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ORIGINAL ARTICLE

Clinical variability of children with anti-*N*-methyl-D-aspartate receptor encephalitis in southern Brazil: a cases series and review of the literature

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Abstract

Purpose Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated disease of the central nervous system (CNS). The aim of this study was to describe the variability of clinical presentation in anti-NMDAR encephalitis, treatment and outcomes in a case series of children and adolescents.

Methods Retrospectively analyse patients diagnosed with anti-NMDAR encephalitis, from 2010 to 2018.

Results The study population consisted of nine children with anti-NMDAR encephalitis from southern Brazil, six females and three males, aged 5 months to 16 years (mean 5 years). The time of follow-up varied between 1 and 7 years, with a mean of 3 years. The most frequent first manifestation consisted of seizures. All patients described had psychiatric symptoms and a wide spectrum of neurologic findings. Five patients had unilateral symptoms. Magnetic resonance imaging and electroencephalogram were normal in most patients. Cerebrospinal fluid pleocytosis occurred in five patients. All patients were administered immunoglobulin and/or steroids. Seven patients (78%) required cyclophosphamide and/or rituximab. Almost half of the patients fully recovered from all symptoms.

Conclusions A wide variety of symptoms were observed in this study and, although unilateral symptoms are rarely reported in the literature, a high frequency was observed among Brazilian children. Alternatives to first-line therapy should be considered in patients with clinical suspicion, even if they have not had a good response with first-line therapy.

Keywords Anti-N-methyl-D-aspartate receptor · Encephalitis · Paediatrics · Autoimmune

Introduction

Since its first description in 2007, by Dalmau et al. [1], anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been widely studied. It is an immune-mediated disease associated with immunoglobulin against the GluN1 subunit of NMDAR [2]. Epidemiologic studies suggest that anti-NMDAR encephalitis is the predominant cause of autoimmune encephalitis after demyelinating acute encephalitis [3].

A wide spectrum of symptoms may present in this disease, including cognitive, behavioural, autonomic, sleep disturbance and movement disorders [4]. Studies of anti-NMDAR encephalitis in children mainly consist of small- to medium-sized case series.

The aim of this study was to better understand the disease spectrum in children, describe the variability of clinical presentation of anti-NMDAR encephalitis and discuss its treatment and outcomes.

Methods

This is a retrospective study of children with a diagnosis of anti-NMDAR encephalitis, from 2010 to 2018, in the paediatric neurology units of 3 reference hospitals in Paraná state (Hospital Pequeno Principe, Hospital Waldemar Monastier and Hospital de Clínicas da Universidade Federal do

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Paraná). The estimated paediatric population served by these hospitals was 3,000,000 in 2018.

The sample included patients younger than 18 years. The diagnosis was based on the presence of anti-NMDAR antibodies in cerebrospinal fluid (CSF) after clinical suspicion and exclusion of other diagnoses.

Relevant data, such as age, gender, symptoms, course of the disease, imaging, electrophysiological study and treatment response, were recorded.

The treatment response was classified as total, partial or absent according to the objective improvement in neurological findings during drug therapy.

This study was approved by the Ethics Committee of Hospital Pequeno Príncipe.

Results

The sample consisted of nine patients (six females and three males) aged 5 months to 16 years (mean 5 years). The time of follow-up varied between 1 and 7 years, with a mean of 3 years. None of the related patients had other identified encephalitis aetiologies.

Five (56%) patients presented with seizure as the first manifestation, and two (22%) patients presented with irritability (Table 1). All patients presented with neurologic or psychiatric findings during disease. Seventy-eight percent ($N = 7$) presented with seizures and 89 % ($N = 8$) with movement disorders. Thirty-three percent ($N = 3$) presented with neurodevelopmental regression. Fifty-six percent ($N = 5$) presented with unilateral neurological symptoms: two patients with hemicoreia, one patient with hemidystonia and three patients with spastic hemiplegia (3/9). Twenty-two percent ($N = 2$) presented with hallucinations, 11 % ($N = 1$) presented with delusions, 67 % ($N = 6$) presented with bizarre behaviour and 56 % ($N = 5$) with mutism or aphasia (Table 1).

Electroencephalogram (EEG) was normal during admission and all course of disease in six cases (67%). From those patients with abnormalities in EEG, one patient (11%) presented with a disturbance in background rhythm and 2 (22%) with epileptic activities (Table 1).

Brain magnetic resonance imaging (MRI) was performed in all cases. One (11%) patient had cerebral hyperintensity areas, including posterior periventricular and right thalamus capping, and one (11%) patient had frontotemporal atrophy (Table 1).

