Received: 12 October 2021 | Accepted: 14 April 2022

DOI: 10.1111/dmcn.15261

ORIGINAL ARTICLE

Neuroimaging and neurological outcome of children with acute encephalitis

Heidi M. Pöyhönen[1,2] | **Mikko J. Nyman**[3] | **Ville T. Peltola**[2,4] | **Eliisa S. Löyttyniemi**[5] | **Tuire T. Lähdesmäki**[1,2]

[1]Department of Paediatric Neurology, Turku University Hospital, Turku, Finland

[2]Departments of Paediatrics and Paediatric Neurology, University of Turku, Turku, Finland

[3]Department of Radiology, Turku University Hospital, Turku, Finland

[4]Department of Paediatrics and Adolescent Medicine, Turku University Hospital, Turku, Finland

[5]Department of Biostatistics, University of Turku, Turku, Finland

Correspondence
Heidi Pöyhönen, Department of Paediatrics and Adolescent Medicine, Turku University Hospital, PL 52, 20521 Turku, Finland.
Email: hmlaut@utu.fi

Funding information
Arvo ja Lea Ylppö Foundation; Finnish Pediatric Neurology Association; Maire Taponen Foundation; Suomalais-Norjalainen Lääketieteen Säätiö; the State Research Funding of the Turku University Hospital District; Turku University Foundation; Turun Yliopistollisen Keskussairaalan Koulutus- ja Tutkimus säätiö; University Foundation; Turku University Hospital; Päivikki and Sakari Sohlberg Foundation; Paulo Foundation; Orion Research Foundation; Foundation for Medical Research; Research Foundation; Finnish Medical Foundation; Finnish Cultural Foundation

Abstract

Aim: To investigate the severity of acute phase magnetic resonance imaging (MRI) findings and severity of acute illness as risk factors for disability after recovery from encephalitis.

Method: Children with encephalitis ($n = 98$; median age 6 years 10 months, interquartile range 3 years–11 years 6 months; 59 males, 39 females) treated in Turku University Hospital during the years 1995 to 2016 were identified in this retrospective cohort study. The acute phase (<2 months of symptom onset) brain MRIs were re-evaluated and classified based on the severity of neuroimaging finding by a neuroradiologist. Neurological outcome at discharge, at short-term (<3 months from discharge) follow-up, and at long-term (>1 year from discharge) follow-up was assessed from medical records using the Glasgow Outcome Scale.

Results: Long-term recovery was poor in 24 of 82 (29%) children with follow-up data. Two children died, eight had severe disability, and 14 had moderate disability. Acute phase MRI was available for re-evaluation from 74 of 82 patients with follow-up data. The increasing severity of MRI findings was associated with need for ventilator therapy and with poor recovery.

Interpretation: The risk for poor recovery in paediatric encephalitis is high, and it is associated with the severity of MRI findings.

Encephalitis is an infective or inflammatory disorder of the brain causing acute encephalopathy. Several clinical subtypes can be recognized based on major signs and symptoms, neuroimaging findings, microbial causative agents, and autoantibodies detected in cerebrospinal fluid (CSF) or serum. Other aetiologies, as with febrile infection-related epilepsy syndrome (FIRES) or acute necrotizing encephalopathy, may cause acute encephalopathy and meet the diagnostic criteria of acute encephalitis.

Paediatric encephalitis is estimated to cause up to a 13% risk of death and 78% risk of neurological sequelae during 1 to 5 years of follow-up.[1–8] In a few studies reporting the

Abbreviations: AIE, Autoimmune encephalitis; CSF, Cerebrospinal fluid; FIRES, Febrile infection-related epilepsy syndrome; GOS, Glasgow Outcome Scale; ICU, Intensive care unit.

degree of disability using both standardized performance methods and at least 1 year of follow-up after hospital discharge, the rate of moderate or severe disability affecting school performance or causing dependence has been reported as 13% to 33%.[9–12]

Neuroimaging findings in childhood encephalitis differ from adults,[13–16] and range from normal magnetic resonance imaging (MRI) to severe haemorrhagic/necrotizing lesions and brain edema.[17] The association between abnormal brain MRI findings with severe clinical presentation and short-term outcome of encephalitis has been reported.[1,18] The severity of brain MRI findings is also directly correlated with length of hospitalization.[17] Poor long-term outcome is associated with abnormal brain MRI,[5,6,10] and parenchymal involvement,[12] areas with diffusion restriction,[11] and focal cortical findings[4,19] on brain MRI.

Other risk factors, such as young age,[2,3,8] microbial aetiology (especially herpes simplex virus),[11,12] recurrent seizures,[4,6,19] and need for intensive care unit (ICU)[11] or ventilator therapy[20] are also associated with poor outcome. Need for extra support at school before encephalitis may predispose to longer hospitalization.[21]

We aimed to study the prevalence of long-term neurological disability after recovery from paediatric encephalitis and acute infective encephalopathy, and the association of acute phase neuroimaging findings with long-term disability. We hypothesized that the severity of acute phase brain MRI findings was associated with long-term neurological disability measured by the Glasgow Outcome Scale (GOS).

