Open Journal of
Clinical & Medical
Case Reports

Volume 2 (2016)
Issue 5

ISSN 2379-1039

Multimodal Imaging for Characterizing Neoplasia in Anti-NMDA Receptor encephalitis

Michael J. Bradshaw, MD*; Fredrick D. Oakley, MD, PhD; Adam Nagy, MD; Mark Tedford, MD; Kelly M. Brown, MD; Siddharama Pawate, MD

***Michael J. Bradshaw, MD**
Department of Neurology, Vanderbilt University Medical Center, USA
Email: Michael.j.bradshaw@vanderbilt.edu

Abstract

Autoimmune encephalitis should be considered in all cases of encephalitis, and recognition of the clinical features is critical for neurologists, internists and other physicians. Classic features seen in NMDAR-autoantibody encephalitis were well illustrated by this case and include subacute neuropsychiatric manifestations (hallucinations, memory loss), movement disorders and seizures, often in the absence of fevers. This case also demonstrates the characteristic EEG changes, known as extreme delta brush. Sending both cerebrospinal fluid and serum for NMDAR autoantibodies is important in the diagnostic approach, as we demonstrate here. We highlight the importance of multimodal imaging, when necessary, to characterize suspected malignancy in cases of NMDAR-antibody encephalitis, which surgeons may require in order to proceed with intervention.

Keywords

N-Methyl-D-Aspartate; NMDA; Autoimmune encephalitis; Teratoma; Paraneoplastic

Introduction

Encephalitis is inflammation of the brain parenchyma with associated neurologic dysfunction. While viral etiolgoies are the most common, the next most frequently identified category are autoimmune encephalitides, which are important to include in the differential diagnosis of encephalitis [1]. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a potentially reversible autoimmune, sometimes paraneoplastic condition caused by auto antibodies targeting the NMDAR. This leads to internalization of the synaptic NMDAR and causes neuropsychiatric manifestations and often seizures [2]. Since the discovery of NMDAR encephalitis, a number of other antibody-mediated encephalitides have been identified, most of which respond favorably to immunotherapy [3]. We present a case that demonstrates many features of the illness and highlights importance of multimodal imaging, when necessary, to characterize suspected malignancy in cases of NMDAR-antibody encephalitis, which surgeons may require in order to proceed with intervention.

Case Report

A 29-year-old middle-eastern woman presented with subacute headaches, memory loss, behavioral changes, auditory hallucinations and seizures.

Over the week prior to admission, she developed new headaches, auditory hallucinations consisting of "background music" playing constantly, emotional lability and suffered several generalized tonic-clonic seizures. On admission, she was afebrile, tachycardic and intermittently catatonic with diffuse, symmetric hyperreflexia.

Lumbar puncture revealed 106 nucleated cells with 87% lymphocytes; protein and glucose were normal. The remaining evaluation was unremarkable. She was treated with levetiracetam and empiric acyclovir until CSF herpes-simplex virus and varicella zoster virus PCR returned negative. Intravenous methylprednisolone and intravenous immune globulin (IVIg) were given for suspected autoimmune encephalitis.

She deteriorated with myoclonic facial movements that lacked EEG correlate, dysautonomia (episodes of sinus tachycardia and apnea), increasing encephalopathy and frequent clinical seizures, for which she was loaded with fosphenytoin, transferred to the ICU and intubated. Electroencephalography demonstrated extreme delta brush pattern in the bilateral frontal lobes (Figure 1). Anti-NMDAR immunoglobulin G (IgG) autoantibodies were undetectable in the serum but were found in the cerebrospinal fluid at 1:20; other classes of immunoglobulins were not tested. Contrasted brain MRI was normal, but 18-fluorodeoxyglucose positron-emission tomography (PET) revealed hypothalamic hypermetabolism and severe hypometabolism in the bilateral occipital cortices (Figure 2). CT chest/abdomen/pelvis revealed a cystic adnexal mass, and MRI of the pelvis characterized this as an ovarian teratoma (Figure 3). Upon review with the gynecology service, the patient underwent exploratory laparotomy. The pelvic mass was removed and identified as a mature cystic teratoma (Figure 4). Within 24 hours, the patient's neurologic status improved. She completed five days of intravenous methylprednisolone and IVIg and was given two doses of rituximab 14 days apart (the second dose was given after discharge). After a four-week hospitalization she returned to neurologic baseline apart from some asthenia secondary to deconditioning and was discharged to inpatient rehabilitation. Now more than seven months from presentation, the patient is doing well off immunomodulatory therapy with moderate memory difficulty as her only sequela.

