AFMN BIOMEDICINE

REVIEW ARTICLE

EPILEPSY IN CHILDREN WITH CENTRAL NERVOUS SYSTEM INFECTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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In childhood, infections of the central nervous system may lead to neurodevelopmental disorders and complications such as epilepsy. The present study aimed to evaluate epilepsy in children with central nervous system (CNS) infections.

The present systematic review and meta-analysis included five cohort studies from international databases, PubMed, Scopus, Web of Science, and Embase, from January 1, 2010, to May 10, 2025, using keywords aligned with the study objective. The statistical analysis was performed using Stata/MP v17 and a random-effect model.

The risk ratio of epilepsy in children with etiologically diagnosed CNS infections was 0.23 (ES = 0.23; 95% CI 0.01 to 0.45; I^2 = 99.52%, P < 0.05).

Based on the results of the present study, there is a high risk of epilepsy associated with brain infections.

Keywords: epilepsy, children, central nervous system, infections

Submitted: January 18, 2025 **Accepted:** October 26, 2025
Published online: December 22, 2025

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INTRODUCTION

Central nervous system (CNS) infections in children can be fatal or result in neurological complications. The neurological prognosis varies depending on the causative agent. A better understanding of the causative agents will help predict the neurological outcome in children (1). Studies have examined intractable seizures following meningitis and encephalitis. Evidence suggests that most children who develop acute bacterial meningitis are at high risk of developing seizures. Children who develop long-term neurological impairment after infection are at high risk of developing epilepsy (2, 3). Studies have shown that seizures are also highly prevalent in children with acute viral encephalitis, increasing the risk of developing epilepsy and intractable seizures (4, 5).

Currently, the factors that cause epilepsy in children have not been precisely determined. Based on evidence, the use of certain medications by the mother during pregnancy, environmental and genetic factors, neurobiological and perinatal factors are among the factors that cause epilepsy in children. Environmental factors are one of the most important risk factors, especially CNS infections (6-9).

Studies showed that the effects of CNS infection in children are different from those in adults (1, 10). CNS infections in children can occur at different times and through different routes. It was shown that maternal infections during pregnancy are directly linked to fetal brain abnormalities (11, 12). Infections trigger inflammatory pathways that release different inflammatory cytokines and cause morphological changes. Neonates can develop encephalitis during passage through an infected birth canal. Permanent neurological deficits result from brain infections that cause neurological dysfunction during central nervous system development, often preceding cellular damage directly related to viral replication (13). Children typically do not show the symptoms of CNS infections. These neurological signs of infection can be mild and slow-acting, making them easy to miss. Any delay in diagnosing a CNS infection in children or infants can have negative consequences. According to some research, brain infections during infancy or childhood damage the developing central nervous system and may increase the risk of epilepsy in adulthood (14-16).

Given the importance of the subject, the challenges and uncertainty of pathogenesis of epilepsy in childhood, the present study aimed to investigate neurogenic epilepsy in children having infection and stroke.

METHODS

A comprehensive search was conducted between January 1, 2010, and May 25, 2025, using keywords relevant to the study objectives, in the international databases PubMed, Scopus, Web of Science, and Embase. The present article was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Searches were also conducted in other databases using keywords similar to Mesh keywords.

Search strategy keywords:

(((((("Epilepsy"[Mesh] OR "Epilepsy, Benign Neonatal"[Mesh]) OR ("Epilepsy/Complications"[Mesh] OR "Epilepsy/Diagnosis"[Mesh] OR "Epilepsy/Diagnostic imaging"[Mesh] OR "Epilepsy/Epidemiology"[Mesh] OR "Epilepsy/Etiology"[Mesh] OR "Epilepsy/Genetics"[Mesh] OR "Epilepsy/Pathology"[Mesh] OR "Epilepsy/Prevention and control"[Mesh] OR "Epilepsy/Therapy"[Mesh])) AND "Neurodevelopmental disorders"[Mesh]) AND ("Child"[Mesh] OR "Only Child"[Mesh])) AND ("Central nervous system"[Mesh] OR "Central nervous system parasitic infections"[Mesh] OR "Central nervous system bacterial infections"[Mesh] OR "Central nervous system viral diseases"[Mesh])) AND "Infections"[Mesh].