What this paper adds

- Poor long-term recovery was found in 29% of children with encephalitis.
- Severe disability measured by Glasgow Outcome Scale was found in 8%.
- The most severe neuroimaging findings were a risk factor for severe acute illness and poor long-term recovery.

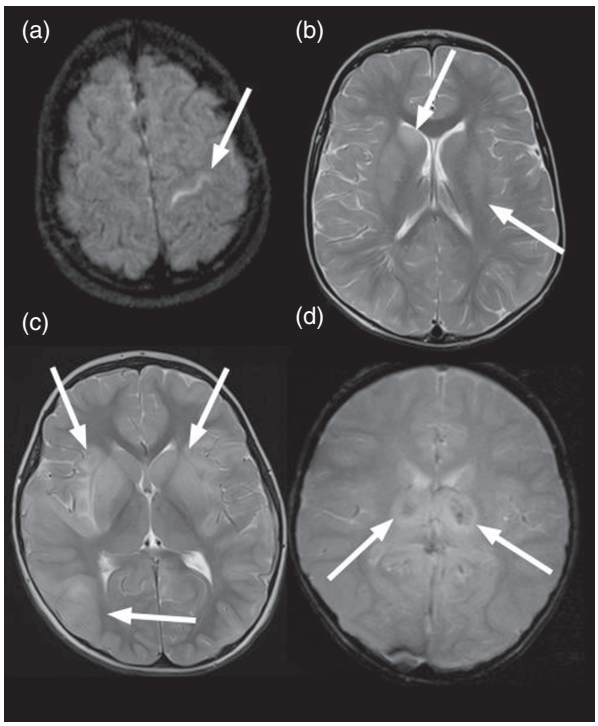

FIGURE 1 Examples of the abnormal brain magnetic resonance imaging findings in different severity categories: (a) meningeal enhancement (category 2), (b) multiple focal brain lesions (category 3), (c) confluent brain lesions (category 4), (d) hemorrhagic brain lesions (category 5).

METHOD

The patients treated for acute encephalitis at 0 to 16 years of age in our institution, during the years 1995 to 2016, were retrospectively identified from the electronic medical record system using the International Classification of Diseases, 10th Revision (ICD-10) codes referring to a diagnosis of acute central nervous system infection (A80–89, G00–09, and G51–52). Medical records of all patients with one or several of the above-listed diagnoses were examined to confirm the diagnosis of encephalitis.

The diagnosis of encephalitis was determined as acute encephalopathy (altered level of consciousness, altered behaviour, or ataxia) lasting 24 hours or longer, occurring with or without findings of acute neurological defect, with previous or concurrent symptoms of infectious disease (fever, respiratory tract symptoms, or gastrointestinal symptoms), and either CSF, electroencephalogram (EEG), or neuroimaging findings consistent with encephalitis. CSF findings consistent with encephalitis were pleocytosis (CSF leukocyte count >5x10^6/L), elevated protein concentration (>400 mg/L in children aged 2 years–13 years 11 months and >450 mg/L in children aged 14 years–15 years 11 months), or positive polymerase chain reaction test for known causative microbial agent of encephalitis. General and/or focal disorder with or without epileptiform activity were regarded as EEG findings consistent with encephalitis. Cortical or basal ganglia oedema, diffusion restriction, haemorrhage, hydrocephalus and parenchymal, meningeal, or cranial nerve enhancement were considered encephalitis-related pathology on brain MRI.

To confirm brain MRI findings consistent with acute encephalitis, a neuroradiologist (MN) blinded to the outcome results re-evaluated the MRI scans for any encephalitis-related pathology. The severity of MRI findings in acute phase (<2 months of symptoms onset) was classified according to Bykowski et al.:[17] (1) normal MRI, (2) meningeal enhancement and/or focal non-enhancing lesion, (3) multifocal lesions, (4) confluent lesions, and (5) lesions plus diffusion restriction, haemorrhage, or hydrocephalus. We also

classified isolated cranial nerve enhancement in category 2. Figure 1 shows examples of brain MRI findings of the different severity categories.

Microbial aetiology was investigated by standard laboratory methods used during the patient's acute disease episode and findings were divided by two clinicians (HP and VP) into two groups: (1) confirmed or probable, and (2) uncertain or unknown. Microbial aetiology was defined as 'confirmed' when there was a positive polymerase chain reaction or immunoglobulin M (IgM) antibody result in the CSF for a typical encephalitis-causing pathogen and 'probable' when there was a positive CSF antigen test for any pathogen; an antibody response in the CSF for an atypical encephalitis pathogen; or a positive IgM antibody result in a single serum sample, a seroconversion, or an increase in immunoglobulin G (IgG) antibody levels in paired sera for a typical encephalitis-causing pathogen. Also, in a case with an onset of clinically diagnosed varicella 4 days before development of encephalitis, the aetiology was defined as probable. The aetiology was defined as 'uncertain' when a potential encephalitis-causing pathogen was detected by polymerase chain reaction or antigen test from nasopharyngeal, pharyngeal, tracheal, or faecal specimen, or by high IgG antibodies in a single serum sample. In statistical analyses, respiratory viruses (rhinovirus, enterovirus, adenovirus, parainfluenza virus, or influenza A or B virus) were defined as one category of microbial aetiology, and each other microbe as a separate category.

