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CLINICAL AND MOLECULAR CHARACTERIZATION OF A PATIENT WITH SYNDROMIC CRANIOSYNOSTOSIS, A CASE REPORT

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ABSTRACT

Introduction: *Craniosynostosis is a craniofacial disorder characterized by premature fusion of one or more cranial sutures, inhibiting bone growth perpendicular to the affected suture. In syndromic craniosynostosis, anomalies of the limbs, heart and central nervous system may be present, in addition to genetic mutations affecting the cranial vault. Its etiology is associated with paternal age, teratogenic factors and external pressure on the skull; the main genes causing syndromic craniosynostosis are the growth factor receptors (FGFR1, FGFR2, and FGFR3, TWIST1 and EFNB1), for these reasons it is of utmost importance to recognize the existing types of syndromic craniosynostosis, and its clinical and molecular characteristics to reach an optimal and accurate diagnosis.*

Objective: *to present the clinical and molecular characterization of an individual with syndromic craniosynostosis in a case.*

Methodology:*an objective description of the clinical case and a review with analysis of a total of 24 articles, including review and original articles, as well as clinical cases, of which 18 bibliographies were used because the other articles were not relevant to this study. The sources of information were indexed journals as well as search engines such as PubMed, Google Scholar and Cochrane; the terms used to search for information were: syndrome, craniosynostosis, gene, mutation, FGFR.*

Results: *the present report shows a clinical case of syndromic craniosynostosis. The diagnosis was made during an evaluation by means of radiographic analysis in a 15-year-old female patient, and corroborated by genetic blood tests with the following results: heterozygous variant at position 755 of the c.DNA, where a variant in Cytosine is visualized by a Guanine. This determines a change at the level of the FGFR2 protein.*

Conclusions: *the case report describes the clinical and molecular diagnosis of a 15-year-old female patient, revealing a heterozygous genetic variant in the FGFR2 gene (c.755>G), associated with changes in the FGFR2 protein. This finding is relevant, as similar variants have not been reported in Ecuador or South America, underscoring the need for further research on syndromic craniosynostosis and Apert syndrome. A multidisciplinary approach to treatment is recommended, involving various medical specialties to ensure proper brain development and improved esthetics. In addition, the existence of similar cases in Indonesia and Congo is mentioned, suggesting a possible founder effect related to the migration of people with character.*

KEY WORDS: *syndrome, craniosynostosis, gene, mutation, FGFR*

INTRODUCTION

Craniosynostosis is a pathologic craniofacial disorder and is defined as the premature fusion of one or more cranial sutures. Cranial sutures are fibrous joints consisting of unossified mesenchymal cells that play an important role in the development of healthy craniofacial skeletons. Early fusion of these sutures results in incomplete brain development(1).

During cranial vault development, condensation of undifferentiated mesenchymal cells surrounding the sutures begins. After condensation has begun, cells begin to proliferate from the osteogenic fronts; the main regulatory pathway for this differentiation is the fibroblast growth factor (FGF) signaling pathway. Bone overgrowth from non-mineralized bone matrix

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or early arrest of brain development may be the cause of premature suture fusion and may lead to morphological, physiological and functional abnormalities, such as craniosynostosis(2,3).

Craniosynostoses usually inhibits the growth of bone that is perpendicular to the affected suture. These premature fusions may affect a single cranial suture or occur in varied patterns of multiple suture closure combinations; it may occur as part of a syndrome or in isolation. However, this growth arrest is usually compensated for by increased growth of other skull bones not neighboring the premature one. This results in an altered skull shape and dysmorphic facial features that depend on the involvement of the specific suture, in syndromic craniosynostosis (CS) multiple sutures are usually affected (Virchow's Law)(4).

Cases of craniosynostosis are typically divided into groups; syndromic and non-syndromic, more than 70% of patients have been diagnosed with non-syndromic craniosynostosis, although autosomal dominant inheritance is responsible for the majority of syndromic cases(5).

In syndromic cases, additional findings of craniosynostosis may be seen including anomalies of the limbs, heart and central nervous system, as well as encompassing a variety of diagnoses and genetic mutations affecting the cranial vault with anomalies at embryologically distinct anatomical sites(6).

