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Prevalence of Different Types of Craniosynostosis in Isfahan, Iran

Ali Riazi¹, Mostafa Allami², Alireza Arabi³, Mehrdad Larry^{1*}¹Department of Neurosurgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran²School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran³National Center for Health Insurance Research, Tehran, Iran***Corresponding Author:** Mehrdad Larry, M.D., Neurosurgery Resident, Department of Neurosurgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98-9128504065 Email: mehrdad.larry@gmail.com

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Abstract

Background: Craniosynostosis is a congenital deformity of the skull that occurs at birth.**Objectives:** This study aimed to investigate the frequency of different types of craniosynostosis in Isfahan, Iran.**Methods:** In this retrospective study, the records of all patients referred to the pediatric neurosurgery clinic of Imam Hossein children's hospital in Isfahan, Iran from 2013 to 2018 were diagnosed with craniosynostosis. Incomplete files were excluded. Demographic information of patients and type of delivery, underlying diseases of their parents, diseases of maternal pregnancy, type of craniosynostosis, syndromic or non-syndromic craniosynostosis were collected. Data were analyzed using SPSS software version 22.**Results:** The diagnosis of craniosynostosis in 63% of cases (n=121) was a single suture and in 37% of cases (n=72) was a complex suture. There was no significant difference in the frequency distribution of craniosynostosis in males and females ($P>0.05$).**Conclusion:** Due to the prevalence of 16 cases per 100,000, we can reduce the complications of this disease by educating doctors and parents.**Keywords:** Craniosynostosis, Prevalence, Epidemiology

1. Background

Primary craniosynostosis is a congenital anomaly that occurs as a result of premature closure of one or more of the skull sutures, with an approximate incidence of one in every 2100 to 2500 live births.^{1,2} Skull growth normally occurs at the surface perpendicular to the sutures, but in craniosynostosis it is restricted only to the suture that has been closed prematurely, leading to deformity in the Calvaria at birth.^{3,4}

Anatomically, craniosynostosis is divided into two forms: single (involvement of one skull suture) and complex (involvement of several sutures), and each of these two types is divided into sub-branches based on the location of the sutures involved.⁵ Craniosynostosis occurs in most cases alone, but can occasionally be associated with a variety of syndromes, including about 150. The most common craniosynostosis syndromes are Crouzon syndrome, Apert syndrome, Pfeiffer syndrome, Muenke syndrome, and Saethre-Chotzen syndrome.^{6,7}

The most common form of craniosynostosis is sagittal craniosynostosis, which is caused by premature closure of the sagittal suture. Its prevalence is one in 5000 live births and accounts for approximately 40% to 55% of non-syndromic cases of craniosynostosis. Sagittal craniosynostosis is predominantly seen in males. Most

cases are monocotyledonous and appear to be familial in 6% of cases.⁸ Coronal craniosynostosis is the second most common non-syndromic form of craniosynostosis, with a prevalence of approximately one in 10000 live births. Coronal craniosynostosis is divided into unicoronal and bicoronal. It is often seen in females and studies have shown that in 8% to 15% of non-syndromic types of craniosynostosis, there is a family history.⁸ Another form of non-syndromic craniosynostosis is the metopic type,⁹ which is the third most common type.¹⁰ Metopic synostosis prevalence is approximated at 67 per 1000000 births, the male to female ratio is 3.3:1, and no relation with paternal or maternal age has been stated.^{11,12} Lambdoid Craniosynostosis accounts for 3% to 5% of craniosynostosis cases and its prevalence is approximately one in 33000 live births and rarely has a family history. In 5% of nonsyndromic cases of craniosynostosis, two or more of the two skulls become involved in premature closure, which is called complex craniosynostosis.⁸

The prevalence of cranial suture involvement in craniosynostosis is as follows: Sagittal sutures are the most common sutures involved, followed by coronal (unilateral), coronal (bilateral), metopic, and least commonly lambdoid sutures.¹³ However, a study published by Singer et al. in 1999 found that over a 14-year period

from 1980 to 1994, the prevalence of craniosynostosis in Australia increased by 4% per year and that the most common types of craniosynostosis studied were sagittal and lambdoid, respectively.¹⁴ However, the results of some new studies have shown that in recent decades the incidence of metopic sinusitis has increased significantly and has changed its position to the second most common form of craniosynostosis.^{1,5,9,15}

