Original article

Childhood encephalitis in Sweden: Etiology, clinical presentation and outcome

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ABSTRACT

Acute encephalitis is a relatively uncommon but potentially harmful CNS inflammation usually caused by infection. The diagnosis is difficult to establish and the etiology often remains unclear. Furthermore, the long-term prognosis of acute encephalitis in children is poorly described. In this study, we characterize childhood encephalitis from a Swedish perspective in regard to etiology, clinical presentation and sequelae.

We retrospectively studied all children (n = 93) who were admitted for acute encephalitis at Karolinska University Hospital in Stockholm during 2000–2004. A confirmed etiological agent was identified in eight cases and a probable one in 37; in 48 cases no etiological agent could be found. Tick-borne encephalitis virus, enterovirus, respiratory syncytial virus, varicella zoster virus and influenza virus predominated and represented 67% of all the confirmed or probable etiologies. Encephalopathy was present in 80% of the children, 81% had fever, 44% had focal neurological findings, and seizures occurred in 40%. EEG abnormalities were seen in 90% and abnormal neuroimaging was present in 30%. The cerebrospinal fluid showed pleocytosis in 55%. There was no mortality, but 60% of the children had persisting symptoms at the time of discharge, 41% of which were moderate to severe.

We conclude that the etiology of encephalitis among Swedish children is at large the same as in other European countries with similar vaccination programs. Fever and encephalopathy were seen in a majority of children and the most sensitive tool for making the diagnosis was EEG examination. Furthermore, many children display persisting sequelae at discharge for which the strongest predictive factor was focal neurological findings at presentation.

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1. Introduction

Encephalitis is an inflammation affecting the parenchyma of the brain. The highest frequency and the more severe cases of acute encephalitis are often seen in younger children. 1–5 Most cases are thought to be caused by viruses, but bacteria, fungi, parasites and post-infectious and/or autoimmune forms are also seen. 6–8 The frequency and distribution of viruses and other agents causing encephalitis vary according to the geographical region with large differences between Europe, Asia and the USA. This etiological diversity is in part due to variation in climate, presence of epidemics,
arthropod-borne infections and variations in immunization programs.1,5–10

Clinically, acute encephalitis varies from being a self-limiting disorder with no sequelae to being a severe illness with life-long morbidity or even mortality.2,4,11,12 The classical presentation of encephalitis consists of fever, headache and an altered mental state together with seizures and focal neurological findings in some cases.1,6,7,10,11 The diagnosis is based on the medical history and clinical picture together with results of specific investigations such as EEG, neuroimaging and examination of the cerebrospinal fluid (CSF). However, a definitive etiological diagnosis relies on detecting the agent in the brain (biopsy or autopsy) and/or CSF. Such an agent is often difficult to establish and antibody detection in the CSF, or a significant rise of antibodies in serum, is therefore often considered to be diagnostic. This may cause some difficulties in determining whether the pathogen is only a coincidental finding or if there is a causal relationship with the encephalitis. In as many as 65% of all patients with encephalitis the definite cause of the illness cannot be determined.1,5,6,8,9,11

Only a few studies have performed long-term follow-up of children with encephalitis but discharge data indicate that many children still have symptoms at the time of discharge from hospital.1,2,6,11–14 Furthermore, these symptoms, e.g. headache, tiredness and cognitive problems, may persist for several months.10,12,13,15 Some long-term follow-up studies also indicate that many children suffer from severe sequelae such as epilepsy, paroxysmal motor function disorder and moderate to severe learning difficulties.2,4,14 Several factors have been suggested as indicative of a negative prognosis, such as young age,2 deteriorating EEG pattern,4 degree of blood-brain barrier damage,5 presence of focal neurological signs,13 abnormal neuroimaging11 and low score on the Glasgow coma scale.4,12

Establishing a correct diagnosis is of great importance in order to optimize the treatment for the individual but also from an epidemiological perspective where preventive measures such as immunization programs and vector control play a part in preventing the disease. The etiology of encephalitis among Swedish children has not been described in detail, and the aim of this study is to characterize childhood encephalitis from a Swedish perspective with regard to etiology, clinical presentation and presence of sequelae.

