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N-Methyl-D-Aspartate Receptor Antibodies in Pediatric Dyskinetic Encephalitis Lethargica

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Encephalitis lethargica (EL) describes an encephalitis with psychiatric, sleep, and extrapyramidal movement disorders. Dyskinetic and Parkinsonian forms have been described. EL shares clinical features with the anti–N-methyl-D-aspartate receptor (NMDAR-Ab) encephalitis. We studied 20 sera from pediatric patients with contemporary EL. Ten sera (from 2 males and 8 females, aged 1.3–13 years) and 6/6 cerebrospinal fluid samples were positive for NMDAR-Ab. NMDAR-Ab–positive patients had dyskinesias, agitation, seizures, and insomnia, whereas Parkinsonism and somnolence dominated in the NMDAR-Ab–negative children. We were unable to identify any tumors. The dyskinetic form of EL is an NMDAR-Ab encephalitis and can affect very young children.

Ann Neurol 2009;66:704–709

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Potential conflict of interest: A.V. and her department receive payments and royalties for antibody assays.

Pfizer had no role in study design, data collection, data analysis, data interpretation, or the writing of the manuscript.

Received May 19, 2009, and in revised form Jul 1, 2009. Accepted for publication Jul 10, 2009. Published online, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21807

Epidemics of "lethargic encephalitis" (encephalitis lethargica [EL]) have been described for centuries, classically by Von Economo.[1] Von Economo described 3 classic forms: akinetic mutism, somnolent-ophthalmoplegic, and hyperkinetic.[1] EL describes an encephalitis with dominant psychiatric features (catatonia, agitation, compulsive behaviors), extrapyramidal movement disorders (chorea, oculogyric crises, dystonia, Parkinsonism), and sleep disturbance (insomnia or hypersomnolence).[1,2] Seizures, autonomic dysfunction, encephalopathy, and cognitive features are less common. Some dyskinetic EL cases have been called "immune-mediated chorea encephalopathy syndrome."[3] We previously reported 20 cases, predominantly in children, suggesting this phenotype is not rare.[4] The absence of viral antigens in the central nervous system (CNS), the benefit of immunotherapies, the presence of antineuronal antibodies, and cerebrospinal fluid (CSF) oligoclonal bands suggest that EL is an immune-mediated phenomenon.[2,4–8]

Recently, an encephalitis has been described with dominant psychiatric features, dyskinesias (particularly orofacial), seizures, and autonomic and respiratory features, largely in young females with ovarian teratomas with good responses to tumor surgery,[9–12] and with serum and CSF autoantibodies to the extracellular domain of NR1/NR2 subunits of the N-methyl-D-aspartate receptor (NMDAR-Ab).[12] A recent larger study found NMDAR-Abs in both sexes, and 40% of cases were nonparaneoplastic.[13] We asked whether contemporary EL is associated with NMDAR-Ab.

Materials and Methods

Patients and Controls

Twenty patients (12 female; range, 1.3–15 years; Tables 1 and 2) were studied over 9 years. All patients had encephalitis defined as neurological dysfunction with CNS inflammation on brain magnetic resonance imaging (MRI) or CSF analysis. Their condition was defined as EL because of the dominant movement and psychiatric disorders, and clinical similarity with historical descriptions of EL.[1,4,6] Excluded diagnoses included infectious encephalitis (herpes simplex virus, mycoplasma pneumonia, Epstein-Barr virus), autoimmune disorders (systemic lupus erythematosus, antiphospholipid syndrome), and metabolic disorders. Ten of 20 patients were described previously, and some had antibodies directed against soluble brain proteins using Western blotting,[4,14] as indicated in Tables 1 and 2. The antigens were later identified as ubiquitous intracellular glycolytic enzymes, and we now believe that these antibodies reflect nonspecific autoimmunity. All serum and CSF samples were taken during the first 3 weeks of the encephalitis before any immunotherapies. These were intravenous methyl-prednisolone followed by oral prednisolone (n = 13) or intravenous

Table 1. **Clinical Details and Outcome of EL Patients With Positive NMDAR-Ab (n = 10)**

