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REVIEW: A Review on Different Manifestations of Crouzon Syndrome

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ABSTRACT

Introduction: Crouzon syndrome (CS), the most common craniosynostosis condition, which could lead to several developmental complications. This study aimed to review the different manifestations of CS.

Material and Methods: In order to find the relevant articles, the databases of PubMed, Scopus, Web of Science, and Cochrane Library were searched using the term “Craniofacial Dysostosis” and its relevant entry terms. All English-language articles regarding the CS were included in the study. After removing the duplicate articles, two authors independently screened the title and abstracts of the included articles. Disagreements were resolved through voting and discussion with the third author. Then full-text of articles were screened and the articles were categorized depending on regarding their main topic.

Results: The search yielded 449 results in different databases. After removing the duplicates, 331 results remained. Then, 182 were excluded as not completely relevant by screening the abstracts. The remaining 149 studies were assessed for the eligibility criteria. Of them, 74 were excluded due to the following reasons: (1) unavailable full text; (2) discussing other types of craniosynostoses syndromes; and (3) not having clear results. Finally, 75 studies which were included in this study.

Conclusion: CS is caused by mutations in the FGFR2 gene and is inherited in an autosomal dominant pattern. Diagnosis is based on the characteristic physical features, as well as imaging studies and genetic testing. Treatment involves surgery to correct the craniosynostosis and facial abnormalities. Early and appropriate treatment can help to improve the quality of life for affected individuals.

Introduction

Craniosynostosis is a condition that affects the growth of the skull bones in infants and children. The condition occurs when the cranial sutures fuse prematurely, leading to abnormalities in the shape and size of the skull. Craniosynostosis can occur as an isolated condition or as part of a syndrome (1, 2). There are various types of craniosynostosis syndromes, including Apert, Crouzon, Pfeiffer, Carpenter, Saethre-Chotzen, and Jackson-Weiss syndromes (3). Crouzon syndrome (CS), the most common craniosynostosis condition, is a rare genetic disorder with a prevalence of approximately

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one in 25,000 to 60,000 live births, which affects the development of the skull and face (4). The condition is caused by mutations in the fibroblast growth factor receptor 2 (FGFR2) gene, which is involved in the development and maintenance of bones and other tissues in the body. CS is inherited in an autosomal dominant pattern. In some cases, however, the condition can arise spontaneously due to new mutations in the FGFR2 gene (5-7). The characteristic features of CS include craniosynostosis, which leads to an abnormally shaped skull, and facial abnormalities such as bulging eyes, a small upper jaw, and a beaked nose. Children with CS may also have dental problems, hearing loss, and developmental delays (8-10).

The diagnosis of CS is made based on the characteristic physical features of the condition, as well as imaging studies such as X-rays, CT scans, and MRI scans. Genetic testing can also be performed to confirm the diagnosis and identify the specific mutation in the FGFR2 gene (11, 12). Treatment for CS involves surgery to correct the craniosynostosis and facial abnormalities. The goal of surgery is to improve the appearance of the face and head, as well as to alleviate any neurological symptoms that may be present. Surgery may also be necessary to correct dental problems and hearing loss (13-15).

Early diagnosis and appropriate treatment of CS can help to improve the quality of life for affected individuals. It is important for individuals with CS to receive ongoing medical care, including regular monitoring and treatment of any associated conditions (16). This study aimed to provide information on different manifestations of CS.

Methods

In order to find the relevant articles regarding CS, the English-language papers published until January 21, 2023 were searched by two authors in the databases of PubMed, Scopus, Web of Science, and Cochrane Library. Related terms were searched in the Medical Subject Headings (MeSH) database, and finally, the term “Craniofacial Dysostosis” and its relevant entry terms were selected as the main search keywords.

All English-language articles regarding the CS were included in the study. The following articles were excluded: reviews, case reports, editorials, guidelines, letter to the editors, and abstracts from conferences; articles not written in English; duplicate articles; articles with no available full text; and articles regarding other craniosynostoses syndromes.

