Infectious and Autoantibody-Associated Encephalitis: Clinical Features and Long-term Outcome

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abstract

BACKGROUND AND OBJECTIVES: Pediatric encephalitis has a wide range of etiologies, clinical presentations, and outcomes. This study seeks to classify and characterize infectious, immune-mediated/autoantibody-associated and unknown forms of encephalitis, including relative frequencies, clinical and radiologic phenotypes, and long-term outcome.

METHODS: By using consensus definitions and a retrospective single-center cohort of 164 Australian children, we performed clinical and radiologic phenotyping blinded to etiology and outcomes, and we tested archived acute sera for autoantibodies to N-methyl-D-aspartate receptor, voltage-gated potassium channel complex, and other neuronal antigens. Through telephone interviews, we defined outcomes by using the Liverpool Outcome Score (for encephalitis).

RESULTS: An infectious encephalitis occurred in 30%, infection-associated encephalopathy in 8%, immune-mediated/autoantibody-associated encephalitis in 34%, and unknown encephalitis in 28%. In descending order of frequency, the larger subgroups were acute disseminated encephalomyelitis (21%), enterovirus (12%), Mycoplasma pneumoniae (7%), N-methyl-D-aspartate receptor antibody (6%), herpes simplex virus (5%), and voltage-gated potassium channel complex antibody (4%). Movement disorders, psychiatric symptoms, agitation, speech dysfunction, cerebrospinal fluid oligoclonal bands, MRI limbic encephalitis, and clinical relapse were more common in patients with autoantibodies. An abnormal outcome occurred in 49% of patients after a median follow-up of 5.8 years. Herpes simplex virus and unknown forms had the worst outcomes. According to our multivariate analysis, an abnormal outcome was more common in patients with status epilepticus, magnetic resonance diffusion restriction, and ICU admission.

CONCLUSIONS: We have defined clinical and radiologic phenotypes of infectious and immune-mediated/autoantibody-associated encephalitis. In this resource-rich cohort, immune-mediated/autoantibody-associated etiologies are common, and the recognition and treatment of these entities should be a clinical priority.

WHAT'S KNOWN ON THIS SUBJECT: Encephalitis is a serious and disabling condition. There are infectious and immune-mediated causes of encephalitis, but many cases remain undiagnosed.

WHAT THIS STUDY ADDS: This large single-center study on childhood encephalitis provides insight into the relative frequency and clinico-radiologic phenotypes of infectious, autoantibody-associated, and unknown encephalitis. Risk factors for an abnormal outcome are also defined.
Encephalitis is inflammation of the brain parenchyma and has many infectious and immune-mediated etiologies. Acute encephalitis can be life threatening and results in permanent neuropsychiatric and cognitive impairments in a significant proportion of survivors. Inflammatory forms of encephalitis such as acute disseminated encephalomyelitis (ADEM) have been known for some time, but in the past decade other autoimmune forms of encephalitis have been recognized, defined by the presence of autoantibodies against cell surface antigens. Autoantibody detection is important as immune suppression is ineffective against cell surface antigens. Autoantibody detection is important as immune suppression alone may improve outcomes, particularly when given early in the disease. A recent study suggested that N-methyl-D-aspartate receptor antibody (NMDAR-Ab) encephalitis, the best-known autoimmune form, is more common than herpes simplex virus (HSV) encephalitis in children and young adults, and a prospective study of adults (n = 134) and children (n = 69) with encephalitis found that infectious encephalitis and immune-mediated forms were identified in 42% and 21% of the cohort, respectively.

However, most of the previous larger studies of encephalitis in children were undertaken before the advent of neuronal autoantibody testing. We studied clinical and radiologic features, serum autoantibodies in acute archived samples, and long-term outcomes in a large retrospective cohort of pediatric encephalitis from a single center.

**METHODS**

**Patients, Definitions, and Clinical Data**

**Patients**

We report patients with encephalitis seen between January 1998 and October 2010 at the Children’s Hospital at Westmead, the largest tertiary children’s hospital in New South Wales, Australia. Patients either presented directly to the hospital emergency department or were referred from district hospitals in western Sydney and New South Wales (referral base ~4.5 million people). Patients were identified retrospectively from International Classification of Diseases, 10th Revision coding of encephalitis or encephalomyelitis at discharge, plus screening of consultant correspondence from the Department of Neurology database and review of cerebrospinal fluid (CSF) polymerase chain reaction testing from the Department of Infectious Diseases and Microbiology. The following patients were excluded: neonates (<1 month old), patients >16 years old, known or suspected cases of immunodeficiency, and viral or bacterial meningitis without encephalitis. Infection-associated encephalopathy (influenza and rotavirus) cases were included. A total of 164 patients fulfilled the diagnostic criteria for acute encephalitis, according to the following definitions.