Age/Sex	1st Symptoms	Psychiatric Symptoms	Early Movement Disorder	Late Movement Disorder	Sleep Disorder	Other	Outcome
1.3/F[a]	Encephalopathy, unresponsive	—	Chorea	Chorea	—	Hypotonia, mutism, regression,	Relapse, chorea, DD
3/F	Chorea, aggression	Agitation, SIB	Chorea	Parkinsonism, stereotypies	Sleep inversion	Seizures, mutism, encephalopathy	Memory loss, relapse
3/F[a]	Seizures	Screaming	Chorea	Chorea and dystonia	—	Encephalopathy, confusion, mutism	Complete recovery
5/F	Agitation, insomnia	Agitation	Chorea and dystonia	Chorea and dystonia	Insomnia	Memory loss, language impairment	Cognitive impairment, memory loss, inattention
7/F	Hemichorea, OGC, seizures	Catatonia, agitation, tricillomania, echolalia	Chorea, dystonia, stereotypies, orolingual dyskinesia	Dystonia, Parkinsonism, waxy flexibility	Insomnia	Seizures, social disinterest, mutism, memory loss, tachycardia[b]	Dystonia, Parkinsonism, cognitive impairment, social disinterest, emotional lability
7/F	Confusion, inappropriate laughter	Agitation, aggression, emotional lability, tricillomania	Dystonia, chorea	Dystonia, chorea	Sleep inversion	Encephalopathy, poor eye contact, mutism, hypoventilation[b]	Emotional lability, OCB
8/F	Dystonia	Agitation, emotional lability, impulsive	Dystonia, hemiballismus	Dystonia	Insomnia	Seizures, urinary incontinence, mutism	Emotional lability
8/M[c]	Irritable, aggression	Agitation, echolalia, palilalia, coprolalia, SIB	Hemiballismus, stereotypies	Dystonia, Parkinsonism, orolingual dyskinesia, OGC	Insomnia	—	Complete recovery
11/F[ad]	Agitation, panic attacks	Catatonia, panic attacks	Orolingual dyskinesia, stereotypies	Orolingual dyskinesia	Insomnia	Seizures, hyperventilation[b]	Complete recovery
13/M[c]	Agitation, visual hallucinations	Catatonia, aggression, compulsive touching	Stereotypies, hemiballismus, dystonia	Parkinsonism, stereotypies, waxy flexibility	Insomnia	Mutism, hypertension[b]	Complete recovery

[a]Patients with positive antineuronal antibodies defined using Western blotting as described.[4]
[b]Autonomic features.
[c]Previously described EL patients.[2]
[d]Previously described EL patients.[4]
NMDAR-Ab = antibodies to N-methyl-D-aspartate receptor; F = female; M = male; DD = developmental delay; SIB = self-injurious behavior; OGC = oculogyric crises; OCB = obsessive-compulsive behavior.

immunoglobulin (n = 2). Patients were followed-up for a variable period. Nineteen sera from children with opsoclonus myoclonus syndrome (aged 18 months to 10 years) provided controls.

NMDAR, Voltage-Gated Potassium Channel, Glutamic Acid Decarboxylase, and Glycine-Receptor Antibody Assays

The NMDAR-Ab assay was based on the work of Dalmau et al.[12] NR1/NR2B subunits of NMDAR and enhanced green fluorescent protein were cotransfected into human embryonic kidney cells, and human immunoglobulin G binding was detected with secondary antibody (Alexa Fluor red-conjugated). The cells were fixed briefly without permeabilization. Sera were tested initially at 1:20 and CSF samples undiluted or at 1:4, depending on availability. The results were scored visually using immunofluorescence as described for aquaporin-4 assays (for techniques see Waters et al. 2008[15]). Glycine-receptor–transfected cells[16] were run in parallel to assess NMDAR-Ab specificity. Voltage-gated potassium channel (VGKC) and glutamic acid decarboxylase (GAD) antibody assays used techniques in routine clinical use.

