Journal of Pediatric Surgery (2010) **45**, 1550–1553

ELSEVIER

Journal of Pediatric Surgery

www.elsevier.com/locate/jpedsurg

Anti–*N*-methyl-D-aspartate receptor encephalitis associated with an ovarian teratoma in an adolescent female ☆

Aaron P. Lesher [a], Thomas J. Myers [a], Fred Tecklenburg [b], Christian J. Streck [a,*]

[a] *Division of Pediatric Surgery, Department of Surgery, Medical University of South Carolina, Charleston, SC 29425, USA*
[b] *Department of Pediatrics-Critical Care, Medical University of South Carolina, Charleston, SC 29425, USA*

Received 11 February 2010; revised 1 April 2010; accepted 5 April 2010

Key words:
Encephalitis;
NMDA receptor antibodies;
Ovarian teratoma;
Children;
Paraneoplastic syndrome

Abstract Anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a recently described paraneoplastic syndrome with prominent neuropsychiatric symptoms. We report a case of NMDA receptor encephalitis in a 15-year-old female related to the development of NMDA receptor autoantibodies triggered by an ovarian teratoma. Removal of the mature teratoma proved curative with eventual resolution of the paraneoplastic disease process and associated psychiatric symptoms. Increasingly, reports of anti-NMDA receptor encephalitis associated with ovarian teratomas in pediatric patients, as well as a novel assay to measure these antibodies, suggest an etiology for this disease process that may be amenable to prompt surgical excision. The clinical presentation, diagnosis, and surgical management of the disease, as well as a review of the literature, are included.

1. Case report

A 15-year-old previously healthy Hispanic female presented to a local referring hospital with transient loss of consciousness and seizure-like activity. Initial evaluation, including routine laboratory tests and computed tomographic (CT) imaging of the head, was unremarkable. She was discharged home with outpatient neurology follow-up. The following day, she began having visual hallucinations and bizarre psychotic behavior. She was further evaluated by an electroencephalogram that demonstrated bitemporal sharp spikes, started on antiseizure medication, and readmitted for inpatient observation. She was transferred to our Children's Hospital for further evaluation and treatment when her symptoms progressed, including worsening emotional lability, increasing disorientation, and a progressive dyskinetic movement disorder. Inpatient consultations with neurology, psychiatry, and infectious disease were obtained. Workup of her delirium, including repeat electroencephalogram and head CT, revealed no underlying pathologic condition. Magnetic resonance imaging of the brain demonstrated a subtle hyper-T2 signal of the mesial temporal lobes bilaterally. Lumbar puncture; blood cultures; serum viral studies, including herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and Varicella-Zoster Virus; toxicology; and metabolic evaluation did not reveal an etiology. The patient became increasingly agitated with little response to intravenous benzodiazepines, sedatives, and antipsychotics and required antihypertensive medication for new-onset hypertension. On hospital day 6, the patient developed acute nonoliguric renal failure. Evaluation of her hypertension and

☆ No financial conflicts of interest to disclose.

* Corresponding author. Tel.: +1 843 792 3853; fax: +1 843 792 3858.
E-mail address: streck@musc.edu (C.J. Streck).

0022-3468/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.jpedsurg.2010.04.002

acute renal failure included a renal ultrasound and biopsy that were unremarkable. Despite empiric antiviral therapy, broad-spectrum antibiotics, and stress-dose steroids for suspected autoimmune encephalitis, the patient's mental status continued to deteriorate requiring intensive care unit observation.

While in the intensive care unit, a review of the patient's extensive evaluation revealed an incidental finding of a 6.0 × 4.0 × 4.3-cm left ovarian mass on her renal ultrasound (Fig. 1). The Pediatric Surgery Service was consulted, and an abdominal CT scan demonstrated a solid left adnexal mass with evidence of calcification consistent with an ovarian teratoma (Fig. 2). Because of concern for a paraneoplastic syndrome, serum and cerebrospinal fluid samples were sent for analysis of anti–*N*-methyl-D-aspartate (NMDA) receptor antibodies. Serum β-human chorionic gonadotropin and α fetoprotein were measured and were normal. A diagnostic laparoscopy revealed a solid left ovarian mass. The contralateral ovary was normal appearing. Pelvic fluid sampling and a laparoscopic left oophorectomy were performed given the extensive tumor involvement of the ovary. Pathologic examination confirmed the diagnosis of a mature ovarian teratoma. The results of the anti-NMDA receptor antibody assay later revealed high antibody titers in cerebrospinal fluid and serum. Three doses of intravenous immunoglobulin were given in the first postoperative week with minimal improvement in her agitation. The patient remained confused and disoriented with periods of improvement and decline for approximately 2 weeks, at which time she had a rapid improvement in her mental status and progressed to her predisease state over the next few days. An

