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Epilepsy in Individuals with Craniosynostosis: A Comprehensive Review

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ABSTRACT

Untreated craniosynostosis can lead to a variety of problems, including cognitive and psychological problems, as well as craniofacial deformities. However, its association with epileptic seizures is still unclear. This review aimed to assess the occurrence of epilepsy among people with craniosynostosis. Several databases, including the Cochrane Library, Science Direct, Web of Science, EBSCO, and PubMed, were searched for relevant studies. Rayyan QCRI was used to screen the titles and abstracts of articles before comprehensive evaluation of the full texts. A total of 11 studies, involving 21,456 craniosynostosis patients, were included in the analysis. The majority of these patients were male. The highest reported prevalence of preoperative seizures was 12.2%, while the lowest was 2.5%. For postoperative epilepsy, the highest rate was also 12.2%, and the lowest was 0.24%. There is a significant gap in research concerning epileptic seizures due to craniosynostosis. While metabolic or hemodynamic complications following craniosynostosis surgery are more frequently documented, neurological issues such as epilepsy require vigilant monitoring. The findings suggest that patients with syndromic craniosynostosis tend to experience more severe complications compared to those with non-syndromic forms.

Keywords: Seizures, Craniofacial, Craniosynostosis, Epilepsy

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Introduction

During the developmental stages of infancy and childhood, the skull expands to accommodate the growing brain. This growth primarily occurs along the cranial sutures, which are small mesenchymal gaps between the various bones of the skull. These sutures include the metopic and sagittal sutures, which divide the frontal and parietal bones, the coronal sutures separating the frontal and parietal bones, and the lambdoid sutures separating the parietal bones from the occipital bone [1].

Craniosynostosis is a condition where one or more cranial sutures fuse prematurely, causing skull deformities. This is due to the combination of halted growth along the fused suture and compensatory overgrowth at the remaining unfused sutures [2]. If left untreated, craniosynostosis can result in limited skull growth and lead to significant cranial and facial deformities [3].

People with craniofacial abnormalities are more likely to experience neurocognitive challenges compared to the general population, such as lower IQ, learning difficulties, language delays, and behavioral problems. The exact

cause of these challenges is unclear, but it is thought that limited cranial growth and increased intracranial pressure may contribute to craniocerebral disproportion [4].

A recent systematic review and meta-analysis found that 84,665 children globally are born with craniosynostosis every year, with 72,857 of these having non-syndromic craniosynostosis [5]. Surgery is often performed early to correct skull deformities, lower the risk of intracranial hypertension, and improve psychosocial well-being [3].

Surgeons generally prefer early surgery to capitalize on the skull's growth potential. If signs of raised intracranial pressure—such as enlarged fontanelles, optic atrophy, seizures, or multiple suture synostosis—are present, prompt surgery is typically advised [6]. However, there is limited research on complications of craniosynostosis, particularly regarding epileptic seizures, which are mainly discussed in clinical series [7, 8].

To the best of our knowledge, no systematic review has specifically addressed the prevalence of epilepsy in individuals with craniosynostosis. This study aims to explore patient demographics, the prevalence of epilepsy, and the potential causes of this condition, examining both pre- and post-operative seizures.

Materials and Methods

This review was conducted adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure comprehensive and transparent reporting of findings.

Study design

The research was carried out as a systematic review combined with a meta-analysis approach.

Study duration

The review was conducted over a period from July to August 2022.

Study focus

This study evaluates existing research on individuals diagnosed with craniosynostosis who experience epileptic seizures, both before surgery and after undergoing corrective procedures.

Literature search strategy

An extensive search was carried out across five major databases: PubMed, Science Direct, Web of Science, EBSCO, and Cochrane Library. The search was confined to studies published in English, and the search criteria were tailored for each specific database. The following key terms were utilized: "craniosynostosis," "syndromic craniosynostosis," "non-syndromic craniosynostosis," "epilepsy," "seizures," "epileptic seizures," and "convulsions," which were combined using Boolean operators "AND" and "OR." The search targeted full-text, freely available articles, with a focus on human-based studies.

