Seizure 20 (2011) 266–270

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Case report

Anti-NMDA receptor encephalitis presenting with imaging findings and clinical features mimicking Rasmussen syndrome

Hansel Greiner [a], James L. Leach [b], Ki-Hyeong Lee [a], Darcy A. Krueger [a,*]

[a] Department of Pediatrics, Division of Child Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

ARTICLE INFO

Article history:
Received 15 September 2010
Accepted 1 November 2010

Keywords:
NMDA receptor
Encephalitis
Children
Rasmussen syndrome
Neuroimaging
Treatment

ABSTRACT

Background: Antibody mediated anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a recently reported diagnosis of clinical importance. Recognition of the syndrome, especially in pediatric populations, is difficult and often undiagnosed and/or confused with neurological disorders with similar clinical features.

Results: We report a case of an 11 year old female with explosive-onset epilepsy and predominantly unilateral frontal lobe abnormalities on magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) neuroimaging. A diagnosis of Rasmussen syndrome (RS) was considered. Cerebrospinal fluid analysis revealed strong positivity for NMDA receptor antibodies. Screening for occult ovarian teratoma with computed tomography (CT) and MRI initially did not demonstrate associated tumor. Treatment with steroids and plasma exchange improved her clinical course and subsequent MRI showed resolution.

Conclusion: NMDA receptor encephalitis has variable neuroimaging manifestations, and can mimic other entities. We emphasize the clinical syndrome of NMDA receptor encephalitis and consideration of the diagnosis in evaluating a child with explosive-onset epilepsy, unilateral imaging abnormalities, and neurocognitive decline.

1. Introduction

Anti-NMDA-receptor (NMDAR) encephalitis is an acute autoimmune paraneoplastic syndrome that can occur with or without identifiable associated tumors, commonly presenting in young women with occult ovarian teratoma. The clinical features were initially described in 1997 in a 19 year old woman with limbic encephalitis which improved after removal of an ovarian teratoma.[1] The identification of disease-causing antibodies was not made until 2007.[2] NMDAR encephalitis is characterized by prominent subacute, progressive neuropsychiatric signs and symptoms, including depression and catatonia, and can progress to death or disability in many cases.[3] Seizures, headaches, disordered sleep and movement disorders, including orofacial dyskinesias, also occur in a majority of patients. In addition, patients may develop hypoventilation, dysautonomia, and coma.[2] The overall clinical course is variable, ranging from full recovery to death. Relapses may occur. The syndrome has been most frequently reported in young women, but identification of NMDAR encephalitis occurring in children as young as 2 and 3 years of age is increasing.[4,5] However, in males and prepubertal girls, the association with tumor is more rare than that reported in adults.[4]

The differential diagnosis in presenting cases leads clinicians to a broad and extensive evaluation. NMDAR encephalitis has no specific findings on standard brain magnetic resonance imaging (MRI), cerebrospinal fluid analysis (CSF), or electroencephalogram (EEG) evaluation. Nonspecific abnormalities on fluid attenuated inversion recovery (FLAIR) sequences of MRI are common, not only in the medial temporal lobes but also in the basal ganglia, cerebellum, and cerebral cortex.[3] CSF pleocytosis is seen in 89–95% of reported cases. CSF oligoclonal bands are less frequently seen but have been consistently reported.[3,4,6] EEG typically shows focal delta or theta waves, and subclinical seizures are frequently reported. Due to these nonspecific findings, children may be misdiagnosed with infectious encephalitis or autoimmune disorders other than NMDAR encephalitis. In a study by Gable et al. of 10 cases of NMDAR encephalitis, four of whom were children, MRI, CSF, and EEG did not differentiate anti-NMDA-receptor encephalitis from viral etiologies, but some differences were noted in clinical presentation.[6] For instance, in differentiating Herpes Simplex Virus

* Corresponding author at: Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 2015, Cincinnati, OH 45229, USA. Tel.: +1 513 636 9214; fax: +1 513 636 1888.
E-mail address: Darcy.Krueger@cchmc.org (D.A. Krueger).

