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Case of a Two-Year-Old Boy With Recurrent Seizures, Abnormal Movements, and Central Hypoventilation

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Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first described in young women with ovarian teratoma. Typical presentations include subacute onset of neuropsychiatric symptoms, seizures, altered awareness, movement disorders, and autonomic dysfunction. Growing evidence indicates that anti-NMDAR encephalitis is one of the most common causes of encephalitis in children and young adults. We present a case of a 2 year-old boy with anti-NMDAR encephalitis to illustrate and discuss the differences in neurological presentation, frequency of symptoms, and association with underlying tumor between children and adults.
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Case History

A 2-year-old boy was transferred from another facility with recurrent seizures, abnormal movements, and failure to wean off mechanical ventilation. The patient had been healthy until approximately 4 weeks before transfer with a self-limited episode of extension and stiffening of the right arm and leg lasting for 30 minutes. He was evaluated in the emergency department at another hospital. An electroencephalogram (EEG) revealed occasional subclinical seizures. He was thought to be at high risk for recurrent unprovoked seizures and administration of levetiracetam was started.

Over the next several days, he had recurrent right-sided seizures that included right arm and leg stiffening, occasional upward eye deviation or head deviation to the left or both, and subsequent transient right-sided weakness consistent with Todd paralysis. At 2 weeks after symptom onset, the parents reported decreased interaction, spontaneous speech, and ability to feed himself. He also was observed to have had episodes of spontaneous laughing and crying without clear reason. The right-sided weakness became persistent associated with intermittent dystonic posturing of his right arm. Over the subsequent weeks, he became increasingly confused with a significantly disrupted sleep-wake cycle.

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Evaluations before transfer included repeated normal brain magnetic resonance (MR) imaging (MRI) and MR spectroscopy studies. Continuous EEG showed focal rhythmic activity in the left hemisphere but no EEG correlate for near-continuous right-sided dystonic posturing. Laboratory studies included evaluation of lactate, pyruvate, carbohydrate-deficient transferrin, biotinidase, ammonia, plasma amino acids, urine organic acids, ceruloplasmin, copper, CPK, PPT1 and TPP1 for neuronal ceroid lipofuscinosis, TSH and T4, and alpha-fetoprotein levels. Array comparative genomic hybridization (CGH) and methylation studies for Prader-Willi or Angelman syndrome were normal. Cerebrospinal fluid (CSF) analysis revealed a white blood cell count of 18 cells/μL (reference: 0-10), 91% lymphocytes, red blood cell count of 1 cell/μL, glucose of 61, and a protein of 25. Repeat CSF studies performed 3 weeks from clinical presentation showed white blood cell of 1, red blood cell of 2, glucose of 77, and protein of 37. Investigations for infectious etiologies included serum and CSF serology or polymerase chain reaction studies for *Tropheryma whipplei*, Lyme disease, La Crosse encephalitis, eastern equine encephalitis, St. Louis encephalitis, and West Nile virus. A CSF amino acid panel found mildly elevated glutamine and phenylalanine levels, but this was not felt to be consistent with a particular disorder.

Antiepileptic medications including levetiracetam, topiramate, and clobazam were titrated up to maximal doses with minimal effect for presumed seizures. A dose of prednisone (1 mg/kg/d) was initiated after an unrevealing workup for infectious etiologies. The patient was intubated and continued to have presumed seizures despite propofol or pentobarbital infusion. A third brain MRI, repeated 5

