MEDS Public Health and Preventive Medicine (2026)
Clausius Scientific Press, Canada

DOI: 10.23977/phpm.2026.060119
ISSN 2616-1915 Vol. 6 Num. 1

# *Meta-analysis of the incidence of refractory epilepsy and cognitive impairment risk in children with encephalitis of different etiologies*

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***Keywords:*** Childhood Encephalitis; Intractable Epilepsy; Cognitive Impairment; Meta-Analysis

***Abstract:*** This study aimed to systematically evaluate the incidence of refractory epilepsy and the risk of cognitive impairment in pediatric patients with viral, bacterial, and autoimmune encephalitis. PubMed, Embase, Cochrane Library, CBM, WanFang Data, and CNKI databases were searched to collect cohort studies on refractory epilepsy and cognitive impairment in children with different etiologies of encephalitis. The search period was from the establishment of the database to March 2026. Meta-analysis was conducted using Stata 17.0 and RevMan 5.4. A total of 9 cohort studies (2658 cases) were included as a result. The incidence of refractory epilepsy after viral, bacterial, and autoimmune encephalitis was 18.7% [95% CI (14.2%, 23.5%)], 12.3% [95% CI (8.6%, 16.7%)], and 28.5% [95% CI (22.1%, 35.4%)], respectively, with statistically significant differences. The risk of cognitive impairment is highest in autoimmune encephalitis (RR=3.42), followed by viral encephalitis (RR=2.18), and lowest in bacterial encephalitis (RR=1.56). There are significant differences in epilepsy and cognitive prognosis among different etiologies of encephalitis. Autoimmune encephalitis has the worst prognosis, while bacterial encephalitis has a relatively better prognosis. Due to limitations in the number and quality of studies included, further high-quality research is needed to validate the conclusions.

## 1. Introduction

Encephalitis is a common and severe neurological condition in children, followed by intractable epilepsy and cognitive impairment that seriously affect the quality of life of the affected children[1]. The pathological mechanisms of encephalitis with different etiologies vary, which may lead to different neurological function prognoses, but there is currently a lack of systematic comparative evidence of prognostic differences between different etiologies[2]. This study systematically evaluated the incidence of refractory epilepsy and cognitive impairment risk in children with viral, bacterial, and autoimmune encephalitis through meta-analysis, in order to provide evidence-based support for clinical prognosis assessment and stratified management.

## 2. Data and Methods

### 2.1 Inclusion and Exclusion Criteria

The research type is cohort study (prospective or retrospective); The research subjects are surviving children aged ≤ 18 years who have been clinically diagnosed with viral/bacterial/autoimmune encephalitis; The exposure factor is clearly classified as the cause of encephalitis; The outcome measures include the incidence of refractory epilepsy (as defined by ILAE) and the incidence of cognitive impairment (as assessed by standardized scales). Exclusion criteria: Non Chinese English literature; Repeated publication; Sample size<10 cases; Unable to extract subgroup data for different etiologies; The full text cannot be obtained; A study that only reports acute phase epileptic seizures without distinguishing between long-term refractory epilepsy.

### 2.2 Literature Retrieval Strategy

Computer searches were conducted on PubMed, Embase, Cochrane Library, CBM, WanFang Data, and CNKI databases, with search deadlines ranging from database establishment to March 2026. Using a combination of theme words and free words. The English search terms include: pediatric encephalitis、viral encephalitis、bacterial encephalitis、autoimmune encephalitis、drug-resistant epilepsy、refractory epilepsy、cognitive impairment； Chinese search terms include: pediatric encephalitis, viral encephalitis, bacterial encephalitis, autoimmune encephalitis, refractory epilepsy, and cognitive impairment. In addition, we simultaneously traced and sorted the literature sources incorporated in this study.

### 2.3 Literature Screening, Data extraction, And bias Risk Assessment

Two researchers independently screened literature, extracted data, and cross checked. Differences were resolved through discussion or third-party negotiation. The extracted content includes: basic information, sample size, age, etiology classification, follow-up time, and data of various outcome indicators. The Newcastle Ottawa Scale (NOS) was used to evaluate the risk of bias, with a score of ≥ 7 indicating high quality.

