

Craniosynostosis's Five-Year Epidemiologic Findings in Isfahan

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Abstract

Background: Craniosynostosis, is defined as the premature fusion of the cranial sutures, which can cause impair brain development and cognitive problems.

Objectives: The purpose of this study was to assess the epidemiological features of children with craniosynostosis. This assessment includes the characteristics of the patients, their parents as well as their socioeconomic status.

Methods: This cross-sectional study was performed from 2015 to 2020 in Imam Hossein Children's Hospital, Isfahan, Iran. For this purpose, 220 patients under craniosynostosis treatment were included. Accordingly, multidisciplinary team examined the participants. Furthermore, a CT-scan was performed on all patients. Participants underwent surgical intervention. The recorded information was classified into four sections: 1. characteristic data of children with craniosynostosis 2. Family history and parental information, including underlying diseases and drug history 3. Socioeconomic status 4. Treatment and surgery.

Results: According to findings, 151 (68.7 %) of participants were male and 171 (77.9%) had term delivery. The average birth weight was 2.92 kg and head circumference were 34.4 cm. The mean age of children at the time of surgery was 7.74 months and the mortality rate was 3 (1.4%). Moreover, 90% were operated once and 10% were operated two or three times. The most common type of craniosynostosis was Metopic 59 (59.4%). In relation to parenteral data, 96 (43.6%) of parents had consanguineous marriage and 6.4% had 1st and 2nd degree family with craniosynostosis.

Conclusion: To conclude, attention must be directed towards the potential risk of craniosynostosis in offspring born to consanguineous couples. Moreover, parents must receive guidelines for managing children affected by craniosynostosis.

Keywords: Craniosynostosis, Epidemiology, Neurosurgery

1. Background

Craniosynostosis represents the premature fusion of one or more cranial sutures. It is a common malformation that occurs in about 1 in 2,000 to 2500 live births.¹ There are various complications associated with craniosynostosis, including increased Intracranial Pressure (ICP), which occurs in 8% of patients.^{2,3} Abnormalities related to speech, behavior, cognitive, and neurodevelopmental status are seen in children diagnosed with craniosynostosis. However, the exact relationship between structural and developmental problems remains unknown.^{4,5} The diagnosis of premature fusion of calvarial bones in one or more cranial sutures is based primarily on physical examination. However, Computed Tomography (CT) can accurately show the fusion and the general condition of the skull sutures. A CT-scan can also delineate associated problems, including hydrocephalus and bony abnormalities. Genetic testing is used in syndromic types.⁶⁻⁸ A multidisciplinary team is needed to manage craniosynostosis patients.^{9,10} However, the only definitive treatment is

surgery, which both prevents increased ICP and improves the look of the patient's head. The most common surgical procedure is open surgery, which is done on all types of craniosynostosis.^{2,11}

Numerous studies are available, providing data on the role of genetics in craniosynostosis, its treatment approaches, and different surgical methods. Yet, information on its risk factors such as socioeconomic status, pregnancy-related conditions, and other comorbidities is limited. Maternal consumption of anticonvulsant drugs, in particular sodium valproate, is a known risk factor for craniosynostosis in children.^{12,13} Maternal diseases, such as thyroid problems, can also be associated with developing craniosynostosis.¹⁴ Studies have shown that the socioeconomic status of parents and unhealthy behaviors like smoking in mothers are related to craniosynostosis development in their children.^{15,16} Therefore, in addition to treatment and genetic characteristics, it is critical to examine the parenteral

conditions, especially during pregnancy. Underlying diseases and socioeconomic status are specifically noteworthy in our investigations. Since new studies show an increase in craniosynostosis prevalence, it is getting more important to examine these risk factors.¹⁷

2. Objectives

The present study evaluates the characteristic features of children with craniosynostosis. Parental factors including underlying diseases, drug use, and socioeconomic status were also investigated.

3. Methods

3.1. Study Design and Ethics

This cross-sectional study was performed from 2015 to 2020 in Imam Hossein Children's Hospital, Isfahan, Iran. The information of individuals was kept confidential. The Research Center of Isfahan University of Medical Sciences approved the research protocol. The current study was approved by the Isfahan University of Medical Sciences Ethics Committee with the code of IR.MUI.MED.REC.1399.472.

3.2. Study Population

Participants in the present study were children with a definitive diagnosis of craniosynostosis. The diagnosis was made by a physical examination performed by a pediatric neurosurgeon and confirmed using a three-dimensional CT-scan. All patients in the study underwent open craniosynostosis surgery. A total of 220 participants

were included in the study.

3.3. Study Procedure

Hospital records of patients diagnosed with craniosynostosis, who were referred to Imam Hossein Children's Hospital between the years 2015 and 2020 were used in this study. A multidisciplinary team examined all participants. In addition, a CT-scan was performed on all patients. It is worth mentioning that all participants underwent surgical intervention. The recorded information was classified into four sections: 1. Characteristic data of children with craniosynostosis 2. Family history and parental information, including underlying diseases and drug history 3. Socioeconomic status 4. Treatment and surgery.

