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Crouzon syndrome: Genetic and intervention review

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ABSTRACT

Crouzon syndrome exhibits considerable phenotypic heterogeneity, in the aetiology of which genetics play an important role. *FGFR2* mediates extracellular signals into cells and the mutations in the *FGFR2* gene cause this syndrome occurrence. Activated *FGFs/FGFR2* signaling disrupts the balance of differentiation, cell proliferation, and apoptosis via its downstream signal pathways. However, very little is known about the cellular and molecular factors leading to severity of this phenotype. Revealing the molecular pathology of craniosynostosis will be a great value for genetic counselling, diagnosis, prognosis and early intervention programs. This mini-review summarizes the fundamental and recent scientific literature on genetic disorder of Crouzon syndrome and presents a graduated strategy for the genetic approach, diagnosis and the management of this complex craniofacial defect.

1. Introduction

Craniosynostosis is a birth defect characterized by premature fusion of one or more of the calvarial sutures before the completion of brain growth and development, leading to restricted growth of the skull, brain, face and central nervous system development. More than 100 craniosynostosis syndromes have been reported with an estimated birth with an incidence of 1:2500 live births.[1] Among craniosynostoses, the syndromic craniosynostoses are valued to comprise 15% of all cases. To date, there are over 180 craniosynostosis syndromes identified. About 8% of cases are familial or inherited.[2]

Crouzon syndrome (CS) is the most frequently seen syndromic. It is related to multiple fibroblast growth factor receptor 2 (*FGFR2*) mutations.[2] *FGFR2* belongs to a family of four FGFR. *FGFR1* to *FGFR3* have a signaling function in cranial sutures and play a crucial role in embryonic development of the limbs.[3] This syndrome was first reported by Louis Edouard Octave Crouzon in 1912 when a triad of calvarial deformities with craniofacial dysostosis, exophthalmos and facial anomalies was defined in a mother and her son.[4]

Crouzon syndrome occurs in approximately 16.5 cases per million live births (1: 60,000).[5] It is considered the most common craniosynostosis syndrome as it represents approximately 4.8% of all craniosynostosis cases at birth. It has an autosomal dominant inheritance pattern, but variable expressivity and incomplete penetrance are known. CS commonly starts at the first three years of life.[4] Craniosynostosis can be suspected during antenatal stage via ultrasound scan otherwise is often detected at birth from its classic crouzonoid features of the newborn. The crouzonoid features include craniosynostosis, midface hypoplasia, proptosis and, in a few cases, a beaked nose. One of the cases stated at birth was described by Gopal et al., in 2017, where all the features of craniosynostosis as well as feature of ocular proptosis was reported with the presence of pseudocleft, enlarged ears without hearing loss and a shallow nasal septum without any deviation.[5]

The frequent manifestation of CS includes coronal craniosynostosis with other cranial sutures fusion, brachycephaly, hypertelorism, frontal bossing, strabismus, orbital proptosis mandibular prognathism and maxillary hypoplasia. These features either become more prominent or may regress over time. Hearing loss is common (55%) and there is 30% incidence of C2 and C3 spinal fusion.[6] Other manifestation could be progressive hydrocephalus (30%), often with tonsillar herniation and sacrococcygeal tail. Extremity and mental capacity are usually normal in these patients. However, when the premature closure of the cranial suture lines impairs brain development due to persistent increased intracranial pressure (ICP) it can lead to mental retardation.[7] Differential diagnosis of CS includes Apert syndrome and Pfeiffer syndrome. Apert syndrome will have all the manifestation that will be seen in CS except for the syndactyly of hands and feet. However, Anderson in 1998 reported that CS phenotypes exhibit hand dysmorphogenesis and their

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contention that overlap may exists between CS and Apert syndrome. In case of Pfeiffer syndrome, broad big toes, broad thumbs with partial and variable syndactyly will be presented in addition to the features of CS.[8,9] Although Crouzon and Pfeiffer syndromes have historically been considered as distinct conditions, recent genotype-phenotype studies had shown them to have a closely overlapping spectrum of FGFR*2* mutations, suggesting these two conditions to be a continuum.

2. Genetic disorder

As CS does not affect intellectual abilities and reproductive fitness, 70% of CS patients have an affected parent while the others are due to de novo occurrences. In about 50%–60% of cases, a mutation usually acting through a gain-of-function mechanism, can be identified.[10] A person affected by CS has a 50% chance of passing the defective gene to offspring. A negative *FGFR2* study does not exclude clinical diagnosis of CS.

