon syndrome	9	40.9
Apert syndrome	8	36.4
Pfeiffer syndrome	2	9.1
Frontonasal dysplasia	2	9.1
Antley-Bixler syndrome	1	4.5

Table 3: Diagnosis and measurements of craniosynostosis patients

Sl. No	Age	Sex	Diagnosis	Cranio Facial Surgery	IPD (cm)	IICD (cm)	IOD (cm)	IOCD (cm)	Exophthalmometry (mm)	
									Right Eye	Left Eye
1	2	M	Apert	Yes	6.2	4	2.5	8	7	9
2	5	M	Crouzon	Yes	6	3	2	10	20	21
3	1	F	Apert	No	6.5	3.5	2	10	17	18

4	2	M	Apert	No	5.5	3	2	9	14	13
5	0.5	M	Apert	Yes	6.5	3.7	3.5	9.5	16	14
6	5	F	Crouzon	Yes	6.5	3	2.2	10	27	25
7	5	F	Crouzon	Yes	6.5	3.5	2	9	23	28
8	2	M	Crouzon	Yes	6.9	3.6	2.27	9.6	24	24
9	0.67	M	Apert	No	7.5	4.5	2.5	11	25	20
10	15	F	Crouzon	No	7	4	2.5	10.3	23	24
11	8	F	Pfeiffer	No	6	3.2	2	9	18	17
12	24	F	Crouzon	Yes	8	4.5	3.5	12.1	30	32
13	1.5	F	Pfeiffer	No	6.5	3.61	2	8.5	18	17
14	0.67	M	Crouzon	No	5.6	3.5	1.9	7.8	19	20
15	0.17	F	FND	No	5.7	3.8	2.4	8.4	13	12
16	13	F	Crouzon	Yes	7.6	3.2	2.2	11	27	24
17	4	M	Apert	No	6.35	3.5	1.7	9.5	12	13
18	0.83	M	Apert	No	5	3.2	1.9	8	12	13
19	9	M	Apert	No	6.9	4	2.5	10	20	21
20	8	M	Crouzon	No	7.1	3.7	2.8	9.7	24	23
21	0.25	M	AB	No	6	3.5	2.2	8	16	16
22	4	F	FND	No	6.5	4.5	2.65	9.1	17	18
Mean and Standard deviation of measurements (SD in brackets)					6.47 (0.72)	3.64 (0.47)	2.33 (0.47)	9.43 (1.10)	18.81 (5.64)	18.95 (5.76)

Abbreviations used: FND: Fronto nasal dysplasia, AB: Antley-Bixler, IOD: Inter orbital distance, IICD: Inter Inner canthal distance, IPD: Inter papillary distance, IOCD: Inter outer canthal distance

Table 4: Frequency of ophthalmic abnormalities

Ocular abnormality	Syndromic CFS(n-22)	Percentage (%)
Telecanthus	6	27.3
Hypertelorism	12	54.5
Proptosis	14	63.6
EOM abnormalities	16	72.7
Ametropia	9	40.9
Anterior segment abnormalities	14	63.6
Optic disc abnormalities	14	63.6
Strabismus in straight gaze	7	31.8
Visual impairment	4	19.2

Table 5: Distribution of ophthalmic manifestations in Apert syndrome

Ophthalmic manifestation	Frequency (n = 8)	Percentage (%)
Hypertelorism	4	50
Telecanthus	3	37.5
Down-slanting palpebral fissure	4	50
Axial proptosis	2	25
Non-axial proptosis	1	12.5
EOM Abnormality	5	62.5
Strabismus in primary gaze	1	12.5
V pattern	3	37.5
Excyclorotation	5	62.5
Ametropia	1	12.5
Anterior Segment Abnormality	5	62.5
Optic disc changes	5	62.5

Table 6: Distribution of Ophthalmic manifestation in Crouzon syndrome

Ophthalmic manifestation	Frequency (n = 9)	Percentage (%)
Hypertelorism	6	66.7
Telecanthus	2	22.2
Down-slanting palpebral fissure	8	88.9
Axial proptosis	2	22.2
Non-axial proptosis	7	77.8
EOM Abnormality	9	100
Strabismus in primary gaze	6	66.7
V pattern	9	100
Excyclorotation	5	55.6
Ametropia	4	44.4
Anterior Segment Abnormality	7	77.8
Optic disc changes	7	77.8
Visual impairment	3	33.3

Discussion

We have in this study, analysed the ophthalmic involvement of patients with syndromic craniosynostosis. To the best of our knowledge and understanding, this is the first study in India that gives a

compiled data on ophthalmic manifestations in syndromic craniosynostosis.