**Definitions**

We used the Granderod encephalitis case definitions, with minor modifications. Encephalitis was defined as an acute encephalopathy with ≥2 of the following: fever ≥38°C, seizures or focal neurologic signs, CSF pleocytosis (≥5 white blood cells/μL) or elevated CSF neopterin (≥30 nmol/L), EEG consistent with encephalitis (presence of slowing in this study), or MRI findings suggestive of encephalitis. CSF neopterin, which is produced secondary to α- or γ-interferon stimulation, was included as an alternative to CSF pleocytosis because it has been shown to be a useful marker of central nervous system (CNS) inflammation. Encephalopathy was defined as an altered or reduced level of consciousness and a change in personality or behavior or confusion lasting >24 hours. We did not use lethargy and irritability as sole features of encephalopathy because of the nonspecific nature of these features in sick children unless supported by EEG features of encephalopathy.

**Clinical Data During Acute Encephalitis**

In total, 179 clinical or investigation variables were recorded in every patient (Supplemental Information). CSF results were available in 157 (96%) patients, and EEG reports from the first week of admission were available in 130 (79%) patients. We obtained follow-up information by telephone interview in 144 (88%) cases in 2011 and 2012 by using the Liverpool Outcome Score (LOS) questionnaire, supplemented by clinical records. All patients were followed up for a minimum of 12 months after encephalitis, and the LOS was recorded as follows: 1 = death, 2 = severe, 3 = moderate, 4 = mild, and 5 = normal, and specific domains of abnormal outcome were also recorded. The outcome score describes the patient’s abilities compared with peers, with mild describing impairments without dependence on carers, whereas severe describes complete dependence on carers. Clinical relapses were recorded separately.

**MRI**

We had access to 1.5-Tesla MRI brain scans for review in 149 (91%) patients. MRI data were reviewed, blinded to clinical and diagnostic information, by pediatric neuroradiologists (R.C.D., S.C.P.) and a pediatric neuroradiologist (K.P.), and consensus was reached on abnormalities. The mean and median duration of first MRI scan after admission were 4.8 days and 3 days, respectively (range 1–70 days).

**Etiologic Investigation to Determine Encephalitis Causation**

**Infectious Encephalitis and Infection-Associated Encephalopathy**

The CSF, serological, and non-CNS specimen testing for infectious etiologies are summarized in Supplemental Table 3. Testing of up
to 42 different microorganisms was carried out as clinically indicated. The mean and median etiologic tests (including autoantibodies) per patient were 14 and 13 tests, respectively (range 0–36).

CSF Testing
A CSF was obtained at a mean and median admission duration of 2.9 days and 2 days, respectively (range 1–48 days). Bacterial and viral cultures of the CSF were done on 155 (95%) and 152 (93%) patients, respectively. CSF polymerase chain reaction testing was obtained in 131 (80%) of the total cohort, with patients with ADEM less frequently tested (63%).

Serology
Serological testing for ≥1 microorganisms was performed on 139 (85%) patients. Serological studies for microorganisms used complement fixation tests and immunoglobulin M (IgM) enzyme-linked immunosorbent assays (Table 1).

Non-CNS Specimens
These tests include blood culture (n = 144, 87.8%), nasopharyngeal aspirate (n = 69, 42%), stool and rectal swab (n = 68, 41%), throat swab (n = 47, 29%), and skin swab (n = 5, 3%) (Supplemental Table 3).