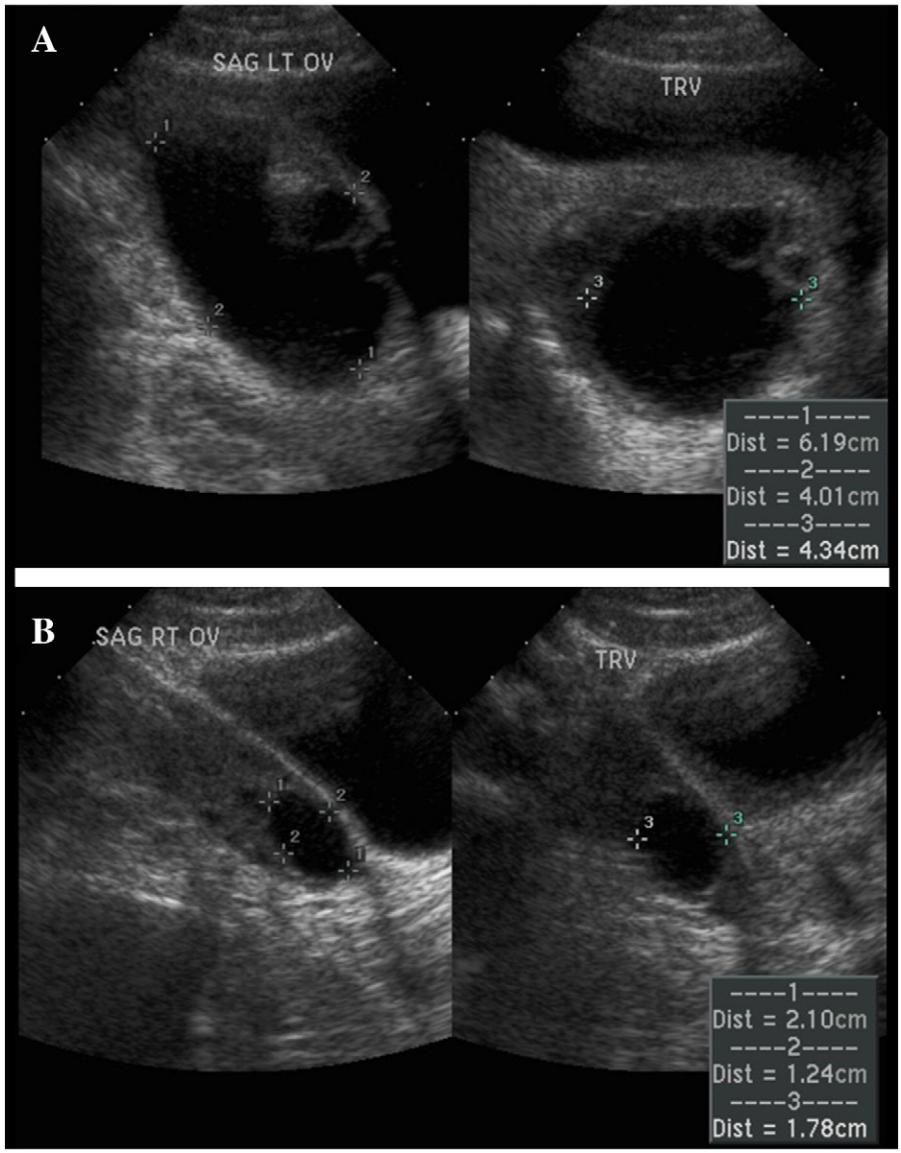

Fig. 1 Transabdominal ultrasonography demonstrates a 6.2 × 4.0 × 4.3-cm cystic mass in the left ovary (panel A) compared to a normal-appearing right ovary (panel B).