1059-1311/$ – see front matter © 2010 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2010.11.013

Type 1 (HSV-1) Encephalitis, HSV-1 cases were generally older with less psychiatric disturbances, and less likely to have movement disorders and dysautonomia. In another recently described case of NMDAR encephalitis occurring in a 15 year old girl, the initial presentation was consistent with the NMDAR encephalitis syndrome, but the patient subsequently experienced 10 relapses associated with extensive longitudinal myelitis and optic neuritis, mimicking neuromyelitis optica.[7]

Here we describe presentation of NMDAR encephalitis in an 11 year-old female with explosive-onset epilepsy and unilateral imaging findings mimicking Rasmussen syndrome (RS).

2. Case report

A previously healthy 11 year-old right handed white female was transferred to our tertiary referral medical center for evaluation and treatment of explosive onset of daily seizures and psychiatric disturbances. Symptoms began with daily holocranial headaches, neck pain, dysthymia, and hypersomnia for one week. She then had a generalized tonic–clonic seizure at school. She was brought to a local hospital, where initial evaluation included head computed tomography (CT) that was normal and lumbar puncture (LP) revealed a mild pleocytosis (18 wbc/dl) and mildly elevated protein (67 g/dl). HSV-1 PCR was negative. She remained hospitalized for the next three weeks due to daily seizures. Seizures typically began with left leg tonic stiffening, then spread to right leg and subsequently generalized. Multiple anticonvulsant regimens during this period were largely ineffective in controlling seizure activity. The patient also developed marked personality change, with profound abulia, periods of catatonia, and bradykinesia. Serial brain MRI over a three week interval revealed an enlarging area of focal FLAIR abnormality in the right frontal lobe, which was not seen on the initial study (Fig. 1). Bilateral medial frontal lobe involvement was also noted (Fig. 2). This contralateral finding was not prominent on the subsequent study, and was felt to be related to edema from her seizures which were occurring daily at that time. Brain biopsy was proposed in hopes for more accurate diagnosis, but parents elected to transfer the patient to our center for a second opinion.

Transfer occurred three weeks after seizure onset (day 20). Upon arrival, her physical exam was remarkable for profound abulia, aprosody and paucity of speech. Choreoathetotic movements of the left hand and mirror movements of the left hand were also noted. A second LP was performed and demonstrated a mild elevation of opening pressure (22 cm water) but the pleocytosis noted on the prior LP had resolved (2 wbc/dl). A serum and CSF workup for autoimmune and paraneoplastic disorders was sent. A 24 h EEG revealed focal delta/theta slowing centrally (Fig. 3). On

