Pediatric Neurology 55 (2016) 37–45

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Utility of Neurodiagnostic Studies in the Diagnosis of Autoimmune Encephalitis in Children

Dara V. Albert DO [a,b,1], Charles P. Pluto MD, PhD [b,c,1], Amanda Weber DO [a], Jorge Vidaurre MD [a,b], Fatima Barbar-Smiley MD, MPH [d], Rabheh Abdul Aziz MD [d], Kyla Driest MD [b,d], Sharon Bout-Tabaku MD, MSCE [b,d], Lynne Ruess MD [b,c], Jerome A. Rusin MD [b,c], Bethanie Morgan-Followell MD [a,b,*]

[a] *Section of Child Neurology, Department of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio*
[b] *College of Medicine, The Ohio State University, Columbus, Ohio*
[c] *Department of Radiology, Nationwide Children's Hospital, Columbus, Ohio*
[d] *Section of Rheumatology, Department of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio*

ABSTRACT

BACKGROUND: Autoimmune encephalitis is currently a clinical diagnosis without widely accepted diagnostic criteria, often leading to a delay in diagnosis. The utility of magnetic resonance imaging (MRI) and electroencephalography (EEG) in this disease is unknown. The objective of this study was to identify disease-specific patterns of neurodiagnostic studies (MRI and EEG) for autoimmune encephalitis in children. **METHODS:** We completed a retrospective chart review of encephalopathic patients seen at a large pediatric hospital over a four year interval. Clinical presentation, autoantibody status, and MRI and EEG findings were identified and compared. Individuals with autoantibodies were considered "definite" cases, whereas those without antibodies or those with only thyroperoxidase antibodies were characterized as "suspected." **RESULTS:** Eighteen patients met the inclusion criteria and autoantibodies were identified in nine of these. The patients with definite autoimmune encephalitis had MRI abnormalities within limbic structures, most notably the anteromedial temporal lobes (56%). Only individuals with suspected disease had nontemporal lobe cortical lesions. Sixteen patients had an EEG and 13 (81%) of these were abnormal. The most common findings were abnormal background rhythm (63%), generalized slowing (50%), focal slowing (43%), and focal epileptiform discharges (31%). Sleep spindle abnormalities occurred in 38% of patients. There were no specific differences in the EEG findings between the definite and suspected cases. Focal EEG findings only correlated with a focal lesion on MRI in a single definite case. **CONCLUSIONS:** Pediatric patients with definite autoimmune encephalitis have a narrow spectrum of MRI abnormalities. Conversely, EEG abnormalities are mostly nonspecific. All patients in our cohort had abnormalities on one or both of these neurodiagnostic studies.

Keywords: autoimmune encephalitis, magnetic resonance imaging (MRI), electroencephalogram (EEG), NMDA antibody, GAD65 antibody, TPO antibody

Pediatr Neurol 2016; 55: 37-45

Introduction

Autoimmune encephalitis is an increasingly identified cause of encephalitis when no infectious agent is apparent. As many as 77% of children with autoimmune encephalitis will have seizures during the course of the illness; thus, the terms "autoimmune encephalitis" and "autoimmune epilepsy" have significant overlap, although each may exist independently.[1,2] Clinical signs and symptoms that suggest

Disclosures: All authors report no disclosures.
Funding: None.
Article History:
Received October 22, 2015; Accepted in final form October 31, 2015
* Communications should be addressed to: Dr. Bethanie Morgan-Followell; Section of Child Neurology; Nationwide Children's Hospital; 700 Children's Drive; Columbus, OH 43205.
E-mail address: Bethanie.morgan@nationwidechildrens.org
[1]Co-first authors.

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http://dx.doi.org/10.1016/j.pediatrneurol.2015.10.016

autoimmune encephalitis and autoimmune epilepsy have been described, but confirmation of these diagnoses rely on the identification of neuronal surface antibodies (NSAbs) and an intracellular antibody, glutamic acid decarboxylase (GAD). Presently, only a handful of antibodies that are considered to be pathogenic have been identified. In addition, testing is not commercially available for all antibodies associated with autoimmune encephalitis and epilepsy. Given the limited availability of biomarkers that support a definitive diagnosis, patients often fall into the category of suspected autoimmune encephalitis or epilepsy. The diagnosis of suspected immune-mediated disease relies on nonspecific clinical symptoms and is, in many ways, a diagnosis of exclusion. Thus, prompt identification of patients with autoimmune encephalitis or epilepsy is often difficult. Nevertheless, prompt diagnosis is imperative as the literature has shown that early treatment improves outcomes.[3] As more pathogenic antibodies are identified and testing becomes widely available, the time to diagnosis and treatment may decrease. While awaiting these developments, we can seek to maximize the yield of current neurodiagnostic testing, specifically magnetic resonance imaging (MRI) and electroencephalography (EEG).

