Incidence of Childhood Meningoencephalitis in Children With a Suspected Meningoencephalitis in the Netherlands

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The etiology of childhood meningoencephalitis has changed significantly over the past decades with the introduction of national immunization programs against previous common causes of childhood meningoencephalitis.[1–5] Pathogens that are not included in these vaccination programs (*Escherichia coli*, group B streptococci, enteroviruses and herpes simplex viruses) are now considered the leading causes of childhood meningoencephalitis.[6–10] Despite the significant decrease in the total incidence of childhood meningoencephalitis following effective national immunization programs, morbidity and mortality rates remain high in childhood meningoencephalitis cases, especially in newborns and in low-income countries.[11–14]

Although rare, autoimmune processes are associated with encephalitis in children, most commonly acute disseminated encephalomyelitis and anti-N-methyl-d-aspartate receptor encephalitis.[15] Despite improvements in diagnostic possibilities, in large proportions of children with a suspected meningoencephalitis, no pathogen is identified. More specifically, the incidence of viral meningoencephalitis may be underestimated as viral pathogens are not routinely tested for.[16,17]

Early recognition of childhood meningoencephalitis remains challenging because of the nonspecific clinical presentation, such as fever, headache, irritability, vomiting and diarrhea.[18–20] Additional diagnostic tools to recognize (the etiology of) meningoencephalitis such as blood inflammation markers, cerebrospinal fluid (CSF) characteristics and neuroimaging abnormalities have been used to aid clinical decision-making. Previous studies on the use of these diagnostic techniques were mostly performed for specific pathogens or in small study populations, making it difficult to evaluate their current value as accurate predictors for diagnosing a specific cause of meningoencephalitis in children.[21–24]

In this study, we aim to determine the incidence of meningoencephalitis in children in the northern part of the Netherlands. We used data collected as part of a multicenter prospective cohort study, evaluating the etiology and diagnostics performed in children with a suspected meningoencephalitis. We aimed to identify clinical, biochemical, and neuroimaging abnormalities possibly associated with the diagnosis of a bacterial, viral or autoimmune-mediated meningoencephalitis. Lastly, possible factors associated with mortality and neurologic sequelae on discharge were evaluated.

METHODS

Data Collection and Study Population

We used data collected as part of the Pediatric and Adult Causes of Encephalitis and Meningitis (PACEM) study. The PACEM study is a prospective multicenter cohort study evaluating children and adults with a suspected meningoencephalitis. The study was conducted in 3 hospitals in the Northern part of the Netherlands: Amsterdam University Medical Centers, location Academic Medical Center (a tertiary care teaching hospital), Onze Lieve Vrouwe Gasthuis (a city-based secondary care hospital) in Amsterdam and the Flevoziekenhuis in Almere (a province-based secondary care hospital).

For this pediatric study, we evaluated all children <18 years old with a clinically suspected meningoencephalitis, who had a CSF analysis performed between January 2012 and July 2015. Reasons for exclusion from the analysis were multiple admissions during the inclusion period, loss of follow-up due to transfer to a nonparticipating hospital. In addition, all children with a preexisting neurologic disease or malignancy were excluded. All data were obtained from the electronic medical records of the included children.

Definitions

The medical records of all included children were reviewed to allow for unification of the clinical and diagnostic evaluations and final diagnoses. All records were reviewed by 2 independent researchers and diagnosed as a proven infectious meningoencephalitis, a proven autoimmune encephalitis, a possible infectious meningoencephalitis, or no meningoencephalitis. This scoring system was based on previously reported clinical symptoms, biochemical characteristics and abnormalities associated with childhood meningoencephalitis (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E611).[6,7,16,18,21,25]

Proven Infectious Meningoencephalitis

A proven infectious meningoencephalitis was defined as the isolation of a pathogen using culture or polymerase chain

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reaction (PCR) from CSF, blood, feces or nasal-throat swab in combination with CSF pleocytosis and/or a clinical suspicion. Children presenting with one or more of the following symptoms, a decreased Glasgow Coma Scale ≤7 or altered consciousness, seizures, neck stiffness and/or generalized or focal neurologic impairments,[18,20,25–27] were considered highly suspect of a meningoencephalitis. Proven cases of infectious meningoencephalitis were categorized as bacterial, viral or neuroborreliosis. We considered a proven case of neuroborreliosis in case of a positive *Borrelia burgdorferi* PCR in CSF in combination with CSF pleocytosis.[28–30]

