Review Article

Epilepsy in Patients with Craniosynostosis: A Systematic Review

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Abstract

If left untreated, craniosynostosis can cause neuropsychological impairments, psychosocial problems, and craniofacial deformities. Its association with epileptic seizures is unknown. This review investigated the incidence of epilepsy in patients with craniosynostosis. The Cochrane Library, Science Direct, Web of Science, EBSCO, and PubMed were all searched. Rayyan QCRI was used to filter study article titles and abstracts before full-text evaluations were conducted. In total, 11 studies involving 21456 patients with craniosynostosis were examined; more than half of the patients were men. The highest reported rate of preoperative epileptic seizures was 12.2%, and the lowest rate was 2.5%. The highest rate of post-operative epilepsy was 12.2%, and the lowest was 0.24%. There is a lack of literature on epileptic seizures as an outcome among craniosynostosis patients. The metabolic or hemodynamic events following craniosynostosis corrective surgeries were more significant. However, neurological manifestations, including epilepsy, require close monitoring. We found that syndromic craniosynostosis patients experienced more significant problems than non-syndromic patients.

Keywords: Craniofacial, Craniosynostosis, Epilepsy, Seizures

Introduction

Within infancy and youth, the calvaria (skull vault) expands to create room for the growing brain. The cranial sutures, which are tiny fissures of developing mesenchyme located between numerous bones, are where this growth primarily occurs. The metopic and sagittal sutures, respectively, split the frontal and parietal bones midway. Coronal sutures separate the frontal and parietal bones, and lambdoid sutures separate the parietal bones from the lone occipital bone [1].

The condition known as cranial synostosis is the early fusion of one or more of the cranial sutures; secondary deformation of the skull shape is caused by a confluence of insufficient growth parallel to the fused suture and compensatory overgrowth at the non-fused sutures [2]. If left untreated, craniosynostosis can result in probable cranial growth restriction as well as subsequent cranial and facial deformities [3].

It is well-established that the craniofacial population is more susceptible to neurocognitive deficiencies than the general population, including lower generalized intelligence quotients, learning challenges, language delays, and behavioral issues. While the exact cause of this is unknown, there is evidence that cranial growth limitation and the subsequent intracranial pressure play a part in craniocerebral disproportion [4].

A recent systematic review and meta-analysis documented that there are 84,665 children born with craniosynostosis worldwide annually, including 72,857 children with non-syndromic craniosynostosis [5]. Infant surgery is frequently performed to modify the abnormal form of the skull, lower the risk of intracranial hypertension, and improve psychosocial health [3].

Many surgeons elect to perform their procedures at a young age to benefit from the beneficial effects of brain growth on

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skull shape. If there is any sign of raised intracranial pressure, such as enlarged fontanelles, progressive optic atrophy, convulsions, or multiple-suture synostosis, most surgeons perform surgery as quickly as possible [6]. There is a lack of literature reporting the complications of craniosynostosis, especially epileptic seizures, and most of them are included in clinical series [7, 8].

As far as we are aware, there has never been a systematic review that looked at the prevalence of epilepsy in people with craniosynostosis. This study's objective is to present patient demographics, the prevalence of epilepsy, and potential causes of the condition. Our study included both pre- and post-operative epileptic seizures.

Materials and Methods

This systematic review was conducted following the demonstrated guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA).

Study Design

This was a systematic review and meta-analysis.

Study Duration

From July to August 2022.

Study Condition

The published research on patients with craniosynostosis who experience epileptic seizures and those who have corrective surgery but experience post-operative seizures is examined in this study.

Search Strategy

To find the relevant literature, a thorough literature search was conducted in five main databases, including PubMed, Web of Science, Science Direct, EBSCO, and Cochrane Library. Our search was restricted to the English language, and it was customized as needed for each database. The following keywords, which were converted into Mesh terms in PubMed, were used to identify the appropriate studies: "craniosynostosis," "syndromic craniosynostosis," "non-syndromic craniosynostosis," "Epilepsy," "seizures," "epileptic seizures," and "convulsions." The appropriate keywords were paired with "OR" and "AND" Boolean operators. The search results comprised English, full-text publications, freely available articles, and human trials.