The inclusion criteria for this review were as follows:

- Predominantly cohort and retrospective cohort studies, as well as research designs that provided either qualitative or quantitative data on the occurrence of pre-operative and post-operative epilepsy in patients diagnosed with craniosynostosis.

Exclusion criteria were as follows:

- Studies not published in English.
- Studies that were not freely accessible.

Data collection

To remove any duplicate entries from the search results, Rayyan (QCRI) [9] was utilized. The results were filtered based on pre-established inclusion and exclusion criteria, after which the titles and abstracts were examined for relevance. Full texts of the studies that met the inclusion criteria were further evaluated by the reviewers. Any discrepancies or conflicts were resolved through discussions among the authors. A data extraction form was created to collect key details from eligible studies. The extracted data included the study's title, authors, year of publication, design, study population, participant demographics (such as gender), the prevalence of pre- and post-operative epilepsy, craniosynostosis type, and significant findings.

Bias risk evaluation

The risk of bias in the included studies was assessed using the ROBINS-I tool for non-randomized studies [10]. Any inconsistencies in quality evaluation were identified and addressed by the reviewers.

Data synthesis strategy

Summary tables were created to provide an overview of the study components and results from the included studies. After the data extraction phase, decisions were made on how to utilize the available data. Studies that fulfilled the inclusion criteria but did not provide information on the prevalence of epileptic seizures were excluded from further analysis.

Results and Discussion

Search outcomes

Out of the 460 studies identified in the initial search, 53 duplicates were removed. After screening the titles and abstracts of 407 studies, 290 were excluded. 7 articles, out of 117 requested for retrieval, could not be located. Ultimately, 110 articles underwent full-text evaluation. Among these, 78 studies were excluded due to irrelevant outcomes, 21 were excluded for lacking data on the frequency of epileptic seizures, and 11 were excluded because they did not meet the required population criteria. This review ultimately included ten studies that met all inclusion criteria. A summary of the study selection process is shown in **Figure 1**.

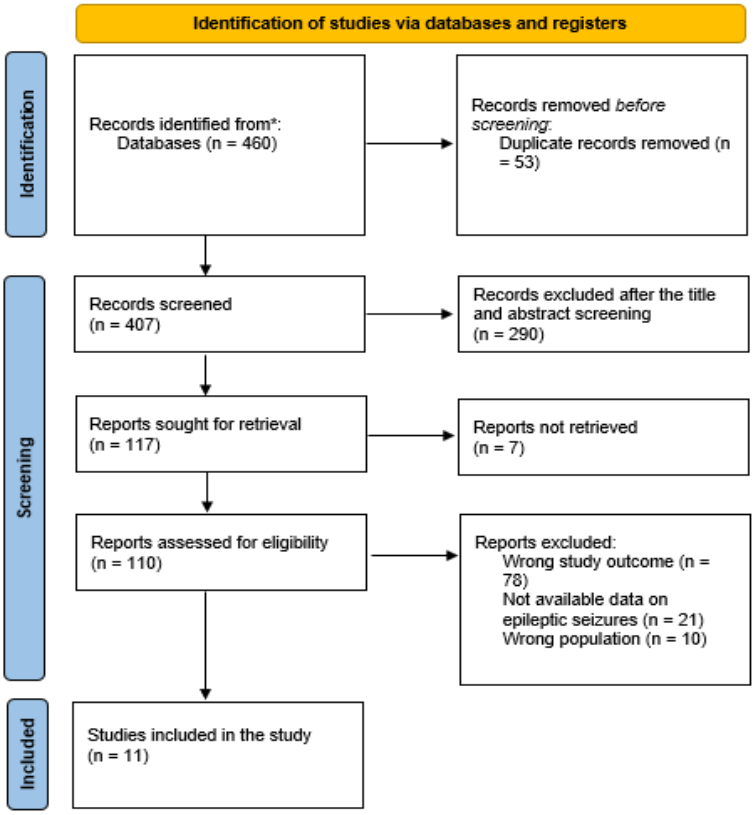

Figure 1. PRISMA flow chart presenting the study selection results

Overview of the included studies

This review incorporated data from 11 research articles, collectively analyzing 21,456 patients diagnosed with craniosynostosis. The majority of the study populations consisted of male patients. Geographically, eight of the included studies were carried out in the United States [10-17], while one study each was performed in Brazil [18], India [19], and Turkey [20].