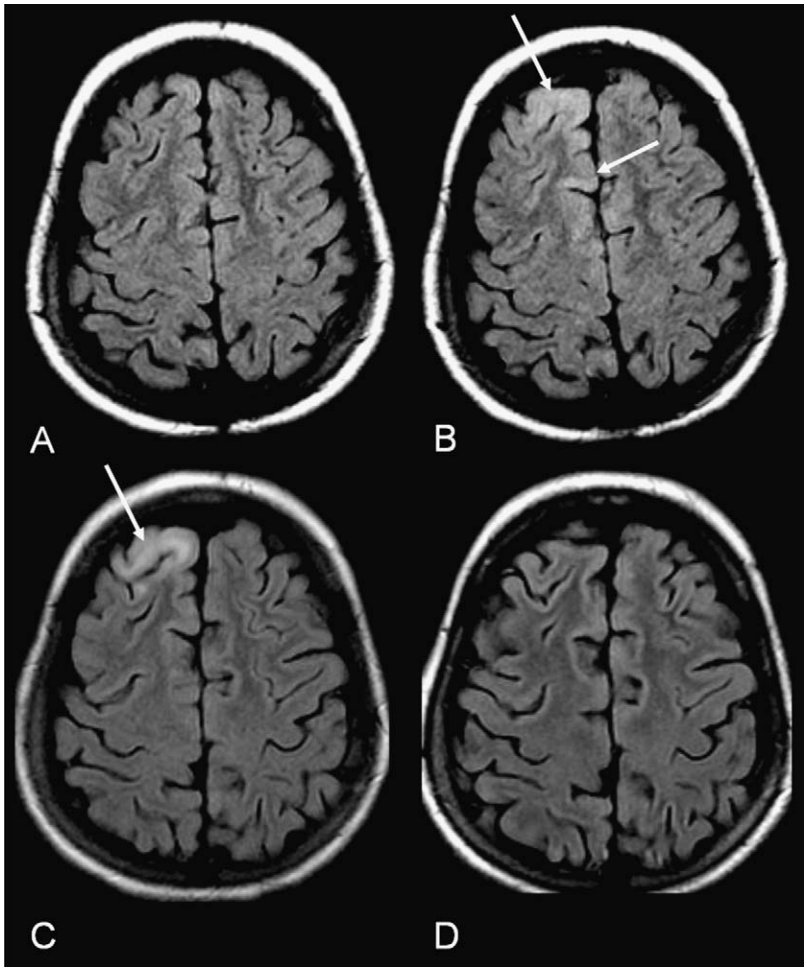

Fig. 1. Superior frontal-lobe brain MRI. Axial T2 FLAIR images (1.5 T, 5 mm slice thickness, TR: 10,002 ms, TE: 121 ms, TI: 2200 ms): (A) at initial presentation, (B) 3 days after presentation, (C) 20 days after presentation, (D) 88 days after presentation. At initial presentation (A) no definitive signal abnormality is identified in the superior frontal lobes. Repeat scan 3 days later (B) demonstrates abnormal increased cortical signal and gyral swelling involving the superior frontal gyrus (arrows, B). There was no diffusion restriction or abnormal enhancement. At 20 days after presentation (C) the signal abnormality is more defined anteriorly and extends into the subcortical white matter (arrow, C). The more posterior superior frontal gyrus signal has resolved. At longer term follow up (D, 88 days after initial presentation), there is complete resolution of the signal abnormality.

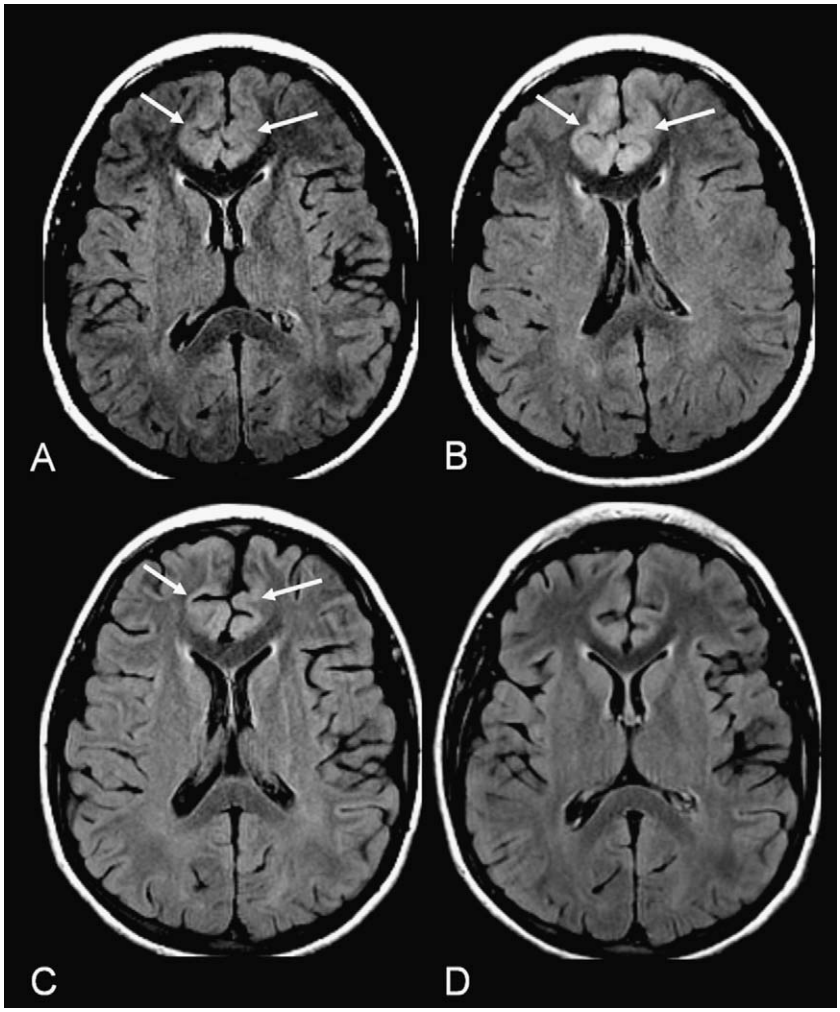

Fig. 2. Medial frontal lobe brain MRI. Axial T2 FLAIR images (1.5 T, 5 mm slice thickness, TR: 10,002 ms, TE: 121 ms, TI: 2200 ms): (A) At initial presentation, (B) 3 days after presentation, (C) 20 days after presentation, (D) 88 days after presentation. Subtle bilateral inferior medial frontal cortical signal abnormality was noted at presentation (A, arrows). This progressed over three days with increasing signal and gyral swelling (B, arrows). No diffusion restriction or enhancement was noted. At 20 days after presentation there is marked resolution of signal and gyral swelling with minimal increased signal remaining (C, arrows). At long term follow-up (88 days after presentation) there is complete resolution of the signal changes (D).

