Epidemiology and Etiology of Severe Childhood Encephalitis in The Netherlands

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Background: Limited data are available on childhood encephalitis. Our study aimed to increase insight on clinical presentation, etiology, and clinical outcome of children with severe encephalitis in the Netherlands.

Methods: We identified patients through the Dutch Pediatric Intensive Care Evaluation database and included children diagnosed with encephalitis <18 years of age admitted to 1 of the 8 pediatric intensive care units (PICU) in the Netherlands between January 2003 and December 2013. We analyzed demographic characteristics, clinical symptoms, neurologic imaging, etiology, treatment and mortality.

Results: We included 121 children with a median age of 4.6 years (IQR 1.3–9.8). The most frequently described clinical features were headache (82.1%), decreased consciousness (79.8%) and seizures (69.8%). In 44.6% of the children, no causative agent was identified. Viral- and immune-mediated encephalitis were diagnosed in 33.1% and 10.7% of the patients. A herpes simplex virus infection (13.2%) was mainly seen in children <5 years of age, median age, 1.73 years (IQR 0.77–5.01), while immune-mediated encephalitis mostly affected older children, median age of 10.4 years (IQR, 3.72–14.18). An age of ≥ 5 years at initial presentation was associated with a lower mortality (OR 0.2 [CI 0.08–0.78]). The detection of a bacterial (OR 9.4 [CI 2.18–40.46]) or viral (OR 3.7 [CI 1.16–11.73]) pathogen was associated with a higher mortality.

Conclusions: In almost half of the Dutch children presenting with severe encephalitis, a causative pathogen could not be identified, underlining the need for enhancement of microbiologic diagnostics. The detection of a bacterial or viral pathogen was associated with a higher mortality.

Key Words: encephalitis, children, epidemiology, outcome, pediatric intensive care

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Encephalitis is a severe central nervous system infection of the brain parenchyma leading to neurologic dysfunction, such as headaches and altered levels of consciousness.[1] Childhood encephalitis is associated with long-term morbidity in up to 50% of the affected patients, but mortality rates improve significantly with early start of treatment.[2–4] Early recognition of childhood encephalitis is therefore vital to improve clinical outcome, but often proves to be difficult as symptoms are wide-ranged and nonspecific.[5] These symptoms may include malaise, fever, headaches, seizures and decreased consciousness.[6] Accurate numbers on the incidence and causes of childhood encephalitis are incompletely defined. The lack of data on this subject stems from a few problems. Firstly, there are only a few quality population studies available on encephalitis because of the rarity of this disease. Most of these studies are performed in a broad population and do not specifically focus on children. Furthermore, because a large proportion of encephalitis cases have an unknown cause, it is possible that previously reported incidence numbers are underestimations. Furthermore, the large proportion of unknown causes makes it difficult to assess regional differences and the possible impact of specific etiologic causative pathogens.[7–10]

Research specifically focusing on the etiology of childhood encephalitis in the Western world is needed, as diagnostic and detection techniques have improved leading to an increased ability to identify causative pathogens that were previously undetectable.[11] Previous studies have mainly focused on the epidemiology and etiology of childhood encephalitis in low resource settings and their results may therefore not be representative for the Western world.[12] The etiology of childhood encephalitis has changed significantly in developed countries with the start of extensive vaccination programs targeting previously common causes of childhood encephalitis, such as varicella zoster virus (VZV) and measles.[13–15]

Herpes simplex virus (HSV) is the most frequently identified viral pathogen in children with encephalitis in the Western world followed by VZV. Enteroviruses have emerged as an important cause of viral encephalitis in Asia, specifically China.[16–18] Despite being an important cause of encephalitis, the frequency of occurrences of these viruses may be underestimated.[19,20] Apart from viral and bacterial causes, immune-mediated processes, such as N-methyl D-aspartate receptor antibody (anti-NMDAR) encephalitis, have been reported to be the cause of encephalitis in up to 34% of cases. Immune-mediated encephalitis represents an important disease entity as it has been linked to high mortality rates. The need

to differentiate between infectious and immune-mediated disease is further highlighted by the differences in treatment.[21–23]

In this study, we describe the clinical symptoms, demographics and mortality in children admitted to a pediatric intensive care unit (PICU). Furthermore, we evaluated associations between clinical and diagnostic indicators and mortality in children with encephalitis.

