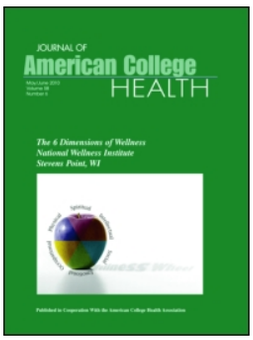

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Anti-N-methyl-D-aspartate receptor antibody encephalitis: an important cause of encephalitis in young adults. A report of two cases.

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Anti-N-methyl-D-aspartate receptor antibody encephalitis: an important cause of encephalitis in young adults. A report of two cases.

Abstract

Encephalitis is a clinical syndrome which can include altered mental status, motor and sensory deficits, altered behavior including personality changes, speech and movement disorders and seizures. While the overall incidence of encephalitis is not known, it is common enough that most pediatric and adolescent medicine physicians will have seen at least one case. Peak times of risk include the newborn period and middle-to-late adolescence.[1] It is important for clinicians to have a working knowledge of the broad range of encephalitis etiologies: viral, post-viral, toxic, auto-immune and paraneoplastic. We discuss two cases of encephalitis in young adult women with ovarian teratoma and production of anti-N-methyl-D-aspartate receptor (NMDAR) antibodies.

Keywords: encephalitis, altered mental status, anti-NMDA receptor antibodies, auto-immune encephalitis, paraneoplastic encephalitis.

Introduction

Anti-NMDAR encephalitis was first described by Dalmau et al in 2007.[1] In one case series, The California Encephalitis Project, it surpassed the incidence of any viral cause of encephalitis for which a clear diagnosis could be established.[2] Indeed, anti-NMDAR encephalitis was diagnosed with a frequency more than four times that for HSV-1-, West Nile Virus- or VZV-associated encephalitis.[2] A feature which can sometimes distinguish anti-NMDAR encephalitis from other causes is the relative prominence of psychiatric symptoms. These can include hallucinations, bizarre behavior, panic attacks, marked personality changes, catatonia-like states, aggression and amnesia. [2] Seizures are common. [2] As anti-NMDAR encephalitis is a para-neoplastic syndrome, the evaluation of patients suspected of having it generally must include a thoughtful search for an underlying tumor; in women, often a teratoma.

Case 1 Clinical Presentation

At time of presentation, patient was an 18 year old Caucasian-Hispanic female undergraduate student. She had no significant past medical history. She had recently graduated near the top of her class from a highly competitive "magnet" high school. The patient reported one week of headache, localizing to the frontal region. On the day of presentation, while sitting in class, she experienced acute onset of "jaw twitching" associated with inability to manage oral secretions. These symptoms resolved spontaneously after an indeterminate period of time. A second episode of jaw twitching occurred later the same day associated with loss of lower extremity motor coordination and a fall. The patient denied loss of consciousness.

On physical exam, the patient was afebrile, normotensive and had a heart rate of 99bpm. She was awake, alert, speaking in full sentences with an appropriate affect. Her neurological exam revealed no gross deficits. There was no nuchal rigidity. Due to the unusual nature of the two reported episodes, and a concern for new-onset seizures possibly secondary to an infectious etiology, the patient was rapidly transported to the local hospital. Within 12 hours of presentation to the hospital, patient had multiple episodes of seizure-like activity, marked confusion and rapidly deteriorating level of consciousness.

Case 2 Clinical Presentation

At time of presentation, patient was a 34 year old Caucasian female post-baccalaureate pre-medical student, nearing the end of her studies, already admitted to medical school. The patient had no significant past medical history.

Approximately one week prior to presentation, the patient reported an episode of "fainting" while showering without significant associated injury. She was briefly evaluated in an emergency room and discharged. The following day, she began experiencing frequent episodes of feeling a "fog in my head" associated with confusion, dry mouth and involuntary "shaking" of her legs. These episodes were reported to last 10-15 minutes with four to five episodes in a 24-hour period. Symptoms persisted for about one and one-half days at which time she additionally began to experience auditory hallucinations: a piano playing or hearing friends, not present with her, conversing. By the third day, the frequency of her episodes of "fog" and confusion had increased as had their duration, persisting for up to one to two hours. The patient presented again to the same emergency room, this time being admitted, her initial evaluation including a

consultation with the psychiatric team which noted “waxing and waning” levels of consciousness.

