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SHORT COMMUNICATION

Psychosis secondary to an incidental teratoma: a "heads-up" for psychiatrists and gynecologists

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Abstract Anti-N-methyl-D-aspartate receptor encephalitis is a potentially fatal form of autoimmune encephalitis that originates secondary to a host immune response to neural tissue within a teratoma. We describe the case of a 17-year old girl who presented with acute onset psychosis, catatonic movements, urinary incontinence, fever, tachycardia, and fluctuating periods of hypotension and hypertension. A CT scan demonstrated an incidental 6 cm ovarian teratoma. The patient fully recovered after ovarian cystectomy, followed by medical management with intravenous immunoglobins and plasmapheresis. Anti-N-methyl-D-aspartate receptor encephalitis is an important differential diagnosis to consider for young patients presenting with acute onset psychiatric symptoms, who develop seizures, movement disorders, or autonomic instability. It is important for psychiatrist and gynecologist to be aware of this diagnosis as delay in recognition can have serious consequences including patient death.

Keywords Anti-N-methyl-D-aspartate receptor encephalitis · Ovarian teratoma · Psychosis

Introduction

The association of an ovarian teratoma and Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has been described and is a serious and potentially fatal condition that occurs in young women and remains under-recognized. Although this syndrome is now believed to be the second most common etiology of autoimmune encephalitis (Titulaer et al. 2013), its existence still remains unknown to many psychiatrists and gynecologists.

Anti-NMDA receptor encephalitis is characterized by acute onset of psychosis, seizures, autonomic instability, and dyskinesia (Dalmau et al. 2011; Shimazaki and Hayasaka 2011). Eighty percent of affected patients are female, and approximately 60% have an underlying ovarian teratoma (Titulaer et al. 2013). The pathophysiology of the syndrome is related to an autoimmune process. Anti-NMDA receptor autoantibodies originate secondary to a host immune response directed against neural tissue within the ovarian teratoma. The generated autoantibodies then bind to host NMDA receptors located in the brain, thus leading to the constellation of clinical symptoms. The disease course can be severe but with prompt diagnosis, intensive care support, and surgical management in combination with immunotherapy, a good prognosis can be achieved (Titulaer et al. 2013).

Case

A 17-year-old disoriented female was admitted to the pediatric intensive care unit. The mother described the girl as a happy, well behaved, honor student up until a week prior to her admission when she started complaining of fatigue and did not want to go to school. She had no history of previous psychiatric disorders or medical problems. Past surgical history

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included a laparotomy and right oophorectomy for an ovarian teratoma at age 11.

On the day of her admission, the patient reportedly became extremely agitated and attempted to jump out of a moving automobile, claiming that "she wanted to see God". The patient was brought by her parents to the emergency room where she exhibited aggressive behavior, tore off her clothes, and attempted to assault her father and other staff in the emergency department. The patient was placed in restraints and treated with 2 mg of intramuscular haloperidol every 6 h as required for acute psychosis.

She was afebrile and normotensive. Physical examination was non-contributory. Reflexes were +2 bilaterally. Hematological indices and serum electrolytes were normal, and a urine toxicology screen was negative. On hospital day 2, she continued to experience emotional outbursts, periods of aggression, as well as episodes of confusion, disorientation, and lethargy. In addition, the patient began to exhibit choreoathetoid movements and lingual facial dyskinesia.

Urine cultures, blood cultures, and cerebral spinal fluid (CSF) cultures were negative, as were tests for autoimmune diseases, rheumatological disorders, endocrine abnormalities, and heavy metal exposure. Polymerase chain reaction results of CSF and serum for herpes simplex virus, cytomegalovirus, and Epstein-Barr virus were negative. However the CSF was positive for oligoclonal bands. A T1- and T2-weighted MRI of the brain was performed and showed no evidence of intracranial abnormalities. A CT scan of the abdomen and pelvis was normal except for an incidental finding of a 6 cm teratoma involving the left ovary.