Neurological outcome was scored according to the GOS: (1) good recovery (resumption of normal activities even though there may be minor neurological or psychological deficits); (2) moderate disability (disabled but independent); (3) severe disability (dependent on others for daily support); (4) persistent vegetative state (no cortical function); and (5) death.[22] The age-appropriate level of function in children was defined according to Beers et al.[23] When assessing children with previous developmental disorders or neurological/neuropsychiatric diseases, premorbid level of function was weighed in relation to the neurological outcome. The assessment of the neurological outcome was performed by a paediatric neurologist (HP) retrospectively according to the medical records at discharge, at short-term (<3 months of discharge) and at long-term (≥1 year from acute encephalitis) clinical follow-up. Based on outcome assessment, children were divided into two groups: good recovery (GOS 1) and poor recovery (GOS 2–5). An increasing GOS category indicated the increasing degree of disability.

Seven subtypes of encephalitis or clinical entities presenting as acute encephalopathies were determined by two paediatric neurologists (HP and TL), based on clinical features of illness during hospitalization and clinical follow-up. These were (1) autoimmune encephalitis (AIE; intrathecal immunological reaction, e.g. elevated CSF IgG index or oligoclonal bands with/without specific autoimmune antibodies, together with typical symptoms, such as acute movement disorder, neuropsychiatric symptoms, and/or autonomic dysfunction); (2) acute necrotizing encephalopathy (typical necrotizing lesions of brain MRI together with *RANBP* gene mutation; (3) acute demyelinating encephalomyelitis (multiple, bilateral, asymmetric, poorly marginated, and demyelinated lesions of deep grey and white matter in brain MRI); (4) cerebellitis (evident cerebellar symptoms, e.g. ataxia or coordination problems without major cortical symptoms and with/without confirmed microbial aetiology); (5) encephalitis with confirmed microbial aetiology (the cases did not meet the criteria of other encephalitis subtypes; a causative agent for encephalitis was found); (6) encephalitis without confirmed microbial aetiology (the cases did not meet the criteria of other encephalitis subtypes; a microbial causative agent for encephalitis was not found); and (7) FIRES.

Statistical analysis

Continuous variables were summarized using median with lower (Q1) and upper (Q3) quartiles, and categorical variables with counts and percentages. The following dependent variables were studied: poor recovery, degree of disability, and neuroimaging severity category (1–5) (ordinal variables). The following predictor variables were studied in the models: need for ICU, need for ventilator therapy, need for antiseizure medication, detected CSF pleocytosis, abnormal EEG, sex, category of probable/confirmed microbial agent, microbial aetiology category, encephalitis subtype (categorial variables), age at acute illness onset, and length of hospitalization (quantitative variables). Univariate association between dependent variables and categorical predictive variables were studied using a χ^2 test or Fisher's exact test when both were categorical variables, and the Mann–Whitney *U* test or Kruskal–Wallis test otherwise. The association between poor long-term recovery (response), and need for ventilator therapy, age, and neuroimaging severity category (predictors) were examined with cumulative logistic regression. Odds ratios (OR) together with 95% confidence intervals are reported. A significance level of 0.05 (two-tailed) was used. The data analysis was done using SAS software (version 9.4 of the SAS System for Windows; SAS Institute, Cary, NC, USA).

Ethics

The study was approved by the Institutional Review Board at the Turku Clinical Research Centre with a statement that an ethic committee review was not needed for this retrospective analysis of data collected during routine patient care.

RESULTS

We identified 98 children fulfilling our criteria for encephalitis. The median age of patients was 6 years 10 months (Q1 3 years, Q3 11 years 6 months), and 59 (60%) patients were male. One child had nephrotic syndrome and

immunosuppressive treatment whereas the others had no significant comorbidities before encephalitis. Nine children had obvious developmental delay (learning or motor disability) before encephalitis onset, and eight children were born preterm (<37 gestational weeks), two of them very preterm (<32 gestational weeks). None of the patients had epilepsy before the onset of encephalitis. Four children had two separate episodes of infection-associated encephalitis, two of them later classified as acute necrotizing encephalopathy due to *RANBP2* mutation.[24]

The most common neurological symptoms at the onset of acute disease were abnormal consciousness in 75, headache in 44, and seizures in 37 children. A total of 58 children had fever, 56 gastrointestinal symptoms, and 30 respiratory symptoms. CSF pleocytosis was detected in 65 of 98 and abnormal EEG in 71 of 88 children studied. The demographic data of patients (n = 98) is shown in Table 1.

Microbial diagnosis was confirmed in 38 children. The aetiologies were human herpes virus 6 or 7 in 10, Mycoplasma pneumoniae in seven, herpes simplex virus in four, Borrelia burgdorferi in four, enterovirus in three, and tick-borne encephalitis virus in three children. Parainfluenza virus, rhinovirus, adenovirus, Epstein–Barr virus, varicella-zoster virus, cytomegalovirus, and Streptococcus pneumoniae, each in one child, were also confirmed aetiologies. In one patient, the polymerase chain reaction test for human herpes virus 7 from CSF and antibody test for tick-borne encephalitis virus from CSF and serum were positive.

