ORIGINAL ARTICLE

STUDY OF RISK FACTORS IN CHILDREN WITH PRIMARY NON-SYNDROMIC CRANIOSYNOSTOSIS

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Abstract

Craniosynostosis (cranio=cranium + syn=together + ostosis=related to bone) is a condition in which one or more of the fibrous sutures in an infant skull prematurely fuses by ossification. Several risk factors for non-syndromic craniosynostosis (NSCS) have been suggested.

Material and Methods: In this observational study we studied the risk factors associated with NSCS in 30 children aged 1 month to 12 years attending pediatric outpatient department in tertiary health care institute in India.

Results: Male:Female ratio was 1.7:1. Twenty-five (83.6%) children belonged to the plains while 5 (16.7%) belonged to the hilly regions from Himachal Pradesh. Ten (33.3%) children were from the rural areas and the rest (66.7%) were from the urban area. The mother's age at conception was below 30 years in 28 (93.3%) patients. On the other hand 16 (53.3%) of the fathers were above 30 years of age.

Conclusion: Paternal age more than 30 years and male gender is associated with non-syndromic craniosynostosis.

Introduction

Craniosynostosis (CS) consists of premature fusion of one or more cranial sutures often resulting in abnormal cranial shapes. (1) In 1851, a German pathologist, Virchow introduced the term "craniostenosis" to describe a variety of abnormalities in calvarial growth. In non-syndromic or isolated craniosynostosis, there is no evident extracranial abnormality such as neurological, ophthalmologic manifestation, facial dysmorphism or asymmetry other than those associated with early sutural fusion. The etiology of non-syndromic craniosynostosis (NSCS) is still largely unknown and the condition is sporadic in most instances. (2) The earliest publications on the underlying cause of CS described some sort of infection, mostly syphilis. (3)Another explanation, persistently appearing in the literature in a variety of ways, is that of mechanical constraint. Both environmental factors (especially intrauterine fetal head constraint) and genes (single gene mutations, chromosome abnormalities and polygenic background) predispose to craniosynostosis. Several risk factors for NSCS have been suggested, including advanced maternal and paternal age, parity, education, ethnicity, altitude, male infant sex intrauterine constraint, prematurity and low birth weight. (4) Some studies have identified white maternal race, maternal smoking, maternal residence at high altitude, maternal use of drugs, certain paternal occupations and fertility treatments as potential risk factors for NSCS. (5)

Craniosynostosis presents with different clinical findings depending on the extent and number of fused sutures. The clinical outcome varies between minor cosmetic deformity to severe head growth restriction with mental retardation and cranial palsies. The diagnosis relies on physical examination and radiographic studies, including plain radiography and computed tomography (CT). We undertook this study to determine the risk factors associated with NSCS.

Methods & Materials

Thirty children of both sexes between the age group of 1 month to 12 years attending the department of pediatric genetic clinic and pediatric growth clinic with the suspected diagnosis of craniosynostosis from July 2012 to June 2013 were studied. Detailed history was taken including socioeconomic history, maternal history, birth history and development history. Socioeconomic status was classified according to the Kuppuswamy Scale of 2007. Development assessment charts were filled for a child with delayed development. Detailed examination was done by the investigator to confirm absence of any associated malformation. The clinical findings were confirmed by the same clinical examiner to maintain inter-examiner variability of the clinical findings related to dysmorphism. Anthropometry was done using standardized anthropometric techniques and instruments. (6) The magnitude of inter-rater error for two head diameters and head circumferences was 0-1mm and the error for inner canthal and outer canthal distance was within 0.0-0.4mm. Spreading caliper was used to measure head length and width up to the accuracy of 1 mm. (7) The maximum occipito-frontal diameter was measured by using fiber glass tape up to the accuracy of 1 mm. Body weight was measured using the electronic weighing scale with least count of 50 grams. Height/length was measured using the stadiometer/infantometer having least count of 1mm.World Health Organization (WHO), Centers for Disease Control (CDC) growth charts were used for the percentile values for the basic anthropometric data. In addition to the basic measurements, Cephalic Index (CI) was calculated by the following formula Cephalic Index = Head width / Head length X 100. Volumetric Spiral CT scans were acquired from base of skull to vertex on a 64-2000 Multi detector CT scan (Ac Qvilons, Toshiba).Images were reconstructed on a Terrerecon Work Station and 3D images of the skull were generated using a volume rendering software. Radiation exposure from CT scan was recorded for all patients (CTDI & DLP levels which are generated from CT console).

SPSS 16 statistical software was used for the statistical analysis. Mean and standard deviations were computed for all anthropometric and radiological measurements. To see the interrelationship between clinical and radiologic parameters, chi square test was applied. P value <0.05 was considered as significant.