2. Patients and methods

2.1. Population

All children admitted during 2000–2004 to Astrid Lindgrens Children’s hospital in Stockholm, serving a population of 220,000 children (0–18 years), were screened retrospectively for diagnoses compatible with encephalitis. Initially, 148 patients were singled out as possible encephalitis out of which 93 fulfilled the inclusion criteria which were

A. Age 1 month–18 years
B. Signs of cerebral dysfunction either as
   1. encephalopathy defined as altered consciousness, personality or behavioral changes lasting for more than 24 hr, or
   2. abnormal EEG finding compatible with encephalitis, plus at least one of the following:
      - Abnormal results of neuroimaging compatible with encephalitis.
      - Positive focal neurological findings.
      - Seizures.
C. Signs of inflammation, defined either as pleocytosis (≥6 white blood cells/μL), fever (>38 °C) or elevated infectious parameters (CRP, WBC). Mild symptoms from eyes, nose or throat were not considered to be sufficient.

Children with another verified cause of symptoms such as bacterial meningitis or other underlying neurological or metabolic disease that per se could explain the symptoms were excluded. Pure ataxia was not considered sufficient neurology for inclusion.

2.2. Laboratory examinations

Most children underwent routine laboratory tests of serum at the time of admission including serology, CRP and WBC. When there is a clinical suspicion of encephalitis a standard procedure for etiological sampling is used in our hospital. During the studied period, the CSF samples were investigated by PCR for herpes simplex virus type 1 and 2 (HSV-1, HSV-2), varicella zoster virus (VZV) and enteroviruses in all children who underwent lumbar puncture due to a suspicion of an infection in the CNS. Due to the clinical picture and test results, the CSF of some children was further investigated by PCR for human herpes virus 6 (HHV-6) and in one case also for Mycoplasma pneumoniae. Most of the CSF samples were also subjected to viral isolation. The timing of the lumbar puncture varied, but in most children it was performed at the time of admission, and in all patients during the first week. In children with present or recent respiratory tract infection, nasopharyngeal samples were investigated for respiratory viruses by immunofluorescence (IF) for respiratory syncytial virus (RSV) and influenza virus, followed by viral isolation. In children with gastrointestinal tract symptoms, or recent history of such an infection, fecal samples were investigated by Enzyme ImmunoAssay (EIA) for rotavirus and adenoviruses and by PCR for norovirus, followed by viral isolation. Paired sera were taken for antibody determination (however, when a possible etiological agent was found a second sample was not always taken). The presence of IgM antibodies in serum samples was used to determine recent infection with Tick-borne encephalitis virus (TBEV), for all other etiological diagnosis rise of IgG antibodies were requested.

When a viral agent was detected in the CSF, this was defined as confirmed etiology. In a large number of cases no etiological agent was found in the CSF, but findings were made in throat swabs, blood culture, feces or in nasopharynx. These cases were labelled as probable etiology. Results of examination of the CSF such as elevated lactate levels (>2.5 mmol/L), elevated protein levels (>0.5 g/L) and presence of pleocytosis were recorded.
2.3. Clinical findings

Demographic characteristics (sex and age) were analyzed as well as seasonal distribution.

Clinical signs and symptoms at the time of admission such as fever (>38 °C), presence of encephalopathy, seizures, focal neurological symptoms and the presence of other infectious symptoms or prodromal illness were also analyzed. The duration of hospitalization and persisting symptoms at the time of discharge were recorded. Symptoms at the time of discharge were classified into (a) no symptoms, (b) mild symptoms such as headache, fatigue or mild concentration problems and (c) moderate to severe symptoms such as persisting motor dysfunction (e.g. pareses, severe ataxia and balance disturbance), moderate to severe cognitive impairment or epilepsy.

