J Neurol (2015) 262:1859–1866
DOI 10.1007/s00415-015-7781-9

ORIGINAL COMMUNICATION

Treatment and outcome of children and adolescents with *N*-methyl-D-aspartate receptor encephalitis

Anastasia Zekeridou[1] · Evgenia Karantoni[1,4] · Aurélien Viaccoz[1,2,3] · François Ducray[1,2,3] · Cyril Gitiaux[5] · Frédéric Villega[6] · Kumaran Deiva[7] · Veronique Rogemond[1,2] · Elodie Mathias[1,2] · Géraldine Picard[1] · Marc Tardieu[7] · Jean-Christophe Antoine[1,8] · Jean-Yves Delattre[4] · Jerome Honnorat[1,2,3,9]

Received: 17 February 2015 / Revised: 6 May 2015 / Accepted: 8 May 2015 / Published online: 19 May 2015

Abstract The objective of this study is to describe the treatment and outcome of children and adolescents with *N*-methyl-D-aspartate receptor (NMDA-R) encephalitis. A retrospective study of children and adolescents with NMDA-R encephalitis was performed by the French Paraneoplastic Neurological Syndrome Reference Center between January 1, 2007 and December 31, 2012. The modified Rankin scale (mRS) was used to assess outcome. Thirty-six children and adolescents with NMDA-R encephalitis were studied. All of the patients received first-line immunotherapy (corticosteroids, intravenous immunoglobulins or plasma exchange), and 81 % received second-line immunotherapy (rituximab or cyclophosphamide). Median time between first-line and second-line treatment was 26 days. During the first 24 months, 30 of 36 patients (83 %) achieved a good outcome (mRS $\leq$ 2) and 20 of 36 patients (56 %) achieved complete recovery (mRS = 0). Median time to good outcome and to complete recovery was 6 and 24 months, respectively. Three patients (8 %) relapsed, one patient died. In multivariate analysis, age >12 years was a predictor of good outcome and initial mRS $\leq$ 3 was a predictor of complete recovery. Despite a higher rate of patients who received second-line immunotherapy, the outcome of the patients in the present series was very similar to the outcome reported in previous series. The present study highlights the need for clinical trials to determine the optimal treatment of NMDA-R encephalitis.

Keywords Pediatric autoimmune encephalitis · NMDA receptor encephalitis

Anastasia Zekeridou and Evgenia Karantoni contributed equally to the manuscript.

✉ Anastasia Zekeridou
anastasia.zek@gmail.com

✉ Jerome Honnorat
jerome.honnorat@chu-lyon.fr

1 French Reference Center of Paraneoplastic Neurological Syndromes, Hospices Civils de Lyon, Hôpital Neurologique, 69677 Bron, France

2 Lyon Neuroscience Research Center, INSERM U1028/CNRS UMR 5292, 69372, Lyon, France

3 Université de Lyon, Université Claude Bernard Lyon 1, 69372 Lyon, France

4 Service de Neurologie Mazarin, Groupe Hospitalier Pitié-Salpêtrière, APHP, UMR S975, CNRS, UMR 7225, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Université Pierre et Marie Curie-Paris 6, Paris, France

5 Service de Neurologie Pédiatrique, Hôpital Necker Enfants Malades, APHP, INSERM U1016-CNRS8104, Université Paris-Descartes, Paris, France

6 Service de Neurologie Pédiatrique, CHU Bordeaux, Bordeaux, France

7 Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud, Neurologie Pédiatrique, Université Paris Sud et INSERM U1012, Orsay, France

8 Service de Neurologie, CHU de Saint-Etienne et Université de Lyon, 42023 Saint-Etienne, France

9 Neuro-Oncologie, Hôpital Neurologique Pierre Wertheimer, 59 Boulevard Pinel, 69677 Bron Cedex, France

Introduction

Since the first description of autoimmune encephalitis with *N*-methyl-D-aspartate receptor autoantibodies (NMDA-R encephalitis) in young women with ovarian teratomas [1], the spectrum of this disease has proved to be much broader, including females without cancer, male patients and children [2–4]. The clinical presentation of children with NMDA-R encephalitis is now well known, with more than 200 pediatric patients reported in the literature [5]. However, the best treatment modalities are not yet clear. A first-line treatment with corticosteroids, plasma exchange or intravenous immunoglobulins followed by a second-line, in the absence of a clinical response, with rituximab and/or cyclophosphamide is currently proposed but has not yet been evaluated prospectively [4]. The rates of a second line of immunotherapy vary according to the series from 14 to 35 % [3–7]. The aim of the present study was to describe a series of 36 children and adolescents with NMDA-R encephalitis and to compare their outcome with data from the literature and adult patients from our center.

