Infectious and Autoimmune Causes of Encephalitis in Children

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BACKGROUND AND OBJECTIVES: Encephalitis can result in neurologic morbidity and mortality in children. Newly recognized infectious and noninfectious causes of encephalitis have become increasingly important over the past decade.

METHODS: We retrospectively reviewed medical records from pediatric patients in Houston diagnosed with encephalitis in both an urban and rural catchment area between 2010 and 2017. We conducted an investigation to understand the etiology, clinical characteristics, and diagnostic testing practices in this population.

RESULTS: We evaluated 231 patients who met the case definition of encephalitis, among which 42% had no recognized etiology. Among those with an identified etiology, the most common were infectious (73; 31%), including viral (n = 51; 22%), with the most frequent being West Nile virus (WNV; n = 12), and bacterial (n = 19; 8%), with the most frequent being Bartonella henselae (n = 7). Among cases of autoimmune encephalitis (n = 60; 26%), the most frequent cause was anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis (n = 31). Autoimmune causes were seen more commonly in female (P, .01) patients. Testing for herpes simplex virus and enterovirus was nearly universal; testing for anti-NMDAR encephalitis, WNV, and Bartonella was less common.

CONCLUSIONS: WNV was the most common infectious cause of encephalitis in our pediatric population despite lower testing frequency for WNV than herpes simplex virus or enterovirus. Increasing testing for anti-NMDAR encephalitis resulted in frequent identification of cases. Increased awareness and testing for WNV and Bartonella would likely result in more identified causes of pediatric encephalitis. Earlier etiologic diagnosis of encephalitis may lead to improve clinical outcomes.

WHAT’S KNOWN ON THIS SUBJECT: Pediatric encephalitides are often severe and lack an identified etiology. Newly recognized viruses and autoimmune causes are considered to be important, but no large recent studies have been conducted to assess their exact role in children.

WHAT THIS STUDY ADDS: We found more encephalitides caused by West Nile virus, Bartonella, and autoimmune disease, despite these conditions being tested for less frequently. Testing for these conditions will improve our understanding of etiology and pathogenesis and may improve patient outcomes.

There are >100 different etiologies that can lead to encephalitis in children; however, most researchers have found that the majority (50%–70%) of patients lack an identified etiology. Encephalitis in the pediatric population may result in substantial morbidity, disability, and even mortality. Because a high proportion of encephalitis patients have an infectious etiology, and these agents differ with respect to geography and ecology, etiologies of encephalitis may have regional variability. Additionally, a number of newly discovered causes of encephalitis, predominantly autoimmune, have been recognized in the past 2 decades, leading to the need for contemporary pediatric prevalence studies. Inflammatory and autoimmune causes of encephalitis may be treatable if identified early in a patient’s course of illness. To understand the prevalence of infectious and noninfectious etiologies of childhood encephalitis, we conducted an analysis of all pediatric cases at a large pediatric hospital system in Houston, Texas.

**METHODS**

**Study Population**

We conducted a retrospective chart review of all patients with an International Classification of Diseases, Ninth Revision (ICD-9) or International Classification of Diseases, 10th Revision (ICD-10) code associated with encephalitis or meningoencephalitis admitted to Texas Children’s Hospital (TCH) from January 1, 2010, to December 31, 2017 (Supplemental Information). The geographic catchment area for TCH is extensive and includes both rural and urban settings. Patients were reviewed and classified as encephalitis if they met the 2013 definition of the International Encephalitis Consortium. To meet the definition for encephalitis, patients needed to have documented altered mental status lasting at least 24 hours with no other explainable cause. Additionally, to be defined as encephalitis, a patient required at least 2 of the following: (1) fever ≥38°C within 3 days of presentation, (2) new onset seizures, (3) new onset of focal neurologic findings, (4) cerebrospinal fluid (CSF) white blood cell count ≥5/mm³, (5) new onset neuroimaging abnormality consistent with encephalitis, or (6) EEG abnormality not associated with another cause. If patients did not have an identified infectious etiology, then their charts were screened and reviewed by 2 of the authors (T.A.E., E.M.) using the recently developed criteria for autoimmune encephalitis. To meet the criteria for autoimmune encephalitis, patients required evidence of altered mental status or neuropsychiatric deficits and at least 1 objective central nervous system abnormality: focal neurologic abnormality, new onset seizures, CSF pleocytosis, or neuroimaging finding suggestive of encephalitis.