Selection Criteria

Our review comprised the studies with the following criteria:

- Mainly cohort and retrospective cohort studies and study designs that provided qualitative or quantitative data about the incidence of pre-and post-operative epilepsy among patients with craniosynostosis.

Exclusion criteria included the following:

- Studies not conducted in the English language.
- Studies with no free access.

Data Extraction

To identify the duplicate components of the search strategy results, we employed Rayyan (QCRI) [9]. By filtering the combined search results according to a set of inclusion/exclusion criteria, the researchers assessed the adequacy of the titles and abstracts. The entire texts of the papers that met the criteria for inclusion were evaluated by the reviewers. To resolve any discrepancies, the writers had INS discussions. The eligible study was added using a data extraction form that was produced. The study's names, authors, year, design, population, participant count, gender, prevalence of pre-and post-operative epilepsy, type of craniosynostosis, and significant findings were all extracted by the authors.

Risk of Bias Assessment

To evaluate the caliber of the included research, the qualitative data synthesis employed the ROBINS-I technique for non-randomized studies [10]. The reviewers looked into and corrected any anomalies in the quality evaluation.

Strategy for Data Synthesis

Summary tables with the information gathered from the eligible studies were produced to give a qualitative overview of the included study components and result data. After the systematic review's data extraction process was completed, choices were made regarding how to make the most of the data present in the included study papers. Studies that complied with the full-text standards for inclusion but lacked information on the prevalence of epileptic seizures were disregarded.

Results and Discussion

Search Results

53 duplicate study articles out of a total of 460 were eliminated after the comprehensive search. 290 studies were removed after 407 studies had their titles and abstracts screened. Only seven articles out of the 117 reports that were sought for retrieval were not found. In the end, 110 studies were screened for full-text evaluation. However, 78 studies were disqualified due to the wrong study outcomes; 21 studies were disqualified due to a lack of information regarding the frequency of epileptic seizures; and 11 studies were disqualified due to the incorrect population type. This systematic review contained ten appropriate study papers. **Figure 1** depicts a summary of the study selection procedure.

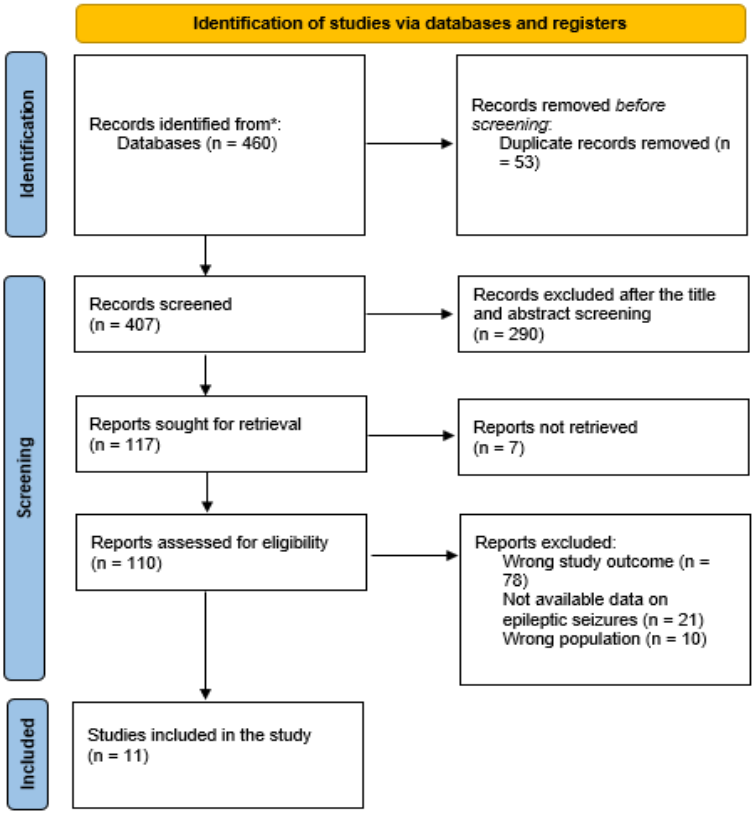

Figure 1. PRISMA flow chart presenting the study selection results.