Patients and methods

NMDA-R-Abs detection

The presence of NMDA-R-Abs was assessed in the patient's cerebrospinal fluid (CSF). Patients were considered positive when they fulfilled both criteria: (1) specific staining pattern of the neuropil in rat brain tissue by immunohistochemistry and (2) positive cell-based assay with human embryonic kidney cells (HEK293) expressing both NR1 and NR2b subunits of the NMDA receptor, as previously described [8, 9].

Patients

112 of the 1921 CSFs evaluated for autoimmune encephalitis suspicion in the French PNS Reference Center between January 1, 2007 and December 31, 2012 were positive for NMDA-R-Abs. Of those patients, 41 were children or adolescents (aged less than 18 years). The clinical data were prospectively collected after diagnosis at least twice a year by phone or mail to the treating physicians. Written consent was obtained from all patients, and this study was approved by the institutional review board of the University Claude Bernard Lyon 1/Hospices Civils de Lyon.

Clinical and paraclinical data

Symptoms were grouped into 8 categories: (1) psychiatric disorders (e.g., behavioral changes, hallucinations, agitation and delirium), (2) seizures, (3) movement disorders, (4) decreased level of consciousness, (5) autonomic dysfunction, (6) sleep disorders, (7) cognitive dysfunction (e.g., speech difficulties, memory deficit and frontal signs) and (8) other. The presenting symptom was defined as the first symptom observed at the onset of the disease. Demographic information, previous medical history, history of current illness, neurologic observation and examination, treatment modalities, neuro-imaging findings, electroencephalography findings, cerebrospinal fluid analyses and tumor screening results were collected from the referring neurologists or pediatricians and recorded. Only the first MRI, EEG and CSF findings were considered. The treatments were administered according to the treating physician's expertise. However, the therapeutic recommendation of French PNS Reference Center was to perform early second-line immunotherapy when the patients did not respond to first-line treatment (for pediatric cases: rituximab with a dose of 375 mg/m^2, to repeat if there is no substantial improvement after 10 days). In this study, we considered the first-line treatments to be corticosteroids, intravenous immunoglobulins (IVIG) and plasma exchange, the second-line treatments to be cyclophosphamide and rituximab and long-term immunosuppressive treatments to be azathioprine or mycophenolate mofetil. Relapses were defined as the appearance of new symptoms or worsening of pre-existing symptoms after improvement or stabilization of the disease for at least 2 months. Patients were considered to have a good outcome when their modified Rankin scale (mRs) score was ≤ 2 and to have complete recovery when their mRs was 0. At the latest, follow-up information at 12 and 24 months was available for 35 and 31 patients, respectively.

Statistical analysis

The statistical program used for analysis was IBM SPSS Statistics, version 2.0. Groups were compared using Fisher's exact test, the *t* test and the Mann–Whitney test. Correction for multiple hypothesis testing was performed according to the Bonferroni method. Correlation between the date of diagnosis and the delay between clinical presentation and treatment was calculated using Spearman's rho rank correlation coefficient. Median time to good outcome and complete recovery was determined according to the Kaplan–Meier method. Patients who did not reach mRS 2 or 0 were censored at last follow-up. A multivariate Cox regression model was used to adjust the effect of factors predictive of better outcome and of complete recovery.

Results

Among the 41 children and adolescents (aged less than 18 years) with NMDA-R encephalitis identified in our database, 5 cases were excluded from this study; three

because the diagnosis was made retrospectively years after the encephalitis using a conserved sample of CSF and two cases because insufficient data were provided by the treating physician. In total, 36 children and adolescents were included in this study (Table 1).

Clinical characteristics

Average age was 10.1 years (median 10.9; range 14.5 months to 17.2 years). Only one tumor (ovarian teratoma) was identified in a 15-year-old girl. The sex ratio was 26 females to 10 males; 22 patients were younger than or equal to 12 years. Prodromal symptoms were present in 52 % (fatigue, cough, fever and/or headache). The most common presenting symptom was seizures (18 cases, 50 %), followed by psychiatric symptoms (11 cases, 31 %), sleeping difficulties and atypical symptoms (Fig. 1). During the course of the disease, psychiatric symptoms and cognitive dysfunction were present in 92 % of the cases, seizures in 86 % and movement disorders in 83 % (Fig. 1). An alteration in behavior was the most frequent psychiatric feature mentioned (64 %), followed by agitation (48 %), hallucinations (24 %) and delirium (12 %). In addition, 21 patients presented oro-mandibular dyskinesias (70 %), 17 limb dystonia (57 %), 9 chorea (30 %), 6 stereotypic movements (20 %), 6 myoclonus (20 %), 3 ballistic movements and opisthotonus (10 %) and 2 tremor and athetosis (7 %). Twenty-two patients had speech difficulties and 20 had signs of memory disturbance, disorientation, apraxia and frontal signs.