Immune-Mediated/Autoantibody-Associated Encephalitis
We used Granerod case definition for confirmed ADEM. Retrospective autoantibody testing on stored acute sera was performed in 103 of the 129 patients with non-ADEM encephalitis (80%). Patients with a preliminary diagnosis of ADEM were excluded from autoantibody testing (n = 35). Antibodies to NMDAR (n = 103), voltage-gated potassium channel complex (VGKC-complex) (n = 102), leucine-rich glioma-inactivated 1 (LGI1) (n = 99), contactin-associated protein-like 2 (CASPR2) (n = 99), glycine receptor (n = 102), and glutamic acid decarboxylase (n = 102) were tested as previously described.11–14 Only 5 patients had combined testing of CSF and serum for autoantibodies (NMDAR only). VGKC-complex antibody positivity was based on titers >150 pM, as suggested in children.15 Dopamine D2 receptor antibody testing (n = 103) was undertaken as described.16

Etiologic Causation
The final etiologic diagnosis was determined by stringent application of the consensus guidelines proposed by Granerod et al.1 Cases were classified as confirmed, probable, or possible. Confirmed cases had detection of the organism or autoantibody in CSF or brain.1 A probable diagnosis was based on serological evidence of acute infection or autoantibody, and a possible diagnosis was based on detection of the organism from a specimen sample outside the CNS, such as stool or nasopharyngeal aspirate.1 As accepted in the literature, we used the term infection-associated encephalopathy rather than encephalitis to denote encephalitis related to influenza virus or rotavirus.17–19 In cases with multiple etiologies (Supplemental Table 4), the agent with the strongest hierarchical association (confirmed > probable > possible) was designated as the etiology of encephalitis.

Ethics
The study was ethically approved (09/CHW/56), and written consent was obtained from the families and patients for a follow-up telephone interview and testing of stored acute samples.

### Table 1 Hierarchical Classification for the Etiology of Encephalitis

<table>
<thead>
<tr>
<th>Etiology of Encephalitisa</th>
<th>Confirmed</th>
<th>Probable</th>
<th>Possible</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious (N = 49, 30%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterovirus</td>
<td>17</td>
<td></td>
<td>3</td>
<td>20 (12)</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>11</td>
<td></td>
<td>11</td>
<td>11 (7)</td>
</tr>
<tr>
<td>HSV</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>5</td>
<td></td>
<td>3</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other infections</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Infection-associated encephalopathy (N = 13, 8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza virus</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5 (3)</td>
</tr>
<tr>
<td>ANE</td>
<td>3</td>
<td></td>
<td></td>
<td>3 (2)</td>
</tr>
<tr>
<td>Immune-mediated or autoantibody-associated (N = 56, 34%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADEM</td>
<td>35</td>
<td></td>
<td></td>
<td>35 (21)</td>
</tr>
<tr>
<td>NMDAR antibody</td>
<td>5</td>
<td>5</td>
<td></td>
<td>10 (6)</td>
</tr>
<tr>
<td>VGKC-complex antibody</td>
<td>4</td>
<td>1</td>
<td></td>
<td>7 (4)</td>
</tr>
<tr>
<td>Dopamine D2 receptor antibody</td>
<td>4</td>
<td></td>
<td></td>
<td>4 (2)</td>
</tr>
<tr>
<td>Unknown (N = 46, 28%)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>29</td>
<td>25</td>
<td>118 (100)</td>
</tr>
</tbody>
</table>

ANE, acute necrotizing encephalopathy.

Table adapted from Granerod et al. (2010).1 Serological testing for ≥1 microorganisms was performed on 159 (85%) patients. Serological studies for microorganisms used complement fixation tests (CFTs) and IgM enzyme-linked immunosorbent assays. Only 14 patients had paired acute and convalescent serology, and no patients had a diagnosis of infectious encephalitis based on a fourfold change in titer. A single raised anti-streptolysin O (group A Streptococcus, n = 1) and a positive IgM and IgG (HSV [n = 3] and Epstein–Barr virus, parvovirus B19 [each, n = 1]) result were used to diagnose probable or possible infectious encephalitis. A positive IgM provided a probable infectious diagnosis for Mycoplasma pneumoniae (n = 11).

a Patients had ≥2 etiologic associations and are presented in Supplemental Table 4.

b HSV-1 (n = 4, CSF PCR confirmed); HSV-2 (n = 1, skin swab polymerase chain reaction positive); 1 patient with probable HSV (reisapaning) also had positive serum NMDAR and D2R antibodies.

c Group A Streptococcus (n = 1, probable); adenovirus (n = 1, probable), Epstein–Barr virus (n = 1, probable), parainfluenza 3 virus (n = 1, probable), parvovirus B19 (n = 1, probable), varicella zoster virus (n = 1, probable).

