BRIEF COMMUNICATION

Postencephalitic epilepsy and drug-resistant epilepsy after infectious and antibody-associated encephalitis in childhood: Clinical and etiologic risk factors

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Summary

To define the risk factors for postencephalitic epilepsy (PE) and drug-resistant epilepsy (DRE) in childhood following infectious and autoimmune encephalitis, we included 147 acute encephalitis patients with a median follow-up of 7.3 years (range 2–15.8 years). PE was defined as the use of antiepileptic drugs (AEDs) for ≥24 months, and DRE was defined as the persistence of seizures despite ≥2 appropriate AEDs at final follow-up. PE and DRE were diagnosed in 31 (21%) and 15 (10%) of patients, respectively. The features during acute encephalitis predictive of DRE (presented as odds ratio [OR] with confidence intervals [CIs]) were status epilepticus (OR 10.8, CI 3.4–34.3), visual disturbance (6.4, 1.4–29.9), focal seizures (6.2, 1.9–20.6), magnetic resonance imaging (MRI) hippocampal/amygdala involvement (5.0, 1.7–15.4), intensive care admission (4.7, 1.4–15.4), use of >3 AEDs (4.5, 1.2–16.1), MRI gadolinium enhancement (4.1, 1.2–14.2), any seizure (3.9, 1.1–14.4), and electroencephalography (EEG) epileptiform discharges (3.9, 1.3–12.0). On multivariable regression analysis, only status epilepticus remained predictive of DRE in all models. DRE was common in herpes simplex virus (3/9, 33%) and unknown (8/40, 20%) encephalitis, but absent in acute disseminated encephalomyelitis (ADEM) (0/32, 0%), enterovirus (0/18), and anti-*N*-methyl-D-aspartate receptor–NMDAR encephalitis (0/9). We have identified risk factors for DRE and demonstrated "high-risk," and "low-risk" etiologies.

KEY WORDS: **Encephalitis, Infection, Autoimmune, Epilepsy, Outcome.**

Postencephalitic epilepsy (PE) following acute childhood encephalitis has been reported in 6.1–16.4% of cohorts with variable definitions of encephalitis, PE, and length of follow-up.[1–5] Previous studies in childhood cohorts have reported the following features during acute encephalitis as risk factors for PE and intractable epilepsy: acute seizures (focal, generalized), status epilepticus, severe encephalopathy, medically induced coma, focal neurologic deficits, number of antiepileptic drugs (AEDs), prolonged hospitalization, abnormal electroencephalography (EEG; slowing, multifocal, or focal spikes), magnetic resonance imaging (MRI) involvement of cortical and subcortical areas, and infectious etiology (herpes simplex virus [HSV], *Mycoplasma pneumoniae*).[1,2,4–7] However, these studies were performed mostly in East Asia, were focused mainly on

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infectious encephalitis, excluded acute disseminated encephalomyelitis (ADEM), and did not include auto-antibody–associated syndromes such as *N*-methyl-D-aspartate receptor (NMDAR) encephalitis.[8] A recent adult study that included antibody-associated encephalitis, identified acute seizures and T2 MRI abnormalities as risk factors for PE, but did not determine the risk of PE according to etiology.[9] Using a large cohort of pediatric patients with encephalitis with both infectious and immune-mediated causes with long follow-up, we identify clinical and etiologic predictors of postencephalitic epilepsy.

Methods

Cohort and data collection

This study performed further data collection, and extended follow-up of a recently published single center, retrospective cohort of 164 children with acute encephalitis, and found the larger causes of encephalitis (in descending order) to be: ADEM (n = 35, 21%), enterovirus (n = 20, 12%), *M. pneumoniae* (n = 11, 7%), NMDAR antibody (n = 10, 6%), and HSV (n = 9, 5%). There were 46 patients (28%) without an identified etiology (unknown).[10] Serum auto-antibody testing for NMDAR, voltage gated potassium channel (VGKC) complex, leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-like 2 (Caspr2), glycine receptor, dopamine-2 receptor, and glutamic acid decarboxylase (GAD) was performed in 103 (80%) of 129 non-ADEM patients. In this present study, in order to focus on the epilepsy outcomes, we extended the minimum length of follow-up to ≥24 months, and the median final follow-up to 7.3 years (range 2–15.8 years). Seizure and epilepsy outcome data with a minimum follow-up of 24 months after acute encephalitis were available in 147 (90%) of 164 patients. Follow-up was unavailable in 17 patients for the following reasons: death (n = 4), lost to follow-up (n = 7), and follow-up <24 months (n = 6). Information regarding the presence of seizures, seizure type, and use of AEDs was obtained from either the last hospital medical record (outpatient, inpatient, or emergency attendance) and/or by telephone interview.