In terms of craniosynostosis type, non-syndromic cases were far more frequently reported compared to syndromic forms. Three studies specifically addressed the occurrence of epileptic seizures before surgical intervention. Ongun *et al*. [20] identified the highest pre-operative seizure prevalence at 12.2%, followed closely by Agochukwu *et al*. [14] with a rate of 12%, while Stanbouly *et al*. [15] recorded the lowest rate of 2.5%.

Seven studies provided information regarding post-operative epilepsy, with seizure rates varying from as high as 12.2% [20] to as low as 0.24% [11].

Quality assessment revealed that 7 studies [10, 12-14, 17, 18, 20] were deemed to have a high risk of bias, while 4 studies [11, 15, 16, 19] were assessed as having a moderate risk of bias **(Table 1)**.

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*. [11]	Retrospective study	USA	6583	4246 (64.5)	NR	8 months	5852 (89.1)	717 (10.9)	NR	16 (0.24%)	The incidence of post-operative seizures and thromboembolic ischemic complications among individuals undergoing surgical management of craniosynostosis was found to be relatively low.	Moderate
Raposo-Amaral *et al*. [18]	Observational retrospective study	Brazil	16	8 (50)	16.2 ± 8.1	NR	0	16 (100)	NR	1 (6.2)	Certain critical post-operative complications have been documented following craniofacial disjunction procedures, such as cerebrospinal fluid (CSF) fistula formation, occurrence of seizures, significant intraoperative blood loss, and fractures involving the zygomatic bone.	High
Menon *et al*. [19]	Retrospective study	India	98	46 (46.9)	NR	2 years	NR	NR	NR	3 (3.1)	Post-operative seizures were observed in a limited subset of the studied population. Additionally, complications arising from significant blood loss and airway management difficulties represented the primary contributors to both morbidity and mortality among these patients.	Moderate
Lam *et al*. [12]	Retrospective study	USA	572	388 (67.8%)	704 ± 479 days	NR	NR	NR	3 (0.52)	9 (1.6)	Only a minority of the patient population experienced post-operative seizures, alongside the occurrence of neuromuscular disorders and immune-related diseases.	High
Ongun *et al*. [20]	Retrospective study	Turkey	41	26 (63.4)	NR	7 months	41 (100)	0	5 (12.2)	5 (12.2)	Patients with craniosynostosis demonstrated a previous history of epilepsy. Additionally, post-operative complications were reported at a similar rate of seizure	High

											occurrence, accompanied by other adverse events such as hypotension, hypothermia, metabolic acidosis, significant blood loss, unexplained fever, and hyperglycemia.	
Naumann *et al*. [13]	Retrospective study	USA	70	43 (61)	NR	NR	NR	NR	NR	1 (1.4)	Seizures occurred in one patient 24 hours post-surgery.	High
González *et al*. [10]	Retrospective study	USA	96	63 (66)	NR	10.5 months	NR	NR	NR	2 (2.1)	In this study, post-operative epilepsy was observed in two patients.	High
Agochukwu *et al*. [14]	Cohort study	USA	58	NR	NR	NR	0	58 (100)	7 (12)	NR	Given the elevated incidence of epilepsy in Muenke syndrome, individuals with this condition may face an increased likelihood of developing both intracranial abnormalities and epilepsy.	High
Stanbouly *et al*. [15]	Retrospective cohort study	USA	4709	2972 (63.1)	1.43 ± 1.28	NR	NR	NR	244 (2.5)	NR	Individuals with craniosynostosis, especially those who also suffer from conditions such as hydrocephalus, OSA, and BC, are at an increased risk of developing epilepsy.	Moderate
Bruce *et al*. [16]	Retrospective cohort study	USA	8417	5531 (657)	NR	6.99 months	7867 (93.5)	550 (6.5)	NR	99 (1.2)	While craniosynostosis surgery remains generally safe, the likelihood of complications during the procedure increases progressively with the patient's age. Post-operative issues, such as seizures, hematoma, bleeding, and pneumonia, are commonly observed in these patients.	Moderate
Lee *et al*. [17]	Retrospective study	USA	796	571 (65	NR	7.6 months	698 (88)	98 (12)	NR	6 (0.8)	A review spanning 30 years revealed that only six patients experienced seizures following surgery.	High

