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Apert and Crouzon Syndromes—Cognitive Development, Brain Abnormalities, and Molecular Aspects

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Apert and Crouzon are the most common craniosynostosis syndromes associated with mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene. We conducted a study to examine the molecular biology, brain abnormalities, and cognitive development of individuals with these syndromes. A retrospective longitudinal review of 14 patients with Apert and Crouzon syndromes seen at the outpatient Craniofacial Surgery Hospital for Rehabilitation of Craniofacial Anomalies in Brazil from January 1999 through August 2010 was performed. Patients between 11 and 36 years of age (mean 18.29 ± 5.80), received cognitive evaluations, cerebral magnetic resonance imaging, and molecular DNA analyses. Eight patients with Apert syndrome (AS) had full scale intelligence quotients (FSIQs) that ranged from 47 to 108 (mean 76.9 ± 20.2), and structural brain abnormalities were identified in five of eight patients. Six patients presented with a gain-of-function mutation (p.Ser252Trp) in *FGFR2* and FSIQs in those patients ranged from 47 to78 (mean 67.2 ± 10.7). One patient with a gain-of-function mutation (p.Pro253Arg) had a FSIQ of 108 and another patient with an atypical splice mutation (940–2A →G) had a FSIQ of 104. Six patients with Crouzon syndrome had with mutations in exons IIIa and IIIc of *FGFR2* and their FSIQs ranged from 82 to 102 (mean 93.5 ± 6.7). These reveal that molecular aspects are another factor that can be considered in studies of global and cognitive development of patients with Apert and Crouzon syndrome (CS).

Key words: syndromic craniosynostosis; intellectual functioning; central nervous system; molecular biology

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INTRODUCTION

Premature fusion of cranial sutures underlies craniosynostosis, which occurs in both nonsyndromic and syndromic forms. Syndromic craniosynostosis is usually associated with limb abnormalities, dysmorphic facial features, and skull deformity. Mutations in the gene encoding fibroblast growth factor receptor 2 (*FGFR2*) account for several severe craniosynostosis conditions, including Apert, Pfeiffer, Crouzon, Beare–Stevenson, and Jackson–Weiss syndromes [Bonaventure and El Ghouzzi, 2003; Cunningham et al., 2007]. *FGFR2* belongs to a family of four fibroblast growth factor receptors, which contain an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with tyrosine kinase activity.

Many craniosynostosis disorders have their origins in specific embryological processes, including brain patterning, migration and fusion of tissues in the face, and bone differentiation in the skull vault [Wilkie and Morriss-Kay, 2001]. Extracranial phenotypes such as limb, cardiac, central nervous system, and tracheal malformations are well described [Cunningham et al., 2007].

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Indeed, Passos-Bueno et al. [1998] showed that mutations in the *FGFR2* locus account for 93% of syndromic craniosynostosis disorders. The spectrum of *FGFR2* mutations that cause craniosynostosis is wider than previously recognized; nevertheless, the IgIIIa and IgIIIc regions linking Ig-like domains of *FGFR2* gene represent mutation hotspots [Kan et al., 2002]. Other mutations in the genes encoding fibroblast growth factor receptor 1 (*FGFR1*), fibroblast growth factor receptor 3 (*FGFR3*), *TWIST1*, and *MSX2* (transcription factors) also cause craniosynostosis [Cunningham et al., 2007; Passos-Bueno et al., 2008].

Apert syndrome (AS) was first described in 1906 by Eugene Apert, and during the last century, progress has been made in understanding and treating this condition [Perlyn et al., 2009]. AS is caused by specific missense mutations in one of two adjacent amino acid residues (p.Ser252Trp or p.Pro253Arg) in the highly conserved region linking Ig-like domains II and III of *FGFR2* [Yu et al., 2000]. Another distinct pathological basis for AS has also been identified [Oldridge et al., 1999]: signaling through keratinocyte growth-factor receptor has been shown to be responsible for syndactyly in AS.

