Int Clin Neurosci J. 2022;9:e30 Original Article

doi:10.34172/icnj.2022.30

Prevalence of Cardiac Anomalies in Children with Syndromic and Non-syndromic Craniosynostosis

Ali Riazi[1], Mahdi Vahidian[2], Mehrdad Larry[2*], Donya Sheibani Tehrani[3], Mostafa Alami[2], Zahra Salehi[2], Maryam Karimi[2], Sarina Loghmani[2]

[1]Department of Neurosurgery, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Department of IT, Shahid Beheshti University, Tehran, Iran

Abstract

Background: Craniosynostosis mostly occurs as a single abnormality; however, it may rarely occur concomitantly with other congenital abnormalities known as syndromic craniosynostosis. Cardiac anomalies are among the most common ones occurring coincidentally with craniosynostosis. Nevertheless, the information about the exact prevalence of cardiac anomalies in craniosynostosis has not been well-understood yet. We aimed to assess the prevalence of different cardiac anomalies that coincidence with craniosynostosis.

Method: This cross-sectional study was done on 145 patients with craniosynostosis from January 2015 to December 2019. 103 patients with a single-suture involvement were placed in the non-syndromic group, and the remaining 42 with pansynostosis or the clinical manifestations of Apert, Pfeiffer, Crouzon, and Carpenter syndromes in the syndromic group. The prevalence of cardiac anomalies was evaluated and compared between the groups.

Results: The prevalence of congenital cardiac anomalies was 22.3% and 50% in non-syndromic and syndromic cases, respectively ($P=0.001$). Syndromic boys predominantly presented cardiac anomalies ($P=0.85$), whereas non-syndromic girls were mostly affected by cardiac anomalies ($P=0.75$). Age was not associated with congenital cardiac anomalies, neither in non-syndromic ($P=0.31$) nor in syndromic ($P=0.26$) patients. The number of affected sutures was not associated with cardiac anomalies ($P>0.05$). Tricuspid regurgitation (TR) (16.7%), patent ductus arteriosus (PDA) (14.3%), and ventricular septal defect (VSD) (11.9%) were the most prominent anomalies found among the syndromic patients, while TR (8.7%), atrial septal defect (ASD) (3.9%), and PDA (3.9%) were common among the non-syndromic ones.

Conclusion: Congenital heart disease is a prevalent abnormality among children with craniosynostosis. Therefore, cardiac assessment in craniosynostosis is strongly recommended.

Keywords: Craniosynostosis; Syndromic; Cardiac; Anomaly; Prevalence

***Correspondence to**
Mehrdad Larry, Neurosurgery Resident, MD-MPH, Department of Neurosurgery, Isfahan University of Medical Sciences, Isfahan, Iran. Email: mehrdad.larry@gmail.com

Published online October 22, 2022

Citation: Riazi A, Vahidian M, Larry M, Sheibani Tehrani D, Alami M, Salehi Z, et al. Prevalence of cardiac anomalies in children with syndromic and non-syndromic craniosynostosis. Clin Neurosci J. 2022;9:e30. doi:10.34172/icnj.2022.30.

Introduction

The cranial sutures are not fused at birth, allowing the brain to grow rapidly through the first year of life and then gradually until adolescence. The metopic suture is the first one, closing about 6-2 months after birth, whereas the others typically fuse in adulthood.[1]

Craniosynostosis is defined as the premature complete or partial fusion of the cranial sutures. Craniosynostosis affects 1 in 2000 live births, which makes it one of the most common craniofacial abnormalities in the United States.[2] usually syndromic craniosynostosis accompanied by facial characteristics, including midface hypoplasia, breaking nose, proptosis, and hypertelorism eyes.[3] This condition can affect one or multiple sutures, including sagittal, uni- or bilateral coronal, metopic, or lambdoidal sutures. The sagittal suture is the most common affected one accounting for 40%-55% of craniosynostosis cases, followed by coronal, metopic, and lambdoid sutures with the prevalence of 20%-25%, 5%-15%, and less than 5%, respectively.[4]