Definition of postencephalitic epilepsy and drug-resistant epilepsy

There is currently no consensus definition for postencephalitic epilepsy (PE), with most studies applying the use of ongoing AEDs as their definition of PE, with variable time thresholds.[1,5,6,9] Because seizures can resolve in the first few months after encephalitis, we used 24 months as our minimum "time threshold.." Thus our operational definition of PE was the need for continued and ongoing use of AEDs ≥24 months after acute encephalitis (including the continued and ongoing use of AED introduced after 24 months). In addition, we defined drug-resistant epilepsy (DRE) as persistence of seizures at final follow-up despite ≥2 appropriate AEDs, as defined previously.[11] As the definition of PE is subjective, as the cessation of AEDs is dependent on many factors (clinician, patients/family concerns, EEG findings), we chose DRE as our primary outcome because the definition of DRE is more widely accepted.

There were two patients who later developed features of genetic generalized epilepsy, who were reviewed by a pediatric epileptologist (DG) and excluded from a diagnosis of PE. One 3-year-old girl with confirmed relapsing NMDAR encephalitis was also excluded because the focal seizures were part of a clinical relapse 4 years after the first episode, and required only short-term AED treatment.[12] This patient remains seizure free 3.5 years after the relapse.

Statistical analysis

Statistical analysis was performed using SAS version 9.3. The association between clinical variables and the outcomes of PE and DRE were assessed using binary logistic regression. All predictors were tested in univariate models and associations described as the odds ratio (OR) for developing the outcome in patients with each predictor relative to those without the predictor, with 95% confidence interval (CI) and p-value. A multivariate model for PE and DRE used all characteristics with a p-value of <0.05 in univariate models as candidate predictors, and then backward selection was used to remove predictors with p-values of >0.05. The area under the receiver operating characteristic (ROC) curve was calculated for the final model. There was no adjustment made for multiple statistical testing.

Results

Seizures during acute encephalitis

Eighty-eight (54%) of 164 patients had seizures during the acute encephalitis illness, and 75 (85%) of these patients received AEDs during hospitalization. Status epilepticus occurred in 28 (17%) of the total cohort, and admission to the intensive care unit (ICU) in 66 (40%). EEG epileptiform discharges with/without slowing were present in 27 (21%) of 130 patients who had an acute EEG.

Postencephalitic epilepsy and drug-resistant epilepsy

At ≥24 month follow-up, 31 patients (21%) fulfilled criteria for PE. By final follow-up (median 7.3 years, range 2–15.8 years), 22 (15%) of 147 patients required ongoing AED use. Two (6%) of the PE patients died (4 and 2.3 years, respectively), one of recurrent refractory status epilepticus, and the other of possible sudden unexplained death in epilepsy (SUDEP).

DRE was diagnosed in 15 (10%) of 147 patients after a median follow-up of 7.3 years (range 2–15.8 years). Of the 15 patients with DRE, 7 patients had daily or weekly seizures, or required epilepsy surgery (Table S1). The median age at encephalitis presentation for the 15 DRE patients (7 male) was 4.2 years (range 0.2–15.1 years). In 12 of these

15 patients (80%) with DRE, the seizures began during the initial episode of encephalitis. However, in three DRE patients, the epilepsy developed 3–6 years after encephalitis; two of these patients had mesial temporal sclerosis (MTS). Epilepsy surgery was performed in two DRE patients: a patient with unknown encephalitis had MTS and required right temporal lobectomy (Engel class Ia, 12 months follow-up postsurgery), and a patient with HSV encephalitis had a right frontal lobectomy (Engel class 1b, 22 months). Patients with DRE had longer acute hospitalization (median 27 days, range 9–618 days), compared to those without DRE (median 12 days, range 3–234 days; p = 0.03). Information regarding seizure type, ongoing seizure frequency, AEDs, and duration of follow-up for the PE and DRE patients is presented in Table S1.

Risk factors for PE and DRE

The clinical and radiologic predictors for PE closely resembled that for DRE and are presented in full in Tables S2 and S3. Table 1 presents the nine clinical and radiologic features during the acute encephalitis that were predictive of DRE (p < 0.05), which are presented as ORs in descending order: status epilepticus, visual disturbance, focal seizures, MRI evidence of hippocampal/amygdala T2/T2 fluid-attenuated inversion recovery (FLAIR) abnormalities, intensive care unit (ICU) admission, use of more than three AEDs in acute encephalitis, MRI evidence of gadolinium enhancement, any seizure, and EEG epileptiform discharges. Due to small event numbers it was difficult to draw firm conclusions from multivariate models; however, status epilepticus was an independent predictor of DRE after backward selection in all models. Other predictors that remained in some models were focal seizures, MRI hippocampal/amygdala involvement, and MRI gadolinium enhancement. In a model derived by manual backward selection starting with predictors whose p-values were <0.05 in univariate models, the final predictors were status epilepticus (OR 6.0, 95% confidence interval [CI] 1.5–24; p = 0.011), focal seizures (OR 5.9, 95% CI 1.4–25; p = 0.016), and MRI gadolinium enhancement (OR 7.9, 95% CI 1.7–37; p = 0.009). This model had area under the ROC curve of 0.84 (95% CI 0.72–0.96).