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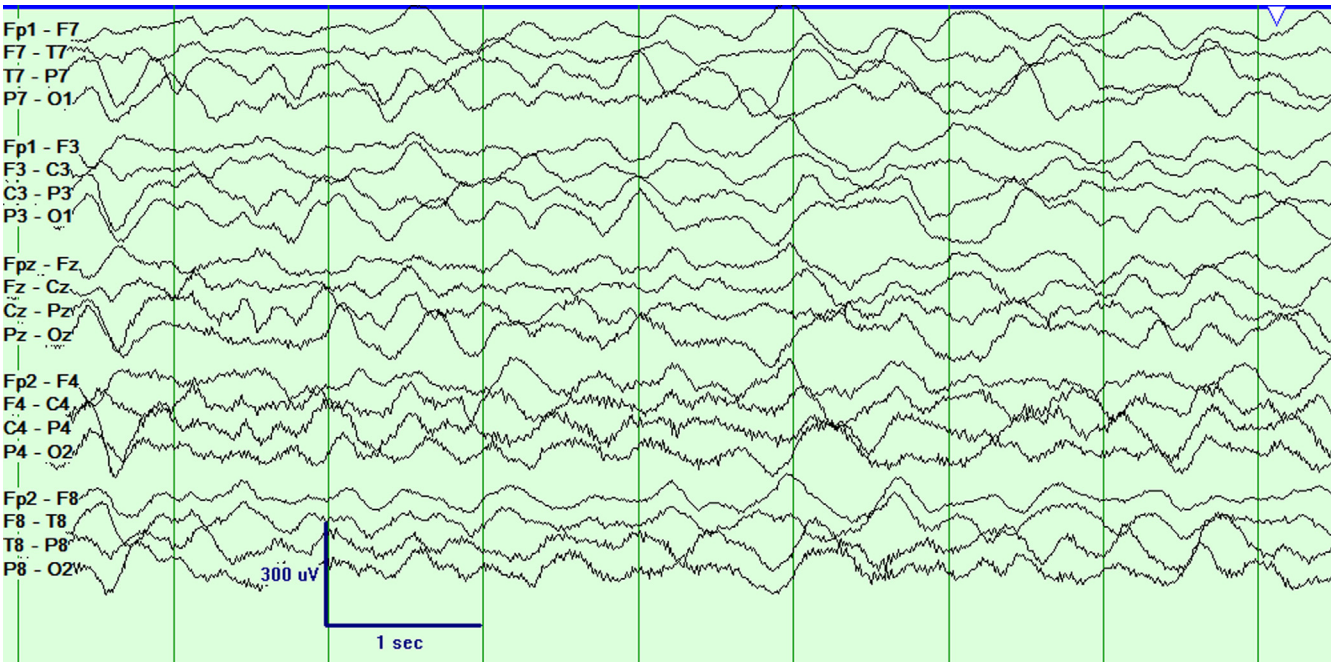

Figure 1 EEG at 1 month from clinical presentation during comatose phase. Extreme delta brush is seen as generalized diffuse delta activity with superimposed beta activity (LFF 1 Hz, HFF 70 Hz, notch 60 Hz, and sensitivity 15 uV/mm). (Color version of figure is available online.)

weeks from presentation, was interpreted as potentially demonstrating subtle volume loss involving the left cerebral hemisphere, raising concern for possible Rasmussen syndrome. At 7 weeks after clinical presentation, intravenous (IV) immunoglobulin (IVIG) treatment was started (5 doses of 0.4 g/kg/d) and improvement was noted in interictal epileptiform discharges on continuous EEG monitoring. Sedation was then discontinued; however, extubation was not successful, and he was transferred to our institution for further evaluation and treatment. Before transfer, serum and CSF samples were submitted for analysis of autoantibodies.

On general examination after transfer, he was found intubated and sedated without dysmorphic features or neurocutaneous stigmata. Near-continuous orofacial dyskinesia with repetitive chewing or grimacing motions were noted around the eyes and jaw as well as hyperkinetic movements of his upper and lower limbs. Continuous video EEG monitoring showed no EEG correlates for his orofacial or appendicular movements. There was persistent diffuse generalized delta slowing with superimposed beta fast activities (Fig. 1). Re-review of serial MRI images showed no cortical asymmetry but demonstrated a few scattered ill-defined areas of subcortical T2 hyperintensity. CSF anti-N-methyl-D-aspartate -receptor (NMDAR) autoantibody returned at markedly elevated titer of 1:64, confirming diagnosis of anti-NMDAR encephalitis.

