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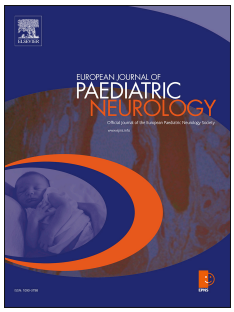

Initial clinical presentation of young children with N-methyl-D-aspartate receptor encephalitis

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Original article

Initial clinical presentation of young children with N-methyl-D-aspartate receptor encephalitis.

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Abstract

Autoimmune encephalitis with anti-N-methyl-D-aspartate receptor autoantibodies (NMDA-R-Abs) is a recently described disease affecting adult and pediatric patients. Symptoms of the disease are now perfectly described in the adult population but the clinical presentation is less known in young children. The aim of the present study was to describe the clinical presentation and the specificities of symptoms presented by young children with NMDA-R-Abs encephalitis to improve diagnosis of this disease, and to compare these to a series of previously published female adult patients. Fifty cases of children younger than twelve years of age diagnosed with NMDA-R-Abs encephalitis between January 1, 2007 and December 31, 2016 (27 females and 23 males) were retrospectively studied. The first neurological symptoms observed in young children with NMDA-R-Abs encephalitis were characterized by seizure (72%), especially focal seizure (42%), within a median of 15 days before other encephalitis symptoms; other patients mostly had behavioral disorders (26%). The seizures were frequently difficult to diagnose because of the transient unilateral dystonic or tonic posturing presentation or sudden unilateral pain in the absence of clonic movements. A post-ictal motor deficit was also frequently observed. This clinical presentation is different from that observed in adult females with NMDA-R-Abs encephalitis who initially present mainly psychiatric disorders (67%) or cognitive impairment (19%), and less frequently seizures (14%). The diagnosis of NMDA-R-Abs encephalitis should be systematically considered in young children of both sexes who present neurological symptoms suggesting recent seizures (focal or generalized) without obvious other etiology.

Key words: autoimmune encephalitis; N-methyl-D-aspartate receptor; child; focal seizures.

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Abbreviations

Abs, antibodies; CSF, cerebrospinal fluid; EEG, electroencephalogram; ENT, ear, nose and throat; FDG-PET, fluoro-D-glucose positron emission tomography; FLAIR, fluid attenuated inversion recovery; HSV, *Herpes Simplex Virus*; IQR, interquartile range; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NMDA, N-methyl-D-aspartate; NMDA-R-Abs, anti-N-methyl-D-aspartate receptor antibodies.

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1. Introduction

Autoimmune encephalitis with anti-N-methyl-D-aspartate receptor antibodies (NMDA-R-Abs) was described for the first time in 2007 in 13 women presenting an ovarian teratoma (1). NMDA-R-Abs encephalitis represents about 4% of all encephalitis (2) and it is the most common autoimmune encephalitis (3, 4). The course of the disease is very well known in the adult population especially in young women who typically present prodromal symptoms followed a few days later by psychiatric disorders then seizures and autonomic dysfunctions (5, 6). Several studies have reported clinical and laboratory data in children and adolescents with NMDA-R-Abs encephalitis (7-11) but none of them has precisely described the course of the disease in young children.

The aim of this study was to describe the clinical and paraclinical presentation as well as outcome of NMDA-R-Abs encephalitis in young children in order to increase the accuracy of the disease diagnosis, knowing that prognosis seems to be related to the early initiation of immunomodulatory treatment (6, 8, 9).

2. Materials and Methods

2.1. Population

We retrospectively studied all the children with NMDA-R-Abs encephalitis younger than 12 years old diagnosed in the French Paraneoplastic Neurological Syndrome Reference Center between January 1, 2007 and December 31, 2016. The diagnosis of NMDA-R-Abs encephalitis was confirmed by the presence of NMDA-R-Abs in the patient's cerebrospinal fluid (CSF), as previously described (7, 13), using two methods: i) specific staining pattern by immunohistochemistry of the hippocampus on rat brain tissue; ii) positive cell-based assay with human embryonic kidney cells (HEK293) expressing GluN1 and GluN2B subunits of the

NMDA receptor (7, 13). The date of diagnosis corresponded to the date of CSF NMDA-R-Abs identification.