2.4. Neuroimaging

In children who underwent neuroimaging these results were recorded. A computer tomography (CT) was performed in 44 patients, whereas magnetic resonance imaging (MRI) was performed in 10, in three children both CT and MRI were performed.

2.5. EEG

Most of the children underwent an EEG examination at some point during their illness. A majority of the EEG examinations were performed at the time of, or shortly after, the admission to hospital, but some were performed at a later stage. All EEG recordings that were found to be compatible with encephalitis were considered to be positive with no regard to when it was performed.

In a small number of cases (9) the result of the EEG examination was unclear and these results were therefore re-evaluated. Episodic or continuous, focal or generalized, slow activity (delta and/or theta) with or without epileptiform discharges were considered as EEG abnormalities compatible with encephalitis.

2.6. Ethical approval

This study was approved by the local ethics committee (Dnr 01-320).

3. Results

Between January 2000 and December 2004, 93 children (60 male and 33 female) met our criteria and were included. The mean age at the time of presentation was 7.5 years (range 5 weeks–17.7 years, Diagram 1).

3.1. Etiology

A confirmed etiological agent was identified in eight cases (9%) and a probable in 37 (40%). In 48 (52%) of the 93 included children, no etiological agent could be found (Table 1). TBEV, enterovirus, RSV, VZV and influenza virus (A and B) predominated and represented 67% of all the confirmed or probable etiologies (18%, 13%, 13%, 11% and 11%, respectively). In the groups infected with enterovirus and rotavirus all children were male. Children infected with rotavirus, RSV, enterovirus and VZV tended to be younger than average (1.5; 1.0; 4.9 and 5.0 years old, respectively, Table 2).

3.2. Clinical presentation

At the time of admission, 80% of the children were encephalopathic, 81% presented with fever and 44% with focal neurological findings. The focal neurological findings included motor dysfunction (such as hemiparesis) in 22 cases, ataxia in 15, dysphasia in 10, nystagmus in six, and three children had cranial nerve dysfunction (two facial nerve paralysis, one abducens nerve paralysis). Focal neurological symptoms were present in all children with HSV-1, Epstein-Barr virus (EBV) and Mycoplasma pneumoniae, and were also found at a high rate in children with VZV and enterovirus infections. None of the children with RSV presented with focal neurological symptoms and only 1/8 with TBEV (presenting symptoms are listed in Table 2).

Seizures occurred in 40%, 3/5 of children with influenza and 2/3 with rotavirus had seizures at the time of admission as
well as half of the children with EBV and HSV-1. None of the children with TBEV had seizures, and it was also rare in children with enterovirus and VZV.

As expected, all cases of Tick-borne encephalitis (TBE) occurred in the summer months (May–August) as did most of the enterovirus infections (June–September, one case in November). All RSV infections occurred in the winter (December–February) as did the influenza infections (November, December and February) (Diagram 2). The mean length of hospitalization was 9 days (range 1–65 days, median 7 days).

### 3.3 EEG, CSF and neuroimaging findings

EEG abnormalities compatible with encephalitis occurred in 90% (77/86) of the children. Abnormal neuroimaging findings compatible with encephalitis (such as diffuse or focal edema or ischemia) were present in 30% (16/54) of examined cases. CSF analysis showed pleocytosis in 55% (46/84) of the patients. All children infected with TBEV, enterovirus, VZV, rotavirus, HSV-1, EBV and Mycoplasma pneumoniae had pleocytosis (Table 1). Only three children had a rise in lactate and in none of them could the etiology be established. Raised CSF protein levels were seen in 28% (22/79) of the cases (normal <0.5 g/L) with a median level of 0.65 (range 0.52–2.36). For 18 of those the rise was only minor (0.52–0.96).