This is the inaugural systematic review examining epileptic seizures as either a preoperative or postoperative outcome in craniosynostosis patients. Recent studies in this area show improved quality, larger sample sizes, and greater reliability when assessing neurodevelopmental outcomes via standardized metrics.

In general, the literature on epileptic seizures in craniosynostosis patients is underdeveloped and fraught with significant methodological issues, including small sample sizes and minimal control group usage. Addressing these gaps through robust, high-quality research is essential for better understanding the connection between craniosynostosis and epilepsy.

Ongun *et al*. identified the highest rates of preoperative and postoperative epilepsy, likely due to their study's smaller sample size. In addition, they documented various post-surgical complications such as hypotension, hypothermia, blood loss, metabolic acidosis, fever of unknown origin, and hyperglycemia [20]. Their findings underscore the clinical importance of monitoring patients for at least 24 hours post-surgery, despite the variety of complications presented in other studies [11, 12, 14, 17, 19, 21, 22].

Raposo-Amaral et al. [18] observed post-operative seizures in a patient with Crouzon syndrome, considering it a severe complication. Additionally, syndromic craniosynostosis patients were found to experience more complications than non-syndromic patients. Syndromic and multi-suture craniosynostoses are known to increase the likelihood of repeat surgeries and surgical issues. This is often due to factors like poor bone quality, significant cranial shape deformations, recurrent raised intracranial pressure (ICP), and genetic links to other conditions, such as airway obstruction. Patients undergoing extensive cranial remodelling surgeries or those with more challenging bone structures—thicker, scarred, or highly vascular—typically experience longer, more complex surgeries, raising the risk for complications such as excessive bleeding, venous embolism, dural tears, and infections [23-25].

Several factors limit the interpretation of this study's findings. One major constraint is the reliance on retrospective data, which prevents the identification of direct cause-and-effect relationships between craniosynostosis and epileptic seizures. Furthermore, by including only peer-reviewed English-language studies, we may have introduced a bias toward publication. Additionally, variations in research methodologies across studies must be considered when evaluating the overall findings, which could limit the generalizability of the results.

Although this review provides an initial overview of the relationship between craniosynostosis and seizures, further detailed investigations are essential. Future research should prioritize exploring the epidemiology of syndromic craniosynostosis and its potential role in seizure development. Moreover, comprehensive global studies are needed to quantify the burden of craniosynostosis, incorporating measures like life-years lost and the long-term disability caused by the condition [26].

Additionally, future investigations should assess the availability of specialized surgeons, such as neurosurgeons, pediatric surgeons, plastic surgeons, and general surgeons, across different regions and countries. Addressing the gap between surgical workforce availability and the need for craniosynostosis surgeries would be crucial, given the current shortage of trained surgeons worldwide [27, 28].

Conclusion

This systematic review highlighted a noticeable gap in the existing research regarding epileptic seizures as a clinical outcome in patients diagnosed with craniosynostosis. The current body of literature appears to lack depth and remains insufficient in addressing this specific aspect. Our analysis indicated that post-operative metabolic and hemodynamic disturbances were among the more prominent complications following craniosynostosis surgical interventions. Nevertheless, neurological outcomes, particularly the occurrence of epilepsy, warrant vigilant observation in the post-surgical period. Furthermore, our findings suggest that patients with syndromic craniosynostosis are more prone to experiencing adverse events compared to those with non-syndromic forms. Syndromic and multi-suture craniosynostoses remain established predictors for increased surgical challenges, higher rates of complications, and the likelihood of repeated operative procedures.

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