In general, patients affected by syndromic craniosynostosis are thought to have involvement of multiple sutures with significant potential for restricted brain growth, increased intracranial pressure (ICP) and facial dysmorphias in the context of a spectrum of additional anatomic abnormalities, are also more likely to have ventricular expansion, hydrocephalus, expanded subarachnoid space and cerebellar tonsillar herniation compared to patients with sporadic single suture synostosis(7).

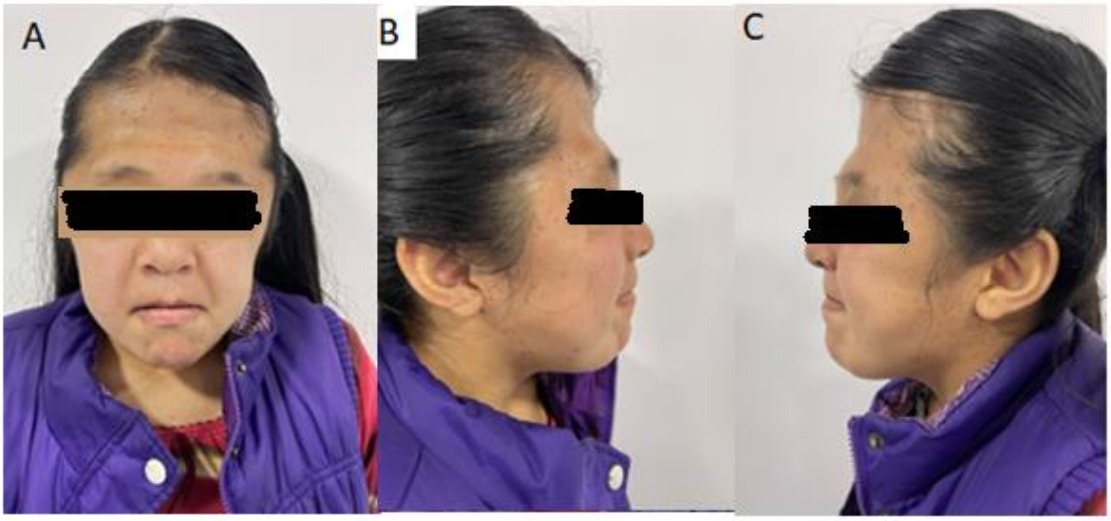
The TWIST protein has been shown to play a key role in the regulation and differentiation of sutural mesenchymal cells to form the skull(8).

The FGF family has 23 members that bind to different receptors (FGFR1 and FGFR2) to induce cellular responses, whereas FGFR1 signaling regulates osteogenic differentiation, FGFR2 signaling directs stem cell proliferation. In syndromic craniosynostosis, mutations are mainly found in FGFR2. It is of utmost importance to recognize the existing types of syndromic craniosynostosis, and their clinical and molecular characteristics to reach an optimal and accurate diagnosis(9,10).

DESCRIPTION OF THE CASE

The finding of syndromic craniosynostosis was made when clinically observing the craniofacial characteristics of a 15 year old female patient, in a diagnostic evaluation upon admission to the Multidisciplinary Clinic of Cleft Lip and Palate of the Catholic University of Cuenca, for dental treatment consultation.