Patients were excluded if they were <90 days old at time of admission or if they were >18 years of age. Only incident patients were included. We retained patients who were first seen at an outside hospital and then transferred to TCH if they had medical records from the initial hospitalization. Patients who were transferred to our hospital and had missing information regarding diagnostic testing or length of stay from the outside hospital were excluded from this study (Fig 1).

**Data Collection**

We acquired data on demographic factors, immune compromise, tests ordered and conducted to determine the cause of encephalitis, and CSF laboratory values. We created a variable for admission season (summer defined as the 6 months with highest temperature in Houston, May 1 to October 31). All patients were classified as infectious or noninfectious and further clarified as autoimmune and immune mediated, infectious including viral, bacterial, other (eg, parasitic or fungal), or unknown. Viral diseases were identified by CSF polymerase chain reaction (PCR) or serology (immunoglobulin G [IgG] and immunoglobulin M [IgM]) identification as relevant; cases were also identified by blood sample PCR or serology in the presence of encephalitis if no CSF result was available. Arboviral diseases were diagnosed via a panel of testing that included IgM for West Nile virus (WNV), St Louis encephalitis virus, California encephalitis virus, eastern equine encephalitis virus (EEEV), and western equine encephalitis virus (WEEV). Patients with encephalitis associated with respiratory viruses (influenza A and B, parainfluenza 1–3, human metapneumovirus, adenovirus, and respiratory syncytial virus) were identified through nasal wash PCR detection of a viral agent during the hospitalization for encephalitis. Bacterial causes of disease were identified either through culture or via relevant serological testing for Bartonella, Ehrlichia, and Rickettsia. Patients were considered positive for an autoimmune condition if the CSF antibody test was present in an abnormal range in the absence of any other identified cause of encephalitis. Hashimoto’s encephalopathy and patients with acute disseminated encephalomyelitis (ADEM) were included if they met previously published guidelines and reviewed by coauthors (T.A.E. and T.L.). ADEM was classified as autoimmune or immune mediated on the basis of recent literature implicating multiple white matter disease autoantibodies in this disease process. Time to diagnosis was calculated by subtracting the first date of admission, at TCH or at an outside facility, from the date positive results were obtained that were used to classify the etiologic cause of disease.

**Statistical Methodology**

We conducted comparisons of categorical variables with \( \chi^2 \) testing with statistical significance set at the 0.05 level. For cells with <5
observations, we used Fisher exact test. All statistics were calculated by using Stata 14.0 (Stata Corp, College Station, TX). This study was reviewed and approved by Baylor College of Medicine Institutional Review Board H-35069.

**RESULTS**

Through ICD-9 and ICD-10 coding-based searches of the hospital database, we identified 409 patients who were >90 days of age and had a discharge diagnosis of encephalitis. After applying the International Encephalitis Consortium case definition, 231 patients with encephalitis were retained (Fig 1). Half of the patients (133; 58%) had 1 of 29 identified etiologies of encephalitis, and 42% had no identified cause. The most common identified etiologies were infectious (73 out of 133; 55%) versus noninfectious or autoimmune (n = 60 out of 133; 45%) (Table 1).

Among the infectious causes of encephalitis, viral causes were most incident (n = 51 out of 73; 70%), with almost one-fifth (n = 13 out of 73; 18%) diagnosed with arboviral encephalitis, including 12 confirmed cases of WNV and 1 case of California encephalitis virus. Although we did not confirm or include them in our case numbers, we also identified IgG-positive probable cases of WNV (n = 8) and St Louis encephalitis virus (n = 1). Three patients had positive IgM for EEEV with low-level antibody detection. Two of these patients were subsequently tested by plaque reduction neutralization using convalescent sera; both were negative.

