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BRIEF REPORT

Variability in the Use of Novel Diagnostic Technology in Children With Suspected Encephalitis and in the Management of Emerging Encephalitides by Pediatric Infectious Disease Providers

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We surveyed pediatric infectious disease physicians through the Infectious Disease Society of America's Emerging Infections Network regarding the diagnosis and management of encephalitis. We identified practice variations, particularly with the use of new diagnostic modalities and management of autoimmune encephalitides. These findings may inform the creation of updated management guidelines.

Key words. encephalitis; metagenomic next generation sequencing; multiplex polymerase chain reaction; pediatric; survey.

Encephalitis is a devastating disease, which may produce severe neurodevelopmental abnormalities and extreme morbidity in survivors [1]. Unfortunately, a myriad of pathogens are associated with this illness, many of which are difficult to diagnose and are without effective therapies [2–4]. In addition, noninfectious causes of encephalitis may have overlapping signs and symptoms with infectious causes, further complicating attempts at effective diagnosis [5]. Since the publication of the most recent Infectious Disease Society of America (IDSA) guidelines addressing encephalitis in 2008 [4], many changes in the diagnosis and epidemiology of pediatric encephalitis have emerged. Multiplex polymerase chain reaction (PCR) testing [6] and metagenomic next-generation sequencing (mNGS) [3] of the cerebrospinal fluid (CSF) have increasingly entered clinical practice. Autochthonous transmission of tropical neurotropic viral pathogens has arisen in several US states as well (eg, Chikungunya virus) [7]. Increasingly, clinicians are appreciating the emerging disease burden caused by autoimmune encephalitides [8]. These developments have greatly changed the diagnostic approach for this disease. In an effort to characterize how clinicians are adapting to these changes, we surveyed pediatric infectious disease physicians via the IDSA's Emerging Infections Network (EIN) to ascertain their approach to several evolving clinical issues related to the management of encephalitis in children.

METHODS

An 11-question, confidential, web-based survey link was distributed to 370 pediatric infectious disease physician members of the EIN of the IDSA and remained open between January 29 and February 17, 2020 (Supplementary File). Nonresponders received 2 reminders approximately 1 week apart. Only responses from providers caring for children with suspected encephalitis were analyzed. Respondents were characterized by the region of the country in which they practiced, years of experience since fellowship, their place of employment, and their primary hospital type. The survey assessed respondents' approaches to the use of multiplex PCR and mNGS testing in the CSF, their likelihood of testing for autochthonous tropical viral pathogens in the United States in a hypothetical scenario, their role and comfort level in evaluating and caring for children with autoimmune encephalitides, as well as criteria for initiating immunomodulatory agents in a child with suspected encephalitis. A Chi-square test was used to compare frequencies (SAS v.9.4).

RESULTS

Responses were received from 222 of 370 members (60%); the response rate was based only on members who had ever responded to an EIN survey [9]. Of the 222 respondents, 196 (88%) reported caring for children with suspected encephalitis and form the basis for the report. Of note, respondents were more likely than nonrespondents to have fewer than 5 years of pediatric infectious disease experience (25% vs 14%, $P = .04$). A majority of respondents worked in an academic medical setting (65%).

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Fifty-six percent of respondents reported that the use of multiplex PCR testing of CSF was not subject to institutional restrictions; 20% reported that this testing was not used at their institution. Multiplex PCR testing of CSF in the initial evaluation of most children with suspected encephalitis was reported by 110 (56%) of respondents, with 65% of these (71 of the 110 respondents) conducting pathogen-specific testing to confirm results (Table 1). Sixty respondents (31%) would likely require diagnoses to be excluded by standard testing (eg, cultures, herpes simplex virus PCR) prior to the use of a multiplex PCR assay. Additionally, 25 of these 60 respondents (42%) would only pursue multiplex PCR testing if a child were not clinically improving.

CSF mNGS had been used by 47% of providers (Table 2). Overall, if CSF mNGS were available in a timely and cost-effective manner, 74% of respondents (n = 145) stated that they would use it only if likely diagnoses were excluded via standard testing, of whom 64% (93 of these 145 respondents) would only use mNGS if a child were not improving. Of note, 11% of providers reported being unaware of mNGS of the CSF, 13% were unsure how best to use the test, and 40% were aware of the test but had never ordered it. Metagenomic NGS results without an identified pathogen were interpreted to mean no infection would be present by only 2% of respondents, while 68% felt the results would not exclude an infection (Table 2).

For autoimmune encephalitis, 33% of pediatric Infectious disease physicians were primarily responsible for the diagnostic evaluation, but only 55% of those surveyed reported feeling comfortable diagnosing this condition. Pediatric neurology services were listed as primarily responsible for diagnosis by 84% of respondents (respondents could select multiple services with primary responsibility for the diagnostic evaluation). Marked variation existed regarding the decision-making used prior to the initiation of immunomodulatory agents in a child with suspected encephalitis. Negative results from pathogen-specific testing were required by 87% of respondents, and a request from the neurology and/or rheumatology services was required by 64%. Defervescence was required by 11% of respondents, normal CSF indices by 23%, and reassuring magnetic resonance imaging of the brain (absence of necrosis and enhancement and diffusion-weighted abnormalities) by 50%.

Regarding the need for testing for autochthonous tropical viruses in the United States in a hypothetical pediatric patient with suspected encephalitis and no travel history, 42% of respondents reported that they would be somewhat likely or very likely to screen for such infections, 26% were somewhat unlikely or very unlikely to pursue such testing or reported conditional requirements for testing, and 18% were uncertain.

