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Delineation of craniosynostosis in Saudi Arabia

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Abstract

Background: Craniosynostosis (CS) is defined as an early premature fusion of cranial sutures resulted to congenital skull deformity and affecting approximately 1 in 2500 children. Clinical assessment of CS may considered a difficult challenge due to the complex phenotype variability between cases. Phenotypically, CS classified into isolated (non-syndromic) or syndromic with frequent majority of 85% to the reported non-syndromic. The most common phenotype involving single suture is the sagittal synostosis, followed by coronal synostosis, metopic synostosis and lambdoid synostosis of the non-syndromic cases. Approximately 15% of the syndromic is affected with more than one suture.

Methods: A retrospective chart review for Craniosynostosis patients were referred to the Molecular Pathology laboratory, Pathology and Laboratory Medicine department between 2010-2016 for molecular genetic studies of FGFR1, FGFR2, FGFR3 and TWIST genes. All patients were diagnosed and investigated at King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia.

Results: Eighteen (18) patients were clinically diagnosed with Craniosynostosis. The age of onset ranged from birth to 10 years and with predominant Female to Male ratio of 1.6:1. Fourteen (14) patients (82.4%) were confirmed by missense mutations within FGFR2 (57.1%) and FGFR3 (35.7%) genes but no mutations were detected within FGFR1 and TWIST genes in four cases. Several mutations were detected with FGFR2 gene such c.755C>G p.Ser252Trp, c.833G>T p.Cys278Phe, c.1024T>C (p.Cys342Arg), c.1029G>C p.Ala344Pro and 1061C>G p.Ser354Cys. The most common mutation of c. c.749C>G p.Pro250Arg was detected within FGFR3 gene.

Conclusion: Craniosynostosis has a wide variable clinical heterogeneity that might be correlated with phenotype/genotype presentation. Negative molecular investigation should not rule out the disease if clinical and radiological investigations support the diagnosis. Further molecular investigation is required to better classify the unknown causes of unexplained craniosynostosis cases. A larger data registry is essential to better describe the craniosynostosis genotype/phenotype in Saudi Arabia.

Introduction

Early fusion of cranial sutures results in congenital skull deformity called craniosynostosis. It is a quite common condition affecting approximately 1 in 2500 children [1,2]. It is categorized into syndromic or non-syndromic, primary and secondary, with non-syndromic craniosynostosis account for the majority (85%) of craniosynostosis cases [3]. In primary craniosynostosis, the main presenting feature is abnormal skull shape, hence it is relatively straight forward in diagnosis. Single suture craniosynostosis account for the majority of primary craniosynostosis with multiple suture account for only 15% of cases. The Intracranial Pressure (ICP) in primary craniosynostosis is usually normal in the majority of cases with high ICP accounting for 20% of single suture primary craniosynostosis [4,5]. Secondary craniosynostosis caused by underling systemic diseases such as sickle cell diseases and thalassemia or underling metabolic diseases such as Hurler's syndrome and hyperthyroidism [6,7]. Cardiac defect, skeletal defect, psychomotor retardation or digital anomalies in patient presenting with craniosynostosis raise the index of suspicion of syndromic craniosynostosis with more than 180 syndromes and multiple genes have been reported to date [8].

Currently, no validated pharmaceutical intervention that may prevent the craniosynostosis and the mainstay of treatment is surgical intervention via skull re-shaping [9-11]. Craniosynostosis genetic investigation, in particular, the basic molecular genetic analysis including the karyotyping and array Comparative Genomic Hybridization (CGH) are essential because the clinical course, the prognosis and the primary causes all can be obtained by the result of molecular genetic analysis [12]. Indeed, the genetic causes identified by the current molecular genetic evaluation was approximately 45% [12,13]. Moreover, the role of molecular genetic analysis not only in treatment, it is also preventive measures via genetic consultations and patient education regarding the risk of recurrence in future siblings. However, not all types of craniosynostosis necessitate a molecular genetic evaluation. Due to low recurrence risk and less complication, patients with metopic, sagittal and lambdoid craniosynostosis usually don't need a genetic evaluation [14]. The most common genetic alteration associated with craniosynostosis are FGFR-, TWIST1-, and EFNB1- related syndromes [12].

To our knowledge, there is no single study had investigated the molecular genetic analysis of craniosynostosis patients. Thus, the aim of this study is report our findings and compare it to other studies.

Methods

This hospital-based retrospective chart review study was conducted at King Abdul-Aziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia. Craniosynostosis patients were referred to the Molecular Pathology laboratory, Pathology and Laboratory Medicine department between 2010-2016 for molecular genetic studies of FGFR1, FGFR2, FGFR3 and TWIST genes. All patients were diagnosed and investigated at King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia. Ethical approval for the study was obtained from the Ethics Committee of the King Abdullah International Medical Research Center (KAIMRC).