Inclusion criteria: PICO was the basis for the inclusion criteria (Table 1). All human studies, English language, type of brain infections, various brain infections, epilepsy and neurodevelopmental outcomes, prospective and retrospective studies, randomized controlled trial were included.

Table 1. *PICO method for choosing research*

PICO strategy	
Population (P)	Children aged <18 years with brain infections
Exposure (E)	CNS infections
Comparison (C)	Non-brain infections
Outcomes (O)	Risks of epilepsy

Exclusion criteria involved: Case studies of specific cancers, case reports, exploring other diagnostic options, incomplete or atypical data reporting, review studies, case report studies, laboratory studies, animal studies, letters to the editor, conference papers, and studies without full text. Using a pre-made table, two independent, blinded authors extracted data from a few chosen studies. After review and discussion with the third author of any discrepancies, a summary of the collected information was created.

The columns of the table were: first author, year of publication, design of study, number of children in case and control group, gender, mean of age, pathogens, follow-up, and outcome.

Quality assessment was performed in three domains: selection, comparison, and outcome using the Newcastle-Ottawa Scale (NOS) (17). "High quality" was defined by the NOS tool as scores greater than 7.

Statistical analyses were performed with random effects models using Stata MP.v17 software. Effect sizes were calculated using 95-CI and RMEL method.

RESULTS

Three hundred eighty-one articles that met the search criteria were found after a thorough literature search in the databases. One hundred thirty-nine articles were excluded based on exclusion criteria or title irrelevance to the study aim. In total, 242 articles were reviewed for abstracts and excluded if they did not meet the inclusion criteria. The full text of 25 articles was reviewed by two separate, blinded authors and then screened for inclusion and exclusion criteria. Only five articles were selected for review of this study after meeting the inclusion criteria (Figure 1).