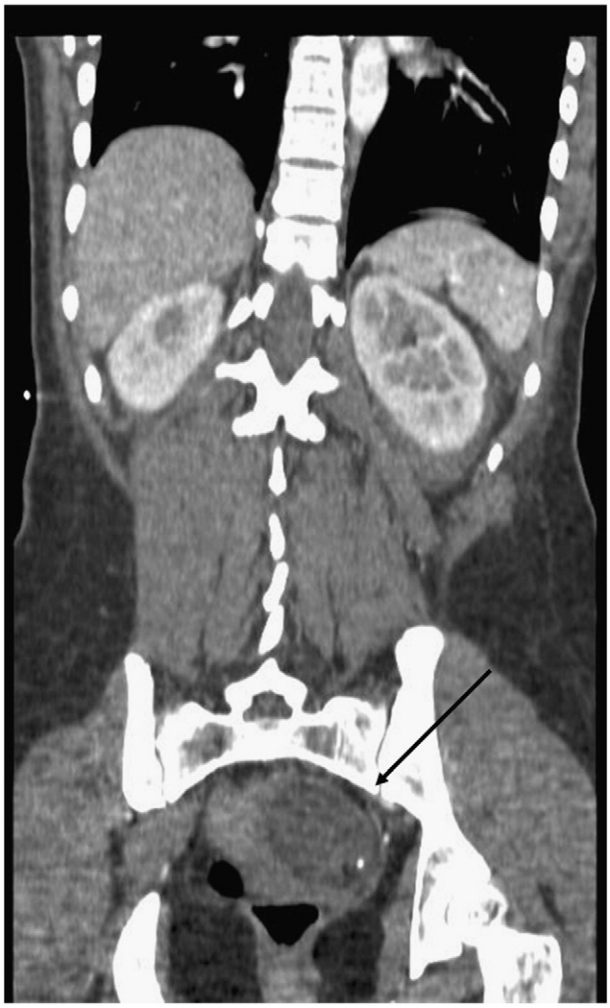

Fig. 2 A coronal reconstruction of a CT scan of the patient's abdomen and pelvis reveals a cystic left adnexal mass with an internal focus of fat and high attenuation material suggesting an ovarian teratoma (black arrow).

outpatient follow-up appointment revealed an active, alert teenager without residual neurologic deficit.

2. Discussion

We present a case of an adolescent female with paraneoplastic anti-NMDA receptor encephalitis. Paraneoplastic syndromes in children are uncommon and are traditionally associated with Wilm's tumor and neuroblastoma [1]. Recent work by Dalmau and colleagues [2] has uncovered an autoimmune paraneoplastic process that accounts for a severe form of encephalitis previously undescribed. Patients present with a recognizable syndrome predominantly characterized by escalating confusion, amnesia, agitation, and paranoid or delusional thoughts. In this disease process, autoantibodies to the NMDA Receptor 1 subunit of the NMDA receptor are detectable in serum and cerebrospinal fluid. The NMDA receptors are ligand-gated cation channels primarily expressed in the hippocampus and forebrain and are implicated in memory and learning [3]. Drugs interacting with the NMDA receptor, including ketamine and phencyclidine, induce paranoia, dissociative symptoms, and hallucinations, which are common symptoms in anti-NMDA receptor encephalitis.

The incidence of paraneoplastic anti-NMDA receptor encephalitis is not known. The first substantial case series described 12 patients with 3 similarities: all were young females (14-44 years of age) with prominent neuropsychiatric symptoms, ovarian (n = 11) or mediastinal (n = 1) teratomas, with detectable quantities of serum or cerebrospinal fluid antibodies that interacted with the cell membrane of rat hippocampal neurons in vitro [2]. In this report, initial presenting symptoms ranged from short-term memory loss and confusion to acute psychiatric syndrome with paranoia and behavioral changes. Eleven patients had partial or generalized seizures, and 10 patients required mechanical ventilation because of central hypoventilation. Nine patients underwent teratoma resection with 8 patients demonstrating neurologic improvement. One patient died without improvement of neurologic symptoms. Clinical improvement in patients correlated with falling serum and cerebrospinal fluid anti-NMDA receptor antibody levels. A subsequent larger series of 100 patients with anti-NMDA receptor encephalitis documented 58 cases associated with tumors, 49 of which were ovarian teratomas [4]. Patients in this series who underwent tumor excision within 4 months of the onset of neurologic symptoms had a significantly better outcome than patients without tumor or those with late or no tumor removal.

A recent report of 81 patients with anti-NMDA receptor encephalitis revealed that 40% were younger than 18 years, with a median age of 14 years [5]. Older female patients had a higher frequency of ovarian teratomas than younger patients, with 31% of girls younger than 18 years old having teratomas compared with 56% of females older than 18 years. Only 9% of females younger than 14 years had associated teratomas. Most patients presented with behavioral or personality changes with progression to seizures in 77%, 84% with stereotyped movements, 86% with autonomic instability, and 23% with central hypoventilation. Patients were treated with immunotherapy with teratoma removal if applicable. Full recovery was more common in patients with immunotherapy and teratoma excision than those without teratoma [5]. Although not all patients presenting with NMDA receptor encephalitis are female with ovarian teratomas, the frequency of these patients mandates screening of these patients with ultrasound, CT scans, or magnetic resonance imaging to rule out a causative tumor.

