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Original article

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

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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.

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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]

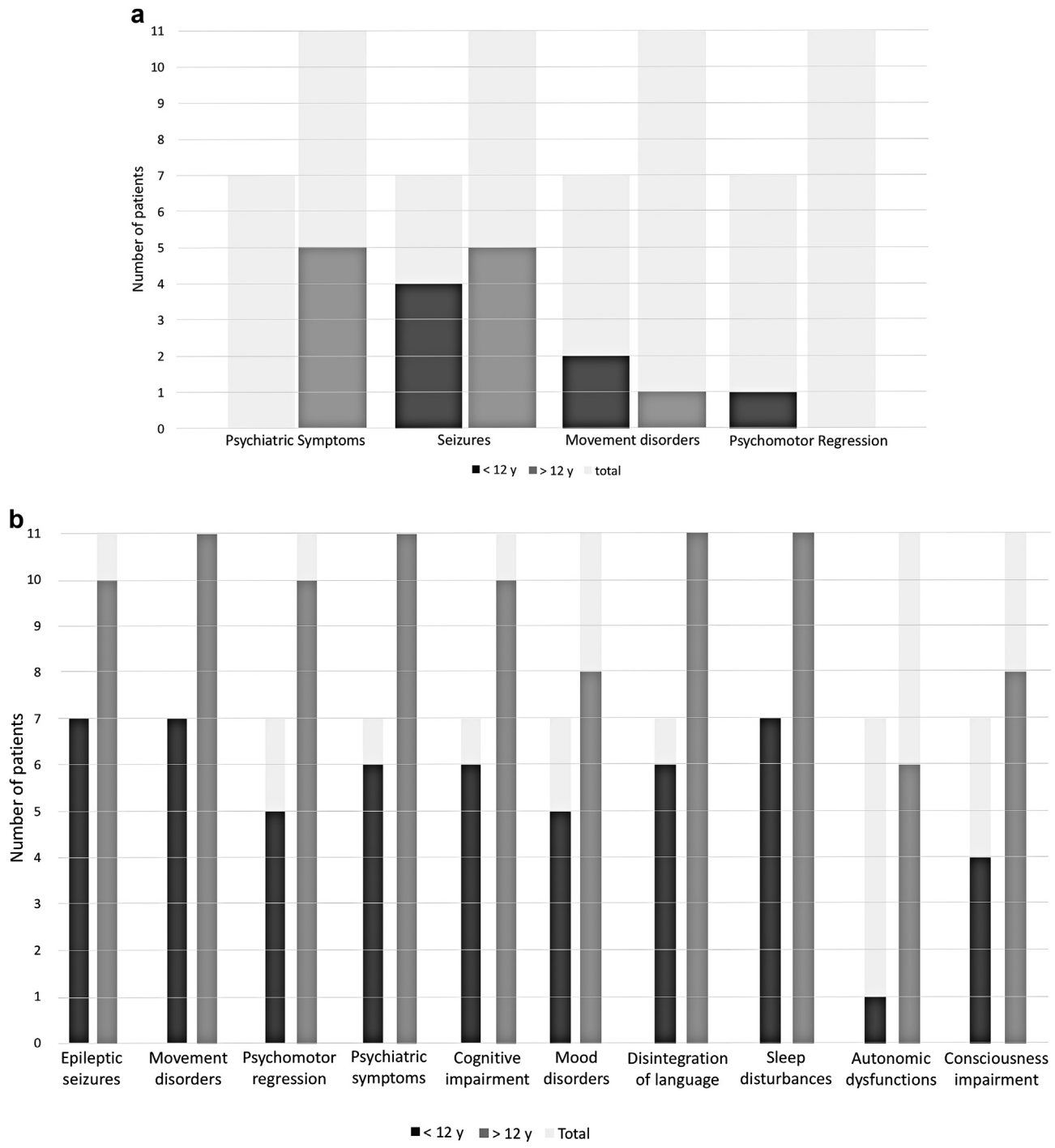

Fig. 1 – a: Presenting symptoms categorized according to the age at disease onset (less or more than 12 years). b: Symptoms during the acute phase categorized according to the age at disease onset (less or more than 12 years).

