Crouzon Syndrome: Variability in clinical severity at a presentation a clinico-radiological evaluation.

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Abstract

Background/Aims: Crouzon syndrome (CS) was first described in 1912 by a French neurologist Octave Crouzon (1874-1938), as a hereditary syndrome of craniofacial dysostosis, which included a triad of skull deformities, facial anomalies, and proptosis. Here, the authors present 5 cases of CS of different clinical severity at the time of presentation. Case Report: The demographic, ophthalmic, radiological, and systemic findings of 5 patients with CS with variable clinical severity at presentation will be discussed in detail. Conclusion: CS can present with different clinical manifestations involving the skull, orbits, and eyes. The clinical and radiological findings of this syndrome vary in severity from a mild presentation with subtle manifestations, to a severe form with marked midface, brain, orbital, eye, cardiac, and respiratory complications. Management of patients with CS requires a multidisciplinary approach, by a team of craniofacial experts. Early surgical intervention is highly recommended in many patients with CS.

Keywords: Crouzon syndrome, Craniofacial dysostosis, Skull sutures, Orbit, Proptosis, Hydrocephalus.

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Introduction

Crouzon syndrome was first described in 1912 by a French neurologist Octave Crouzon (1874-1938), as a hereditary syndrome of craniofacial dysostosis, which included a triad of skull deformities, facial anomalies, and proptosis [1]. It is one of the craniosynostosis syndromes. It is a rare genetic disorder that has a worldwide prevalence rate of 1 in 25,000 live births [2,3]. It is transmitted as an autosomal dominant inheritance, but in 25% of cases, it may occur sporadically because of a fresh mutation. The genetic defect is caused by mutation of Fibroblast Growth Factor Receptor 2 (FGFR2) on chromosome locus 10q25-q26, resulting in early fusion of skull bones during fetal development [4-6].

The underlying pathological process in CS is premature closure of the sagittal, coronal and occasionally lambdoid sutures beginning in the first year and completed by 2-3 years of life. No single skull shape is a diagnostic of CS because the eventual shape of the head depends on the time and sequence in which the skull sutures fused. The skull deformity in CS may be brachycephaly, oxycephaly or trigonocephaly. CS is distinguishable from other craniosynostosis syndromes by lack of hand and/or foot abnormalities [7].

The appearance of an infant or a child with CS can vary in severity from a mild presentation with subtle midface manifestations to severe form with multiple fused cranial sutures and marked brain, midface, orbital, and eye problems. The earlier the onset, the more dramatic the effect of these malformations on subsequent cranial and brain growth and development; whereas late synostosis cranial sutures may render a nearly normal-shaped skull [8]. In this study, the authors present 5 cases with clinical and radiological features of, but, of different clinical severity at the time of presentation.

Case Reports

Five patients with diagnostic features of CS of different clinical severity will be presented.

Case 1 (The most severe)

A female newborn presented on the same day of delivery to the Ophthalmology Department with severe bilateral proptosis, associated with other facial abnormalities. Her mother was a primipara, and her pregnancy was uneventful. There was no history of drug intake or radiation exposure during pregnancy. The parents were first cousins. Ophthalmic examination revealed bilateral severe proptosis, hypertelorism, undeveloped eyelids, severely chemotic conjunctiva with subconjunctival hemorrhage, edematous cornea (exposure keratopathy), and unreactive pupils. Fundus could not be seen because of the hazy ocular media. Externally, eye manifestations were associated with bulging of the frontal and temporal bones; hypoplasia of the superior maxilla; prognathism of the lower jaw; short broad, and hooked nose; and low set ears (Figure 1a). The pediatric examination revealed the presence of congenital heart septal defect and upper respiratory tract anomalies. No digital (fingers and toes) abnormalities were seen (No Syndactyly).

Orbital and brain Computed Tomography (CT) revealed extremely shallow bony orbits with massive bilateral proptosis; small facial bones compared with skull vault and markedly dilated cerebral ventricles (hydrocephalus) with hypertrophy of the left hemicrania (Figure 1b and 1c). The patient died 4 days after birth because of the associated severe cerebral anomalies, congenital heart defects, and upper respiratory tract obstruction.