Results

Mean age of the patients was 29.5 ±37.6 months with age range of 3 months- 12 years. Male: Female ratio was 1.7:1. Twenty-five (83.6%) children belonged to the plains of which12 (40%) were from Punjab, 7 (23%) were from Haryana and 6 (20%) were from

Chandigarh while 5 (16.7%) belonged to the hilly regions from Himachal Pradesh (p=0.36) Ten (33.3%) children were from the rural areas and the rest (66.7%) were from the urban area (p=0.540). Twenty four (80%) children belonged to the upper middle income group, five (16.7%) were in lower middle income group and only one child (3.3%) was from the high income group. There was no family with a similarly affected child. Moreover, no history of consanguinity was found in any of the families. The mother's age at conception was below 30 years in 28 (93.3%) patients. On the other hand 16 (53.3%) of the fathers were above 30 years of age. History of maternal infections during the antenatal period was found in 3 (10%) children. In addition, two mothers were on long term medications. There was no history of use of medications other than iron and folic acid during the antenatal period in other females. Although the smoking habits among the mothers were enquired, none of the mothers reported smoking habit. Five (17.9%) mothers had a history of previous abortions. Twin gestations were found in two mothers .The perinatal details are depicted in table 1. The details of sutures fused are given in Table 2.

Table 1: Perinatal details of the children

	Parameters	No. of patients (%)
1. Gestational age	Term	26 (86.7%)
	Preterm	4 (13.3%)
2. Mode of delivery	Normal Vaginal delivery	20 (66.7%)
	LSCS	10 (33.3%)
	Assisted/ instrumental	0
3. Birth weight	Appropriate for age	20 (66.7%)
	Low birth weight	8 (26.7%)
	Large for date	2 (6.7%)
4. APGAR Score	Normal	28 (93.3%)
	Low	02 (6.7%)
5. Post-natal complications	Birth Asphyxia	02 (6.7%)
	Seizures	01 (3.3%)
	Neonatal Jaundice	01 (3.3%)
	Birth Trauma	0

Table 2: Craniosynostosis phenotype based on the 3-D CT scan

Radiological parameters	Male	Female	Total (%)	P value
Number of sutures fused 1) No suture fused 2) Single suture fused 3) Multiple sutures fused	 0 (0%) 13(43.3%) 6 (20%)	 2(6.7%) 3(10%) 6(20%)	 2 (6.7%) 16 (53.3%) 12 (40. %)	
Total	**19 (63.3%)**	**11 (36.7%)**	**30 (100%)**	**0.037**
Monosutural 1) Metopic 2) Sagittal 3) Coronal 4) Lambdoid	 8(50%) 4(25%) 1(6.25%) 0	 0 2(12.5%) 1(6.25%) 0	 8 (50%) 6 (37.5%) 2 (12.5%) 0	
Total Monosutural	13 (81%)	03 (19%)	16	0.126
Polysutural a) Metopic + coronal b) Sagittal + coronal c) Coronal + lambdoid d) Metopic + sagittal +coronal e) Metopic+ sagittal + lambdoid f) Sagittal + coronal +lambdoid g) Metopic + sagittal + coronal + lambdoid	 1(8.3%) 0 1(8.3%) 1(8.3%) 1(8.3%) 0 2(16.6%)	 0 1(8.3%) 0 1(8.3%) 1(8.3%) 2(16.6%) 1(8.3%)	 1(8.3%) 1(8.3%) 1(8.3%) 2(16.6%) 2(16.6%) 2(16.6%) 3 (25%)	
Total Polysutural	**06**	**06**	**12**	**0.126**

Discussion

There are very few published studies from India on craniosynostosis. Some studies from outside

India studied risk factors associated with craniosynostosis with varying results. One study found the increasing maternal age appears to increase risk of craniosynostosis. (8) However other studies did not find a significant relationship between maternal age and risk of CS. (9) Increase age of the father has been linked to some syndromic craniosynostosis syndromes. (10) One study identified older age of the father as a risk factor (11) but other studies did not find any relation with non-syndromic CS and paternal age. (12) One study from India has found significant association of craniosynostosis with advancing parental age [OR 2.17(95% CI 1.08 to 4.360)]. (13) The explanation for this could be that advanced paternal age is associated with increased chance of mutation in the sperm which leads to increased risk of child born with genetic disorder like craniosynostosis. Present studies also support the findings.

Various studies have found child's gender to be associated with the craniosynostosis. One study has found predilection for dolichocephaly, scaphocephaly (sagittal) and metopic synostosis in males (14) while in brachycephaly and plagiocephaly (coronal CS) there is a female predilection. (10) However, not all studies have observed this association. (15) In the present study we have found the increase association of male gender.

Several studies found several risk factors including parity, intrauterine constraint, prematurity and low birth weight. (5)Mothers who live or work at high altitudes and also smoke may have an increased risk for having a child with CS, especially for coronal and metopic synostosis. (16) In the present study we did not found any such association.

We conclude that paternal age more than 30 years and male gender is associated with non-syndromic craniosynostosis. Further studies are required to validate these findings.

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