Craniosynostosis mostly occurs as a single abnormality referred to as non-syndromic; however, in 15-30% of the cases, it may occur concomitantly with other abnormalities in the limb, heart, central nervous system, or trachea, which is known as syndromic craniosynostosis.[5] Over 150 syndromes have been introduced to be associated with craniosynostosis.[6-8]

The most frequently diagnosed craniosynostosis-associated syndromes include Muenke (1 in 10 000-1 in 30 000), Crouzon (1 in 25 000), Pfeiffer (1 in 100 000),

© 2022 The Author(s). This is an open access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Apert (1 in 100 000), and Saethre-Chotzen (1 in 25 000-50 000) syndromes.[9]

Outbreaks appear to be exacerbated during craniosynostosis. Shunt with the presence of a hemodynamically significant congenital heart defect (CHD) can lead to increased pulmonary arterial flow and pressure. The onset and severity of pulmonary arterial hypertension (PAH) are quite variable according to the type of CHD, and in an extreme form can lead to Eisenmenger syndrome with irreversible PAH, contraindicated to any further correction.[10]

Cardiac anomalies are among the prevalent congenital abnormalities found coincidentally with craniosynostosis; nevertheless, the information about comparing congenital cardiac anomalies incidence in syndromic and non-syndromic cases is limited. We aimed to investigate congenital cardiac anomalies in a census study on a large number of syndromic versus non-syndromic children admitted for correctional surgery of craniosynostosis.

Methods

The current cross-sectional study was done using the census method on 145 children with the documented diagnosis of craniosynostosis admitted to Imam Hussein Hospital affiliated to Isfahan University of Medical Sciences from January 2015 to December 2019.

All of the patients with the documented diagnosis of craniosynostosis (syndromic or non-syndromic/ primary or secondary craniosynostosis) made by an expert pediatric neurosurgeon were included the study. We excluded records that were incomplete (more than 20%) and no echocardiography was available at the time of admission.

The included patients were retrieved through a census selection following the diagnosis of craniosynostosis made by a physical examination and confirmed by paraclinical imaging (cranial computed tomography [CT scan]). The patients were divided into two groups of syndromic and non-syndromic groups based on the presence or absence of congenital abnormality in any other parts of the body other than cardiac anomalies.

All children with pansynostosis and a few children with typical clinical characteristics compatible with Apert, Pfeiffer, Crouzon, and Carpenter syndromes, were considered as syndromic. Other children with isolated craniosynostosis were in the non-syndromic group.

Cardiac echocardiography is becoming an essential diagnostic tool for a variety of cardiac pathologies. It is safe and non-invasive technique. Rotation of the transducer counterclockwise from the apical four-chamber orientation gives the apical two-chamber view. In this orientation, the anterior, inferior, and apical walls of the left ventricle are visualized, along with the left atrium and its appendage.[11]

The patients' age, sex, affected suture(s), numbers of affected suture(s), and the echocardiographic abnormalities, including ventricular septal defect (VSD), tricuspid regurgitation (TR), pulmonary insufficiency, pulmonary embolism, tetralogy of Fallot (TOF), pulmonary hypertension, patent ductus arteriosus (PDA), mitral regurgitation, anomaly of left pulmonary artery, double outlet right atrium, mitral valve prolapsed (MVP), coarctation of aorta, left ventricular hypertrophy, biventricular hypertrophy, atrial septal defect (ASD) and aortic insufficiency were recruited from the medical records.

Eventually, the obtained information was entered into the Statistical Package for Social Sciences (SPSS, version 22, IBM Corporation, Armonk, NY, USA). The descriptive data were represented mean, standard deviation, absolute numbers, and percentages. Chi-square and Fisher's exact tests were used to analyze the data. $P < 0.05$ was considered as a significant level.

Results

The current study was done on 145 children with craniosynostosis, among which 103 were non-syndromic and 42 were syndromic. The studied population had a mean ± SD age of 6.13 ± 5.30 months and 61.4% were male patients.