2.2. Data collection

Data were prospectively collected from patients' physicians at diagnosis and during follow up. However, as NMDA-R-Abs encephalitis is infrequent in young children and physicians are not always systematic in the description of the symptoms, we systematically reviewed and discussed with the physician in charge of the patient all data available, every symptom and the chronology of them. Prodromal symptoms were those presented by patients before the first neurological symptom. The first neurological symptom was defined as the symptom observed at the onset of the disease, and complete clinical presentation was defined as the symptoms presented during the course of the disease. We defined 8 categories of symptoms: 1) psychiatric disorders, such as behavioral disorders, hallucinations, anxiety, or mood disorders; 2) seizures, such as focal seizures, generalized tonic-clonic seizures, or status epilepticus – focalized or generalized; 3) abnormal movements, such as dyskinesia, dystonia, chorea, or myoclonus; 4) decreased level of consciousness; 5) autonomic dysfunction, such as systemic hypotension or hypertension, bradycardia, tachycardia, apnea, or fever with no infection; 6) sleep disorders; 7) cognitive dysfunction, such as memory deficits, speech disorders, frontal signs, confusional state, or muteness; 8) other.

The modified Rankin scale (mRS) was used to assess the disability caused by the disease (12). The results of ancillary tests (lumbar puncture, neuro-imaging, electroencephalography – EEG, and tumor screening) were also collected.

Treatment was administered according to the treating physician's judgment. The first-line treatment could be intravenous corticosteroids, and/or intravenous immunoglobulins, and/or plasma exchange, and/or immunoadsorption. The second-line treatment corresponded to

rituximab and/or cyclophosphamide. The long-term immunosuppressive treatment was mycophenolate mofetil and/or azathioprine, and intrathecal immunotherapy corresponded to intrathecal injection of methotrexate and methylprednisolone.

Patients were considered to have a good outcome when mRS ≤ 2 and they were considered to have complete recovery when mRS = 0. Relapse was defined as the appearance of a new symptom or worsening of a pre-existing symptom after improvement or stabilization of the disease for at least 2 months.

In addition, the clinical characteristics, results of complementary exams, treatment, and outcome of the young children included in the present study were compared to those of the 58 adult female patients included in the study reported by Viaccoz et al. (13).

2.3. Ethics

Written informed consent was obtained from all patients and patients' parents, and this study was approved by the institutional review board of the University Claude Bernard Lyon 1 and the Hospices Civils de Lyon.

2.4. Statistical analysis

Statistical analyses were performed using SAS software (SAS 9.3, SAS Institute Inc., Cary, NC, USA). Qualitative variables were expressed as percentages and were compared using the Chi-squared test or the Fisher's exact test if the Chi-squared test was not applicable. Quantitative variables were expressed as median and interquartile range [IQR] and were compared using the Mann-Whitney test.

3. Results

3.1. Population

Fifty children were included in the study (Fig. 1). The median age at diagnosis was 5.9 years (interquartile range, IQR [3.8-8.3]), 27/50 patients (54%) were female, and most were of caucasian (40%) or african (34%) ethnicity.

3.2. Clinical presentation

Prodromal symptoms were present in 20 patients (40%): fever in 10/20 patients (50%), headache and ear, nose and throat (ENT) disorders in 6/20 (30%), digestive disorders in 5/20 (25%), cough and sleep disorders in 2/20 patients (10%), and deterioration of the general state of health in only 1 patient. Skin disorders were not notified. Among those with prodromal symptoms, the median interval between prodromal and first neurological symptom was 7 (IQR [1-9.3]) days.