On hospital day 3, her condition worsened. The patient developed urinary incontinence, began experiencing alternating periods of tachycardia and bradycardia, periods of hypotension and hypertension, and became febrile. Her blood pressure ranged from 90 to 159 mmHg systolic over 42–91 mmHg diastolic, pulse ranged from 56 to 149 beats per minute, and temperature from 98.2–101.0 F. The infectious disease service initiated treatment with intravenous vancomycin, ceftriaxone, and acyclovir for suspicion of an infectious encephalitis. Despite the antibiotic and antiviral therapy, she continued to spike daily fevers and to manifest signs of autonomic instability (Fig. 1).

On hospital day 5, the patient's mental status deteriorated as she was no longer able to recognize her mother. She would moan and shout incoherent words and respond only to painful stimuli. The patient continued to display choreoathetoid movements, lingual facial dyskinesia, and was unable to tolerate food orally.

At this time, the gynecology service was consulted for possible anti-NMDA receptor encephalitis secondary to the ovarian teratoma. Test for anti-NDMA receptor antibodies in the serum and CSF were sent; however, results were still pending. The decision was made to take the patient to the operating room for an ovarian cystectomy on hospital day 5. Findings at diagnostic laparoscopy revealed a surgically absent right ovary and a 4 × 6 cm teratoma that appeared to encompass

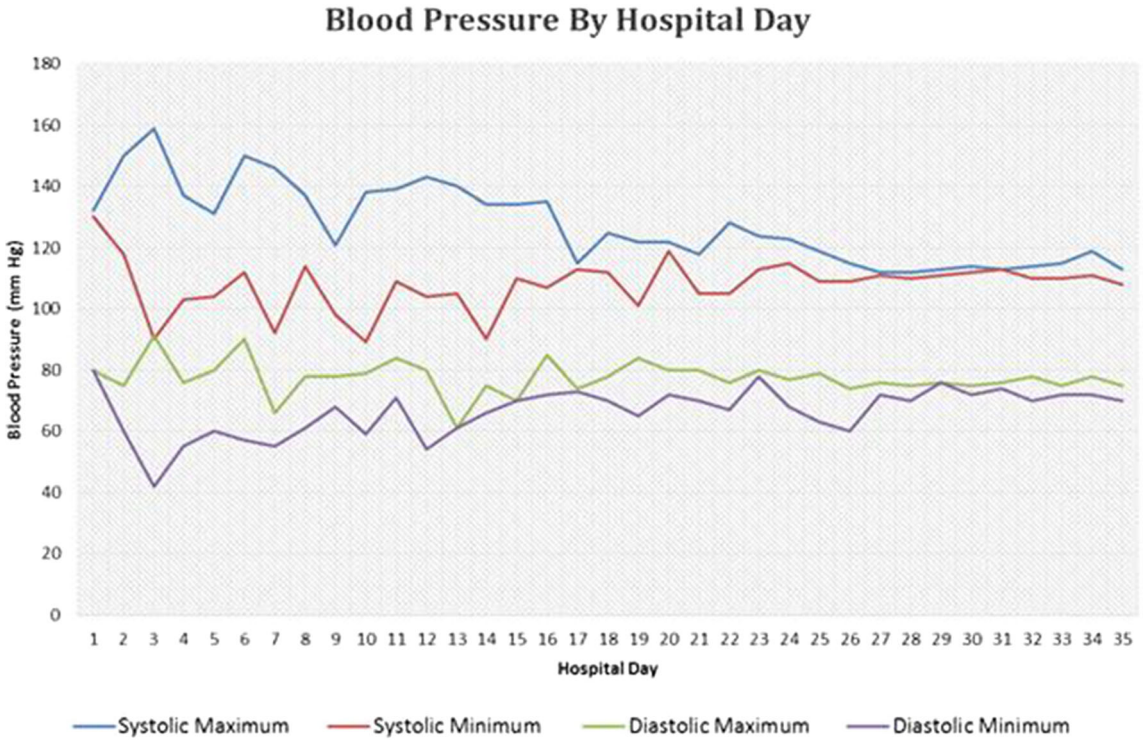

Fig. 1 Blood pressure by hospital day

the entire left ovary. In order to avoid possible spillage and maximize ovarian conservation of her only remaining ovary, the procedure was converted to an open laparotomy. The teratoma was enucleated from the ovarian tissue and removed en bloc with no spillage of contents. The surgical procedure was uncomplicated. The pathology report revealed a mature ovarian teratoma measuring 8.5 × 6.5 × 4.5 cm. The structure contained four teeth and yellow sebaceous material mixed with black hair and skin like structures. Interestingly, none of the represented pathology sections noted the presence of neuronal tissue.