Discussion

Autoimmune encephalitis should be considered in all cases of encephalitis, and recognition of the clinical features is critical. Those seen in NMDAR-autoantibody encephalitis were well illustrated by this case and include subacute neuropsychiatric manifestations (behavioral abnormalities, hallucinations, memory loss) and seizures, often in the absence of fevers [4]. These are often followed by movement disorders, catatonia, autonomic instability and coma.

In approaching the diagnosis, autoantibodies targeting the NMDAR should be sought in the serum and CSF, as 15% of patients will only have autoantibodies detectable in the CSF [5], as in this case. Most patients will have abnormalities on EEG, typically areas of nonspecific slowing. The extreme delta brush pattern, which consists of 1-3 Hz delta activity with superimposed 20-30Hz beta activity is relatively unique to NMDAR encephalitis [6]. Brain MRI may be less sensitive than PET scan, which may demonstrate fronto-temporal hypermetabolism with occipital hypometabolism, as in this case [7].

This case illustrates the need for an interdisciplinary approach to the management of patients

with autoimmune encephalitis (e.g. neurology, critical care, surgery). We highlight that in order for surgeons to proceed with intervention, multimodal imaging may be necessary for characterizing suspected malignancy in cases of NMDAR encephalitis. Ovarian teratomas are discovered in approximately 50% [8,9] of affected females over the age of 18 and, while pelvic ultrasound is often the first-line imaging modality, MRI is the most sensitive [10]. Teratomas are the most common malignancies associated with NMDAR encephalitis, but other tumors have been reported as well, including breast carcinoma, small cell lung cancer, ovarian neuroendocrine tumors, sex cord stromal tumors, pancreatic pseudopapillary neoplasia, neuroblastoma and Hodgkin lymphoma among others. Men and older adults are less likely to have an underlying malignancy [11]. Prompt removal of any underlying tumor is an important therapeutic intervention.

If the clinical suspicion is high and infectious etiologies have been excluded, empiric immunotherapy should be considered while awaiting confirmatory autoantibodies. First-line therapy includes tumor removal, intravenous corticosteroids (generally methylpredinsolone 1g daily for five days) and IVIg (0.4g/kg daily for five days) or plasma exchange. Patients who do not improve with first-line treatment require second-line immunotherapy including rituximab and/or cyclophosphamide, which should be considered if there is no improvement in the first ten days [4]. The optimal duration of therapy has not been well defined, but should generally continue at least until there is substantial clinical improvement, which may take up to 18 months [5]. Some 15-24% of patients with NMDA receptor encephalitis will relapse, possibly after several years, which may occur in the setting of occult teratoma or teratoma recurrence or in the absence of malignancy. Therefore, some authors have suggested treatment with immunosuppression (mycophenolatemofetil or azathioprine) for at least a year [12].

Figures

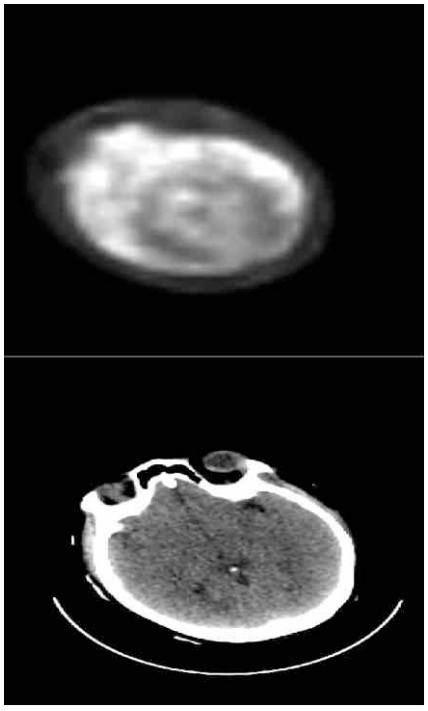

Figure 1: Electroencephalogram - This demonstrated bifrontally predominant, rhythmic, delta activity with superimposed beta activity characteristic of extreme delta brush seen in NMDAR-autoantibody encephalitis.