With regard to other viral causes, human herpesvirus (HHV) was also frequently identified, with herpes simplex virus 1 (HSV-1) (n = 10), human herpesvirus 6 (HHV-6) (n = 4), Varicella Zoster virus (n = 3), Epstein-Barr virus (n = 2), and herpes simplex virus 2 (HSV-2) (n = 1) infections diagnosed. Seven encephalitis cases were diagnosed with enterovirus. Respiratory viruses isolated from nasal wash in patients with encephalitis were also found, including influenza (n = 6), parainfluenza (n = 2), and adenovirus (n = 2). One case was diagnosed with lymphocytic choriomeningitis virus (LCMV) (n = 1).

Bacterial encephalitis was present at a lower rate than other causes; however, it was still responsible for 19 of 133 (14%) patients identified in our study. The leading identified cause of bacterial encephalitis was *Bartonella henselae* (n = 7). Patients with antibodies to *Rickettsia rickettsii* (n = 2) were also present in this group. *Streptococcus pneumoniae* (n = 5), *Neisseria meningitidis* (n = 1), *Serratia marcescens* (n = 1), *Bacillus cereus* (n = 1), *Staphylococcus aureus* (n = 1), and *Haemophilus influenzae* (n = 1) were all grown in culture from the CSF of patients with meningoencephalitis who met the clinical definition for this study (Table 2).

In addition to viral and bacterial causes of encephalitis, we also identified fungal etiologies associated with *Cryptococcus neoformans* (n = 1) and *Candida lusitaniae* (n = 1), and 1 patient diagnosed with primary amebic meningoencephalitis, the...
result of infection with the parasite *Naegleria fowleri*.

Autoimmune and immune-mediated causes of encephalitis represented 45% (*n = 60 out of 133*) of all patients with an identified etiology (Table 2). Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was the most frequently identified single cause of encephalitis (*n = 31 out of 60; 52%). Another condition broadly classified as autoimmune, ADEM, was the second most common identified cause of encephalitis in this population (*n = 18 out of 60; 30%); Hashimoto’s encephalitis (*n = 6*) was the seventh most common cause of encephalitis. We also identified instances of autoimmune encephalitis related to anti-voltage-gated potassium channel (anti-VGKC), anti-glutamic acid decarboxylase (anti-GAD), and anti-crossveinless 2/collapsin response mediator protein 5 (anti-CV2/CRMP5) antibodies. Cumulatively, non-anti-NMDAR causes represented 48% of identified autoimmune encephalitis.

There were a total of 9 deaths (4%) recorded in this retrospective cohort, including the patient with *N. fowleri*. Of these, the majority (*n = 5*) had unknown causes despite each receiving extensive testing, including anti-NMDAR, herpes, *Bartonella*, WNV and other arboviruses, and other infectious and noninfectious etiologies. The other 3 deaths were caused by enterovirus, HSV-1, and HHV-6, respectively. The patient with HHV-6 was a recipient of a medically complex bone marrow transplant, so it was unclear as to the influence of HHV-6 in this fatal outcome.

With regard to diagnostic testing practices, PCR testing for HSV-1 and HSV-2 was common (90%). These test results were frequently negative, with only 11 (HSV-1 = 10, HSV-2 = 1) positive (11 out of 197; 5.6%). Overall, 70% of those who had CSP cultures negative for bacterial growth had an arboviral panel ordered. There was a trend toward more testing for WNV in the summer than in winter (76% vs 62%, *P* = .03). Of those with no known cause of encephalitis, almost half (*n = 42, 43%*) were not tested for anti-NMDAR antibodies; however, this test had the highest probability of returning a positive result (27%). The frequency of anti-NMDAR test administration dramatically increased throughout the study, from 29% tested in 2010 to 76% in 2017 (Fig 2), helping to reduce the percentage of unknown etiology from 52% in year 2010 to 36% in 2016 to 2017.