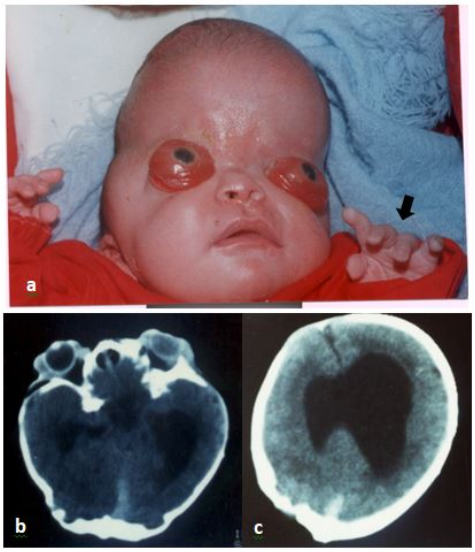

Figure 1. (a): *Aclinical photograph of a female newborn with bilateral severe proptosis, associated with chemotic conjunctiva, exposure keratopathy, low set ears, bulging of the frontal and temporal bones, hypoplasia of superior maxilla, prognathism of the lower jaw, broad, hooked nose, and normal fingers (black arrows);* ***(b):*** *Axial orbital CT showing extremely shallow orbits with severe bilateral proptosis;* ***(c):*** *Brain CT showing dilated cerebral ventricles "hydrocephalus" with diffuse indentation of inner table of skull and hypertrophy of the left hemicrania*.

* This case was reported by the same author in 1998 [9].

Case 2

A 6-year-old boy presented with his parents to the Pediatric Neurology Clinic, with the chief complaint of recurrent attacks of headache and seizures. He is the 2nd child of clinically healthy parents of consanguineous marriage and there was no history of similar anomalies in the first sibling or near relatives. No history of systemic illness or drug use was reported by the patient's father. The mother reported normal pregnancy and there was no history of drug intake or radiation exposure during pregnancy. The child was born by a full-term normal delivery. The child was not on any medications and denied any medical allergies. The abnormal cranial and facial features started developing slowly after birth, and the enlarged size of the head was noticed by the mother within the first few months of child's life. The severity had gradually increased till the age of 7 months when has was diagnosed as CS. No cosmetic maxillofacial surgery had been done.

On ophthalmic examination, the child presented with bilateral blind proptotic globes with bilateral corneal scarring; down slanting of palpebral fissures; hypertelorism; right upper lid ptosis; and V-pattern exotropia (Figure 2a). His visual acuity was No Light Perception (NPL) in both eyes. Fundus examination could not be done due to associated corneal scarring, however, a previous medical report of fundus examination and photography at earlier stage revealed bilateral optic atrophy. On general examination, the child had short stature. Head examination revealed enlarged cranial vault with frontal bossing, parrot-beaked nose, depressed nasal bridge, hypoplastic maxilla, relative prognathism of the lower jaw, nasal septal deviation, and low set ears (Figure 2a and 2b). Audiogram examination revealed bilateral conductive deafness. Dental examination revealed a narrow high arched palate, with crowding of the anterior teeth. No digital abnormalities were present (No Syndactyly). On Visual Evoked Potential (VEP), he had bilateral optic atrophy. On audiogram examination, he had a bilateral dense conductive deafness. He had severe mental retardation. Other systemic examinations including cardiovascular, respiratory and abdominal examinations were unremarkable. Routine hematological and biochemical tests were within normal limits.

On radiographic investigation, the anteroposterior and lateral skull radiographs (Figure 2c and 2d) revealed the "scaphocephalic" skull shape, fused cranial sutures, hypoplastic maxilla, and prominent cranial markings of the inner surface of the cranial vault seen as multiple radiolucencies, known as "beaten metal or beaten copper/ silver" appearance due to increased ICP as a result of premature closure of cranial sutures. Orbital CT scan showed bilateral proptosis. Brain CT showing dilated cerebral ventricles "hydrocephalus" with diffuse indentation of inner table of skull and hypertrophy of the left hemicrania. No other anomalies were noted in radiographs of the metacarpal bones and fingers, chest, and spine. Based on the clinical, dental, ophthalmological, and radiological findings, the diagnosis of Crouzon syndrome was made.