Proven Autoimmune Encephalitis

Autoimmune encephalitis was defined as proven, if any of the following parameters was present: detection of intrathecal antibodies (anti-myelin oligodendrocyte glycoprotein, anti-N-methyl-d-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, glycine receptor, glutamic acid decarboxylase, Hu, Ma1 and Ma2[31–34]), abnormalities on neuroimaging assessments or high clinical suspicion. We used a scoring system like the one used in case of a proven infectious meningoencephalitis.[35–37]

Possible Infectious or Autoimmune Meningoencephalitis

We considered a possible meningoencephalitis in the event no pathogen could be identified in CSF, blood, feces, urine or nasal-throat swab in combination with a clinical suspicion based on the presence of at least two supportive findings from two different categories (clinical symptoms, and biochemical and neuroimaging results). In addition to the aforementioned criteria, all other plausible diagnoses needed to be excluded. A pleocytosis, a decreased glucose CSF-blood ratio, an increased total protein in CSF were considered supportive biochemical findings. Age-specific cutoff values were used to define biochemical abnormalities, as described in the clinical symptoms and biochemical characteristics section (below).[6,21,35,38–40] Abnormalities on cerebral ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) were considered supportive neuroimaging findings. Abnormalities on neuroimaging investigations were only considered suspect of a meningoencephalitis, when reported as such by the radiologist at the time of admission or during hospital stay.[36,37]

No Meningoencephalitis

This study examined all children with a suspected meningoencephalitis. Children were classified as no meningoencephalitis when none of the previously described criteria were met or in case an alternative diagnosis was made at the time of admission or during the subsequent hospital stay.

Etiology

Causative pathogens were identified using the results of performed diagnostic tests at the time of admission or during subsequent hospital stay.

Bacterial and viral pathogens were isolated at the respective medical microbiology laboratories of each participating hospital using routine bacterial, blood, CSF, feces, urine or nasal-throat swab cultures and/or real-time PCR. Similar testing protocols were performed across participating hospitals. Testing protocols were not revised during the study period.

Clinical Symptoms and Biochemical Characteristics

Information on clinical symptoms at admission was obtained via screening of the respective medical records. The following clinical symptoms were evaluated: fever (defined as temperature >38.5 °C), hypothermia (defined as temperature <36.5 °C), vomiting, diarrhea (a significant change in defecation pattern from normal), coughing, skin rash, apnea (defined as the cessation of breathing for >10 seconds), irritability (children <2 years of age) and signs or symptoms of otitis media. Additionally, the following biochemical characteristics were assessed: C-reactive protein (CRP) and white blood cell count (WBC) were assessed as possible predictors of infection in blood. CSF characteristics were described as follows: WBC (μ/L), protein levels (mg/L) and glucose CSF-blood ratio. Age-specific cutoff values were used to evaluate WBC and protein levels.[41] Decreased glucose CSF-blood ratio was defined as <60%. Traumatic punctures (defined as erythrocyte count >5000 cells/mL in CSF) were excluded in the final analysis of CSF characteristics.

Neuroimaging

Data on abnormalities in neuroimaging were obtained using available information on performed cerebral ultrasound, CT and MRI scan at admission or during subsequent hospital stay. The performed CT and MRI scans were reviewed during hospital stay by the on-call radiologist at the time.

Clinical Outcomes

Mortality and neurologic functioning at the time of hospital discharge were considered primary outcome measures. The following neurologic findings were assessed at discharge: level of consciousness, general motor functioning, sensory functioning and loss of hearing (as tested via Automated Auditory Brainstem Response). Transfer to the intensive care unit, duration of hospital stay (days) and need for supportive therapy such as mechanical ventilation and circulatory support were evaluated as indicators of disease severity.