Characteristics of the Included Studies

A total of 11 studies were included in this review, with 21456 patients diagnosed with craniosynostosis, and more than half of them were males. Eight studies were conducted in the United States (USA) [10-17], one in Brazil [18], one in India [19], and one in Turkey [20]. We found that the non-syndromic craniosynostosis weighed much more than the syndromic incidence. Three studies reported preoperative/history of epileptic seizures; the highest rate (12.2%) was reported by Ongun *et al.* [20], followed by Agochukwu *et al.* (12%) [14], and the lowest rate (2.5%) was reported by Stanbouly *et al*., [15]. Post-operative epilepsy was reported in seven studies; the highest rate (12.2%) [20] and the lowest (0.24%) [11]. Seven studies [10, 12-14, 17, 18, 20] found a high risk of bias, while four studies reported a moderate risk [11, 15, 16, 19].

Table 1. Summary of characteristics of the included studies.

Study	Study design	Country	Total Participants	Male (%)	Mean age (y)	Median age	Non-syndromic (%)	Syndromic (%)	Seizure history/ Preoperative (%)	Post-operative seizure (%)	Key findings	ROBINS-I
King *et al*., 2022 [11]	Retrospective study	USA	6583	4246 (64.5)	NR	8 months	5852 (89.1)	717 (10.9)	NR	16 (0.24%)	A minimal rate of associated post-operative seizures or thromboembolic ischemic events among patients with craniosynostosis.	Moderate
Raposo-Amaral *et al*., 2018 [18]	Observational retrospective study	Brazil	16	8 (50)	16.2 ± 8.1	NR	0	16 (100)	NR	1 (6.2)	Some serious post-operative complications including CSF fistula, seizures, major blood loss, and zygomatic fracture after craniofacial disjunction.	High

Menon *et al*., 2022 [19]	Retrospective study	India	98	46 (46.9)	NR	2 years	NR	NR	NR	3 (3.1)	A small portion of the population had post-operative seizures. Complications due to blood loss and airway issues were the leading cause of morbidity and mortality.	Moderate
Lam *et al*., 2016 [12]	Retrospective study	USA	572	388 (67.8%)	704 ± 479 days	NR	NR	NR	3 (0.52)	9 (1.6)	A small portion of the population has post-operative seizures, neuromuscular disorders, and immune diseases.	High
Ongun *et al*., 2018 [20]	Retrospective study	Turkey	41	26 (63.4)	NR	7 months	41 (100)	0	5 (12.2)	5 (12.2)	A history of epilepsy among craniosynostosis. Post-operative complications also included the incidence of seizures with the same percentage, hypotension, hypothermia, metabolic acidosis, blood loss, fever of unknown origin, and hyperglycemia.	High
Naumann *et al*., 2012 [13]	Retrospective study	USA	70	43 (61)	NR	NR	NR	NR	NR	1 (1.4)	One patient developed seizures 24 hours after surgery.	High
González *et al*., 2022 [10]	Retrospective study	USA	96	63 (66)	NR	10.5 months	NR	NR	NR	2 (2.1)	Two patients developed post-operative epilepsy in this study.	High
Agochukwu *et al*., 2012 [14]	Cohort study	USA	58	NR	NR	NR	0	58 (100)	7 (12)	NR	Due to the high prevalence of epilepsy in Muenke syndrome, these patients may be at risk for both intracranial abnormalities and epilepsy.	High
Stanbouly *et al*., 2022 [15]	Retrospective cohort study	USA	4709	2972 (63.1)	1.43 ± 1.28	NR	NR	NR	244 (2.5)	NR	Patients with craniosynostosis who frequently have concomitant conditions, particularly hydrocephalus, OSA, and BC, have a higher chance of developing epilepsy.	Moderate
Bruce *et al*., 2018 [16]	Retrospective cohort study	USA	8417	5531 (657)	NR	6.99 months	7867 (93.5)	550 (6.5)	NR	99 (1.2)	Repair of craniosynostosis is still safe, but the chance of problems at the time of intervention rises linearly with age. Patients with craniosynostosis develop post-operative complications, including seizures, hematoma, post-operative bleeding, and pneumonia.	Moderate
Lee *et al*., 2012 [17]	Retrospective study	USA	796	571 (65	NR	7.6 months	698 (88)	98 (12)	NR	6 (0.8)	Analyzing a 30-year review demonstrated only six patients with post-operative seizures.	High