the basis of progressively more pronounced unilateral MRI findings and an explosive onset of seizures, the diagnosis of RS was considered. Positron emission tomography (PET) showed a focal area of hypermetabolism in the right frontal lobe (Fig. 4) correlating to the FLAIR signal abnormality noted on MRI (Fig. 1). A computed tomography (CT) scan of the chest, abdomen, and pelvis evaluating for occult malignancy did not identify any tumor. However, the pelvic CT and subsequent thin-slice MRI of same region did demonstrate a small paratubal cyst (Fig. 5). Serum testing for NMDAR antibodies was negative but strongly positive in the CSF for NR1/NR2 subunits. Serum testing for other antibodies associated with CNS paraneoplastic syndromes was negative, including Hu, Ma1, Ma2, CV2, VGKC, and amphiphysin. Initial neuropsychometric testing revealed significant deficits in processing speed and working memory.

Prior to identification of anti-NMDAR antibodies in the CSF, the patient was started on empiric high-dose intravenous methylprednisolone. In the ensuing week, she experienced intermittent episodes of hypoventilation and tachycardia. No further clinical seizures were seen. After the third day of corticosteroid there was a plateau in her psychiatric symptoms and she occasionally spoke voluntarily. After completion of five days of corticosteroid treatment, an incomplete return to baseline prompted initiation of five sessions of plasma exchanges performed on alternating days. At the end of these two courses of therapy, she continued to be seizure free, choreoathetotic movements ceased, affect was improved but still not back to baseline, and subtle left leg weakness was noted. She was discharged from the hospital in stable condition after a total of eight weeks following initial presentation at the outside hospital.

At three-month follow-up, the patient's parents reported that she continued to have improvement of personality and cognition, although both still were not back to baseline. She was now independent with activities of daily living. Neuropsychometric testing revealed ongoing deficits in processing speed and working memory, but these were significantly improved. She continued to have subtle left leg weakness. Parents reported at this time a three-day history of hypersomnia and fatigue concerning for possible relapse, prompting follow-up MRI of the brain. The prior FLAIR abnormality in the right frontal lobe was completely resolved (Fig. 1). Still, a five day course of oral corticosteroids was prescribed, with resolution of clinical symptoms. At six-month followup, routine imaging surveillance with ultrasound demonstrated bilateral 1 cm echogenic lesions in the ovaries. Exploratory laporotomy was performed and the lesions were surgically removed under ultrasound guidance which were confirmed to be ovarian teratomas by subsequent histological analysis.

