Short Communication | Journal of Neurological Disorders | 2020 | Vol.8 No.7

The Clinical Spectrum of Autoimmune Epilepsy in Children: With Cases Illustrations

Muhammad Akbar Malik[1*]

[1]Department of Pediatric Neurology, The Children's Hospital, Pakistan

ABSTRACT

There are many causes of seizures in autoimmune disorders of brain, and the first clinical Seizures are among the most common neurological manifestation. Occasionally seizures can be the presenting symptom, convert into epilepsy, may be detected up to 14% of epilepsy patient, which could herald a life-threatening progression of the underlying illness. However, existing criteria for autoimmune epilepsy are too reliant on antibody testing and response to immunotherapy, which might delay the diagnosis. Because autoantibody test results and response to therapy are not available at disease onset, the initial diagnostic approach should be on neurological assessment and conventional tests that are accessible to most clinicians. Through logical differential diagnosis, levels of evidence for autoimmune epilepsy (possible, probable, or definite) may be achieved, which can lead to prompt immunotherapy. Prompt recognition of these disorders is mandatory to offer the patient adopted therapeutic options. Neuronal surface antibody and intracellular antibody syndromes encompass a variety of disorders associated with severe epilepsy. These share clinical and neuroradiological features that pose challenges related to their recognition and treatment. On that basis, a target treatment can be started, anti-seizure drugs augmented with corticosteroids and intravenous immunoglobulin or plasma exchange as a first-line immunotherapy, followed by second-line drugs including rituximab, cyclophosphamide or mycophenolate mophetil, if the case. In children a prompt diagnosis and a targeted treatment may lead to a better clinical outcome.

Keywords: Epilepsy, Autoimmune, Antibodies, FIRES, VGKC, NMDAR, GAD, Pediatrics.

METHODS

We describe 13 representative children seen at our tertiary institution over a period of 3.5 years with suspected autoimmune epilepsy. Autoimmune epilepsy was suspected clinically when there was any of the following:

(1) Recognizable syndromes such as NMDAR encephalitis or limbic encephalitis, (2) evidence of CNS inflammation in cerebrospinal fluid or on magnetic resonance imaging (MRI), (3) the presence of other autoimmune diseases, or (4) positive response to immunotherapy. We tested these patients for neuronal surface antibodies (voltage gated potassium channel [VGKC]-complex, leucine rich glioma inactivated 1 [LGI1], contactin-associated protein-like 2 [CASPR2], and NMDAR) and glutamic acid decarboxylase (GAD) antibodies. We modified the J Neurol Neurosurg Psychiatry, 83, 2012, 638 guidelines that were designed to classify adults with neuronal surface antibody syndromes (NSAS), to be more appropriate for children with suspected autoimmune epilepsy. Using the modified guidelines, the 13 patients were classified into definite, probable, possible, unlikely, or unknown autoimmune epilepsy according to the presence of neuronal surface or GAD antibodies, and the response to immune therapy when given. Key Findings: Of the 13 patients, 11 were females, and the mean age was 6 years (range 1–13 years). Three patients had classical NMDAR encephalitis, two had VGKC encephalitis, two had limbic encephalitis with negative antibodies, three had epilepsy with other autoimmune diseases (one with high titer GAD antibodies), two had fever-induced refractory epileptic encephalopathy in school-aged children (FIRES), and one epileptic encephalopathy associated with VGKC antibodies. Seven patients of the 13 children with suspected autoimmune epilepsy were positive for neuronal surface antibodies (NMDAR, n = 3; VGKC-complex, n = 3; and GAD, n = 1). Immunotherapy was given to nine cases, and a positive response was more common in patients with positive neuronal surface antibodies (5/5) compared to those with negative antibodies (2/4). Applying the proposed guidelines, the classification of autoimmune epilepsy was definite in five, probable in one, possible in three, unlikely in two, and unknown in two patients.

SIGNIFICANCE

Neuronal surface antibodies and GAD antibodies are present in a proportion of children with suspected autoimmune epilepsy and may define a treatable subgroup of childhood epilepsy. The proposed guidelines can be useful in the recognition of children with seizures of autoimmune etiology.

RESULTS

The 13 patients with seizures of suspected autoimmune origin (11 female, age range 1–13 years, mean age 6 years) are presented. All patients had other potential causes for their seizures excluded. All 13 patients had new onset seizures and at least one supportive feature of CNS inflammation or the presence of other autoimmune diseases. Three patients had the clinical characteristics of NMDAR encephalitis (all with CSF and serum NMDAR antibodies), two had encephalitis associated with VGKC-complex antibodies, two had features suggestive of limbic encephalitis (with negative antibodies), three had epilepsy in association with other autoimmune diseases (one with GAD antibodies), two had FIRES, and one had epileptic encephalopathy with CNS inflammation (VGKCantibody positive). Seven patients (53.9%) of the 13 were positive for one of

the tested antibodies including NMDAR (n = 3), VGKCcomplex (n = 3), and GAD (n = 1). Immunotherapy wasgiven in nine patients: five with positive neuronal antibodies and four negative. The immune therapy was steroids alone (n = 4), steroids and intravenous immunoglobulin (IVIG)(n = 3), steroids, IVIG and mycophenolate (n = 1) and steroids, IVIG, and rituximab (n = 1). All five patients with positive neuronal antibodies who received any immune therapy improved after receiving therapy, whereas only two of four with negative neuronal antibodies improved after receiving immune therapy. Three of the four patients who did not receive immunotherapy had poor outcome including ongoing epilepsy, and cognitive and psychiatric impairment.