The final diagnosis was encephalitis without confirmed microbial aetiology in 42, encephalitis with confirmed microbial aetiology in 25, acute demyelinating encephalomyelitis in 10, cerebellitis in eight, and AIE in seven children. In clinical follow-up, the diagnosis of six children turned out to be infection-related encephalopathies: three cases of FIRES[25,26] and three cases of acute necrotizing encephalopathy due to *RANBP2* mutation.[24] AIE presented with acute movement disorder, neuropsychiatric symptoms, and/or autonomic dysfunction together with intrathecal immune reaction, and one child also had positive voltage-gated potassium channel complex antibodies in serum.

AIE-related autoantibodies were studied in 12 children, treated in the years 2010 to 2017. The studied autoantibodies were N-methyl-D-aspartate receptor antibodies from 11, voltage-gate potassium channel antibodies from six, antiglutamate receptor antibodies from three, and contactin-associated protein 2 antibodies from two children. Autoantibodies were studied if AIE was suspected by typical clinical features and/or intrathecal immune reaction, and/or the microbial aetiology of encephalitis was unclear.

MRI was performed on 88 children during the acute phase (<2 months of symptoms onset) of encephalitis. MRI was considered normal in 39 (44%) children. Meningeal or cranial nerve enhancement and/or focal T2-hyperintense lesion was documented in 14 (26%), multifocal T2-hyperintense lesions in 18 (20%), confluent T2-hyperintense lesions in four (5%), and T2-hyperintense lesions plus diffusion restriction, haemorrhage, or hydrocephalus in 13 (15%) children. In five patients with normal MRI, neuroimaging was performed during the first 2 days after the onset of symptoms without re-imaging later.

GOS based on clinical follow-up was defined for all the 98 patients at discharge, for 91 patients at short-term follow-up, and for 82 patients at long-term follow-up. MRI was available from 75 of these 82 children. The median long-term follow-up time was 6 years (Q1 2 years 8 months, Q3 11 years 6 months, mean 7 years 6 months, range 1–23 years). The recovery was poor (GOS 2–5) at short-term follow-up in 29 of 91 (32%) children (GOS median 2, Q1 1, Q3 2); and at long-term follow-up in 24 of 82 (29%) children (GOS median 2, Q1 1, Q3 2). Nine patients with good recovery at discharge had moderate disability at short-term follow-up. Seven of 15 children (47%) with severe disability at discharge had good

TABLE 1 Demographic data of children with encephalitis (n = 98)

Data	*n* (%)
Age, years:months, median (Q1, Q3)	6:10 (3:0, 11:6)
Sex, male	59 (60)
Evident developmental delay	9 (9)
Born preterm	8 (8)
Need for ICU	55 (56)
Need for antiseizure medication	30 (31)
Need for ventilator therapy	14 (14)
Length of hospitalization, days, median (Q1, Q3)	8 (6.0, 12.0)
Probable or confirmed microbial aetiology	38 (39)
CSF pleocytosis	65 (66)
Abnormal EEG	71/88 (81)
Treatment	
Doxycycline	90 (92)
Ceftriaxone	25 (25)
Acyclovir	83 (85)
High-dose steroid	25 (26)
Intravenous immunoglobulin	20 (20)
Symptoms	
Abnormal consciousness or alertness	75 (75)
Fever	58 (59)
Gastrointestinal	56 (57)
Headache	44 (46)
Seizures	37 (38)
Difficulties in balance	31 (32)
Respiratory symptoms	30 (31)
Motor paresis	23 (24)
Difficulties in speech	22 (23)
Psychiatric symptoms	12 (12)
Movement disorder	8 (8)
Neck stiffness	8 (8)

Abbreviations: ICU, intensive care unit; CSF, cerebrospinal fluid; EEG, electroencephalogram.

recovery at long-term follow-up. The recovery status of patients is shown in Figure S1.

Poor long-term recovery was associated with increasing neuroimaging severity category ($p = 0.04$) (Table 2), need for antiseizure medication ($p < 0.001$), and need for ventilator therapy ($p < 0.001$). Degree of disability was associated with increasing neuroimaging severity category ($p = 0.01$) and need for ICU ($p = 0.006$). The severity of MRI findings was higher in males, in children with ICU admission, and in children with ventilator therapy (Table 2). Ventilator therapy had the strongest association with the degree of disability (OR 7.75; 95% CI 1.59–37.9; $p = 0.01$) over the neuroimaging severity category ($p = 0.2$) in multivariate analysis. Sex, preterm birth, developmental delay before encephalitis, age at encephalitis, length of hospitalization, or microbial aetiology were not related to poor long-term recovery or degree of disability in univariate analyses. The recovery of children in different encephalitis subtypes is shown in Table 3.

Of 10 children with the most severe sequelae (severe disability or death), the microbial aetiology of encephalitis was confirmed in three: herpes simplex virus in two and Mycoplasma pneumoniae in one. Three patients' acute illness was later diagnosed as FIRES and one had suspected AIE with no confirmed autoantibodies. Two cases were diagnosed as encephalitis without confirmed microbial aetiology. Long-term sequelae of eight patients with severe disability included epilepsy in seven, learning disability in five, neuropsychiatric disorders or personality change in six, and motor disability in one patient. In all cases, these residual symptoms occurred together with each other.