METHODS

Study Population

We performed a retrospective cohort study in which all children <18 years of age were included. All children were admitted because of encephalitis to 1 of the 8 PICUs in the Netherlands between January 1, 2003 and December 31, 2013.

All children were diagnosed with encephalitis by their treating physicians, based on clinical signs and symptoms either on admission to the PICU, or during the subsequent hospital stay. Therefore, all included cases of encephalitis were based on a clinical diagnosis and no accurate distinction between cases of meningo-encephalitis or pure encephalitis cases could be made. All 8 PICUs in the Netherlands, that is, the Academic Medical Centre Amsterdam (AMC), Erasmus University Medical Centre, Leiden University Medical Centre, Maastricht University Medical Centre, Radboud University Nijmegen Medical Centre, University Medical Centre Groningen, University Medical Centre Utrecht and VU University Medical Centre participated in this study.

Patients were identified using the search term "encephalitis" via the Dutch Pediatric Intensive Care Evaluation national database, in which data such as diagnosed illness, length of stay, severity of disease and mortality of children admitted to a PICU in the Netherlands are collected. We collected data from the Pediatric Intensive Care Evaluation database and medical patient records using standardized case report forms. Primary encephalitis was defined as a direct infection of the brain by a bacterial, viral or auto-immune infection. An auto-immune infection was considered proven when antibodies could be detected during subsequent hospital stay and follow-up. A secondary encephalitis was defined as a clinically diagnosed encephalitis occurring after a primary infection, trauma or immune-mediated disease, during a subsequent hospital stay. Only primary cases of encephalitis were included. All secondary admissions to a PICU during the same disease episode were excluded. For the purpose of statistical analyses, we classified children into 3 age groups: children <1 year of age, children between 1 year and 4 years, children ≥ 5 years of age.

Clinical Symptoms, Neurologic Imaging and Outcomes

We evaluated the following clinical characteristics: fever (defined as a temperature > 38.5°C), decreased consciousness (Glasgow coma scale score ≤ 7), meningeal irritation, seizures and apnea (defined as an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor and/or marked hypertonia). Only signs and symptoms present at hospital admission were used.

Standardized reports on abnormalities in neurologic imaging and functioning were collected using available information on computed tomography (CT), magnetic resonance imaging (MRI) and electroencephalograms (EEG). All diagnostic images were commissioned either on admittance to the PICU or during the subsequent hospital stay. It is possible that multiple tests were performed in the same child on admission, for instance, a CT scan followed by an MRI scan. We have only evaluated data on the neuroimaging tests performed at the time of admission. All neuro-imaging tests

were performed because the treating physician considered a diagnosis of meningo-encephalitis. Abnormal findings that were caused by a meningo-encephalitis (which were all abnormal findings) were included in this study.

Clinical outcome was evaluated by the mortality rate during the index admission. The outcomes of individual cases were reviewed by retrospectively evaluating medical records. Through this method, we tried to distinguish children who died during admission and subsequent hospital stay, from children who had already died before reaching the respective PICUs. Because of the previously reported worse outcome in patients with comorbidities, especially immunocompromised individuals, a statistical analysis was performed to assess the impact of all major comorbidities on mortality.[10] Deaths occurring during secondary hospital admissions, were not included in the mortality rate. Length of hospital stay in days was used as a secondary measurement of clinical outcome.

Etiology

Data on the presence of a causative infectious pathogen were collected using data from the medical microbiology laboratory of each participating hospital. We defined infectious encephalitis as a clinical diagnosis combined with the identification of a viral or bacterial pathogen, in blood or cerebrospinal fluid (CSF) cultures or a positive plasma or CSF result using polymerase chain reaction (PCR).