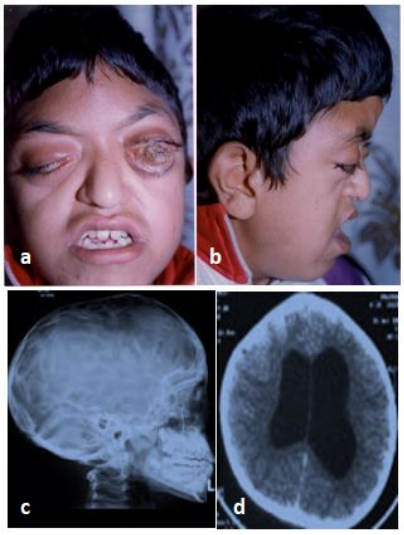

Figure 2. (a,b): *A 6-year-old male child showing severe bilateral proptosis, right ptosis, right exotropia, left severe corneal scarring, short, broad, hooked nose with a flattened nasal bridge, low set ears,hypoplasia of the superior maxilla, and prognathism of the lower jaw;* ***(c):*** *Lateral skull radiograph showing fusion of skull sutures and "beaten copper/silver" appearance;* ***(d):*** *Brain CT showing dilated cerebral ventricles "hydrocephalus"with diffuse indentation of inner table of skull and hypertrophy of the left hemicrania.*

Case 3

A 4-month-old male infant presented with his parents to the Pediatric Department, because of abnormal cranial and facial appearance, and enlarged head size. He is the first child of

clinically healthy parents of consanguineous marriage. Past medical history revealed that these features started developing slowly after birth. The prenatal, delivery and postnatal history were found to be insignificant. The mother reported normal pregnancy and there was no history of drug intake or radiation exposure during pregnancy. Family history revealed no abnormalities.

General examination showed enlarged cranial vault with frontal bossing, maxillary hypoplasia and a relative, mandibular prognathism, depressed nasal bridge and low-set ears (Figure 3a and 3b). Intraoral examination revealed a high-arched palate. His hands and feet were found to be normal (No Syndactyly). Because of his abnormal ocular features, he was referred to the pediatric ophthalmology clinic for further evaluation. Ocular examination revealed bilateral proptosis, and divergent squint (exotropia).

The skull radiographs revealed the 'scaphocephalic' skull shape, hypoplastic maxilla, and prominent cranial markings of the inner surface of the cranial vault seen as multiple radiolucencies, known as "beaten metal or beaten copper/ silver" appearance (Figure 3c-3e). Orbital CT scan showed bilateral proptosis (Figure 3f). Brain CT showing dilated cerebral ventricles "hydrocephalus" with diffuse indentation of the inner table of the skull and hypertrophy of the left hemicrania (Figure 3g). Three-dimensional CT scans of the skull showed fused sagittal, lambdoid, and coronal sutures, with shallow orbits (Figure 3i and 3j). Another systemic examination was unremarkable. Routine hematological and biochemical tests were within normal limits. The diagnosis of Crouzon syndrome was made on the basis of clinical, ocular, and radiological findings.