On hospital day 6, postoperative day 1, the patient remained disoriented and catatonic. She continued to spike fevers and displayed signs of autonomic instability. Her blood pressure ranged from 112 to 150/57–90 mmHg and her pulse ranged from 68 to 124 beats per minute. Empiric medical treatment was started for anti-NMDA receptor encephalitis. The patient was given Solumedrol 250 mg IV q 6 h, intravenous immunoglobulin (IVIG) 1 g/kg over 12 h, and underwent plasmapheresis (4.5 L with 2% albumin) every other day for a total of 6 treatments.

The patient began to show signs of improvement after the fourth treatment of IVIG on hospital day 14, postoperative day 9. The choreoathetoid movements and lingual facial dyskinesia gradually disappeared and the patient was able to recognize and respond to her mother. Results of the serum and CSF anti-NDMA antibodies sent on hospital day 2 were available on hospital day 15, postoperative day 10. Both were reported as positive. This confirmed the diagnosis of anti-NDMA receptor encephalitis.

Her vital signs began to normalize by hospital day 25, postoperative day 20, after which she no longer had fever, hypertension, or tachycardia. At this time, the patient began interacting with health care workers and became oriented to her surroundings. Prior to discharge on hospital day 34, postoperative day 29, the patient was ambulating, interacting with her family members, doing homework, and applying make-up. The patient completed 6 treatments of IVIG. Two months after discharge, she made the honor roll and was preparing for her regional exams. At 14 months follow-up, she has shown no signs of relapse.

Discussion

Pathophysiology of anti-NMDA receptor encephalitis

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a rare neurological syndrome caused by autoantibodies directed against the N-methyl-D-aspartate receptor.

NMDA receptors are ubiquitous in the brain, with the highest density localized to the limbic system and in particular the hippocampus (Granerod et al. 2010). Symptoms of encephalitis manifest when anti-NMDA receptor autoantibodies bind to target regions on the NR1 subunit of NMDA receptors (Hughes et al. 2010). The binding of these autoantibodies leads to a profound loss of surface NMDA receptors secondary to receptor internalization by autophagy (Dalmau et al. 2011; Hughes et al. 2010). Similar antagonism of the NMDA receptor by drugs such as ketamine and phencyclidine (PCP) have been shown to produce anti-NMDA receptor encephalitis-like symptoms, including psychosis, autonomic instability, dystonia, hypertension, and cardiac arrhythmias (Dalmau et al. 2008). In the case of our patient, the anti-NMDA receptor autoantibodies originated from a host immune response to neural tissue found in the ovarian teratoma.

Clinical features

Anti-NMDA receptor encephalitis is a multistage illness. Patients initially present with prodromal flu-like symptoms including headache, fever, nausea, vomiting, diarrhea, or upper respiratory tract infections (Dalmau et al. 2011). Following the prodromal symptoms, a second phase ensues. Patients experience psychiatric symptoms that can be quite varied, but often include anxiety, insomnia, grandiose delusions, delirium, hallucinations, psychosis, aphasia, and violent behavior (Dalmau et al. 2011). After 2–3 weeks, a period of decreased responsiveness follows. The patient may alternate between periods of catatonia and agitation. During this phase, seizures, movement disorders, and autonomic instability are common manifestations (Dalmau et al. 2011). The seizures are typically complex and generalized, but in some cases, status epilepticus has been reported (Titulaer et al. 2013). The abnormal repetitive movements associated with anti-NMDA receptor encephalitis include oral-lingual facial dyskinesia, trunk choreoathetosis, rigidity, oculogyric crisis, and opisthotonus postures (Shimazaki and Hayasaka 2011). Frequent manifestations of autonomic instability include hypotension or hypertension, tachycardia or bradycardia, cardiac arrhythmias, hyperthermia, urinary incontinence, and hypoventilation. If left untreated, the patient can develop respiratory depression and even death. (Titulaer et al. 2013; Dalmau et al. 2011; Shimazaki and Hayasaka 2011).