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 contiguous body segment, and persisted during sleep. Complex stereotypies consisted of raising and lowering of the arm, finger wiggling, or of bizarre movements which, aimlessly, reproduced learned movements, such as playing piano or harp, dance figures or rolling-pills. A characteristic stereotypic pattern was that of perseveration: after the voluntary

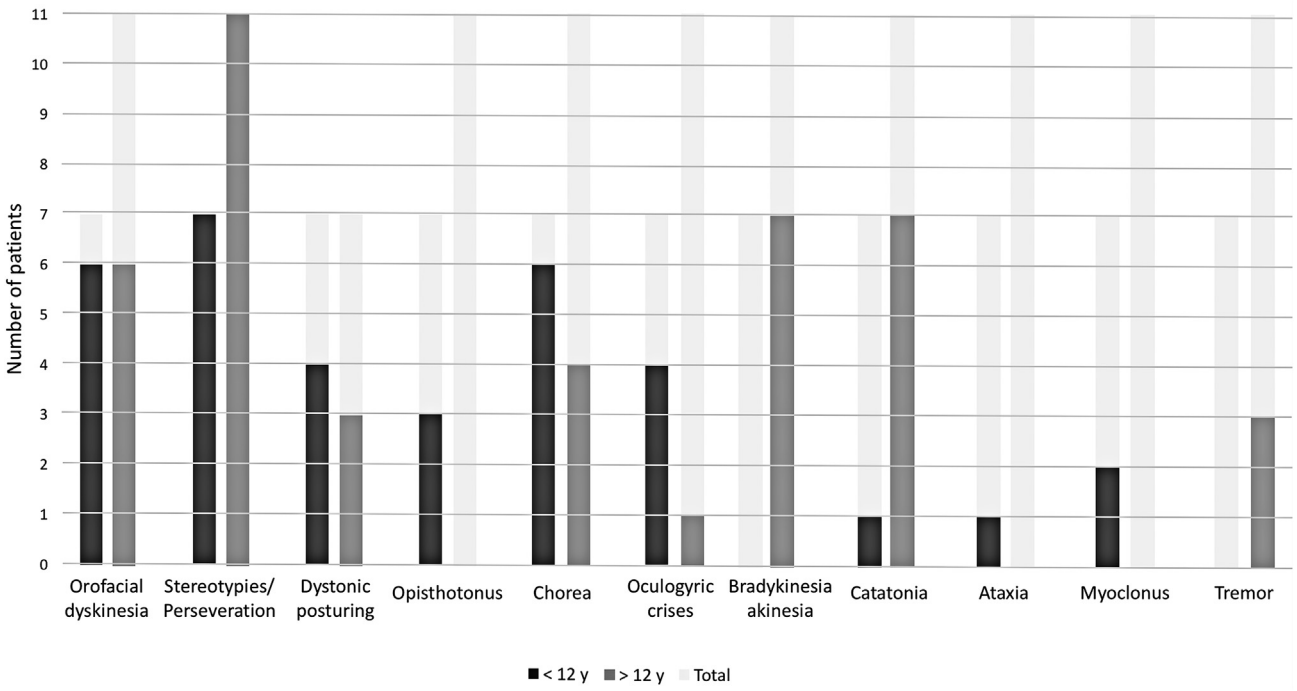

Fig. 2 – Movement disorders categorized according to the age at disease onset (less or more than 12 years).

initiation of a motor task the patient repeated it iteratively; interestingly we observed in different patients two typical patterns: moving the hair behind ear, and scratching the nose.

Orofacial dyskinesia was another distinctive motor phenomenon observed in 12 patients. It was characterized by sustained and repetitive sucking, rabbit mouth movements, clicking, rolling and protrusion of the tongue, grimacing, jaw opening and closing.

Dystonia, characterized by sustained or intermittent muscle contractions causing abnormal and repetitive movements, or postures, was present in 7 patients. Dystonic posturing had variable distribution but mainly involved the trunk, in 3 children the trunk dystonia was extremely severe and determined spontaneous opisthotonus.

Excessive, irregular, non-repetitive and randomly distributed choreic movements have been observed in 10 patients. Abnormal eye movements with oculogyric crises, squint, offset eyeballs, have been documented in 5.

In 8 patients (7 teenagers and 1 girl aged 8 years) the clinical picture was dominated by akinesia, plastic hypertonia with waxy flexibility and passively induced postures, unresponsiveness, stupor, and mutism, associated with stereotypic movements, perseveration, and alternating with bouts of excitement, severe agitation, verbigeration, and delusions.

3.2. *Epileptic seizures*

Epileptic seizures were reported in almost all patients at disease onset (11/18) or during the acute phase (17/18), with video-EEG recording obtained in 5 patients: focal motor (2) or focal non motor (3). One patient, already described, had focal motor seizures intermingled with focal hyperkinesia in a single complex motor phenomenon.[15] In three patients, the seizures semiology was extremely subtle (ie. only staring or rapid eye deviation) and the diagnosis of epilepsy required video EEG recordings. Video EEG monitoring also made clear that in 5 patients at least part of the paroxysmal events labeled as epileptic by caregivers and physicians, actually were paroxysmal MDs or non-epileptic episodes of unresponsiveness.