In contrast to AS, Lajeunie et al. [2006] showed that the spectrum of *FGFR2* mutations that cause Crouzon syndrome (CS) is broad. In vitro differences between normal and CS fibroblasts suggested that clinical features may be caused by an imbalance between transforming growth factor beta and basic fibroblast growth factor, which alter the microenvironment where morphogenesis takes place [Bodo et al., 1999; Baroni et al., 2002]. The genotype–phenotype correlation is well discussed in the literature [Patton et al., 1988].

Current research in craniosynostosis has focused on uncovering genetic and neuropsychologic correlates [Da Costa et al., 2005]. Identification of syndromes caused by chromosomal micro deletions and characterization, both molecular and clinical, is contributing to a better understanding of the connections between genes and cognition [Baroni et al., 2002]. Animal models with disease-causing mutations have also increased understanding of clinical phenotypes and have helped elucidate the roles of genes in human cognitive capacities [Benítez, 2009].

Behavioral phenotypes are characteristic patterns of motor, cognitive, linguistic, and social abnormalities that are associated with biological disorders; environmental factors are also known to be important in their development [Ruggieri and Arberas, 2003]. It is clear that global approaches will be the most effective means to tackle questions surrounding craniofacial anomalies, including elucidation of causes, treatments, or preventative measures [Kaplan, 1991; WHO, 2002].

AS and CS are the most common of the craniosynostosis syndromes that have *FGFR2* gene mutations [Cohen, 1995; 2004; Kress et al., 2000], and cognitive development of patients has been related to structural brain abnormalities, timing of surgery, and social aspects. Studies that correlate abnormalities in brain development to genetic mutations will lead to improved understanding of these conditions. Therefore, the objective of this study was to elucidate the molecular underpinnings of AS and CS and present the data in context with information on structural brain abnormalities and cognitive development of these patients.

METHODS

A retrospective longitudinal study was performed on 14 patients with craniosynostosis syndromes (eight with AS and six with CS) seen at the outpatient Craniofacial Surgery Hospital for Rehabilitation of Craniofacial Anomalies at the University of Sao Paulo, Brazil from January 1999 through August 2010. Patients between 11 and 36 years of age (mean 18.3 ± 5.8) underwent evaluation by an interdisciplinary team, including genetic diagnostics, clinical examinations, and magnetic resonance imaging (MRI). This project was approved by the ethical evaluation of human being research review board (N°006/2009 – SVAPEPE – CEP, February 18, 2009).

MRI was performed using a 0.5 T system (Flexart, Toshiba, Japan) with a head coil. T1 weighted spin-echo, T1 weighted inversion recovery, and T2 weighted fast spin-echo and fluid-attenuated inversion recovery were used for imaging. Sagittal, coronal, and axial planes were imaged.

Ventriculomegaly was defined as non-progressive enlargement of the ventricular system without signs of hypertensive dilation, such as periventricular lucency. Hypoplasia of the corpus callosum (CC) was defined as reduction in extension or thickness of the CC seen in the sagittal and coronal planes. Abnormalities of the septum pellucidum were classified as hypoplasia when thickness of the septum pellucidum was reduced in the coronal T2 and axial flair images. Cavum vergae was defined as a cavity posterior to the septum pellucidum. Encephalomalacia presented as hyperintense T2 signal and hypointense T1 signal. These criteria for brain abnormalities were established previously [Yacubian-Fernandes et al., 2004].

Cognitive evaluation was obtained using the Wechsler Intelligence Scale for Children (WISC-III) [Wechsler, 1994)], a standardized test that measures intellectual functioning in children aged 6 to 16 years, and the Wechsler Adult Intelligence Scale (WAIS) [Wechsler, 1981], a test designed to measure intelligence in adults and older adolescents. The intelligence quotients (IQs) were obtained as verbal intelligence quotients (VIQs), performance intelligence quotients (PIQs), and full scale intelligence quotients (FSIQs).

