AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS SHORT RESEARCH REPORT

Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis: have you checked the ovaries?

KIRSTY CLEVERLY[1], PIETRO GAMBADAURO[2] & RAMESAN NAVARATNARAJAH[1]

[1]*Department of Obstetrics and Gynaecology, The Royal London Hospital, Bart's Health NHS Trust, London, UK, and*
[2]*Department of Learning, Informatics, Management and Ethics (LIME), Karolinska Institute, Stockholm, Sweden*

Key words
Encephalitis, ovarian neoplasms, receptors *N*-methyl-D-aspartate, teratoma, autoantibodies, anti-*N*-methyl-D-aspartate receptor encephalitis, paraneoplastic syndromes, laparoscopy

Correspondence
Kirsty Cleverly, Department of Obstetrics and Gynaecology, Royal London Hospital, Whitechapel Road, London E1 1BB, UK.
E-mail: kirsty.cleverly@bartshealth.nhs.uk

Conflicts of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Cleverly K, Gambadauro P, Navaratnarajah R. Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis: have you checked the ovaries? Acta Obstet Gynecol Scand 2014; 93:712–715.

Received: 20 February 2014
Accepted: 25 March 2014

DOI: 10.1111/aogs.12386

Abstract

Anti-*N*-methyl-D-aspartate receptor encephalitis is an autoimmune disorder that can occur as a paraneoplastic phenomenon related to ovarian teratomas. It is a serious but reversible condition with improved outcomes following prompt tumor removal. We report two cases from our recent experience. In the first case a small poorly described lesion, confirmed as a teratoma only at histology, was managed by laparoscopic oopohorectomy. In the second case a large teratoma was managed by laparoscopic cystectomy. Postoperatively both women made a good recovery. Gynecologists may be called upon to perform ovarian surgery outside of normal surgical indications, in young women who will often lack capacity to consent. Fertility-sparing ovarian cystectomy is possible in some cases, but will be challenging for small deeply buried tumors. Blind bilateral oophorectomy has been performed successfully in extreme cases. Information of the benefit of ovarian surgery will be essential to the surgeon during preoperative counseling.

Abbreviations: FLAIR, fluid attenuated inversion recovery; NMDAR, *N*-methyl-D-aspartate receptor.

Introduction

Autoimmune encephalitis can occur as a paraneoplastic phenomenon. An interesting association has been reported among paraneoplastic encephalitis, the presence of an ovarian teratoma and antibodies to the *N*-methyl-D-aspartate receptor (NMDAR) (1).

Anti-NMDAR encephalitis is typically seen in females of reproductive age presenting with a characteristic neuropsychiatric sequence (Table 1) (2) and high levels of antibodies against the NMDAR in blood and cerebrospinal fluid. It is a life-threatening but potentially reversible condition. The association of ovarian teratoma and improved outcomes with tumor removal makes this uncommon syndrome an important topic for general gynecologists. The body of literature on anti-NMDAR encephalitis is composed of case reports and case series. The NMDAR is formed of two subunits (NR1 and NR2) that bind glycine and glutamate, respectively. The receptor plays a crucial role in synaptic plasticity and memory function. In anti-NMDAR encephalitis, symptoms follow the rise of antibody titers in the serum and cerebrospinal fluid. The presence of such antibodies is significantly related to the finding of a teratoma (3).

Teratomas are pluripotent and may contain neural tissue that expresses the NMDAR. In a case series of 25

Table 1. Clinical features of anti-*N*-methyl-D-aspartate receptor encephalitis.

Prodrome	Flu-like symptoms
Stage 1	Apathy Fear Depression Psychosis Cognitive impairment
Stage 2	Tonic clonic seizures Loss of verbal output Inability to follow verbal commands Athetoid movements Catatonic state
Stage 3	Autonomic instability Cardiac arrhythmias Hypoventilation (may require intubation) Dyskinesia Extrapyramidal signs Oro-lingual facial dyskinesias

patients with anti-NMDAR encephalitis who had a teratoma, all tumors contained neural tissue expressing NMDAR (4). An immune response against this ectopic nervous tissue could result in abnormally high NMDAR antibody titers. Symptoms result from the antibodies cross-reacting with the native NMDAR in neural tissue, leading to its destruction and down-regulation. Case series have suggested that 58% of patients will have an ovarian teratoma (4). Anti-NMDAR encephalitis can be life-threatening with cause of death from autonomic instability leading to acute respiratory distress, hospital-acquired sepsis or cardiac arrest. Most patients have a prolonged hospital admission often in an intensive care setting. In one cohort of 360 patients, 75% recovered with mild disability, the remainder died or were left with a serious disability (3).