Table 2. **Clinical Details and Outcome of EL Patients With Negative NMDAR-Ab (n = 10)**

Age/Sex	1st Symptoms	Psychiatric Symptoms	Early Movement Disorder	Late Movement Disorder	Sleep Disorder	Other	Outcome
5/F	Confusion, confabulation	Emotional lability, perseveration	Parkinsonism	Parkinsonism	Insomnia	Pyramidal weakness	Insomnia, inattention
5/M[ab]	Bradykinesia, lethargy	—	Parkinsonism	Parkinsonism	Somnolence	Ophthalmoplegia, ptosis, mutism, nocturnal bradycardia[c]	Complete recovery
6/F	Paralysis	—	Orolingual dyskinesia	Orolingual dyskinesia	—	Axonal neuropathy	Ventilation dependence, profound paralysis
7/F[ab]	Anxiety	Anxiety, depression	Rigidity	Rigidity	Sleep inversion	Mutism	Anxiety
8/M	Lethargy, Parkinsonism	—	Parkinsonism	Parkinsonism	Somnolence	Encephalopathy	Complete recovery
9/F[ab]	Dystonia	Disinhibition, compulsive touching	Hemi-Parkinsonism, hemiballismus, OGC	Hemi-Parkinsonism, hemiballismus	Sleep inversion	Ophthalmoplegia, mutism, hiccough[c]	Dystonia, cognitive impairment
10/M[ab]	Somnolence	Depression	Parkinsonism, motor tics	Parkinsonism, motor tics	Somnolence	Mutism	Depression
14/M[ab]	Dystonia	Agitation	Dystonia	Dystonia, Parkinsonism	Somnolence	Encephalopathy, mutism, confusion	Dystonia, cognitive impairment
15/M[ab]	Paranoia, anxiety	Paranoia, anxiety, agitation	Parkinsonism, OGC	Parkinsonism	Somnolence	Hiccough, pupillary abnormalities[c]	Complete recovery
15/M[ab]	Paranoia, OGC	Catatonia, paranoia, agitation, compulsions	Orolingual dyskinesia, blepharoclonus, OGC	Dystonia, Parkinsonism	Sleep inversion	Poor eye contact, mutism	Mutism, catatonic schizophrenia, cognitive impairment

[a]Previously described EL patients.[4]
[b]Patients with positive antineuronal antibodies defined using Western blotting as described.[4]
[c]Autonomic features.
NMDAR-Ab = antibodies to N-methyl-D-aspartate receptor; F = female; M = male; OGC = oculogyric crises.

Results

The clinical phenotypes of all 20 patients are given in Tables 1 and 2. They presented mainly with psychiatric, behavioral, movement, or sleep disorders. Psychiatric symptoms included agitation and compulsive behaviors. Movements disorders were dyskinetic (hyperkinetic form of EL) or Parkinsonism (akinetic form of EL). Sleep disorders presented as insomnia, sleep inversion, or somnolence. Seizures occurred in 25%, usually associated with an encephalopathy.

Ten of 20 EL patients had serum NMDAR-Ab (see Fig for examples). All 6 available CSF samples from these patients were also positive, but titers in matched serum and CSF samples were highly variable, with ratios of serum/CSF titers ranging between 4 (very high intrathecal synthesis; Fig A, B) and 320 (negligible intrathecal synthesis; Fig C, D) in 1 6-year-old female. Subsequent CSF samples from this patient were negative. Results of all comparisons are shown in Figure E.

No NMDAR-Abs were found in the 19 children with opsoclonus myoclonus. None of the EL patients had GAD antibodies, but 1 NMDAR-Ab–positive patient had a low titer of Voltage-gated potassium channel antibodies (173pM) and 1 NMDAR-Ab–negative patient had weak binding to glycine receptor. EL patients were divided into NMDAR-Ab–positive (Table 1) and –negative (Table 2) groups; the more distinctive clinical features are compared in Table 3.