### 3.4 Symptoms at discharge

Three children were referred to another hospital before discharge, in all cases due to geographical reasons. In the remaining group of 90 there were no mortalities, but at discharge 54 (60%) children still had symptoms. Some of these were mild such as feeling of fatigue in 32 cases, and more severe in 22 where a combination of symptoms such as moderate cognitive impairment including concentration problems and loss of memory function (n = 12), impaired motor function e.g. hemiparesis (n = 11), ataxia (n = 10), dysphasia (n = 5) and epilepsy (n = 6) persisted at the time of discharge from hospital. All children with encephalitis caused by RSV had made a full recovery at the time of discharge, whereas most of the children with TBEV (6/8), enterovirus (4/6), VZV (3/5), rotavirus (2/3), HSV-1 (2/2) and EBV (2/2) infections still had symptoms when discharged from hospital. The persisting symptoms in these groups were mainly fatigue in the group with TBE, ataxia, fatigue and personality changes in the enterovirus group, ataxia in the children with VZV, irritability in the rotavirus group and memory dysfunction in the children with HSV-1. Of the children with EBV, one suffered from anxiety and one of ataxia together with cognitive problems and epilepsy at the time of discharge from hospital (Table 2). Of the children who had focal neurological symptoms at presentation, 84% (32/38) still had some persisting symptoms at the time of discharge from hospital, compared to 42% (22/52) of those without focal neurological symptoms.

Seizures at presentation were not predictive for persisting symptoms at discharge (58% in either group). Of the children with encephalopathy at presentation, 63% had persisting symptoms at the time of discharge, compared to 50% of the children who were found not to be encephalopathic. There was no clear correlation between age and persisting symptoms, but a tendency that children who made a full recovery

