Outcome and Prognostic Factors of Pediatric Encephalitis in Thailand

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Abstract

Encephalitis, a severe central nervous system infection, poses significant morbidity and mortality risks. Etiologically, this condition can arise from infections or immune-mediated mechanisms, with varying causative agents across regions. Despite limited studies on pediatric encephalitis in Thailand, our retrospective cohort study aimed to discern the characteristics, outcomes, and prognostic factors influencing clinical results. We examined patients under 15 years of age admitted to Maharat Nakhon Ratchasima Hospital from January 1, 2007 to December 31, 2022, recording baseline data encompassing clinical manifestations, etiology, investigations, and treatments. The study defined outcomes in terms of morbidity, subsequent epilepsy incidence, and mortality rates evaluated via the modified Rankin Scale. Among 183 enrolled patients (age range 5 days to 15 years, mean age 7.4 years), males comprised 54.1%. Viral encephalitis (35.52%) and immune-mediated encephalitis (22.4%) emerged as the prevailing etiologies, with herpes simplex, dengue, and influenza virus as prominent viral pathogens. Anti-N-methyl-D-aspartame receptor encephalitis (56.1%) led among immune-mediated cases. Initially, 94.53% of patients displayed moderate-to-severe disability, while 45.7% exhibited clinical improvement within 6 months. Subsequent epilepsy ensued in 38.8% of cases, with an overall mortality rate of 19%, notably higher in viral encephalitis instances. Our findings underscore a predilection for viral pathogens in pediatric encephalitis cases, contributing to inferior prognoses. This study accentuates the necessity of understanding etiological patterns and prognostic markers to enhance clinical outcomes in this vulnerable population segment.

Keywords
- pediatric encephalitis
- etiology
- outcome
- prognostic factors

Introduction

Pediatric encephalitis is one of the severe conditions that lead to high morbidity and mortality.[1–4] The pathogenesis of encephalitis is inflammation of the brain parenchyma. The etiology of encephalitis can be classified into infection and inflammation process. Infectious etiology is defined as viral, bacterial, tuberculosis (TB), fungal, and presumed infection, but the limitation of investigation resulted in the suboptimal identification of pathogens of infection.[2] There is an emerging diagnosis of inflammatory etiology of encephalitis, such as immune encephalitis and anti-N-methyl-D-aspartame receptor (NMDAR) encephalitis. Previous studies in developed and developing countries show that the infectious etiology was common in viral pathogens, and the immune etiology was as common as the anti-NMDAR encephalitis.[5–8]

The outcomes of pediatric encephalitis, such as subsequent epilepsy and disability, were severe. The mortality rate varied from 0.5 to 31%. The prognostic factors were the

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etiology of encephalitis and the need for pediatric intensive care unit (PICU) admission.[1–3]

In Thailand, existing studies have primarily focused on the etiology and prognosis of encephalitis but with limited emphasis on the pediatric population. Our study aimed to fill this gap by investigating the etiology and outcomes of pediatric encephalitis, as well as identifying prognostic factors. By comparing our findings with previous research, we sought to delineate the differences and contribute to the understanding of this condition specifically in children.

Method

Conducted as a retrospective cohort study, our research received approval from the Institutional Review Board (IRB102/2023) and adhered to the guidelines outlined in the Helsinki Declaration. We enrolled patients under 15 years of age who were diagnosed with encephalitis and admitted to Maharat Nakhon Ratchasima Hospital between January 1, 2007, and December 31, 2022. Encephalitis diagnoses were established through a comprehensive assessment of clinical, laboratory, neuroimaging, and serological data following the criteria set forth by the International Encephalitis Consortium (IEC 2013).[1,2] Baseline characteristics including clinical manifestations, etiology, investigative procedures, and treatment regimens were meticulously documented.

We excluded congenital infections such as cytomegalovirus, toxoplasmosis, syphilis, hepatitis B, and rubella from our study.

Viral pathogens were identified using polymerase chain reaction (PCR) technology. TB diagnosis involved PCR and culture of TB in cerebrospinal fluid. Bacterial infections were diagnosed through cerebrospinal fluid culture. Immune encephalitis, like anti- NMDAR encephalitis, was diagnosed using a cell-based assay technique. Due to constraints related to PCR technology and financial limitations, PCR testing was restricted to a selected group of pathogens, including herpes simplex virus (HSV), enterovirus, dengue virus, influenza virus, respiratory syncytial virus (RSV), and Japanese encephalitis (JE).

The outcomes assessed included morbidity, subsequent epilepsy, and mortality rates. Morbidity was determined using a modified Rankin Scale (MRS) as outlined in ►**Appendix A**. Morbidity was evaluated at diagnosis, 6 months, 12 months, and beyond 12 months during the follow-up period. Subsequent epilepsy was classified according to the International League Against Epilepsy guidelines. Mortality rates were classified as short-term (within 30 days of initial diagnosis) and long-term (after 30 days of initial diagnosis).