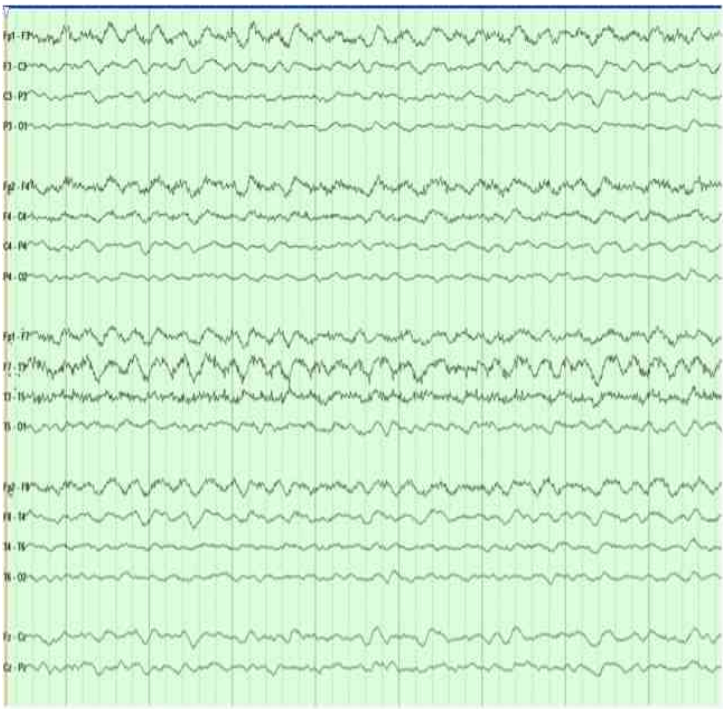

Figure 2: Brain fluorodexoyglucose positron emission tomography (FDG-PET) and CT - There was severe reduction of metabolic activity within the bilateral occipital cortices with hypothalamic hypermetabolism.