The clinical characteristics of the patients were compared according to sex and age (Table 1). No significant difference was noted in the prodromal symptoms and clinical presentation at onset. After correction for multiple testing, the only significant difference which was identified was the more frequent autonomic dysfunction in females

Table 1 Overview of clinical features, ancillary tests and treatment of the patients based on sex and age distribution

	Total ($n = 36$)	Female ($n = 26$)	Male ($n = 10$)	p	<12 years ($n = 22$)	>12 years ($n = 14$)	p
Age (years)	10.1 (1–17.2)	10.8	8.3	ns	NA	NA	NA
Prodromal symptoms	13/25 (52 %)	9/16 (56 %)	4/9 (44 %)	ns	7/15 (47 %)	6/10 (60 %)	ns
Presenting symptom, *n* (%)							
Psychiatric disorders	11(31 %)	9 (35 %)	2 (20 %)	ns	5 (23 %)	6 (43 %)	ns
Seizures	18 (50 %)	11 (42 %)	7 (70 %)	ns	13 (59 %)	5 (36 %)	ns
Movement disorders	2 (6 %)	2 (8 %)	0	ns	0	2 (14 %)	ns
Decreased level of consciousness	1 (3 %)	1 (4 %)	0	ns	0	1 (7 %)	ns
Sleep disorders	6 (17 %)	5 (19 %)	1 (10 %)	ns	5 (23 %)	1 (7 %)	ns
Cognitive disorders	1 (3 %)	1 (4 %)	0	ns	1 (5 %)	0	ns
Other	6 (17 %)	4 (15 %)	2 (20 %)	ns	4 (18 %)	2 (14 %)	ns
Complete clinical syndrome, *n* (%)							
Psychiatric symptoms	33 (92 %)	25 (96 %)	8 (80 %)	ns	20 (91 %)	14 (93 %)	ns
Seizures	31 (86 %)	23 (88 %)	8 (80 %)	ns	19 (86 %)	12 (80 %)	ns
Movement disorders	30 (83 %)	23 (88 %)	7 (70 %)	ns	17 (77 %)	14 (21 %)	ns
Decreased level of consciousness	22 (61 %)	16 (62 %)	6 (60 %)	ns	15 (68 %)	8 (53 %)	ns
Autonomic dysfunction	13 (36 %)	13 (50 %)	0	**<0.01**	5 (23 %)	9 (60 %)	**0.02**
Sleep disorders	23 (64 %)	18 (69 %)	5 (50 %)	ns	16 (73 %)	8 (53 %)	ns
Cognitive disorders	33 (92 %)	24 (92 %)	9 (90 %)	ns	20 (91 %)	14 (93 %)	ns
Other	16 (44 %)	10 (38 %)	5 (50 %)	ns	11 (50 %)	4 (29 %)	ns
Tumor, *n* (%)	1 (3 %)	1 (4 %)	0	ns	0	1 (7 %)	ns
Relapse, *n* (%)	3 (8 %)	3 (12 %)	0	ns	2 (9 %)	1 (8 %)	ns
ICU stay	18 (50 %)	15 (58 %)	3 (30 %)	ns	10 (45 %)	8 (57 %)	ns
Ancillary tests							
MRI (abnormal)/assessable cases, *n* (%)	11/35 (31 %)	7/26 (27 %)	4/9(44 %)	ns	7/21 (33 %)	4/14 (29 %)	ns
EEG (abnormal)/assessable cases, *n* (%)	32/35 (91 %)	23/26 (88 %)	9/9(100 %)	ns	21/22 (95 %)	11/13 (85 %)	ns
CSF (abnormal)/assessable cases, *n* (%)	32/35 (91 %)	25/25 (100 %)	7/10 (70 %)	**0.02**	18/21 (86 %)	14/14 (100 %)	ns