A total of 18 patients were managed at our institution during the 6-year period of the study and formed the basis of the present study. Data collection included age, gender, craniofacial, ophthalmological, otolaryngological, cardiovascular, musculoskeletal, developmental and molecular genetic features. Moreover, all patients included in this study had undergone cranial vault reshaping surgery. To reflect the most possible precise outcome of the present study, the patient's hospital records either chart or electronic (Best Care Medical System) of cytogenetic and molecular pathology, clinical examinations, investigations, and surgery were the only source used to collect the data.

Statistical analysis

Means and standard deviations were used to summarize continuous variables. Frequencies and proportions were used to present the categorical clinical characteristics. The $\chi 2$ test (or Fisher exact test) was used to compare data. All tests were two sided and a $P<0.05$ was considered statistically significant. The Statistical Package for Social Sciences (IBMSPSS, Oklahoma, USA, version 21) was used for data management and analysis.

Results

The study included eighteen (18) patients were clinically diagnosed with craniosynostosis. The age of onset ranged from birth to 10 years and with predominant Female to Male ratio of 1.6:1. Fourteen (14) patients (82.4%) were confirmed by missense mutations within FGFR2 (57.1%) and FGFR3 (35.7%) genes but no mutations were detected within FGFR1 and TWIST genes in four cases. Several mutations were detected within exon 8 and exon 2 of FGFR2 gene such c.755C>G p.Ser252Trp (exon 8), c.833G>T p.Cys278Phe (exon 2), c.1024T>C (p.Cys342Arg) (Exon 8), c.1029G>C p.Ala344Pro (exon 8) and 1061C>G p.Ser354Cys (exon 8). The most common mutation of c.749C>G p.Pro250Arg was detected within exon 7 of FGFR3 gene (Table 1).

The varieties of craniofacial features that have been found in our patients are described in Table 2. The most common craniofacial feature was midface deficiency followed by brachycephaly 41% and 30% respectively. On the other hand, the least common were retrognathia and dolichocephaly 6%. The cardiovascular features found in our patients are Atrial Septal Defect (ASD) secundum type and peripheral pulmonary stenosis Table 3. The different otolaryngological features associated with craniosynostosis patients are illustrated in Table 4. The most common was otitis media with effusion (30%). Hearing loss has been found in two patients (12%). The developmental features of craniosynostosis patients are described in Table 5. Global developmental delay and speech delay accounted for 36%. Moreover, mental developmental delay and low school performance accounted for 12%.

The radiological features showed that mild brain edema and optic nerve swelling due to increased intracranial pressure in one patient and multiple area of encephalomalacia and multiple venous infarct in another patient Table 6. The musculoskeletal features that identified in our patients are described in Table 7. The most common feature was syndactyly of hand and feet bilateral and symmetrical (12%). Big left toe and bilateral big toes were identified in two patients.

Table 8 illustrate the ophthalmological features in our pa-

tients. Ocular proptosis was the most common (30%) followed by papilledema (24%). Amblyopia and myopia accounted for 18% and 12% respectively.

Table 9 describes other features identified in our patients are febrile seizure (6%), bronchial asthma (12%) and adenotonsillectomy (12%).

Table 1: Summary of genes detected mutations.

Gene	Mutation	Number of cases
FGFR2	c.755C>G, p.Ser252Trp	5
FGFR2	c.833G>T, p.Cys278Phe	1
FGFR2	c.1209G>C, p.Ala344Pro	1
FGFR2	c.1024T>C, p.Cys342Arg	2
FGFR2	c.1061C>G, p.Ser354Cys	1
FGFR3	c.749C>G, p.Pro250Arg	5
FGFR3	c.1263A>G, p.Arg421Arg	3

Table 2: Craniofacial features.

Craniofacial Features	(%)N
Cleft Palate	3(18)
Brachycephaly	5(30)
Midface deficiency	7(41)
Maxillary hypoplasia	2(12)
Dental malocclusion	2(12)
Turricephaly (oxycephaly)	3(18)
Micrognathia	3(18)
Retrognathia with hypoplastic mandibular condyle	1(6)
Bossing of forehead	2(12)
Depressed nasal bridge	2(12)
Dolichocephaly	1(6)
Plagiocephaly	2(12)

Table 3: Cardiovasucular features.

Cardiovascular Features	(%)N
"Atrial Spetal Defet" ASD secundum type	1(6)
Peripheral pulmonary stenosis	1(6)

Table 4: Otolaryngological features.

Otolaryngological Feature	N (%)
Posteriorly rotated ears	1(6)
Low Set ear	2(12)
Bilateral conductive hearing los	2(12)
Otitis media with effusion	5(30)
Subglotitic stenosis	1(6)
Laryngeal cleft	1(6)

Table 5: Developmental features.

Developmental feature	N(%)
Global Developmental delay	3(18)
Speech Delay	3(18)
Mental developmental delay	1(6)
Low school performance	1(6)

Table 6: Radiological features.

Radiological feature	(%)N
Mild brain edema and optic nerve swelling	1(6)
Multiple area of encephalmomalasica and multiple venous infarct	1(6)

Table 7: Musculoskeletal system.