DISCUSSION

Nearly a third of the children had poor short- and long-term recovery after having encephalitis. The mortality rate was 2%. Severe disability causing dependence on others was found in 8%, which is in line with previous studies evaluating the outcome after paediatric encephalitis with standardized methods.[9–12] The rate of vegetative state in previous studies has been 1% to 5%,[9,12] but in our patients there was none.

Neurological symptoms and signs causing remarkable disability may remain undetectable at discharge. These symptoms do not necessarily affect the patient's function until the child returns home, to school, and to hobbies. In our series, over one-sixth of patients with good recovery at discharge were later found to be disabled, but almost half of the children with severe disability at discharge had good recovery at long-term follow-up.

Increasing severity of MRI findings was a risk factor for poor outcome. The most severe MRI findings were associated with the need for ICU and ventilator therapy. The patients with most severe MRI findings were thus prone to severe clinical acute illness and later poor long-term neurological outcome. The association between the most severe neuroimaging findings and disease severity was also found in previous studies.[11,17] However, one-fifth of our patients with normal acute phase MRI had poor outcome at long-term follow-up.

Later re-imaging might have revealed encephalitis-related abnormalities in patients with normal MRI performed early after symptom onset. In practice, follow-up MRI is not performed routinely if a child has good clinical recovery. All

TABLE 2 Patients details according to the severity of MRI findings score

	MRI findings score					*p*
	1, *n* = 39	**2, *n* = 14**	**3, *n* = 18**	**4, *n* = 4**	**5, *n* = 13**	
Poor recovery at discharge	14 (36)	9 (64)	8 (44)	4 (100)	10 (77)	0.02
Poor recovery at <3 months follow-up	8/37 (22)	5 (36)	4/14 (29)	1 (25)	9 (69)	0.04
Poor recovery at >1 year follow-up	7/30 (23)	3/13 (23)	4/16 (25)	3 (75)	7/11 (64)	0.04
Age, years:months, median, (Q1, Q3)	7:6 (2:7, 13:1)	8:10 (6:0, 13:11)	6:0 (3:5, 10:1)	2:4 (0:6, 5:11)	5:4 (1:2, 11:1)	0.1
Sex						
Male	19/53 (36)	8/53 (15)	17/53 (32)	3/53 (6)	6/53 (11)	0.01
Female	20/35 (57)	6/35 (17)	1/35 (3)	1/35 (3)	7/35 (20)	
ICU admission	19 (49)	7 (50)	12 (67)	3 (75)	12 (93)	0.03
Antiseizure medication usage	12 (31)	3 (21)	4 (22)	3 (75)	7 (54)	0.1
Ventilator therapy	3 (8)	2 (14)	1 (6)	2 (50)	6 (46)	0.004

Data are *n* (%) unless otherwise stated. Magnetic resonance imaging (MRI) findings score (1) normal MRI, (2) meningeal enhancement and/or focal non-enhancing lesion, (3) multifocal lesions, (4) confluent lesions, and (5) lesions plus diffusion restriction, haemorrhage, or hydrocephalus. Associations were tested with Fisher's exact test.
Abbreviations: ICU, intensive care unit.

TABLE 3 Neurological outcome at discharge and at short- and long-term follow-up according to the diagnosis of encephalitis subtype

	Poor recovery at discharge	Poor recovery at <3 months follow-up	Poor recovery at >1 year follow-up	Severe disability or death in long-term follow-up
AIE	4/7 (47)	3/7 (43)	4/7 (47)	1/7 (14)
ADEM	8/10 (80)	5/9 (56)	3/9 (33)	0/9 (0)
ANE	1/3 (33)	1/3 (33)	2/3 (67)	0/3 (0)
Cerebellitis	8/8 (100)	4/8 (50)	3/7 (43)	0/7 (0)
Encephalitis with confirmed microbial causative agent	9/25 (36)	6/24 (25)	4/22 (18)	2/22 (9)
Encephalitis without confirmed microbial causative agent	14/42 (33)	7/37 (19)	5/31 (16)	4/31(13)
FIRES	2/3 (67)	3/3 (100)	3/3 (100)	3/3 (100)
p	0.001	0.02	0.008	<0.001

Data are *n* (%) unless otherwise stated. Associations were tested with Fisher's exact test. Abbreviations: AIE, autoimmune encephalitis; ADEM, acute disseminated encephalomyelitis; ANE, acute necrotizing encephalopathy; FIRES, febrile infection-related epilepsy syndrome.

five patients with normal early MRI and no follow-up imaging had good short- and long-term recovery.

Contrast enhancer was not used in four MRIs; two of them were categorized as normal, one was classified in category 2, and one in category 3. The possibility of a major grading shift based on enhancement was considered low, and these four cases were included in the study.

