Pediatric Anti-*N*-methyl-D-Aspartate Receptor Encephalitis—Clinical Analysis and Novel Findings in a Series of 20 Patients

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Objective To report the clinical features of 20 pediatric patients with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

Study design Review of clinical data, long-term follow-up, and immunologic studies performed in a single center in Spain in the last 4 years.

Results The median age of the patients was 13 years (range, 8 months-18 years), 70% were female. In 12 patients (60%), the initial symptoms were neurologic, usually dyskinesias or seizures, and in the other 40% psychiatric. One month into the disease, all patients had involuntary movements and alterations of behavior and speech. All patients received steroids, intravenous immunoglobulin or plasma exchange, and 7 rituximab or cyclophosphamide. With a median follow up of 17.5 months, 85% had substantial recovery, 10% moderate or severe deficits, and 1 died. Three patients had previous episodes compatible with anti-NMDAR encephalitis, 2 of them with additional relapses after the diagnosis of the disorder. Ovarian teratoma was identified in 2 patients, 1 at onset of encephalitis and the other 1 year later. Two novel observations (1 patient each) include, the identification of an electroencephalographic pattern ("extreme delta brush") considered characteristic of this disorder, and the development of anti-NMDAR encephalitis as post herpes simplex encephalitis choreoathetosis.

Conclusions The initial symptoms of pediatric anti-NMDAR encephalitis vary from those of the adults (more neurologic and less psychiatric in children), the development of a mono-symptomatic illness is extremely rare (except in relapses), and most patients respond to treatment. Our study suggests a link between post herpes simplex encephalitis choreoathetosis and anti-NMDAR encephalitis. *(J Pediatr 2013;162:850-6)*.

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Since its initial description in 2007,[1] anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis has been recognized as the most frequent autoimmune encephalitis in children after acute demyelinating encephalomyelitis.[2] In a center focused on the etiology and epidemiology of encephalitis (California Encephalitis Project) the frequency of anti-NMDAR encephalitis surpassed that of any viral encephalitis.[3] Patients develop serum and cerebrospinal fluid (CSF) antibodies to a restricted epitope region of the NR1 subunit of the NMDAR.[4] In cultures of hippocampal neurons, patients' immunoglobin G (IgG) or CSF produce a substantial decrease of the levels of NMDAR and NMDAR-mediated currents that is reversible upon removal of patients' antibodies. A similar effect was obtained when antibodies were injected in vivo into the hippocampus of rats.[5,6] In pediatrics, increased awareness of this disorder is largely due to single case reports or small series,[7,8] with the largest experience being an American series of 32 patients, 8 from a single institution.[9] This and subsequent studies suggested that the younger the patient, the less likely a tumor would be found, and that the disease onset

CSF	Cerebrospinal fluid
EEG	Electroencephalography
FLAIR	Fluid-attenuated inversion recovery
HSE	Herpes simplex encephalitis
HSV	Herpes simplex virus
IgG	Immunoglobin G
IVIG	Intravenous immunoglobulin
MRI	Magnetic resonance imaging
NMDAR	*N*-methyl-D-aspartate receptor
PCPC	Pediatric Cerebral Performance Category
PCR	Polymerase chain reaction

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in children may be different from that of adults.[9,10] However, in those studies, the retrospective diagnosis of some patients and conservative treatment approach because of the novelty of the disease limited the information on symptom onset, treatment, and outcome. To address these issues, we report our experience with 20 pediatric patients with anti-NMDAR encephalitis focusing on disease presentation, spectrum of symptoms, treatment, and relapses. Moreover, the identification of a patient who developed the disorder 1 month after onset of herpes simplex encephalitis (HSE) provides an explanation for a rare and poorly understood complication of HSE[11-13] that often presents with choreoathetosis and occurs without viral reactivation.