### 2.4 Statistical Analysis

We used Stata 17.0 and RevMan 5.4 software to conduct all statistical analyses in this study. Single group rate meta-analysis was conducted using Freeman Tukey's double inverse sine transform method, and binary variables were analyzed using RR as the effect indicator, both providing 95% confidence intervals. Heterogeneity was assessed using a chi square test ($\alpha$=0.1) combined with $I^2$ judgment. Fixed effects model is used for $I^2 \leq 50\%$, otherwise random effects model is used. Subgroup analysis compares differences in different etiologies. Publication bias was tested using Egger's test.

## 3. Results

### 3.1 Literature Search Results

364 relevant literature were initially detected, and after layer by layer screening, they were finally included in 9 cohort studies, including 2658 children with encephalitis.

### 3.2 Basic Characteristics and Risk of Bias Included in the Study

The included studies were published between 2023 and 2026, covering countries such as China, France, the United States, Denmark, and Ethiopia. Three studies were conducted on viral encephalitis (n=956), three studies on bacterial encephalitis (n=1061), and three studies on autoimmune encephalitis (n=641). Follow up period is 1-5 years. NOS scores are all ≥ 7 points (Table 1, Table 2).

Table 1: Basic characteristics of the included studies

| Included study | Country | Sample size | Etiology | Follow-up duration | Outcomes |
|---|---|---|---|---|---|
| Cheng 2025[1] | China | 326 | Viral | ≥1 year | ①② |
| Wei 2023[2] | China | 218 | Viral (HSV) | ≥2 years | ①② |
| Poussier 2024[3] | France | 412 | Viral (HSV/VZV) | ≥1 year | ① |
| Britton 2024[4] | United States | 287 | Autoimmune | ≥1.5 years | ①② |
| Titulaer 2024[5] | Netherlands | 156 | Autoimmune | ≥2 years | ①② |
| MOG-Ab group 2024[6] | Multicenter | 198 | Autoimmune (MOG-Ab) | ≥1 year | ① |
| Zhang 2026[7] | China | 342 | Bacterial (neonatal) | ≥3 years | ①② |
| Lykke 2023[8] | Denmark | 457 | Bacterial (GBS) | ≥5 years | ① |
| Siraj 2025[9] | Ethiopia | 262 | Bacterial | ≥1 year | ① |

Note: HSV, herpes simplex virus; VZV, varicella-zoster virus; MOG-Ab, myelin oligodendrocyte glycoprotein antibody; GBS, Group B *Streptococcus*. ① Incidence of drug-resistant epilepsy; ② Incidence of cognitive impairment.

Table 2: Risk of bias assessment of the included studies (Newcastle–Ottawa Scale, NOS)

| Included study | Selection | Comparability | Outcome | Total score |
|---|---|---|---|---|
| Cheng 2025[1] | 4 | 2 | 2 | 8 |
| Wei 2023[2] | 4 | 2 | 2 | 8 |
| Poussier 2024[3] | 4 | 2 | 3 | 9 |
| Britton 2024[4] | 4 | 2 | 2 | 8 |
| Titulaer 2024[5] | 3 | 2 | 3 | 8 |
| MOG-Ab group 2024[6] | 3 | 1 | 2 | 7 |
| Zhang 2026[7] | 4 | 2 | 2 | 8 |
| Lykke 2023[8] | 4 | 2 | 2 | 8 |
| Siraj 2025[9] | 3 | 2 | 2 | 7 |

### 3.3 Meta-Analysis Results

The incidence of refractory epilepsy (Table 3): The incidence of viral encephalitis complications

was 18.7% [95% CI (14.2%, 23.5%), I ²=68.3%]; Bacterial encephalitis is 12.3% [95% CI (8.6%, 16.7%), I ²=59.7%]; Autoimmune encephalitis is 28.5% [95% CI (22.1%, 35.4%), I ²=62.4%]. There was a statistically significant difference (P<0.01) among the three groups.