After removing the duplicate articles, two authors independently screened the title and abstracts of the included articles. Disagreements were resolved through voting and discussion with the third author. Then full-text of articles were screened and the articles were categorized depending on regarding their main topic.

Results

The search yielded 449 results in different search engines/databases of PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar. After finding and removing the duplicates, 331 search results remained. After screening the abstract of these 331 articles, 182 were excluded as not completely relevant. The remaining 149 studies were assessed for the eligibility criteria. Of them, 74 were excluded due to the following reasons: (1) unavailable full text; (2) discussing other types of craniosynostoses syndromes; and (3) not having clear results. There remained 75 studies which were included in this study.

Genetics

The function of fibroblast growth factor receptor (FGFR) mutations in the etiology of some eponymous forms of craniosynostosis is now well understood. The most prevalent syndromes associated with craniosynostosis are Pfeifer (FGFR1, FGFR2), Apert (FGFR2), Crouzon (FGFR2), Saethre–Chotzen (TWIST1), Jackson–Weiss (FGFR2), Greig (GL13), and Muenke (FGFR3) (17). CS is an autosomal-dominant inherited craniosynostosis condition caused by heterozygous mutations in the FGFR2

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gene (18-21). FGFR2 is a transmembrane tyrosine kinase that corresponds to the 10q26 gene. Three extracellular immunoglobulin (Ig)-like domains (IgI, IgII, and IgIII), a single transmembrane segment, and a split tyrosine kinase (TKI/TKII) domain make up this protein (22, 23). Exons 8 (IIIa) and 10 (IIIc), which encode the extracellular Ig-like III (IgIII) domain of the receptor, are mutated in about 95% of CS patients (20, 21, 24, 25). Growth factors such as fibroblast growth factor (FGF) and transforming growth factor (TGF) are important regulators in cell growth and differentiation process. Increased ligand affinity and altered ligand specificity can result from FGFR2 mutations, affecting mesenchymal stem cell differentiation and hence causing developmental abnormalities (24, 26).

Form of cranial fossa

The most common shapes of skull in patients with CS are brachycephalic and scaphocephalic. Trigonocephalic and triphyllocephalic (cloverleaf skull) forms are less common (27). Hydrocephalus is one of the complications related to CS. The incidence of hydrocephalus in craniosynostosis is reported as 4%. Hydrocephalus may result in ventricular dilation through constriction of subarachnoid spaces by the premature fusion of the sutures (28). Chiari type I malformation (CM-I) is another manifestation that may be seen in CS patients as a result of missense mutation in FGFR2 gene. It has been reported that the premature fusion of cerebral sutures may be the mechanism leading to the development of CM-I in patients with syndromic craniosynostosis (29).

A chronic tonsillar herniation is another important complication in patients with CS. It was assumed that the pathophysiology underlying the development of this condition is related to the jugular foramen stenosis and the subsequent increased sagittal sinus pressure and venous turgor of the brain. Following this problem, CSF absorption gets defected and results in hydrocephalus (30). Tonsillar herniation is more likely to occur in patients with a lumbar shunt who have some degree of cephalocranial disproportion (31).

A different form of craniosynostosis has been reported which is progressive postnatal. Patients with progressive craniosynostosis mainly had mutations in exon 7 or 9 of FGFR2 which is a common site of CS mutations. The affected individuals have a normal skull shape and open sutures in infancy but develop multiple-suture craniosynostosis postnatally, which requires surgical correction. These cases are important because the patients do not initially display physical manifestations of craniosynostosis, but eventually develop increased intracranial pressure which can have harmful consequences. Because elderly individuals have more time to grow, they present a higher percentage of anterior fontanelle bulging, papilledema, and thumbprinting. These symptoms are also used for monitoring patients and preventing further outcomes (32).

In a study by Caplan et al., encephalocele has been reported as a late complication of frontal bone reconstruction for craniosynostosis, which was successfully managed (33). The histopathologic features of the skull in patients with CS show hemangiomatous anomaly of bone. The reason, however, needs to be further studied (34).