Immune-mediated encephalitis was defined as a heterogeneous group consisting of several forms of encephalitis, for which an auto-immune etiology had been demonstrated or was strongly suspected, based on clinical presentation or abnormalities on neuroimaging. The following types of immune-mediated encephalitis were identified: Acute disseminated encephalomyelitis (ADEM), anti N-methyl D-aspartate receptor (anti-NMDAR) encephalitis, Hashimoto encephalitis or Rasmussen encephalitis.[24]

Cerebrospinal Fluid Characteristics

Cerebrospinal fluid characteristics were described using the following variables: white blood cell count (µ/L), protein levels (mg/L) and glucose levels (we compared glucose levels between CSF and blood). Decreased glucose CSF levels were defined as CSF levels <60% compared with blood glucose levels). We evaluated white blood cell count and protein levels based on the age specific cutoff values as previously described.[25]

Statistical Analysis

SPSS statistical software (version 23.0, SPSS inc, Chicago IL) and R (R version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org) were used for statistical analysis. Continuous variables were expressed as mean plus standard deviation if normally distributed or median and interquartile range (IQR) when data were skewed. For categoric clinical and demographic variables, differences between groups were evaluated using the χ^2 test or Fisher exact test where appropriate. To estimate the prognostic value of epidemiologic characteristics and clinical variables present at admission, odds-ratios with 95% CI were calculated using binary logistic regression. The variables used in the logistic regression model were pre-selected based on possible correlations considered in available literature. Model goodness of fit was assessed by the Hosmer-Lemeshow test. A P-value of $P < 0.05$ was considered statistically significant.

RESULTS

Demographic Characteristics

We identified 161 cases clinically diagnosed with encephalitis who were admitted to a PICU during the study period. Of these,

TABLE 1. Demographic Characteristics and Clinical Symptoms

		Children with encephalitis (n = 121) (n, %)
Demographic characteristics		
Sex (male)		57/121 (47.1)
Age at admission (years, IQR)		4.6 (1.3–9.8)
Comorbidity		28 (23.5)
	Malignancy	5 (4.2)
	Immune deficiency	4 (3.4)
	Prematurity	3 (2.5)
	Metabolic disorder	3 (2.5)
	Other	13 (10.9)
Clinical symptoms		
	Fever	49/95 (51.6)
	Apnea	12/64 (18.8)
Neurologic symptoms		
	Headache	23/28 (82.1)
	Decreased consciousness	71/89 (79.8)
	Meningeal irritation	25/54 (46.3)
	Insults	74/106 (69.8)
	Absent pupil reflex	16/94 (17.0)
	Abnormal eye movements	32/77 (41.6)
	Focal abnormalities	9/66 (13.6)

Demographic characteristics and clinical symptoms of children clinically diagnosed with encephalitis, admitted to a Pediatric Intensive Care Unit (PICU) in the Netherlands between January 1, 2003 and December 31, 2013. Data were obtained by a retrospective review of medical records and presented as median (IQR) or n (%). Decreased consciousness is defined as a GCS-score of <7. GCS= Glasgow coma scale.

40 children were subsequently excluded. Reasons for exclusion were previous inclusion of children on primary admission (n = 11), exclusion of the diagnosis encephalitis at follow-up (n = 20), admittance to a PICU due to logistic reasons rather than clinical need (n = 2), lack of availability of patient files (n = 4) and admission to a PICU outside the established time frame for this study (n = 3). A total of 121 children were included for further analyses, of which 57 were males (47.1%). The median age at the time of admission to a PICU was 4.6 years (IQR 1.3–9.8), with (20.7%) of patients <1 year of age.

In 39 cases (32.5%), hospital stay was complicated by co-infections. These included a range of infections ranging from pneumonia to gastro-enteritis caused by a wide variety of pathogens. No homogenous group of pathogens could be identified.

Comorbidity was reported in 28 children (23.5%), in 2 cases it remained unknown whether there was an underlying illness present. The most frequently reported comorbidities were malignancy (4.2%), immune deficiency (3.4%), prematurity (2.5%) and (not further specified) metabolic disorders (2.5%). Demographic characteristics and clinical symptoms of all included children are shown in Table 1.