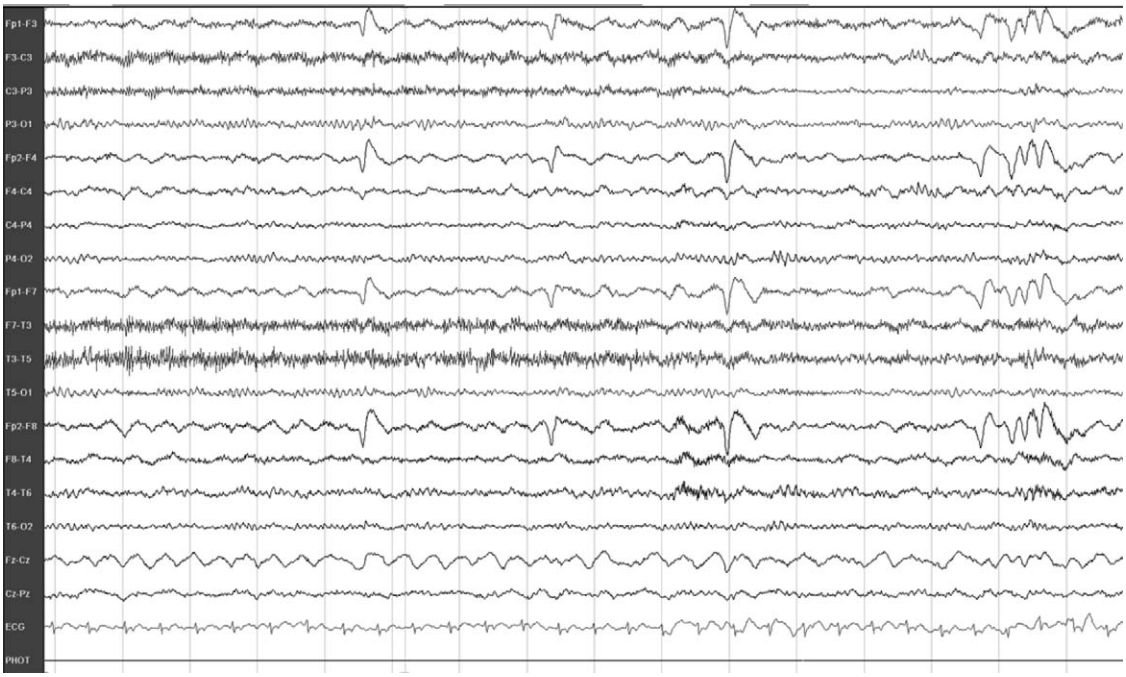

Fig. 3. Electroencephalography (EEG). Routine awake EEG using the 10/20 international system of electrode placement was performed 20 days after seizure onset. Shown is AP bipolar montage, demonstrating central focal slowing.

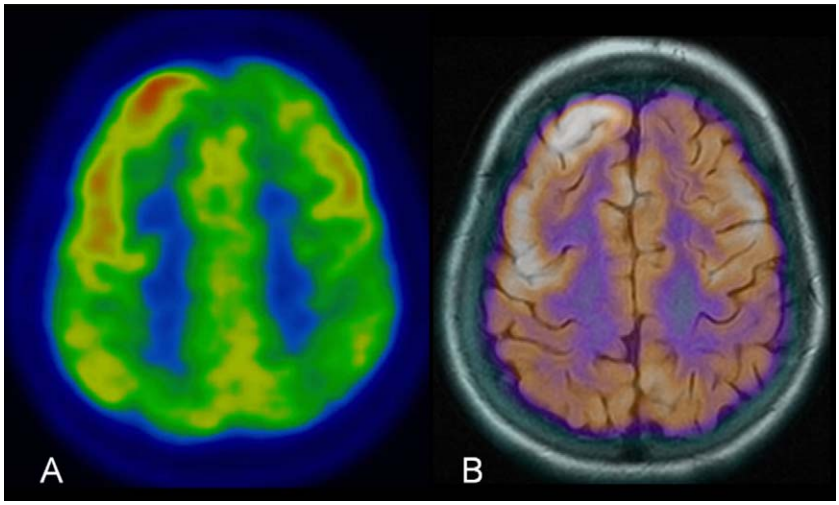

Fig. 4. Positron emission tomography (PET). PET images of the brain obtained after IV administrations of 7.53 mCi F-18 fluorodeoxyglucose (FDG) 24 days after seizure onset. (A) Color coded axial images, (B) PET–MRI fusion (with axial FLAIR sequence performed 20 days after initial presentation). Areas of asymmetric hypermetabolism are noted in the superior right frontal lobe (A, arrows), corresponding to the areas of increased signal on recent MR imaging (B).

3. Discussion

Identification of a recognizable clinical syndrome associated with NMDAR antibodies in the CSF is an important discovery in new onset pediatric epilepsy cases, particularly in girls. Our case represents a mimic of the acute phase of Rasmussen syndrome (RS). In a recent European Consensus Statement on RS, the acute phase is described as a period of frequent seizures and neurological deterioration.[8] While seizures in RS classically present as epilepsia partialis continua (EPC), this is not always the case. Twenty-four percent of patients diagnosed with RS will have supplementary motor area or premotor area-localizing seizures, as in our case.[9] Current proposed diagnostic criteria of non-biopsy-proven RS include focal seizures, unilateral cortical deficits, unilateral EEG findings, and hyperintense FLAIR signal on MRI.[8] Our patient had all of the features consistent with the diagnosis of RS except for unihemispheric cortical atrophy. Reversible brain atrophy has been reported in two women with anti-NMDA-receptor encephalitis.[10] As in our patient, the finding of unilateral focal increased metabolism of glucose on FDG-PET is suggestive of subclinical seizures in RS but has also been described interictally in RS patients.[11] In one published report describing FDG-PET in NMDAR encephalitis, bilateral areas of hypermetabolism were seen.[12]