Diagnosis

This wide constellation of symptoms can be explained by the distribution of NMDA receptors in regions of the brain that are responsible for memory, personality, movement, cognition, and autonomic control. However, due to the variability and non-specific nature of the symptoms, patients are often misdiagnosed (Dalmau et al. 2011). During the initial phases, patients are often thought to have an acute psychiatric disorder and may be referred to a psychiatrist. Many patients are treated with antipsychotic medication, and if they develop rigidly, or

autonomic instability, it is thought to be secondary to neuroleptic malignant syndrome (Dalmau et al. 2011). Patients with hyperthermia and autonomic instability may also be presumed to have an infectious etiology and are treated with antimicrobial therapy. In our patient, infection was one of the early differential diagnoses, and she was treated empirically for both bacterial and viral pathogens.

Non-specific CSF finding include moderate lymphocytic pleocytosis, increased protein, and oligoclonal bands. Oligoclonal bands can be found in up to 60% of patients and may incorrectly lead to a diagnosis of multiple sclerosis (Dalmau et al. 2011). Brain MRI is negative for any findings in 50% of cases, and in the other 50%, T2 or FLAIR signal hyperintensity may be apparent in the hippocampus, frontobasal and insular regions, basal ganglia or brainstem, and cerebellar or cerebral cortex (Dalmau et al. 2011). These changes may be difficult to detect as they are often subtle, transient, and do not correlate to severity of the symptoms (Dalmau et al. 2011). Electroencephalogram (EEG) may show non-specific slow and disorganized activity (Dalmau et al. 2011; Shimazaki and Hayasaka 2011).

Diagnosis is confirmed by detecting antibodies against the NMDA receptor in the patient's serum or CSF. It can take several weeks to obtain results of this test from outside laboratories, and, therefore, a high index of clinical suspicion is needed. In the case of our patient, antibody test results were not available at the time of the ovarian cystectomy procedure. When the gynecology service was consulted for removal of the teratoma, the patient was catatonic, responsive to only painful stimuli, tachycardic, and febrile. Although the patient was in critical condition, we made the decision to proceed with surgery based on the clinical findings of her worsening condition and exclusion of other diagnoses in the differential. Since only a very small amount of neuronal tissue is necessary to trigger an antibody response, its presence within the teratoma may not always be identified by pathologists.

Treatment

The main objective of therapy is to reduce or eliminate the anti-NMDA receptor antibody levels. Initial therapy should be aimed at removing the ovarian teratoma and initiation of immunotherapy (Bai et al. 2016). Early surgical intervention has been shown to improve prognosis (Bai et al. 2016). First line immunotherapy includes corticosteroids, intravenous IgG immunoglobulins, and plasmapheresis. A large observational study of 577 patients with anti-NMDA receptor encephalitis showed neurological improvement in 81% of patients treated with immunotherapy and tumor removal (Titulaer et al. 2013). If no response is seen, second line immunotherapy with rituximab or cyclophosphamide is recommended (Titulaer et al. 2013).

Recovery and prognosis

As patients recover, they experience a reverse order of the symptoms. Recovery may be a slow process, sometimes requiring hospitalization for 3–4 months (Dalmau et al. 2011). Many patients will also require physical and behavioral rehabilitation for several months; however, 75% of patients will recover or have mild sequelae. The other 25% will remain severely disabled or may die. The reported mortality for anti-NMDA receptor encephalitis ranges from 4 to 7% (Titulaer et al. 2013; Dalmau et al. 2011; Acién et al. 2015). Relapses have been reported in approximately 20–25% of patients (Dalmau et al. 2011; Shimazaki and Hayasaka 2011).

Conclusions

It is important that psychiatrists and gynecologists are aware of this condition and promptly consider it among their differential diagnoses when presented with a similar clinical scenario. Delay in diagnosis can have serious consequences, including unnecessary treatment or patient death. In many cases, surgical intervention and initiation of medical therapy may have to be undertaken before the diagnosis can be confirmed by presence of anti-NMDA receptor antibodies in the serum or CSF.

Compliance with ethical standards The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Human and animal rights and informed consent This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from the patient included in the report.

Conflict of interest The authors declare that they have no conflict of interest.

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