The first neurological symptoms of the disease in young children with NMDA-R-Abs encephalitis could be separated into two main categories: seizures and behavioral disorders (Fig. 2). Seizures were the most common first neurological symptom; they were reported in 36/50 patients (72%). Most of those who had seizures had focal seizures (21/36, 58%) and the remaining patients had generalized seizures (15/36, 42%). Two developed suddenly generalized status epilepticus and 13 had repeated generalized seizures with around 1 to 2 seizures per day for a median 10 days (IQR [1-30]) before an increase frequency of seizure leading to confusion with behavioral disorders in 8 cases and status epilepticus in 5 cases. Among those with focal seizures, 19/21 (90%) primarily presented lateralized motor symptoms. The two remaining patients primarily presented painful somato-sensory seizures consisting of 1 to 7 episodes per day of acute pain within the face and an arm, which were of a few seconds in duration. One of these (patient 21) also later demonstrated some clonic motor seizures in the same side. Regarding ictal motor symptoms, two seizure types could be

differentiated. Ten children showed typical clonic seizures on one side, which mainly affected an arm and the face but sometimes also a leg (patient 2). A post-ictal motor deficit was observed in 9/10 patients and was associated with post-ictal aphasia in 2 patients when the seizures arose from the dominant hemisphere. In the nine other patients, the epileptic origin of the clinical symptoms was initially more difficult to diagnose because the children presented transient unilateral dystonic or tonic posturing during a few seconds or minutes, with or without clonic components. This dystonic/tonic attitude could be restricted to one hand (patient 12), one foot (patient 18), or a limb. In one case (patient 11), the children presented acute left leg deficit, rarely associated with clonic movements and an inter-ictal normal examination. A post-ictal motor deficit was frequently observed during hours or days (6/9, 67%). The epileptic origin of these symptoms was confirmed by abnormal EEG and/or characterized epileptic seizure. The median interval between focal seizures and a second symptom of encephalitis was 15 days (IQR [6-21]). The second symptom could be confusion with or without mutism, abnormal movements, abnormal behavior and/or generalized tonic-clonic seizures (Table 1).

Most of the young children who did not have seizures as the first neurological symptom of NMDA-R-Abs encephalitis presented behavioral disorders (13/50, 26%) with agitation and aggressiveness. Almost half of these children (6/13) had seizures as second symptom: 4 generalized tonic-clonic seizures, one focal motor seizures, and one focal somato-sensory seizures with pain. The median interval between the onset of psychiatric disorders and the occurrence of the first seizure was 8.5 days (IQR [5-14]).

The remaining child who did not have seizure or behavioral disorder as the first neurological symptom of the encephalitis presented a cerebellar syndrome followed one month later by

generalized tonic-clonic seizures, abnormal movements, and confusion. No other autoantibodies than NMDA-R-Abs was detected in the serum or the CSF of this child. Abnormal movements were observed in 38 (76%) patients and were characterized by bucco-facial dyskinesia in 33, limb dyskinesia/chorea in 17, and myoclonia in 7 patients.

3. Paraclinical data

The CSF was abnormal in 41/47 patients (87%) with oligoclonal bands in 21/26 (81%) patients, pleiocytosis in 32/42 patients (76%; median 24.5 cells/mm^3, IQR [11-57]) and/or high protein level in 3/35 patients (9%). With the exception of the presence of NMDA-R-Abs, no other abnormality was observed in the CSF, especially no additional antibody.

The EEG was initially abnormal in 42/47 patients (89%). The most common abnormality was an asymmetric slowing (33/42, 79%). Focal spikes were noticed in 31% of patients with an abnormal EEG. Extreme delta brush pattern was reported in none of the patients.

The magnetic resonance imaging (MRI) was abnormal in 18/47 patients (38%) and reported a fluid attenuated inversion recovery (FLAIR) temporal hypersignal in only 6 patients. A cerebral fluorodeoxyglucose positron emission tomography (FDG-PET) was performed in 7 patients and showed no specific abnormality.

A tumor was present in only 1 patient (2%); it was a pineal dysgerminoma in a 10 year-old boy with a teratoma component diagnosed 11 months before the diagnosis of encephalitis.