Selection of Possible Confounders and Effect Modifiers

For statistical analyses, children were divided into 3 age groups: children younger than 1 year, between 1 and 4 years and 5 years of age or older. Comorbidities were evaluated separately as they may impact mortality rates.[39,42] Prematurity was considered a comorbidity and defined as extreme premature (gestational age <28 weeks), very premature (gestational age between 28 and 32 weeks) and moderately premature (gestational age between 32 and 37 weeks).[43]

Statistical Analysis

R studio software (version 3.6.1, https://www.R-project.org; R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. Numerical variables were expressed as mean plus SD if equally distributed or median and interquartile range (IQR) when data were unequally distributed. A χ^2 or Fisher's exact test was used to compare proportions, when appropriate. To detect possible associations between clinical and diagnostic predictors and outcome measures, we performed a univariate binary logistic regression. The predictors tested used in the logistic regression model were preselected based on clinical expertise and correlations previously described.[6,18,22–24] The effect of individual comorbidities on clinical outcomes were assessed separately using a univariate model. Associations were reported as odds ratio (OR) and 95% confidence interval (CI). A P value of <0.005 was considered statistically significant.

RESULTS

Demographic Characteristics

In total, 468 children were screened of whom 432 were included in our analysis. Reasons for exclusion were multiple admissions during the inclusion period (n = 12), transfers to

nonparticipating hospitals (n = 8) and children with a preexisting neurologic disease or malignancy (n = 16). Of the included children, 248 children were males (57.4%). The median age at presentation was 45.5 days (IQR, 11.0–351.2) with 72.2% of children below 1 year old. Comorbidities were reported in 106 children (25.2%). The most frequently reported comorbidity was prematurity (89 of 426 cases, 20.9 %; Table 1).

Etiology

We identified 66 cases of proven meningoencephalitis (15.3%) of which 61 (92.4%) were of infectious origin. We identified 38 cases as possible meningoencephalitis (8.8%). In most cases (328, 75.9%), no meningoencephalitis was diagnosed.

Most infectious meningoencephalitis cases were caused by viral pathogens (37 of 61 cases, 60.7%) followed by bacterial meningoencephalitis (17 of 61 cases, 27.9%). In addition, 2 cases of *B. Burgdorferi*–associated meningoencephalitis (3.3%) were identified (Table 2). In 5 of 61 cases (8.2%) cases presenting with clinical symptoms in addition to biochemical findings associated with a proven meningoencephalitis, no pathogen was identified. Furthermore, we identified 5 cases of autoimmune encephalitis (7.6%). Enteroviruses were the most frequently identified viral pathogens (25 of 37 cases, 67.6%). The most prevalent bacterial pathogens were *Streptococcus agalactiae* and *Neisseria meningitides* (both 4 of 17 bacterial cases, 23.5%). Acute disseminated encephalomyelitis was the most frequent cause of autoimmune encephalitis (2 of 5 cases, 40.0%).

Biochemical Characteristics

CRP was elevated in 37 of 63 (58.7%) children with a proven meningoencephalitis with a median of 13.0 mg/L (IQR, 4.0–50.0). An elevated CRP was seen in 19 of 36 (52.8%) children with a possible meningoencephalitis, with a median of 11.5 mg/L (IQR, 1.00–62.25). Systemic WBC was increased in 55 of 64 (85.9%) children with a proven meningoencephalitis, with a median of 9.35 μ/L (IQR, 6.88–15.45). In 4 of 36 (11.1%) children with a possible meningoencephalitis, the systemic WBC was increased, with a median of 10.90 μ/L (IQR, 8.28–14.13).

CSF WBC count was elevated in 32 of 55 proven meningoencephalitis (58.2%) and in 22 of 32 possible meningoencephalitis (68.8%), with a median of 11.0 cells/L (IQR, 3.5–189.0) and a median of 13.0 cells/L (IQR, 6.00–81.25) for cases of proven and possible meningoencephalitis, respectively. In 16.2%, total protein was increased, with a median of 0.39 g/L (IQR, 0.21–0.68). The CSF/blood glucose ratio was decreased in 88 of 211 cases (41.7%).

