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Expanding Spectrum of Encephalitis With NMDA Receptor Antibodies in Young Children

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Abstract

The authors report here 2 cases of subacute-onset encephalitis with *N*-methyl-*D*-aspartate (NMDA) receptor antibodies. One had a paraneoplastic syndrome associated with a neuroblastoma, whereas the other had no primary tumor. This disease was originally described as a paraneoplastic syndrome in young women with ovarian teratoma. The clinical features of both children resembled the typical symptoms reported for older patients with this disease: psychomotor deterioration, movement disorders, and seizures. One of the reported cases is the first known case of paraneoplastic encephalitis with NMDA antibodies in a child with neuroblastoma. Both cases described here were younger than any of the previously reported cases. Consistent with recently published series, this report suggests that the spectrum of symptoms of encephalitis with NMDA receptor antibodies is probably wider than previously thought.

Keywords

encephalitis, NMDA receptor antibodies, paraneoplastic syndrome

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Encephalitis with antibodies against *N*-methyl-*D*-aspartate (NMDA)-type glutamate receptors was recently recognized as a defined clinical entity. The initial reports concerned exclusively young women with ovarian germinal tumor and encephaltis.[1-9] All had a number of clinical signs in common: cognitive deterioration and abnormal movements of the orofacial region and limbs. The outcome after tumor resection was favorable and the patients displayed slow clinical recovery. These patients also had antibodies against NMDA receptors, consistent with a paraneoplastic syndrome.[10] However, the spectrum of the disease is probably wider. We report here 2 cases of subacute-onset encephalitis with NMDA-receptor antibodies in the absence of teratoma in young children.

Case 1

A 3-year-old boy was admitted to hospital for 4 episodes of generalized febrile seizures, each lasting <5 minutes. Intercurrent neurological examinations were normal. The child's family reported no recent history of illness. On day 5, the child's level of consciousness decreased and abnormal movements were noted. These movements consisted of repetitive episodes of tonic posture of the 4 limbs, extensive movements involving the trunk, and orofacial dyskinesia. On day 9, repeated measurements showed high blood pressure, more than 2 standard deviations above the mean for age. The patient's level of consciousness remained unchanged over the next few weeks. He displayed only motor responses to nociceptive stimulation. Blood tests revealed moderate inflammation (Table 1). Cerebrospinal fluid cell counts (days 7 and 15) and cerebrospinal fluid protein levels were in the normal range. Repeated serological tests on blood and cerebrospinal fluid detected no active infectious disease. Cerebral magnetic resonance imaging (MRI) was carried out on days 10 and 22 and showed enlarged sulci on day 22 that were still present 2 months after the end of the administration of corticosteroids (Figure 1). The patient's clinical status remained poor over the next few weeks, with an agitated coma and abnormal blood pressure levels. Levels of noradrenaline excretion in urine exceeded the upper limit of the normal range on 3 consecutive

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Table 1. Main Values of Cerebrospinal Fluid and Blood Tests During Follow-Up of Case 1

	J1	J7	J15
Cerebrospinal fluid tests			
Cells count/μL	nd[a] (traumatic puncture)	7	2
Proteins (g/L)	1.4	0.12	0.05
Lactate (mmol/L)	nd	1.8	2
Cerebrospinal fluid Ab anti–NMDAr			
Transfected cell-based assay	nd	nd	pos
Blood tests			
White cells (Nbr/μL)	12 400	9300	13 600
Hb (g/dL)	12.3	12.5	12.5
Platelets (Nbr/μL)	346 000	476 000	10 73 000
Neutrophiles (Nbr/μL)	nd	6890	11 180
Lymphocytes (Nbr/μL)	nd	1620	nd
CRP (mg/L)	60	29	<6

NOTES: CRP, C-reactive protein; Hb, hemoglobin level; nd, not done; pos, positive result.