3.4. Treatment and outcome

The diagnosis of NMDA-R-Abs encephalitis was confirmed by the identification of CSF antibodies with a median 25 days (IQR [19-39]) after the first neurological symptom. All patients received a first-line of treatment within a median 19 days (IQR [11-28]) after the first symptom, and 38 (76%) before confirmation of the diagnosis (96% intravenous

immunoglobulins, 86% intravenous corticosteroids, 29% plasma exchange, and 16% immunoadsorption). Forty-two patients (84%) received a second-line of treatment (rituximab alone or associated with cyclophosphamide in 2 cases) according the decision of the local physician. Nine patients (18%) were treated with azathioprine as long-term immunosuppressive treatment in order to prevent relapses, and 7 (14%) received intra-thecal therapy with methotrexate and methylprednisolone.

Thirty-seven patients (74%) were followed for at least 12 months, and 24 (48%) for at least 24 months. At last follow-up, 39 patients (78%) had a good outcome (mRS $\leq$ 2), 27 (54%) had complete recovery (mRS = 0), and 1 patient had died from uncontrolled sepsis.

Comparison between the 27 girls and the 23 boys of the study did not highlight any significant difference regarding demographic and clinical data, results of paraclinical examination, treatment and outcome.

3.5. Comparison with adult patients

We compared the clinical characteristics of the young children included herein with those of 58 adult women (Table 2), that have been previously reported (13). Young children mostly presented seizures (72% *vs.* 14%, $p < 0.0001$) as the first neurological symptom whereas adult women mostly had psychiatric disorders (67% *vs.* 26%, $p < 0.0001$). If a seizure was the first neurological symptom, adult women mainly had generalized seizures (87% of adult women with seizures) contrary to young children who mostly presented focal ones (58% of children with seizures).

Seizures (88% *vs.* 69%, $p = 0.0210$) and abnormal movements (76% *vs.* 55%, $p = 0.0276$) were more frequent in young children than in adult women. Young children had significantly less frequently a tumor than adult women (2% *vs.* 41%, $p < 0.0001$); only one young child had a tumor. Regarding the treatment and outcome, a second-line treatment was more frequently used in young children than in adult women (84% *vs.* 48%, $p < 0.0001$) and,

conversely, adult women had more frequently a relapse than young children (14% *vs.* 0%, p = 0.0358).

We also compared the clinical characteristics of the young children included in our study with those of 13 adult men that have been previously reported (13). The two populations had the same clinical features, except for cognitive impairment that was more frequently presented by men as the first neurological sign of the disease (25% *vs* 0%, p = 0.0058).

4. Discussion

The present study identified the specific characteristics of young children with NMDA-R-Abs encephalitis. As compared to adult patients who are mostly female and present behavioral and cognitive disorders a few days before the main symptoms of encephalitis (5, 6, 13, 14), young children are equally male and female and present mainly seizures as the first neurological symptom. However, the diagnosis of seizures can be difficult because young children may present atypical seizures, such as unilateral tonic/dystonic movements or unilateral acute pain. Furthermore, nearly half of children with focal seizures presented a post-ictal unilateral deficit, and in such cases the epileptic origin is not always easy to prove. The particular clinical presentation of focal seizures found herein (frequent tonic and myoclonic components) is not specific of NMDA-R-Abs encephalitis as it is regularly observed in young children with frontal or temporal epilepsy (15, 16). The clinical characteristics of seizures probably evolve during brain maturation (15, 16) and could explain the tonic-dystonic presentation observed herein in the young children. Epilepsy is observed as the first neurological symptom in only around 14% of adult females with NMDA-R-Abs encephalitis (7, 13, 15) but in the majority of adult male patients (13). This difference could be related to hormonal changes. Indeed, some data suggest that sexual hormones can have an effect on epilepsy (17, 18, 19) and hormonal changes occurring around puberty, and especially sexual

hormone modifications, could then explain the differences of seizure frequency observed between young and older children (9). Alternatively, this age related semiology may be due to the high epileptogenicity of the peri-sylvian cortex of young children (20). Interestingly, young children with genetic mutations of NMDA-R also present seizures of peri-sylvian origin (21), suggesting the role of this receptor in the neuronal excitability of these areas.