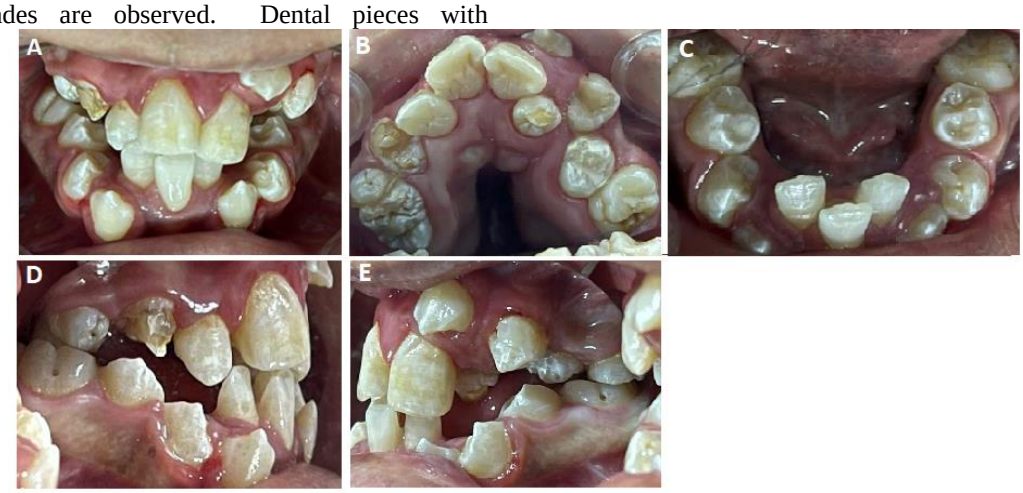
Figure 1. Extraoral clinical photographs (A). Frontal view: Skull with oxycephaly, regular high hairline, broad frontal, hypoplastic supraciliary arches with low hairline implantation, downward directed oblique palpebral fissures, left palpebral ptosis, bilateral epicanthus, hypertelorism, low eyelash implantation and low implantation in the outer third of the eyebrows, depressed low-set nasal root with a wide bridge with bulbous tip with anteverted nostrils, long philtrum grade 2, thin upper lip, thick lower lip, downturned labial commissures and midfacial hypoplasia, square facial shape with facial asymmetry. (B). Left lateral view: high frontal, low hairline, anteroposterior deficiency of maxillary growth and short neck (C). Right lateral view.



Source: The Authors.

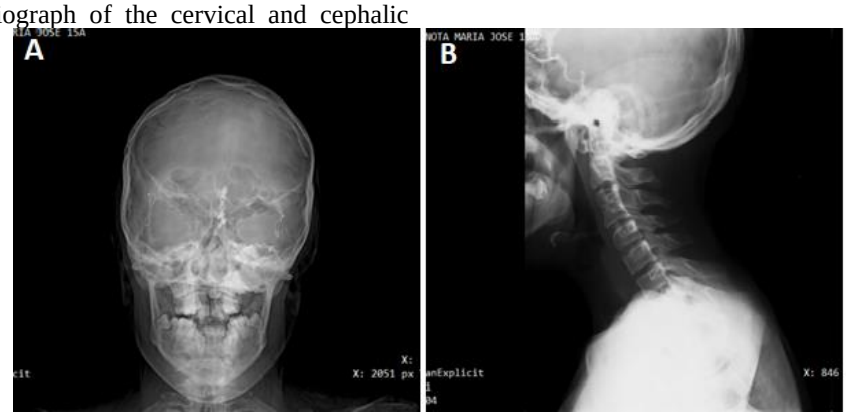
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Figure 2. Intraoral clinical photographs.
A: Occlusal view
B: Upper arch view
C: Lower arch view
D: Right oblique view
E: Left oblique view
Generalized enamel development defects with white, yellow and brown shades are observed. Dental pieces with amelogenesis imperfecta (Type lll-hypocalcified), with periodontal disease associated with defects in enamel formation, as well as dental crowding in both arches. (D) Piece 6.3 is in the mouth, because it is retained. (E) Agenesis of the piece 3.1. Carious lesions with ICDAS 03 at molar level. It presents apparent retention of canines.



Source: The Authors.

Figure 3. Cranial radiographic studies. A. Cranial radiography, showing oxycephaly, brachycephaly, with alteration of the semicircular ducts and lack of pneumatization of the paranasal sinuses. B. Lateral radiograph of the cervical and cephalic spine, showing opacification of the semicircular canals, loss of intervertebral space between the first four vertebrae, rectification of cervical lordosis.



Source: The Authors.

Figure 4. Radiographic and clinical study of hands. Distal complex syndactyly of phalangeal bones of both hands, hypoplasia of distal phalanges of both hands with cutaneous syndactyly.



Source: The Authors.