3.4. Statistical Analysis

The SPSS version 22 statistical software was used for data analysis. Descriptive statistics for qualitative variables were in the form of frequency and percentage and for quantitative variables in the form of mean and standard deviation.

4. Results

4.1. Children with Craniosynostosis

A total of 220 children with craniosynostosis participated in our study, 151 (68.7%) of whom were male and 69 (31.3%) female. The majority of participants (77.9%) had a term delivery, compared to 22.1% who had a preterm delivery. The average birth weight was 2.92 ± 0.70 kg, and the average head circumference was 34.4 ± 2.25 cm.

Table 1. Characteristics of Children with Craniosynostosis

Variables	Subcategory	N (%)
Gender	Male	151 (68.7)
	Female	69 (31.3)
Pregnancy Length	Term	171 (77.9)
	Pre-term	49 (22.1)
Birth order	1st	67 (30.3)
	2nd	102 (46.2)
	3rd	26 (12.1)
	4th	17 (7.6)
	5th	6 (3)
	6th	2 (0.8)
Weight, kg, mean \pm SD (Rang)	At birth	2.92 ± 0.70 (0.98-4.64)
	At operation	7.61 ± 6.08 (2-20)
Head Circumference, cm, mean \pm SD (Rang)	At birth	34.43 ± 2.25 (28-39)
	At operation	40.52 ± 3.34 (32-49)
Age, Month, mean \pm SD (Rang)	At operation	7.74 ± 10.4 (1.1-43)
Major Co-existing diseases	CHD	57 (57.64)
	NICU	29 (29.7)
	Allergy, Asthma	7 (7.04)
	Seizure	5 (5.28)
	Crouzon Syndrome	5 (5.28)
	Other operation with anesthesia	11 (10.56)
Types of Craniosynostosis	Sagittal	47 (21.5)
	Metopic	59 (59.4)
	Coronal	36 (36.52)
	Lambdoid	2 (1.32)
	Pansynostosis	53 (52.58)
	Multisuture	23 (22.88)

CHD: Congenital Heart Disease, cm: Centimeter, Kg: kilogram, NICU: Neonatal intensive care unit, N: Number, SD: Standard Deviation, kg: Kilogram, cm: Centimetre

Table 2. Family History and Parental Information

Variable	Subcategory	N (%)
Mean Age, year, (mean \pm SD)	Mother	29.92 \pm 5.78
	Father	34.12 \pm 2.98
Marriage type	Consanguineous	96 (43.6)
	Unrelated	124 (56.4)
Infertility history	Yes	4 (1.8)
	No	216 (98.2)
Abortion	Yes	27 (12.3)
	No	193 (87.7)
Delivery type	NVD	46 (20.9)
	C/S	173 (78.1)
Family History of Craniosynostosis (1 st , 2 nd relatives)	Yes	14 (6.3)
	No	206 (93.7)
Underlying maternal and pregnancy-related conditions	Thyroid Diseases	23 (10.5)
	Gestational Diabetes	9 (4.1)
	Hypertension	7 (3.2)
	Anemia	3 (1.4)
	Urinary Tract Infection	2 (0.9)
	Anxiety/Depression	2 (0.9)
	Other	1 (0.5)
	Paternal condition	41 (18.7)
Paternal condition	Smoking	41 (18.7)
	Drug Addiction	14 (6.4%)
	Seizure	1 (0.5)
	Other	1 (0.5)

NVD: Natural vaginal delivery, C/S: Cesarean Section

At the time of surgery, the mean age of children was 7.74 \pm 7.84 months (Range = 1.1-43) and the mean head circumference was 40.52 \pm 3.34. The most common type of craniosynostosis was Metopic 59 (59.4%). Also, the major underlying diseases and comorbidities were recorded. The most common disease was Congenital Heart Disease which was seen in 57 (57.64%) participants. Other comorbidities, including kidney, thyroid, and cleft lip and palate, were present in less than 1% of participants. Moreover, 4.8% of children underwent surgeries other than craniosynostosis. More demographic information has been presented in Table 1.

4.2. Family History and Parental Factors

The results of the information of parents of children with craniosynostosis have been shown in Table 2. The mean age of mothers at the time of birth-giving was 29.92 (SD = 5.35) and fathers 34.12 (SD = 5.44). Furthermore, 43.6% of couples had consanguineous marriages, 1.8% had a history of infertility treatment, and 12.3% of mothers reported a history of abortion. Also, among children diagnosed with craniosynostosis, 21% were born by Normal Vaginal Delivery (NVD) and 79% by a Cesarean Section (C/S). Regarding the family history of craniosynostosis, 6.4% (9.9% valid percent) had 1st or 2nd-degree family members with craniosynostosis. The most common maternal problem was thyroid diseases. More information on parental condition is presented in Table 2.

4.3. Socioeconomic Status

Regarding the socioeconomic status of parents, their job was considered as a criterion. In this regard, 93% of the mothers were housewives and had no income, 3.6% were employees, 1.4% had a local business, 0.7% were students, and 0.7% were professors or teachers. In

addition, 46.5% of the fathers had a local business, 26.8% were workers, and the rest included: 15.5% employees, 9.2% farmers, 1.4% unemployed, and 0.7% teachers and professors.