Methods

From January 2008 until February 2012, we identified 61 patients (median age 22 years; range 8 months-76 years) with anti-NMDAR encephalitis whose serum and CSF were referred for antibody testing to Hospital Clinic, University of Barcelona. All patients were suspected of having autoimmune encephalitis after being extensively studied by their physicians. Twenty patients (33%) were younger than 19 years and are the focus of this study. Analysis of serum and CSF for NMDAR antibodies was performed using 2 different tests, immunohistochemistry with rodent brain tissue and a highly specific cell-based assay, following reported criteria.[14] None of the patients had antibodies to other cell surface or synaptic proteins using cell-base assays for the following proteins: AMPA receptor, GABA(B) receptor, mGluR1, mGluR5, LGI1, Caspr2, glycine receptor, and dopamine receptor. All patients were seen by the authors. Disease severity and residual deficits were determined with the Pediatric Cerebral Performance Category (PCPC) scale (**Table I**; available at www.jpeds.com).[15] There was not standardized protocol for ancillary tests; all patients underwent electroencephalography (EEG), magnetic resonance imaging (MRI), CSF analysis, and extensive bacterial and viral studies, including in all instances herpes simplex virus (HSV) among others. Treatment decisions were based on the physician's discretion. Three patients have been previously reported as part of a series of patients with relapses of encephalitis.[16]

The study was approved by the Ethics Committee of the Hospital Clinic. Samples are deposited in a collection of biological samples registered in the Biobank of Institut d'Investigació Biomèdica August Pi i Sunyer, Barcelona.

Results

The median age of the patients was 13 years (8 months-18 years); 14 were Caucasian, 5 Hispanic, and 1 Asian. NMDAR antibodies were identified in the CSF of all patients and serum of 9; the serum of 2 patients was negative and was not available from the other 9. Seventy percent of the patients were female. The ratio female/male varied according to age, so that 33% of patients younger than 12 years and all above this age were female.

Initial Symptom

Eleven patients (55%) developed prodromal symptoms a few days before the onset of the disease, including fever (n = 7), headache (6), and vomiting (4). A 2-year-old girl developed anti-NMDAR encephalitis 1 week after completing treatment

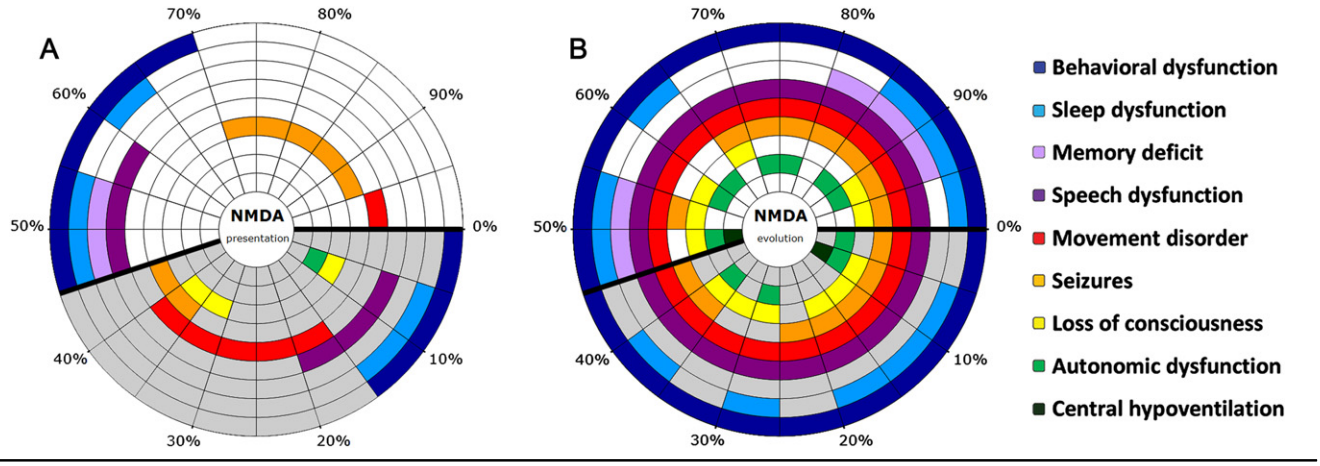

Figure 1. Symptoms at presentation and during the first month of the disease. **A,** The initial symptoms of each patient are shown in a panel; every radial segment represents 1 patient. The percentages assist to determine the percentage of patients with a specific symptom or combination of symptoms, each symptom coded with a different color. Patients >12 years-old are shown in the section with white background, and those ≤12 in the section with grey background. Behavioral dysfunction included agitation and aggression (4 patients), psychosis, delusional thoughts, and hallucinations (3), nonspecific behavioral disturbance (3), anxiety (2), stereotyped behavior and obsessions (1), and negativism and autolytic thoughts (1). **B,** The symptoms during the first month of the disease; patients are represented in the same order as in **A**.