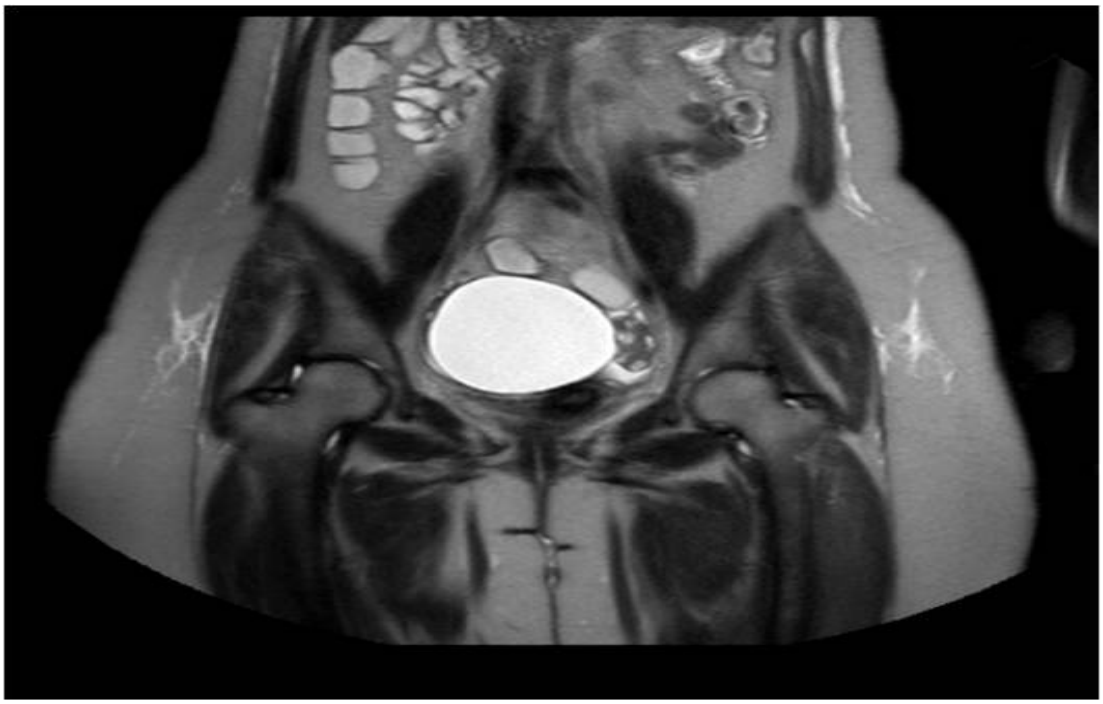

Figure 3: Coronal T2 MRI pelvis - This characterized the mass as a teratoma and led to the exploratory laparotomy.The bladder is decompressed by a foley catheter, the hyperintense cystic component is seen midline arising from the left ovarian teratoma, which is heterogenous in appearance.

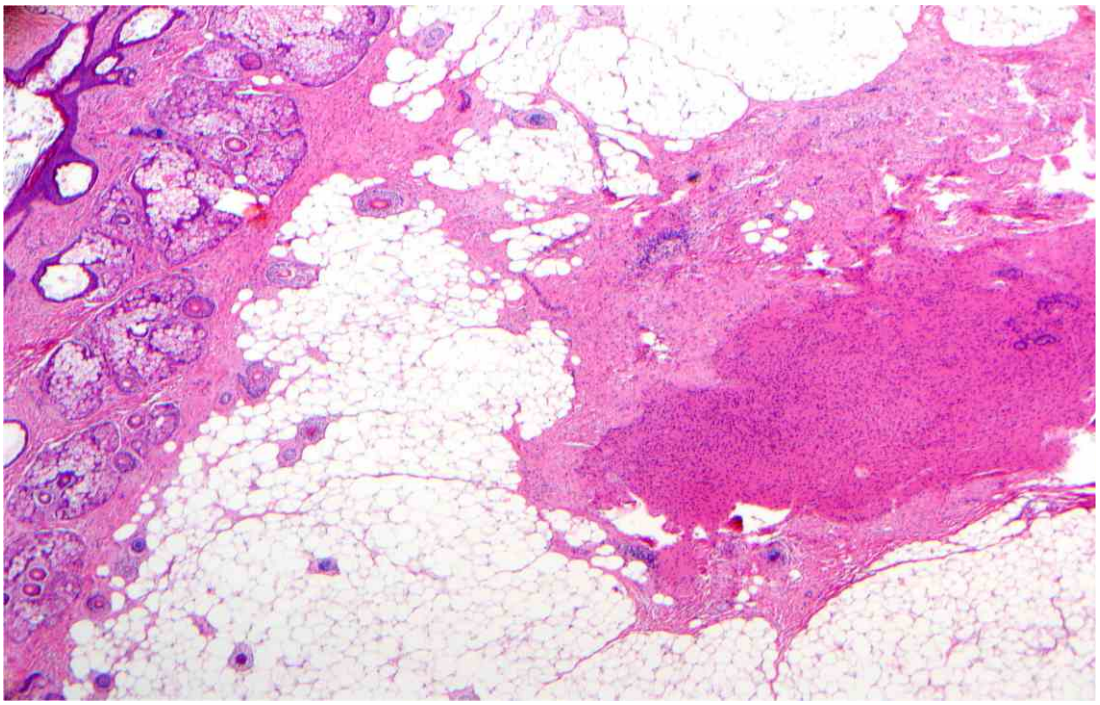

Figure 4: Pathological specimen of the ovarian mass (H&E stain) - This demonstrated a mature teratoma with multiple tissue types. Hair follicles and sebaceous glands are present (left), neural tissue (right) with ependymal-like structures (top-right), adipose tissue (center, lower).