Clinical Symptoms and Neurologic Imaging

The most reported neurologic symptoms were headache (82.1%), decreased consciousness (79.8%) and insults (69.8%). Further details on neurologic symptoms are shown in Table 1. In total, 80 CT scans were performed of which 48 (60.0%) showed abnormalities (diffuse cerebral swelling or edema). A total of 101 MRIs was performed, of which 79 (78.2%) showed abnormalities (diffuse swelling or cytotoxic edema). An EEG was performed in 92 cases, with abnormalities reported in 81 EEGs (88.0%). Generalized alterations were detected in the majority of cases in whom an

TABLE 2. Neuro-Imaging and Functioning

	N (=121) (n, %)
CT	
Number of patients in whom CT was performed	80/121 (66.1)
Number of CT in which cerebral abnormalities were detected	48/80 (60.0)
Findings	
Edema	17/80 (21.2)
Hypo-density	13/80 (16.3)
White/gray matter abnormalities	5/80 (6.3)
Hydrocephalus	1/80 (1.3)
Enlarged ventricular system	9/80 (11.3)
Subdural hematoma	2/80 (2.5)
Cerebral atrophy	3/80 (3.8)
Other	7/80 (8.8)
MRI	
Number of patients in whom MRI was performed	101/121 (83.5)
Number of MRI in which cerebral abnormalities were detected	79/101 (78.2)
Findings	
Edema	17/79 (21.5)
Abnormal signal intensity (not specified)	34/79 (43.0)
White matter abnormalities	15/79 (19.0)
Gray matter abnormalities	13/79 (16.5)
Ischemia	9/79 (11.4)
Hematoma	3/79 (3.8)
Enlarged ventricular system	5/79 (6.3)
Cerebral atrophy	4/79 (5.1)
Hydrocephalus	1/79 (1.3)
Other	11/79 (13.9)
EEG	
Number of patients in whom EEG was performed	92/121 (76.0)
Number of MRI in which cerebral abnormalities were detected	81/92 (88.0)
Findings	
Epileptiform abnormalities	22/81 (27.2)
Focal abnormalities	23/81 (28.4)
Diffuse abnormal EEG	71/81 (87.7)

This table shows the different abnormalities identified using CT, MRI or EEG. Abnormalities are categorized based on data obtained from medical records. It is possible that multiple abnormalities were reported on the same CT, MRI or EEG. Data are presented as N (%).

EEG was performed (87.7%). All identified abnormalities on either CT, MRI or EEG are summarized in Table 2.

Etiology

Causative pathogens were identified using PCR on CSF, blood and feces as well as viral cultures performed on CSF, blood and feces. A lumbar puncture was performed in 108 out of 121 (89.3%) children. We identified 40 positive PCRs on CSF (33.1 %), 19 positive PCRs on blood (15.7%) and 10 positive fecal PCRs (8.3%). Only 4 fecal viral cultures were positive (3.3%). None of the performed viral cultures on CSF or blood gave a positive test result. A causative pathogen was identified in 67 cases (55.4%) (see Table 3). A viral pathogen was identified in 40 children (33.1 %), a bacterial pathogen was identified in 12 children (9.9%). Immune-mediated encephalitis was identified in 13 children (10.7 %). Furthermore, 1 case of parasitic encephalitis (malaria falciparum) and 1 case of fungal encephalitis (aspergillosis) were identified. HSV was the most frequently identified viral pathogen (HSV) in 16 children (13.2%). Furthermore, 6 cases of enterovirus (5.0%) and 5 cases of human herpes virus type 6 (HHV-6) (4.1 %) encephalitis were identified. *Streptococcus pneumoniae*

TABLE 3. Etiology

PCR/ culture performed		N (%)
Bacterial meningo-encephalitis		12
	Streptococcus pneumoniae	7/12 (58.3)
	Escherichia coli	1/12 (8.3)
	Mycobacterium tuberculosis	1/12 (8.3)
	Other*	3/12 (25.0)
Viral encephalitis		40
	HSV	16/40 (40.0)
	CMV	2/40 (5.0)
	EBV	3/40 (7.5)
	Enterovirus	6/40 (15.0)
	Parechovirus	3/40 (7.5)
	HHV-6	5/40 (12.5)
	Measles virus	1/40 (2.5)
	Mumps virus	2/40 (5.0)
	Japanese encephalitis	1/40 (2.5)
	Influenza H1N1 virus	1/40 (2.5)
Immune-mediated encephalitis		13
	ADEM	6/13 (46.1)
	Anti-NMDAR encephalitis	3/13 (23.1)
	Hashimoto encephalitis	2/13 (15.4)
	Rasmussen encephalitis	1/13 (7.7)
	Other	1/13 (7.7)
Other		2
	Aspergillosis	1/2 (50.0)
	Malaria falciparum	1/2 (50.0)

This table shows the identified causative pathogens or underlying immune-mediated disease processes. Pathogens were identified using CSF/blood cultures or PCR. Data are displayed as n (%).