Typical phenotypic characteristics of CS are cranial synostosis and brachycephaly, hypertelorism, low set ears and orbital proptosis. Such abnormalities vary greatly in severity, ranging from mild to severe. Apart from having poor vision that can be caused by increased ICP, optic nerve damage and direct insult to the corneal surface, sudden visual loss in syndromic craniosynostosis children such as in Apert and Crouzon syndrome has been reported.[11] The degree of impairment of the visual system depends upon the severity and combination of ocular abnormalities present. It is also important to be aware of the late-onset pansynostosis of CS, which occurs occasionally, because the slight distortion of the skull shape may disguise the presence of raised ICP.[5,9,12]

Phenotypically, CS is the mildest form of the *FGFR2*-associated disorders.[9] Nucleotide alterations causing amino-acid substitutions (c.1030G > C (Ala344Pro)) at the FGFR2 gene on chromosome 10q25 − q26 lead to the Crouzon phenotype. Approximately 95% of 50 different mutations of CS cases having mutations in just two exons of the gene immunoglobulin-like III (IgIII) [IgIIIa (8) and IgIIIc domains (10)] that encode the extra-cellular IgIII domain of the protein.[13] These mutant dimers, pathologically increased tyrosine kinase activity, are FGF ligand independent. Differences in glycosylation and intracellular trafficking could result in tissue specificity of the mutations. In this syndrome, the IgIII domain mutations Cys342Ala and Cys278Ala showed highly alteration in transformation activity assay. Sharma et al., in 2012 reported that Cys62Ala mutant was moderately transforming, which indicated that mutations of the IgI domain could also be activating.[14] Furthermore, Oldridge et al. presented mutations associated with CS, also in the upstream exon of third immunoglobulin domain that expressed in both tissue isoforms.[15] Acanthosis nigricans is caused by the mutation of A p. Ala391Glu FGFR3, which share craniofacial abnormalities with classic CS All CS patients with associated acanthosis nigricans, have the pathogenic variant c.1172C > A (p.Ala391Glu) in the *FGFR3* gene. Unless a FGFR2 mutation is found, a p. Ala391Glu FGFR3 mutation must be assumed and tested for.[16,17]

No clear link between phenotype and genotype has been identified yet.[18] Phenotypic variability is depending on genetic homozygosity. Increasing homozygosity may be responsible for more severe phenotypic expression.[19] A family with a mild phenotype, in which the *FGFR2* mutation c.943G > T result in substitution of the amino acid p. Ala315Ser, was also detected by Graul-Neumann and his coworker.[18] A mutation that has been identified just recently, c.812G > T, (p.Gly271Val) or c.1851G > C, (p.Leu617Phe) was described. This novel mutation arose de novo which resulted in craniofacial characteristics resembling Pfeiffer/Crouzon syndrome.[20] Recently in 2017, Driessen and his co-worker revealed that the sign and symptoms of CS depends on the rate and order of progression of sutural synostosis. They showed patients with CS and premature closure of the spheno-occipital synchondrosis (SOS) have more severe obstructive sleep apnea (OSA) and maxillary hypoplasia.[21]

Clarification of a genetic lesion has a significant benefit in providing accurate prenatal diagnosis. The underlying genetic aetiology study of craniosynostosis syndromes has evidently provided targets for non-surgical treatment for craniosynostosis. Recently, the understanding of molecular and biochemical signaling specifically of the *FGFR* play a vital role in the investigation of potential pharmacologic and genetic therapy that specifically suppress the activation of these pathways which in turn might be helpful for the treatment of syndromic craniosynostosis patients.[22,23] One study showed that, early union of sutures mediated by Crouzon-like activated FGFR2c mutant using genetically modified mice is prohibited by mitigation of signaling pathways by selective uncoupling among the docking protein Frs2alpha and activated FGFR2c, eventually, led to normal skull expansion and growth.[24] Continuous research and development of gene therapy in the field of craniosynostosis is highly desirable which give to the potential of nonsurgical treatment as well as expanding the exploration of new biotechnologies.

3. Functional issues associated with CS

There are three major functional issues associated with CS namely increased ICP due to lower cranial vault capacity, eye protection disability secondary to severe orbital proptosis and OSA secondary to maxillary hypoplasia.[25] Severe OSA can lead to respiratory depression and life-threatening breathing complications while mild to moderate degree of OSA can create significant problems such as daytime sleepiness, disturbed sleep, inability to concentrate thus affecting the child's developmental growth. Deafness consequence of failure to transmit neural signals to the brain could be present. These issue can be ranged from mild to moderate and it could be asymptomatic or symptomatic based on severity and specific functional component combined.