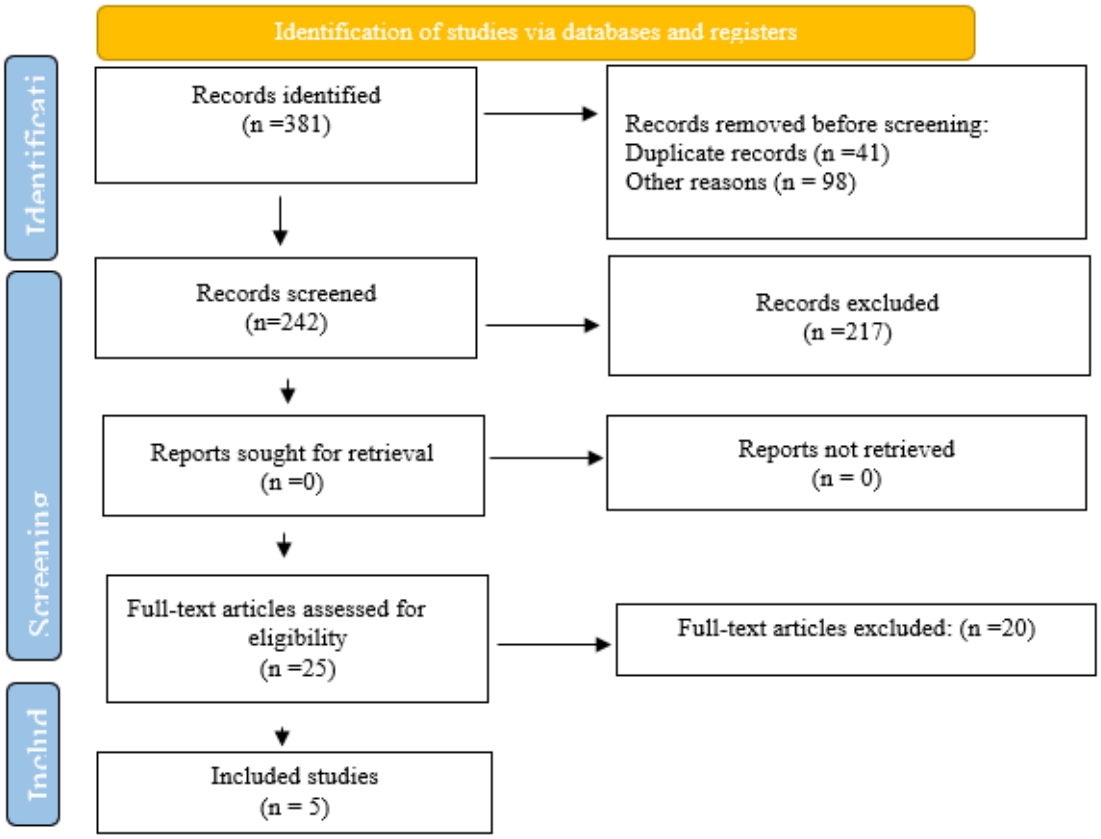

Figure 1. *Flowchart of PRISMA 2020 and selection of studies*

Characteristics of included studies
Study's characteristics were summarized in Table 2.

Table 2. *Main characteristics of the included studies*

Study	Study design	Number of participants		Gender				Mean age	Associated pathogens	Follow-up (years)	Neurodevelopmental outcomes (epilepsy)	
				Case		Control						
		Case	Control	Girl	Boy	Girl	Boy				Case	Control
Sodero et al., 2025 (18)	Prospective	53	27	25	28	9	18	7.4 years	CNS infections	5	37.8 % (8)	0
Valle et al., 2024 (19)	Retrospective	469		NR		NR		7.9	CNS infections	5	7.7% (36)	-
Bergonzini et al., 2024 (20)	Retrospective	94		31	63	-		10	CNS infections	5	62.7% (59)	-
Lykke et al., 2023 (21)	Retrospective	1432	14211	640	792	6342	7869	89 days	Group B Streptococcus	5	3.6% (52)	2.2% (312)
Lin et al., 2019 (7)	Retrospective	145	292	47	98	110	182	3.43 years	Enterovirus, *Herpes simplex* virus, Group B Streptococcus, *S. pneumoniae*	7.7	7.5% (11)	0.3 (1)

Bias assessment
Four studies received a score of 7/9 (High quality) and one study had moderate quality 6/9 (Table 3).

Table 3. *Assessment of quality of a cohort study (Newcastle Ottawa Scale)*

	Selection				Comparability	Outcome		Total
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at the start of the study		Assessment outcome	Length of follow-up	
Sodero et al., 2025 (18)	*	*	*	*	**	*	-	7
Valle et al., 2024 (19)	*	*	*	*	**	*	-	7
Bergonzini et al., 2024 (20)	*	*	*	*	**	*	-	7
Lykke et al., 2023 (21)	*	*	*	*	**	*	-	7
Lin et al., 2019 (7)	*	*	*	*	*	*	-	6

*= 1 score; **= 2 score.

Risk of epilepsy in central nervous system infections in children

The risk ratio of epilepsy in children with etiologically diagnosed CNS infections was 0.23 (ES = 0.23; 95% CI 0.01 to 0.45; I^2 = 99.52%, P < 0.05) (Figure 2).

Children with brain infections were at higher risk for epilepsy for all the different pathogens tested.