* Other bacterial agents included: *Borrelia burgdorferi*; *Streptococcus mitis*; and one not further defined Gram-positive specimen.

anti-NMDAR encephalitis, anti *N*-methyl D-aspartate receptor encephalitis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6.

was the most frequently identified bacterial pathogen as it was identified in 7 children (5.8%). All the evaluated cases were single infections, except for one severe case of immune deficiency, in which multiple viral agents were detected. ADEM was the most frequent cause of immune-mediated encephalitis, as it was diagnosed in 6 children (5.0%).

Cerebrospinal Fluid Characteristics

The median white blood cell count was 26.0 µ/L (IQR, 5.8–279.3). White blood cell count were performed in 96 cases, of which 63 were elevated (65.6%). Protein values were elevated in 62.7%. Decreased glucose values were seen in 77 out of 91 cases (84.6%) (Table 4).

TABLE 4. Cerebrospinal Fluid Characteristics (CSF).

	Children with encephalitis; N (%)
White blood cell count (IQR)	26.0 (5.8–279.3)
Elevated White blood cell count	63/96 (65.6)
Protein (IQR)	0.53 (0.25–1.56)
Elevated protein levels	52/83 (62.7)
Glucose	4.00 (3.40–5.73)
Decreased glucose levels	77/91 (84.6)

This table shows information on cerebrospinal fluid characteristics (CSF). Data are presented as median (IQR) or n (%).

White blood cell count (WBC) is shown as µ/L; Protein is shown as mg/L; Glucose level is shown as % proportional to blood glucose levels. As CSF levels <60% of blood glucose levels are considered as decreased.

TABLE 5. Association Between Clinical Symptoms, Neurologic Imaging, Etiologic Groups and Mortality

	Outcome (death)	
Demographic characteristics	OR	95% CI
Age at hospital admission:		
Children < 1 year of age	1	
Children between 1-4 years	0.6	(0.18 - 1.67)
Children ≥ 5 years of age	0.2	(0.08 - 0.78)
Gender (male)	1	
Gender (female)	1.5	(0.60 - 3.60)
Clinical symptoms		
Fever	0.5	(0.17 - 1.36)
Decreased consciousness	0.7	(0.22 - 2.31)
Neuroimaging		
Abnormalities on CT-scan	1.4	(0.45 - 4.16)
Abnormalities on MRI-scan	14.5	(0.84 - 250.38)
Abnormalities on EEG	2.3	(0.27-19.50)
Etiologic groups		
No PCR performed/No pathogen identified	1	
Viral	3.7	(1.16 - 11.73)
Bacterial	9.4	(2.18 - 40.46)
Auto-immune	1.6	(0.27 - 9.09)
Other	9.4	(0.51 - 174.48)

This table shows the univariate Odds Ratio's (OR) of a binary logistic regression analyses, evaluating the association between mortality and the individual demographic characteristics, clinical symptoms, etiologic groups and abnormalities on neuroimaging.

Data are presented as odds ratio (95% Confidence interval).

Treatment, Supportive Therapy and Outcome

Treatment consisted of different treatment regimens; acyclovir was administered in 94 patients, antibiotics in 93 patients; in 69 patients, steroids were administered and 12 children received immunoglobulins. In 6 of 121 (5.0%) children, empiric treatment consisted of only acyclovir, while in 4 of 121 (3.3%) children only antibiotics were administered. In all other cases, treatment consisted of a multi-drug regimen; 77 of 121 (63.6%) children were treated with acyclovir and antibiotics, while 54 of 121 children received both antibiotics and steroids (44.6%). In 4 cases, treatment consisted of acyclovir, antibiotics, immunoglobulins and steroids.

Supportive intensive care treatment consisted of respiratory support (both invasive and noninvasive), vasoactive drug treatment and renal replacement therapy. A total of 83 (68.3%) children received some level of supportive intensive care treatment. Invasive respiratory support was provided in 73 of 118 children (61.9%), and noninvasive respiratory support in 21 of 118 cases (17.8%). Information on respiratory support was missing in 3 children. Vasoactive drug treatment was provided in 16 of 121 children (13.2%). Mortality during the index admission was 20.8% (25 children of 121 died during initial PICU stay). The length of PICU stay was <1 week for the majority of children (62.0%), with a median PICU stay of 5 days (IQR 3.0–11.5).