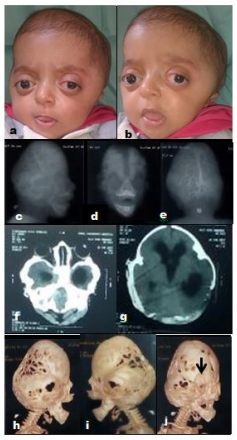

Figure 3. (a,b): *A 4-month-old male infant with Crouzon syndrome showing bilateral proptosis, left exotropia,low set ears, bulging of the frontal and temporal bones, hypoplasia of superior maxilla, prognathism of the lower jaw, broad, hooked nose,* ***(c):*** *Axial orbital CT showing shallow orbits with bilateral proptosis;* ***(d):*** *Brain CT showing dilated cerebral ventricles "hydrocephalus" with diffuse indentation of inner table of skull. Lateral skull radiograph showing fusion of skull sutures and "beaten copper/silver" appearance;* ***(e-g):*** *skull radiographs showing fusion of skull sutures and multiple "beaten copper/silver" appearance;* ***(h-j):*** *Three-dimensional CT scan of skull revealing obliteration of skull sutures and shallow orbit (black arrow).*

Case 4

A 10-year-old girl, who was the first child of a non-consanguineous marriage, presented with her parents to the Otolaryngology Clinic, with the chief complaint of hearing loss. She, also, had a diminution of vision of both eyes and divergent squint (Exotropia), together with abnormal facial features, left ptosis and dental abnormalities. Because of her ocular problems, she was referred to the Pediatric Ophthalmology Clinic for further evaluation.

On general examination, she had a brachycephalic head with bilateral proptosis, beaked-nose with a flattened nasal bridge, nasal septal deviation, hypoplasia of the superior maxilla, and prognathism of the lower jaw (Figure 4a and 4b). Ophthalmic examination revealed bilateral proptosis, V-pattern exotropia, and left ptosis (Figure 4a). Her visual acuity was 3/60 in the right eye and 6/60 in the left eye. Anterior segment biomicroscopy was within normal limits. Fundus examination revealed bilateral optic disc pallor, more in the right eye. Oral and dental examination revealed high-arched palate (Figure 4c), and crowding of the anterior teeth (Figure 4d). No digital abnormalities were detected (No syndactyly). On audiogram examination, she had bilateral conductive deafness. She had moderate mental retardation. Other systemic examinations including cardiovascular, respiratory and abdominal examinations were unremarkable. Routine hematological and biochemical tests were within normal limits.

On radiographic investigation, the lateral skull radiograph revealed closure of cranial sutures with beaten copper/silver" appearance (Figure 4d). Orbital CT scan showed shallow bony orbits with bilateral proptosis, more severe on the right side. Antero-posterior spine radiograph revealed decreased intervertebral space between C5 and C6 vertebrae. The radiographic examination of metacarpal bones and fingers was unremarkable (No syndactyly). No other anomalies were noted in chest radiograph. The diagnosis of Crouzon syndrome was made, on the basis of clinical, dental, ophthalmological, and radiological findings.

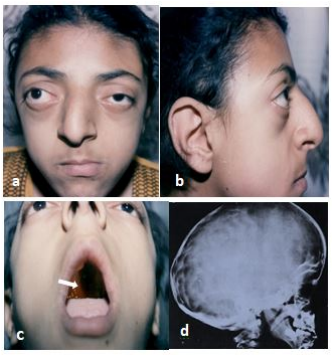

Figure 4. (a,b): *Two clinical photographs of a 10-year-old female child showing bilateral proptosis, V-pattern exotropia, left ptosis, beaked-nose with a flattened nasal bridge, hypoplasia of the superior maxilla, and prognathism of the lower jaw;* ***(c):*** *Intraoral examination showing high arched palate (white arrow);* ***(d):*** *Lateral skull radiograph showing multiple "beaten copper/silver" appearance.*

Case 5

A 12-year-old girl presented with her mother to the Pediatric Ophthalmology Clinic with the chief complaint of diminution of vision of eyes, frequent attacks of headache, and abnormally prominent eyes. She was the third child of clinically healthy parents of non-consanguineous marriage. She was a full-term baby, and there was no history of drug intake or radiation exposure by the mother during pregnancy. There were no reported anomalies in other siblings or near relatives. The child was not on any medications.