Statistically significant differences between the groups are in bold

ns not significant, *NA* not applicable

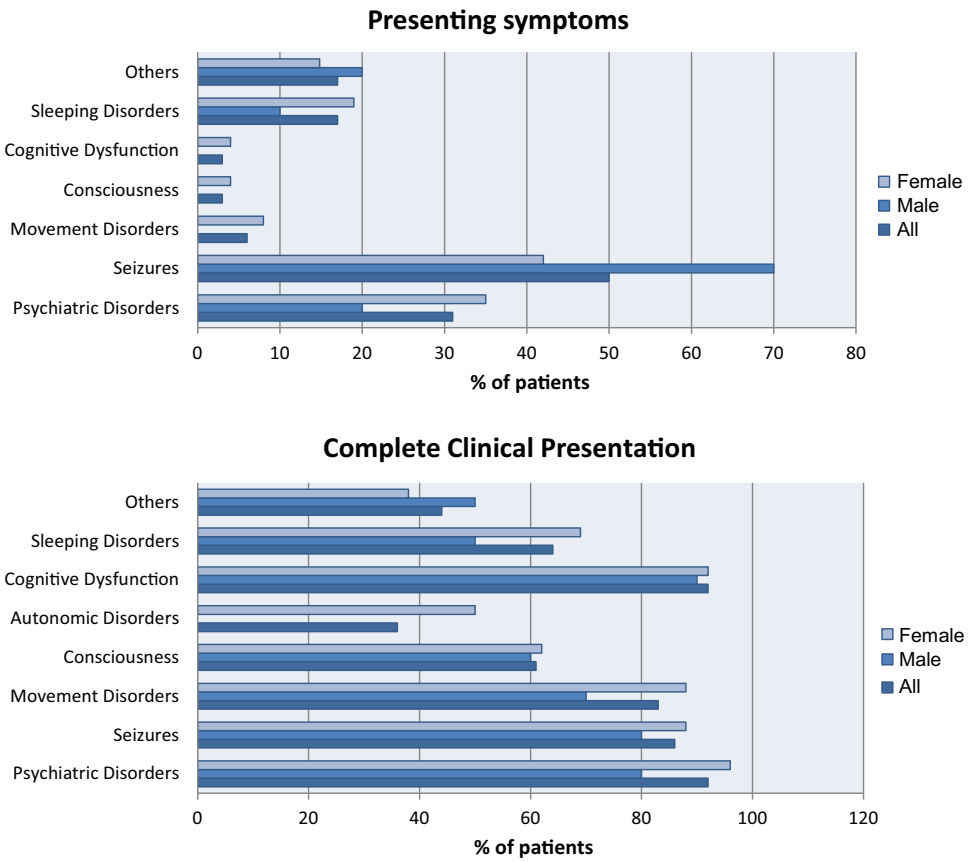

Fig. 1 Summary of presenting symptoms (**a**) and complete clinical presentation (**b**), according to sex

than in males (50 vs 0 %, $p < 0.01$). Chorea was significantly more frequent in the younger patients (52 vs 0 %, $p = 0.003$). No other clinical differences were observed between the groups.

Ancillary tests

The first MRI (performed an average of 27 days from the onset of neurological syndrome; median 10.5 days; range 0–209 days) was abnormal in only 31 % of cases, with FLAIR hyperintensities without gadolinium enhancement in different parts of the brain (hemispheres and basal ganglia) as already described in the literature [10]. The CSF was abnormal in 91 % of cases [evaluated after an average of 50 days from the onset of neurological syndrome (median 11 days; range 0–183 days)]. Twenty-three patients presented pleocytosis (91.6 %), and 7 presented oligoclonal bands (19.4 %). The EEG was abnormal in 92 % of the cases, mostly with a focal or diffuse slowing.

Relapses, treatment and outcome (Table 2)

All the patients received first-line immunotherapy (corticosteroids, intravenous immunoglobulins or plasma exchange); 81 % received second-line immunotherapy (rituximab or cyclophosphamide). The median time between clinical presentation and first-line treatment was 19 days (range 2–183 days). The median time between first- and second-line treatment was 26 days (range 7–198 days). Median time between clinical presentation and first-line treatment and between clinical presentation and second-line treatment tended to be shorter in patients diagnosed after 2010 ($n = 22$) than in patients diagnosed before 2010 ($n = 14$) (16.5 vs 21.5 days, $p = 0.09$ and 37 vs 69 days, $p = 0.03$). In addition, there was a trend towards inverse correlation between the date of diagnosis and the delays between clinical presentation and first-line treatment and between clinical presentation and second-line treatment onset ($\rho = -0.37$, $p = 0.03$ and $r = -0.43$, $p = 0.02$). Treatment delays tended to become shorter over time. As second line of treatment, the physicians used rituximab in 26 patients (72 %) and cyclophosphamide in 5 patients (14 %); 3 of these patients received both treatments (8.3 %). Only 5 patients received azathioprine, and 1 patient received mycophenolate mofetil for long-term immunosuppression. Teratoma ablation was performed in the 15-year-old girl with the ovarian teratoma, 24 days after the onset of neurological symptoms. Three serious adverse events were observed with rituximab treatment: severe allergic reaction in 2 patients and severe sepsis with death