Our patient exhibited many features described in acute RS. Ignoring the psychiatric manifestations of anti-NMDA-receptor encephalitis, or misinterpreting them as part of an epileptic encephalopathy, could have led to a missed diagnosis. The typical course of RS is relentless, and hemispherectomy is offered to patients with a suspected diagnosis. Given the literature indicating clinical improvement in most children with anti-NMDA-receptor

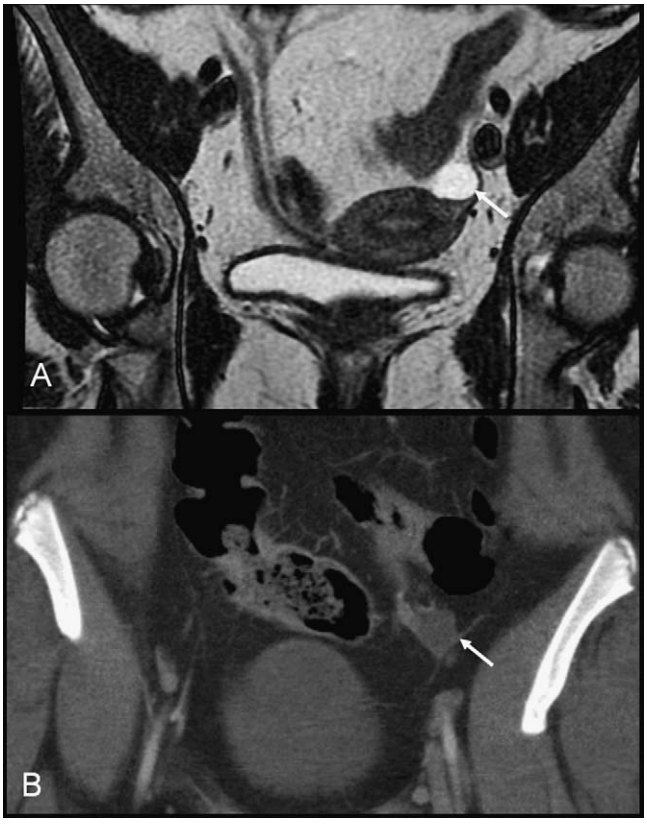

Fig. 5. Pelvis Imaging. (A) Coronal oblique T2 weighted MRI of the pelvis (slice thickness: 3 mm, TR: 5200 ms, TE: 76 ms). (B) Coronal reconstruction, CT scan of the pelvis. A small right sided paratubal cyst (arrows, A and B), but no definite solid tumor, was identified.

encephalitis, a misdiagnosis of RS would be problematic. The workup, treatment, and prognosis of the two disorders differ significantly.

Treatment of NMDAR encephalitis, beyond the decision to remove the associated tumor identified in neoplastic cases, consists of immunomodulatory therapy. Oral and intravenous corticosteroids, intravenous immune globulin and plasmapheresis have all been reported.[4] Cyclophosphamide and rituximab have been used in refractory cases.[4,13] No prospective studies are available to guide the clinician. Relapsing patients may show improvement with repeated treatments.