4. CS diagnosis and investigation

Crouzon syndrome is usually diagnosed during labour or in the antenatal period thorough clinical evaluation, physical assessment, and a diversity of specialized tests. Experienced obstetrician and ultrasonographer may also identify the early sign of premature cranial sutures closure throughout detailed 3 dimensional (3D) or ultrasound scanning procedure.

Wilkie et al., in 2007 proposed protocol of a molecular genetic for the diagnosis of CS which was include the 1st line tests of *FGFR2*-exons IgIIIa, IgIIIc followed by the 2nd line tests of *FGFR2*-exons 3, 5, 11, 14-17; *FGFR3*-Pro250Arg, Ala391 Glu.[26]

Clinically, malformation of the cranium with ocular proptosis and shallow eye sockets are diagnostic features of CS. Ocular proptosis, a feature occurring in 100% of the cases, is secondary to shallow orbits and results in a high incidence of exposure conjunctivitis or keratitis.[5]

Plain film radiography and computed tomography (CT) scan may also help in the diagnosis and evaluation of CS.[27] Enlarged hypophyseal cavity, copper beaten appearance, mandibular prognathism and maxillary hypoplasia can be seen from a lateral skull plain radiograph. The degree of hydrocephalus and detailed image of diffuse depression of the inner table of the skull could be identified by brain CT scan. This can also be used for creating a 3D biomodel for the definite structural assessment, pre-surgical planning and pre-operative surgical procedure simulation.[28]

5. Treatment and care

The treatment of CS is based on the severity of functional and appearance-related needs. Comprehensive assessment by multidisciplinary craniofacial team is necessary for optimization of care.

Intracranial assessment can be done via CT scan, plain film radiography or magnetic resonance imaging (MRI). Cranial bone thinning may give rise to the high index of suspicious to raised ICP. Clinical ophthalmological assessment and other tests which include fundoscopy

and optic nerve evaluation are paramount for eye function preservation. Respiratory problems would necessitate nasoendoscopy to evaluate the nasopharyngeal airway, and polysomnography for OSA if indicated.

5.1. Acute management

Increased ICP with hydrocephalus would need Ventriculoperitoneal (VP) shunts, severe exorbitism may indicate temporary tarsorraphy, and breathing difficulty would necessitate either a tracheostomy or continuous airway pressure device or nasal stent depending on the specific anatomical obstruction and severity of it.

5.2. Surgical management

Surgical intervention of the malformations of the skull in CS can be done as staged or combined based on how severely and functionally the syndromic patients are affected according to their age. For instance, increased ICP could be treated by posterior cranial vault expansion. However, if its combined with orbital proptosis or/and maxillary hypoplasia it may need for fronto-orbital advancement (FOA) with or without cranioplasty or a Monobloc (fronto-orbital and midface) or Le Fort III advancement for a more complex deformity.[25,29,30] Surgery can be done conventionally or together with distraction osteogenesis (DO) technique, indicated for superior structural expansion. Asymptomatic CS patients may undergo orthodontic treatment with or without orthognathic surgery to correct malocclusion and jaw discrepancy upon completion of growth and maturation.

5.3. Genetic counselling and psychosocial support

As CS is a genetic condition with a variable phenotype. A detailed history, family tree and, physical examination of the patient and the parents are important proceedings for making a clinical diagnosis. Furthermore, genetic counselling and information are essential components of care for parents who has an infant with CS. In patients with atypical presentation or parents wishing to have prenatal diagnosis, genetic testing of the index case can be done. Limitations of the genetic testing, including the possibility of a negative pathogenic report or the finding of a variant of unknown significance, must be discussed. Psychosocial support for the family and helping them to come to terms with their child's condition are vital in empowering the families to maximize the child's potential.

6. Complications and relapse

The complication and stability of the result are depending on the complexity of the case, age of the patient, type and number of the surgical technique. Previous operations increase intra-operative issues such as structural deficiency and presence of fibrous tissues. The choice between DO technique over traditional conventional surgery should be made based on the amount of movements and anticipated structural relapse.[31] Complications of surgical interventions include mortality, cerebro-spinal fluid (CSF) leak, intra-operative bleeding, wound infection, post-operative visual loss, distraction device failure and relapse, among others. Nevertheless, these complications are minimal and can be prevented with comprehensive intra-operative surgical assessment, planning and execution.

7. Conclusion

Considerable progress has been made in understanding the cellular and molecular basis of CS. However, the degree of genetic disturbance and how it makes the disorder classified is still not well understood. Genetic phenotype study and genetic evaluation is necessary to determine the degree of complexity and to guide management, genetic counselling and intervention in CS.

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Conflicts of interest

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