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Case Report

A Fatal Refractory Status Epilepticus Due to A GAD65 Positive Autoimmune Limbic Encephalitis

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Abstract

Autoimmune encephalitis is a dysimmune disease characterized by a widely clinical polymorphism, ranging from the insidious onset of cognitive disorder to more complex forms with refractory status epilepticus. We are dealing here with a case of limbic encephalitis, which initially presented with sudden convulsions preceded essentially by some psychiatric manifestations (episodes of disorientation, mood disorder and bizarre behaviors). The classic paraneoplastic investigation was negative. Cerebrospinal fluid (CSF) and serum examination showed elevated titers of glutamic decarboxylase 65 (GAD65) antibodies leading to the diagnosis of non-paraneoplastic limbic encephalitis. Evolution was fatal following a prolonged stay in intensive care unit for a refractory status epilepticus despite immunotherapy regimens including steroid, intravenous immunoglobulin (IVIg), and plasma exchange.

Keywords: Autoimmune; Limbic encephalitis; GAD Antibody; Seizure

1. Introduction

In 1960 the first three cases of subacute encephalitis affecting limbic areas were reported [1]. For these first observations, the paraneoplastic origin was rejected. In 1968 the concept of paraneoplastic limbic encephalitis was established on the basis of three other observations of memory disorder associated with lung cancinoma [2]. Since then, many cases of limbic encephalitis (LE) paraneoplastics have been published and it was considered strictly paraneoplastic until 2004, where LE associated with Voltage gated potassium channel antibodies (anti-VGKC) were

described [3]. It appears more and more that LE is an auto-immune condition usually presents with vague symptoms such as confusion, seizures, psychiatric and memory disturbances. NMDA receptor antibodies, Voltage gated potassium channel antibodies and GAD receptor antibodies are the most common non paraneoplastic antibodies associated with this pathology. We report a case of GAD_{65} Positive Autoimmune Limbic Encephalitis leading to a refractory status epilepticus and its subsequent management during a long ICU admission.

2. Case Report

A 23-year-old man, without any medical backgrounds, was admitted to our hospital because of the occurrence of complex partial seizures. He had a few days history of increasing headaches, diplopia, vomiting, lethargy and aggressive Behaviors. Seizures were treated with IV clonazepam. Cerebrospinal fluid (CSF) examination documented normal glucose and protein content, and no pleocytosis. Suspecting a herpes simplex virus (HSV) encephalitis, IV acyclovir was started and seizures were treated with carbamazepine. Initial laboratory investigations, CT scan and Brain MRI were unremarkable. An electroencephalogram (EEG) showed 4–6 Hz mixed polymorphic theta activity in the left frontal cortex, without focal slowing, spikes or sharp waves.

During the subsequent 72 hours, the patient manifested frequent complex partial seizures despite starting a combined antiepileptic treatment (carbamazepine, phenobarbital, valproic acid, and levetiracetam). An extensive screening for antiviral and antibacterial antibodies in CSF and serum (HSV1 and HSV2, HHV6, Coxsackie, Rubella, Epstein-Barr, Varicella-Zoster, human immunodeficiency virus type 1 and 2, Cytomegalovirus, syphilis, Parvovirus B19, Coxiella burnetii 1 and 2, Legionella, influenza and parainfluenza virus, and enterovirus) was negative. HSV polymerase chain reaction (PCR) was negative leading to discontinuation of acyclovir. A diagnostic search for cancer including imaging and serological studies for various tumor markers was negative. Evaluation of typical antibodies (NMDA, Hu, Yo, Ri, amphiphysin, CV2/CRMP5, Ta /Ma1, VGKC-Ab) present in a paraneoplastic panel also turned out to be negative. The autoimmune etiology has been suspected, so an immunomodulatory treatment with a five-day course of IV immunoglobulin therapy (0.4 g/kg/day) and intravenous methyl-prednisone (1g/kg/day for three days) was initiated.

Over the next few days the patient developed a super-refractory status epilepticus that could be only resolved by general anesthesia (benzodiazepines and propofol). Antibodies markers in CSF and serum showed presence of GAD_{65} autoantibody, and as no improvement was noted, plasma exchange (PE), was then started (10 exchanges in 10 days) without clinical improvement and no decrease in titers of GAD_{65} antibody was noted. When stopping sedation, seizures frequently recur. A vagus nerve stimulator was implanted with an initial response (reduction of seizure frequency) but a secondary resistance appeared. Unfortunately, the occurrence of refractory septic shock at 264 days of hospitalization and the patient died with multiple organ failure.

3.Discussion

Historically, LE has been described as an inflammatory disease predominant on the limbic lobe [1]. This definition was reconsidered given the high frequency of extralimbic symptoms associated with this pathology. The coexistence

of underlying neoplasia in reported cases made the LE as paraneoplastic pathology [2]. Understanding of LE has increased significantly recently, and it is only in the last decade that it was recognized that autoimmune LE with no known or active malignancy represented a growing percentage of all LE diagnoses. Antibody-mediated LE can also be characterized as either group I or group II according to the location of their neuronal antigens, with group I antibodies targeting intracellular antigens which include all known paraneoplastic antigens, and group II antibodies targeting antigens on the cell surface including the VGKC, NMDA receptor and GAD [4, 5]. This distinction is clinically useful for treatment response, association with malignancy, and long-term prognosis [5].

Our patient has clinical signs suggestive of acute autoimmune encephalitis. Association between GAD antibody and non-paraneoplastic LE was initially described by Mata et al. [6]. The goal of treatment with autoimmune LE is immunomodulating therapy to suppress the autoimmune response. Encephalitis associated with GAD antibodies is a severe disorder that occurs in young children as well as adults. In a recent study [7], this nonparaneoplastic disorder is different from anti-VGKC limbic encephalitis, as it occurs in younger individuals, (17-66 years Vs 44-77 years, p=0.003) who present first with seizures.

Since the lack in the literature of randomized controlled trials, immunotherapy treatment with varying combinations of steroids, IVIg, plasma exchange and immunosuppressants [8] is based on case reports and prospective case series. In the same study cited above [7], treatment with corticosteroids, intravenous immunoglobulin or cyclophosphamide did not improve seizure control. That's why other treatment such as monoclonal antibody could be a futuristic alternative. Indeed Dalakas MC et al. [9] used rituximab in treatment of autoimmune neurologic diseases. This anti-CD20 monoclonal antibody causes selective destruction of B lymphocytes and decreased production of antibodies [10, 11].

4. Conclusions

Limbic encephalitis with anti-GAD positive antibodies is an emerging diagnosis among the adult population. Early diagnosis is overriding for the management and in the evocative clinical setting limbic encephalitis should be considered as first-line diagnostic with anti-GAD systematically included in the antibodies screen. Refractory SE is a complication of LE and requires an aggressive care including anti-epileptic regimen, steroid, IVIg, plasma exchange, and immunosuppressive agents in varying combinations. However, response to treatment is variable.

5. Disclosure

The authors have no conflicts of interest to disclose.

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