Genomic DNA was extracted from blood lymphocytes using the Autopure LS kit (Qiagen, Hilden, Alemanha); approximately 350 μg of genomic DNA were extracted from 10 ml of blood. DNA sequencing reactions were processed on the ABI 3730 DNA sequencer (Applied Biosystems, Foster City, CA) and analyzed using the SeqScape v2.6 software. Twenty to forty nanograms of PCR amplified *FGFR2* isoforms IIIa and IIIc were purified with the Exonuclease 1 enzyme (10 U/μL) and Shrimp Alkaline Phosphatase (1 U/μL).

RESULTS

Table I shows results presented according to syndrome type, sex, age, IQ, intellectual outcomes (VIQ, PIQ, and FSIQ), MRI results, and molecular analyses of the *FGFR2* gene. Patients with AS presented VIQs from 48 to 100 (mean 75.5 ± 17.4), PIQs from 51 to 108 (mean 80.4 ± 19.0) and FSIQs from 47 to 108 (mean 76.9 ± 20.2). Structural brain abnormalities were seen in five of eight cases. Six patients with AS had the typical *FGFR2* mutation (p.Ser252Trp gain-of-function mutation) (Table I) and VIQs from 48 to 75 (mean 67.3 ± 10.1), PIQs from 51 to 86 (71.5 ± 11.4), and

TABLE I. Cognitive Profile, Structural Brain Abnormalities on MRI, and Gene Mutations Among Patients With Apert and Crouzon Syndromes

Patient	Syndrome	Age[a] (years/months)	Gender	TEST	VIQ	PIQ	FSIQ	MRI	Nucleotide change[b]	Effects on protein or RNA[b]	Gene or protein regionß
1	Apert	17 y 3 m	M	WAIS	71	74	71	Normal	c.755C>G	p.Ser252Trp	IgII–IgIII linker
2	Apert	8 y 7 m	F	WISC-III	100	108	104	Normal	c.940-2A>G[c]	Splicing	intron 9–splice acceptor
3	Apert	10 y 11 m	M	WISC III	65	71	65	HCC	c.755C>G	p.Ser252Trp	IgII–IgIII linker
4	Apert	7 y 8 m	F	WISC-III	75	73	72	VM + HCC	c.755C>G	p.Ser252Trp	IgII–IgIII linker
5	Apert	7 y 9 m	M	WISC-III	100	106	108	VM + HCC + HSP	c.758C>G	p.Pro253Arg	IgII–IgIII linker
6	Apert	8 y 7 m	F	WISC-III	74	86	78	HCC + HSP	c.755C>G	p.Ser252Trp	IgII–IgIII linker
7	Apert	11 y 11 m	F	WISC-III	48	51	47	HSP	c.755C>G	p.Ser252Trp	IgII–IgIII linker
8	Apert	25 y 11 m	F	WAIS	71	74	70	Normal	c.755C>G	p.Ser252Trp	IgII–IgIII linker
9	Crouzon	16 y 3 m	M	WISC III	101	97	98	Normal	c.938A>G	p.Tyr328Cys	IgIIIc
10	Crouzon	15 y 3 m	M	WISC III	92	95	93	ENC	c.938A>G	p.Tyr328Cys	IgIIIc
11	Crouzon	12 y	F	WISC III	95	93	93	ENC	c.833G>T	p.Cys278Phe	IgIIIa
12	Crouzon	8 y 5 m	M	WISC III	72	96	82	VM	c.1021A>C	p.Thr341Pro[d]	IgIIIc
13	Crouzon	12 y 10 m	M	WISC III	91	98	93	Normal	c.1061C>G	p.Ser354Cys	IgIIIc
14	Crouzon	10 y 11 m	M	WISC III	112	90	102	Normal	c.1025G>A	p.Cys342Tyr	IgIIIc

[a]Age (years/months) at cognitive testing.
[b]Nucleotide and amino acid residue numberings are in accordance with Cohen (21, 58). Mutation nomenclature is in accordance with the recommendations of the Human Genome Variation Society (http://www.hgvs.org/mutnomen/; den Dunnen and Antonarakis, 2000).
[c]Mutations that lead to ectopic expression of the alternative *FGFR2* 2b splice form.
[d]This case was described previously by Passos-Bueno et al. [1997].
M, Male; F, female; WAIS, Wechsler Adult Intelligence Scale; WISC III, Wechsler Intelligence Scale for Children; VIQ, verbal intelligence quotient; PIQ: performance intelligence quotient; FISQ: ful scale intelligence quotient. MRI: magnetic resonance imaging; HCC: hypoplasia of corpus callosum; VM: ventriculomegaly; HSP: hypoplasia of septum pellucidum; ENC: encephalomalacia.