Computed tomography scans of the chest, abdomen, and pelvis and testicular ultrasound for occult neoplasm were unrevealing. A second 5-day course of 0.4 g/kg/d of IVIG and 5 days of 30 mg/kg/d IV methylprednisolone rendered limited improvement. Rituximab therapy (375 mg/m^2), with pulse IV methylprednisolone (30 mg/kg) every 3 days, also had limited clinical response. Multiple extubation attempts failed due to inadequate ventilation, despite non-invasive BiPAP support, suggestive of central hypoventilation. Tracheostomy was performed at 7.5 weeks after presentation.

After several plasma exchanges, the patient demonstrated an improved level of alertness and was weaned off sedation. Weekly administration of IV methylprednisolone continued for 10 weeks followed by once every 3 weeks over the subsequent 3 months. Over the next month, the patient demonstrated gradual clinical improvement: increased sleep duration, reduction in abnormal movements, and purposefully fixated and followed people across his visual field. At 6 months from his initial presentation, and 4 months from his IVIG, plasma exchange, and rituximab treatments, he was able to use several words to express wants but was not yet using 2-word sentences, he was able to manipulate toys with either hand with a resolved right-sided paresis, he was able to ambulate independently, and he no longer demonstrated any abnormal dyskinetic movements. EEG at that time demonstrated mild generalized slowing, reduced amplitude over the left hemisphere, without epileptiform abnormalities (Fig. 2).

Discussion

Description

The constellation of subacute onset of neuropsychiatric symptoms, labile affect and sleep difficulty, seizures, and distinct orofacial dyskinesia, with negative metabolic, infectious, and genetic evaluations is concerning for a primary or paraneoplastic autoimmune process. Although it was first