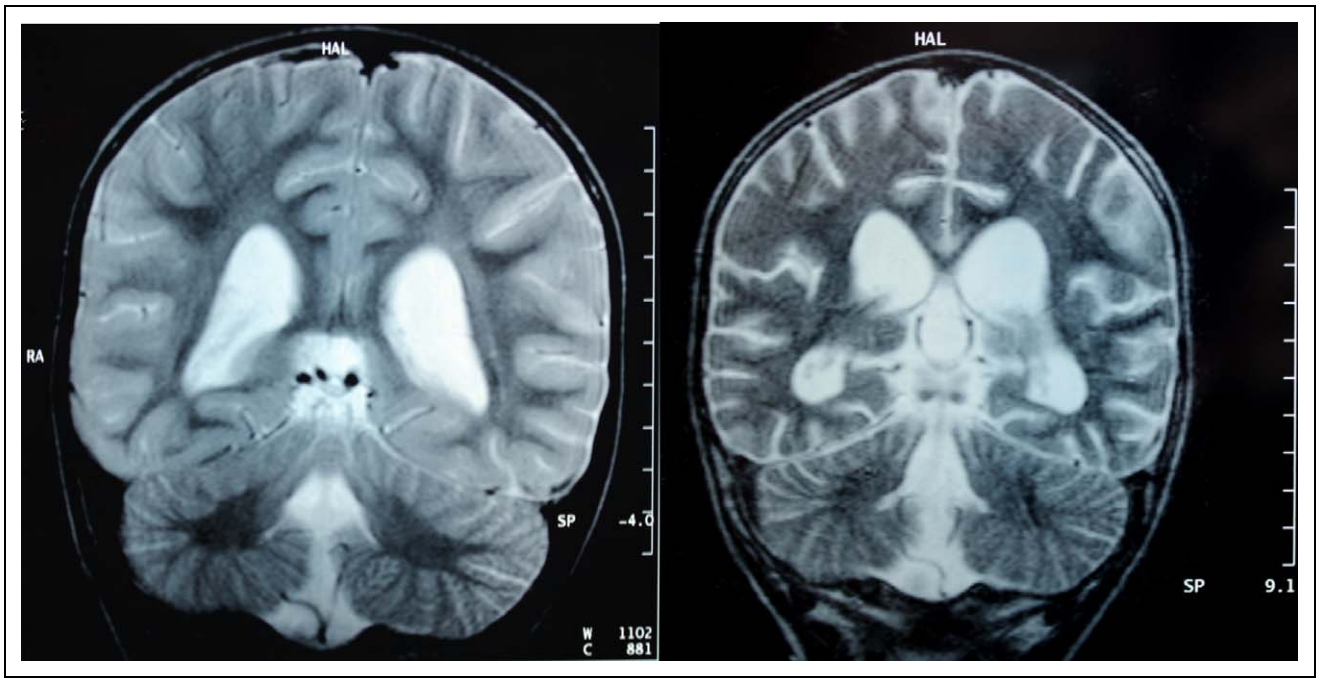

Figure 1. Cerebral magnetic resonance imaging (MRI) scans of patient no 1 (coronal T2) taken on days 10 and 22 showing a diffuse enlargement of sulci with cortical thinning.

days. Abdominal ultrasonic tomography on day 46 revealed the presence of a right adrenal mass with large locoregional adenopathies. (131)I-meta-iodobenzylguanidine scintigraphy results were negative. The abnormal mass was removed on day 57. Ultrastructural examination revealed it to be a neuroblastoma (size = 6 × 3.2 × 2.2 cm) with a ruptured adrenal capsule and invasion of the locoregional lymph nodes and bone marrow. It contained only small amounts of poorly differentiated stroma. *N*-myc was not amplified, and there was no 1p deletion. The patient was treated with pulses of methylprednisolone (days 10 and 12) and antihypertensive drugs (nicardipine, acebutolol). He received complementary oral chemotherapy with VP16 3 days per week for 4 weeks. Plasmapheresis was carried out on days 64 and 66. A slight clinical improvement was observed after treatment: the abnormal movements transiently disappeared and the patient was able to make eye contact and execute simple orders. Chemotherapy was intensified on day 85 because the patient's hypertension became uncontrolled. Carboplatin and VP16 were administered in months 5 and 7. Clinical, biological, and radiological tests showed the patient to be in remission from neuroblastoma. However, his neurological status gradually deteriorated and he died 10 months after the initial symptoms. After 7 years, NMDA-receptor antibodies were retrospectively detected in a cerebrospinal fluid sample from this child with the original method described by Dalmau.[6]