We observed no other clear differences between adult (women) and young cases of NMDA-R-Abs encephalitis except the rarity of associated tumors that was observed in only one child of 10 years of age. Complementary examinations gave no specific results, but some of these may strengthen a clinical presumption of NMDA-R-Abs encephalitis. For instance, an asymmetric electroencephalographic slowing and oligoclonal bands in the CSF are initially frequent in children with NMDA-R-Abs encephalitis but brain MRIs are frequently normal. Taken together, clinical signs and paraclinical data may justify the initiation of immunotherapy without waiting for the definitive diagnosis of autoimmune encephalitis, as suggested by other authors (6, 8, 9). Indeed, in many countries a few weeks are sometimes necessary to obtain results of CSF anti-NMDA-R-Abs tests. However, it is of note that, even though this test is readily available in France and the results obtained in less than 10 days, three quarters of the children included herein received an immunomodulatory treatment before the identification of NMDA-R-Abs, and more than 8/10 received a second line of treatment. As some authors have suggested that an earlier treatment may improve the prognosis (9), we can speculate that the early treatment and the frequency of second-line treatment explain the good outcome of the patients described herein.

The main limitation of the study lies in the retrospective data collection. NMDA-R-Abs encephalitis is infrequent in young children and physicians are not always familiar with the

symptoms, and it was therefore sometimes difficult to define the exact first neurological symptom. It was also difficult to specify retrospectively the chronology of the symptoms; efforts were made to limit the importance of these aspects by careful consideration of all data available, and discussing every symptom with the physician in charge of the patient. We retrospectively interpreted transient dystonic/tonic attitude in some patients as seizures because all of them developed later abnormal EEG and/or characterized epileptic seizures. However, we cannot exclude in these patients, in the absence of EEG performed during symptoms, an abnormal movement without seizure. Further works will be necessary to clarify this point. Another limitation relates to the evaluation of the outcome using the mRS that is sometimes not enough specific, especially in young children who are yet to be independent in activities of daily living. It may therefore be of interest to develop a new specific score allowing a better assessment of the outcome with items evaluating the presence and severity of NMDA-R encephalitis symptoms.

5. Conclusion

The study demonstrates that presentation of NMDA-R-Abs encephalitis is particular in young children and different than in adults. The diagnosis should be systematically considered in both male and female patients, and not only in case of abnormal behavior or abnormal movements as is the case in adult patients, but also in case of neurological symptoms suggesting recent seizures (focal or generalized) in the absence of obvious other etiology. The diagnosis must be also considered in the presence of any neurological deficit without obvious etiology.

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Figures titles and captions

Figure 1. Flow chart presenting the population of the study.

Among the 273 patients included, 101 were prospectively diagnosed children, 57 of whom were aged under 12 years, and among these, NMDA-R-Abs encephalitis was not related to Herpes Simplex Virus (HSV) for 50 patients who were included in the study.

Figure 2. Stages of illness in young children according to the first neurological symptoms: focal seizures, generalized seizures, behavioral disorders and cerebellar ataxia. The first neurological symptom of the disease (D0) might be preceded by prodromal symptoms seven days before (D-7). The complete clinical presentation takes place between 8 and 30 days after the onset of the disease depending on the presenting symptom.

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Table 1. Description of the 21 cases with focal seizures as presenting symptom of the NMDA-R-Abs encephalitis