Time to diagnosis of causal agents differed between major causes of encephalitis (Table 2). Zoonotic and autoimmune causes were identified nearly a week (median = 6 days) after presentation, with some taking longer than one week, whereas more traditionally accepted causes (ie, HSV and enterovirus) were identified in less than half this time (median, 2 days). For bacterial pathogens, positive results varied between culture positive (median, 3 days) and intracellular (median, 6 days). Autoimmune causes took longer to diagnose (median, 6 days) than the majority of infectious causes, particularly for those diseases associated with rarer autoimmune antibodies (median, 32.5 days).
No statistically significant temporal variation was observed related to the causes of pediatric encephalitis. Although vector-borne and zoonotic causes (Bartonella, Rickettsia, California encephalitis, WNV, and LCMV) were more frequently observed in the summer than in the winter (13% of all encephalitis and 22% of identified encephalitis versus 6% and 11%, respectively; odds ratio [OR] = 2.5; \( P = .06 \); 95% confidence interval [CI] = 0.9–8.0), this was not statistically significant. No statistically significant trend in seasonality for anti-NMDAR encephalitis was identified (25% of identified encephalitis in summer versus 21% in winter; OR = 1.3, \( P < .59 \); 95% CI = 0.5–3.1).

We observed some differences in demographic and clinical findings between infectious and autoimmune causes of encephalitis (Table 3). Male patients were more likely to present with infectious cause of encephalitis (66% vs 42%; \( P = .005 \); OR = 2.7, 95% CI = 1.3–5.8), whereas female patients were more likely to have an autoimmune etiology (58% vs 34%). The proportion of autoimmune encephalitis cases relative to infectious encephalitides rose with increasing age (Table 1), although no significant difference was seen when dichotomized by the mean age of the total population of cases (Table 3). Interestingly, this prevalence increase paralleled an increase in autoimmune disease diagnostic testing practices. As far as other differences seen, patients with infectious causes of

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**TABLE 2 Clinical and Laboratory Findings by Cause of Encephalitis**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. Cases</th>
<th>Time From Symptom Onset to Hospitalization, d (range)</th>
<th>Time From Hospitalization to Diagnosis, d (range)</th>
<th>Fever, n (%)</th>
<th>Rash, n (%)</th>
<th>CSF Pleocytosis, n (%)</th>
<th>CSF Lymphocyte, % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Anti-NMDAR</td>
<td>31</td>
<td>8 (0–80)</td>
<td>6 (1–17)</td>
<td>5 (16)</td>
<td>1 (3)</td>
<td>23 (74)</td>
<td>91 (67–95)</td>
</tr>
<tr>
<td>ADEM</td>
<td>18</td>
<td>5 (1–10)</td>
<td>5.5 (0–43)</td>
<td>13 (72)</td>
<td>2 (11)</td>
<td>16 (89)</td>
<td>58.5 (8–83)</td>
</tr>
<tr>
<td>Hashimoto’s</td>
<td>6</td>
<td>1 (0–30)</td>
<td>9.5 (0–13)</td>
<td>2 (33)</td>
<td>0</td>
<td>1 (17)</td>
<td>__________________________</td>
</tr>
<tr>
<td>Other autoimmune(^b)</td>
<td>5</td>
<td>10 (0–60)</td>
<td>32.5 (6–53)</td>
<td>2 (40)</td>
<td>0</td>
<td>1 (20)</td>
<td>__________________________</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Herpesvirus</td>
<td>20</td>
<td>2 (0–21)</td>
<td>2 (1–37)</td>
<td>15 (75)</td>
<td>5 (26)</td>
<td>18 (90)</td>
<td>75 (18–92)</td>
</tr>
<tr>
<td>Arbovirus</td>
<td>13</td>
<td>0 (4–10)</td>
<td>6 (4–13)</td>
<td>12 (92)</td>
<td>5 (39)</td>
<td>12 (92)</td>
<td>52 (15–91)</td>
</tr>
<tr>
<td>Respiratory virus(^b)</td>
<td>10</td>
<td>1 (0–7)</td>
<td>2 (1–24)</td>
<td>9 (90)</td>
<td>1 (10)</td>
<td>5 (50)</td>
<td>74 (2–83)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>7</td>
<td>2 (1–10)</td>
<td>2.5 (1–9)</td>
<td>6 (88)</td>
<td>0</td>
<td>7 (100)</td>
<td>53 (1–96)</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>__________________________</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>7</td>
<td>4 (2–18)</td>
<td>3 (2–9)</td>
<td>6 (88)</td>
<td>0</td>
<td>7 (100)</td>
<td>1 (0–60)</td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td>3</td>
<td>3 (1–20)</td>
<td>4.5 (3–6)</td>
<td>2 (66)</td>
<td>0</td>
<td>3 (100)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>B. henselae</td>
<td>7</td>
<td>1 (0–7)</td>
<td>6 (2–8)</td>
<td>5 (71)</td>
<td>2 (28)</td>
<td>5 (3)</td>
<td>48.5 (10–87)</td>
</tr>
<tr>
<td>Spotted fever group rickettsioses</td>
<td>2</td>
<td>4.5 (4–5)</td>
<td>30.5 (18–43)</td>
<td>2 (100)</td>
<td>1 (50)</td>
<td>2 (100)</td>
<td>35 (30–40)</td>
</tr>
<tr>
<td>Other infectious(^b)</td>
<td>3</td>
<td>5 (0–30)</td>
<td>2.5 (1–4)</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>3 (100)</td>
<td>37 (14–60)</td>
</tr>
</tbody>
</table>