People's race is strongly related to their genetic characteristics, and therefore obvious racial differences between different races can provide a genetic or even cultural underlying factor for craniosynostosis.⁵ The results of studies by Anderson et al. showed that the Asian race is significantly different from the white race in the prevalence of sutures involved in the non-syndromic type of craniosynostosis so that the sagittal form is more common in the white race and the multi-suture form is more common in the Asian race.⁵ Greenwood et al. also concluded that the gene content of non-syndromic types of craniosynostosis seems to be suture specific.⁸ Recent studies have shown an increase in the prevalence of metopic form in the United States and Europe, the main cause of which is still unknown.¹

The results of some studies have indicated that several environmental factors such as parity, prematurity, limited intrauterine space, and the use of tobacco or nitrosatable drugs during maternal pregnancy cause sagittal craniosynostosis. A new study also shows the existence of genes that may be involved in the development of sagittal craniosynostosis.⁸

2. Objectives

It seems that despite the frequency mentioned in several studies that have shown that sagittal type is the most common type of craniosynostosis,⁸ the sagittal form does not seem to be the most common among craniosynostosis patients visited in Isfahan province. Due to these observations and the lack of statistics on the frequency of craniosynostosis in Iran, this study aimed to investigate the frequency of craniosynostosis in patients referred (over a five-year period) to the Pediatric Neurosurgery Clinic of Imam Hossein children's hospital, Isfahan, Iran.

3. Methods

The present study is a descriptive-analytical and cross-sectional study that was conducted between 2013 to 2018 in Imam Hossein Children's Hospital of Isfahan, Iran. The study population was the records of all patients referred to the Pediatric Neurosurgery Clinic with a diagnosis of craniosynostosis. Since in this study the records of all patients were reviewed, sampling was not performed. All patients with complete records in whom the diagnosis of craniosynostosis (both syndromic and non-syndromic) is definitive were included in the study and cases with defective data recording were excluded from the study.

Demographic information of each patient including age, sex, race, ethnicity, place of birth, place of residence, birth

weight, type of delivery, underlying diseases of parents, maternal gestational diseases, type of craniosynostosis, craniosynostosis syndrome, or non-syndrome was collected. In this study, the diagnosis of craniosynostosis was confirmed using brain imaging (three-dimensional CT scan) and in cases of syndromic craniosynostosis, its syndrome was confirmed by a pediatric neurologist and geneticist.

Quantity and percentage indices for qualitative and mean variables and standard deviation for quantitative variables were utilized to determine frequency tables. The chi-square test was used to analyze the data. Statistical analyses were performed by SPSS software version 22. In this study, a statistically significant level of 0.05 was considered.

4. Results

In this study, 64% (n=123) of patients were male and 36% (n=70) were female. Also, most patients (83%; n=161) were full-term infants at birth and there was a significant difference between the two sexes ($P=0.030$); so that 88% (n=108) of male patients were term and this ratio was 76% (n=53) for female patients. The diagnosis of craniosynostosis was 63% (n=121) as a single suture and in 37% (n=72) as a complex; a comparison of male and female patients in this regard is shown in [Figure 1](#). In both sexes, the highest frequency of craniosynostosis was single suture. Among all types of craniosynostosis, 71% (n=136) of the diagnoses included metopic (27%), sagittal and pansynostosis (22% for each), respectively. Among the types of diagnoses of single suture craniosynostosis, metopic (43%; n=52), sagittal (35%; n=42) and unicoronal (21%; n=26) diagnoses had the highest frequency, respectively. Regarding complex diagnoses, the most common types were pansynostosis (58%; n=42), multiple suture synostosis (28%; n=20) and bicoronal (14%; n=10), respectively.

The frequency distribution of craniosynostosis types by sex is shown in [Figure 2](#). In male patients, metopic (34%) and sagittal (25%) and, in female patients, pansynostosis (31%) and unicoronal (24%) were the most common types of craniosynostosis. There was no significant difference between the frequency of craniosynostosis in male and female patients ($P=0.068$); meanwhile, this study was not

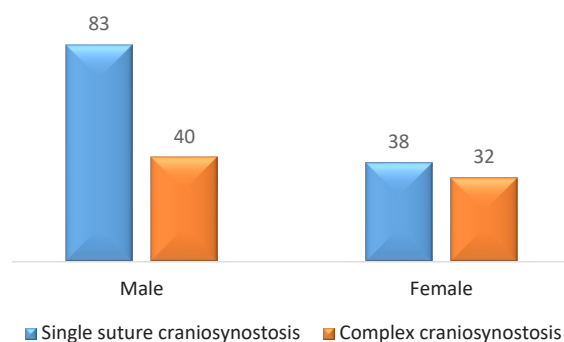


Figure 1. Comparison of different types of craniosynostosis by sex

significant by controlling the difference between male and female patients in terms of term or pre-term ($P=0.077$) (Table 1).