The common presenting symptoms of patients with NMDA receptor encephalitis include neuropsychiatric symptoms, seizures, dyskinesias, loss of consciousness, amnesia, and autonomic dysfunction. Our patient exhibited all of these symptoms over her disease course. However,

unlike the patients described in other series, our patient did not exhibit central hypoventilation. One reason for this could be identification and removal of the tumor relatively early in her clinical course, compared to patients in the literature. Our patient's ovarian teratoma was removed approximately 3 weeks after the onset of symptoms. In one report, neurologic symptoms were present for 3 weeks to 4 months before the diagnosis of teratoma, with time to initial improvement ranging from 3 days to 16 weeks [2]. In addition, our patient demonstrated neurologic improvement on postoperative day one with subsequent waxing and waning. Steady, gradual improvement in her cognitive abilities began approximately 14 days after excision of the teratoma with full return to function by postoperative day 20. Slow improvement with periods of relapse seems to be a characteristic of anti-NMDA encephalitis, likely because of the failure of common immunomodulatory therapies to provide sustained control of the immune response [4]. Removal of the NMDA-expressing tumor has been associated with a decrease in serum and cerebrospinal fluid levels of the pathologic autoantibody [6]. For benign-appearing ovarian masses, cystectomy should be attempted if a plane can be developed between the cystic tumor and normal ovarian tissue. Cystectomy preserves gonadal tissue in the patient of childbearing age with an otherwise benign tumor. In our case, oophorectomy was performed because there was no normal-appearing ovarian tissue. In addition, some authors suggest that symptomatic ovarian masses, as in the case of patients with precocious puberty, warrant oophorectomy [7].

Outcomes of NMDA receptor encephalitis vary from full recovery, to 24-hour institutional care, to death after prolonged hospitalization [2,6,8]. In addition to surgical excision of the teratoma, immunotherapy, including corticosteroids, intravenous immunoglobulin, and plasmapheresis, has been widely used in patients to date [5]. Given the relative novelty of this disease process, there are no randomized, controlled data to support or condemn the use of immunotherapy in this patient population. Our patient did receive 3 doses of intravenous immunoglobulin in the early postoperative period, although no immediate neurologic improvement was noted. However, reports of patients with anti-NMDA receptor encephalitis with and without a teratoma have demonstrated clinical responses to immunomodulatory regimens, including steroids, intravenous immunoglobulin, and plasmapheresis in patients [5,8]. Although the reasons for our patient's successful outcome are unknown, treatment should clearly include prompt evaluation and treatment of suspicious ovarian masses while in the care of a multidisciplinary team.

Awareness and recognition of anti-NMDA receptor encephalitis is of utmost importance to pediatric specialists because complete recovery after surgical resection is possible despite the severity of symptoms. Increasing numbers of case reports in the neurology [2,6,9] and gynecology [10] literature, as well as coverage in the lay press [11], are highlighting the severity of the disease as well as the potential for surgical cure. Adolescents presenting with severe psychotic symptoms or seizures and dyskinesias may have previously been misdiagnosed with psychiatric illness or viral encephalitis. With the development of a reliable assay to measure autoantibody titers, and the clinical awareness to rule out an ovarian mass, otherwise difficult-to-treat neuropsychiatric patients may benefit from prompt diagnosis and treatment of this novel clinical entity.

References

[1] Rees JH. Paraneoplastic syndromes: when to suspect, how to confirm, and how to manage. J Neurol Neurosurg Psychiatry 2004;75(Suppl II): ii43-50.

[2] Dalmau J, Tuzun E, Wu H, et al. Paraneoplastic anti–*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.

[3] Waxman EA, Lynch DR. *N*-methyl-D-aspartate receptor subtypes: multiple roles in excitotoxicity and neurological disease. Neuroscientist 2005;11:37-49.

[4] Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-8.

[5] Florance NR, Davis RL, Lam C, et al. Anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11-8.

[6] Seki M, Suzuki S, Lizuka T, et al. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 2008;79:324-6.

[7] Hayes-Jordan A. Surgical management of the incidentally identified ovarian mass. Semin Pediatr Surg 2005;14:106-10.

[8] Ishiura H, Matsuda S, Higashihara M, et al. Response of the anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. Neurol 2008;71:1921-6.

[9] Sansing LH, Tuzun E, Ko MW, et al. A patient with encephalitis associated with NMDA receptor antibodies. Nat Clin Pract Neurol 2007;3:291-6.

[10] Kort DH, Vallerie AM, DeMarco EF, et al. Paraneoplastic anti–*N*-methyl-D-aspartate receptor encephalitis from mature cystic teratoma. Obstet Gynecol 2009;114:373-6.

[11] Sanders L. Diagnosis: brain drain. New York Times Mag 2008:MM22.