Clinical Phenotype of NMDAR-Ab–Positive EL

Eight of 10 patients were female, including 4 children ≤5 years of age (Table 1). A preceding infection was only reported in 2 patients. The presentation was often dramatic, with agitation, catatonia, mutism, compulsive, and self-injurious behaviors. Dyskinetic movement disorders with chorea, dystonia, hemiballismus, stereotypies, and oculogyric crises occurred within 4 weeks of presentation. Some of the dyskinetic movements were extraordinary, and included lower limb cycling, stereotypical upper limb flailing, prolonged limb posturing with waxy flexibility, and orolingual dyskinetic "rabbit" movements. The movement disorders were usually generalized, dramatic, and impairing; only 1 patient had orolingual dyskinesia as the main movement disorder. Videos of these movements have been provided previously.[2] Parkinsonism only occurred in 4

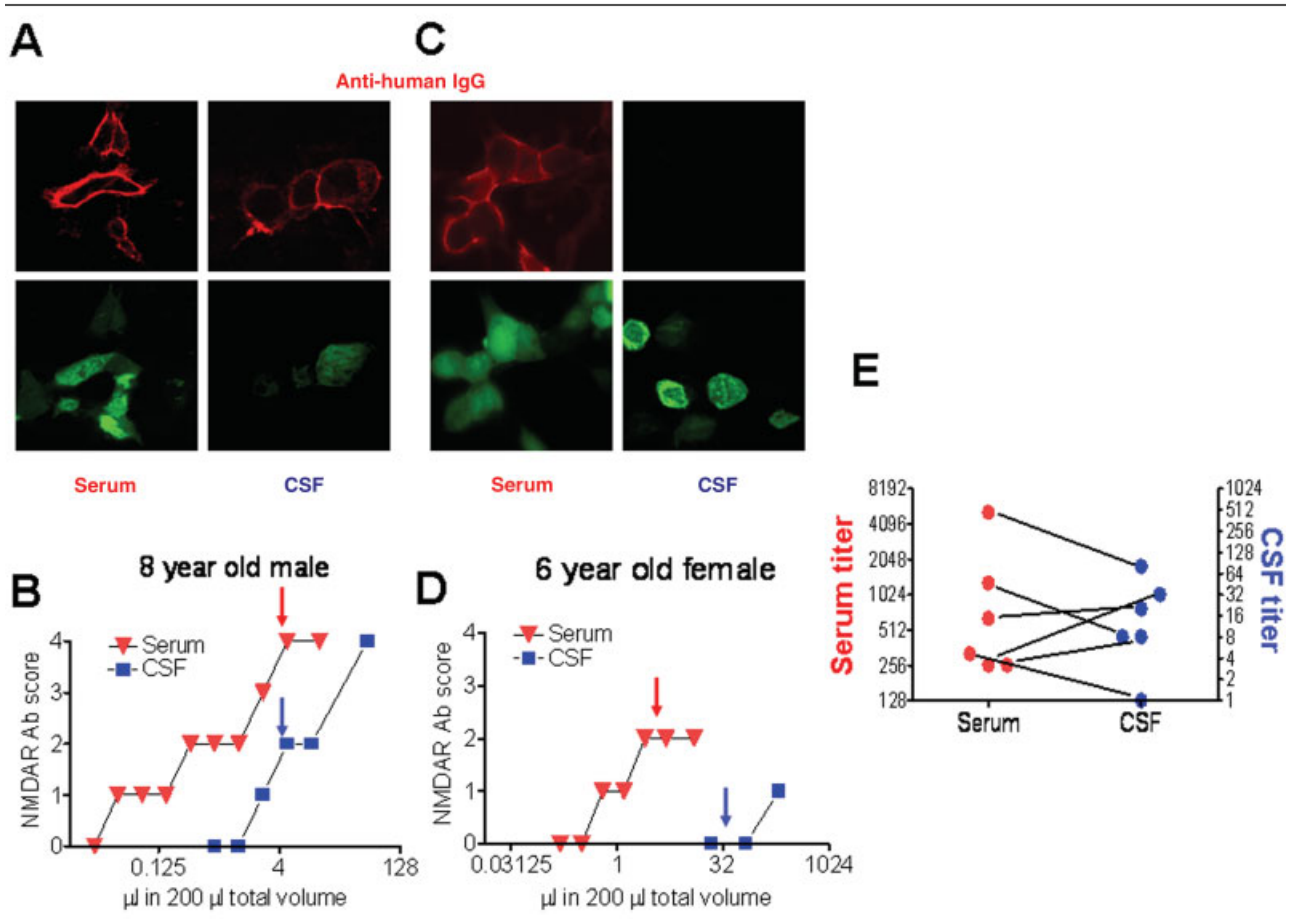

Fig. Titers of antibodies to N-methyl-D-aspartate receptor (NMDAR-Ab) in serum and cerebrospinal fluid (CSF). NR1/NR2B subunits of NMDAR and enhanced green fluorescent protein were transfected into human embryonic kidney cells, and human immunoglobulin G (IgG) binding was detected with secondary antibodies (Alexa Fluor red-conjugated). The results show 1 patient with high serum antibody (score 4 at 1:40) and high CSF antibody (score 2 at 1:40) (A, B), and another patient with moderate serum antibody (score 2 at 1:40 dilution) and very low CSF antibody (score 0 at 1:3 dilution) (C, D). The arrows denote the dilutions used for panels A and C. (E) Relative titers of serum and CSF antibodies in all 6 patients with available CSFs. The titers given are the highest dilution at which binding was scored as 1. Note the different scales of the y axes in E.

NMDAR-Ab patients and always late, 4 weeks after disease onset. Insomnia or sleep inversion was common, but somnolence was not observed (Table 3). Seizures (n = 5) were only found in this group ($p < 0.05$). Four had autonomic dysfunction. Encephalopathy, developmental regression, hypotonia, and social disinterest were common under 10 years of age (Table 1). CSF revealed pleocytosis in 4 of 10 (mean 14 lymphocytes/mm^3; range, 0–58), and oligoclonal bands were abnormal in all 9 patients tested (6 intrathecal synthesis, 3 mirrored