Association Between, Clinical Characteristics, Causative Pathogens, Comorbidities and Mortality

No significant multivariate model to predict mortality based on our chosen predictors could be built. However, a significant lower mortality was seen in children >5 years compared with children <1 year (OR 0.2 [CI 0.08–0.78]). The detection of a proven bacterial (OR 9.4 [CI 2.18–40.46]) or viral (OR 3.7 [CI 1.16–11.73]) pathogen was associated with a higher mortality. Associations are shown in Table 5.

We examined the possible impact of comorbidities on mortality. All of the following comorbidities were evaluated:

TABLE 6.　Diagnostics

Diagnostics		N (%)
Viral cultures (CSF, blood, feces, urine)		
	Performed	85/121 (70.2)
	Positive	9/85 (10.6)
PCR CSF		
	Performed	103/121 (85.1)
	Positive	42/103 (40.8)
	HSV (type 1 and 2)	16/42 (38.1)
	CMV	2/42 (4.8)
	EBV	3/42 (7.1)
	Enterovirus	6/42 (14.3)
	Parechovirus	3/42 (7.1)
	HHV-6	5/42 (11.9)
	Measles virus	1/42 (2.4)
	Mumps virus	1/42 (2.4)
	Streptococcus pneumoniae	3/42 (7.1)
	Mycobacterium tuberculosis	1/42 (2.4)
PCR blood		
	Performed	44/121 (36.4)
	Positive	19/44 (43.2)
	HSV (type 1 and 2)	2/19 (10.5)
	CMV	2/19 (10.5)
	EBV	2/19 (10.5)
	Adenovirus	1/19 (5.3)
	Enterovirus	2/19 (10.5)
	Parechovisrus	3/19 (15.8)
	HHV6	3/19 (15.8)
	Parvovirus	1/19 (10.5)
	Measles virus	1/19 (10.5)
	Mycobactertium tuberculosis	1/19 (10.5)
PCR feces		
	Performed	34/121 (28.1)
	Positive	10/34 (29.4)
	Adenovirus	1/10 (10.0)
	Enterovirus	2/10 (20.0)
	Parechovirus	3/10 (30.0)
	HHV6	1/10 (10.0)
	Rotavirus	2/10 (20.0)
	Norovirus	1/10 (10.0)
PCR urine		
	Performed	4/121 (3.3)
	Positive	1/4 (25.0)
	Mumps virus	1/4 (25.0)

This table contains an overview of all available data on the performed diagnostic tests.

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6.

malignancy, immune deficiency, prematurity and metabolic disorders. Out of the 5 children with malignancy, 1 survived, while out of 4 children with an immune-deficiency, 1 survived. In our study, all prematurely born children survived. Out of 3 children with metabolic disorders, 2 survived. Malignancy (*P*-value, 0.003) and immune deficiency (*P*-value, 0.012) were the only comorbidities associated with a higher mortality.

DISCUSSION

In this nationwide retrospective study, we evaluated the clinical signs and symptoms, etiology and mortality of children <18 years with severe encephalitis in the Netherlands and evaluated associations between symptoms, etiologic factors and outcome. In half of the patients with clinical symptoms of severe encephalitis, no causative agent could be detected. Viruses were the most frequently identified cause of infectious encephalitis. A lower mortality was seen in children ≥5 years of age, compared with children <1 year of age. Furthermore, the detection of a bacterial or viral pathogen was associated with a higher mortality.

In accordance with previous studies, we were able to identify a causative pathogen in only half of the children presenting with severe encephalitis.[13,14,26] When a causative pathogen could be identified, viruses and more specifically HSV, were the most frequently detected cause of infectious encephalitis in children. These findings correlate with the etiology of childhood encephalitis previously described in western countries.[16,17,27] However, in contrast to previous studies from Scandinavia and Eastern Europe, we did not monitor any cases of tick-borne or VZV encephalitis in our study. This difference may be explained by differences in vaccination coverage as well as geographic and environmental differences.[9,27,28] HSV encephalitis was specifically frequent in children <5 years, while immune-mediated encephalitis was more often seen in older children.[13]

We reported a mortality rate of 20.8%, which is higher than previously reported rates.[4,13,26] However, it is difficult to compare these results, as we included all possible causative pathogens in our study, whereas most previous studies solely focused on a specific pathogen, with mortality rates differing for different causes of encephalitis.[2,4,29,30] The high mortality rate in our study might have resulted from our recruitment solely of children admitted to an intensive care unit, with a large population (23.5 %) burdened with several severe co-morbidities such as malignancy and prematurity.