The neuroimaging severity scoring has several limitations. White matter lesion volume was not quantified, which makes the scoring subjective, but makes it easier to use in clinical work. Lesion severity may not always correlate with this classification; sometimes patchy lesions may be more severe than confluent ones, and diffusion-weighted imaging lesions may not be a sign of severe disease. Our results still support the general severity pattern of the MRI findings based on the Bykowski classification.[17] Broader lesions are generally more severe than smaller ones. Diffusion-weighted imaging restriction, haemorrhage, and parenchymal enhancement are generally associated with more severe disease. Minimum MRI protocol to perform this classification is T2-weighted imaging, diffusion-weighted imaging, hemo/susceptibility-weighted imaging, T1-weighted imaging, and T1+C-weighted imaging. Including flair images would also be beneficial.

The rates of poor outcome after acute demyelinating encephalomyelitis (33%) and AIE (47%) were congruent with Pillai et al.'s results.[11] Encephalitis without confirmed microbial aetiology had the most favourable long-term outcome in our study, but the most unfavourable outcome in the other study.[11] This group's heterogeneity in our study was wide, including a variety of cases who did not meet the criteria of other subtypes and probably both infective and immunologic aetiologies.

All patients with cerebellitis had poor recovery at discharge, but over half recovered well later, which is in line with previous studies.[27,28] Even the patients with poor outcome had only moderate disability. This may reflect that cerebellitis mainly causes motor and coordination problems[27,28] that are already easily recognizable in a hospital environment.

The categorization of encephalitis subtypes differs between studies. FIRES, which had the worst outcome in our study, was not defined as a separate category in Pillai et al.'s study. Herpes simplex virus aetiology, which had the most unfavourable outcome in Pillai et al.'s study, was included in the category of confirmed microbial aetiology in our study.[11] This makes comparison between different studies difficult.

Our criteria for different encephalitis subtypes were based on clinical symptoms and certain neuroimaging or CSF findings at the acute phase. The diagnostic methods of AIE varied between individual patients because of the wide timespan of our data. The autoantibodies were only examined in 12 children. It is thus possible that we missed some AIE cases from our data.

FIRES was related to the poorest long-term outcome, with severe disability in all three patients, which is in line with previous studies.[25,26] The diagnosis of FIRES-like autoimmune epilepsy is usually stated later in the clinical follow-up. One child with FIRES had pleocytosis, and two children had encephalitis-related MRI abnormalities classified in neuroimaging severity category 2, thus meeting the inclusion criteria of our encephalitis study. In addition, one patient had confirmed microbial aetiology (positive Mycoplasma pneumoniae IgM antibodies in serum sample) during the acute phase of illness. As the aetiology of FIRES is not yet fully understood, we included these patients in the study. With exclusion of these three patients, the rate of severe disability would be only slightly lower (6% vs 8%), and the overall rate of good recovery would not be remarkably higher (72% vs 71%).

The microbial aetiology was not associated with neurological outcome, which may reflect the diverse aetiology and the small sample size; only 38 of our patients with encephalitis had confirmed microbial aetiology. Also, the microbial aetiology was not related to severity of neuroimaging findings, which is consistent with a previous study.[17]

Our inclusion criteria demanded encephalopathy lasting more than 24 hours, with CSF, MRI, or EEG abnormality related to encephalitis. The proportion of MRI abnormalities

was high, reflecting a true brain disorder. Our criteria excluded transient encephalopathies during febrile illness caused by, for example, hypoglycaemia, dehydration, and febrile seizures. Our inclusion criteria may have worsened the overall outcome of the study by exclusion of some milder cases.

The main strength of our study was the use of the standardized outcome score to assess neurological disability. It enabled us to compare the variable symptoms reported by separate patients and studies, and define the functional impairment of these symptoms in everyday life. Because this method considers a child's premorbid level of function, it can also be used on patients with premorbid disability, without an obligation to exclude these patients from the study.

Only a few previous studies report long-term outcome evaluated with standardized methods.[9–12] We focused on the functional long-term neurological outcome, instead of the sequelae at discharge or short-term clinical follow-up. We used the original GOS, instead of its revision, GOS Extended,[29] for outcome measures. We wanted to identify children with most severe disabilities, not to divide the mildest symptoms into separate categories of upper and lower good recovery. Thus, we found the original GOS sufficient for our purposes. Because the original GOS only measures functional outcome, it may not recognize some postencephalitic cognitive problems.[30,31] More definite neuropsychological examinations are needed to find specific problems (e.g. difficulties in executive function and memory).

Our study has some limitations. The data were collected retrospectively from the medical record system, which, although used consistently in our hospital, is prone to human errors when recording a diagnosis. The timing of the long-term follow-up varied from 1 to 23 years, making it difficult to differentiate all environmental factors affecting patients' neurological outcome from the effects of encephalitis. In young children, the differentiation of developmental disorders and encephalitis-related symptoms can be challenging, even though the development was normal before the acute illness. In our study, two children with severe disability and seven children with poor outcome were under 2 years of age when they had acute encephalitis. However, the use of standardized outcome measures also increased the reliability of evaluation in these patients.

CONCLUSIONS

The risk for poor outcome, disability, or death was high after paediatric encephalitis. The severity of neuroimaging findings was associated with severe illness and poor long-term outcome. However, a normal MRI during the acute phase does not exclude poor long-term outcome. Clinical follow-up should, therefore, be offered to all children after having encephalitis.