References

1. Armangue T, Leypoldt F, Dalmau J. Autoimmune encephalitis as differential diagnosis of infectious encephalitis. Current opinion in neurology. 2014;27(3):361-8. doi: 10.1097/WCO.0000000000000087. PubMed PMID: 24792345; PubMed Central PMCID: PMC4132825.

2. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Annals of neurology. 2005;58(4):594-604. doi: 10.1002/ana.20614. PubMed PMID: 16178029; PubMed Central PMCID: PMC2245881.

3. Linnoila JJ, Rosenfeld MR, Dalmau J. Neuronal surface antibody-mediated autoimmune encephalitis. Seminars in neurology. 2014;34(4):458-66. doi: 10.1055/s-0034-1390394. PubMed PMID: 25369441.

4. Mann AP, Grebenciucova E, Lukas RV. Anti-N-methyl-D-aspartate-receptor encephalitis: diagnosis, optimal management, and challenges. Therapeutics and clinical risk management. 2014;10:517-25. doi: 10.2147/TCRM.S61967. PubMed PMID: 25061311; PubMed Central PMCID: PMC4085332.

5. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. The Lancet Neurology. 2013;12(2):157-65. doi: 10.1016/S1474-4422(12)70310-1. PubMed PMID: 23290630; PubMed Central PMCID: PMC3563251.

6. Veciana M, Becerra JL, Fossas P, Muriana D, Sansa G, Santamarina E, et al. EEG extreme delta brush: An ictal pattern in patients with anti-NMDA receptor encephalitis. Epilepsy & behavior : E&B. 2015. doi: 10.1016/j.yebeh.2015.04.032. PubMed PMID: 26071995.

7. Leypoldt F, Buchert R, Kleiter I, Marienhagen J, Gelderblom M, Magnus T, et al. Fluorodeoxyglucose positron emission tomography in anti-N-methyl-D-aspartate receptor encephalitis: distinct pattern of disease. Journal of neurology, neurosurgery, and psychiatry. 2012;83(7):681-6. doi: 10.1136/jnnp-2011-301969. PubMed PMID: 22566598; PubMed Central PMCID: PMC3740122.

8. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Annals of neurology. 2009;66(1):11-8. doi: 10.1002/ana.21756. PubMed PMID: 19670433; PubMed Central PMCID: PMCPMC2826225.

9. 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(19):1735-9. doi: 10.1212/WNL.0b013e3181fc2a06. PubMed PMID: 21060097.

10. Perera DS, Prabhakar HB. Imaging of the adnexal mass. Clinical obstetrics and gynecology. 2015;58(1):28-46. doi: 10.1097/GRF.0000000000000083. PubMed PMID: 25608251.

11. Titulaer MJ, McCracken L, Gabilondo I, Iizuka T, Kawachi I, Bataller L, et al. Late-onset anti-NMDA receptor encephalitis. Neurology. 2013;81(12):1058-63. doi: 10.1212/WNL.0b013e3182a4a49c. PubMed PMID: 23946310; PubMed Central PMCID: PMCPMC3795591.

12. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. The Lancet Neurology. 2011;10(1):63-74. doi: 10.1016/S1474-4422(10)70253-2. PubMed PMID: 21163445; PubMed Central PMCID: PMCPMC3158385.

Manuscript Information: Received: November 29, 2015; Accepted: March 07, 2016; Published: March 10, 2016

Authors Information: Michael J. Bradshaw, MD[1*]; Fredrick D. Oakley, MD, PhD[2]; Adam Nagy, MD[1]; Mark Tedford, MD[1]; Kelly M. Brown, MD[1]; Siddharama Pawate, MD[1]

[1]Department of Neurology, Vanderbilt University Medical Center, USA
[2]Department of Pathology, Vanderbilt University Medical Center, USA

Citation: Bradshaw MJ, Oakley FD, Nagy A, Tedford M, Brown KM, Pawate S. Multimodal imaging for characterizing neoplasia in anti-NMDA receptor encephalitis. Open J Clin Med Case Rep. 2016; 1087

Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.

Visit the journal website at **www.jclinmedcasereports.com**