Head examination revealed enlarged cranial vault with frontal bossing, maxillary hypoplasia, and a relative mandibular prognathism (Figure 5a and 5b). Dental examination revealed a narrow high arched palate (Figure 5d) (black arrow) and crowding of the anterior teeth (Figure 5d). Ophthalmic examination revealed that the best-corrected visual acuity was 6/12 in the right eye and 6/24 in left eye. Also, there was bilateral proptosis, and hypertelorism (Figure 5a and 5b), and the rest of anterior segment examination of both eyes was unremarkable. Fundus examination revealed bilateral normal optic discs. Cycloplegic refraction showed bilateral myopic astigmatism of-2.75/-1.75 axis 5° (for right eye), and-4.25/-2.50 axis 175° (for left eye), which was corrected with glasses (Figure 5c). She had mild mental retardation. Other systemic examinations including cardiovascular, respiratory and abdominal examinations were unremarkable. Routine hematological and biochemical tests were within normal limits.

On radiographic investigation, the lateral skull radiograph revealed closure of cranial sutures with beaten copper/silver" appearance (Figure 5c). Orbital CT scan revealed shallow orbits, with bilateral proptosis more of the left eye. Brain CT showed diffuse indentation of the inner table of skull.

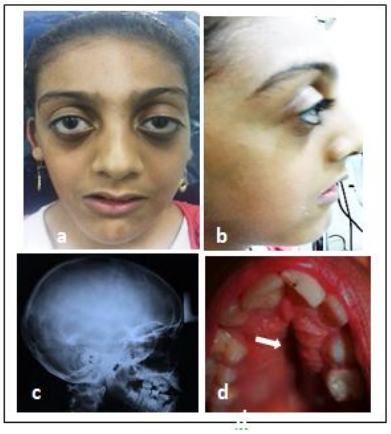

Figure 5. (a,b): *Two clinical photographs of a 12-year-old female child showing bilateral proptosis, maxillary hypoplasia, and a relative, mandibular prognathism;* ***(c):*** *Lateral skull radiograph showing multiple "beaten copper/silver" appearance;* ***(d):*** *Intraoral examination showing high arched palate (white arrow), and dental irregularities*

The radiographic examination of metacarpal bones and fingers were unremarkable (No Syndactyly). No other anomalies were noted in radiographs of the chest and spine. The diagnosis of Crouzon syndrome was made on the basis of clinical, dental, ophthalmological, and radiological findings. A comparison between the 5 patients in this study is shown in Table 1.

Table 1. *A comparison between the 5 patients in this study.*

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
(1) History					
a. History of consanguinity	+ve	+ve	+ve	-ve	-ve
b. Parents	Healthy	Healthy	Healthy	Healthy	Healthy
c. Mother	Primipara	Multipara	Multipara	Multipara	Multipara
d. Pregnancy	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful
e. Labor	Full-term	Full-term	Full-term	Full-term	Full-term
f. Family history	-ve	-ve	-ve	-ve	-ve
g. Age at presentation	1st day	6 years	4 months	10 years	12 years
h. Chief complaint	abnormal facial appearance	recurrent attacks of headache and seizures	abnormal facial appearance	Hearing loss and abnormal position of eyes	diminution of vision and attacks of headache
(2) Clinical Examination					
A. Eye signs					
i. Degree of proptosis	Most severe	Severe	Severe	Moderate	Mild
ii. Eye position	Outside orbital cavities	Exotropia	Exotropia	Exotropia	Normal

iii. Other eye signs	Absent eyelids Chemotic conjunctiva; Corneal edema; Hypertelorism	Ptosis Corneal scarring Optic atrophy Hypertelorism	Optic disc pallor	Ptosis Optic disc pallor Hypertelorism	Myopic astigmatism
B. Ear signs	Low-set ears	Low-set ears+Conductive deafness	Low-set ears	Low-set ears+Conductive deafness	- ve
C. Other signs					
i. High-arched palate	+ve	+ve	+ve	+ve	-ve
ii. Dental anomalies	-ve (Newborn)	+ve	-ve (4 months)	+ve	+ve
iii. Cervical synostosis	-ve	-ve	-ve	+ve	-ve
iv. Hydrocephalus	+ve	+ve	+ve	-ve	-ve
v. Digital anomalies (Syndactyly)	-ve	-ve	-ve	-ve	-ve