pattern). MRI during the first weeks was normal in 7; 3 had subtle cortical grey matter enhancement, which was absent on subsequent imaging. One patient has clear cerebral atrophy on follow-up imaging. The mean time to maximum deficit was 5.5 weeks, and the mean inpatient stay was 13.6 weeks (range, 6–35 weeks). At follow-up (mean, 27 months; range, 6-84), 4 patients had made a complete recovery, 6 patients had significant motor, cognitive, or psychiatric impairments, and 2 of these had a relapsing course. Two NMDAR-Ab–positive female patients with ongoing impairments had ovarian imaging with negative findings.

Clinical Phenotype of NMDAR-Ab–Negative EL

NMDAR-Ab–negative patients were more often male, and none was <5 years of age (Tables 2 and 3). Seven of 10 patients reported a postinfectious onset. Agitation was not common, and the early and dominant movement disorder was typically Parkinsonism. Somnolence was the commonest sleep disturbance, and no patients had seizures (Tables 2 and 3). Autonomic features occurred in 3 patients. MRI was normal in 7 patients, and 3 had basal ganglia and substantia nigra/midbrain lesions. NMDAR-Ab–negative patients had a shorter disease course, with a mean time to maximum

Table 3. **Comparisons Between Clinical Phenomenology of NMDAR-Ab–Positive and NMDAR-Ab–Negative Patients**

Clinical Features	NMDAR-Ab Positive	NMDAR-Ab Negative	Significance (Fisher Exact 2-Tail Test, Except[a])
Male:female	2:8	6:4	NS
Median age, y (range)	6 (1–13)	8.5 (5–15)	NS[a]
Agitation	9/10	4/10	$P=0.06$
Catatonia	3/10	1/10	NS
Mutism	7/10	6/10	NS
Early dyskinesias	10/10	4/10	$P<0.05$
Early Parkinsonism	0/10	6/10	$P<0.05$
Insomnia	7/10	1/10	$P<0.05$
Somnolence	0/10	5/10	$P<0.05$
Autonomic dysfunction	4/10	3/10	NS
Seizures	5/10	0/10	$P<0.05$
Complete recovery	4/10	3/10	NS

Early dyskinesias include chorea, dystonia, hemiballismus, stereotypies, orolingual dyskinesias, and tics within 1st 4 weeks. Early Parkinsonism describes bradykinesia plus rigidity, rest tremor, or postural instability within the 1st 4 weeks.
[a]Mann-Whitney U test.
NMDAR-Ab = antibodies to N-methyl-D-aspartate receptor; NS = nonsignificant.

deficit of 2.45 weeks and mean in-patient stay of 7.1 weeks (range, 2–26 weeks). Only 3 made a complete recovery; 7 had persistent motor, cognitive, or psychiatric impairments.