Patients (No)	Sexe	Age (years)	Seizure patterns	Frequence of seizures	Post-ictal status	Delay between seizures and encephalitis (days)	Evolution of patients
1	M	12	Motor clonic Right face and limbs	2 to 3/day	Right hemiparesis Aphasia	5	Status epilepticus
2	F	4	Motor clonic Left leg	< 1/day	Right leg deficit	9	Generalized seizures Abnormal behavior
3	F	6	Motor clonic Right limbs	1/day	Normal	6	Confusion, mutism
4	M	3	Motor clonic Right hand	3 episodes	Right hand deficit	35	Confusion, mutism
5	M	2	Motor clonic Right face and limbs	1/day	Hemiparesis	17	Confusion
6	M	5	Motor clonic Right face and arm before generalization	One	Hemiparesis	0	Confusion
7	M	3	Motor clonic Left arm	1/day	Left arm deficit	34	Confusion
8	M	5	Motor clonic Left arm and leg	4/day	Hemiparesis	13	Confusion
9	F	3	Motor clonic Right face, arm and leg	1/day	Aphasia	48	Abnormal behavior
10	F	10	Motor clonic Right arm and leg	1 to 4/day	Apraxia	21	Bucco-facial dystonia mutism
11	F	8	Motor Acute left limbs deficit, rarely clonic	3 to 4/day	Normal	19	Abnormal behavior
12	M	4	Motor dystonic Right hand	2 to 3/day	Right hemiparesis	15	Confusion, mutism
13	F	5	Motor dystonic Left hand	1/day	Normal	7	Confusion
14	M	11	Motor clonic/dystonic Left arm and leg	1 to 4/day	Hemiparesis	32	Confusion
15	F	3	Motor dystonic Left arm and leg	1/day	Hemiparesis	5	Abnormal behavior
16	F	3	Motor dystonic Right arm and leg	1 to 3/day	Normal	17	Abnormal behavior
17	F	2	Motor dystonic Right arm and leg	> 10/day	Hemiparesis Aphasia	20	Abnormal movements
18	F	7	Motor clonic/dystonic Right foot	2/day	Right foot deficit before hemiparesis	12	Confusion
19	M	4	Motor dystonic Right leg	> 7/day	Right leg deficit	30	Generalized seizures
20	M	9	Sensitive Left face and limb acute pain	1/day	Normal	3	Generalized seizures confusion
21	F	11	Sensitive and motor Right face and arm acute pain with arm dystonic attitude	6 to 7/day	Right arm deficit	6	Confusion

Table 2. Comparison of young children and adult women with NMDA-R-Abs encephalitis.

	Young children n=50 (%)	**Adult women n=58 (%)**	*p* value
Female, n (%)	27 (54)	58 (100)	< 0.0001
Caucasian, n (%)	20 (40)	44 (76)	0.0002
Prodromal symptoms, n (%)	20 (40)	34/55 (62)	0.0321
Headache	6/20 (30)	21/34 (62)	0.0472
Fever	10/20 (50)	NA	
Deterioration of the general state of health	1/20 (5)	NA	
Digestive disorders	5/20 (25)	9/34 (27)	NS
Skin disorders	0	NA	
ENT disorders	6/20 (30)	NA	
Cough	2/20 (10)	NA	
Sleep disorders	2/20 (10)	NA	
First neurological symptom, n (%)			
Psychiatric disorders	13 (26)	39 (67)	< 0.0001
Seizures	36 (72)	8 (14)	< 0.0001
Focal seizures	21/36 (58)	1/8 (13)	0.0459
Generalized seizures	15/36 (42)	7/8 (87)	0.0459
Abnormal movements	0	NA	
Decreased level of consciousness	0	NA	
Cognitive impairment	0	11 (19)	0.0008
Ataxia	1 (2)	NA	
Complete clinical symptoms, n (%)			
Psychiatric disorders	48 (96)	53 (91)	NS
Seizures	44 (88)	40 (69)	0.0210
Abnormal movements	38 (76)	32 (55)	0.0276
Decreased level of consciousness	36 (72)	30 (52)	0.0472
Autonomic dysfunction	12 (24)	20 (35)	NS
Cognitive impairment	43 (86)	48 (83)	NS
Initial ancillary tests, n (%)			
Abnormal CSF	41/48 (85)	45/55 (82)	NS
Abnormal EEG	43/48 (90)	38/49 (78)	NS
Abnormal MRI	18/48 (38)	19/57 (33)	NS
Tumor, n (%)	1 (2)	24 (41)	< 0.0001
Treatment, n (%)			
Corticosteroids	42/49 (86)	44 (76)	NS
Intravenous immunoglobulins	47/49 (96)	49 (95)	NS
Plasma exchange	14/49 (29)	12 (21)	NS
Immunoadsorption	8/49 (16)	NA	
Second-line treatment	42 (84)	28 (48)	0.0001
Long-term immunotherapy	9 (18)	17 (29)	NS
Intra-thecal treatment	7 (14)	NA	
Outcome, n (%)			
Good outcome (mRS ≤ 2)	39 (78)	35/43 (81)	NS
Complete recovery	27 (54)	26/42 (62)	NS
Relapse	0	8 (14)	0.007
Death	1 (2)	3 (5)	NS