During the first two days of the patient’s hospitalization, her symptoms progressed to include what was described as “prominent paranoia”. Over the course of the ensuing days her symptoms progressed further; ultimately, the patient was largely unresponsive to verbal commands.

Work-up

Both patients underwent a thorough work-up for common infectious causes of encephalitis, including lumbar puncture, blood studies and head CT. Both patients additionally had blood studies sent for auto-immune and toxic etiologies. Other than abnormal white blood cell and glucose counts in the CSF of one patient, these studies were negative.

Further evaluation led to the identification in both patients of ovarian tumors; in Case One unilateral, Case Two bilateral. Due to progressive clinical deterioration, both patients had their tumors urgently surgically removed, pathology revealing findings consistent with teratoma. Blood and CSF samples were sent to the laboratory of Dr. Josep Dalmau of the University of Pennsylvania and the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) of the University of Barcelona, Spain, for detection of antibodies specific to the NMDAR. Diagnosis was confirmed by detection of IgG antibodies to the NR1 (also known as the GluN1) subunit of NMDAR in serum and CSF in both patients. (Note: serum IgM and IgA antibodies against NMDAR are not believed to have clinical value in this disease.)

Treatment

In addition to ovarian teratomaectomy, both patients received aggressive support in an intensive care setting over the course of several weeks. In addition, they each received high-dose intravenous steroids; intravenous immunoglobulin infusions times three courses; and, ultimately, due to the lack of clinical improvement, plasma exchange, also times three courses. Case one additionally received intravenous rituximab. For more information regarding current recommendations for treatment of anti-NMDAR and other forms of paraneoplastic encephalitis, please see the 2011 *The Lancet Neurology* review by Dalmau, Lancaster and Martinez-Hernandez.[4]

Clinical Course

Following treatment, both patients showed gradual improvement in their symptoms over months. Case One required approximately three months hospitalization followed by additional in-patient rehabilitation. Case Two's hospitalization and time in a rehab facility were briefer. At six months post-treatment, both patients continued to struggle with neurologic sequelae, including impaired short term memory and difficulties with concentration. Patient Two also experienced bilateral hearing deficit. At one year post-treatment, both patients had recovered sufficiently as to return to their courses of study though Case One continued to require weekly sessions with a learning specialist, not required in her pre-morbid state.

Discussion

Paraneoplastic neurologic syndromes are a heterogeneous group of neurologic disorders associated with various cancer types and caused by mechanisms other than metastases, metabolic or nutritional deficits, clotting defects or treatment side effects. The two patients described in this brief report reveal an important cause of paraneoplastic encephalitis in young people: the production of anti-NMDA receptor antibodies.

NMDAR encephalitis has been reported to frequently be associated with very serious complications, including death. Early identification and aggressive treatment of the patients described here likely was beneficial to their clinical outcomes, though each required prolonged hospitalization and recovery.

Some of the clinical features of NMDAR encephalitis are fairly specific, in particular neuropsychiatric symptoms such as mood disturbance and hallucinations, which we saw in each of our patients. Other symptoms of NMDAR encephalitis, some also present in our patients, can include insomnia; memory impairment; seizures; changes in level of consciousness; dyskinesia, dystonia and muscle rigidity; autonomic disturbance; language dysfunction.[5]

An age and gender-related association with teratoma incidence has been reported, where teratoma is more likely to occur in female patients over the age of twelve years with anti-NMDAR encephalitis.[5] Our patients followed this pattern.

The specific pathophysiologic phenomena causing encephalitis symptoms in patients producing NMDAR antibodies has been linked to the functional loss of NMDARs, a type of glutamate receptor, and the resultant impact on synaptic function in areas such as the hippocampus.[6]

In the evaluation of children, adolescents and adults in their 20's and 30's presenting with symptoms suggestive of acute encephalitis, it is important for the clinician to consider paraneoplastic syndromes, specifically NMDAR encephalitis, as exemplified in these patients.

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