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\(^a\) No observations on this variable were available.  
\(^b\) Other autoimmune causes included anti-VGKC (2), anti-GAD (2), and anti-D2/C2/CRMP5 (1). Respiratory viruses included influenza (n = 6), parainfluenza (n = 2), and adenovirus (n = 2). Other infectious causes included C. lusitaniae, C. neoformans, and N. fowleri.

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No statistically significant trend in seasonality for anti-NMDAR encephalitis was identified (25% of identified encephalitis in summer versus 21% in winter; OR = 1.3, \( P < .59 \); 95% CI = 0.5–3.1).
encephalitis were more likely to be immunocompromised (16% vs 3%; \( P = .02, \text{OR} = 5.7, 95\% \text{CI} = 1.2–54.1 \)) and have an abnormal brain MRI (78% vs 56%, \( P = .008, \text{OR} = 2.8, 95\% \text{CI} = 1.2–6.5 \)) when compared with autoimmune encephalitis.

**DISCUSSION**

This study is one of the largest investigations of the etiology of encephalitis in children since the discovery of anti-NMDAR encephalitis. Through this study, we had many intriguing findings, particularly the prevalence of autoimmune causes and significant numbers of patients diagnosed with vector-borne viral (WNV) and atypical bacterial (B. henselae and spotted fever group rickettsioses) infections. With 42% of all patients having no etiologic diagnosis, future research should be focused on improving use of existing tests as well as etiologic discoveries by using novel tools like next-generation sequencing. Quality improvement and educational projects should emphasize the importance of comprehensive and standardized diagnostic testing in pediatric cases of encephalitis.

Infections were the most frequently diagnosed causes of encephalitis. On the basis of our findings, the importance of vector-borne and zoonotic agents as etiologies of encephalitis in certain regions of the United States should be emphasized. Despite being underrepresented in diagnostic testing, vector-borne and zoonotic infectious agents were frequently identified, representing 17% (23 out of 133) of identified causes of encephalitis in our study population. We tested for WNV at a high relative rate compared with other studies involving both pediatric and adult populations, and it seems axiomatic that this increased testing frequency led to the higher number of WNV-positive results.\(^{16,17}\) Like most parts of the United States, Houston is endemic for WNV and other arboviral diseases.\(^{18}\) This study contained 2 high-incidence outbreak years in 2012 and 2014 when WNV cases in Houston were elevated.\(^{19–21}\)