Patients were classified according to the proposed modified guidelines, and their classification is presented in Table 3. Five patients had definite, one had probable, three had possible, two had unlikely, and two had unknown autoimmune epilepsy. We present the case histories for 8 of the 13 patients in details in the Data S1 as representative examples.

DISCUSSION

The recognition of immune mechanisms in neurologic disorders is important as this can prompt early treatment and may lead to better outcomes. The identification of specific and potentially pathogenic NSAbs is increasing, and the spectrum of the clinical syndromes associated with NSAbs is widening (Zuliani et al., 2012). Recently guidelines have been developed to help in the diagnosis and management of adults with suspected NSAS (Zuliani et al., 2012). In children the lack of large studies regarding NSAbs and their related syndromes makes it harder to identify these cases; therefore, guidelines may help in the identification of NSAS particularly when seizures are an important feature.

In this paper, we describe 13 representative patients with seizures of suspected autoimmune etiology and we propose features for identification of these pediatric patients, and a classification system testing the strength of evidence of autoimmune epilepsy based on the presence of neuronal antibodies and response to immunotherapy.

There were some general features common to the cohort. Females were over-represented in this cohort, as is often described in autoimmune disorders in general. The seizures were often focal, and generally occurred in association with encephalopathy or other features of CNS dysfunction. Three cases had typical features of NMDAR encephalitis in children, as represented by case 3 description in the Data S1. The patients with NMDAR encephalitis generally had focal epilepsy, and the presence of psychiatric manifestations, behavior alteration, and movement disorder was a strong indicator of NMDAR encephalitis. However, it is possible that NMDAR Abs are present in children with epilepsy in the Abs absence of the classic phenotype as has been described in adults (Niehusmann et al., 2009), and therefore testing for NMDAR in children with suspected autoimmune seizures may provide further information about the spectrum of NMDAR antibody-associated disease. Two cases had VGKC-complex Ab-associated encephalitis, characterized by fever-associated focal seizures and status epilepticus; one was previously reported (case 5) and the clinical phenotype of the second case (case 4) was similar to our previously reported pediatric patients with VGKC-complex Ab-associated encephalitis (Suleiman et al., 2011a). The seizure semiology was suggestive of temporal lobe onset, a finding that is commonly seen in both adults and children with this syndrome (Vincent et al., 2004; Suleiman et al., 2011a). In case 4, mycoplasma immunoglobulin M (IgM) was positive and was consistent with acute infection.

Mycoplasma infection has been described in association with NMDAR encephalitis in children and may be a trigger of autoimmune CNS disorders (Florance et al., 2009). However, mycoplasma pneumonia is a common respiratory infection in children and positive mycoplasma serology may therefore be incidental in some patients (Waites & Talkington, 2004). Antibodies against LGI1 or CASPR2, which have been identified as the target of VGKC-complex Abs in adults, were negative in this case, a finding that is common in children with positive VGKC-complex Abs. It is possible that in children, VGKC-complex Abs are targeted against other antigens in the VGKC-complex that are yet to be identified. Patients with VGKC-complex Ab-associated encephalitis often respond to immune therapy, but spontaneous improvement can also occur (Irani et al., 2010) as was the case in this patient.

Case 6 had a syndrome of limbic encephalitis; however, NSAbs and GAD Abs were negative, possibly due to late testing and because the patient received no immunotherapy, the classification was “unknown.” Early recognition, testing, and treatment might have improved her outcome. Case 7 had a limbic encephalitis syndrome and was negative for NSAbs but responded to immune therapy (classification possible). Antibodies against AMPAR and GABABR (not tested) or other unrecognized NSAbs could be the cause of limbic encephalitis in these patients. The diagnosis of limbic encephalitis can be challenging in children, where its existence is reported but probably underrecognized (Haberlandt et al., 2011). The diagnosis of limbic encephalitis is partly clinical, with new-onset temporal lobe seizures and cognitive disturbance sometimes associated with radiologic mesial temporal or hippocampal changes. Because hippocampal signal change is described in a proportion of children with febrile status epilepticus (Shinnar et al., 2012), it is difficult to discriminate radiologic seizure-induced hippocampal swelling from limbic encephalitis.