We analyzed prognostic factors that could impact clinical outcomes, including etiology, age group, various treatments, disease severity categorized by MRS, status epilepticus, and admission to the PICU.

Percentages and mean/median values were utilized in the descriptive analysis. Prognostic factors and potential etiological influences on prognosis were identified through multivariate analysis. A p-value below 0.05 indicates statistical significance.

Results

A total of 183 patients aged between 5 days and 15 years (with a mean age of 7.4 years) were included in the study, with 54.1% being male. Viral encephalitis (64.5%) and immune-mediated encephalitis (28.96%) were identified as the predominant etiologies. Seizures and altered consciousness were the most common clinical manifestations, with 81.97% of patients experiencing status epilepticus during their hospital stay. Despite the majority of patients exhibiting cerebrospinal fluid pleocytosis, 11.48% tested negative on serological and immunologic assessments due to laboratory constraints. Neuroimaging (either CT brain or MRI brain) was performed in only 50.82% of cases due to investigative limitations. Treatment consisted of intravenous antibiotics or intravenous acyclovir in 71.04% of patients, while those with seronegative results received supportive care. Despite the majority of patients experiencing severe encephalopathy and significant neurological deficits with seizures, only 42.08% were admitted to the PICU due to resource constraints within the hospital. Demographic information is presented in ►**Table 1**.

The primary viral pathogens identified included HSV, dengue virus, and influenza virus, with another 64.5% comprising various other viruses such as enterovirus, RSV, and unidentified pathogens detected through PCR analysis. Patients with suspected viral encephalitis based on clinical and laboratory findings—including evidence of viral infection in complete blood count results and negative hemocultures—were categorized within this broader "other virus" grouping. Due to restrictions within the encephalitis panel PCR testing capabilities, only HSV, influenza, dengue, RSV, and enterovirus could be specifically evaluated.

The most prevalent bacterial infections were *Streptococcal pneumoniae* and *Mycoplasma pneumoniae*. TB infection was identified in 4% of patients, as illustrated in ►**Fig. 1**.

Regarding immune-mediated etiologies, anti-NMDAR encephalitis accounted for 56% of cases, followed by acute disseminated encephalomyelitis (ADEM) at 37%. Other etiologies, such as systemic lupus erythematosus, comprised 7% of cases, as shown in ►**Fig. 2**.

Upon initial diagnosis, 94.53% of patients exhibited moderate-to-severe disability, with 42.6% presenting comatose and severely disabled. By 6 months, 45.7% demonstrated clinical improvement. However, at 1 year follow-up, patients still displayed mild-to-moderate disability, with only 7.65% achieving complete recovery. By the 2-year mark, 71% exhibited mild disability on the MRS, while nearly complete recovery was observed in only 19% of patients, as illustrated in ►**Fig. 3**.

Seizures manifested as the initial clinical symptom in 46.45% of cases, with 81.97% eventually experiencing episodes of status epilepticus. Upon follow-up, 38.8% of patients progressed to develop epilepsy.

The short-term mortality rate was 19%, primarily attributed to causes such as brain herniation and multiorgan failure. Etiology of viral encephalitis was found to have a significant impact on mortality rates, while the presence of

Table 1 Summary of demographic characteristics

	N = 183 (%)
Sex	
Male	99 (54.10)
Female	84 (45.90)
Age 5 d–15 y Mean age 7.4 y (SD = 4.88)	
Age group	
Age 0–5 y	77 (42.07)
Age 6–10 y	43 (23.50)
Age 11–15 y	63 (34.43)
Etiology of encephalitis	
Bacterial	24 (13.1)
Virus	118 (64.5)
Immune-mediated	41 (22.4)
Developing status epilepticus	
Yes	150 (81.97)
No	33 (18.03)
First presenting symptoms	
Seizure	85 (46.45)
Alteration of consciousness	74 (40.44)
Others	24 (13.11)
CSF pleocytosis	
Yes	133 (72.68)
No	50 (27.33)
Neuroimaging	
CT brain	47 (25.68)
MRI brain	46 (25.14)
Not done	90 (49.18)
Treatment	
IV Antibiotics	66 (36.07)
IV Acyclovir	64 (34.97)
Immunosuppressive drug	53 (28.96)
Combine both cephalosporin such as cefotaxime and ceftriaxone/immunosuppressive drug	0 (0)
Need of PICU	
Yes	77 (42.08)
No	106 (57.92)
MRS at first diagnosis	
Severe disability	78 (42.62%)
Moderate disability	95 (51.91%)
Mild disability	10 (5.46%)
No disability	0 (0)

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; MRS, modified Rankin Scale; PICU, pediatric intensive care unit; SD, standard deviation.