The utility of neurodiagnostic studies, namely, brain MRI and EEG, in the setting of autoimmune encephalitis is unclear. Several recent reports have described MRI findings of autoimmune encephalitis in adults, but relatively little is published about MRI findings of autoimmune encephalitis in children.[4-7] Results of MRI can range from completely normal to significantly abnormal. Increased T2 signal abnormality in the limbic regions has been described.[6] Many individuals have EEG abnormalities and several authors have attempted to elucidate common findings.[1,2,6,8-12] Unfortunately, most have found relatively nonspecific EEG abnormalities such as generalized slowing and epileptiform discharges.[5,13]

We examined brain MRIs and EEGs of 18 children with either definite or suspected autoimmune encephalitis. The primary objective of this retrospective analysis was to identify disease-specific patterns of neurodiagnostic studies (MRI and EEG) for autoimmune encephalitis in children. We hypothesized that common features may emerge that would aid in the diagnosis and also that there might be differences in findings between those with definite versus suspected autoimmune encephalitis.

Methods

This study was approved by the Nationwide Children's Hospital Institutional Review Board for Human Research.

The medical records of children with definite or suspected autoimmune encephalitis who were evaluated in our institution from January 2009 to December 2013 were reviewed by five of the authors (AW, KD, FB-S, RAA, and SB-T). We identified 244 patients with "encephalitis" (International Classification of Diseases, Ninth Revision 323.01 to 323.9) or "encephalopathy" (International Classification of Diseases, Ninth Revision 348.30 to 348.39) as a primary or secondary diagnosis in the electronic medical record. We developed inclusion criteria based on the available pediatric literature in autoimmune encephalitis or epilepsy (Fig 1).[13,14] Demographic information and clinical data including signs and symptoms at presentation and follow-up, laboratory results, and treatment regimens were recorded. This information was then reviewed by a neuroimmunologist (BM-F) to ensure that the criteria were appropriate.

All MRIs were performed on 1.5- or 3-T GE imaging units; gadopentetate dimeglumine (Magnevist) MRI contrast was used. All MRIs were independently reviewed by two pediatric neuroradiologists (CPP and JAR). The radiologists then reviewed all the cases together, and any examinations with questionable findings were reviewed by a third pediatric radiologist (LR) who was blinded to the findings in question.

EEGs were performed using the standard 10/20 international system of electrode placement. When patients had more than one EEG, only the initial EEG was reviewed. If a patient had more than 24 hours of video EEG monitoring, only the first 24 hours were reviewed. All EEGs were reviewed by two neurophysiologists (DVA and JV). The neurophysiologists were aware that the patients had the diagnosis of either definite or suspected autoimmune encephalitis, but were blinded to the clinical information at the time of review.

Results

Clinical and laboratory findings

There were 244 pediatric patients identified by review of the electronic medical record; 18 met inclusion criteria (Fig 1). There were 12 (67%) females and 6 (33%) males. The mean age was 10.1 years at presentation. Ethnic background of the patients were as follows: 6 (33%) patients were Caucasian, 7 (39%) were African-American, and the remaining 5 (28%) were other or of mixed heritage. The most common presenting symptom was seizure (56%). Fever was documented on clinical presentation in 33%. Seventeen of 18 patients had cerebrospinal fluid (CSF) examination. Ten (56%) of those had five or more leukocytes per cubic millimeter. Six (33%) of 17 had CSF protein greater than 45 mg/dL. Both leukocytes and protein were adjusted for number of red blood cells (RBCs) using the standard correction calculation (allowance of one leukocyte for every 700 RBCs and protein increases 1.1 mg/dL for every 1000 RBCs). Eight patients had testing for oligoclonal bands. Unpaired oligoclonal bands were present in the CSF of four. Six patients had other autoimmune disorders: one type I diabetes mellitus, three transient thyroiditis associated with anti-thyroperoxidase (TPO) antibodies, one alopecia areata, and one type I diabetes mellitus and Grave disease. Mean duration of follow-up was 25 months (range 1 to 79 months).

Antibody testing was performed at the discretion of the treating physician and was, therefore, highly variable. NSAbs were identified in five patients, and all these were anti–N-methyl-D-aspartate (NMDA) receptor antibodies. GAD antibodies (GAD65) were identified in four patients (Table 1). In all, we identified nine definite cases of autoimmune encephalitis via antibody testing in either serum or CSF. All other cases were classified as suspected cases based on the fulfillment of clinical inclusion criteria. Given the poorly understood significance of TPO antibodies, patients with TPO antibodies alone were classified as suspected.

Anti-TPO antibodies were identified in four patients. Anti-GAD65 antibodies were concurrently present in two of these patients. Three patients were diagnosed with thyroiditis associated with anti-TPO antibodies by the consultant endocrinologist. Two had a transient elevation in serum thyroid-stimulating hormone (TSH) level without elevation in serum T3 or T4 level, whereas the third had normal levels of both TSH and T3/T4. Two (one with elevated TSH level, one with normal TSH level) had findings on ultrasonography of the neck suggestive of thyroiditis.