d Associated infections (probable/possible) in 2 of 3 patients.

f 5 of the 7 VGKC-positive patients had Mycoplasma pneumoniae IgM detected (see Supplemental Table 4).
Statistical Analysis

For comparison of clinical variables between the different major etiologic groups, we used SAS version 9.3 (SAS Institute, Inc, Cary, NC). Categorical variables were compared with the exact χ² test and described in terms of proportions and Wilson confidence intervals (CIs); continuous variables were compared with the Kruskal–Wallis test and described in terms of median and range (Supplemental Tables 5–8). We assessed the relationship of clinical variables to outcome by using univariate and multivariate logistic regression analyses. All variables with a univariate P < .05 were included as potential predictors in a multivariate model that used a stepwise backward selection procedure in SPSS (IBM SPSS Statistics, IBM Corporation). We described these associations by using odds ratios (ORs) and Wald CIs. We assessed the association between clinical variables to autoantibody status by using the χ² test and described it in terms of ORs and 95% CIs. We made no adjustment for multiple statistical testing.

RESULTS

All Encephalitis (n = 164)
Overview of Etiologies (Table 1)

A total of 164 children were diagnosed with acute encephalitis. An etiology was proposed in 118 (72%) patients, of whom 64 (39%) were confirmed, 29 (18%) probable, and 25 (15%) possible. In 46 (28%) patients, the cause was unknown. The etiologic groups were infectious encephalitis, n = 49 (30%); infection-associated encephalopathy, n = 13 (8%); and immune-mediated/autoantibody-associated encephalitis, n = 56 (34%). Complete autoantibody and some infectious serological findings are presented in Table 1. Potential dual or multiple etiology occurred in 11 (7%) patients (Supplemental Table 4), including 8 with Mycoplasma pneumoniae.

Demographics and Seasonality

The median age at presentation was 5.5 years (range 5 weeks–15.1 years), and 94 (57%) patients were male. Figure 1 demonstrates that young children are more frequently affected. The majority of encephalitis cases (n = 57, 35%) presented during the Australian winter season (June–August, data not shown).

Clinical Features, CSF, EEG, and MRI

Figure 2 and Supplemental Table 5 compare the clinical features, which in descending order of frequency were fever (n = 126, 77%), seizures (n = 88, 54%), headache (n = 71, 43%), weakness or pyramidal signs (n = 61, 37%), any respiratory symptoms (n = 57, 35%), and agitation (n = 56, 34%). CSF pleocytosis was present in 110 out of 155 (71%) patients and elevated CSF protein in 50 out of 154 (33%) patients. CSF neopterin was elevated in 36/47 (77%) tested patients. Oligoclonal bands were measured in 53 (32%), and intrathecal oligoclonal bands were detected in only 2 patients (1 with NMDAR encephalitis, 1 unknown) and mirrored oligoclonal bands in another 16 (5 infectious, 10 immune-mediated [ADEM 4, NMDAR 4, dopamine receptor D2 (D2R) 2], 1 unknown). Five patients with positive serum NMDAR antibody also had CSF testing and were confirmed CSF NMDAR antibody positive. CSF findings by subgroup are presented in Supplemental Table 6. The EEG was abnormal in 115 out of 130 (88%) patients; EEG slowing was found in 111 out of 130 (85%) and epileptiform discharges in 27 out of 130 (21%) patients, respectively. Figure 3 and Supplemental Table 7 describe the MRI features. The MRI brain (T2-weighted fluid-attenuated inversion recovery) was abnormal in 121 out of 149 (81%) of patients.

Duration of Stay, Therapy, and Outcome

The mean and median length of stay for patients were 27 and 13 days, respectively (range 1–618 days). Admission to the ICU was necessary in 66 (40%) patients, with the majority needing management of
FIGURE 2
Clinical features at any stage in all encephalitis and major etiologic subgroups \( (n \geq 7) \). Data including statistical significance is in Supplemental Table 5.
EV, enterovirus; GI, gastrointestinal; MycoP, *Mycoplasma pneumoniae*; Unk, unknown.
FIGURE 3
MRI features according to neuroanatomical location and sequence characteristics in all encephalitis and the major etiologic subgroups (n ≥ 7). Data including statistical significance are in Supplemental Table 7. EV, enterovirus; FLAIR, fluid-attenuated inversion recovery; MycoP, Mycoplasma pneumoniae; T1-W, T1-weighted; T2-W, T2-weighted; Unk, unknown.
encephalopathy, seizures, or both. Of the 164 patients, 147 (87%) received antibiotics or antiviral therapy. The mean and median duration of follow-up were 6.6 years and 5.8 years, respectively (range 1.1–14.4 years). There were 5 deaths (4 in the hospital).