### Table 1 – Frequency of etiological findings, pleocytosis, abnormal neuroimaging and EEG abnormalities in children with acute encephalitis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number (%)</th>
<th>Pleocytosis (%)</th>
<th>EEG (%)</th>
<th>CT/MRI (%)</th>
<th>Microbiological method (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All included</td>
<td>93</td>
<td>46/84 (55)</td>
<td>77/86</td>
<td>16/54 (30)</td>
<td></td>
</tr>
<tr>
<td>Etiology not found</td>
<td>48 (52)</td>
<td>19/44 (43)</td>
<td>41/45</td>
<td>9/28 (32)</td>
<td></td>
</tr>
<tr>
<td>Confirmed/probable etiology</td>
<td>45 (48)</td>
<td>27/40 (68)</td>
<td>36/41</td>
<td>7/26 (27)</td>
<td></td>
</tr>
<tr>
<td>TBEV</td>
<td>8 (9)</td>
<td>8/8</td>
<td>6/6</td>
<td>0/2</td>
<td>IgM+IgG ab in serum(4), IgM ab in serum(4)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>6 (7)</td>
<td>6/6</td>
<td>4/5</td>
<td>0/2</td>
<td>Pos in CSF with PCR(4), IgM+IgG ab in serum(2)</td>
</tr>
<tr>
<td>RSV</td>
<td>6 (7)</td>
<td>0/4</td>
<td>5/6</td>
<td>1/3</td>
<td>Respiratory tract sample pos with IF(6)</td>
</tr>
<tr>
<td>VZV</td>
<td>5 (5)</td>
<td>4/4</td>
<td>4/5</td>
<td>0/2</td>
<td>IgM+IgG ab in serum(1), clinical diagnosis only(4)</td>
</tr>
<tr>
<td>Influenza A/B</td>
<td>5 (5)</td>
<td>1/4</td>
<td>4/4</td>
<td>1/3</td>
<td>Respiratory tract sample pos with IF(5), also IgM+IgG ab in serum(2)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>3 (3)</td>
<td>2/2</td>
<td>2/3</td>
<td>1/2</td>
<td>Positive in faeces with EIA(3)</td>
</tr>
<tr>
<td>HSV-1</td>
<td>2 (2)</td>
<td>2/2</td>
<td>2/2</td>
<td>1/2</td>
<td>Pos in CSF with PCR(2)</td>
</tr>
<tr>
<td>EBV</td>
<td>2 (2)</td>
<td>2/2</td>
<td>2/2</td>
<td>1/2</td>
<td>IgM+IgG ab in serum(2)</td>
</tr>
<tr>
<td>HHV-6</td>
<td>1 (1)</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>Pos in CSF with PCR(1)</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>1 (1)</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>IgM+IgG ab in serum(1)</td>
</tr>
<tr>
<td>Morbillivirus</td>
<td>1 (1)</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>IgM+IgG ab in serum(1)</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>1 (1)</td>
<td>0/1</td>
<td>1/1</td>
<td>1/1</td>
<td>Respiratory tract sample pos with IF(1)</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>2 (2)</td>
<td>2/2</td>
<td>2/2</td>
<td>1/2</td>
<td>Pos in CSF with PCR(1), IgM+IgG ab in serum(1)</td>
</tr>
<tr>
<td>Norovirus</td>
<td>1 (1)</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>Pos in faeces with PCR(1)</td>
</tr>
<tr>
<td>Bartonella Elisabethae</td>
<td>1 (1)</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>IgM+IgG ab in serum(1)</td>
</tr>
</tbody>
</table>
Table 2 – The etiology and clinical symptoms at presentation and at discharge in children with acute encephalitis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number (%)</th>
<th>Mean age in years (range)</th>
<th>Encephalopathy* (%)</th>
<th>Fever (%)</th>
<th>Seizures (%)</th>
<th>Focal neurological symptoms (%)</th>
<th>Symptoms at discharge (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All included</td>
<td>93 (100)</td>
<td>7.5 (0.1–17.7)</td>
<td>74 (80)</td>
<td>75 (81)</td>
<td>37 (40)</td>
<td>41 (44)</td>
<td>54/90 (60)</td>
</tr>
<tr>
<td>Etiology not found</td>
<td>48 (52)</td>
<td>8.1 (0.2–17.7)</td>
<td>38 (80)</td>
<td>39 (81)</td>
<td>21 (44)</td>