All patients were screened for ovarian, testicular, abdominal, pelvic and thoracic tumours, and none presented any of these identified diseases.

Two (22%) patients had a good response to first-line therapy (corticosteroid administered with or without immunoglobulin). None of the patients presented worsening of symptoms after using corticosteroids. All patients treated with immunoglobulin had a partial response (5/7) or no response (2/7). Second-line therapy was administered in seven patients. A total response was present in three patients who used rituximab (3/3) and in one who used cyclophosphamide (1/6). Partial response was observed in five patients who use cyclophosphamide. No treatment response was reported after cyclosporine (1/1).

Five (56%) patients fully recovered from all symptoms, two (22%) patients had slight sequelae and two (22%) with significant sequelae. Recovery was not related to age, sex, symptoms, EEG findings or MRI.

Discussion

Anti-NMDAR encephalitis is a rare disorder and reports mainly consist of small- to medium-sized case series in children (Table 2), with few cases reported in Brazil [5]. This case series is part of a larger Brazilian case series of anti-NMDAR encephalitis in children. Our estimated incidence in Paraná state is 0.3/million children per year. This incidence is lower than findings in other studies [6, 7]. The discrepancy is likely due to misdiagnosis and difficulties in accessing health services.

Prevalence rates differ from other similar studies due to the predominance of younger patients in this series (seven patients less than 4 years old). The gender distribution is similar to that in other studies [4, 6–15].

Although flu-like symptoms are common in adults, variable prevalence rates are observed in younger populations, with prevalence varying from 18 to 80% prevalence identified in these studies [4, 6, 8, 9, 11–15].

As shown in the literature, the most frequent initial manifestations have been seizures and cognitive symptoms [4]. In our study, five patients had seizures as first symptoms, and two additional patients had seizures during the disease course. Children usually present with prominent neurological-based symptoms, though seizures can occur throughout the course of disease [16].

Movement disorders, including dystonia, can be precipitated by autoimmune CNS lesions. Basal ganglia involvement is a common finding in children and adults with anti-NMDAR encephalitis [17]. Anti-NMDAR antibodies induce downregulation of postsynaptic NMDAR in hippocampal neurons in rats [17, 18]. A high prevalence of movement disorders is expected, as identified in our and previous case series, ranging from 44 to 100% [4, 6–15].

Although most of the study subjects had generalised symptoms, a high frequency of unilateral symptoms was observed in that study. Hemiparesis as a major symptom in children younger than 12 years old was shown in a previous study [8]. Hemidystonia, as an isolated manifestation, was also described in a 19-year-old woman with anti-NMDAR

Table 1 Demographic data, first symptom, clinical findings, complementary exams, treatment and disclosure of Brazilian children with anti-NMDAR encephalitis

Patient	1	2	3	4	5	6	7	8	9
Sex	F	F	F	F	M	M	F	M	F
Age of onset (years)	10	16	2	3	2	3	3	0	2
First symptom	Seizure	Motor apraxia	Seizures	Seizures	Left hemiparesis	Seizures	Irritability/somnolence	Fever and seizures	Dystonia
Clinical findings									
Prodromic symptoms									
Fever	−	−	−	+	−	−	−	+	−
Headache	−	+	−	−	−	−	−	−	−
Vomits	−	−	−	+	−	−	−	−	−
Abnormality (psychiatric) behaviour or cognitive dysfunction									
Agitation/irritability	+	+	+	+	+	+	+	+	+
Hallucination/psychosis	+	+	−	−	−	−	−	−	−
Insomnia	+	−	−	−	+	+	+	+	−
Lethargy	−	−	+	−	+	−	+	−	+
Speech dysfunction									
Apraxia	−	+	−	−	−	−	−	−	−
Aphasia	−	−	+	+	−	+	−	−	+
Mutism	+	−	−	−	−	−	−	−	−
Seizures	+	+	+	+	−	+	−	+	+
Movement disorder, dyskinesia or rigidity/abN posture									
Chorea	+	−	−	+	+	−	−	+	+
Dystonia	+	−	−	+	−	+	−	+	+
Orofacial dyskinesia	+	+	+	−	+	+	−	−	+
Spastic hemiplegia	−	−	−	+	+	+	−	−	−
Tics	+	−	−	−	−	−	−	−	−
Decreased level consciousness	−	−	−	−	+	−	+	−	+
Autonomic dysfunction	−	−	−	−	−	−	+	−	−
Others									
Neurodevelopmental regression	−	−	−	−	−	+	−	+	+
Paraesthesia	−	+	−	−	−	−	−	−	−
Dysarthria	+	+	−	−	−	−	−	−	−
Complementary exams									
MRI	N	N	N	N	N	Hyperintensity areas*	N	Frontotemporal atrophy	N
EEG	Occipital SW	N	N	N	N	N	N	BA depressed	Frequent SW
Treatment performed									
Time of illness of first treatment (days)	33	19	15	24	50	90	3	45	9
Methylprednisolone	+	+	+	+	+	+	+	+	+
Immunoglobulin	−	+	−	+	+	+	+	+	+
Cyclosporine	+	−	−	−	−	−	−	−	−
Cyclophosphamide	+	+	−	+	−	+	+	+	−
Rituximab	+	−	−	+	−	−	−	−	+
Follow-up									
Outcome	Fully recovered	Slight memory impairment	Fully recovered	Fully recovered	Slight left hand hemidystonia	Irritability, spastic double hemiplegia	Fully recovered	Developmental delay	Fully recovered