Most non-syndromic patients were boys (68%), whereas syndromic ones were predominantly girls (54.8%). The mean ± SD age of syndromic and non-syndromic patients was 5.22 ± 3.30 and 8.36 ± 8.03 months, respectively. The two groups were remarkably different in age ($P = 0.024$) and sex distribution ($P = 0.011$).

The prevalence of congenital cardiac anomalies was 22.3% and 50% in non-syndromic and syndromic cases, respectively ($P = 0.001$). The detailed information about the type of anomalies is represented in Table 1.

As shown in Table 2, 69.6% of non-syndromic boys with craniosynostosis had cardiac anomalies ($P = 0.85$), while girls were predominantly involved in syndromic patients ($P = 0.75$). In addition, age was not associated with congenital cardiac anomalies, neither in non-syndromic ($P = 0.31$) nor in syndromic ($P = 0.26$) patients. The number of affected sutures was not associated with cardiac anomalies ($P > 0.05$).

As shown in Table 2, the presence of cardiac anomaly was not associated with age, sex and also the affected sutures in neither syndromic nor non-syndromic children.

Discussion

To the best of our knowledge, the current study is the first to investigate and compare the coincidence of cardiac anomalies with craniosynostosis in a large population of children admitted to the neurosurgery ward for the correctional surgery of craniosynostosis.

Consistent with the literature, we found a slight male

Table 1. The Comparison of Congenital Cardiac Anomalies Between Syndromic and Non-syndromic Cases With Craniosynostosis

Variables	Non-syndromic Craniosynostosis (n = 103)	Syndromic Craniosynostosis (n = 42)	*P* Value
	No. (%)	No. (%)	
Ventricular septal defect (yes/no)	1 (0.9)/102 (99.1)	5 (11.9)/37 (88.1)	0.008
Tricuspid regurgitation (yes/no)	9 (8.7)/94 (91.3)	7 (16.7)/35 (83.3)	0.24
Pulmonary insufficiency (yes/no)	2 (1.9)/101 (98.1)	3 (7.1)/39 (92.9)	0.14
Pulmonary stenosis (yes/no)	3 (2.9)/100 (97.1)	2 (4.8)/40 (95.2)	0.62
Pulmonary embolism (yes/no)	1 (0.9)/102 (99.1)	2 (4.8)/40 (95.2)	0.20
Tetralogy of Fallot (yes/no)	0 (0)/100 (103)	1 (2.4)/41 (97.6)	0.29
Pulmonary hypertension (yes/no)	2 (1.9)/101 (98.1)	1 (2.4)/41 (97.6)	0.99
Patent ductus arteriosus (yes/no)	4 (3.9)/99 (96.1)	6 (14.3)/36 (85.7)	0.035
Mitral regurgitation (yes/no)	1 (0.9)/102 (99.1)	0 (0)/42 (100)	0.99
Anomaly of left pulmonary artery (yes/no)	1 (0.9)/102 (99.1)	1 (2.4)/41 (97.6)	0.49
Double outlet right atrium (yes/no)	0 (0)/103 (100)	1 (2.4)/41 (97.6)	0.29
Mitral valve prolapse (yes/no)	0 (0)/103 (100)	1 (2.4)/41 (97.6)	0.29
Coarctation of the aorta (yes/no)	0 (0)/103 (100)	1 (2.4)/41 (97.6)	0.29
Left ventricular hypertrophy (yes/no)	0 (0)/103 (100)	1 (2.4)/41 (97.6)	0.29
Biventricular hypertrophy (yes/no)	0 (0)/103 (100)	1 (2.4)/41 (97.6)	0.29
Atrial septal defect (yes/no)	4 (3.9)/99 (96.1)	1 (2.4)/41 (97.6)	0.99
Aortic insufficiency (yes/no)	0 (0)/103 (100)	1 (2.4)/41 (97.6)	0.29