<td>22 (46) (dysphasia n = 3, motor and coordination impairment n = 13, balance impairment n = 4, ataxia n = 8, nystagmus n = 2, cognitive impairment n = 2, facial nerve paralysis n = 2, vision impairment n = 1)</td>
<td>30/47 (64) (fatigue n = 19, motor impairment n = 7, epilepsy n = 4, ataxia n = 4, cognitive impairment n = 8, dysphasia n = 2, headache n = 3, facial paresis n = 1)</td>
</tr>
<tr>
<td>Confirmed/probable etiology</td>
<td>45 (48)</td>
<td>6.9 (0.1–17.1)</td>
<td>36 (80)</td>
<td>36 (80)</td>
<td>16 (36)</td>
<td>19 (42)</td>
<td>24/43 (55)</td>
</tr>
<tr>
<td>TBEV</td>
<td>8</td>
<td>8.3 (3.4–12.5)</td>
<td>7/8</td>
<td>7/8</td>
<td>0/8</td>
<td>1/8 (dysphasia, ataxia)</td>
<td>6/8 (fatigue n = 5, hallucinosis n = 1, aggression n = 1)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>6</td>
<td>4.9 (0.5–8.1)</td>
<td>6/6</td>
<td>5/6</td>
<td>1/6</td>
<td>3/6 (ataxia in all 3, weakness; nystagmus; tremor)</td>
<td>4/6 (ataxia n = 2, fatigue n = 2, personality change n = 2)</td>
</tr>
<tr>
<td>RSV</td>
<td>6</td>
<td>1.0 (0.1–1.11)</td>
<td>5/6</td>
<td>5/6</td>
<td>2/6</td>
<td>3/5 (ataxia in all 3, dysphasia; nystagmus)</td>
<td>3/5 (ataxia n = 3, dysphasia n = 1, mood changes n = 1)</td>
</tr>
<tr>
<td>VZV</td>
<td>5</td>
<td>5.0 (0.4–11.8)</td>
<td>4/5</td>
<td>4/5</td>
<td>1/5</td>
<td>2/5 (dysphasia, weakness left side; vision impairment)</td>
<td>2/5 (fatigue, concentration impairment, irritability n = 1, nystagmus, ataxia n = 1)</td>
</tr>
<tr>
<td>Influenza A/B</td>
<td>5</td>
<td>10.1 (0.0–12.6)</td>
<td>3/5</td>
<td>5/5</td>
<td>3/5</td>
<td>2/5 (dysphasia, weakness left side; vision impairment)</td>
<td>2/5 (irritability n = 2, dysphasia, motor impairment n = 1)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>3</td>
<td>1.5 (0.2–2.9)</td>
<td>3/3</td>
<td>3/3</td>
<td>2/3</td>
<td>1/3 (speech and motor impairment, paresis of n. adducense)</td>
<td>2/3 (irritability n = 2, dysphasia, motor impairment n = 1)</td>
</tr>
<tr>
<td>HSV-1</td>
<td>2</td>
<td>14.11 (14.5–15.5)</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>2/2 (dysphasia, hemiplegia right side, nystagmus)</td>
<td>2/2 (memory impairment n = 2, fatigue, irritability n = 1)</td>
</tr>
<tr>
<td>EBV</td>
<td>2</td>
<td>14.10 (12.7–17.1)</td>
<td>2/2</td>
<td>1/2</td>
<td>1/2</td>
<td>2/2 (dysphasia, weakness, cognitive impairment; hyperkinesia, ataxia, nystagmus)</td>
<td>2/2 (cognitive impairment, epilepsy, ataxia n = 1, anxiety n = 1)</td>
</tr>
<tr>
<td>HHV-6</td>
<td>1</td>
<td>1.3</td>
<td>0/1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1 (hemiplegia)</td>
<td>0/1</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>1</td>
<td>1.9</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1 (weakness in legs)</td>
<td>0/1</td>
</tr>
<tr>
<td>Morbilli virus</td>
<td>1</td>
<td>0.9</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>1</td>
<td>3.4</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1 (weakness in legs)</td>
<td>1/1</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>2</td>
<td>9.2 (6.1–12.2)</td>
<td>2/2</td>
<td>1/2</td>
<td>0/2</td>
<td>2/2 (ataxia, vertigo; weakness)</td>
<td>1/1 (weakness in legs)</td>
</tr>
<tr>
<td>Norovirus</td>
<td>1</td>
<td>9.3</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>1/1 (weakness left hand, dysphasia)</td>
<td>1/1</td>
</tr>
<tr>
<td>Bartonella Elisabethae</td>
<td>1</td>
<td>13.4</td>
<td>0/1</td>
<td>0/1</td>
<td>1/1</td>
<td>1/1 (weakness left hand, dysphasia)</td>
<td>0/1</td>
</tr>
</tbody>
</table>