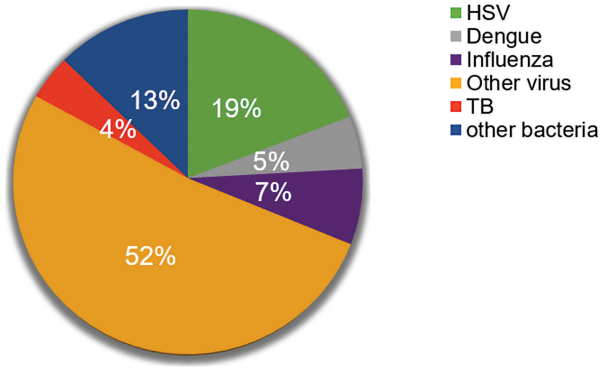

Fig. 1 Distribution of infectious pathogens as etiological factors.

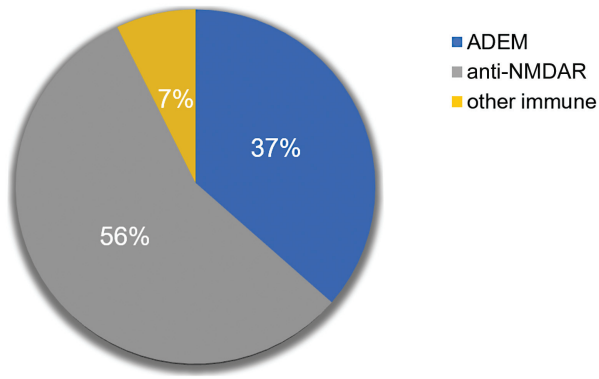

Fig. 2 Etiological factors of immune-mediated encephalitis.

status epilepticus did not show a significant effect, as evidenced in ►**Table 2**.

Discussion

Pediatric encephalitis represents a critical medical emergency associated with high morbidity and mortality rates according to references.[9,10] The understanding of pediatric encephalitis etiology has advanced significantly. Over 80% of our patients were successfully identified. Our study highlighted infectious etiology as the primary cause in 59.56% of cases, followed by immune-related causes as the second most prevalent.

In our hospital study, limitations were observed in diagnosing encephalitis, with 11.48% of patients presuming an infectious etiology based on clinical presentation, despite negative serology results.

In our research, HSV, influenza, and dengue were frequently identified as the primary viral pathogens. This differs from the findings of Britton et al in Australia, where enterovirus and parechovirus were commonly found.[11] However, our results are consistent with those of Brisca et al, which also highlighted HSV as a prevalent viral pathogen.[12]

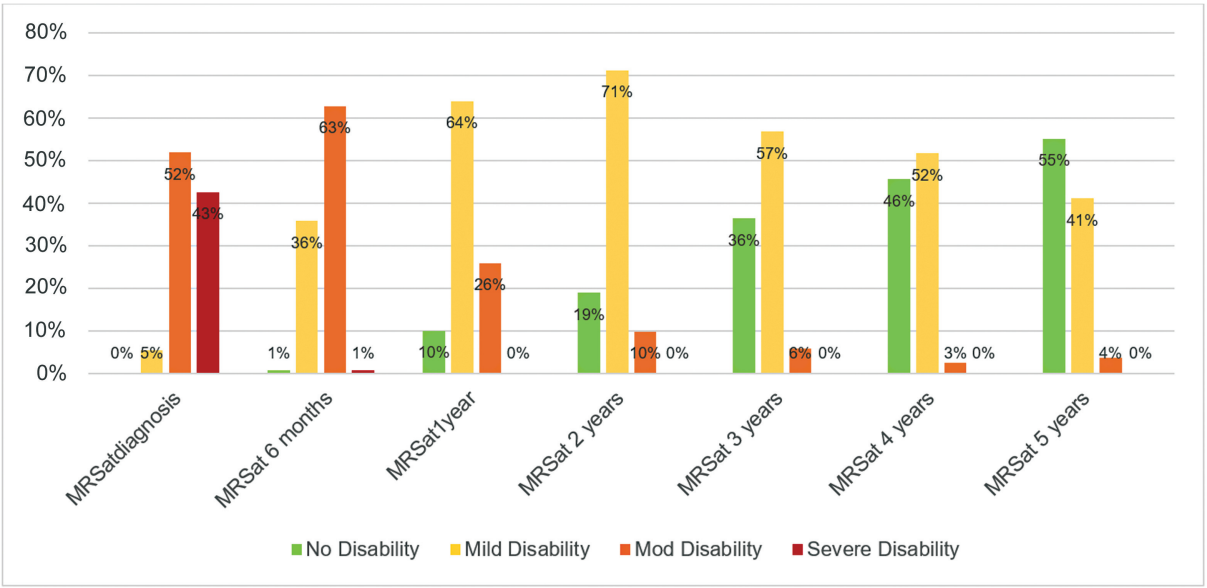

Fig. 3 Disability status at diagnosis and follow-up periods.