We found 3 patients with positive IgM for EEEV, and 2 were able to be ruled out by subsequent plaque reduction neutralization using convalescent specimens. EEEV is rare in this region and is associated with severe course of disease; all 3 of these patients recovered relatively quickly, with no neurologic sequelae.\(^{22}\) For these reasons, these patients were not considered true EEEV cases and were classified as unknown. It is possible these low detectable antibodies represent cross-reaction with other alphaviruses. WEEV could be possible in this population\(^{23}\) and potentially be cross-reactive with EEEV; however, only 1 of the 3 patients positive for EEEV was also positive for WEEV at a low-level titer. Although we are in a high-risk area for arboviral disease, it is likely that arboviruses may be an underrepresented cause of encephalitis and that they should be high on the list of differential diagnoses in certain regions of the country and particular seasons.

*B. henselae* (3% of all patients) represented the fifth most common cause of encephalitis in our population. Researchers of one other study of encephalitis in both pediatric and adult patients only reported *B. henselae* in <1% of their diagnosed patients.\(^{24}\) Two patients had antibodies to spotted fever group rickettsioses as well. Conventionally, these bacterial infections (along with *Bartonella* and *Ehrlichia*) would be considered probable in the absence of a second convalescent phase test. Researchers of recent studies have shown more infections with *Rickettsia* as well as confirmed autochthonous transmission of spotted fever group rickettsioses in Houston.\(^{25,26}\) In these studies, relatively few instances of *Rickettsia* infections were followed with convalescent serological testing, although in every case in which convalescent testing was conducted, fourfold conversion confirming infection occurred.\(^{27}\) For this reason we chose to include these infections as causes of encephalitis. One patient with LCMV was also observed; this agent, which was once considered a common cause of encephalitis in the United States, was rarely tested for in our population (n = 12) and is typically thought of in immunocompromised hosts.\(^{28,29}\)

With regard to autoimmune causes of encephalitis, anti-NMDAR was the most frequent cause. The prevalent frequency of anti-NMDAR encephalitis was expected to be more common than any other single cause. In the California Encephalitis Project, 32 of 761 cases (4%) of encephalitis in patients \( \geq 30 \) years of age tested positive for anti-NMDAR antibodies, compared with our study, in which 31 of 231 (13%) patients with encephalitis \( < 18 \) years were found to be positive.\(^{30}\) The frequency with which

| TABLE 3 Demographic and Clinical Differences Between Infectious and Autoimmune Encephalitis |
|-----------------------------------------------|------------------|------------------|-----|-------------------|
| **Etiology**                   | **Infectious Encephalitis** | **Autoimmune Encephalitis** | \( P \) | \( OR (95\% CI) \) |
| Male sex                      | \( n = 78, \% (n) \) | \( n = 60, \% (n) \) |     |                   |
| Age 8 y or older              | 48 (66)           | 25 (42)          | 0.05 | 2.7 (1.3–5.8)     |
| Race or ethnicity other       | 28 (38)           | 32 (53)          | 0.8  | 0.54 (0.3–1.2)    |
| Immune compromised*           | 12 (16)           | 2 (3)            | 0.2  | 5.7 (1.2–54.1)    |
| New onset seizure             | 45 (62)           | 39 (65)          | 0.7  | 0.87 (0.4–1.9)    |
| Abnormal MRI                  | 53 out of 68 (78) | 33 out of 58 (56)| 0.008| 2.8 (1.2–6.5)     |
| Abnormal EEG                  | 47 out of 53 (89) | 33 out of 42 (79)| 0.18 | 2.1 (0.6–8.0)     |
| Hospitalized 7 d or longer    | 56 (77)           | 54 (90)          | 0.04 | 0.37 (0.1–1.1)    |