DISCUSSION

We found marked variability in the approach to evaluation and management of children with suspected encephalitis by pediatric infectious disease physicians. The diagnostic approach to children with encephalitis varied greatly in the ways newer diagnostic modalities, such as mNGS and multiplex PCR testing

Table 1. Approach to the Use of Multiplex Polymerase Chain Reaction Testing in the Cerebrospinal Fluid of Children With Suspected Encephalitis by 196 Pediatric Infectious Disease Physicians

Diagnostic Approach	Number (%) of Respondents
Would not use	8 (4%)
Would use only if likely diagnoses excluded with standard testing (eg, culture, HSV PCR)	35 (18%)
Would use only if likely diagnoses excluded with standard testing AND the child was not improving	25 (13%)
Would use in the initial evaluation of most children with suspected encephalitis, WITH pathogen-specific confirmatory testing	71 (36%)
Would use in the initial evaluation of most children with suspected encephalitis, WITHOUT pathogen-specific confirmatory testing	39 (20%)
Not sure	5 (3%)
Other approach	11 (6%)
Did not answer question	2 (1%)

Abbreviations: HSV, herpes simplex virus; PCR, polymerase chain reaction.

Table 2. Approach to the Use of Metagenomic Next-Generation Sequencing of the Cerebrospinal Fluid in Children With Suspected Encephalitis by 196 Pediatric Infectious Disease Physicians

Topic	Number (%) of Respondents
Prior experience with mNGS	
Unaware of mNGS	22 (11%)
Aware of mNGS, never used it	79 (40%)
Used mNGS, never found it useful	37 (19%)
Used mNGS, found it useful in select situations	53 (27%)
Used mNGS, usually find it useful	2 (1%)
Did not answer question	3 (1%)
How mNGS of CSF would be used if available in a timely and cost-effective manner	
Would not use	7 (4%)
Would use only if likely diagnoses excluded with standard testing (eg, culture, HSV PCR)	52 (27%)
Would use only if likely diagnoses excluded with standard testing AND the child was not improving	93 (47%)
Would use as standard test in the initial evaluation of most children with suspected encephalitis	12 (6%)
Not sure	25 (13%)
Other approach	5 (3%)
Did not answer question	2 (1%)
Interpretation of negative CSF mNGS results in a child with suspected encephalitis	
No infection	4 (2%)
Infection unlikely, but cannot exclude infection	44 (22%)
Infection less likely, but cannot exclude infection	91 (46%)
Would not change initial suspicion of infection	30 (15%)
Unsure	25 (13%)
Did not answer question	2 (1%)

Abbreviations: mNGS, metagenomic next-generation sequencing; CSF, cerebrospinal fluid; HSV, herpes simplex virus; PCR, polymerase chain reaction.

of CSF, were implemented. Providers reported differences in multiplex PCR test availability and use, test ordering restrictions, and test interpretation with regard to pathogen-specific confirmatory testing [10].

Around half of the providers surveyed had used mNGS testing of CSF, though disagreement existed about the optimal timing and the interpretation of results. In particular, negative results from mNGS testing were interpreted with differing levels of confidence to exclude infectious causes. Due to the transient and, at times, relatively brief presence of many viral encephalitis pathogens in the CSF (eg, flaviviruses) [11], mNGS and multiplex PCR testing may be somewhat limited in utility, and serological testing of the blood and/or the CSF (or more invasive approaches, such as brain biopsy) [3] may be needed to augment the diagnostic approach in such instances [3].

Given the large number of infectious causes of encephalitis without effective treatments, providers may also not feel obligated to pursue a specific diagnosis with mNGS or multiplex PCR testing, particularly once treatable and common causes have been excluded, especially when the child is clinically improving. Indeed, nearly three-fourths of our respondents reported that they would only use mNGS on CSF in a child with suspected encephalitis if likely diagnoses were excluded by standard testing, and nearly two-thirds of those respondents would additionally only pursue such testing if the child were not improving. However, the unbiased approach to diagnosis afforded by mNGS offers the potential to identify novel and emerging neurotropic pathogens which may otherwise evade detection [3].

Our survey also highlights not only the important role many infectious disease physicians play in the evaluation of autoimmune encephalitis but also their relative lack of comfort with this diagnosis. Though not a primary infectious process, these survey findings highlight the need for enhanced training, updated directives in clinical guidelines, and a clearer delineation of duties amongst pediatric providers caring for children with autoimmune encephalitides. Similarly, the criteria used to guide the initiation of immunomodulatory agents in children with suspected encephalitis varied tremendously. Many of the respondents would require the absence of findings that could be concerning for infectious encephalitis (eg, fever, abnormal brain magnetic resonance imaging (MRI), and abnormal CSF indices) but are also common in the autoimmune encephalitides and, therefore, may delay definitive therapy in these cases.[8]

Clinical management guidelines for encephalitis from the IDSA were last published in 2008 [4], though the International Encephalitis Consortium has published diagnostic guidance in a consensus statement from 2013 [12]. Guidelines should be updated to address the uncertainties we identified with the use of mNGS, multiplex PCR testing, testing for autochthonous tropical viruses, and autoimmune encephalitis evaluation and management. Incorporating these new technologic advances and emerging clinical challenges into updated guidelines, guided by current research, may help optimize and standardize the approach of pediatric infectious disease physicians to this challenging patient population.

CONCLUSIONS

Tremendous variability exists regarding the use of novel diagnostic tools in children with suspected encephalitis and the management of emerging encephalitides, such as autoimmune encephalitis, by pediatric infectious disease physicians. Revised and updated clinical guidelines addressing these gaps in knowledge may help standardize care of children with suspected encephalitis.

Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society online*.

Notes

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