Neuroimaging Findings

A cranial ultrasound was performed in 60 cases (13.9%), of which 7 of 60 (11.7%) in children with a proven meningoencephalitis, in 8 of 60 (13.3%) children with a possible meningoencephalitis and in 45 of 60 (75%) in children with no meningoencephalitis. Abnormalities were seen in 14.3% (1 of 7) children with a proven meningoencephalitis and in 2 of 8 (25.0 %) possible meningoencephalitis cases. Abnormalities on ultrasound were seen in 10 of 45 (22.2%) children with no meningoencephalitis. A CT or MRI scan was performed on admission in 73 cases (16.9%), of which 7 of 15 (46.7%) in children with a proven meningoencephalitis. Additionally, 1of 6 (16.7%) children with a possible meningoencephalitis and 13 of 52 (25.0%) children with no meningoencephalitis showed abnormalities. An additional CT or MRI scan was performed in 70 cases (16.2%) of which 31 showed abnormalities (44.3%). In children with a proven meningoencephalitis, abnormalities were seen in 8 of 15 (53.3%); 2 of 6 (33.3%) of additionally performed CT or MRI scans in children with a possible meningoencephalitis showed abnormalities. Lastly, a second CT or MRI scan performed in children with no meningoencephalitis showed abnormalities in 21 of 49 (42.9%; Table 3).

Mortality, Neurologic Deficits at Discharge and Hospital Severity Score

Data on mortality were available in 406 cases, of which 10 patients died (2.5%). Of the 65 patients with a proven meningoencephalitis, 3 patients died (4.6%). Of the 32 patients with a possible meningoencephalitis, 1 patient died (3.1%). Of the 309 patients without a meningoencephalitis, 6 patients died (1.9%). There were no significant differences in the mortality rates between these groups.

Information on neurologic outcomes was available in all patients; in 14 of 432 cases, neurologic deficits were reported (3.2%). The most frequently described neurologic deficit at hospital discharge was hearing impairment (2 of 14 cases, 14.3%). There were no significant differences in neurologic deficits between patients with a proven, possible or no meningoencephalitis.

The hospital severity score was assessed by intensive care unit admission, the need for mechanical ventilation and the need for circulatory support. The need for intensive care unit admission was significantly increased in patients with a proven meningoencephalitis [OR, 2.39 (CI, 1.11–4.90)]. No correlation between proven meningoencephalitis and an increased need for mechanical ventilation or circulatory support could be shown.

We were unable to demonstrate a significant effect of prematurity on mortality or on the occurrence of new neurologic deficits.

Associations Between Demographics, Clinical Characteristics, Biochemical Markers, Neuroimaging, Clinical Outcomes and Etiology of Proven Meningoencephalitis

An increased CRP [OR, 5.24 (CI, 1.43–28.90)], an increased WBC in CSF [OR, 19.69 (CI, 4.16–186.51)] and an increased total protein [OR, 14.75 (CI, 3.99–60.99)] were associated with the presence of a bacterial pathogen in CSF. The detection of a viral pathogen was significantly associated with fever at admission [OR, 11.14 (CI, 2.78–97.15)], an increased intrathecal WBC [OR, 2.67 (CI, 1.13–6.17)] and a decreased glucose CSF/blood ratio [OR, 3.04 (CI, 1.09–8.97)]. An autoimmune encephalitis was associated with older age (>5 years) [OR, 25.07 (CI, 2.42–1242.31)], focal neurologic symptoms at presentation [OR, 12.55 (CI, 1.00–116.03)] and abnormalities on neuroimaging [OR, 18.20 (CI, 2.01–224.76)]. Lastly, autoimmune encephalitis was associated with neurologic deficits at discharge [OR, 14.49 (CI, 1.22–111.61); Table 4].

DISCUSSION

In this multicenter study, we evaluated the incidence and etiology of childhood meningoencephalitis in the Netherlands. In most of the suspected cases, no meningoencephalitis was diagnosed. Viral pathogens were the most frequently identified cause of proven infectious meningoencephalitis. Autoimmune encephalitis was associated with older age, focal neurologic symptoms, neuroimaging abnormalities and neurologic deficits at hospital discharge.