3.3. *Psychiatric symptoms*

Psychiatric symptoms or behavioral disorders were associated in 17 patients; these were mostly characterized by irritability, temper tantrum, persistent inconsolable crying, and severe behavioral regression in children and by excitement, motor agitation, paranoid thoughts, swear words, delusions, and hallucinations, and depressive mood in teenagers.

3.4. *Cognitive symptoms*

In most of our patients, symptoms were so severe soon after disease onset that formal neuropsychological assessment was impossible. For the 10 patients first assessed during the acute phase of their illness, but when the clinical condition had stabilized sufficiently to make formal testing possible, deficits were found in all domains investigated, although severity varied. Cognitive impairment (16/18), disintegration of language (17/18 patients) with jargoning, unintelligible whispered voice, and echolalia were almost consistently present. Details on cognitive profiles during the acute phase and on evolution have been already reported.[16]

3.5. Associated symptoms

During the acute stage of the disease, sleep disturbances (mainly insomnia) were invariably associated. Impairment of consciousness (12/18), and autonomic dysfunctions (7/18), such as tachypnea, tachycardia, or bradycardia, were also present.

3.6. Treatment and evolution

Immunomodulatory treatment: all patients received early first-line immunotherapy, with intravenous pulses of methylprednisolone combined with intravenous immunoglobulin (IVIg); the treatment was started a median of 2 weeks (range 2–12) from symptom onset, and was followed by oral steroids tapering over 6 months. The first-line treatment was well tolerated and effective in 14/18 patients, with symptoms improvement after a median time of 4 weeks from starting therapy (range 2–108). All these patients resumed normal life, albeit in a subset of them neuropsychological difficulties persisted, mainly evident as poor academic performance and impaired social relationships.[16] Despite the good response to first-line treatment 4 out of the 14 patients who were given only first-line treatment relapsed within two years from the first episode, and required a new course of MPN and IVIg, followed by rituximab, which was effective and well tolerated. Four out of 18 patients did not respond to first-line immunotherapy and quickly underwent second-line treatment with rituximab. The treatment was effective, but complicated by lethal sepsis in one 16-year-old boy.

Symptomatic treatment: in all patients, our first choice was benzodiazepine (midazolam, lorazepam) given their potential effect in hyperkinetic MDs, in catatonia, as well as in favoring sleep. Intravenous continuous midazolam was required in 8 patients who featured severe dystonic postures and movements, or catatonia. Further symptomatic treatment included Tetrabenazine, Trihexyphenidyl and Pimozide for the treatment of MDs, antiepileptic drugs (Levetiracetam, Oxcarbazepine), sleep inducers (mirtazapine, trazodone), and, in a minority of patients, atypical antipsychotic (Risperidone, Aripiprazole, Olanzapine, and Clonidine).

4. Discussion

We reviewed the clinical characteristics of a cohort of pediatric patients observed along a seven years period. The clinical presentation varied according to the age: all the children presented with prominent neurological symptoms, whereas psychiatric disorders were prominent in teenagers. However, during the first weeks after the onset all the patients developed a full blown clinical syndrome which associated at least 4 of the 6 typical symptoms of anti-NMDAR encephalitis, variously combined in each patient. These clinical pictures, together with the paraclinical findings (i.e. EEG and CSF) were consistent with the suspicion of NMDAR encephalitis, which was confirmed by the detection of specific antibodies. Our data further support the reliability of the diagnostic criteria proposed by Graus et al.,[17] and verified in a cohort of 29 children by Ho et al.[7]

Our study was mainly focused at describing the characteristics of MDs, that are among the most consistently reported symptoms in anti-NMDAR encephalitis. In the large cohort reported by Titulaer et al., MD was the first symptom in about 35% of children younger than 12 years and in about a quarter of those aged 12–18 years. During the first month of disease MDs were reported in above 80% of patients in both age groups.[6] A full range of hyperkinetic and hypokinetic movements have been described, with variable distribution and fluctuating course.[10,11,13] In our series, MDs were reported as the presenting symptom in 2 of the 7 children aged less than 12 years and in 1 of the 11 teenagers. These figures however might underestimate the proportion of patients with MDs at onset, given that the video EEG recordings often clarified that the paroxysmal phenomena reported in anamnesis as epileptic seizures were in fact non-epileptic events (mainly rhythmic hitting movements of a body segment or non-epileptic episodes of unresponsiveness).