FSIQs from 47 to78 (mean 67.2 ± 10.7). Another common mutation was found in one AS patient (p.Pro253Arg gain-of-function mutation) (Table I) and was associated with three structural brain abnormalities (ventriculomegaly, hypoplasia of the corpus callosum, and septum pellucidum) and a VIQ of 100, PIQ of 106, and FSIQ of 108. One case that had an atypical mutation, a disruption of the acceptor splice site of exon 9 (940–2A →G) (Table I), had a structurally normal brain on MRI, a VIQ of 100, PIQ of 108, and FSIQ of 104.

Six patients with CS had with mutations in exons IIIa and IIIc of the *FGFR2* gene (Table I). Brain abnormalities, including one case of ventriculomegaly and two cases of encephalomalacia, a postsurgical abnormality, were observed. VIQs of these patients ranged from 72 to 112 (mean 93.8 ± 13.2), PIQs ranged from 93 to 98 (mean 94.8 ± 2.9), and FSIQs from 82 to 102 (mean 93.5 ± 6.7).

DISCUSSION

We present the results of a study of 14 patients that presented before other factors related to IQ were investigated [Yacubian-Fernandes et al., 2005, 2007]. Data revealed that VIQ, PIQ, and FSIQ results were similar within patient groups, and in all measurements (VIQ, PIQ, and FSIQ), patients with CS outperformed those with AS. Patients with CS without brain malformations demonstrated intellectual functioning at the lower end of average. Among patients with AS, two had FSIQs that were substantially higher than the others. One patient with a splice mutation (940–2A →G) had a structurally normal brain on MRI and an FSIQ of 104, and the other patient with a p.Pro253Arg mutation had three structural brain abnormalities (ventriculomegaly, hypoplasia of the corpus callosum, and septum pellucidum) and an FSIQ of 108.

Patients with AS displayed three known mutations, p. Ser252Trp, p.Pro253Arg, or mutations of the splice site of *FGFR2* exon IIIc [Passos-Bueno et al., 1997]. Compared with patients with the p.Pro253Arg mutation, patients with AS with the p.SerS252Trp mutation had more severe ocular phenotypes [Jadico et al., 2006]. In contrast to data presented here, Lajeunie et al. [1999] concluded that the p.Pro253Arg mutation is associated with more severe disease with regard to syndactyly and cognitive outcomes. In our analysis, only one case had a p.Pro253Arg mutation; this patient had a FSIQ of 108, higher than the IQs of patients with p.SerS252Trp mutations.

Many studies have tried to correlate IQ among patients with AS to abnormalities of the central nervous system [Yacubian-Fernandes et al., 2004], such as hypoplasia of the septum pellucidum [de Leon et al., 1987] and high intracranial pressure [Marucci et al., 2008]. Malformation of limbic structures can indicate cognitive impairment not only in AS, but also in patients with callosal abnormalities. Indeed, studies of AS revealed that patients commonly had malformations of the corpus callosum, limbic structures, or both [de Leon et al., 1987; Cohen and Kreiborg, 1990]. Other findings frequently observed included megalencephaly, gyral abnormalities, encephalocele, pyramidal tract abnormalities, hypoplasia of cerebral white matter, and heterotopic gray matter. Progressive hydrocephalus seems to be uncommon and has frequently been confused with non-progressive ventriculomegaly [Cohen and Kreiborg, 1990; Murovic et al., 1993].

Raybaud and Di Rocco [2007] suggested that three categories of brain abnormalities accompany syndromic craniosynostosis: global mechanical distortion of the brain, chronic tonsillar herniation (Chiari I deformity), and abnormalities that involve white matter. In comparison, in this study, the most common findings were related to abnormalities of white matter.