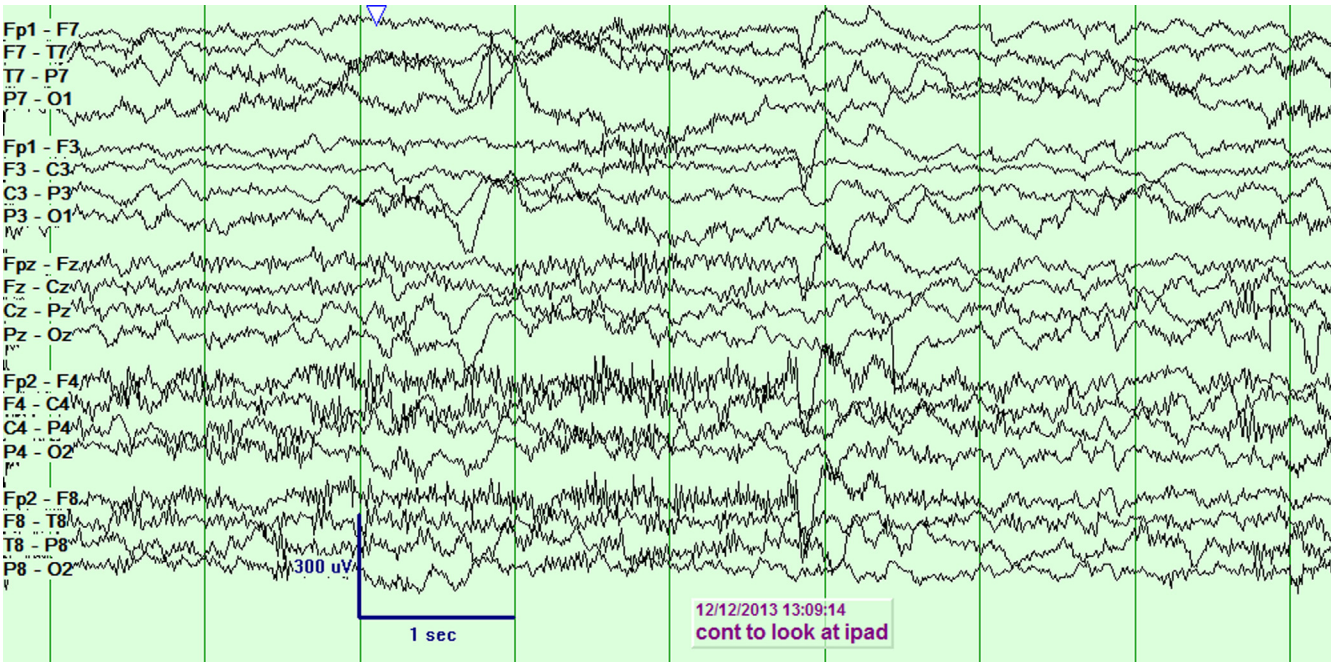

Figure 2 EEG at 6 months after presentation during clinical recovery, with resolution of generalized slowing (LFF 1 HZ, HFF 70 Hz, notch 60 Hz, and sensitivity 15 uV/mm). (Color version of figure is available online.)

recognized in young women with ovarian teratoma, anti-NMDAR encephalitis is now recognized as one of the most common causes of encephalitis in children.[1] There is also emerging evidence that this condition may actually be the most common of a set of closely related encephalopathies seen in the context of teratoma or other neoplasm with autoantibodies directed at postsynaptic neurotransmitter receptors.

Epidemiology

The true incidence of anti-NMDAR encephalitis remains unknown, but it is likely more common than previously suspected. There is a predilection for females in the adolescent and adult patient population, which is less so observed in younger children.[2] A population-based prospective study in the United Kingdom found anti-NMDAR encephalitis to be the sixth leading cause of encephalitis in children and adults (4%), following unknown cause in 37%, herpes simplex virus encephalitis in 19%, acute disseminated encephalomyelitis in 11%, *Mycobacterium tuberculosis* in 5%, and varicella-zoster virus in 5%.[3] Association with tumor is age and gender dependent.[2,4,5] The largest pediatric case-series compiled to date demonstrate children are significantly less likely to have an associated tumor.[5,6]

Clinical Presentation

Anti-NMDAR encephalitis presents in distinct phases beginning with a prodromal phase, followed by psychosis or seizures or both, leading to a phase of unresponsiveness that can be similar to akinetic mutism or catatonia.[4,7] Prodromal symptoms are seen in about half of children. The symptoms include fever, headache, upper respiratory symptoms, vomiting, or diarrhea lasting up to 2 weeks.[4-6,8] Most patients then exhibit psychiatric or behavioral changes, which in adult patients manifest as anxiety, agitation, paranoia, and visual or auditory hallucinations.[4] Of the patients who present *without* behavioral changes, dystonia, or dyskinesias or progressive speech loss, or both, were the presenting symptoms. In children, temper tantrums, agitation, aggression, and progressive speech deterioration are often the initial symptoms of disease, whereas adolescents can present with hypersexual, aggressive, or manic behavior.[5]

Seizures occur in 77% of children and are typically focal, but primary or secondarily generalized seizures have also been observed. Status epilepticus is common.[9,10] Most patients have progressive decreases in level of consciousness. An associated movement disorder and symptoms of autonomic instability may manifest early during clinical course but often emerge during the comatose phase.

The associated movement disorder occurs in 84%. Orolinguofacial dyskinesias, choreoathetoid movements, and dystonic posturing or muscle rigidity or hypertonicity continue without respect to sleep-wake cycle. Oculogyric crisis, opisthotonos, and dystonia, associated with tachycardia and hypertension, may represent an autonomic storm phenomenon.[11] Autonomic instability is less common in children than in adults, but it still occurs in approximately 40% of patients younger than 12 years and needs to be considered as a cause of recurrent fever (as in the patient presented earlier, who underwent repetitive evaluations for fever of unknown origin and empiric courses of broad-spectrum antibiotics without identified infections). Central

hypoventilation is less common in the pediatric population, observed in 15% of patients younger than 12 years vs 40% of adult patients. Central hypoventilation can prompt intubation even when the patient's level of consciousness is still relatively preserved, or first noticed when a patient cannot be weaned from mechanical ventilation after elective sedation for seizure control.[12]