Table 2 Comparison of relapses, outcome and treatments among different series

	Titualer et al. [5] ($n = 211$)	Florance et al. [2] ($n = 32$)	Armangue et al. [6] ($n = 20$)	Irani et al. [3] ($n = 10$)	Wright et al. [7] ($n = 31$)	Our series ($n = 36$)
First-line treatment (Median time to first-line treatment)	95 % (21 days)	97 % (NA)	100 % (NA)	80 %* (NA)	100 %	100 % (19 days)
Second-line treatment (Median time from first-line to second-line treatment)	32 % (NA)	23 % (NA)	35 % (NA)	14 %* (NA)	33 %	81 % (26 days)
Type of first-line treatment						
Corticosteroids	84 %	NA	100 %	75 %	100 %	86 %
Intravenous immunoglobulins	69 %	NA	75 %	34 %	71 %	89 %
Plasma exchange	33 %	NA	5 %	30 %	29 %	39 %
Type of second-line treatment						
Rituximab	24 %	19 %	25 %	5 %*	19 %	72 %
Cyclophosphamide	16 %	16 %	10 %	9 %*	19 %	14 %
Long-term immunosuppression	6 %	NA	15 %	9 %*	3.2 %	17 %
Relapses after diagnosis	12 %*	25 %	10 %	29 %*	23 %	8 %
Good outcome						
At 12 months	77 %	74 %**	85 %***	NA	NA	83 %
At 24 months	87 %	NA	NA	NA	NA	83 %

NA not available, * Adults and children, ** Only 4.5 months of follow-up, *** 17.5 months of follow-up

10 days after rituximab treatment in one patient. The latter patient, who was intubated in the intensive care unit, previously presented multi-resistant pulmonary infections. In the 26 patients treated with rituximab, the median duration between the first administration of rituximab and the first sign of improvement was 24 days (range 5–150 days). Three patients presented a relapse (at 4, 12 and 24 months after the onset of NMDA-R-Ab encephalitis); 1 patient had received first-line immunotherapy only while 2 patients had already received a second-line immunotherapy before their relapse. We did not observe multiple relapses. One child had presented 8 years before the diagnosis of NMDA-R encephalitis a first episode of encephalitis without a clear diagnosis.

At last follow-up, 30 patients (83 %) had a good outcome (mRS ≤ 2) and 20 patients (56 %) recovered completely (mRS $= 0$) (Fig. 2). Median time between treatment onset and good outcome was 6 months and median time between treatment onset and complete recovery was 24 months. In univariate analysis, factors associated with good outcome were: age >12 years ($p = 0.04$), no stay in the intensive care unit ($p = 0.08$), initial mRS ≤ 3 ($p = 0.004$) and treatment with first-line treatment only ($p = 0.01$). Factors associated with complete recovery were no stay in intensive care unit ($p = 0.01$) and initial mRS ≤ 3 ($p < 0.001$). In multivariate analysis, only age >12 years remained significant ($p = 0.03$) for good outcome and initial Rankin ≤ 3 for complete recovery ($p < 0.01$) (Table 3).

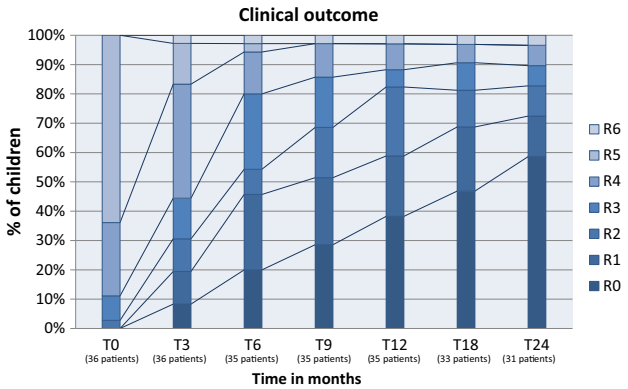

Fig. 2 Clinical outcome. Evolution of modified Rankin score (mRS) during follow-up