+ Present, − absent, *BA* basal activity, *F* female, *M* male, *N* normal, *SW* sharped waves

*Posterior periventricular capping, right thalamus

Table 2 Demographic and clinical findings of main paediatric series cases of anti-NMDAR encephalitis

Article		Florance et al. 2009	Dale et al. 2009	Armangue et al. 2013	Hacohen et al. 2013	Wright et al. 2015	Sartori et al. 2015	Brenton et al. 2016	Wang et al. 2017	Ho et al. 2018	Konuskan et al. 2018	Brujin et al. 2018	This study
Period		May 08 to Dec 08	NR (9 years)	Jan 08 to Feb 12	2007 to 2010	Nov 10 to Dec 11	May 07 to Nov 13	Jan 10 to Aug 13	Mar 14 to Nov 16	Jan 09 to Dec 15	2012 to 2016	Jan 08 to Mar 17	2010 to 2018
Country		USA	Australia	Spain	England	England	Italy	USA	China	Hong Kong	Turkey	Netherlands	Brazil
Number of cases		32	10	20	13	31	20	10	51	15	16	28	9
Demographic data	Female	81%	80%	70%	NR	74%	50%	80%	59%	67%	50%	75%	67%
	Age (years)	14 (1.9–18)	7 (1.3–13)	13 (0.6–18)	9 (1.8–17)	11 (6–17)	8 (3–17)	13 (6–17)	8 (0.3–14)	12 (1–17)	6 (0.5–14)	14 (1–17)	5 (0.4–16)
First manifestation	Neurologic	13%	50%	60%	NR	NR	70%	50%	27%	40%	81%	57%	89%
	Psychiatric	88%	50%	40%	NR	90%	30%	80%	51%	60%	62%	36%	11%
Symptoms	Prodromic symptoms	48%	NR	55%	30%	NR	32%	70%	29%	80%	18%	64%	33%
	Seizures	77%	50%	90%	77%	68%	85%	90%	67%	93%	88%	96%	78%
	Psychiatric	88%	90%	100%	77%	90%	50%*	100%	88%	93%	100%	86%	100%
	Speech dysfunction	3%	50%	100%	NR	19%	100%	80%	55%	87%	13%	86%	67%
	Movement disorder	84%	100%	100%	54%	68%	100%	70%	78%	80%	44%	86%	89%
	Alteration in mental status	NR	0%	NR	NR	NR	95%	100%	59%	67%	69%	54%	33%
	Autonomic dysfunction	86%	40%	NR	NR	39%	90%	70%	24%	33%	NR	54%	11%
CSF	Pleocytosis	87%	40%	70%	NR	45%	56%	100%	29%	73%	60%	78%	56%
EEG	Normal	0%	NR	10%	8%	7%	0%	NR	14%	13%	13%	4%	78%
	Extreme delta brush	NR	NR	5%	NR	0%	NR	10%	NR	0%	19%	NR	0%
MRI	Normal	69%	70%	55%	69%	65%	55%	70%	64%	80%	63%	64%	78%
Tumour		27%	0%	10%	8%	3%	0%	20%	2%	0%	NR	19%	0%
Treatment	First line	97%	100%	100%	NR	100%	100%	100%	100%	100%	94%	100%	100%
	Second line	22%	NR	35%	NR	32%	45%	90%	47%	20%	44%	46%	78%
Outcome	Full recovery	29%	40%	60%	NR	63%	NR	60%	67%	82%	50%	64%	56%
	Partial improvement	45%	0%	25%	NR	33%	NR	40%	20%	9%	NR	23%	22%
	Severe sequels	26%	60%	10%	NR	14%	NR	0%	14%	9%	NR	13%	22%
	Death	0%	0%	5%	NR	0%	NR	0%	0%	0%	0%	0%	0%

Reference: [4, 6–15]

encephalitis, pointing to a possibility of presenting the disease in the form of unilateral symptoms, especially in young people [17].