This is further underlined by the significantly higher mortality in children with malignancy and immune deficiency. A possible association between an immunocompromised status and worse outcome has previously been reported.[10] Further research should be performed examining the impact of comorbidities on the prevalence and outcome of encephalitis, as we were unable to do so because of the small sample sizes of these sub-groups.

We were unable to establish significant associations between clinical symptoms, abnormalities on neuroimaging or EEG and the diagnosis of an infectious or immune-mediated encephalitis. Previous studies have identified EEG abnormalities as a predictor for the presence of encephalitis.[31,32] However, previous studies have linked abnormalities on neuroimaging to a worse clinical outcome, but were not been able to replicate these associations in our study.[33,34] The discrepancy in findings may be explained by a difference in available data and the study design. Only few data on neuroimaging and EEG reports were available in our study and may have been underreported. Furthermore, differences may originate from a differently described outcome measure. We have only compared abnormalities on imaging, using mortality as the primary outcome.

This is the first and largest multi-center study collecting data across all the PICUs in the Netherlands during a 10-year period; however, some limitations need to be addressed. Our study was limited by the small sample size in which the etiology of encephalitis could be determined. Due to the retrospective design of our study, we had to rely on data from patient files as written by physicians at the time of admission; this may have led to a gap in available data. The diagnosis of encephalitis is based on the interpretation of the treating physician; we were dependent on a correct clinical interpretation of signs and symptoms to identify cases of encephalitis. Therefore, incorrect assessment of clinical signs and symptoms may have led to an under- or overestimation of encephalitis cases. An international accepted standard definition of encephalitis should be implemented to provide more uniform data, as well as to minimize the room for individual interpretation and human error when diagnosing encephalitis in children.

Diagnostic techniques for the detection of causative pathogens in childhood encephalitis have improved significantly in the past decades.[11,35] However, continued research and development of diagnostic techniques to further improve rapid pathogen detection

in childhood encephalitis should remain a high priority as was demonstrated by high mortality rate shown in our study.

REFERENCES

1. Tunkel AR, Glaser CA, Bloch KC, et al.; Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;47:303–327.

2. Aygün AD, Kabakuş N, Celik I, et al. Long-term neurological outcome of acute encephalitis. *J Trop Pediatr*. 2001;47:243–247.

3. Bale JF Jr. Virus and immune-mediated encephalitides: epidemiology, diagnosis, treatment, and prevention. *Pediatr Neurol*. 2015;53:3–12.

4. Khandaker G, Jung J, Britton PN, et al. Long-term outcomes of infective encephalitis in children: a systematic review and meta-analysis. *Dev Med Child Neurol*. 2016;58:1108–1115.

5. DuBray K, Anglemyer A, LaBeaud AD, et al. Epidemiology, outcomes and predictors of recovery in childhood encephalitis: a hospital-based study. *Pediatr Infect Dis J*. 2013;32:839–844.

6. Thompson C, Kneen R, Riordan A, et al. Encephalitis in children. *Arch Dis Child*. 2012;97:150–161.

7. Granerod J, Cousens S, Davies NW, et al. New estimates of incidence of encephalitis in England. *Emerg Infect Dis*. 2013;19:1455–1462.

8. Stone MJ, Hawkins CP. A medical overview of encephalitis. *Neuropsychol Rehabil*. 2007;17:429–449.

9. Fafangel M, Cassini A, Colzani E, et al. Estimating the annual burden of tick-borne encephalitis to inform vaccination policy, Slovenia, 2009 to 2013. *Euro Surveill*. 2017;22:30509.

10. Granerod J, Ambrose HE, Davies NW, et al.; UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010;10:835–844.

11. Read SJ, Jeffery KJ, Bangham CR. Aseptic meningitis and encephalitis: the role of PCR in the diagnostic laboratory. *J Clin Microbiol*. 1997;35:691–696.