Comparison with adult patients

We also compared the clinical characteristics of these 36 children with those of 71 adult patients with NMDA-R-Ab encephalitis at our center (13 males and 58 females). Fewer tumors were observed in the children than in the adults (3 vs 34 %, $p < 0.0001$). Children presented seizures as first symptom more frequently than adults (50 vs 23 %, $p < 0.01$) and less psychiatric symptoms at disease onset (31 vs 57 %, $p = 0.01$). Children had significantly more abnormal movements (83 vs 55 % $p = 0.005$), and in particular limb dystonia (57 vs 27 %, $p = 0.04$). Second-line treatment was used less frequently in the adult population of our center than in the children (54 vs 81 %,

Table 3 Factors associated with good outcome and complete recovery in univariate analysis

	Median time to good outcome in months (mRS $\leq$ 2)	p	Median time to complete recovery in months (mRS = 0)	
Second-line treatment (no vs yes)	3 vs 9	0.01	12 vs 24	NS
ICU stay (no vs yes)	3 vs 9	0.08	12 vs NR	$p = 0.04$
Age >12 years (yes vs no)	6 vs 9	0.04*	NR vs 24	NS
Initial ranking (3 $\leq$ vs $\geq$ 4)	3 vs 9	0.004	4.5 vs 24	$p < 0.0001$*

* Factors remaining significant in multivariate analysis; *NR* not reached, *NS* not significant

$p = 0.01$). The outcomes of 63 adults with sufficient data and all of the children were compared, and we observed no significant difference in the total rate of recovery at 24 months (58 vs 70 %). However, the 14 children older than 12 years appeared to recover better than the adults ($p = 0.015$).

Discussion

The clinical presentation and the outcome in the present series of children and adolescents with NMDA-R-Ab encephalitis were similar to others already published [2, 3, 5, 7]. We observed fewer tumors in children and young adolescents in comparison with adults and more seizures with fewer psychiatric symptoms as the initial presenting symptom. The overall clinical presentation was also different between children and adults, with more abnormal movements, particularly limb dystonia, in children. The ancillary tests were comparable with other series, which highlights the low specificity of MRI findings (abnormal in only 31 % without a specific pattern) and the frequently abnormal EEG and CSF findings (92 and 91 %, respectively) [2, 6].

The main difference between our study and previous studies was the more frequent use of second-line immunotherapy (83 vs 14–35 %), especially Rituximab, which was used in 72 % of our patients compared to 5–25 % in previous series (Table 2). This higher rate of second-line treatment is likely to be explained by the fact that the treatment recommendation of the French PNS Reference Center was to use second-line immunotherapy if rapid improvement after first-line treatment was not achieved. Yet, despite the recommendation to 'treat early' the median time from first- to second-line immunotherapy was 26 days (range was 7–198 days). Paradoxically, even though the patients in our study received more frequently second-line immunotherapy, their outcome appeared to be very similar to the outcome reported in previous series. The relapse rate in our patients (8 %) was also similar to the 12 % rate reported in the largest previous study [5, 7]. These observations could suggest that a more systematic use of second-line immunotherapy is not associated with a better outcome in NMDA-R encephalitis. However, because of its retrospective design and the limited number of patients, the conclusions regarding the impact of second-line treatment in the present series must be taken cautiously. Some characteristics of the patients in our series might be different from those of previously published patients. For example, the frequency of ICU stay in our series (50 %) was lower than that in the largest previous series (69 %) [5]. The interaction between date of diagnosis and speed of use of first-line and second-line immunotherapy also complicates the interpretation of the impact of treatment on outcome. It is also important to point out that rituximab was not administered systematically but that there was clearly a selection in what was administered to whom and when. Most patients who received second-line immunotherapy were patients who did not recover after first-line treatment which explains why having received first-line treatment only was a predictor of good outcome. The fact that the Rituximab dosage that was proposed in our series sits on the lower end of the spectrum that is used for children with CNS inflammatory disorders is another limitation [11]. Since B cell depletion was not monitored the lack of effective dosing could contribute to the observation of the lack of effect of its wider usage. Finally, mRS is a poorly sensitive outcome measure when evaluating cognitive and neurodevelopmental difficulties, particularly in very young children.

