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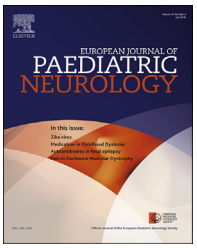

Original article

Pediatric NMDAR encephalitis: A single center observation study with a closer look at movement disorders

Tiziana Granata [a,*], *Sara Matricardi* [a], *Francesca Ragona* [a], *Elena Freri* [a], *Federica Zibordi* [a], *Francesca Andreetta* [b], *Simona Binelli* [c], *Nardo Nardocci* [a]

[a] *Department of Pediatric Neuroscience, Foundation IRCCS Neurological Institute "C. Besta", Milan, Italy*
[b] *Neuromuscular Diseases and Neuroimmunology Unit, Foundation IRCCS Neurological Institute "C. Besta", Milan, Italy*
[c] *Clinical Neurophysiology and Epilepsy Center, Foundation IRCCS Neurological Institute C. Besta, Italy*

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ABSTRACT

Anti-N-Methyl-D-aspartate-receptor (NMDAR) encephalitis is the most frequent autoimmune encephalitis in pediatric age. This retrospective observational study was aimed at describing the clinical characteristics of the disease in a cohort of children and teenagers. Eighteen patients (10 females and 8 males), with a median age of 12.4 years at symptom onset were enrolled. The clinical presentation of the disease was marked by neurological manifestations in 13 patients and by severe psychiatric and behavioral symptoms in 5. The symptoms at onset varied according to the age: all the children presented with prominent neurological symptoms, whereas psychiatric symptoms were prominent in teenagers. Regardless the age, movement disorders (MDs) were distinctive symptoms during the acute stage of the disease. Several MDs might coexist in a given patient, and persist during sleep. The complexity, and the oddness of MDs often challenged their definition and the differential diagnosis with psychiatric manifestations and epileptic seizures. Stereotyped motor phenomena were the most typical MDs, and were recorded in all patients. Among them, perseveration, reproduction of acquired complex motor activities, and orofacial dyskinesia were the most distinctive features. In children, hyperkinetic MDs dominate; in teenagers, by contrast, a constellation of symptoms consistent with catatonia was the most frequent syndrome observed. The management of the several symptoms requires their accurate recognition, definition and assessment, and the knowledge of the potential side effects of antiepileptic and psychotropic drugs which could either mimic or worsen symptoms of encephalitis.

* *Corresponding author*. Department of Pediatric Neuroscience, Foundation IRCCS Neurological Institute C. Besta, Via Celoria 11, 20133, Milan, Italy. Fax: +39 02 23942181.
E-mail address: tiziana.granata@istituto-besta.it (T. Granata).

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1. Introduction

During the last decade, an increasing number of antineuronal autoantibodies direct against membranous epitopes have been discovered, associated with various neurologic syndromes which include movement disorders (MDs) as prominent symptom.[1]

In pediatric age, the most frequent autoimmune encephalitis is anti-N-Methyl-D-aspartate-receptor (NMDAR) encephalitis. This is a treatable disease, characterized by the fairly abrupt onset of a constellation of symptoms attributable to diffuse brain dysfunction. The symptoms at onset vary according to the age: in adults, psychiatric and cognitive disturbances are the more frequent presenting symptoms, whereas seizures and movement disorders usually mark the onset of the disease in children. In the following few weeks, almost all patients, regardless to age and modality of onset, featured at least four symptoms among: epileptic seizures, movement disorders, psychomotor regression, psychosis, speech dysfunction, memory deficit, sleep disorders, autonomic instability, and decreased consciousness.[2–7]

The accurate recognition and definition of the several symptoms is mandatory to prompt a timely diagnosis, and treatment, both immunomodulating and symptomatic.

We report our experience with a cohort of children and adolescents with anti-NMDAR encephalitis observed at a third level center, with the aim of describing the clinical characteristics of the disease with a special focus on MDs, and the challenge of their definition and differential diagnosis.