Recent neurobiological evidence supports the model that white matter abnormalities are primary disorders. The L1 cell adhesion molecule (*L1CAM*) gene plays a major role in development of white matter. To operate, *L1CAM* must interaction with *FGFRs*. Because defects in *FGFRs* lead to craniosynostosis syndromes, *FGFR* defects may generate skull abnormalities and, by lack of interaction with *L1CAM*, produce primary defects in white matter [Raybaud and Di Rocco, 2007].

General conditions such as upper airway obstruction and hearing impairment can also interfere with normal neuropsychological development [Mitsukawa et al., 2004; Arduino-Meirelles et al., 2006; Hunter et al., 2009]. Da Costa et al. [2006] documented lower intellectual functioning in children with syndromic craniosynostosis (mean IQ 83.1 ± 21.9) when compared to nonsyndromic craniosynostosis (mean IQ 104.7 ± 15.8). The majority of children with syndromic craniosynostosis (77%) were of normal intelligence; however, children who have syndromic craniosynostosis had 1.9 times higher risk for having intellectual disabilities defined as FSIQ < 85 compared with the general population ($P < 0.001$) [Maliepaard et al., 2014]. In a study of intellectual and academic functioning of school-age children with single-suture craniosynostosis, Speltz et al. [2015] concluded that the most neurodevelopmentally vulnerable are those with unicoronal and lambdoid fusions.

In the study by Da Costa et al. [2006], children with nonsyndromic craniosynostosis did not display obvious evidence of intellectual dysfunction, and age and gender did not have an effect on intellectual outcomes. CS and AS have been associated with moderate cognitive impairment in other studies [Aguado et al., 1999]. Although the median IQ of CS patients was higher than that of AS patients, it was still lower than the average IQ in the general population. In addition, central nervous system abnormalities and high intracranial pressure are less frequent in CS compared to AS [Cohen and Kreiborg, 1996].

In both syndromes, environmental factors such as social aspects, quality of life, level of education of the parents, and occurrence of institutionalization have been correlated with cognitive performance [Ruggieri and Arberas, 2003; Yacubian-Fernandes et al., 2005, 2007; Bannink et al., 2010]. Another factor, well described in the literature, is early surgery, which has been associated with better cognitive performance, presumably by relieving high intracranial pressure [Renier et al., 1996; Thompson et al., 1997].

Many studies reference the necessity of complex neurophysiology and assess functions such as attention, concentration, memory, visual perception, language, arithmetic processes, praxis, executive functions, reasoning, and general intelligence [Aguado et al., 1999]. Using VIQ, PIQ, and FSIQ as objective measures to quantify cognitive functioning is also recognized in the literature [Patton et al., 1988; Murovic et al., 1993; Renier et al., 1996; Shipster et al., 2002; Da Costa et al., 2006]. Shipster et al. [2002] described eight children with AS with moderate or severe language difficulties that

were not associated with general cognitive deficits. However, cognitive development in patients with AS and CS is still not well understood, although multimodal influences of different factors have been described [Renier et al., 1996; Yacubian-Fernandes et al., 2004, 2005]. Multifactorial studies of development in patients with AS [Renier et al., 1996] revealed that performing surgery before 1 year of age was a primary factor associated with a final IQ greater than 70.

New methods of neuroimaging are revealing relationships between brain architecture, genetic mutations, and cerebral connectivity. Indeed, volumetric measurements of cerebral lobes or regions of interest are being used to define cerebral phenotypes associated with neurogenetic disorders with increasing precision [Schaer and Eliez, 2007]. The contribution of structural brain imaging in advancing our understanding of pathogenic processes underlying brain development may prove useful for defining many different syndromes [Schaer and Eliez, 2007].

This study presents information on cognitive development, structural brain abnormalities and molecular analyses of patients with AS and CS. At present, we do not have a clear understanding of the relationship among IQ, genetics and brain malformations. The data reveal that molecular aspects are another factor that can be considered in studies of the global and cognitive development of these patients.

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