Table 2 Results of multivariate analysis

Factors	Adjusted OR (95%CI)	*p*-Value
Etiology of encephalitis		0.002
Immune	–	
Virus	13.25 (2.49, 70.48)	
Bacteria	18.78 (3.19, 110.59)	
Others	6.86 (1.32, 35.55)	
Status epilepticus		0.931
Yes	–	
No	0.96 (0.36, 2.56)	

Abbreviations: CI, confidence interval; OR, odds ratio.

Similarly, a study conducted by Hasbun et al in the United States identified enterovirus as a common pathogen.[13]

Erickson et al.'s study revealed that infectious causes accounted for 31%, with 22% attributed to viral infections, notably the predominant West Nile virus.[9] In contrast, Goto et al's research in Japan identified influenza as the most common viral pathogen,[14] differing from our study where influenza ranked as the second most prevalent. Studies from China and India indicated JE virus as the primary pathogen, with implications for health policies concerning vaccine-preventable diseases.[10]

Our study, which aligned with de Blauw et al's research in the Netherlands,[15] found HSV and bacteria to be common pathogens. In contrast, studies in Thailand have identified dengue and HSV infections as the primary causes of pediatric encephalitis, differing from Western countries where enterovirus and HSV are more prevalent. Chokephaibulkit et al's study in Thailand highlighted dengue, JE, and HSV as the top three etiologies.[16] Although our study associated with HSV, dengue, and influenza, JE infection was not a significant factor due to temporal differences, indicating JE vaccination was not a limiting factor during our study period.

The etiology of encephalitis can vary based on factors such as geographic distribution, seasonality, and age groups specific to different regions. Genetic susceptibility may also play a role, with influenza encephalitis being more common in Asian populations.[10–17]

Bacterial and TB infections accounted for 19% of cases, with TB infection identified in encephalitis cases due to endemic TB. This contrasts with previous studies that had limited reports on TB infection associated with encephalitis.[18,19]

In terms of immune-mediated etiologies, anti-NMDAR encephalitis was found to be the most prevalent, followed by ADEM. This finding is consistent with studies by Britton et al, which reported immune etiologies in 25% of cases, predominantly involving ADEM and anti-NMDAR encephalitis.[11]

In our analysis, we observed that younger patients were predominantly diagnosed with infectious etiology, whereas older individuals were more commonly associated with immune-related processes. This finding aligns with studies conducted by Britton et al. and Erickson et al.[9,11] The characteristic clinical presentations in our study included seizures, status epilepticus, fever, and alterations in consciousness, which corroborated with findings from previous research studies.[9,11–17,20]

In reference to changes in the MRS or patient disabilities, there was no observed variance compared with a prior study indicating that encephalitis-induced neurodeficits significantly influenced the sequelae of encephalitis.[17,18]

Our study revealed a high prevalence of clinical severity among patients, with the majority experiencing seizures progressing to status epilepticus (81.97%). Of these cases, 42.08% necessitated admission to a PICU—a rate lower than that reported in prior research due to resource constraints

limiting admissions despite the serious nature of the illness. The study exhibited an overall mortality rate of 19%, consistent with findings by Hon et al and Elenga et al, who reported mortality rates of 25 to 30%.[21,22] In contrast, a U.S. study documented a notably lower mortality rate of 0.5%.[13] Comparing our results with prior studies revealed a correlation in mortality rates, aligning with the range of 0.5 to 31% observed in previous research.[21–23]

The identified prognostic factor associated with mortality was the etiology of viral encephalitis, reflecting findings consistent with prior research. Previous studies have demonstrated that viral encephalitis etiology is linked to a worse prognosis, influencing patient outcomes.[19–23]

Our study revealed nonsignificant impacts on mortality from factors such as age group, admission to the PICU, and the occurrence of status epilepticus episodes. This deviates from the findings of a previous study by Hatachi et al, which noted unfavorable outcomes associated with PICU admission within 2 days.[17] Similarly, a study conducted in Nepal aimed to assess the relationship between coma scores and adverse outcomes but, akin to our findings, found no significant correlation.[23]

Conclusion

This study identified Dengue and HSV as common viral etiologies of encephalitis. High morbidity and mortality rates were observed, with the viral etiology of encephalitis playing a crucial role in shaping patient outcomes.

Conflict of Interest

None declared.

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Appendix A The Modifies Rankin Scale (MRS) was classified as below

0: No symptoms.
1: No significant disability. Able to carry out all usual activities, despite some symptoms.
2: Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3: Moderate disability. Requires some help, but able to walk unassisted.
4: Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5: Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6: Dead.