This is the first systematic review to focus on epileptic seizures as a preoperative or post-operative outcome among patients with craniosynostosis. The more recent studies had higher quality with larger sample sizes and, consequently, were more reliable in reporting the neurodevelopmental outcomes on standardized measures.

In general, we found that the available literature on epileptic seizures as an outcome in patients with craniosynostosis is much less comprehensive and susceptible to a number of important methodological challenges, including small sample sizes and the limited usage of control groups. Improving our understanding of the association between craniosynostosis and the incidence of epilepsy using high-quality methodological approaches constitutes a research priority.

Ongun *et al.* reported the highest incidence of pre- and post-operative epilepsy, which could be mainly attributed to the small sample size. They also reported post-operative complications of hypotension, hypothermia, metabolic acidosis, blood loss, fever of unknown origin, and hyperglycemia [20]. The evaluation of incidents in the reported cohort showed clinically significant metabolic or hemodynamic events, despite the wide range of problems described in the literature [11, 12, 14, 17, 19, 21, 22]. These findings imply that those children require close monitoring for at least 24 hours following surgery.

Raposo-Amaral *et al.* reported the incidence of post-operative seizures in one patient with Crouzon syndrome and considered it a life-threatening condition [18]. We also found that patients with syndromic craniosynostosis were

associated with more complications than non-syndromic patients. Syndromic and multi-suture craniosynostoses are known risk factors for more frequent reoperations and surgical complications. Less favourable bone quality, more dramatic head shape alterations, frequent issues with raised intracranial pressure (ICP), or inherited factors that connect them to other defects such as airway blockage may be the cause of this. Patients who required complex cranial remodelling surgery or had difficult bone dissection because their bones were of poorer quality (thick, scarred, vascular, or spiculated) generally underwent longer procedures that were more likely to cause complications like extensive bleeding, venous embolism, dural tear, or infection [23-25].

A number of restrictions should be taken into consideration when interpreting the study's findings. Our study has several limitations, as the inclusion of retrospective studies restricted our ability to establish any causative relationships between epileptic seizures and craniosynostosis. It is recognized that the inclusion criteria, which were restricted to peer-reviewed, published studies in English, may have generated a publication bias. The breadth of this review is also constrained by methodological issues and discrepancies that should be taken into account when interpreting the results, as allowed by the available literature.

This study provides a preliminary review of the association between craniosynostosis and epileptic seizures. However, future research is required for extensive investigations. Studies should focus on defining the epidemiology of syndromic craniosynostosis and its relation to the incidence of seizures. More research is needed to examine the worldwide burden of craniosynostosis, which also takes into account the morbidity and mortality caused by the condition, using metrics such as years of life lost and years of life with disability [26].

Other studies should also estimate the number of neurosurgeons, plastic surgeons, pediatric surgeons, and general surgeons doing craniosynostosis surgery on a national, regional, and international scale. Understanding the disparity between the workforce and epidemiology would help efforts to expand surgical capacity, considering the global scarcity of surgeons [27, 28].

Conclusion

This systematic review detected a lack in the literature on epileptic seizures as an outcome among craniosynostosis patients. The demonstrated literature was found to be non-comprehensive. We found that the metabolic or hemodynamic events following craniosynostosis corrective surgeries were more significant; however, the neurological manifestations, including epilepsy, require close monitoring. Additionally, we reported that syndromic craniosynostosis patients experienced greater problems than non-syndromic patients. There are known risk factors for more frequent reoperations and surgical complications, including syndromic and multi-suture craniosynostoses.

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