Table 2. The Association of Congenital Cardiac Anomaly With Age, Sex, and Type of Affected Suture in Syndromic and Non-syndromic Children With Craniosynostosis

Congenital Cardiac Anomaly	Non-syndromic			Syndromic		
	Positive	Negative	*P* Value	Positive	Negative	*P* Value
Age (month), mean ± SD	4.61 ± 2.62	5.40 ± 3.46	0.31	6.81 ± 4.26	10.45 ± 9.90	0.26
Sex (female/male), %	30.4/ 69.6	32.5/ 67.5	0.85	57.1/ 42.9	52.4/ 47.6	0.75
Affected sutures, mean ± SD	1.09 ± 0.28	1.10 ± 0.30	0.85	2.80 ± 1.09	2.80 ± 0.44	0.99
Coronal suture (affected/non-affected), %	26.1/ 73.9	35/ 65	0.46			
Sagittal suture (affected/non-affected), %	47.8/ 52.2	31.2/ 68.8	0.14			
Metopic suture (affected/non-affected), %	26.1/ 73.9	34.5/ 62.5	0.31			

predominance in craniosynostosis[12,13]; however, with respect to being syndromic or non-syndromic, the mere incidence of craniosynostosis was remarkably more among non-syndromic boys versus syndromic girls. Nevertheless, we found no association between congenital cardiac anomaly and craniosynostosis. The incidence of congenital cardiac anomaly was significantly higher among the syndromic patients, whereas, a statistically remarkable difference was found only in terms of VSD and PDA.

TR, followed by ASD and PDA, were the most common types of congenital heart diseases among the non-syndromic children with craniosynostosis. We also found that the age, sex, type, and numbers of affected sutures were not correlated with cardiac anomalies in non-syndromic children suffering from craniosynostosis; however, in line with previous studies, the sagittal suture was the most prevalent affected one.

We found no study dedicated to cardiac anomalies among the non-syndromic craniosynostosis; however, the presence of congenital heart disease among the non-syndromic children was not a weird finding. Da Costa and colleagues longitudinally assessed the neurodevelopmental trend among children with non-syndromic craniosynostosis and represented cyanotic heart diseases as a common finding in this group of patients.[14] Congenital heart diseases and non-syndromic craniosynostosis associated with incidental de novo mutations have been reported in limited cases reports by Homsy et al,[15] Iossifov,[16] Zaidi et al,[17] and Timberlake and colleagues[1]; however, none assessed further correlations.

TR, PDA, and VSD were the most prominent anomalies among syndromic children with craniosynostosis. In a similar pattern to the non-syndromic ones, we found no correlation between age, sex, and numbers of affected sutures and the coincidence of congenital heart disease among syndromic children with craniosynostosis, as well. Frank-ter Haar syndrome is one of the syndromes

associated with the *SH3PXD2B* gene mutation located on chromosome 5q35.1. This syndrome is accompanied by craniosynostosis as well as skeletal, cardiac, craniofacial, and ocular anomalies. VSD, MVP, and aortic regurgitation are the most prominent cardiac abnormalities in this syndromic type of craniosynostosis.[18]

Carpenter syndrome is another type of syndromic craniosynostosis accompanying by diverse cardiac anomalies among which ASD, VSD, TOF, PDA, and pulmonary stenosis are the most prevalent ones. Along with the cardiac anomalies, other skeletal, craniofacial, and renal malformations are present in this syndrome.[19]

Shprintzen-Goldberg craniosynostosis syndrome accompanies cardiac anomalies, including aortic root dilatation and MPV, and skeletal malformation such as scoliosis, pectus excavatum or carinatum, craniofacial abnormalities, including midfacial hypoplasia, dolichocephaly, hypertelorism, low set ears, prominent forehead, micrognathia and down slanting palpebral fissures. Inguinal and umbilical hernia are the other congenital manifestations of this syndromic craniosynostosis.[20]

Apert syndrome is another autosomal dominant disorder mostly known by craniosynostosis and craniofacial anomalies and symmetrical syndactyly of hands and feet. Cardiac anomalies occur in 10% of the cases, whereas TOF was the most common type of cardiac anomaly in this syndrome.[21]