2. Materials and methods

In this retrospective observational cohort study, we enrolled all pediatric patients diagnosed with anti-NMDAR encephalitis between 2010 and 2017, and followed-up (median follow-up: 34 months, range 3–86 months, mean follow-up: 36.8 ± 26.2 months) at the Department of Pediatric Neuroscience, Foundation I.R.C.C.S. Neurological Institute "C. Besta", Milan. The diagnosis was based on clinical findings and presence of anti-NMDAR antibodies in serum and cerebrospinal fluid (CSF). In one patient, the diagnosis was retrospectively done (and confirmed on detection of antibodies on stored CSF) at the relapse of the disease, which first had manifested in 2005.

All patients underwent extensive and longitudinal neurological evaluation and videotaping. Neurological disability was assessed with the modified Rankin Scale for children (mRS).[8]

Serial video-EEG recordings, brain magnetic resonance imaging (MRI), and screening for tumors were also performed. For the purpose of this study, we reviewed all available video data: video-EEG polygraphy, long-term video EEG monitoring, and videotaping has taken by parents or personnel. We classified seizures according to the 2017 Revised Classification of seizures,[9] and movement disorders according to the conventional terminology: orofacial dyskinesia, stereotyped movements, perseveration, dystonia, choreo-atetosis, eye movement abnormalities, bradykinesia/akinesia, catatonia, ataxia, myoclonus, and tremor.[10,11] Based on our own experience and data from literature[6] which suggest the age dependency of symptoms in anti-NMDAR encephalitis, we grouped patients according to their age at onset of the disease (less and above 12 years).

For all patients, written consent to be included in the present study was obtained from parents or caregivers.

The study was conducted according to the Declaration of Helsinki Criteria and it has been approved by the Foundation I.R.C.C.S. Neurological Institute "C. Besta" ethics committee.

3. Results

The series comprised 18 patients (10 females and 8 males), with a median age of 12.4 years at symptom onset. Eleven patients were older than 12 years (in the following "teenagers", median age of 14 years, range 12–17.5) and 7 patients younger (in the following "children", median age of 5.7 years, range 3.1–8). The longitudinal screening for associated tumor detected an ovarian teratoma in a 13 years old girl, 21 months after the onset of the encephalopathy.

The clinical presentation of the disease was marked by neurological manifestations (epileptic seizures, movement disorders, or psychomotor regression) in 13 patients and by severe psychiatric and behavioral symptoms (anxiety, depressed mood, temper tantrums, inappropriate behavior, paranoid thoughts, delusions and hallucinations) in 5 (Fig. 1a). The symptoms at onset varied according to the age: all the children presented with prominent neurological symptoms, whereas psychiatric symptoms were prominent in teenagers.

During the acute phase, within 4 weeks after the first symptom, all the patients had at least 4 of the typical symptoms of anti-NMDAR encephalitis, variously combined in each patient (Fig. 1b); 15 patients had a severe neurological impairment with a mRS score above 4, and one child required intensive care. At this stage, MDs were present in all patients.

3.1. *Movement disorders*

The types of MD, categorized according to the age, are summarized in Fig. 2. All patients featured more than one MD, that was often variably associated, sometime simultaneous, thus resulting in complex motor patterns. MDs might be present during fluctuating responsiveness in 11 patients and persisted during sleep in 8.

The most frequent and distinctive movements, observed in all patients, were stereotyped movements, termed according to the broad definition of "involuntary or unvoluntary, coordinated, patterned, repetitive, rhythmic, purposeless but seemingly purposeful or ritualistic movement, posture or utterance".[12]

Stereotypies were either simple or complex. Simple stereotypies consisted of cycling of the legs, repetitive thrashing movements of one limb, repetitive flexion-extension of the trunk, head nodding or "no–no" movements. Rhythmic hitting movements of a body segment might be repetitive, rhythmic at slow (1–4 Hz) frequency, and thus consistent with the definition of myorhythmia,[13,14] but in many cases the rhythmic movement increased in frequency, and/or spread to

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