Discussion

A clinical presentation characterized by dominant movement, psychiatric, and sleep disorders is not rare in pediatrics, and is often diagnosed as EL or "immune-mediated chorea encephalopathy syndrome."[3] Although EL patients have antineuronal antibodies detected using Western blotting, it is likely that these antibodies, which bind to intracellular glycolytic enzymes, are markers of autoimmunity, rather than pathogenic autoantibodies.[4,14] By contrast, antibodies that bind to cell surface proteins involved in neurotransmission, such as NMDAR-Ab, are widely held to be pathogenic, and in vitro data support a role in reducing NMDAR surface expression.[13] Our results demonstrate that, using an assay similar to that previously reported,[12] a substantial proportion of contemporary EL patients have antibodies that bind to cell-surface–expressed NMDAR.[12,13] Interestingly, the NMDAR-Ab positive patients predominantly fit into the dyskinetic form of EL,[4,6,17] with early, often bizarre, dyskinetic movement disorders and agitation. The patients with the somnolent-Parkinsonian form of EL, considered to be the classic form by most commentators, were negative for NMDAR-Ab.

The different clinical phenotypes of the NMDAR-Ab–positive and –negative patients suggest different pathogenic targets, and the early Parkinsonian features in the NMDAR-Ab–negative patients suggest the involvement of another, as yet unidentified, antibody, perhaps acting directly on striatal regions. The NMDAR-Ab–positive patients tended to be younger, with dyskinetic movements and agitation, and often had seizures, with Parkinsonian features presenting later (if at all). NMDAR-Ab have been shown to reduce the expression of cell surface NMDA receptors in hippocampal cultures,[13] but it is not clear whether it is the serum or CSF antibodies that play the dominant role in vivo. In fact, the relative levels of serum and CSF NMDAR-Ab in our patients were highly variable, although serum levels were consistently higher than CSF levels.

Although reported cases of anti-NMDAR encephalitis now include both sexes and all age groups, it is still more common in young females, many with ovarian pathology.[13] All but 2 of our NMDAR-Ab–positive EL patients were female, as were the majority of EL cases reported over the past 50 years; ovarian tumors were not routinely excluded at the time, but have been in 2 of our patients with persistent symptoms. In our experience of patients with NMDAR-Ab (Irani and Vincent, in preparation), detectable tumors are uncommon under the age of 20 years, although the majority of the children are female. However, it is also possible that tumors have undergone spontaneous regression, or microscopic tumors may exist that are undetectable using conventional imaging.

Anti-NMDAR encephalitis patients have generally been treated with steroids or intravenous immunoglob-

ulin, and recent reports describe success with plasma exchange and rituximab.[18,19] It is difficult to infer benefit of the ad hoc immunotherapies that some of our EL patients received. However, given the poor outcome in many of our EL patients, and this new evidence for a potentially pathogenic antibody, early aggressive immunotherapies appear warranted. Moreover, our findings draw attention to the pressing need to define specific antibodies in other forms of pediatric psychiatric and movement disorders.

RCD and FB have postdoctoral University of Sydney fellowships, and a Pfizer neuroscience award. SRI is supported by the National Institute for Health Research, Department of Health, UK. Work in AV and BL's laboratory is supported by the Oxford Biomedical Research Centre.

R.C.D. and A.V. were involved in study design, data analysis, and writing of the report. R.C.D., R.W., D.G., and S.P. were involved in clinical assessment of the patients. S.R.I., F.B., B.L., and A.V. performed the experimental analyses and contributed to writing the report. We also thank the patients and families involved in this study.

Dedicated to the late Robert Surtees, mentor, role-model, and Professor of Pediatric Neurology, Great Ormond Street Hospital, London, UK. We thank Prof D. Beeson and Ms S. Maxwell for their help in cloning the NMDAR and Dr Tanja Brenner for technical assistance.

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