The latter syndrome was associated with the deletion of 15q15-22.1. represented as craniosynostosis plus limb abnormalities, craniofacial malformations, including nasal bridge, hypoplastic alae nasae, and micrognathia and TOF.[22] VSD and ASD were the most common types of cardiac anomalies among the patients diagnosed with oculofaciocardiodental syndrome, characterized by the loss of approximately 554 Kb at chromosome 8p23.2-p23.1. This syndrome's other manifestations include temporal hypertrichosis, craniosynostosis with brachycephaly, supraorbital grooving, deafness, and underdevelopment of the midface.[23]

A significant limitation of this study was the failure to genetically study the patients to find the etiology of malformations; nevertheless, we found a significantly high rate of congenital cardiac anomalies among the children with craniosynostosis regardless of syndromic or non-syndromic patterns. Therefore, cardiac assessment for all of the patients with craniosynostosis is strongly recommended.

Limitations

Many patients had two or more congenital cardiac anomalies simultaneously, but it was not initially recorded in the study because of some limitations.

Conclusion

Based on this study, congenital heart disease is a prevalent abnormality among children with craniosynostosis. TR, PDA, and VSD were the most prominent anomalies found among the syndromic, while TR, ASD, and PDA were the most prevalent among the non-syndromic ones. Therefore, cardiac assessment for all patients with craniosynostosis is strongly recommended.

Acknowledgements

We would like to thank all the neurosurgical attending professors, medical residents and nursing staff in data collection and their meticulous patient care.

Conflict of Interest Disclosures

No Conflict of interest.

Ethical Statement

This study complied with the principles of the Declaration of Helsinki. The local ethics review committee of Isfahan University of Medical Sciences approved the study protocol (No. IR.MUI.MED.REC.1399.179). Then, the protocol was entirely explained to the patients' legal guardians and they were reassured about the confidentiality of their information and signed the written informed consent form.

Financial Support

This study was sponsored by Isfahan University of Medical Sciences.

References

1. Timberlake AT, Choi J, Zaidi S, Lu Q, Nelson-Williams C, Brooks ED, et al. Two locus inheritance of non-syndromic midline craniosynostosis via rare SMAD6 and common BMP2 alleles. Elife. 2016;5. doi: 10.7554/eLife.20125.
2. Gonzalez SR, Light JG, Golinko MS. assessment of epidemiological trends in craniosynostosis: limitations of the current classification system. Plast Reconstr Surg Glob Open. 2020;8(3):e2597. doi: 10.1097/gox.0000000000002597.
3. Johnson D, Wilkie AO. Craniosynostosis. Eur J Hum Genet. 2011;19(4):369-76. doi: 10.1038/ejhg.2010.235.
4. Wilkie AOM, Johnson D, Wall SA. Clinical genetics of craniosynostosis. Curr Opin Pediatr. 2017;29(6):622-8. doi: 10.1097/mop.0000000000000542.
5. Ko JM. Genetic syndromes associated with craniosynostosis. J Korean Neurosurg Soc. 2016;59(3):187-91. doi: 10.3340/jkns.2016.59.3.187.
6. Derderian C, Seaward J. Syndromic craniosynostosis. Semin Plast Surg. 2012;26(2):64-75. doi: 10.1055/s-0032-1320064.
7. Addo NK, Javadpour S, Kandasamy J, Sillifant P, May P, Sinha A. Central sleep apnea and associated Chiari malformation in children with syndromic craniosynostosis: treatment and outcome data from a supraregional national craniofacial center. J Neurosurg Pediatr. 2013;11(3):296-301. doi: 10.3171/2012.11.peds12297.
8. Frolov A, Lawson C, Olatunde J, Goodrich JT, Martin Iii JR. Sagittal craniosynostosis with uncommon anatomical pathologies in a 56-year-old male cadaver. Case Rep Pathol. 2019;2019:8034021. doi: 10.1155/2019/8034021.
9. O'Hara J, Ruggiero F, Wilson L, James G, Glass G, Jeelani O, et al. Syndromic craniosynostosis: complexities of clinical care. Mol Syndromol. 2019;10(1-2):83-97. doi: 10.1159/000495739.
10. Kaldararova M, Simkova I, Valkovicova T, Remkova A, Neuschl V. Pulmonary thromboembolism in congenital heart defects with severe pulmonary arterial hypertension. Cor Vasa.