Examination of the frequency distribution of different types of craniosynostosis diagnoses between blood groups showed that in both types of single suture and complex, blood groups A and O had the highest frequency, respectively; so that the blood group of patients in 71% ($n=86$) of cases with the diagnosis of single suture and 66.5% ($n=48$) of cases with the diagnosis of complex belonged to these two blood groups. Meanwhile, there was no significant difference in the frequency distribution of blood groups between the two types of diagnosis of craniosynostosis ($P=0.790$) (Figure 3). In all types of craniosynostosis, patients' RH was positive in 92% of cases ($n=177$). Examination of the frequency distribution of various diagnoses of craniosynostosis in terms of blood RH showed that in both types of single suture and complex, RH+ patients had the highest frequency (91%; $n=110$ in single suture and 93%; $n=67$ in complex. In this regard, there was no significant difference between the two types of diagnosis ($P=0.601$) (Table 2).

The population born in Isfahan province in 2018 was 80556, of which 51% were male ($n=41265$) and 49%

were female ($n=39291$). Accordingly, the prevalence of craniosynostosis in Isfahan province, in the period of five years from 2013 to 2018, was equal to 78 per 100 thousand live births and the annual prevalence was approximately equal to 16 per 100 thousand live births. For male patients living in Isfahan, the prevalence in the period of 5 years was 89.66 per 100 000 live births and for female patients was 66.17 per 100 000 live births. Also, the annual prevalence in both sexes was 17.93 and 13.23 per 100 000 live births, respectively. The prevalence of craniosynostosis in Isfahan province is shown in Table 3.

5. Discussion

Craniosynostosis (craniostenosis) is a premature fusion of the sutures of the cranial vault. A couple of factors can influence the development of the cranial vault throughout embryonic life and after birth, which leads to numerous kinds of craniosynostosis; these can be categorized based on the particular sutures that are fused. Prognosis is developed by initial diagnosis, and it is significant to adopt the right approach to these patients based on the neuroradiological and clinical examination. The first priority is to recognize the kind of craniosynostosis and differentiate between the types that need surgical interventions and those that do not.^{12,16,17}

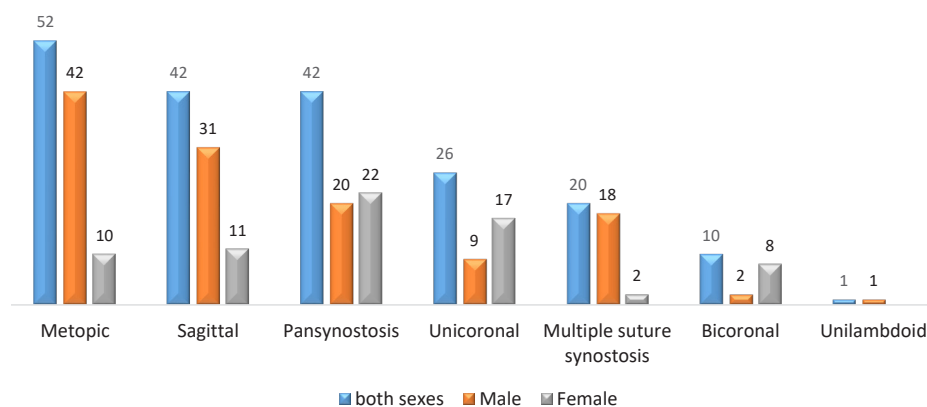


Figure 2. Frequency Distribution of Craniosynostosis in Children by Sex

Table 1. Frequency Distribution of Different Types of Craniosynostosis Diagnoses by Patients by Sex and Gestational Age at Birth