PE and DRE according to etiology

PE and DRE outcomes according to etiology are presented in Figure 1. DRE was most common in patients with HSV (3/9, 33%) and unknown (8/40, 20%) encephalitis, but uncommon in *M. pneumoniae* (1/9, 11%), ADEM (0/32), anti-NMDAR (0/9), and enterovirus (0/18) encephalitis.

Discussion

This is the first childhood study of PE and DRE with a minimum follow-up of 24 months, and included 92% of the survivors from an original cohort of 164 patients diagnosed with acute encephalitis.[10] It is notable that this is also the first pediatric PE and DRE cohort to include immune and auto-antibody–associated etiologies, which have generally not been included in previous studies.

Despite seizures/epilepsy being commonly reported (6–11%) following acute childhood encephalitis, there remains no consensus definition for PE.[2–4] Most recent studies applied duration of AED usage, although different time thresholds were used including >6 months, >12 months, and ≥3 years.[5,6,9] Because most patients with acute symptomatic seizures are treated with AEDs for 3–6 months and weaned by 12 months, we chose a time threshold of AED use of 24 months.[11]

However, given the lack of consensus on PE definitions, and the subjective nature of AED cessation, we chose DRE as our primary outcome, as the definition of DRE is more accepted. At final follow-up (median 7.3 years), 15% of the patients required ongoing AED use, and 10% had DRE.

We identified status epilepticus, focal seizures, and EEG epileptiform discharges during the acute encephalitis episode as risk factors for DRE, which are similar to previous

Table 1. Features during acute encephalitis predictive of drug-resistant epilepsy (DRE) at final follow-up using univariate analysis: categorical predictors with p < 0.05 (all variables in Table S3)

	n (%) developing DRE			
Predictor	Without predictor	With predictor	Odds ratio (95% CI)	p-Value
Seizures	3/68 (4)	12/79 (15)	3.9 (1.1–14.4)	0.043
Focal seizures	4/94 (4)	11/51 (22)	6.2 (1.9–20.6)	0.0030
Status epilepticus	6/121 (5)	9/25 (36)	10.8 (3.4–34.3)	<0.0001
Visual disturbance	12/139 (9)	3/8 (38)	6.4 (1.4–29.9)	0.019
ICU admission	4/87 (5)	11/60 (18)	4.7 (1.4–15.4)	0.012
No. AED >3	7/59 (12)	6/16 (38)	4.5 (1.2–16.1)	0.022
EEG epileptiform discharges	8/92 (9)	7/26 (27)	3.9 (1.3–12.0)	0.019
MRI hippocampus/amygdala involvement	7/104 (7)	8/30 (27)	5.0 (1.7–15.4)	0.0045
MRI gadolinium enhancement	10/100 (10)	5/16 (31)	4.1 (1.2–14.2)	0.026

AED, antiepileptic drug; FLAIR, fluid-attenuated inversion recovery; ICU, intensive care unit; IVIg, intravenous immunoglobulin; T1-W, T1-weighted; T2-W, T2-weighted; WBC, white blood cell.