Airway

Airway obstruction has been reported in approximately 40% of cases with severe craniosynostosis syndrome. The clinical presentation of the airway obstruction in these patients ranges from loud snoring and noisy breathing to frank respiratory distress. CS is more frequently associated with severe airway obstruction than other craniosynostosis syndromes. Cephalometric studies of patients with CS have shown a decrease in nasopharyngeal dimensions. Factors contributing to airway obstruction in CS include midface hypoplasia, adenoid and tonsillar hypertrophy, laryngotracheomalacia, choanal stenosis or atresia, intrinsic lung problems, and neurological problems. In addition, absent pulmonary valve syndrome

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has been reported as the cause of airway obstruction in these patients. The long-term consequences of severe airway obstruction are failure to thrive, feeding difficulties, developmental delay and recurrent respiratory infection. Airway obstruction can also make emergency airway management difficult (35-37). Facial appearance improvement, a possible malocclusion correction, and severe obstructive sleep apnea are the reasons for performing orthognathic surgery in patients with CS. Airway management in CS during the surgery is crucial, thus a correct pre-anesthetic assessment and planned preinduction strategy should be designed to make intubation easier (38).

Ocular manifestations

In CS patients, the floor and the lateral border of bony orbit are both retruded in sagittal plane. However, the orbit's height is higher than normal. Interorbital distances are increased in the transverse plane (39). Ocular manifestations observed in CS patients in different studies include proptosis secondary to shallow orbits, glaucoma, lagophthalmos, hypertelorism, globe subluxation, coloboma, diffuse thick blebs with no leakage, hazy corneas with band keratopathy and exposure, shallow and quiet anterior chambers, posterior synechiae, cataract, flat retina, hyperopia, hypotropia, hypertropia, myopia, increased intracranial pressure, optic edema, papilledema optic nerve hypoplasia, idiopathic orbital inflammatory syndrome, conjunctivitis, visual loss, keratitis, ptosis, nystagmus, strabismus, and amaurosis (39-50). It is worth noting that vision loss can occur suddenly in the absence of other symptoms of intracranial hypertension (51).

There have also been some reports of anomalies in ocular muscles of CS patients, such as anomalous extraocular muscles, bilateral inferior oblique overaction, unilateral congenital absence of the inferior rectus muscle, agenesis of extraocular muscles, absence of the superior and inferior rectus and the oblique muscles. Hypertrophy of the horizontal muscles and extraocular muscle hypoplasia were also reported (41, 44, 47, 52, 53).

Dental phenotype

Although the majority of CS patients have oligodontia, hypodontia, or partial anodontia, supernumerary teeth have been identified in few cases (54-57). These patients may have malposed teeth or teeth that are not structurally normal, such as peg-shaped teeth or macrodontia (54, 55, 58). When compared to a healthy patient, the patient with CS exhibited reduced calcium levels and higher phosphorus, cadmium, and magnesium levels in enamel. Lower calcium, phosphorus, and magnesium levels were found in the dentine, with greater cadmium, lead, iron, sodium, and strontium levels. The calcium-to-phosphorous ratio was found to be considerably lower after statistical analysis. Because the tissues are of poorer quality, they may be more easily demineralized and worn away during physiological dental processes (59). Another characteristic noticed in a large proportion of individuals is Class III malocclusion with or without maxillary crowding (54, 55, 58, 60). In fewer cases, anterior open bite, negative overjet, crossbite, and an increase in interdental space have been documented (54, 59, 60).