Diagnosis

The median time to definitive diagnosis is around 21 days from symptom onset and is often longer in adults (28 days), given the predominance of psychiatric initial presentations.[2] Diagnosis of anti-NMDAR encephalitis requires high index of clinical suspicion, systematic investigation for other etiologies, and confirmatory presence of anti-NMDAR autoantibodies in the serum or CSF or both.[13] CSF analysis typically reveals abnormalities in 80% of patients at presentation, with the majority of the remainder demonstrating abnormal results as their disease progresses. These abnormalities can include a moderate lymphocyte predominate pleocytosis, mildly increased protein levels, and CSF-specific IgG oligoclonal bands in 60% of patients.[4] The findings of MRI of the brain are normal in most patients. Nonspecific or transient T2 or fluid-attenuated inversion recovery (FLAIR) signal hyperintensities can be seen in approximately 50% of patients with anti-NMDAR encephalitis.[4,14,15] As in the patient presented here, neuroimaging can indicate alternative etiologies, often at odds with the clinical presentation, such as Rasmussen syndrome or neuromyelitis optica.[16,17]

EEG demonstrates nonspecific continuous delta-theta activity slowing, prominent during the catatonic phase.[4,5] Continuous, nonreactive, rhythmic delta activity at 1-3 Hz with superimposed bursts of rhythmic 20-30 Hz beta frequency activity termed "extreme delta brush" is present in up to 30% of patients.[18] Extreme delta brush pattern forecasts protracted hospital courses with worse outcomes at discharge. Complicating the management of these patients' seizure disorder is that abnormal repetitive movements are common in anti-NMDAR encephalitis and can mimic the appearance of focal seizures, necessitating prolonged video electroencephalogram monitoring for spell classification and definitive diagnosis.

Definitive diagnosis is made by the presence of anti-NMDAR antibodies in the serum or CSF. Indirect immunofluorescence to rodent or primate hippocampus or cerebellum is often used for screening purposes, but it can be nonspecific.[12] A cell-based assay is also available with much higher sensitivity and specificity in which cells transfected with complementary DNA expressing the NR1 subunit of the NMDAR are exposed to patient serum, with positivity being conferred by indirect immunofluorescence to cell-human antibody complexes. CSF testing has higher sensitivity than serum sample, with only 85% of patients having positive results on serum studies as well as positive results for anti-NMDAR autoimmunity in their CSF.[2,4] In a series of 412 patients with paired samples, no patients were identified with antibodies detected in their serum but *not* in their CSF samples at the time of diagnosis.[12]

Treatment

Early diagnosis and treatment is associated with earlier and more complete recovery.[4,5] Prompt identification and resection of a primary tumor, if present, also speeds recovery and prevents relapses. Among patients without an associated tumor, immunotherapy includes the first-line therapies of high-dose corticosteroids (eg, IV methylprednisolone 20-30 mg/kg/d × 5 days or equivalent), intravenous immunoglobins (eg, 0.4 g/kg/d for 3-5 days), and plasmapheresis. Rituximab and cyclophosphamide are available as second-line agents in refractory cases.[5] In the 31 pediatric cases described by Florance et al,[5] 30 cases were treated with a combination of IVIG high-dose corticosteroids, and plasma exchange. In patients refractory to first-line therapy, treatment with rituximab or cyclophosphamide or both rendered improvement with variable but measurable benefit.

Prognosis

Early recognition and treatment are important, as is escalation to second-line therapy when indicated, as both factors affect length and severity of the initial illness as well as decrease the recurrence rate. In a multicenter observational study of adults and children with anti-NMDAR encephalitis, of whom 210 (out of 574) were younger than 18 years, half demonstrated symptom improvement within 4 weeks of first-line immunotherapy, while the remaining went on to receive second-line immunotherapy or continued with an extended course of first-line immunotherapy.[2] Overall, 81% had a favorable outcome with an all-cause mortality rate of 10%. Recovery at 2-year follow-up was highest among those who responded to first-line treatment (97%), followed by patients who received second-line treatment after unsuccessful first-time therapy (78%), with lowest likelihood of good outcome among those patients who failed first-line therapy and did not receive second-line treatment (55%). As such, second-line agents such as rituximab or cyclophosphamide or both should be pursued in patients who do not respond to corticosteroids, IVIG, and plasmapheresis.