All the patients had some ophthalmic abnormality. Both males and females were almost equally involved with a mean age of 5 years. Orbital measurements were increased when compared to age matched normals and were comparable to studies done by Carr et al [8]. Carr et al[8] compared the Cranio-orbito-zygomatic measurements of unoperated patients with Apert and Crouzon syndrome with age matched controls. Syndromic patients had wider inter-orbital distances, more protrusive globes and shorter medial and lateral orbital walls.

Khan SH et al[7] studied the visual outcomes and amblyogenic risk factors in craniosynostotic syndromes in 141 patients and found that 39.8% of patients had visual impairment defined as VA 6/12 or worse in their better eye. Astigmatism was the most common refractive error, seen in 40.3%, most of which was oblique astigmatism. Anisometropia was seen in 18% of patients. Strabismus was seen in nearly 70% with exotropia being slightly more common than esotropia. Strabismus in our study was comparable to them, however myopia was the most common refractive error in our study and visual impairment was only seen in 19.2%.

Crouzon syndrome: Gray TL et al[9] studied the ophthalmic sequelae in 71 patients, they found ametropia in 77%, hypermetropia was the most common type of refractive error followed by astigmatism. Nystagmus was seen in 7%, strabismus in primary gaze in 39%, exotropia being the commonest form. V pattern was seen in 23%. Visual impairment was seen in 41% and optic atrophy in only 7% of patients.

Hertle RW et al[11] studied the visual function in syndromic patients, 25 of them Crouzon patients. Ametropia was seen in 80%, strabismus in 80%, exotropia being the most common. Visual impairment was seen in 44%, with optic atrophy in only 4% of patients.

In our study, myopia was more common than hypermetropia or astigmatism, unlike the others who found astigmatism to be more common. Nystagmus has been reported in all 3 studies to a comparable extent. In our study, as in the others, exotropia is the commonest form of strabismus in primary gaze. Pattern strabismus especially V exotropia was seen ubiquitously in our patients, while it is reported to a lesser extent in other studies. Optic atrophy either unilateral or bilateral was more in our study, possibly a reflection of the delay in correction of craniofacial anomaly. Visual impairment rates were comparable, but unlike in other studies, optic atrophy was the main cause of visual impairment in our study.

Apert syndrome: Khong JJ et al[12] studied the ophthalmic features in 61 Apert syndrome patients after craniofacial surgery. In their study, ametropia was seen in 69%, Strabismus in primary position in 63%, V pattern in 28%, EOM abnormalities in 28%, Keratopathy in 24% and Optic atrophy in 16%.

Jadico et al[13] studied the phenotypic and genotypic correlations between 18 Apert patients with mutation in 2 different FGFR genes. They found that Astigmatism was the most common refractive error occurring in 55%. Strabismus and EOM abnormalities occurred in nearly 89% of patients.

We found that refractive errors and strabismus in primary gaze were less in our patients compared to the other studies. The occurrence of V pattern, extra-ocular muscle (EOM) abnormalities, keratopathy and optic disc changes were comparable. None of the Apert patients had visual impairment in our study despite 12.5% of the patients having partial optic atrophy. Compared to this Khong JJ et al[12] found nearly 54% of visual impairment either due to Amblyopia or optic nerve involvement.

Of the other syndromes, patients with Antley- Bixler and Pfeiffer syndrome had more sever ocular involvement comparable to that of Crouzon patients.

Limitations

The major limitation of this study is that amblyopia and hence visual impairment could have been under diagnosed as the visual acuity was based on symbol charts in ages < 6 years. Strabismus could have been under-estimated as it is difficult to obtain measurements in these patients. Pattern reversal visually evoked potentials were not taken into consideration in assessing the visual function.

Conclusion

Craniofacial synostosis patients have a significant involvement of the eye and the orbit. It can cause both structural and functional abnormalities. In the syndromic synostosis, ophthalmic manifestations are more common in Crouzon syndrome especially proptosis, visual impairment and optic atrophy. Extra-ocular muscle abnormalities are common in Apert syndrome, while visual impairment and optic atrophy are rare. Hence the management of craniosynostosis patients requires a multi-disciplinary approach, in which the role of an Ophthalmologist is crucial.

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