Figure 4 compares the LOS measures. An abnormal outcome (LOS 1–4) was present in 71 out of 144 (49%) patients, including LOS 1 (death) (n = 5, 4%), LOS 2 (severe) (n = 11, 8%), LOS 3 (moderate) (n = 29, 20%), and LOS 4 (mild) (n = 26, 18%). The most common abnormal outcomes by category (Supplemental Table 8) were learning problems (n = 39, 28%), behavioral problems (n = 33, 24%), epilepsy (n = 25, 18%), and speech problems (n = 24, 17%). Clinical relapse occurred in 9 (5%) patients: HSV encephalitis (n = 1), ADEM (n = 1), NMDAR-Ab encephalitis (n = 3), D2R antibody encephalitis (n = 2), and unknown (n = 2). Patients with NMDAR and D2R antibodies were more likely to relapse (P = .01).

Using univariate analysis, we found that an abnormal long-term outcome was associated with status epilepticus (seizure >30 minutes) (OR 7.74; 95% CI, 2.51–23.89), ICU admission (OR 3.83; 95% CI, 1.91–7.72), diffusion restriction on MRI (OR 2.47; 95% CI, 1.03–5.98), and a movement disorder (OR 2.44; 95% CI, 1.10–5.39). Patients with an infectious prodrome were less likely to have an abnormal outcome (OR 0.28; 95% CI, 0.12–0.63). On multivariate analysis, status epilepticus (OR 3.78; 95% CI, 1.07–13.41, P = .04), diffusion restriction (OR 2.47; 95% CI, 0.95–6.46, P = .06), and ICU admission (OR 2.27; 95% CI, 0.92–5.59, P = .08) each predicted an abnormal outcome.

Subgroup Analysis

According to etiology, the following clinical characteristics were more common (Fig 2): Respiratory symptoms (Mycoplasma, VGKC-complex Ab), gastrointestinal symptoms (enterovirus), seizures (HSV, VGKC-complex Ab), weakness or pyramidal signs (ADEM), agitation and psychiatric symptoms (NMDAR), speech dysfunction (NMDAR), movement disorder (NMDAR), cerebellar (ADEM), sleep disturbance (NMDAR), brainstem (ADEM and enterovirus), and autonomic (NMDAR and enterovirus).

According to etiology, the following MRI features were more common (Fig 3): abnormalities of white matter (HSV, ADEM), cortical gray matter (HSV), basal ganglia (Mycoplasma and ADEM), thalamus (ADEM, HSV), cerebellum and brainstem (ADEM), and limbic encephalitis (NMDAR, VGKC-complex, Mycoplasma). The MRI was least likely to be abnormal (any T2-weighted fluid-attenuated inversion recovery abnormality) in NMDAR encephalitis. Abnormalities detected with diffusion-weighted sequencing, T1 sequences, contrast enhancement, hemorrhage, and cystic necrosis were all more common in HSV (Fig 3 and Supplemental Table 7). HSV and unknown encephalitis had the worst outcomes, and ADEM had the best outcome (Fig 4).

Of the smaller subgroups (Table 1), all 4 patients with D2R antibody–associated encephalitis had dystonia–Parkinsonism, and 3 out of 4 had localized basal ganglia involvement on MRI (basal ganglia encephalitis).16 Three patients had acute necrotizing encephalopathy with the typical radiologic features.18,20 There were no other
characteristic clinicoradiologic features in the other small subgroups.