Radiographic features

Over the years, several imaging methods have been proven to be useful in radiographic assessment of CS patients. Three-dimensional computed tomography (CT) can help evaluate congenital malformations of the brain as well as the surgical approach and postoperative assessment of craniofacial anomalies in children. When CS patients were examined using this method, different observations were made such as different synostoses, exophthalmos, midfacial retrusion, asymmetrical calvarium thickening, and diffuse indentation of the inner table of the skull (3, 12, 61-63). Some features such as abnormally shaped cranium, increased interorbital distance, ocular proptosis, and mild ventriculomegaly could be observed in sonographic examinations during second trimester of pregnancy (64). Lateral, antero-

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posterior, and posteroanterior radiographs of skull could be useful in observation of shallow orbits, depressed nasal bridge, hypertelorism, copper beaten skull, uneven calvarial thickening, and the absence of coronal and lambdoid sutures (3, 62, 65). Decreased intervertebral space between C5 and C6 vertebrae was seen in anteroposterior spine radiograph of a CS patient in a study by Mohan et al. (63). Panoramic images are also helpful to assess the size of jaws and the presence of deciduous and succedaneous teeth (3, 63, 65).

Comorbidity with acanthosis nigricans

Acanthosis nigricans is a rare dermal disease, characterized by pigmented hyperkeratotic patches in body folds area. In older studies the association between acanthosis nigricans and CS was not clear (66, 67). Acanthosis nigricans can be seen in different clinical settings such as syndromic, obesity-associated, inherited, para-neoplastic, drug-induced and mixed conditions (68). In recent years it has been specified that CS with acanthosis nigricans is resulted by the pathogenic variant c.1172C>A (p.Ala319Glu) in the FGFR3 gene (69). CS with acanthosis nigricans (CAN) is different from CS and it is considered an independent clinical entity (70). CAN is autosomal-dominant with a paternal age effect. The crouzonoid features usually are the first recognized features. A choanal atresia is commonly seen and significantly indicates CAN. Symptoms related to the acanthosis nigricans in 80% of the cases presented at the first decade. These symptoms always present before puberty and their pattern is not limited to the body folds. Important systemic conditions especially those involving the kidney must be recognized early.

An uncommon subtype named Crouzono-dermoskeletal syndrome (CDSS) has been introduced based on clinical and molecular findings, which is characterized by acanthosis nigricans, vertebral anomalies and dental cementomas. Additional features are hydro-cephalus, choanal atresia and minor skeletal changes (71). CDSS consists 1-2% of all craniosynostosis syndromes. It has a female predominance but the manifestations are identical in both genders. CDSS is different from classic CS, but shares some phenotypic features such as bilateral coronal craniosyn-ostosis, midfacial hypoplasia, exophthalmos, parrot beak nose, mandibular prognathism, and posteriorly angled ears (72).

Psychosocial

CS patients do not have psychosocial issues until physical symptoms develop (55, 73). Although the exact age of development of the condition is unknown, symptoms typically appear in childhood (74). Children with the syndrome are socially isolated, mocked at school, and abused because of their appearance (75). Children's desire to continue their education and participation in the society has been noted in some cases, and they have become isolated persons who prefer to have limited contact with others at home (55, 75). The family, particularly parents, are the most influential people in preventing negative repercussions. Parents can instill self-assurance and support in their children. Some of the suggested solutions include public awareness, early start of psychotherapy sessions, and enrollment in special schools (75). Early diagnosis and performing any therapeutic or cosmetic interventions (due to the child's primary difficulties) have been found to enhance the psychosocial status of these children, allowing them to socialize and communicate more effectively than untreated children (55, 58, 73). For example, an ear prosthetic, had a major impact on the mental health and quality of life of a patient who had lost his hearing and had an abnormal anatomy in his ear (58).

Conclusion

In conclusion, CS is a rare genetic disorder that affects the development of the skull and face. The condition is caused by mutations in the FGFR2 gene and is inherited in an autosomal dominant pattern. Diagnosis is based on the characteristic physical features of the condition, as well as imaging studies

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and genetic testing. Treatment involves surgery to correct the craniosynostosis and facial abnormalities. Early and appropriate treatment can help to improve the quality of life for affected individuals.

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Conflicts of Interest

None to declare.

Authors' Contribution

Design: N.S. and M.A.; Search: M.A.; Data extraction: N.S., A.L., A.M., I.M.T., and M.A.; First draft: A.L., A.M., and I.M.T.; Final revision: N.S. and M.A.; supervision: M.A. All authors read and approved the final version of the manuscript.

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