Table 2. Main Values of Cerebrospinal Fluid and Blood Tests During Follow-Up of Case 2

	J1	J6	J18	J70
Cerebrospinal fluid tests				
White cells count/μL	87	139	7	1
Lymphocytes (%)	43	87	nd	nd
Proteins (g/L)	0.37	0.61	0.42	0.26
Lactates (mmol/L)	1.5	nd	nd	1.8
Cerebrospinal fluid Ab anti-NMDAr				
Transfected cell-based assay	nd	nd	pos	neg
Immunohistochemistry (rodent brain hippocampus)	nd	nd	pos	pos
Blood tests				
White cells (nbr/μL)	18 770	12 670	4590	nd
Hb (g/dL)	10.2	9.2	10.1	nd
Platelets (nbr/μL)	424 000	379 000	253 000	nd
Neutrophiles (nbr/μL)	13 890	6650	1420	nd
Lymphocytes (nbr/μL)	3380	3660	2300	nd
VS (mm)	nd	nd	20	nd
CRP (mg/L)	nd	108	10	nd
Blood Ab anti-NMDAr				
Transfected cell-based assay	nd	nd	pos	neg
Immunohistochemistry (rodent brain hippocampus)	nd	nd	pos	pos

NOTES: CRP, C-reactive protein; Hb, hemoglobin level; nd, not done; neg, negative result; pos, positive result.

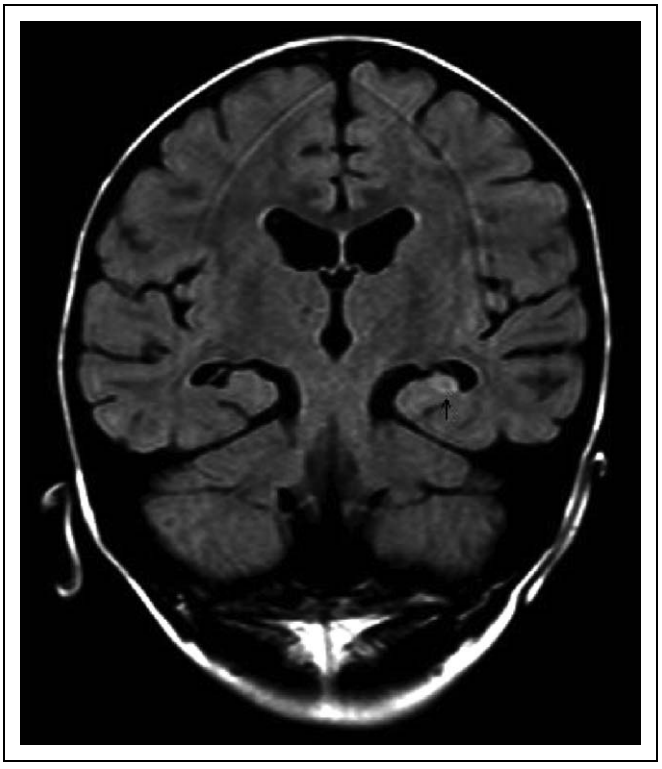

Figure 2. Cerebral magnetic resonance imaging (MRI) scan of patient no 2 (coronal fluid-attenuated inversion recovery) showing a left hippocampal high signal intensity.