ACKNOWLEDGEMENTS

Annika Tihveräinen is acknowledged for language editing. This work was supported by Arvo and Lea Ylppö Foundation, Finnish Paediatric Neurology Association (Märta Donner Grant), Finnish Cultural Foundation, the Finnish Medical Foundation, Finnish-Norwegian Research Foundation for Medicine (Suomalais-Norjalainen Lääketieteen Säätiö), Juhani Aho Foundation for Medical Research, Maire Taponen Foundation, Orion Research Foundation, The Paulo Foundation, Päivikki and Sakari Sohlberg Foundation, The State Research Funding of the Turku University Hospital District, Turku University Foundation, and Tyks Foundation.

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Turku CRC.

ORCID

Heidi M. Pöyhönen https://orcid.org/0000-0002-7984-258X
Mikko J. Nyman https://orcid.org/0000-0002-2104-6302
Ville T. Peltola https://orcid.org/0000-0003-3529-2747
Eliisa S. Löyttyniemi https://orcid.org/0000-0002-7278-6511
Tuire T. Lähdesmäki https://orcid.org/0000-0002-8447-2958

REFERENCES

1. Klein SK., Hom DL., Anderson MR., Latrizza AT., Toltzis P. Predictive factors of short-term neurologic outcome in children with encephalitis. Pediatr Neurol 1994;11(4):308–12. https://doi.org/10.1016/0887-8994(94)90007-8.
2. IFF T., Donati F., Vassella F., Schaad UB., Bianchetti MG. Acute encephalitis in Swiss children: Aetiology and outcome. Eur J Paediatr Neurol 1998;2(5):233–7. https://doi.org/10.1016/S1090-3798(98)80036-6.
3. Clarke M., Newton RW., Klapper PE., Sutcliffe H., Laing I., Wallace G. Childhood encephalopathy: Viruses, immune response, and outcome. Dev Med Child Neurol 2006;48(4):294–399. https://doi.org/10.1017/S0012162206000636.
4. Wang IJ., Lee PI., Huang LM., Chen CJ., Chen CL., Lee WT. The correlation between neurological evaluations and neurological outcome in acute encephalitis: A hospital-based study. Eur J Paediatr Neurol 2007;11(2):63–9. https://doi.org/10.1016/j.ejpn.2006.09.010.
5. Michaeli O., Kassis I., Shachor-Meyouhas Y., Shahar E., Ravid S. Long-term motor and cognitive outcome of acute encephalitis. Pediatrics 2014;133(3):e546-52. https://doi.org/10.1542/peds.2013-3010.
6. Rao S., Elkon B., Flett KB., Moss AFD., Bernard TJ., Stroud B., et al. Long-Term Outcomes and Risk Factors Associated With Acute Encephalitis in Children. J Pediatric Infect Dis Soc 2017;6(1):20–7. https://doi.org/10.1093/jpids/piv075.
7. Khandaker G., Jung J., Britton PN., King C., Yin JK., Jones CA. Long-term outcomes of infective encephalitis in children: a systematic review and meta-analysis. Dev Med Child Neurol 2016;58(11):1108–15. https://doi.org/10.1111/dmcn.13197.
8. Elenga N., Roux A., Cuadro-Alvarez E., Martin E., Kallel H., Defo A. Etiology and prognosis of encephalitis in French Guianese children: a retrospective record-based study. J Infect Public Health 2020;13(7):1051–3. https://doi.org/10.1016/j.jiph.2020.01.315.
9. Mailles A., De Broucker T., Costanzo P., Martinez-Almoyna L., Vaillant V., Stahl JP. Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France. Clin Infect Dis 2012;54(10):1455–64. https://doi.org/10.1093/cid/cis226.