With prompt treatment and intensive care support outcome can be good. Medical treatment is with corticosteroids, intravenous immunoglobulins, plasma exchange and monoclonal antibodies directed against CD-20 B lymphocytes (such as rituximab). Antibody titers are highest in those patients with an identifiable tumor, but removal results in a rapid fall in antibody titers, better response to medical therapy and an improved outcome. In one series ($n = 105$) immunotherapy led to substantial clinical improvement in 80% of patients after tumor removal, compared with 48% where no lesion was identified (3). Relapses, seen in 20–25%, are more common in cases where an identified tumor has not been removed (3), which if done within 4 months shortens symptom duration and reduces relapse frequency (4).

Case reports

A retrospective analysis of serum found to be positive for anti-NMDAR in the immunology department of our tertiary referral unit showed 13 female cases over the last 4 years. Of these women, 62% had imaging of the pelvis to look for ovarian pathology (63% with MRI and 38% with ultrasonography). We present the two women in which an ovarian teratoma was identified.

Case 1

A 25-year-old woman was visiting the UK from Hungary and was brought to the emergency department with a 3-week history of behavior change, agitation and paranoia. She was confused and disorientated with no focal neurological deficit. She had one generalized tonic clonic seizure on admission. A lumbar puncture showed lymphocytosis with normal protein and negative culture. She was started on acyclovir, phenytoin and lamotrigine with a provisional diagnosis of viral encephalitis. The MRI showed bilateral hippocampal changes with increased T2 fluid attenuated inversion recovery (FLAIR) signal in the hippocampi. NMDAR antibodies were positive, immunoglobulin A levels were mildly elevated (0.61) and other immunoglobulins and protein electrophoresis were normal. All other autoantibodies and tumor markers were negative or normal.

Presumed diagnosis changed to autoimmune encephalitis and prednisolone was commenced. Her cognitive state deteriorated with increasing agitation, incomprehensible vocalization, characteristic orofacial hyperkinetic movements and only intermittent tracking and blinking response to visual threat. Presumed diagnosis changed to autoimmune encephalitis and she was commenced on intravenous immunoglobulin with plasma exchange.

An MRI of the pelvis demonstrated a fat-containing lesion of the left ovary, too small to measure and difficult to further characterize. A CT scan of chest and abdomen was normal. She did not have capacity to consent for an oophorectomy. Consent was obtained after a discussion between the neurology and gynecology teams, the next of kin and a Hungarian health advocate. She underwent an uncomplicated laparoscopic left oophorectomy on day 19 of admission. Histopathology reported a mature cystic teratoma containing skin, fat, cartilage and sweat glands. She was admitted to the intensive care unit for aspiration pneumonia and during her stay there had episodes of autonomic instability with tachycardia and intermittent T-wave abnormalities. She made a steady recovery and was stepped down to the neurology ward on day 37. At discharge she was conversing reasonably and was repatriated on day 49.

Case 2

A 22-year-old woman presented to the neurology team with behavioral and movement disorders and generalized tonic clonic seizures. She was transferred to our intensive care unit requiring intubation and was diagnosed with anti-NMDAR encephalitis. She was managed with rituximab. A pelvic MRI demonstrated a 95 × 133-mm complex ovarian mass, likely a teratoma. A laparoscopic ovarian cystectomy was performed 28 days later with intact tumor removal. Histopathology showed a stage 1a immature teratoma containing a large immature neuronal component and germinal centers. Peritoneal washings were negative. She was discharged with neurology rehabilitation 4 months later.

Discussion

Gynecologists need to be aware of anti-NMDAR encephalitis because they will be called upon to remove tumors that fall outside the normal surgical indications, often in women who lack capacity to consent to surgery. The surgeon must be confident of the diagnosis and that a surgical intervention will improve neurological outcome.

NMDAR encephalitis is an under-recognized condition. With the advent of markers the antibody is being sought and found with increasing frequency. One retrospective study over 5 years found anti-NMDAR antibodies in six of seven cases of "encephalitis of unknown origin" (5). Two of three of these patients had an ovarian teratoma, one detected 3 years after symptom onset. Diagnosis can be challenging and key differentials must have been considered and reliably excluded before any surgical intervention. Investigations to exclude an infective (bacterial, viral, prion) or autoimmune encephalitis, Wernicke's or Hashimoto's encephalopathy and neoplastic lesions (primary, secondary, lymphoma) should be considered (6).