**Clinicoradiologic Correlation With Autoantibody Positivity**

Using univariate analysis in patients with non-ADEM encephalitis tested for autoantibody (n = 103), we found that an autoantibody-associated encephalitis was more likely (in descending order) with clinical relapse (OR 13.5; 95% CI, 2.46–74.04, P < .0001), movement disorder (OR 11.2; 95% CI, 3.82–32.9, P < .0001), CSF intrathecal or mirrored oligoclonal bands (OR 7.89; 95% CI, 1.53–40.5, P = .02), speech dysfunction (OR 5.92; 95% CI, 2.03–17.2, P < .0001), psychiatric symptoms (OR 4.79; 95% CI, 1.73–13.2, P = .002), agitation (OR 3.64; 95% CI, 1.34–9.94, P = .009), and MRI limbic encephalitis phenotype (OR 5.22; 95% CI, 1.27–21.5, P = .03). Antibody-associated encephalitis was less common with headache (OR 0.35; 95% CI, 0.12–0.98, P = .04) or MRI thalamic involvement (OR 0.21; 95% CI, 0.05–0.98, P = .03).

**Immunotherapy and Outcome**

A total of 60 out of 164 patients (37%) received immunotherapy (corticosteroids, n = 59; intravenous immunoglobulin, n = 16; rituximab, n = 2), most commonly for ADEM (27 out of 35), NMDAR-Ab encephalitis (6 out of 10), enterovirus (6 out of 20), and unknown (9 out of 46) subgroups. Abnormal outcome was not different in the patients who received immunotherapy compared with those who did not (OR 1.17; 95% CI, 0.60–2.31, P = .64). The mean length of stay was longer in patients who received immune therapy (41 days vs 19 days, P = .02).

**DISCUSSION**

This single-center cohort, followed up for a median of 5.8 years, is the most comprehensive retrospective analysis of pediatric encephalitis to date. In a resource-rich setting, we have defined the relative frequency of acute encephalitis syndromes by etiology, with emphasis on the emerging treatable autoantibody-associated encephalitides. Despite long follow-up, the study confirms the high morbidity in survivors of encephalitis, the significant proportion who lack a diagnosis, the need to identify the autoantibody-associated syndromes, and the need to improve the acute management and rehabilitation of these patients with the hope of reducing long-term residual neurocognitive impairments. Immune-mediated/autoantibody-associated encephalitides were the most common etiologic group. Although by definition ADEM is an encephalomyelitis, it is notable that many previous encephalitis cohorts do not include ADEM but generally focus on infectious encephalitis alone.6–8,21 NMDAR-Ab encephalitis was diagnosed in 6% of patients, who had typical clinical features of the disease, with dominant movement, psychic, sleep, speech, and autonomic features. The number could be an underestimate, because serum testing was performed on only 103 out of 129 (81%) of the patients without ADEM. Indeed, 4 of the 46 patients with unknown encephalitis had a phenotype reminiscent of NMDAR-Ab encephalitis but were negative for serum antibody. CSF might have been helpful,14,22 although that is not our experience. VGKC-complex antibodies were first reported in adults with limbic encephalitis.11 Subsequently, it was found that the VGKC-complex antibodies bound not to the VGKC subunits themselves but to proteins, namely LGI1 and CASPR2,12,23 which are complexed with the VGKC subunits in vivo. In this report, 7 (4%) of children had VGKC-complex antibodies, but only 2 had evidence of limbic encephalitis on imaging, and they were not positive for LGI1 or CASPR2 antibodies, as is often true for pediatric cases with positive VGKC-complex Ab.12,23–25 Although 150 pM has been proposed as a positive result for VGKC-complex Ab in children, levels >400 pM are more relevant in adults,15,26 and only 2 children had these levels. Nevertheless, VGKC-complex antibodies appear to be associated with inflammatory disorders (Hacohen et al in preparation). The association seen here of positive VGKC-complex Ab with *Mycoplasma pneumoniae* and with respiratory symptoms (5 out of 7) suggests that VGKC-complex Ab could be induced as part of the immune response to *Mycoplasma pneumoniae*. *Mycoplasma pneumoniae*-associated encephalitis occurred in 7% of our cohort, although the diagnostic specificity of mycoplasma IgM has been questioned.27 Antibodies to D2R were found in only 4 patients with dystonia–Parkinsonism and basal ganglia lesions, representing a small subgroup (2%).16 There were no patients with antibodies to glutamic acid decarboxylase and only 1 patient with glycine R antibody (who also had VGKC-complex antibodies and *Mycoplasma*), and reported pediatric cases with these antibodies are rare. Nine (20%) of the patients with unknown encephalitis did not have serum available for autoantibody testing, and comprehensive testing may help to ensure recognition of known autoantibodies and to define some of the “unknown” patients in the future. For example, γ-aminobutyric acid A receptor antibodies have recently been found in patients with acute-onset severe epilepsy and encephalitis,28 and it will be interesting to test pediatric patients with encephalitis for this autoantibody.