2013;55(2):e170-e5. doi: 10.1016/j.crvasa.2013.03.006.
11. Ahmed I, Sasikumar N. Echocardiography imaging techniques. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
12. Lee HQ, Hutson JM, Wray AC, Lo PA, Chong DK, Holmes AD, et al. Changing epidemiology of nonsyndromic craniosynostosis and revisiting the risk factors. J Craniofac Surg. 2012;23(5):1245-51. doi: 10.1097/SCS.0b013e318252d893.
13. Synèse BJ, Francis RW, Tony AR, Willy R, Mamiarisoa R, Clément A. Epidemiologic and surgical approach of cranyosynostosis: a case of Madagascar and review of literature. J Adv Res Med Health Sci. 2019;5(9):1-6. doi: 10.53555/nnmhs.v5i9.793.
14. Da Costa AC, Anderson VA, Holmes AD, Lo P, Wray AC, Chong DK, et al. Longitudinal study of the neurodevelopmental characteristics of treated and untreated nonsyndromic craniosynostosis in infancy. Childs Nerv Syst. 2013;29(6):985-95. doi: 10.1007/s00381-012-2017-0.
15. Homsy J, Zaidi S, Shen Y, Ware JS, Samocha KE, Karczewski KJ, et al. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. Science. 2015;350(6265):1262-6. doi: 10.1126/science.aac9396.
16. Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, et al. The contribution of de novo coding mutations to autism spectrum disorder. Nature. 2014;515(7526):216-21. doi: 10.1038/nature13908.
17. Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, et al. De novo mutations in histone-modifying genes in congenital heart disease. Nature. 2013;498(7453):220-3. doi: 10.1038/nature12141.
18. Bendon CL, Fenwick AL, Hurst JA, Nürnberg G, Nürnberg P, Wall SA, et al. Frank-ter Haar syndrome associated with sagittal craniosynostosis and raised intracranial pressure. BMC Med Genet. 2012;13:104. doi: 10.1186/1471-2350-13-104.
19. Perlyn CA, Marsh JL. Craniofacial dysmorphology of Carpenter syndrome: lessons from three affected siblings. Plast Reconstr Surg. 2008;121(3):971-81. doi: 10.1097/01.prs.0000299284.92862.6c.
20. Al Kaissi A, Marrakchi Z, Nassib NM, Hofstaetter J, Grill F, Ganger R, et al. Craniosynostosis, Scheuermann's disease, and intellectual disability resembling Shprintzen-Goldberg syndrome: a report on a family over 4 generations: case report. Medicine (Baltimore). 2017;96(12):e6199. doi: 10.1097/md.0000000000006199.
21. Lionel KR, Sundararajan SK, Moorthy RK, Mariappan R. An infant with Apert syndrome and tetralogy of Fallot for craniosynostosis correction: anesthetic challenges. J Neuroanaesth Crit Care. 2021;8(1):60-2. doi: 10.1055/s-0039-1692735.
22. O'Byrne JJ, Laffan E, Murray DJ, Reardon W. Oculo-facio-cardio-dental syndrome with craniosynostosis, temporal hypertrichosis, and deafness. Am J Med Genet A. 2017;173(5):1374-7. doi: 10.1002/ajmg.a.38128.
23. Shur N, Cowan J, Wheeler PG. Craniosynostosis and congenital heart anomalies associated with a maternal deletion of 15q15-22.1. Am J Med Genet A. 2003;120A(4):542-6. doi: 10.1002/ajmg.a.20093.