Among children with anti-NMDAR encephalitis, recovery may be slow and gradual with a median time to initial improvement up to 6 weeks (range: 2-28 weeks).[5] Recovery takes place in multiple stages that typically occur in the reverse order of symptom presentation.[2] Relapses have been observed in patients with apparent recovery. Approximately 12% of patients experienced clinical relapses, with one-third of these having multiple relapses. These were typically less severe (67%); however, a few patients had relapses that were clinically more intense than their initial presentations (10%). Although patients without an associated tumor had a higher frequency of relapses, in all cases the use of initial immunotherapy was associated with fewer relapses overall.[2]

Summary, Recommendations, and Differences Between Pediatric and Adult Presentations

The recognition of anti-NMDAR encephalitis as a common cause of encephalitis should increase the suspicion for this diagnosis in cases, of all ages, with acute-onset behavioral changes and movement or speech abnormalities or both and new-onset pharmacoresistant seizures. Obtaining CSF for detection of anti-NMDAR antibodies should be considered even if serum serology shows no remarkable findings. Although there are no strict guidelines for determining failure to first-line therapy, improvement is seen in half of patients at 4 weeks, and it is common practice to consider second-line therapy at that time. Early recognition and treatment is important as is escalation to second-line therapy when indicated.

References

1. Armangue T, Petit-Pedrol M, Dalmau J: Autoimmune encephalitis in children. J Child Neurol 27:1460-1469, 2012
2. Titulaer MJ, McCracken L, Gabilondo I, et al: Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. Lancet Neurol 12:157-165, 2013
3. Granerod J, Ambrose HE, Davies NW, et al: Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. Lancet Infect Dis 10:835-844, 2010
4. Dalmau J, Gleichman AJ, Hughes EG, et al: Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. Lancet Neurol 7:1091-1098, 2008
5. Florance NR, Davis RL, Lam C, et al: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 66:11-18, 2009
6. Irani SR, Bera K, Waters P, et al: N-methyl-D-aspartate antibody encephalitis: Temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 133(Pt 6):1655-1667, 2010
7. Peery HE, Day GS, Dunn S, et al: Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun Rev 11:863-872, 2012
8. Day GS, High SM, Cot B, et al: Anti-NMDA-receptor encephalitis: Case report and literature review of an under-recognized condition. J Gen Intern Med 26:811-816, 2011
9. Bayreuther C, Bourg V, Dellamonica J, et al: Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. Epileptic Disord 11:261-265, 2009
10. Johnson N, Henry C, Fessler AJ, et al: Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. Neurology 75:1480-1482, 2010
11. Kleinig TJ, Thompson PD, Matar W, et al: The distinctive movement disorder of ovarian teratoma-associated encephalitis. Mov Disord 23:1256-1261, 2008
12. Dalmau J, Lancaster E, Martinez-Hernandez E, et al: Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10:63-74, 2011
13. Gable MS, Gavali S, Radner A, et al: Anti-NMDA receptor encephalitis: Report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol Infect Dis 28:1421-1429, 2009
14. Dalmau J, Tuzun E, Wu HY, et al: Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61:25-36, 2007
15. Iizuka T, Sakai F, Ide T, et al: Anti-NMDA receptor encephalitis in Japan: Long-term outcome without tumor removal. Neurology 70:504-511, 2008
16. Greiner H, Leach JL, Lee KH, et al: Anti-NMDA receptor encephalitis presenting with imaging findings and clinical features mimicking Rasmussen syndrome. Seizure 20:266-270, 2011
17. Kruer MC, Koch TK, Bourdette DN, et al: NMDA receptor encephalitis mimicking seronegative neuromyelitis optica. Neurology 74:1473-1475, 2010
18. Schmitt SE, Pargeon K, Frechette ES, et al: Extreme delta brush: A unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 79:1094-1100, 2012