Most children who presented with a suspected central nervous system infection were ultimately not diagnosed with meningoencephalitis. This is in line with previous long-term studies focusing on hospital admission rates of proven meningoencephalitis cases in which authors have demonstrated a low average rate of meningoencephalitis cases in Western countries, which correlates to a decline in the prevalence of specific pathogens such as *Haemophilus influenzae* and measles caused by nationwide vaccination programs.[3] In contrast, previous studies have shown an increase in

TABLE 1. Demographics + Clinical Symptoms of Children With a Suspected Meningoencephalitis on Admission

Demographic Characteristics, n (%)			Proven ME	Possible ME	No ME
Total		n = 432 (100.0)			
Male gender		248 (57.4)	35 (53.0)	23 (61.0)	190 (57.9)
Age (days), median (IQR)		45.5 (11.0–351.2)	82.0 (17.0–876.5)	55.0 (12.0–350.0)	43.0 (9.0–312.0)
Comorbidities		106 (25.2)	6 (9.4)	10 (26.3)	90 (28.3)
	Prematurity	89/426 (20.9)	6/89	9/89	74/89
	Gestational age <28 weeks	9/89 (10.1)	1/6 (16.7)	1/9 (11.1)	7/74 (9.5)
	Gestational age between 28 and 32 weeks	33/89 (37.1)	4/6 (66.7)	4/9 (44.4)	25/74 (33.8)
	Gestational age between 32 and 37 weeks	47/89 (52.8)	1/6 (16.7)	4/9 (44.4)	42/74 (56.8)
Clinical symptoms					
	Fever	253/400 (63.3)	49/63 (77.8)	21/31 (67.7)	183/306 (59.8)
	Nausea	96/364 (26.4)	18/53 (34.0)	9/27 (33.3)	69/284 (24.3)
	Skin rash	58/312 (22.8)	15/53 (28.3)	8/27 (29.6)	35/232 (15.1)
	Petechia	11/58 (19.0)	4/53 (7.5)	2/27 (7.4)	5/232 (2.2)
	Diarrhea	49/379 (12.9)	9/56 (16.1)	5/30 (16.7)	35/293 (11.9)
Neurological symptoms					
	Irritability (age <2 years)	158/314 (50.3)	27/46 (58.7)	18/28 (64.3)	113/240 (47.1)
	Decreased consciousness (GCS ≤7)	19/94 (20.2)	5/20 (25.0)	2/14 (14.3)	12/60 (20.0)
	Meningeal irritation/neck stiffness	44/220 (20.0)	9/39 (23.1)	5/19 (26.3)	30/162 (18.5)
	Aphasia	4/59 (6.8)	2/4 (50.0)	0/4 (0.0)	2/4 (50.0)
	Ataxia	6/55 (10.9)	2/6 (33.3)	1/6 (16.7)	3/6 (50.0)
Seizures		48/407 (11.8)	8/59 (13.6)	4/33 (12.1)	36/315 (11.4)
	Focal	5/48 (10.4)	1/5 (20.0)	2/5 (40.0)	2/5 (40.0)
	Generalized	15/48 (31.3)	2/15 (13.3)	0/15 (0.0)	13/15 (86.7)
	Status epilepticus	8/48 (16.7)	1/8 (12.5)	0/8 (0.0)	7/8 (87.5)
Cranial nerve palsy		10/128 (7.8)	2/24 (8.3)	1/15 (6.7)	7/89 (7.9)
	N. III	3/10 (30.0)	1/3 (33.3)	0/3 (0.0)	2/3 (66.7)
	N. VI	2/10 (20.0)	0/2 (0.0)	0/2 (0.0)	2/2 (100.0)
	N. VII	5/10 (50.0)	1/5 (20.0)	1/5 (20.0)	3/5 (60.0)

Data are obtained by a review of medical records and presented as n (%) or median (IQR). Decreased consciousness is defined as a GCS of ≤7.
GCS indicates Glasgow Coma Scale; ME, meningoencephalitis.

