Craniosynostosis:

An Ambiguous Cause to a Prevalent Problem

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Abstract

Craniosynostosis, a birth defect involving the pre-mature conjoining of sutures of one’s skull that results in craniofacial deformity, and possibly cognitive impairment. This review explores five scientific research articles that state results pertaining to the causes and treatments of craniosynostosis. These articles provide various suggestions for identifying and treating craniosynostosis such as: genetics, pre/post-natal development, and reconstructive plastic surgery. Although this research is backed by extensive findings, there still lies an ambiguity behind the exact cause of craniosynostosis, and, therefore, it cannot be prevented in future cases. In spite of the significant improvements in reconstructive plastic surgery, this process continues to display dangerous results that in rare cases may cause death. The purpose of this review is to analyze the possible causes and treatments of craniosynostosis, and to suggest that all probable causes play a factor in the abnormal development of an affected individual’s skull; it also offers suggestions for future treatment that may replace surgical treatment.

Introduction

Craniosynostosis is a birth defect involving the pre-mature conjoining of sutures of one’s skull that results in craniofacial deformity, and possibly cognitive impairment. Numerous studies (Panigrahi, 2011; Andrew et al., 2010; Heather et al., 2010; Nathaniel et al. 2010; Marie, Coffin, & Hurley, 2005) were conducted regarding patients, particularly children, diagnosed with craniosynostosis. These studies examined the possible causes that could have instigated this craniofacial anomaly. Although there is no clear deficiency that correlates directly with the source of craniosynostosis, there is evidence of genetic defects and dysfunctional pre/post-natal development within some craniosynostotic children. For instance, in these studies it was found that craniosynostotic children had an abnormal FGFR gene (fibroblast growth factor receptor) (gene affecting cranial development) and a defective TWIST gene (another gene affecting cranial development). Yet, the parents and siblings of these children provided no evidence of genetic abnormalities. For children without genetic deficiencies, their pre/post-natal development was observed. In fact, the conductors of one study (Nathaniel et al., 2011) noticed that abnormal head positioning in a woman’s utero or in infancy produced an abnormal skull shape.
Craniosynostotic children have no clear-cut diagnosis pertaining to their craniofacial deformities. Is it genetics? Were they positioned incorrectly? And equally important, how can it be fixed? Not only does identifying the cause of craniosynostosis deserve recognition, but also methods of treating (correcting) these deformities. Currently, the only treatment available for these affected patients is plastic reconstructive surgery, which is substantially pain-inducing, and may cause severe mental consequences, or in rare cases, death. Considering all possible causes, treatments, and outcomes, this review was written to identify the most rational cause and treatment of craniosynostosis. First off, this research review will investigate the genetic aspect of craniosynostosis, specifically FGFR & TWIST, then explore pre/post-natal development, and finally examine methods of treatment.

Genetic Defects (FGFR & TWIST)

A gene is an inherited characteristic of an individual’s genetic make-up passed down through generations. The human body is estimated to contain 20,000-100,000 genes, and each of these genes contains a specific sequence of proteins that basically shapes the entire body, some of which determine the physical appearance. Two major genes affecting the structure of the human body are FGFR (fibroblast growth factor receptor) & TWIST; these genes play a key role in cranial development. For instance, in one study (Andrew et al., 2011) it was found that fifty-seven percent (n = 84) of the craniosynostotic children had an abnormal FGFR gene and nineteen percent contained a defective TWIST gene. However, it was also found that these affected children’s parents carried no evidence of defective FGFR & TWIST genes. These scientific researchers conducted the experiment by drawing samples of blood from each craniosynostotic child and their immediate family (parents & siblings). With this study the researchers proved that chromosomal (genetic) abnormalities caused craniofacial dystopia (in some individuals), but it also proved that the cause is multifactorial. This also contradicts the very definition of a gene. If a gene is an inherited characteristic, then why were these children’s FGFR & TWIST genes different?