4.4. Treatment and Surgery

All children included in the study underwent craniosynostosis surgery. The mean age at surgery was 7.74 months. The mortality rate was 1.4% (N = 3). Moreover, 90% had a one-time surgery, and 10% went under two or three operations. The main reason for redoing the surgery was due to the appearance of the head and face.

5. Discussion

Craniosynostosis refers to the premature closure of the cranial sutures.¹⁸ Craniosynostosis divides into two main groups, syndromic and non-syndromic.¹⁹ Different sutures are involved in both types. One of the most common complications of craniosynostosis is an increased ICP. The risk of increased ICP is proportional to the number of sutures involved.^{20,21} The exact mechanism for premature closure of cranial sutures is unknown. However, mutations in specific genes are identified in most patients. Mutations in fibroblast growth factor receptor (FGFR-1, FGFR-2, FGFR-3), TWIST, and MSX2 have been detected.²² Also, based on past epidemiological studies, the most common involved sutures are 1. Sagittal (40%-58%), 2. Coronal (20%-29%), 3. Metopic (4%-10%), 4. Lambdoidal (2%-4%) and multiple sutures account for approximately 5% of craniosynostosis. In the present study, the frequency of the types of involved sutures is different from the available data. Multiple or pansynostosis involvement was responsible for 34.3% of cases. Metopic suture was also the most common involved suture (27%) [Sagittal (21.5%), Coronal (16.6%), Lambdoid (0.6%)]. Besides, 26.5% of participants had Congenital Heart

diseases, which indicates a higher prevalence of the syndromic type in the Middle East region. Furthermore, the prevalence of craniosynostosis amongst males was more than twice as females, which requires further analysis. No abnormal change in the head circumference was observed at birth, and for this reason it cannot be considered as a predicting factor at the birth time.

Also, the mortality rate from craniosynostosis surgery in Iran was similar to that in the United States.²³ The mortality rate was 1.4% (3 of 220), indicating that craniosynostosis surgery is a safe treatment. Redoing the surgery is usually done because of the patient's appearance improvement. Accordingly, its costs should be considered as a factor in the decision making of families.

Previous studies have suggested a variety of risk factors for craniosynostosis. A study by Bengt Källén in 2005, shows that the use of anticonvulsant drugs is strongly associated with craniosynostosis.¹² Sodium valproate has specifically been linked to the involvement of metopic suture synostosis.¹³ Also, smoking has a moderate risk of developing craniosynostosis.¹⁶ Tobacco use was not observed in any of the mothers participating in our study. However, 18.7% of fathers were smokers, which can be a risk factor (with second-hand smoker effect). Furthermore, the most common maternal problem was thyroid diseases, which is consistent with previous studies. Sonja A Rasmussen et al. showed that maternal thyroid disease, especially Graves' disease, could be associated with craniosynostosis.¹⁴ Another noteworthy point was the high rate of consanguineous marriage (1st and 2nd-degree family) among the participants. Accordingly, 43.6% of parents had a consanguineous marriage, which could be a reason for the high prevalence of syndromic types in Iran.

Bradley et al. had shown that paternal occupation, such as agriculture and forestry, could be a moderate risk for craniosynostosis.¹⁵ In our study, 93% of mothers were housewives and had no income. Also, more than a third of the fathers' occupations were workers or peasants. The results of this part of the study are noteworthy in two ways: 1. Possible risk factors and 2. Treatment costs. Since 93% of mothers did not have any income and fathers had low-paying jobs, special attention should be paid to the costs of treating children with craniosynostosis. In particular, the lack of cosmetic surgery for these children can have major effects on their quality of life in the future. Anxiety, depression, and isolation from the society are the main problems these children can face throughout their lives. Also, due to a lack of sufficient education in parents, they may not be able to identify the disease as a real problematic issue that needs their supportive care.

6. Conclusion

Previous Studies on craniosynostosis have focused on treatment and genetics. However, in recent years, it has

been shown that other epidemiological factors such as different regional areas, underlying diseases, drug use by parents, and socioeconomic factors can have a significant role in the development and treatment of this disease. Therefore, the present study provides comprehensive information about children with craniosynostosis and their parents, which could be useful for managing craniosynostosis and help the treatment team.

Research Highlights

What Is Already Known?

The demographic characteristics of patients with craniosynostosis in Iran, especially in Isfahan, have not been extensively reported; thus, a comprehensive understanding of this matter is lacking.

What Does This Study Add?

Most patients are male; approximately half of their parents have engaged in consanguineous marriages. The mortality rate among these patients is less than 1.5%.

Author Contributions

Authors contributed equally to this work.

Conflict of Interest Disclosures

All authors declared that they have no conflict of interest.

Ethical Approval

The current study was approved by the Isfahan University of Medical Sciences Ethics Committee with the code of IR.MUI.MED.REC.1399.472.

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