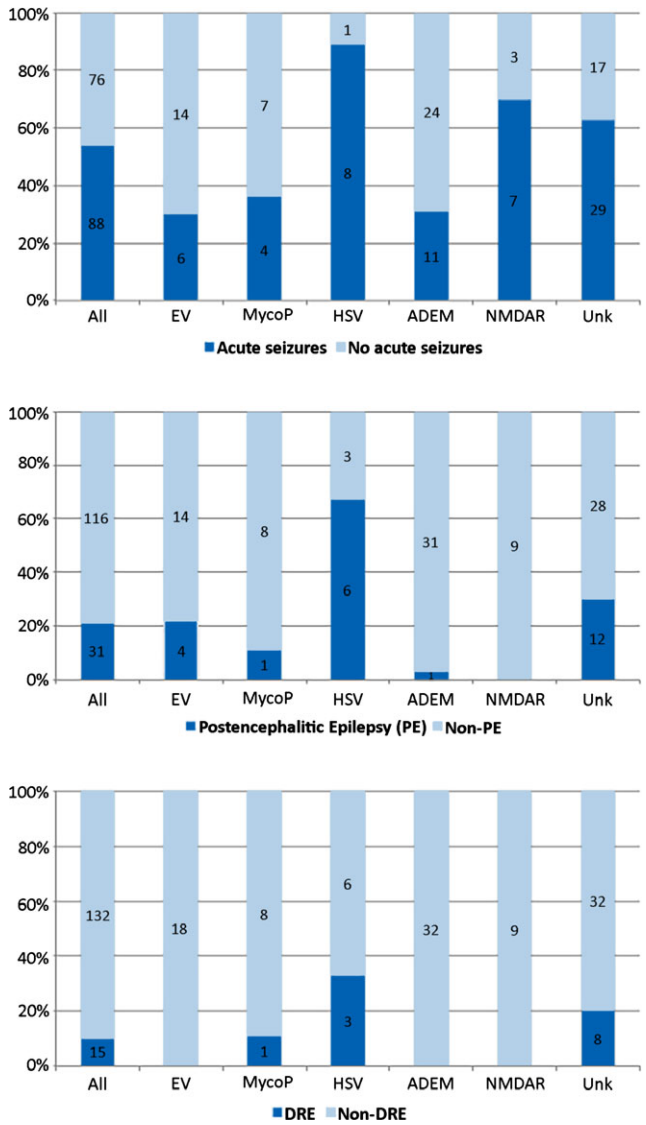

Figure 1.

Percentage of patients with acute seizures (upper graph), with postencephalitic epilepsy (PE) (middle graph), and drug-resistant epilepsy (DRE) (lower graph) is presented, comparing total cohort (All) with the larger ($n \geq 9$) etiologic subgroups. ADEM, acute disseminated encephalomyelitis; EV, enterovirus; HSV, herpes simplex virus; MycoP, *Mycoplasma pneumoniae*; NMDAR, *N*-methyl D-aspartate receptor; Unk, unknown. (The numbers on the bar charts represent the actual number of patients.)

studies of PE in children.[1,2,6,7] Similarly to Rismanchi et al.,[7] we identified additional risk factors for DRE as admission to ICU and use of >3 AEDs in hospital. The MRI risk factors for DRE were T2/T2 FLAIR hyperintensity involving the hippocampus/amygdala, which may be a manifestation of status epilepticus, or represent limbic encephalitis, a recognized precedent of temporal lobe epilepsy and mesial temporal sclerosis in adulthood.[13] The other MRI feature of DRE was gadolinium enhancement, which is a typical neuroimaging feature of HSV encephalitis.

The risk of DRE varied according to etiology, with HSV and unknown encephalitis being "high risk," whereas enterovirus, ADEM, and NMDAR encephalitis were low risk in this cohort. Surprisingly, DRE was also rare in *M. pneumoniae* encephalitis, unlike in a previous report.[6]

The limitations of this study include the retrospective diagnosis of encephalitis and limited detail on the EEG phenotype for PE and DRE. Antibody testing was unavailable for the newer antibodies such as to γ-aminobutyric acid $(GABA)_A$ receptor, which have been reported in patients with encephalitis and refractory seizures and status epilepticus, some of whom were children, and these or other "untested" antibodies could have explained some of the "unknowns."[14,15] Identifying these autoimmune subgroups in the future will be important, as early targeted treatment can improve outcomes. Our study advances the understanding of risk factors for PE and DRE that will help in prognostic advice and careful surveillance of high-risk patients.

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Disclosure

No authors describe a conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author Contributions

Sekhar C Pillai: acquisition of all original clinical and radiologic data, implementation of definitions, and drafting and revising manuscript. Shekeeb S Mohammad: support in acquisition of epilepsy definitions and investigations; drafting and revising of manuscript. Yael Hacohen: technical work (auto-antibody assays) and drafting and revising of manuscript. Esther Tantsis: acquisition of some clinical data and patient follow-up, and revising of manuscript. Kristina Prelog: blinded review of all radiologic data, and revising of manuscript. Elizabeth Barnes: all statistical support and analysis, and revising of manuscript. Deepak Gill: epilepsy definitions and advice with epilepsy diagnosis. Ming J Lim: technical work (antibody), and drafting and revising manuscript. Fabienne Brilot: technical work (antibody), and drafting and revising manuscript. Angela Vincent: technical work (antibody), and drafting and revising manuscript. Russell C Dale: conception of study, supervision and implementation of study, and drafting and revising of manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Seizure type, frequency, and antiepileptic drug (AED) use in patients with drug-resistant epilepsy (DRE) and patients with postencephalitic epilepsy (PE) not fulfilling DRE criteria at final follow-up.

Table S2. Features during acute encephalitis predictive of postencephalitic epilepsy (PE) at ≥24 months using univariate analysis: categorical predictors.

Table S3. Features during acute encephalitis predictive of drug-resistant epilepsy (DRE) at final follow-up using univariate analysis: categorical predictors.