*Encephalopathy defined as altered consciousness, personality or behavioural changes lasting for more than 24 h.*
were younger than average (no symptoms at time of discharge 5.1 years old, mild symptoms 8.1 years and moderate to severe symptoms 7.1 years old). Of the children with pleocytosis in the CSF, 76% had persisting symptoms at discharge, as compared to 50% in the group without pleocytosis. Likewise, positive neuroimaging findings were also predictive of persisting sequelae, 80% of the children with positive findings on CT or MRI had sequelae as compared to 58% in the group with no neuroimaging findings.

4. Discussion

In the management of acute infection-associated encephalopathies, a broad perspective concerning etiology and pathogenesis is needed. In children, a confirmed or probable microbial etiology is in most studies established in 30–65%,1,3,5–9 which is in line with the findings of the present study where a pathogen was identified in 48% of the cases. Some of these represent direct invasive CNS-infection whereas others, such as Bartonella, are more likely indirect dysimmune/autoimmune reactions in the CNS triggered by an extra-CNS infection or immunization. Acute disseminated encephalomyelitis (ADEM) and its subtype acute hemorrhagic leukoencephalopathy (AHLE), Sydenham’s chorea and PAN-DAS are such examples.16–19

In the present study, four children who were diagnosed with ADEM also met our inclusion criteria. The diagnosis was based on clinical and MRI-findings, and in one patient (with AHLE) brain biopsy was also performed. They all had typical multifocal lesions in white matter in cerebrum, cerebellum, brainstem and/or spinal cord. Two of the patients developed coma and three were tetraparetic. None had seizures. All four were treated with high-dose steroids and showed good clinical recovery and remission on MRI. In the AHLE case, recovery was slow and left the patient with cognitive sequelae and general moderate brain atrophy. One case was associated with Mycoplasma pneumoniae and one with influenza B (the AHLE case). Another two patients diagnosed with ADEM were excluded from our study because they did not meet our inclusion criteria (no “inflammatory signs”, criteria C), both of them also had only one white matter lesion. In retrospect, arterial infarction and neoplasia can be suspected as alternative diagnoses in these two cases.

Infections in the nervous system are potentially very harmful or even lethal, and are the most common cause of non-traumatic coma in children, accounting for 40–60% of all cases.20,21 In the present study, younger children were relatively more often affected and the majority of cases were under the age of 10. Also, there was a difference between genders as boys accounted for nearly 2/3 of all the children with encephalitis. Infections caused by TBEV, enterovirus, RSV, VZV and influenza predominated, which is in line with previous studies from other European countries with similar vaccination programs.3,5,7 In contrast, it differs from the etiological pattern described in Asian countries where other viruses dominate.1,8,9,12,13 Interestingly, although the etiological pattern varies, the incidence of childhood encephalitis is relatively constant worldwide. It has also been shown that introduction of immunization programs against some of the common causes of encephalitis alters the etiological pattern without affecting the total incidence.7 This may be suggestive of an individual vulnerability that may cause an encephalopathic illness when infected with some of our common viruses. Such a genetic predisposition increasing CNS susceptibility has indeed been identified in children for HSV-1.22 Whether encephalitis cases with an unknown etiology are caused by CNS-invasive infection and, if so, are caused by the same pathogens as in the groups with a confirmed or probable etiology is obviously unclear. It is known that seroconversion may occur late or not at all, and that a lumbar puncture at the time of admission may fail to detect a seroconversion. Also, even in severe viral encephalitis, PCR for detection of viral DNA can be negative early in the course.23

In the present study focal neurological findings represent the strongest predictive factor for short-term outcome as 84% (32/38) of these children had persisting symptoms at the time of discharge. The overall incidence of persisting symptoms at the time of discharge was 60% and 41% of these had moderate to severe sequelae, indicating the severity and clinical importance of this type of infections.

The golden standards for diagnosing encephalitis have traditionally been EEG, examination of the cerebrospinal fluid and to some extent neuroimaging. Around 90% of the children in our study had an abnormal EEG compatible with
encephalitis, thereby confirming EEG as the most sensitive tool for diagnosing encephalitis. The timing of the examination is of importance for EEG as well as for CSF-investigations and neuroimaging as abnormalities may develop over time and repeated investigations will increase sensitivity.

Knowledge of the long-term outcome and prognosis is limited as few studies have addressed these questions. In Greece, 25% of children had mild to moderate sequelae 4 years after encephalitis infection. In contrast, a study from Taiwan displayed more severe sequelae including epilepsy, mental retardation and quadriparesis. Also, a mortality rate of 4% was seen in the latter study. This underlines the different geographical patterns of disease, to a large extent likely caused by an etiological diversity. The present study provides short-term outcome in a Swedish setting, and indicates sequelae at discharge in 60% of the patients. As may be expected, the etiological agent is of great importance for the occurrence of persisting sequelae. Whereas all children with encephalitis caused by RSV had made a full recovery at the time of discharge, most of the children with TBE, enterovirus, VZV, rotavirus, HSV-1 and EBV infections still had symptoms. The presence of long-term sequelae in a western setting remains to be studied.

In conclusion, this study offers a description of the present etiology, clinical presentation and short-term outcome of childhood encephalitis in a western setting. However, the large group of cases with unknown etiology, the lack of reliable prognostic markers and the lack of data on long-term outcome all indicate the need for further studies in this field.

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