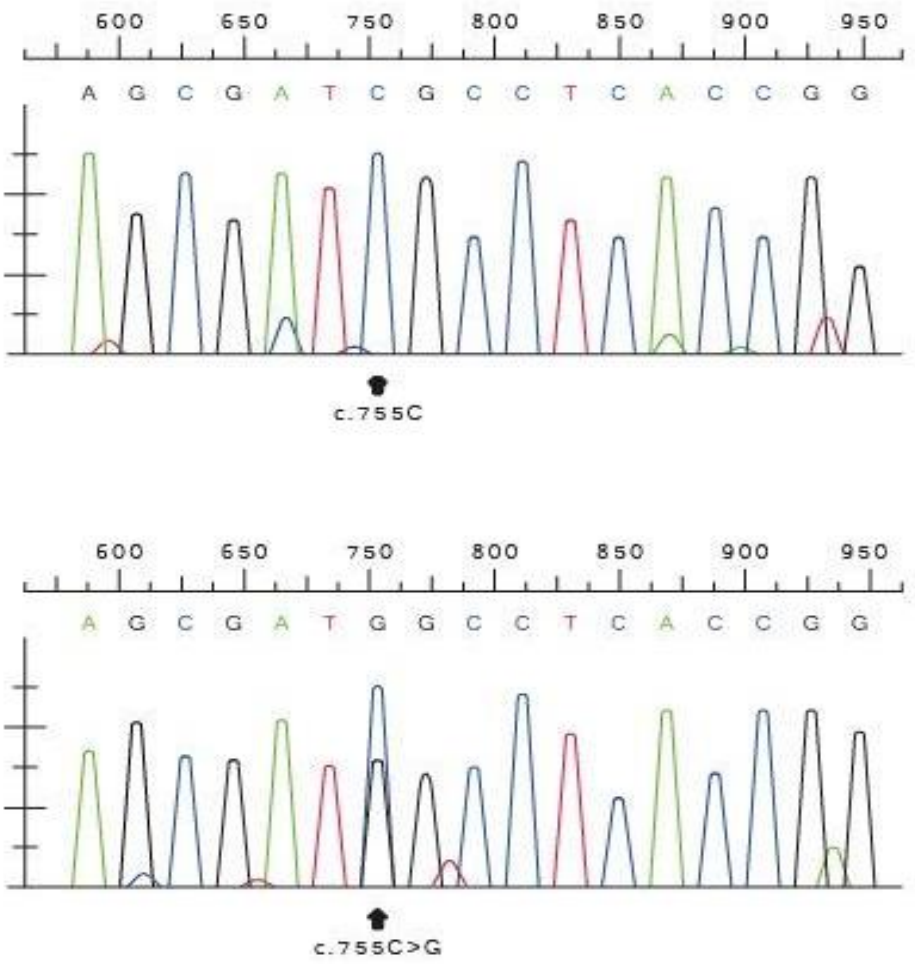
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Figure 5. Radiographic and clinical studies of the feet. A. Complex bony syndactyly of the distal phalangeal bones of both feet, lateral deviation of all the proximal and distal phalangeal bones. B. Complex cutaneous syndactyly of the toes and hypoplasia of the first toe of both feet, the toes are widened.



Source: The Authors.

Figure 6. Molecular confirmation of the genetic study.



Source: The Authors.

In Figure 6 we can see an electropherogram with normal sequence: normal sequence of the FGFR2 gene at position 755 of c.DNA, the presence of a cytosine in the homozygous state is observed. Electropherogram of the patient's sequence: she presents a heterozygous variant at position 755 of the c.DNA, where a variant in the aforementioned cytosine is visualized by a guanine, which determines a change at the level of the FGFR2 protein (p. Ser252Trp).