TABLE 2. Etiology and Age Distribution of Children With a Proven and Possible Meningoencephalitis, n (%)

Total Proven Meningoencephalitis (%)		66/432 (15.3)
Infectious meningoencephalitis		61/66 (92.4)
Bacterial meningoencephalitis		17/61 (27.9)
	Streptococcus agalactiae	4/17 (23.5)
	Streptococcus pneumonia	2/17 (11.7)
	Neisseria meningitidis	4/17 (23.5)
	Other*	7/17 (41.2)
Viral meningoencephalitis		37/61 (60.7)
	Enterovirus	25/37 (67.6)
	Adenovirus	4/37 (10.8)
	Human parechovirus	3/37 (8.1)
	VZV	2/37 (5.4)
	HHV6	2/37 (5.4)
	HSV (type 1)	1/37 (2.7)
B. burgdorferi associated meningoencephalitis		2/61 (3.3)
No pathogen detected in CSF		5/61 (8.2)
Autoimmune encephalitis		5/66 (7.6)
	ADEM	2/5 (40.0)
	Anti-NMDA	1/5 (20.0)
Possible meningoencephalitis		38 (8.8)
Median age at diagnosis of		
Bacterial meningoencephalitis (median days, IQR)		99.0 (10.0–300.0)
Viral meningoencephalitis (median days, IQR)		29.0 (16.0–204.0)
Autoimmune meningoencephalitis (median years, IQR)		10.0 (9.0–14.0)
Possible meningoencephalitis (median days, IQR)		55.0 (12.0–350.0)

Data are presented as n (%) and IQR.
*Other is a grouped category of several bacterial pathogens that could only be identified once. The distinction between proven, possible and no meningoencephalitis was made based on the definitions described in the Methods section.
ADEM indicates acute disseminated encephalomyelitis; anti-NMDA, anti-N-methyl-d-aspartate receptor encephalitis; HHV6, human herpesvirus 6; HSV-1, herpes simplex virus type 1; VZV, varicella zoster virus.

Table 3. Neuroimaging of Children With a Suspected Meningoencephalitis on Admission

Total, n (%) Imaging at Presentation		432 (100.0)	Proven ME	Possible ME	No ME
Cranial ultrasonography	Performed	60/432 (13.9)	7/60 (11.7)	8/60 (13.3)	45/60 (75.0)
	Abnormal	13/60 (21.6)	1/7 (14.3)	2/8 (25.0)	10/45 (22.2)
	Subdural hematoma	7/13 (53.8)	0/7 (0.0)	0/8 (0.0)	7/10 (70.0)
	Subdural empyema	1/13 (7.7)	1/7 (14.3)	0/8 (0.0)	0/10 (0.0)
	Flaring (unspecified)	4/13 (30.8)	0/7 (0.0)	2/8 (25.0)	2/10 (20.0)
	Dilated ventricular system	1/13 (7.7)	0/7 (0.0)	0/8 (0.0)	1/10 (10.0)
CT/MRI	Performed	73/432 (16.9)	15/78 (21.8)	6/78 (7.7)	52/78 (66.7)
	Abnormal	35/73 (47.9)	7/15 (46.7)	1/6 (16.7)	13/52 (25.0)
	Abscess	1/35 (2.9)	1/7 (14.3)	0/6 (0.0)	0/13 (0.0)
	Edema	1/35 (2.9)	1/7 (14.3)	0/6 (0.0)	0/13 (0.0)
	Hydrocephalus	4/35 (11.4)	0/7 (0.0)	1/6 (16.7)	3/13 (23.1)
	Hypodensity	5/35 (14.3)	2/7 (28.6)	0/6 (0.0)	3/13 (23.1)
	Subdural empyema	2/35 (5.7)	2/7 (28.6)	0/6 (0.0)	0/13 (0.0)
	Mastoid/sinus opacification	8/35 (22.9)	1/7 (14.3)	0/6 (0.0)	7/13 (53.8)
Second CT/MRI during hospitalization					
CT/MRI	Performed	70/432 (16.2)	15/70 (21.4)	6/70 (8.6)	49/70 (70.0)
	Abnormal	31/70 (44.3)	8/15 (53.3)	2/6 (33.3)	21/49 (42.9)
	Abscess	1/31 (3.2)	1/8 (12.5)	0/6 (0.0)	0/21 (0.0)
	Edema	1/31 (3.2)	1/8 (12.5)	0/6 (0.0)	0/21 (0.0)
	Hydrocephalus	3/31 (9.7)	0/8 (0.0)	0/6 (0.0)	3/21 (14.3)
	Hypodensity	2/31 (6.5)	0/8 (0.0)	0/6 (0.0)	2/21 (9.5)
	Subdural effusion	2/31 (6.5)	1/8 (12.5)	0/6 (0.0)	1/21 (4.8)
	Subdural empyema	2/31 (6.5)	2/8 (25.0)	0/6 (0.0)	0/21 (0.0)
	Mastoid/sinus opacification	4/31 (12.9)	1/8 (12.5)	0/6 (0.0)	3/21 (14.3)