Discussion

Skull bones articulate through areas called sutures. These fibrous joints are constituted by mesenchyme that must remain unmineralized (unfused) until physiological skull growth is finalized. A tightly regulated mechanism prevents premature and persistent osteogenesis, preserving suture patency. Mechanisms of suture growth must modulate osteogenesis at the right site and timing until growth is complete. Sutures function as key growth centers of the skull during the early years of life. Hence, as the embryonic brain grows, a proportional amount of skull growth is needed at the sutures in order to create the necessary space for the expanding brain. The main role of sutures is to ultimately permit brain growth by coordinating skull expansion in the presence of a developing brain. Suture patency is therefore critical at this stage of life [10].

Craniosynostosis, defined as the premature closure of one or more of the cranial vault sutures, results in a variety of associated skull and subsequent facial deformities secondary to skull growth restrictions that may severely impact on child wellbeing, potentially increasing ICP, commonly resulting in visual disturbances, frequent headaches and learning developmental delays. In addition, the inability of the skull to create the adequate space for brain growth by expanding perpendicularly to the fused sutures results in a compensatory expansion of the cranial vault in a direction parallel to these sutures, with a compensatory overgrowth at other suture sites, progressively rendering an abnormal head shape. The head shape will be a product of the direction and number of the affected sutures, together with the order and timing in which these sutures synostosis. Craniosynostosis can be expressed as an isolated clinical feature, or in association with other clinical features, as a part of about 100 syndromes. Patients with syndromic craniosynostosis are much more complicated than isolated cases, requiring a multidisciplinary team to treat all their problems effectively. Crouzon syndrome (CS) is an example of such group, and accounts for approximately 4.5% of all cases of craniosynostosis [11,12].

Clinically, CS varies greatly in range and severity from case to case, including among the affected family members. However, in most affected infants, the facial and ocular abnormalities typically include protrusion of the eyeballs (proptosis) due to shallow orbital cavities; outward deviation of the eyes (exotropia); widely spaced eyes (hypertelorism); and a small, underdeveloped upper jaw (hypoplastic maxilla), with protrusion of the lower jaw (relative mandibular prognathism) [13,14].

Other reported anomalies of CS include overcrowding of teeth; narrow, high arched palate or cleft palate, bifid uvula; low set ears, pinna defects, narrow or absent ear canals, deformed middle ears, congenital otosclerosis, with conductive deafness. Approximately one-third of patients with CS suffers from hearing loss [15]. Optic atrophy has been reported in 30 to 80% of patients [16]. Some patients with CS may present with headache and seizures because of the raised ICP secondary to the early closure of cranial sutures. Approximately 73% of patients have chronic tonsillar herniation, of these, 47%intervention has been recommended [17]. Mental retardation has been reported due to the premature closure of the cranial sutures which may impair brain development [16]. Cervical fusions are present in approximately 18% of patients (C2-C3 and C5-C6 are equally affected) [18].

In our study, the typical facial appearance characterized by shallow orbits with proptosis, hypertelorism, parrot-beaked nose, hypoplastic maxilla, and relative mandibular prognathism (“crouzonoid” facies), was present in all cases. All patients had proptosis of different severity. The most severe degree of proptosis was evident in case 1 in whom the orbital CT revealed extremely shallow bony orbits (both globes were nearly outside the two orbital cavities), and was associated with undeveloped eyelids, chemotic conjunctiva with subconjunctival hemorrhage, and exposure Keratopathy which is evident in Figure 1. Proptosis was associated with bilateral corneal scarring in case 2 and with V-pattern exotropia in cases 2, 3 and 4 (Figures 2-4). Four patients had a high arched palate and 3 had dental anomalies. Two patients had mental retardation of different severity. Two patients had hearing loss. Radiologically, 3 cases had synostosis of all cranial sutures, 2 cases had synostosis of the sagittal and coronal sutures, and one patient had cervical synostosis.