\* Cell value <3, so Fisher exact was used to calculate 2-tailed \( P \) value.
we identified other autoimmune causes (29 out of 60; 48%) was somewhat unexpected. Next to anti-NMDAR encephalitis, ADEM and Hashimoto’s encephalitis were among the most frequently identified autoimmune causes of encephalitis. Although we identified encephalitis in the presence of a positive VGKC assay in 6 patients, only 1 patient had associated subunit antibodies (leucine rich glioma inactivated 1)31 identified; consequently, those other patients were classified as unknown. Effective therapies exist for these autoimmune conditions, and health care providers should consider testing for anti-VGKC, anti-GAD, and anti-CV2/CRMP5 antibodies when attempting to diagnose the underlying cause of encephalitis.

We observed several trends in temporality. Zoonotic causes were of substantial importance in the summer months and nearly negligible in winter months, although this was not significant, most likely because of sample size considerations. Although this was expected, the lack of seasonality in anti-NMDAR and enterovirus was not. Researchers of previous studies of these conditions had indicated some seasonality in anti-NMDAR encephalitis and enteroviral meningitis, which were not observed in our study.26,27,31 It is possible that the near-tropical climate of Houston resulted in an amelioration of seasonality in these conditions, as has been previously observed with enterovirus meningitis.34

Our study had several limitations worth discussing. One limitation inherent to retrospective chart reviews is that clinical data available for abstraction may have had errors or omissions at time of hospitalization. Our unique geographic location is a strength but may limit generalizability outside of the southern region of the United States; however, many of the causes identified in our study, especially the autoimmune conditions, have not been proven to vary significantly with geography. Properly separating meningitis and encephalitis cases can be difficult, especially with bacterial meningitis cases, hence our use of a strict case definition to improve the rigor and reproducibility of our study.

Despite some limitations, our study has many strengths. This study represents a large population of pediatric encephalitic patients drawn primarily from a diverse (in terms of national origin) population in the United States.35 Houston has a subtropical climate and is different from other areas where similar studies have been conducted. This ecologic difference is evident in the higher-than-expected incidence of vector-borne diseases in our study. Another strength is that our data are contemporary, allowing us to examine the contributions of anti-NMDAR autoimmune encephalitis, previously identified as the most common single cause of encephalitis in pediatric patients, although only truly recognized in 2007.6,30 Our hospital multidisciplinary efforts often led to comprehensive diagnostic testing for both traditional and more-novel causes of encephalitis. Finally, our strategy of applying the more-stringent and accepted consensus case definition for encephalitis provided rigor by excluding those patients who did not meet validated criteria, an important strength in consideration of recent evidence suggesting the lack of suitability of International Classification of Diseases (ICD) codes without such verification for identifying encephalitis.36

CONCLUSIONS
This study represents a contemporary investigation into encephalitis among a large population of children. Increased awareness and more frequent testing for anti-NMDAR encephalitis, WNV, and Bartonella would likely result in more identified causes of pediatric encephalitis. Pediatric institutions and physicians should consider immune-mediated encephalitis etiologies as children with neurologic dysfunction present to medical attention. These conditions may be more effectively treated if identified early in their course, and outcomes would be improved. Further research using innovative means is needed to promote the discovery of novel etiologies.

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ABBREVIATIONS
ADEM: acute disseminated encephalomyelitis
CI: confidence interval
CSF: cerebrospinal fluid
CV2/CRMP5: crossveinless 2/collagenous 2/GRMP5
EEEV: eastern equine encephalitis virus
GAD: glutamic acid decarboxylase
HHV: human herpesvirus
HSV-1: herpes simplex virus 1
HSV-2: herpes simplex virus 2
ICD: International Classification of Diseases
ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Classification of Diseases, Tenth Revision
IgG: immunoglobulin G
IgM: immunoglobulin M
LCMV: lymphocytic choriomeningitis virus
NMDAR: N-methyl-D-aspartate receptor
OR: odds ratio
PCR: polymerase chain reaction
TCH: Texas Children’s Hospital
WEEV: western equine encephalitis virus
WNV: West Nile virus

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