10. DuBray K., Anglemyer A., LaBeaud a D., Flori H., Bloch K., Joaquin KS., et al. Epidemiology, outcomes and predictors of recovery in childhood encephalitis: a hospital-based study. Pediatr Infect Dis J 2013;32(8):839–44. https://doi.org/10.1097/INF.0b013e318290614f.
11. Pillai SC., Hacohen Y., Tantsis E., Prelog K., Merheb V., Kesson A., et al. Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. Pediatrics 2015;135(4):e974–84. https://doi.org/10.1542/peds.2014-2702.
12. Chen T., Liu G. Long-term outcome of acute central nervous system infection in children. Pediatr Investig 2018;2(3):155–63. https://doi.org/10.1002/ped4.12054.
13. Koelfen W., Freund M., Gückel F., Rohr H., Schultze C. MRI of encephalitis in children: Comparison of CT and MRI in the acute stage with long-term follow-up. Neuroradiology 1996;38(1):73–9. https://doi.org/10.1007/s002340050201.
14. Leonard JR., Moran CJ., Cross DWT., Wippold FJ., Schlesinger Y., Storch GA. MR imaging of herpes simplex type I encephalitis in infants and young children: A separate pattern of findings. Am J Roentgenol 2000;174(6):1651–5. https://doi.org/10.2214/ajr.174.6.1741651.
15. Beattie GC., Glaser CA., Sheriff H., Messenger S., Preas CP., Shahkarami M., et al. Encephalitis With Thalamic and Basal Ganglia Abnormalities: Etiologies, Neuroimaging, and Potential Role of Respiratory Viruses. Clin Infect Dis 2013;56(6):825–32. https://doi.org/10.1093/cid/cis990.
16. To TM., Soldatos A., Sheriff H., Schmid DS., Espinosa N., Cosentino G., et al. Insights into pediatric herpes simplex encephalitis from a cohort of 21 children from the California encephalitis project, 1998-2011. Pediatr Infect Dis J 2014;33(12):1287–8. https://doi.org/10.1097/INF.0000000000000422.
17. Bykowski J., Kruk P., Gold JJ., Glaser CA., Sheriff H., Crawford JR. Acute Pediatric Encephalitis Neuroimaging: Single-Institution Series as Part of the California Encephalitis Project. Pediatr Neurol 2015;52(6):606–14. https://doi.org/10.1016/j.pediatrneurol.2015.02.024.
18. Ilias A., Galanakis E., Raissaki M., Kalmanti M. Childhood encephalitis in Crete, Greece. J Child Neurol 2006;21(10):910–2. https://doi.org/10.1177/08830738060210101701.
19. Lee WT., Yu TW., Chang WC., Shau WY. Risk factors for postencephalitic epilepsy in children: A hospital-based study in Taiwan. Eur J Paediatr Neurol 2007;11(5):302–9. https://doi.org/10.1016/j.ejpn.2007.02.011.
20. Hon KLE., Tsang YCK., Chan LCN., Tsang HW., Wong KYK., Wu YHG., et al. Outcome of Encephalitis in Pediatric Intensive Care Unit. Indian J Pediatr 2016;83(10):1098–103. https://doi.org/10.1007/s12098-016-2068-4.
21. Fowler Å., Ygberg S., Svensson E., Bergman K., Cooray G., Wickström R. Prospective Evaluation of Childhood Encephalitis. Pediatr Infect Dis J 2020;39:e417–e422. https://doi.org/10.1097/inf.0000000000002842.
22. Jennett B., Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1(7905):480–4. https://doi.org/10.1016/S0140-6736(75)92830-5.
23. Beers SR., Wisniewski SR., Garcia-Filion P., Tian Y., Hahner T., Berger RP., et al. Validity of a pediatric version of the glasgow outcome scale-extended. J Neurotrauma 2012;29(6):1126–39. https://doi.org/10.1089/neu.2011.2272.
24. Lönnqvist T., Isohanni P., Valanne L., Olli-Lähdesmäki T., Suomalainen A., Pihko H. Dominant encephalopathy mimicking mitochondrial disease. Neurology 2011;76(1):101–3. https://doi.org/10.1212/WNL.0b013e318203e908.
25. Van Baalen A., Häusler M., Boor R., Rohr A., Sperner J., Kurlemann G., et al. Febrile infection-related epilepsy syndrome (FIRES): A non-encephalitic encephalopathy in childhood. Epilepsia 2010;51(7):1323–8. https://doi.org/10.1111/j.1528-1167.2010.02535.x.
26. Hon KL., Leung AKC., Torres AR. Febrile Infection-Related Epilepsy Syndrome (FIRES): An Overview of Treatment and Recent Patents. Recent Pat Inflamm Allergy Drug Discov 2018;12(2):128–35. https://doi.org/10.2174/1872213x12666180508122450.
27. Kornreich L., Shkalim-Zemer V., Levinsky Y., Abdallah W., Ganelin-Cohen E., Straussberg R. Acute Cerebellitis in Children: A Many-Faceted Disease. J Child Neurol 2016;31(8):991–7.
28. Yildirim M., Gocmen R., Konuskan B., Parlak S., Yalnizoglu D., Anlar B. Acute Cerebellitis or Postinfectious Cerebellar Ataxia? Clinical and Imaging Features in Acute Cerebellitis. J Child Neurol 2020;35(6):380–8. https://doi.org/10.1177/0883073820901407.
29. Jennett B., Snoek J., Bond MR., Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry 1981;44(4):285–93. https://doi.org/10.1136/jnnp.44.4.285.
30. Fowler Å., Forsman L., Eriksson M., Wickström R. Tick-borne encephalitis carries a high risk of incomplete recovery in children. J Pediatr 2013;163(2):555–60. https://doi.org/10.1016/j.jpeds.2013.01.037.
31. Pöyhönen H., Setänen S., Isaksson N., Nyman M., Nyman A., Peltola V., et al. Neurological and Cognitive Performance After Childhood Encephalitis. Front Pediatr 2021;9:646684. https://doi.org/10.3389/fped.2021.646684.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Flow-chart showing recovery of patients with encephalitis (n = 98) at discharge, at short-term, and at long-term follow-up.

How to cite this article: Pöyhönen HM, Nyman MJ, Peltola VT, Löyttyniemi ES, Lähdesmäki TT. Neuroimaging and neurological outcome of children with acute encephalitis. Dev Med Child Neurol. 2022;64:1262–1269. https://doi.org/10.1111/dmcn.15261