This table shows the different abnormalities identified using ultrasonography or CT/MRI and categorized based on data obtained from medical records. It is possible that multiple abnormalities were reported on the same ultrasound or CT/MRI. Data are presented as n (%).

ME indicates meningoencephalitis.

Table 4. Associations Between Demographics, Clinical Characteristics, Biochemical Characteristics, Neuroimaging, Clinical Outcomes and Different Etiologic Groups

	Bacterial Meningoencephalitis	Viral Meningoencephalitis	Autoimmune Encephalitis
Demographic characteristics			
Age <1 year	1	1	1
Age between 1 and 5 years	1.30 (0.35–8.42)	1.15 (0.46–3.51)	2.11 (0.04–26.90)
Age >5 years	1.43 (0.38–9.24)	2.21 (0.75–9.42)	25.07 (2.42–1242.31)*
Clinical characteristics			
Fever	0.96 (0.31–3.33)	11.14 (2.78–97.15)*	0.38 (0.03–3.39)
Headache	1.69 (0.17–8.63)	1.07 (0.19–3.86)	5.16 (0.42–46.60)
Irritability (age <2 years)	1.76 (0.44–8.36)	2.11 (0.90–5.24)	0.00 (0.00–1.50)
Meningeal irritation	0.56 (0.01–4.57)	1.47 (0.45–4.26)	0.00 (0.00–6.18)
Seizures	1.25 (0.13–5.90)	1.27 (0.37–3.56)	0.00 (0.00–11.51)
Focal neurological symptoms	0.00 (0.00–5.50)	1.12 (0.12–5.00)	12.55 (1.00–116.03)*
Decreased consciousness	2.01 (0.03–40.63)	1.22 (0.19–5.51)	0.00 (0.00–20.52)
Biochemical characteristics			
Increased CRP	5.24 (1.43–28.90)*	1.07 (0.51–2.25)	0.35 (0.01–4.44)
Increased WBC (blood)	3.77 (0.99–12.28)	1.05 (0.26–3.18)	0.00 (0.00–6.82)
Increased WBC (CSF)	19.69 (4.16–186.51)*	2.67 (1.13–6.17)*	4.81 (0.54–58.44)
Increased total protein (CSF)	14.75 (3.99–60.99)*	0.52 (0.06–2.21)	1.88 (0.04–19.66)
Decreased CSF/blood glucose ratio	3.97 (0.92–23.95)	3.04 (1.09–8.97)*	0.70 (0.01–13.58)
Neuroimaging			
Abnormalities on cranial US	0.00 (0.00–7.35)	0.00 (0.00–3.16)	0.00 (0.00–27.51)
Abnormalities on CT/MRI	0.70 (0.02–4.77)	1.41 (0.34–4.37)	18.20 (2.01–224.76)*
Outcomes			
Death	0.00 (0.00–10.21)	2.64 (0.26–13.97)	0.00 (0.00–37.85)
Neurological deficits on discharge	4.43 (0.44–22.82)	0.00 (0.00–3.16)	14.49 (1.22–111.61)*
ICU admission	1.63 (0.29–6.14)	1.18 (0.34–3.26)	5.11 (0.42–45.75)
Circulatory support	7.08 (2.11–22.83)*	1.06 (0.26–3.25)	0.00 (0.00–6.90)
Mechanical ventilation	2.95 (0.65–10.56)	1.02 (0.25–3.13)	5.29 (0.43–47.54)

This table shows the univariate OR of a binary logistic regression analysis, evaluating the associations between clinical characteristics, biochemical characteristics, abnormalities on neuroimaging, clinical outcomes and different etiologic groups. Data are reported as OR (95% CI).