Though the optimal treatment of NMDA-R encephalitis remains to be determined, there is strong evidence that second-line immunotherapy is important in patients who do not respond to first-line immunotherapy and remain symptomatic [5, 7]. Rituximab is a human/murine chimeric monoclonal antibody primarily used to treat non-Hodgkin's B cell lymphoma. Given the presumed direct pathogenic role of NMDA-R-Abs in this disease, as suggested by experimental studies, and the characteristic perivascular clusters of B lymphocytes in the brains of patients with NMDA-R-Abs encephalitis, some authors have suggested that rituximab could be a useful treatment, with a better outcome when administered early in the disease [8, 11–15]. Rituximab depletes B cells from the circulation and from

the brain parenchyma [16, 17]. It has been used with increasing frequency in both systemic autoimmune diseases and neurological ones, such as myasthenia gravis, neuromyelitis optica, stiff man syndrome or opsoclonus–myoclonus syndrome in both adults and children [11, 18–22]. Yet, the possible severe infectious and allergic adverse events reported with the use of the rituximab in pediatric cases and the lack of prospective studies in autoimmune neurological diseases should be pondered before its use [11].

Cyclophosphamide, a chemotherapeutic agent known for its efficiency in immune-mediated neurological and systemic diseases, has also been proposed in patients with NMDA-R-Ab encephalitis. In our series, 5 patients were treated with cyclophosphamide, three in combination with rituximab. The 2 patients treated with cyclophosphamide alone as a second-line treatment recovered completely after 15 and 16 months and presented no relapses, suggesting that this treatment could be efficient [23]. Yet, rituximab and cyclophosphamide can have severe side effects; in our series, we observed 2 severe allergic reactions with rituximab and one case of severe sepsis with death 10 days after rituximab treatment in a patient who presented multi-resistant pulmonary infections.

Regarding prognostic factors, we observed that age was an independent factor of good outcome. Older children recovered better and more quickly than younger children even though we observed no significant differences in their treatment modalities. These adolescents also recovered better than the adult population of our center as already described [5]. It has been suggested that the outcome of the pediatric cases of NMDA-R encephalitis is probably associated to the disease presentation rather than the treatment used and that the different subtypes of clinical presentation should be used for the stratification of treatment in NMDA-R encephalitis patients [24].

In conclusion, our study highlights the need for performing clinical trials in NMDA-R-Ab encephalitis. Such studies should determine who should receive second-line immunotherapy, which second-line treatment should be given and when this treatment should be started. Given the different outcomes for patients of different ages, age should certainly be used as a stratifying factor.

Acknowledgments We would like to thank all of the physicians, patients and relatives who helped to collect the clinical data. CSF samples were collected with the help of Neurobiotec Bank and the Hospices Civils de Lyon.

Conflicts of interest On behalf of all authors, the corresponding authors state that there is no conflict of interest.

Ethical standard This study has been approved by the institutional review board and ethics committee of the University Claude Bernard Lyon 1/Hospices Civils de Lyon.

References

1. Dalmau J, Tu E, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR (2007) Paraneoplastic anti—*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61:25–36. doi:10.1002/ana.21050
2. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, Campen CJ, Moss H, Peter N, Gleichman AJ, Glaser CA, Lynch DR, Rosenfeld MR, Dalmau J (2009) Anti—*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 66:11–18. doi:10.1002/ana.21756
3. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, Friese Ma, Galea I, Kullmann DM, Beeson D, Lang B, Bien CG, Vincent A (2010) *N*-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 133:1655–1667. doi:10.1093/brain/awq113
4. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10:63–74. doi:10.1016/S1474-4422(10)70253-2
5. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E, Gresa-Arribas N, Ryan-Florance N, Torrents A, Saiz A, Rosenfeld MR, Balice-Gordon R, Graus F, Dalmau J (2013) Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 12:157–165. doi:10.1016/S1474-4422(12)70310-1
6. Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, Dalmau J (2013) Pediatric anti-*N*-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr 162:850–856. doi:10.1016/j.jpeds.2012.10.011
7. Wright S, Hacohen Y, Jacobson L, Agrawal S, Gupta R, Philip S, Smith M, Lim M, Wassmer E, Vincent A (2015) *N*-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. Arch Dis Child. doi:10.1136/archdischild-2014-306795
8. Mikasova L, De Rossi P, Bouchet D, Georges F, Rogemond V, Didelot A, Meissirel C, Honnorat J, Groc L (2012) Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. Brain 135:1606–1621. doi:10.1093/brain/aws092
9. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Dessain SK, Rosenfeld MR, Balice-gordon R, Lynch DR (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7:1091–1098. doi:10.1016/S1474-4422(08)70224-2.Anti-NMDA-receptor
10. Hacohen Y, Absoud M, Hemingway C, Jacobson L, Lin J-P, Pike M, Pullaperuma S, Siddiqui A, Wassmer E, Waters P, Irani SR, Buckley C, Vincent A, Lim M (2014) NMDA receptor antibodies associated with distinct white matter syndromes. Neurol Neuroimmunol Neuroinflamm 1:e2. doi:10.1212/NXI.0000000000000002
11. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, Muscal E, Deiva K, Andersen E, Eyre MR, Eleftheriou D, Brogan Pa, Kneen R, Alper G, Anlar B, Wassmer E, Heineman K, Hemingway C, Riney CJ, Kornberg A, Tardieu M, Stocco A, Banwell B, Gorman MP, Benseler SM, Lim M (2014) Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 83:142–150. doi:10.1212/WNL.0000000000000570
12. Manto M, Dalmau J, Didelot A, Rogemond V, Honnorat J (2010) In vivo effects of antibodies from patients with anti-NMDA