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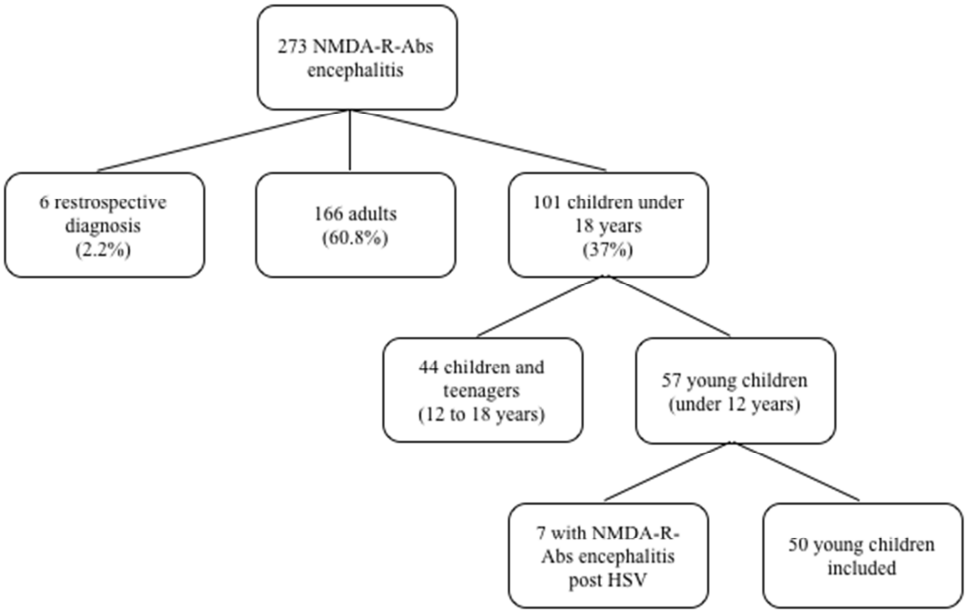

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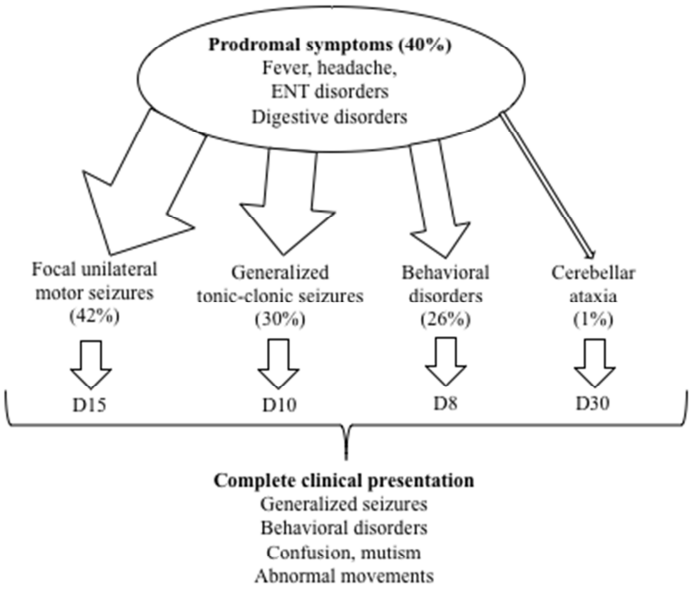

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Highlights :

In this article we describe the clinical presentation of 50 children younger than twelve years of age with NMDA-R-Abs encephalitis. The difference with adult female cases is that the most frequent first neurological symptom is seizures and especially focal seizure sometimes difficult to diagnose because of few presentation with transient unilateral dystonic or tonic posturing in the absence of clonic movements.

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