During the first month of the disease, MDs were actually observed and recorded in all our patients. The review of our video documentation, taken during this acute phase, highlighted peculiar and distinctive characteristics of MDs. Before discussing our data, two preliminary remarks are required. First, the complexity, and the oddness of MDs often challenged the differential diagnosis with "psychiatric" symptoms and with epileptic seizures. The differential diagnosis was particularly puzzling when motor phenomena were repetitive, stereotyped, persisted during sleep, or when epileptic and non-epileptic events were closely intermingled.[15] Prolonged clinical observation and, as stated above, long term video EEG monitoring were often crucial to define the symptoms and to choose the appropriate treatment.

Second, in many cases, the MDs were hardly classifiable in conventional categories, and more than once we had to force their definition. This difficulty also stemmed from the frequent coexistence of different MDs, which might simultaneously involve different segments of the body (for example rhythmic tremor of one hand and myoclonic jerks on the contralateral upper limb, orofacial dyskinesia and "rolling pills", waxy flexibility of one arm and complex stereotypes on the contralateral) causing complex, difficult to define, motor pictures.

In our series, the most frequent MDs were stereotyped MDs, bradykinesia, dystonia, and chorea, whereas tremor and myoclonus were extremely rare. Orofacial dyskinesia and abnormal eye movements, were further consistently observed motor symptoms, confirming, in line with previous reports, as distinctive motor phenomena in anti-NMDAR encephalitis.[10,11,13] Both hypokinetic and hyperkinetic MDs were often associated with prolonged periods of unresponsiveness; stereotyped MDs persisted during sleep in 8 patients.

The distribution of the MDs varied according to the age of patients, with the exception of stereotypies, which were present in all 18 patients, albeit their semiology varied at the different ages. Under the term stereotypes we included prolonged (usually lasting many minutes, or even hours) repetitive motor activity: either simple (for example repetitive hitting movements of a body segment) or complex (for example, raising and lowering the arm, finger wiggling), as well as motor or verbal perseveration, and the episodes of

purposeless mimic of learned fine motor movements and well-coordinated complex activities. The different distribution of these MDs may be related to the distribution of dopaminergic receptors which varies with age,[18] but also with the acquired individual skillset. Simple stereotypes, are due to disinhibition of innate motor pattern and therefore may manifest at any age, whereas perseveration and complex motor activity are due to the disruption of the higher-order frontal cortex – basal ganglia network and require the pre-existence of learned motor patterns.

The above described MDs were differently combined in the different patients, but they clustered in two age-related pictures which entailed different issues in differential diagnosis, and symptomatic treatment. Children mostly had multifocal hyperkinetic movement with chorea, rhythmic motions of the limbs, simple motor stereotypies and dystonic posturing or opisthotonus. In this age group the most distinctive motor pattern was the unusual association of chorea, dystonia and stereotypies, rarely observed in any other neurological conditions. The movement disorders were in the context of a disturbed behavior characterized by irritability, restlessness, persistent inconsolable crying, and severe behavioral regression with loss of motor and cognitive skills and of language. The storming onset of the described severe clinical picture, that was often preceded by fever or trivial infections, was suggestive of acquired encephalopathy, and the diagnostic work up was mainly focused on differential diagnosis with infectious encephalitis and rarely with the decompensation of unrecognized metabolic or degenerative disease. The most challenging diagnostic issue in hyperkinetic patients was the recognition of epileptic versus non-epileptic motor events. The treatment of the often incoercible, and sometimes threatening hyperkinesia and dystonia (which impaired feeding and worsened the dysvegetative symptoms) was demanding, particularly in very young children, and might require polytherapy and continuous infusion of Midazolam.

The vast majority of teenagers, by contrast, mainly featured hypokinesia with muscle rigidity, waxy flexibility, posturing, stereotypes, motor perseverations, and aimless reproduction of complex motor activities. The hypokinetic symptoms were associated with stupor, unresponsiveness, with language limited to fragmented, unintelligible verbal production and suddenly alternated with bouts of severe agitation, and excitement. This constellation of symptoms, which is consistent with the syndromic definition of catatonia, might be misjudged as non-convulsive status epilepticus and, more frequently, as the onset of psychiatric disease.[19]

The treatment of the several symptoms in anti-NMDAR encephalitis deserves a comment. It is acknowledged that early initiation of appropriate immunotherapy is the mainstay of therapy and that recovery of symptoms may be achieved by restoring the NMDAR activity. Nonetheless, symptomatic treatment is always required. The management of the several symptoms benefits from multidisciplinary expertise, it requires the accurate recognition, definition and assessment of the several symptoms, the knowledge of potential side effects of antiepileptic and psychotropic drugs which could either mimic or worsen symptoms of encephalitis[20].

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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