The next line of investigation is screening for a causative neoplasm. Ovarian teratomas are the most commonly associated lesion, with MRI being the best standard imaging technique. In the largest published case series (n = 400), only seven non-ovarian tumors were found (3). Other neoplasms provoking the condition are rare, but include mediastinal tumors (7), small cell carcinomas of the lung (4), and sex cord stromal tumors (6). The low frequency of non-ovarian pathology has led to a recommendation that whole body screening may not be necessary. Potentially difficult situations may arise when a request is made for surgical intervention outside the normal indications. In case 1 we describe a very small tumor not definitively described as a teratoma on radiological imaging and too small for visual detection and removal by cystectomy. In such situations we believe it to be reasonable to search for an alternative trigger with additional imaging of the chest and abdomen before oophorectomy.

There is no evidence to indicate the best surgical approach. Logic would suggest that removal of the tumor without spillage would result in the best outcome but more cases with longer follow-up are needed to confirm this. Most case reports describe management with oophorectomy (1). However, the patient group is typically young and consideration must be made to fertility-sparing ovarian conservation. Although laparoscopic cystectomy of large teratomas is feasible (8), removing a small dermoid cyst that is deeply embedded in the ovary can be challenging. A case report of localization by laparoscopic ultrasonography of a 10-mm tumor with removal by cystectomy has been described (9).

Ovarian surgery has potential implications for future fertility. As there is no time for ovarian stimulation it is not possible to freeze oocytes or embryos. A possible alternative could be cryopreservation of ovarian cortex, a promising technique that has been successfully used as an option for fertility preservation in cancer patients (10). Multidisciplinary communication involving the patients advocate is a vital part of preoperative planning. With improved recovery rate following teratoma removal and the rise of new options for fertility preservation, a question arises as to whether blind bilateral oophorectomy should be performed without preoperative tumor identification. Previously unidentified tumors have been found at post-mortem, suggesting that the provoking teratoma may be missed with current imaging techniques (4). After 6 months of nonconvulsive status epilepticus one patient underwent bilateral oophorectomy. Microscopic teratomas were found followed by prompt recovery (11). However, cases have also been described where a similar approach resulted in no teratoma being identified at histopathology (12).

Anti-NMDAR receptor encephalitis is a serious condition that may be completely reversed with optimal medical care and unconventional gynecological surgery. A registry of cases should be formed to identify the true incidence and treatment options of this condition.

Funding

No specific funding source.

References

1. Dalmau J, Tuzun E, Wu H, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61:25–36.

2. Peery HE, Day GS, Dunn S, Fritzler MJ, Pruss H, De Souza C, et al. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun Rev. 2012;11:863–72.
3. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10:63–74.
4. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7:1091–8.
5. Pruss H, Dalmau J, Harms L, Holtje M, Ahnert-Hilger G, Borowski K, et al. Retrospective analysis of NMDA Receptor antibodies in encephalitis of unknown origin. Neurology. 2010;75:1735–9.
6. Day GS, High SM, Cot B, Tang-Wai DF. Anti-NMDA-receptor encephalitis: case report and literature review of an under-recognized condition. J Gen Intern Med. 2011;26:811–6.
7. Stover DG, Eisenberg R, Johnson DH. Anti-*N*-methyl-D-aspartate receptor encephalitis in a young woman with a mature mediastinal teratoma. J Thorac Oncol. 2010;5:1872–3.
8. Campo S, Marone M, Gambadauro P, Garcea N. Laparoscopic conservative excision of a rare asymptomatic 11-cm ovarian dermoid cyst containing a mandible with seven teeth. Gynaecol Endosc. 2000;9:65–8.
9. Asai S, Ishimoto H, Yabuno A, Asada H, Seki M, Iwata S. Laparoscopic cystectomy of ovarian teratoma in anti-NMDAR encephalitis: 2 case reports. J Minim Invasive Gynecol. 2011;18:135–7.
10. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. N Engl J Med. 2009;360:902–11.
11. Johnson N, Henry C, Fessler AJ, Dalmau J. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. Neurology. 2010;75:1480–2.
12. Parratt KL, Allan M, Lewis SJ, Dalmau J, Halmagyi GM, Spies JM. Acute psychiatric illness in a young woman: an unusual form of encephalitis. Med J Aust. 2009;191:284–6.