Muskeloskelatal feature	(%)N
Syndactyly of hand and feet Bilateral and symmetrical	2(12)
Big left toe	1(6)
Bilaterl big toes	1(6)

Table 8: Ophthalmological Features.

Ophthalmological feature	N (%)
Amblyopia	3(18)
Squint	2(12)
Papilledema	4(24)
Abnormal retinal vasculature	1(6)
Myopia	2(12)
Astigmatism	1(6)
Exotropia	1(6)
Esotropia	1(6)
Shallow Orbit	3(18)
Hypertoloerism	1(6)
Ocular Proptosis	5(30)

Table 9: Other features.

Other feature	(%)N
Febrile Seziure	1(6)
Bronichal Asthma	2(12)
Adentonsillectomy	2(12)

Discussion

We investigated the craniosynostosis cases managed at our hospital from January 2010 to December 2016. Eighteen (18) patients were clinically diagnosed with craniosynostosis. The age of onset ranged from birth to 10 years and with predominant Female to Male ratio of 1.6:1. Fourteen (14) patients (82.4%) were confirmed by missense mutations within *FGFR2* (57.1%) and *FGFR3* (35.7%) genes but no mutations were detected within *FGFR1* and TWIST genes in four cases. Several mutations were detected within exon 8 and exon 2 of *FGFR2* gene such c.755C>G p.Ser252Trp (exon 8), c.833G>T p.Cys278Phe (exon 2), c.1024T>C (p.Cys342Arg) (Exon 8), c.1029G>C p.Ala344Pro (exon 8) and 1061C>G p.Ser354Cys (exon 8). The most common mutation of c. c.749C>G p.Pro250Arg was detected within exon 7 of FGFR3 gene. The concept of genetic factors as the underlying cause of craniosynostosis was first reported in a mother and child who had same phenotype by Octave Crouzon [15].

The first gene identified in craniosynostosis syndrome was MSX2. Mutation in MSX2 cause the rare Boston-type craniosynostosis. After that, the implicated genes underlying the craniosynostosis syndromes were identified including (FGFR1, FGFR2, FGFR3, TWIST1, EFNB1, MSX2 and RAB23) [16].

References

1. Boulet SL, Rasmussen SA, Honein MA. A population-based study of craniosynostosis in metropolitan Atlanta, 1989-2003. American Journal of Medical Genetics Part A. 2008; 146: 984-91.
2. Lajeunie E, Merrer ML, Bonaïti-Pellie C, Marchac D, Renier D. Genetic study of nonsyndromic coronal craniosynostosis. American journal of medical genetics. 1995; 55: 500-4.
3. Boyadjiev SA. Genetic analysis of non-syndromic craniosynostosis. Orthodontics & craniofacial research. 2007; 10: 129-37.
4. Renier D, Sainte-Rose C, Marchac D, Hirsch JF. Intracranial pressure in craniostenosis. J Neurosurg. 1982; 57: 370-7.
5. Thompson DN, Malcolm GP, Jones BM, Harkness WJ, Hayward RD. Intracranial pressure in single-suture craniosynostosis. Pediatr Neurosurg. 1995; 22: 235-40.
6. Khanna PC, Thapa MM, Iyer RS, Prasad SS. Pictorial essay: The many faces of craniosynostosis. Indian J Radiol Imaging. 2011; 21: 49.
7. Robin NH, Falk MJ, Haldeman-Englert CR. FGFR-related craniosynostosis syndromes. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews® [Internet] Seattle, WA: University of Washington. 1993-2016.
8. Panigrahi I. Craniosynostosis genetics: The mystery unfolds. Indian J Hum Genet. 2011; 17: 48.
9. Johnson D, Wilkie AO. Craniosynostosis. European Journal of Human Genetics. 2011; 19: 369-76.
10. Forrest CR, Hopper RA. Craniofacial syndromes and surgery. Plastic and reconstructive surgery. 2013; 131: 86e-109e.
11. Kirmi O, Lo SJ, Johnson D, Anslow P. Craniosynostosis: a radiological and surgical perspective. Semin Ultrasound CT MR. 2009; 30: 492-512.
12. Muenke M, Kress W, Collmann H, Solomon B, editors. Craniosynostoses: Molecular genetics, principles of diagnosis and treatment. Karger Medical and Scientific Publishers. 2011.
13. Wilkie AO, Bochukova EG, Hansen R, Taylor IB, Rannan-Eliya SV, et al. Clinical dividends from the molecular genetic diagnosis of craniosynostosis. American Journal of Medical Genetics Part A. 2006; 140: 2631-9.
14. Johanson D et al. Crnaioynostosis. Eur J Hum Genet. 2011; 19.
15. Crouzon O. Dysostose cranio-faciale hereditaire. Presse Méd. 1912; 20:737-739.
16. Wilkie AOM, Byren JC, Hurst JA, Jayamohan J, Johnson D, et al. Prevalence and Complications of Single-Gene and Chromosomal Disorders in Craniosynostosis. PEDIATRICS. 2010; 126: e391-e400.