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DISCUSSION

Syndromic craniosynostosis is defined as a clinical genetic disorder associated with the fusion of the cranial sutures, which play an important role in the formation of the craniofacial skeleton; however, alterations in the early fusion of these sutures produce an incomplete development of the brain mass and the entire maxillofacial set, and alterations are also described in the upper and lower extremities. In the present report, we present the case of a 15 year old female, who was initially clinically diagnosed with syndromic craniosynostosis and corroborated by molecular genetic diagnosis by finding a mutation in the fibroblast growth factor receptor number two (FGFR2). As for the clinical features observed, in addition to syndromic craniosynostosis, there is symmetrical syndactyly in feet and hands, alterations at the level of the mid-facial line and a history of psychomotor developmental delay. These characteristics are reported by Wang JC in his research, who exposes more than 180 syndromes associated with CS, the five most common being: Apert syndrome and Crouzon syndrome with alteration of FGFR2, Pfeiffer syndrome with alteration in FGFR2 and FGFR1, Muenke syndrome (FGFR3) and Saethre-Chotzen (TWIST1)1. Similarly, the study by Ko JM agrees that the FGFR2, FGFR3, FGFR1 genes are the main causes of the genetic syndromes associated with syndromic craniosynostosis, in addition to TWIST1 and EFNB17. Likewise, the research by Celie et al. agrees with the bibliographic study carried out, since it establishes that the main syndromes associated with CS such as Apert, Crouzon, Pfeiffer and others not only affect the sutures, but are also related to other signs in the upper and lower extremities such as hands, feet, skeletal and cardiac defects, as well as neurodevelopmental delay(11).

Similarly, in the study by Abraham P, et al. it is observed that among the main characteristics of patients with CS are anomalies in the tissues that make up the face and skull, as well as an alteration in the normal growth of the head due to premature closure of the sutures, where it is observed that the main pathophysiological signaling pathway affected corresponds to the fibroblast growth factor(15).

However, in the study by Yee ST, et al. it is observed that in the clinical presentation of CS, anterior scaphocephaly, plagiocephaly, trigonocephaly and brachycephaly can be identified, for which specific genetic tests are recommended, which in the present study were performed to reach the reported diagnosis. Lumaka A, et al., in Indonesia and Congo, respectively, have already reported cases similar to the present one, in which a clinical and molecular diagnosis was made in patients with Apert syndrome, and the same genetic variant identified in our patient with syndromic craniosynostosis was found, thus confirming the genotype-phenotype correlation of Apert syndrome with a genetic variant in the FGFR2 gene(12,16-18).

All the aforementioned studies state that the definitive diagnosis of syndromic craniosynostosis is associated with genetic tests specifically directed at FGFR1, FGFR2, FGFR3 and even TWIST1. However, the study by Goldstein et al. states that the main findings identified in patients with CS also include hydrocephalus, herniation in the cerebellar tonsil, renal alterations, as well as alterations of the axial skeleton(13,14).

In view of the above, it is nowadays important to always have clinical diagnostic studies and to have them corroborated by genetic studies, since these type of pathologies are similar to each other and sometimes a definitive diagnosis cannot be reached. It is important to mention that years ago it was not as easy to perform molecular studies and genetic tests as it is today, so it is much easier to reach a definitive diagnosis.

CONCLUSIONS

The present case report has allowed to identify the clinical and molecular diagnosis of a 15-year-old female patient, through clinical, radiographic and genetic studies, concluding with the presence of a genetic variant in heterozygous state at position 755 of c.DNA in the FGFR2 gene, where a change of a cytosine by a guanine (c.755>G) is visualized, which determines a change at the FGFR2 protein level. However, it should be considered that in the literature there are no similar investigations that have reported this genetic variant in Ecuador or South American countries, so the present study is relevant, novel and contributes to the knowledge, promoting the initiation of new research in the future that will allow the development of appropriate protocols in the management of patients with syndromic craniosynostosis as well as patients with Apert syndrome, as in this case.

Due to the importance of the reported manifestations, it is recommended that treatment should always be multidisciplinary (neurology, neurosurgery, cardiology, plastic surgery, maxillofacial surgery, pediatric dentistry, genetics, traumatology, nephrology, psychology, among others); It is suggested that if the possibility of the presence of a generally congenital CS is observed, clinical and radiological studies, as well as molecular analyses, should be carried out in order to diagnose the presence of syndromic craniosynostosis and reach a specific diagnosis, as in the case of Apert syndrome, in order to achieve normal brain development in the patient through early, appropriate and timely treatment, providing sufficient space inside the skull and a better aesthetic appearance.

In addition, it is important to note that similar cases are reported in countries such as Indonesia and the Congo, which are geographically located in continents distant from Ecuador, which could suggest that at some point in history there may have been migration of people with these same genetic characteristics, so we could be talking about a founder effect in these countries.

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Conflict of Interest Statement

The authors report no conflicts of interest.

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