Infectious encephalitis was found in 30%, and the most common infection was enterovirus (12%). Even with broad testing for HSV (84% of patients), HSV encephalitis was
diagnosed in only 5%, confirming recent reports that HSV encephalitis is less common in children than adults with encephalitis.\textsuperscript{4,29,30} Despite early acyclovir therapy (not described), the outcomes after HSV encephalitis were poor, as described in recent pediatric cohorts.\textsuperscript{30,31} Interestingly, 1 patient with HSV encephalitis relapsed with chorea and had NMDAR and D2R antibodies.\textsuperscript{32} The emerging theme of postviral autoimmunity is increasingly recognized, and it emphasizes the importance of considering immunotherapies in post-HSV relapses.\textsuperscript{32–34} There were some patients with \( \geq 2 \) etiologic associations (Supplemental Table 4), and these patients provide a challenge for diagnosis and illustrate the overlap between infectious and autoantibody-associated syndromes.\textsuperscript{32,35–38}

There were notable etiologic absences in this cohort, such as no \textit{Mycobacterium tuberculosis} encephalitis. Unlike in the United Kingdom,\textsuperscript{5} \textit{Mycobacterium tuberculosis} is rare in Australian children. We also did not observe any confirmed varicella encephalitis, a result probably related partly to the introduction of routine varicella vaccination during the study period. As is true for most resource-rich countries, we no longer observe measles or mumps encephalitis because of vaccination. Other etiologies not seen in our cohort include arboviruses and \textit{Bartonella}.

There were small subgroups of infection-associated encephalopathy (8%) associated with influenza and rotavirus, and these were kept as a separate group, by convention.\textsuperscript{18,39} Acute necrotizing encephalopathy, which is an infection-associated encephalopathy, is observed more frequently in Japanese and East Asian children, presumably because of their differing genetic vulnerability.\textsuperscript{18}

The main limitation of the study was the retrospective design and therefore incomplete investigation and the potential incomplete ascertainment of milder or atypical cases. Despite these limitations, the study confirms that encephalitis is a serious disease with an abnormal outcome in \( \sim 50\% \), particularly in cognitive and behavioral domains, with 3\% mortality. In general, the predictors of poor outcomes were ICU admission and status epilepticus, as in previous studies.\textsuperscript{40–42} In addition, we found diffusion restriction on MRI, a marker of cytotoxic injury, correlated with abnormal outcomes. The use of immunotherapy was not associated with better outcomes, but the patients receiving immune therapy had longer admissions, suggesting that these patients had a more complicated course. Immunotherapy has only recently become established in the treatment of autoantibody-associated encephalitis (other than ADEM).\textsuperscript{3} and prospective studies are needed to determine the benefit of immunotherapy in patients with encephalitis irrespective of whether an autoantibody is detected. The percentage of unknown encephalitis (28\%) in this study is the lowest among substantial pediatric cohorts,\textsuperscript{6–8,40,41} but it represents an important subgroup that is comparable in size to the prospective UK cohort in adults and children.\textsuperscript{5}

There were no distinguishing clinical or radiologic characteristics of the unknown subgroup, mainly because of the likely heterogenous etiologies. The unknown encephalitis group may contain both encephalitis of viral origin (untested or unknown) and autoimmune etiologies. The poor outcome in this group emphasizes the importance of future research in this area.

\textbf{ACKNOWLEDGMENTS}

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\textsuperscript{3} was involved in clinical data acquisition and analysis; Dr Davies was involved in study design and edited drafts; Dr Prelog performed radiological phenotyping and edited drafts; Drs Tantsis, Gill, Webster, Menzies, Ardem-Holmes, Gupta, Procopis, Troedson, Antony, Ouvrier, and Polfrit were involved in clinical data acquisition and analysis and edited drafts; Dr Barnes performed statistical analysis and edited drafts; Dr Vincent supervised autoantibody testing and edited first and subsequent drafts; Dr Dale conceived and designed the study, supervised all clinical aspects of the study, performed radiological phenotyping, wrote the first draft, and edited subsequent drafts; and all authors approved the final manuscript as submitted.

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REFERENCES


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