Case 2

A 4-and-a-half year-old boy was admitted to hospital after 3 episodes of generalized febrile tonic-clonic seizures of short duration followed by a prolonged postictal state. He had no previous illness. On day 3, marked behavioral disorders associated with speech and memory dysfunction were observed. The patient also had orofacial dyskinesia. Over the next few days, he displayed alternate periods of agitation and drowsiness. He was unable to speak and could not focus his attention when awake. He had a mild fever over a period of 10 days. Clinical examination findings were otherwise normal, but with initially high levels in blood tests for inflammation (Table 2). Lumbar punctures were performed on days 1, 6, 18, and 70 and showed no sign of bacterial or viral infection. Cerebral MRI was carried out on day 18 and showed a left localized hippocampal high signal intensity on fluid-attenuated inversion recovery sequence (Figure 2). Anti-NMDA receptor antibodies were detected in both cerebrospinal fluid and blood samples on day 18 with the original method described by Dalmau.[6] After treatment, from day 70 onward, the cerebrospinal fluid was free of NMDA receptor antibodies, as shown by tests with NR2B and NR1 transfected cells, but antineuropil antibodies continued to be detected by immunohistochemistry on cross sections of rodent brain hippocampus. High doses of corticosteroids were administered from day 11 to day 13 (30 mg/kg per day, on 3 consecutive days) without significant improvement. Intravenous immunoglobulin treatment was given from day 22 to day 24 (1 g/kg, 3 consecutive days) and on day 70. This treatment was combined with the intravenous administration of CD20 antibodies (rituximab, 350 mg/m^2) on day 26. The patient displayed gradual clinical recovery over a period of 2 months. He was able to speak normally after 1 month and could focus his attention on normal tasks after 2 months. He continued to display slightly impulsive behavior and had a slight immediate memory deficit, but the final outcome was good.

Discussion

The concept of encephalitis with NMDA receptor antibodies has recently changed. Initially reported only in young women with ovarian teratoma, this disease has since been reported associated with a small-cell lung tumor,[2] and, increasingly, in the absence of evidence for a tumor.[11-13] Indeed, almost half the newly identified cases in 2008 and reported by Dalmau[14] were not linked to tumors. This may be accounted for by involution of the tumor at diagnosis, the use of radiological protocols insufficiently sensitive to detect the primary tumor, or inadequate follow-up. However, the absence of a primary tumor in an increasing number of cases is also consistent with other types of immunological stimulation, such as viral diseases, to account for the breech of normal immune tolerance.

These 2 cases of encephalitis presented a broader spectrum of symptoms than previously described, but both patients had the common recognizable clinical signs of the disease: (1) abnormal behavior, (2) abnormal movements of the limbs and face, including dyskinesia of the orofacial region, and (3) slow clinical recovery, with a favorable outcome in a high proportion of cases.

Case 1 was unusual in terms of his age, being the youngest patient with this condition reported to date, and in the occurrence of encephalitis together with NMDA receptor antibodies and neuroblastoma. Several lines of evidence are consistent with the occurrence of a paraneoplastic syndrome in this patient: (1) the occurrence of encephalitis and neuroblastoma at the same time, (2) clinical improvement after tumor resection, (3) worsening of the neurological symptoms after tumor relapse, and (4) the presence of antibodies against the NMDA receptor.

Case 2 was unusual not only in terms of his young age but also in the absence of a primary tumor and the favorable outcome achieved on treatment with a combination of immunoglobulins and rituximab, as previously reported,[11] despite the short follow-up period of only 4 months. The history of this child closely resembled that of a group of 6 children from our center described in a previous report.[15] All had severe encephalitis with coma and movement disorders. Three had transient orofacial dyskinesia. Unfortunately, we no longer have cerebrospinal fluid and blood samples for these 6 children, so it is not possible to demonstrate the presence of NMDA receptor antibodies retrospectively. However, all these children displayed the relevant principal signs of the disease: abnormal movements, cognitive dysfunction, and slow clinical recovery. These findings suggest that this clinically defined entity may be related to anti-NMDA receptor encephalitis.

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Declaration of Conflicting Interest

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