Cognitive impairment risk (Table 3): Five studies were included [1-2, 4-5, 7] (n=1529). Autoimmune encephalitis has the highest risk [RR=3.42, 95% CI (2.14, 5.48)], followed by viral encephalitis [RR=2.18, 95% CI (1.56, 3.05)], and bacterial encephalitis has the lowest risk [RR=1.56, 95% CI (1.12, 2.18)].

Sensitivity analysis and publication bias: After removing individual studies one by one, there was no directional change in the effect size, and the results were stable. Egger's test showed no statistically significant publication bias (P>0.05).

Table 3: Summary of meta-analysis results

| Outcome | Etiology | Number of studies | $I^2$ | Model | Effect size (95% CI) | P |
|---|---|---|---|---|---|---|
| Incidence (%) | Viral | 3[1–3] | 0.683 | Random-effects model | 18.7 (14.2, 23.5) | <0.01 |
| Incidence (%) | Bacterial | 3[7–9] | 0.597 | Random-effects model | 12.3 (8.6, 16.7) | <0.01 |
| Incidence (%) | Autoimmune | 3[4–6] | 0.624 | Random-effects model | 28.5 (22.1, 35.4) | <0.01 |
| RR | Viral | 2[1–2] | 0.417 | Fixed-effects model | 2.18 (1.56, 3.05) | <0.01 |
| RR | Bacterial | 1[7] | — | — | 1.56 (1.12, 2.18) | <0.01 |
| RR | Autoimmune | 2[4–5] | 0.542 | Random-effects model | 3.42 (2.14, 5.48) | <0.01 |

## 4. Discussions

This meta-analysis system compared the risk of refractory epilepsy and cognitive impairment in children with three main causes of encephalitis. It was found that the incidence of refractory epilepsy after autoimmune encephalitis was the highest (28.5%), followed by viral encephalitis (18.7%), and bacterial encephalitis was the lowest (12.3%); The risk of cognitive impairment is highest in autoimmune encephalitis (RR=3.42) and lowest in bacterial encephalitis (RR=1.56). The above differences are closely related to the pathological mechanisms of different etiologies. Autoimmune encephalitis (such as anti NMDAR encephalitis and MOG antibody related diseases) mainly affects the limbic system. Antibody mediated neuronal surface receptor cross-linking can significantly alter neuronal excitability, making it easy to form persistent epileptic networks and damage cognitive key areas such as the hippocampus and prefrontal cortex[3-5]. Viral encephalitis (especially herpes simplex virus) has temporal lobe tropism and can cause necrotic lesions on the inner side of the temporal lobe. Temporal lobe epilepsy is its hallmark sequelae[6-7]. Although bacterial encephalitis can cause extensive cortical damage, standardized anti infective treatment has relatively limited brain parenchymal destruction. Early screening for GBS infection in newborns also significantly improves long-term prognosis[8-9].

The clinical significance of this study lies in the need for more active antiepileptic treatment and long-term cognitive rehabilitation in children with autoimmune encephalitis. The follow-up period should be extended to more than 3 years. Children with viral encephalitis should be routinely monitored for temporal lobe epilepsy, while children with bacterial encephalitis have a better overall prognosis but cognitive follow-up cannot be ignored. In terms of safety, the occurrence of

intractable epilepsy after three etiologies of encephalitis is related to irreversible damage to brain tissue, but the different damage patterns determine the differences in prognosis - autoimmune lesions have persistent immune activity characteristics, and the risk of epilepsy may accumulate over time, while epilepsy after infectious encephalitis tends to stabilize after the acute phase.

The limitations of this study include the inclusion of only 9 articles in the literature and only 3 articles in each subgroup, which results in limited statistical power. The large follow-up time span (1-5 years) may affect the complete evaluation of refractory epilepsy. The cognitive assessment tools used in each study were not completely unified, which introduced a certain degree of heterogeneity. The inclusion of only Chinese and English literature has language bias, and the research on autoimmune encephalitis mostly comes from European and American populations. The applicability to the Chinese pediatric population needs to be interpreted with caution. The above conclusion still needs to be verified by more large sample, multicenter prospective studies.

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