receptor encephalitis: further evidence of synaptic glutamatergic dysfunction. Orphanet J Rare Dis 5:31. doi:10.1186/1750-1172-5-31
13. Lancaster E, Dalmau J (2012) Neuronal autoantigens-pathogenesis, associated disorders and antibody testing. Nat Rev Neurol 8:380–390. doi:10.1038/nrneurol.2012.99
14. Camdessanché J-P, Streichenberger N, Cavillon G, Rogemond V, Jousserand G, Honnorat J, Convers P, Antoine J-C (2011) Brain immunohistopathological study in a patient with anti-NMDAR encephalitis. Eur J Neurol 18:929–931. doi:10.1111/j.1468-1331.2010.03180.x
15. Martinez-Hernandez E, Horvath J, Shiloh-Malawsky Y, Sangha N, Martinez-Lage M, Dalmau J (2011) Analysis of complement and plasma cells in the brain of patients with anti-NMDAR encephalitis. Neurology 77:589–593
16. Kosmidis ML, Dalakas MC (2010) Practical considerations on the use of rituximab in autoimmune neurological disorders. Ther Adv Neurol Disord 3:93–105. doi:10.1177/1756285609356135
17. Martin Mdel P, Cravens PD, Winger R, Kieseier BC, Cepok S, Eagar TN, Zamvil SS, Weber MS (2009) Depletion of B lymphocytes from cerebral perivascular spaces by rituximab. Arch Neurol 66:1016–1021
18. Binstadt B, Caldas A, Turvey S, Weinstein H, Jackson J, Fuhlbrigge R, Sundel R (2003) Rituximab therapy for multisystem autoimmune diseases in pediatric patients. J Pediatr 143:598–604
19. Nowak RJ, Dicapua DB, Zebardast N, Goldstein JM (2011) Response of patients with refractory myasthenia gravis to rituximab: a retrospective study. Ther Adv Neurol Disord 4:259–266. doi:10.1177/1756285611411503
20. Kim S-H, Huh S-Y, Lee SJ, Joung A, Kim HJ (2013) A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol 70:1110–1117. doi:10.1001/jamaneurol.2013.3071
21. Fekete R, Jankovic J (2012) Childhood stiff-person syndrome improved with rituximab. Case Rep Neurol 4:92–96. doi:10.1159/000339446
22. Battaglia T, De Grandis E, Mirabelli-Badenier M, Boeri L, Morcaldi G, Barabino P, Intra C, Naselli F, Pistoia V, Veneselli E, Conte M (2012) Response to rituximab in 3 children with opsoclonus-myoclonus syndrome resistant to conventional treatments. Eur J Paediatr Neurol 16:192–195. doi:10.1016/j.ejpn.2011.05.013
23. Tatencloux S, Chretien P, Rogemond V, Honnorat J, Tardieu M, Deiva K (2015) Intrathecal treatment of anti-*N*-methyl-D-aspartate receptor encephalitis in children. Dev Med Child Neurol. 57(1):95-99. doi:10.1111/dmcn.12545
24. DeSena AD, Greenberg BM, Graves D (2014) Three phenotypes of anti-*N*-methyl-D-aspartate receptor antibody encephalitis in children: prevalence of symptoms and prognosis. Pediatr Neurol 51:542–549. doi:10.1016/j.pediatrneurol.2014.04.030