In children, paraneoplastic disorders have generally been considered extremely rare. NMDAR encephalitis in children is more likely to be nonparaneoplastic than paraneoplastic. However, as highlighted in this case, the neoplasm may be undetectable by imaging at clinical presentation. Given the rapid contribution of literature to this topic since it was described, the prevalence of NMDAR encephalitis is likely to be underappreciated. This may be especially true of patients with NMDAR antibodies who present with less severe symptomology, since the diagnosis is usually considered only in severe and puzzling cases. In a study of 19 young women with unexplained new onset epilepsy, five had NMDAR antibodies.[14] Four out of these five had psychiatric disturbances consistent with the syndrome. It would be interesting to know if NMDAR encephalitis accounts for a similarly high proportion of unexplained new-onset epilepsy in children. In 1992 Sebire et al. published a case series of children with a syndrome of intense dyskinesia, sleep disturbances, seizures, and regression, who made an unexpected excellent recovery.[15] Recently, Poloni et al. described four children with the "Sebire syndrome", and discovered two new cases of NMDAR encephalitis in this group.[16] They postulate a link between NMDAR encephalitis and encephalitis lethargica as well. This data suggests that children with otherwise unexplained new-onset epilepsy, especially with explosive onset and associated with neuropsychiatric decline, dyskinesias, or other encephalopathic symptoms, should be tested for NMDAR antibodies so as to provide more accurate prognosis and guide appropriate treatment. Our case demonstrates the importance of continued imaging surveillance in presumed nonneoplastic NMDAR encephalitis. Imaging surveillance should be included in the plan of care regardless of response to immunomodulatory therapy or absence of relapse; in our patient associated bilateral ovarian teratomas became detectable during a clinically-improved period without relapse.

References

1. Nokura K, Yamamoto H, Okawara Y, Koga H, Osawa H, Sakai K. Reversible limbic encephalitis caused by ovarian teratoma. *Acta Neurologica Scandinavica* 1997;**95**:367–73.
2. Sansing L, Tuzun E, Ko M, Baccon J, Lynch D, Dalmau J. A patient with encephalitis associated with NMDA receptor antibodies. *Nature Clinical Practice Neurology* 2007;**3**:291–6.
3. Dalmau J, Gleichman A, Hughes E, Rossi J, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurology* 2008;**7**:1091–8.
4. Florance N, Davis R, 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**:11–8.
5. Lebas A, Husson B, Didelot A, Honnorat J, Tardieu M. Expanding spectrum of encephalitis with NMDA receptor antibodies in young children. *Journal of Child Neurology* 2010;**25**:742–5.
6. Gable M, Gavali S, Radner A, Tilley D, Lee B, Dyner L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *European Journal of Clinical Microbiology and Infectious Diseases* 2009;**28**:1421–9.
7. Kruer M, Koch T, Bourdette D, Chabas D, Waubant E, Mueller S, et al. NMDA receptor encephalitis mimicking seronegative neuromyelitis optica. *Neurology* 2010;**74**:1473–5.
8. Bien C, Granata T, Antozzi C, Cross J, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain* 2005;**128**:454–71.
9. Oguni H, Andermann F, Rasmussen TB. The natural history of the syndrome of chronic encephalitis and epilepsy: a study of the MNHI series of forty-eight cases. In: Andermann F, editor. *Encephalitis and epilepsy: Rasmussen's syndrome*. London: Butterworth-Heinemann; 1991. p. 7–25.
10. Iizuka T, Yoshii S, Kan S, Hamada J, Dalmau J, Sakai F, et al. Reversible brain atrophy in anti-NMDA receptor encephalitis: a long-term observational study. *Journal of Neurology* 2010. [Epub ahead of print].
11. Lee J, Juhasz C, Kaddurah A, Chugani H. Patterns of cerebral glucose metabolism in early and late stages of Rasmussen's syndrome. *Journal of Child Neurology* 2001;**16**:798–805.
12. Mohr B, Minoshima S. F-18 fluorodeoxyglucose PET/CT findings in a case of anti-NMDA receptor encephalitis. *Clinical Nuclear Medicine* 2010;**35**:461–3.
13. Ishiura H, Matsuda S, Higashihara M, Hasegawa M, Hida A, Hanajima R, et al. Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. *Neurology* 2008;**71**:1921–3.
14. Niehusmann P, Dalmau J, Rudlowski C, Vincent A, Elger C, Rossi J, et al. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. *Archives of Neurology* 2009;**66**:458–64.
15. Sebire G, Devictor D, Huault G, Aicardi J, Landrieu P, Tardieu M. Coma associated with intense bursts of abnormal movements and long-lasting cognitive disturbances: an acute encephalopathy of obscure origin. *Journal of Pediatrics* 1992;**121**:845–51.
16. Poloni C, Korff C, Ricotti V, King M, Perez E, Mayor-Dubois C, et al. Severe childhood encephalopathy with dyskinesia and prolonged cognitive disturbances: evidence for anti-N-methyl-D-aspartate receptor encephalitis. *Developmental Medicine and Child Neurology* 2010;**52**:e78–82.