Types of Craniosynostosis	Gender No. (%)			P Value	Gestational Age at Birth No. (%)			P Value
	Male	Female	Total		Term	Preterm	Total	
Single suture craniosynostosis	83 (69)	38 (31)	121 (100)	0.068*	102 (84)	19 (16)	121 (100)	0.077*
Metopic	42 (81)	10 (19)	52 (100)		43 (83)	9 (17)	52 (100)	
Sagittal	31 (74)	11 (26)	42 (100)		36 (86)	6 (14)	42 (100)	
Unicoronal	9 (35)	17 (65)	26 (100)		22 (85)	4 (15)	26 (100)	
Unilambdoid	1 (100)	-	1 (100)		1 (100)	-	1 (100)	
Complex craniosynostosis	40 (56)	32 (44)	72 (100)		59 (82)	13 (18)	72 (100)	
Pansynostosis	20 (48)	22 (52)	42 (100)		36 (86)	6 (14)	42 (100)	
Multiple suture synostosis	18 (90)	2 (10)	20 (100)		15 (75)	5 (25)	20 (100)	
Bicoronal	2 (20)	8 (80)	10 (100)		8 (80)	2 (20)	10 (100)	
Total	123 (64)	70 (36)	193 (100)		161 (83)	32 (17)	193 (100)	

*Comparison was performed using chi-square test between two types of diagnosis: Single suture craniosynostosis and complex craniosynostosis.

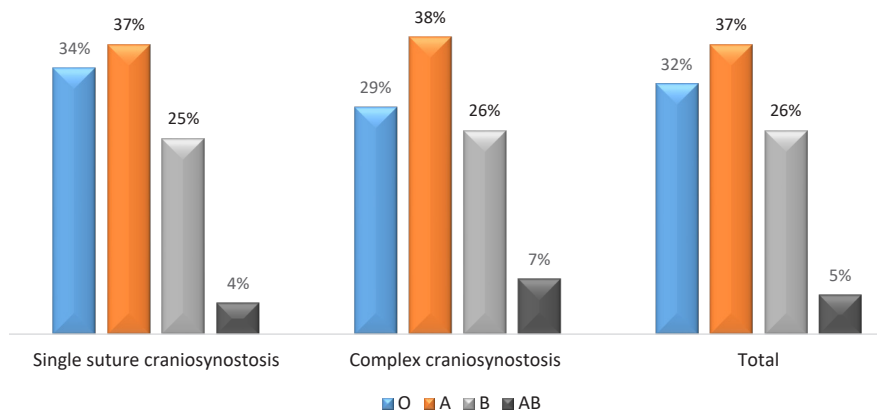


Figure 3. Frequency Distribution of Craniosynostosis by Blood Groups

Table 2. Frequency distribution of different types of craniosynostosis diagnoses in patients by blood type and RH

Types of Craniosynostosis	Blood Type No. (%)					P Value	Rh No. (%)			
	A	B	AB	O	Total		Rh+	Rh-	Total	P Value
Single suture craniosynostosis	45 (37)	30 (25)	5 (4)	41 (34)	121 (100)	0.790*	110 (91)	11 (9)	121 (100)	0.601*
Metopic	20 (38)	13 (25)	2 (4)	17 (33)	52 (100)		45 (87)	7 (13)	52 (100)	
Sagittal	15 (36)	9 (21)	3 (7)	15 (36)	42 (100)		41 (98)	1 (2)	42 (100)	
Unicoronal	10 (39)	8 (31)	-	8 (31)	26 (100)		23 (88)	3 (12)	26 (100)	
Unilambdoid	-	-	-	1(100)	1 (100)		1 (100)	-	1 (100)	
Complex craniosynostosis	27 (38)	19 (26)	5 (7)	21 (29)	72 (100)		67 (93)	5 (7)	72 (100)	
Pansynostosis	18 (43)	9 (21)	3 (7)	12 (29)	42 (100)		39 (93)	3 (7)	42 (100)	
Multiple suture synostosis	7 (35)	7 (35)	1 (5)	5 (25)	20 (100)		19 (95)	1 (5)	20 (100)	
Bicoronal	2 (20)	3 (30)	1 (10)	4 (40)	10 (100)		9 (90)	1 (10)	10 (100)	
Total	72 (37)	49 (26)	10 (5)	62 (32)	193 (100)		177 (92)	16 (8)	193 (100)	

*Comparison was performed using Chi-square test between two types of diagnosis: Single suture craniosynostosis and Complex craniosynostosis.