Psychiatric symptoms in this disease vary widely, from psychosis to catatonia. The psychiatric presentation is associated with the presence of antibodies against the NMDAR NR1a subunit, present in anti-NMDAR encephalitis, as well as the NR2a and NR2b subunits, present in limbic encephalitis and systematic lupus erythematosus [19]. As expected from physiopathology, a high prevalence of psychiatric symptoms in anti-NMDAR is described in previous studies, with ranges from 77 to 100% (Table 2) [4, 6–15]. In this study, psychiatric symptoms occurred in all the study patients.

Cerebrospinal fluid (CSF) was abnormal with pleocytosis in approximately half of the patients, as reported in previous studies, with ranges from 29 to 80% (Table 2) [4, 6–15], showing that normal CSF does not exclude anti-NMDAR encephalitis.

While extreme delta brush on EEG is reported in one out of three cases in adults [20], none of the patients in our series presented with this pattern in EEG. Other studies in paediatric populations show that, in contrast to adults, extreme delta brush is rarely reported (Table 2) [4, 6–15].

MRI was normal in most of the patients, as reported in previous studies, showing a rate from 33 to 80% [4, 6–15]. Hyperintensities in T2/FLAIR in brain MRI occur in a variety of regions, including the brainstem, basal ganglia, hippocampi, cerebellar cortex and cerebral cortex [19], as observed in one of the patients in this study. The other patient presented with frontotemporal atrophy in brain MRI. High densities of NMDAR are present in the frontotemporal area and atrophy can be justified by the presence of anti-NMDAR antibodies in this region [21]. All patients with MRI findings were younger than 5 years old, in agreement with Sartori et al., suggesting that younger children have a higher prevalence of image abnormalities than older ones [12].

None of the studied patients had malignancy. Although there is a low prevalence of tumours in children with anti-NMDAR encephalitis (Table 2), due to and the severity of the tumours, screening is still indicated, specifically for teratomas [4, 6–15].

Even though all patients received first-line therapy with corticosteroid, administered with or without immunoglobulin, only one patient had a full recovery and one a major improvement of symptoms. These data differ from previous findings, in which most patients had a good response after first-line therapy [4, 6–15]. The patients included in this study presented with severe disease symptoms, justifying the poor response after first-line therapy. Patients with less severe disease might be underdiagnosed and not transferred to our services.

Second-line therapy was performed in 78% of the patients. Six patients used cyclophosphamide as second-line therapy. Of those, 2 had full responses and 4 patients had partial responses. All patients who used rituximab (patients 1, 4 and 9) fully recovered from the symptoms. The positive response to second-line therapy is in agreement with previous studies that indicated the importance of escalating immunotherapy in patients who do not show improvement with first-line therapy. Rituximab is previously described as resulting in better outcomes, as shown in our study. Unfortunately, the high cost of this medication limits its widespread use [6, 13].

Neurologic and psychiatric sequelae in patients with anti-NMDAR encephalitis have no relation with age, sex, time of first treatment or findings in complementary exams and imaging studies. Most patients with this disease, when properly treated, recover completely or have slight sequelae in their therapy [4, 6–15]. A full recovery from the symptoms occurred in nearly half of the patients, similar to previous studies whose complete recovery occurred in 29 to 82% patients (Table 2) [4, 6–15]. Two of our patients experienced significant sequelae: one was likely related to intercurrence during treatment and other had a relatively short follow-up. The treatment has a chance of ongoing improvement until 18 months, with a possibility of complete response [15].

As this is a retrospective study, a limitation is that we did not investigate all patients with encephalitis of unknown aetiology, so there might be undiagnosed cases of anti-NMDAR encephalitis. The low number of patients is also a limitation of this study, limiting the statistical analysis.

This study follows a group of patients younger than those in previous studies, and even though most of the patients had normal EEG, they had the more severe disease, with poor outcomes after first-line therapy. Recover was not related to age, sex, symptoms, MRI or EEG findings. Regardless, the patients showed a good response to second-line therapy.

Although unilateral symptoms are rarely reported in the literature, a high frequency was observed among Brazilian children, highlighting the importance of clinical suspicions even in uncommon presentations. Additional studies are needed to identify the higher prevalence of unilateral symptoms in young children.

Clinical suspicions are essential for adequate treatment and a favourable outcome, even though underdiagnoses remain a challenge in our region. In addition, even if patients have not had a good response with first-line therapy, alternatives to first-line therapy should be considered.

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Rosana Herminia Scola: study design, drafting and critical revision of the manuscript for important intellectual content

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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