In addition to genetic defects and inheritance, the possibility of passing down craniosynostosis should also be observed. Nathaniel et al. (2011) followed 29 individuals with apparent craniofacial deformities. The researchers observed these individuals throughout their mother’s pregnancy up until early adulthood, in part to study the long-term effects of the FGFR & TWIST genes and their effect on inheritance. In genetics, alleles are present. All alleles carry the possibility of two to three different physical outcomes. For example, if one parent carries the allele for black hair, and the other parent carries the allele for blonde hair, then the child has a 50% chance of acquiring black hair (dominant), a 25% chance of acquiring blonde (recessive), and in rare cases a 25% chance of neither. A higher percentage rate, however, may not imply dominance. In terms of craniosynostosis and the twenty-nine individuals studied, six of these twenty-nine individuals displayed defective alleles within the FGFR & TWIST genes. These defective alleles portrayed dominant characteristics even in the presence of normal characteristics. Simply put, the defects dominate over the normal. This study proved that whether the parents carried abnormal FGFR & TWIST genes does not matter; those diagnosed with craniosynostosis will carry a mutated FGFR & TWIST gene that has a 50% of reoccurring within their children, and 50% chance of not reoccurring, but only if the craniosynostotic individual displays genetic deficiencies. Another study (Panigrahi, 2011) concluded after genetic research of craniosynostotic children that “if only child is affected and there are no clinical features in parents or other family members, then the disease may be sporadic with negligible risk of
recurrence,” meaning that as long as the affected individual’s immediate family displays no abnormal characteristics pertaining to craniosynostosis, the likelihood of future genetic inheritance should be neglected.

Now, the question is under which circumstance(s) researchers should focus on genetics. Cranial development continues in humans until they reach adulthood (around age 25); however, humans reach pivotal moments of cranial development within this age bracket. In most cases, an individual will hit one of these cranial peaks during infancy and again during their teenage years. Thus, a scientific researcher or medical professional should primarily focus on a patient’s genetic make-up if the patient with craniosynostosis is a child (ages 5-12), and/or when the patient is not undergoing substantial cranial development.

**Pre/Post-Natal Development**

As briefly mentioned earlier, a craniosynostotic individual’s cranial development plays a pivotal role in facial symmetry and cognitive function. In all cases, timing is everything. When a baby is developing in a mother’s uterus, the newly formed brain of that baby is carrying out all necessary functions such as growth. During cultivation, the brain sends signals to all parts of the body, commanding it to perform certain acts. In relation to an individual’s skull, the brain is also in charge of telling the body when to join the sutures of the skull, but what if the brain sends the signal too early? Herein lies the problem. Referring back to the FGFR & TWIST genes, in some cases the brain commands these genes and possibly others to close one or multiple sutures too soon. This pre-mature conjoining of skull sutures causes facial asymmetry, which may then cause intellectual disability. This is called craniosynostosis. As a visual example, picture an individual with one side of their face higher than the other.

However, another question is posed when craniosynostosis is evident, but genetic defects are not. Under this circumstance, scientific researchers and medical professionals must observe the position in which the developing baby is situated. Craniosynostosis surfaces in this case when an external force (the pressure of a mother’s womb) presses against a side of the baby’s skull, causing that one side to close prematurely, which, in turn, causes the unaffected side to overgrow or under grow. Nathaniel, et al. state that “abnormal head positioning in utero or in infancy may produce an abnormal skull shape (plagiocephaly); the abnormality often resolves with appropriate head positioning but occasionally results in craniosynostosis.” It is possible for medical professionals to manipulate or change the position of the baby during their development in the womb, but this process is often disregarded because it poses danger to the baby and its mother. When the position is left unchanged, the doctors allow the baby to be born naturally as if they were a normal developing child, and then continue observing the child once it is born. In one study (Heather et al., 2010) the researchers examined the pre/post-natal development of craniosynostotic babies. They followed these children several years after birth, recording any odd cranial positioning. The researchers were looking to find body re-correcting properties. They wanted to see if the body would fix the imperfections that occurred during fetal development during the post-natal period. In the end, researchers noticed that the unaffected side of the skull grew at a larger rate than the overgrown side, and at a slower rate than the under grown side. This evidence means that the body did indeed attempt to correct itself, but failed due to the continuing growth of the abnormal side. In order to correct and compensate for inaccurate suture closure, medical doctors should create a cranial helmet that applies pressure in designated areas around the skull until pressure is no longer necessary. Each unique individual would have a
Craniosynostosis continues to stand as a consistent problem with no apparent cause.
Currently, scientific researchers and medical professionals are pointing towards genetic abnormalities as the probable cause. Although there is evidence supporting this probable cause, it is not sufficient enough to acknowledge it as the cause of craniosynostosis, but rather a key factor affecting cranial development. Another major factor is pre/post-natal development, and the external forces acting upon an individual’s skull that push the plates of the skull in different directions causing abnormal growth. When craniosynostosis occurs, the only method of correction is craniofacial surgery; surgical procedures of this caliber often bring about more complications than before surgery, and pose a threat to the patient’s health. Although alternatives to surgery are available, there is little known information about the role of FGFR & TWIST in cranial development, and natal re-positioning threatens the health of the mother and child, so these methods should be researched further before implementation. Overall, future research should be aimed at the development of cranial helmets or caps because these would yield safer and more effective results.
References


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