Table 3. Frequency and Prevalence* Types of Craniosynostosis Diagnoses in Patients Living in Isfahan

Types of Craniosynostosis	Male			Female			Total		
	No. (%)	General Prevalence	Annual Prevalence	No. (%)	General Prevalence	Annual Prevalence	No. (%)	General Prevalence	Annual Prevalence
Single suture craniosynostosis	24 (65)	58.16	11.63	14 (54)	35.63	7.13	38 (60)	17.47	9.43
Metopic	9 (24)	21.81	4.36	3 (12)	7.64	1.53	12 (19)	14.90	2.98
Sagittal	10 (27)	24.23	4.85	4 (15)	10.18	2.04	14 (22)	17.38	3.48
Unicoronal	4 (11)	9.69	1.94	7 (27)	17.82	3.56	11 (17.5)	13.66	2.73
Unilambdoid	1 (3)	2.42	0.48	-	-	-	1 (2)	1.24	0.25
Complex craniosynostosis	13 (35)	31.50	6.30	12 (47)	30.54	6.11	25 (40)	31.03	6.21
Pansynostosis	4 (11)	9.69	1.94	3 (23)	15.27	3.05	10 (16)	12.41	2.48
Multiple suture synostosis	9 (24)	21.81	4.36	2 (8)	5.09	1.02	11 (17.5)	13.66	2.73
Bicoronal	-	-	-	4 (15)	10.18	2.04	4 (6)	4.97	0.99
Total	37 (100)	89.66	17.93	26 (100)	66.17	13.23	63 (100)	78.21	15.64

*Prevalence rates per 100000 live births.

In the current study, 86% of patients were diagnosed with craniosynostosis at birth and only 14% were preterm. In this regard, there was a significant difference between the two sexes. Speltz et al¹⁸ indicated craniosynostosis patients with a mean age of 6.5 ± 3.9 months at diagnosis; meanwhile, Zakhary et al¹⁹ indicated mean age of 8.9 months (range 5-30 months) at the surgery. Similar to the present study, these studies do not include patients over 2

years of age.

In the present study, the most common types of craniosynostosis were Metopic, Sagittal, and Pansynostosis, respectively. Ghali et al²⁰ and Byun et al²¹ in their studies reported that sagittal type is the most common type which is not consistent with the findings of the present study. Meanwhile, Bennett et al¹⁰ showed that metopic synostosis was the second most common type of craniosynostosis

Research Highlights

What Is Already Known?

Some of the demographic characteristics of patients with craniosynostosis were known, and the appropriate measures and solutions for its treatment are adopted according to the characteristics of the patients.

What Does This Study Add?

Early diagnosis, knowledge of the characteristics of the disease, periodic examinations, familiarization of parents with this disease and its causes can lead to minimal complications and better treatment results.

between 2004 and 2014. The diagnosis of craniosynostosis in 63% was single suture and in 37% of patients was complex, and in both sexes, the highest frequency of craniosynostosis was assigned to single suture. Among the diagnoses of single suture craniosynostosis, metopic, sagittal, and unicoronal diagnoses and in complex diagnoses, pansynostosis, multiple suture synostosis, and bicoronal diagnoses had the highest frequency, respectively. In the study of Byun et al,²¹ a total of 266 patients treated from 1996 to 2016 were retrospectively reviewed. The results showed that 10.15% were bicoronal, 10.53% metopic, 18.04% unicoronal, 18.80% were unilamboid, and 25.19% patients were sagittal.

In this study, no significant difference was observed between craniosynostosis in males and females. Bennett et al¹⁰ showed that the male gender was associated with metopic craniosynostosis.

The annual prevalence of craniosynostosis in Isfahan province, Iran was approximately equal to 16 per 100 000 live births. According to KOSIS report, the number of new births in Korea has gradually decreased since 2000, but CRS diagnoses have generally increased, especially from 2010 onwards.²² Accordingly, careful screening examinations, as well as better knowledge of parents and physicians, have led to the increased craniosynostosis diagnosis.

6. Conclusion

To diagnose craniosynostosis early, doctors must be fully aware of this disease. Furthermore, parents must be adequately educated. With proper and timely diagnosis, craniosynostosis patients can be treated with better results and minimal complications. It is recommended that the pediatrician monitor the growth of the baby's head during periodic check-ups.

Author Contributions

AR contributed as the main author with the concept of planning the study. AR and ML contributed in study design, patient selection and follow ups. MA and ML performed the statistical analysis and interpreted the data. ML and AA write the manuscript and AR mentored the edition of the final version.

Conflict of Interest Disclosures

All authors declared that they have no conflict of interest.

Ethical Approval

This study was approved by Isfahan University of Medical Sciences Ethics Committee with code of IR.MUI.MED.REC.1397.253.

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