12. Badoe E, Wilmshurst JM. An overview of the effect and epidemiology of viral central nervous system infections in African children. *Semin Pediatr Neurol*. 2014;21:26–29.

13. Iro MA, Sadarangani M, Goldacre R, et al. 30-year trends in admission rates for encephalitis in children in England and effect of improved diagnostics and measles-mumps-rubella vaccination: a population-based observational study. *Lancet Infect Dis*. 2017;17:422–430.

14. Britton PN, Khoury L, Booy R, et al. Encephalitis in Australian children: contemporary trends in hospitalisation. *Arch Dis Child*. 2016;101:51–56.

15. Koskiniemi M, Vaheri A. Effect of measles, mumps, rubella vaccination on pattern of encephalitis in children. *Lancet*. 1989;1:31–34.

16. Vora NM, Holman RC, Mehal JM, et al. Burden of encephalitis-associated hospitalizations in the United States, 1998-2010. *Neurology*. 2014;82:443–451.

17. Boucher A, Herrmann JL, Morand P, et al. Epidemiology of infectious encephalitis causes in 2016. *Med Mal Infect*. 2017;47:221–235.

18. Ai J, Xie Z, Liu G, et al. Etiology and prognosis of acute viral encephalitis and meningitis in Chinese children: a multicentre prospective study. *BMC Infect Dis*. 2017;17:494.

19. Donoso Mantke O, Vaheri A, Ambrose H, et al. Analysis of the surveillance situation for viral encephalitis and meningitis in Europe. *Euro Surveill*. 2008;13:8017.

20. Sahu RN, Kumar R, Mahapatra AK. Central nervous system infection in the pediatric population. *J Pediatr Neurosci*. 2009;4:20–24.

21. Tenembaum S, Chitnis T, Ness J, et al.; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. *Neurology*. 2007;68(16 suppl 2):S23–S36.

22. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63–74.

23. Pillai SC, Hacohen Y, Tantsis E, et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. *Pediatrics*. 2015;135:e974–e984.

24. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. *J Child Neurol*. 2012;27:1460–1469.

25. Kestenbaum LA, Ebberson J, Zorc JJ, et al. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics*. 2010;125:257–264.

26. Bitnun A, Richardson SE. Childhood encephalitis in Canada in 2015. *Can J Infect Dis Med Microbiol*. 2015;26:69–72.

27. Fowler A, Stödberg T, Eriksson M, et al. Childhood encephalitis in Sweden: etiology, clinical presentation and outcome. *Eur J Paediatr Neurol*. 2008;12:484–490.

28. Koskiniemi M, Korppi M, Mustonen K, et al. Epidemiology of encephalitis in children. A prospective multicentre study. *Eur J Pediatr*. 1997;156:541–545.

29. Elbers JM, Bitnun A, Richardson SE, et al. A 12-year prospective study of childhood herpes simplex encephalitis: is there a broader spectrum of disease? *Pediatrics*. 2007;119:e399–e407.

30. Fowler A, Stödberg T, Eriksson M, et al. Long-term outcomes of acute encephalitis in childhood. *Pediatrics*. 2010;126:e828–e835.

31. Mohammad SS, Soe SM, Pillai SC, et al. Etiological associations and outcome predictors of acute electroencephalography in childhood encephalitis. *Clin Neurophysiol*. 2016;127:3217–3224.

32. Schmolck H, Maritz E, Kletzin I, et al. Neurologic, neuropsychologic, and electroencephalographic findings after European tick-borne encephalitis in children. *J Child Neurol*. 2005;20:500–508.

33. Michaeli O, Kassis I, Shachor-Meyouhas Y, et al. Long-term motor and cognitive outcome of acute encephalitis. *Pediatrics*. 2014;133:e546–e552.

34. Wong AM, Lin JJ, Toh CH, et al. Childhood encephalitis: relationship between diffusion abnormalities and clinical outcome. *Neuroradiology*. 2015;57:55–62.

35. Javali M, Acharya P, Mehta A, et al. Use of multiplex PCR based molecular diagnostics in diagnosis of suspected CNS infections in tertiary care setting—a retrospective study. *Clin Neurol Neurosurg*. 2017;161:110–116.