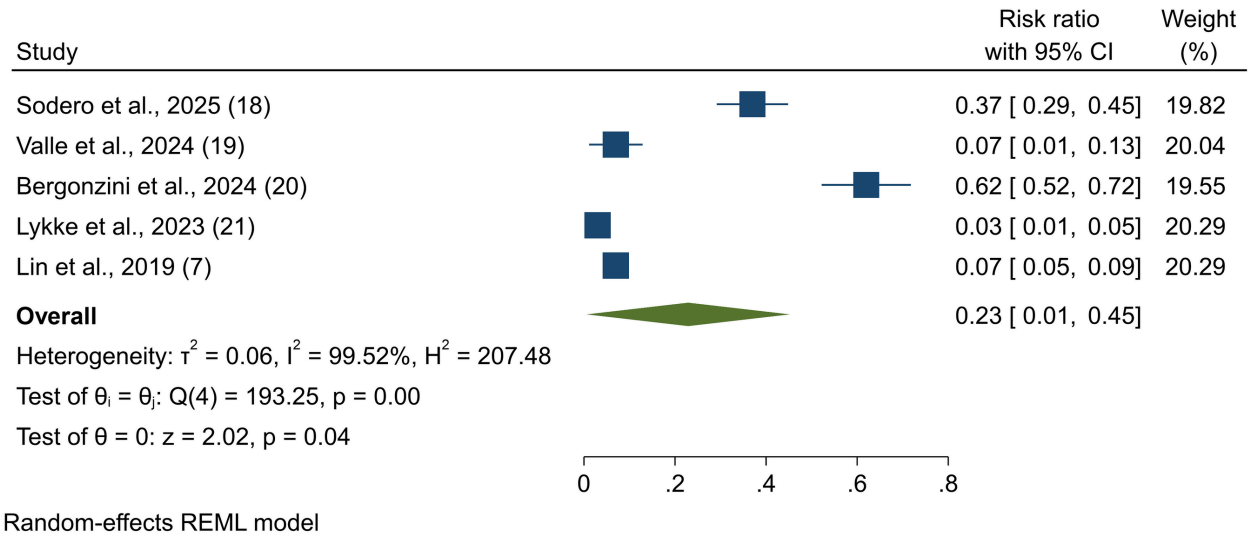

Figure 2. *Forest plot showed event rate of epilepsy in childhood brain infections*

DISCUSSION

Identifying and understanding the association between childhood brain infections and epilepsy is crucial for both treatment and neurodevelopmental prognosis (22). Studies have shown that enteroviruses are the leading cause of brain infections, followed by group B Streptococcus, S. pneumoniae, and Herpes simplex virus (22). Very few studies have addressed the association between epilepsy and infections caused by specific neurotropic pathogens in children. In the present study, five studies were eligible for inclusion and high heterogeneity was observed between studies in terms of methodology. The study population was small in most studies; therefore, the results of the present study should be interpreted with caution.

According to the present meta-analysis, the risk ratio of epilepsy in children involved in infection was 0.23. Brain infections in suspected children should be carefully evaluated as they can increase the risk of epilepsy in children (23). According to the results of the study, the long-term effects of bacterial meningitis can include intractable seizures and epilepsy, and Streptococcus pneumoniae was associated with a relatively higher risk of these conditions (24). Studies have shown that brain infections at this age may also impair children's social and communication skills. For this reason, brain infections may also affect neurodevelopmental disorders in addition to epilepsy (7). Examining these findings is very important due to the lack of studies. In addition to further investigation, studies should use larger samples and more rigorous experimental designs.

Epilepsy research continues to provide new medical treatments to increase the number of people who can fully control seizures and to reduce the side effects of treatments. In the present study, the risk of epilepsy in children with central nervous system infections was 0.23. Therefore, children diagnosed with brain infection should be monitored as they are at higher risk of developing epilepsy. Early assessment and identification of epilepsy and early intervention and treatment are of great importance. Based on the present meta-analysis, epilepsy has a high risk associated with brain infections.

Acknowledgements

This study was not supported by any sponsor of funder.

Competing Interest

The authors declared no relevant conflicts of interest.

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