Upper and lower respiratory tract obstructions may present in patients with CS. Nasal septal deviation, coanal atresia or stenosis, nasopharyngeal narrowing may cause respiratory obstruction [19,20]. The respiratory problems may also be related to the tracheal abnormalities. Complete cartilaginous trachea is very rare and is always associated with craniosynostosis syndromes [21]. In our study, 2 patients (cases 1 and 2) had respiratory tract anomalies. One patient (Case 1) died because of severe upper and lower respiratory tract obstruction, associated with other congenital cardiac and cerebral anomalies.

The diagnosis of CS in our study was based on clinical, facial, dental, ophthalmological, and radiological features. The combination of craniosynostosis, especially of the sagittal and coronal sutures; typical facial features; and lack of hand/foot anomalies (Syndactyly) would strongly suggest the diagnosis of CS; and also, helps to distinguish CS from other conditions which may have similar facial appearances such as Apert syndrome (Acrocephalosyndactyly), Pfeiffer, and Jackson-Weiss syndromes [22]. Syndactyly was absent in all patients in our study. The diagnosis of CS can also be confirmed by the finding of a mutation in the FGFR2 gene. With the advent of molecular technology, the gene for CS could be localized to the fibroblast growth factor receptor II gene (FGFR 2) at the chromosomal locus 10q 25.3-q26, which results in the early fusion of the skull bones during the development of the fetus. More than 30 different mutations within the gene have been documented in separate families [4-6].

Patients with CS are often best cared for by a team of craniofacial experts, including, oromaxillofacial surgeon, plastic surgeon, neurosurgeon, neuroradiologist, Craniofacial anesthetist, clinical Geneticist, pediatric ophthalmologist, dentist, otolaryngologist, psychologist, and Speech therapist; so that, various problems can be comprehensively addressed. The goal of treatment is to stage reconstruction to coincide with facial growth patterns, visceral function, and psychosocial development. Early craniotomy with frontal bone advancement is most often indicated to prevent or treat increased ICP; front-orbital and midfacial advancements help in the cosmetic reconstruction of facial dysmorphisms; shunting procedures for hydrocephalus; tracheostomy for airway obstruction; myringotomy for drainage of middle ear secretions secondary to distorted nasopharynx; and orthodontic management [23-29]. No cosmetic craniofacial operations had been done for the patients in our study.

Prognosis in patients with CS depends upon the cranio-malformation severity and the associated congenital anomalies in other systems. Craniosynostosis can result in brain compression and mental retardation in severely affected patients unless the increased ICT is relieved by early craniotomy. High ICT may lead to death. Optic nerve compression may lead to optic atrophy and blindness. Visual impairment can also result from corneal exposure due to severe proptosis (Exposure keratopathy and corneal opacity or scarring). Conductive deafness is common because of ear canal stenosis or atresia. Airway obstruction can lead to acute respiratory distress [19-21]. In our study, one patient died because of the associated severe respiratory, cardiac and cerebral anomalies; one patient was bilaterally blind because of corneal scarring and optic atrophy; 2 patients were mentally retarded, and 2 patients had conductive deafness.

Conclusion

CS can present with different clinical manifestations involving the skull, orbits, and eyes. The clinical and radiological findings vary in severity from mild presentation with subtle manifestations (like cases 4 and 5), to severe form with marked midface, brain, orbital, and eye complications (like cases 1, 2 and 3). Management of patients with CS requires a multidisciplinary approach, by a team of craniofacial experts. Early surgical intervention is highly recommended in many patients with CS. Early diagnosis and prompt treatment, not only provides good cosmetic and functional results but also prevent the dangerous complications of increased ICP and visual loss in the majority of those children

Declaration

Ethical approval

The study had been approved by the Health Research Ethics Committee. Informed consent was obtained from all parents of children who participated in this study. Also, they agreed on the use of clinical photos of their children for research and publication in the literature. All consent forms signed by the parents were written in Arabic (The main people language in Egypt).

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