*Significant association.

US indicates ultrasound.

the incidence of all-cause encephalitis, which could not be demonstrated in this study.[4] This might be explained by differences in the selection of study participants as we included all children with a suspected central nervous system infection, while other studies focused on inclusion of proven meningoencephalitis patients.[18–20,44]

We identified viruses as the most prevalent causative pathogens in cases of infectious meningoencephalitis. This might be explained by the young age of children included in our study (72.2% <1 year of age). The high prevalence of viral pathogens in young children has been demonstrated in previous literature.[6,9,10,19] The high proportion of viral pathogen cases might additionally be explained by differences in the definitions of meningoencephalitis. We used culture and PCR results on several different materials (CSF, blood, feces and nasal-throat swabs) instead of solely focusing on pathogens identified in CSF. Enteroviruses were the most frequently identified viral pathogen, in accordance with previous studies.[19,45,46]

In addition to a high prevalence of viral pathogens, we identified a relatively large proportion of children with a bacterial meningoencephalitis compared with previous studies (27.9%).[47,48] This might be explained by the large proportion of neonates included, in contrast to previous reports. This might have contributed to the relatively large proportion of *Streptococcus agalactiae* cases.[8,49]

Abnormalities on neuroimaging (CT/MRI) were reported in a small proportion of proven meningoencephalitis cases in our study (21.8%). This might be explained by the large proportion of viral meningoencephalitis cases in addition to the fact that in most cases only a CT scan was performed.[50] Additionally, we were only able to identify 3 cases of parechovirus infections, which have previously been associated with possible abnormalities on neuroimaging.[51,52] Lastly, a low percentage of testing (16.9% of cases) might have contributed to underreporting of abnormalities.[53]

In comparison with previous studies, we were unable to show a correlation between mortality and a proven meningoencephalitis. High mortality rates have previously been found for both bacterial and autoimmune meningoencephalitis cases.[54–56] This difference could be explained by the large proportion of viral meningoencephalitis cases in our study. However, we were able to show a correlation between neurologic deficits at discharge in children with a proven autoimmune encephalitis, which is in line with previous studies demonstrating high rates of neurologic sequelae in children with autoimmune encephalitis.[22,27,57]

In this multicenter study, we have provided an up-to-date report on the epidemiology of childhood meningoencephalitis in the Netherlands. By combining data on causative pathogens, biochemical characteristics, abnormalities on neuroimaging and available data on clinical outcomes at discharge in children with a suspected meningoencephalitis, we were able to provide an accurate picture of childhood meningoencephalitis in the vaccination era. However, a few limitations need to be addressed. We were fully dependent on data recorded in medical records at the time of admission. This may have led to gaps in available data and differences in clinical interpretation between treating physicians. We have tried to mitigate these differences in the interpretation of the diagnosis of meningoencephalitis, by asking 2 independent clinicians to separately review the final diagnoses for this study. Furthermore, due to the small sample of identified cases of meningoencephalitis, we were unable to build a significant multivariate model for the evaluation of the effects of clinical, biochemical and neuroimaging markers on etiology, mortality and neurologic outcomes.

Lastly, because of our retrospective study design, we were unable to include data on long-term neurologic outcomes in children with a viral meningoencephalitis. A topic that has been sparsely covered in available literature which warrants additional research.

In conclusion, meningoencephalitis was diagnosed in a small proportion of children with a suspected central nervous system infection. Most cases of proven infectious meningoencephalitis were caused by viral pathogens (enteroviruses). Autoimmune encephalitis was associated with neurologic deficits at discharge.

This study extends on previous literature and provides additional details regarding the prevalence, diagnosis and outcomes of childhood meningoencephalitis in the Netherlands, while underling important areas in need of additional research. These specifically include focus on improvement of diagnostic techniques and the formulation of a globally accepted definition of meningoencephalitis.

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