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Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis

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ABSTRACT

Objective: The aim of this study was to describe the clinical features and specificities of adult male patients with NMDA receptor antibodies (NMDAr-Abs) encephalitis.

Methods: Observational study of 13 adult male patients who were diagnosed with NMDAr-Abs encephalitis at the French Paraneoplastic Neurological Syndrome Reference Center.

Results: Adult male patients frequently presented initially with a seizure (8/13, 61.5%). Seizures were partial in 5/8 patients and were followed only a few days later (median 12 days; range 2–17 days) by psychiatric or cognitive symptoms. Conversely, adult female patients rarely presented with a seizure initially (8/58, 14%, $p < 0.001$), and most of their seizures were generalized and were rapidly followed (median 2 days; range 1–7 days) by behavioral and psychiatric features. Additionally, in male patients the disease was rarely associated with a tumor (1/13 or 8%, a perineal schwannoma); in contrast, 41% of female patients had an associated tumor (95% of which were ovarian teratomas; $p = 0.02$ male vs female association with tumor). The incidences of abnormalities in ancillary tests, treatment modalities, clinical evolution, and outcome were equal for both subgroups.

Conclusion: Adult male patients who have partial seizures, normal MRI results, and no clear etiology should be tested for NMDAr-Abs to avoid any delays in treatment initiation. Adult female patients who had a seizure as the first symptom are infrequent when NMDAr-Abs encephalitis is diagnosed; additionally, their clinical pattern is different from male patients, with more generalized seizures and rapid development of behavioral and psychiatric symptoms. The differences in hormonal influence could contribute to this difference in clinical pattern. *Neurology*® 2014;82:556–563

GLOSSARY

GTCS = generalized tonic-clonic seizures; **mRS** = modified Rankin Scale; **NMDAr-Abs** = NMDA receptor antibodies; **PS** = partial seizures.

NMDA receptor antibodies (NMDAr-Abs) encephalitis was initially described in 2007 in women who had mature ovarian teratomas.[1] NMDAr-Abs target the NR1 subunit of the receptor and are responsible for the internalization of NMDArs and the subsequent alteration of synaptic function.[2,3] Up to now, approximately 600 cases have been reported in the literature,[4–9] and the typical clinical course of adult female patients is well known and follows a relatively straightforward progression. The prodromal signs, which include fever, respiratory tract infections, gastrointestinal symptoms, and headache,[5] appear a few days prior to the first neurologic symptoms of the disease. The first symptoms are mainly psychiatric, with behavioral features or cognitive disturbances, and are followed by seizure, movement disorders such as orofacial dyskinesia, a fluctuating level of consciousness, dysautonomia, and central hypoventilation.[4] Due to the relatively low prevalence of the disease in males, male patients are usually pooled together with female patients,[4–7] and only a few clinical studies and case reports detail the complete clinical symptoms and biological

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Supplemental data at www.neurology.org

From the French Reference Center on Paraneoplastic Neurological Syndrome (A.V, V.D., F.D., G.P., G.C., V.R., J.-C.A., J.-Y.D., J.H.), Hospices Civils de Lyon, Hôpital Neurologique, Neuro-Oncology, Bron; Lyon Neuroscience Research Center (A.V., V.D., F.D., J.-C.A., J.H.), INSERM U1028/CNRS UMR 5292, Lyon; Université de Lyon—Université Claude Bernard Lyon 1 (A.V., V.D., F.D., J.H.), Lyon; Service de Neurologie (J.-C.A.), CHU de Saint-Etienne, Saint-Etienne; and Service de Neurologie Mazarin (J.-Y.D.), Groupe Hospitalier Pitié-Salpêtrière, APHP, Université Pierre et Marie Curie-Paris 6, Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, UMR S975, CNRS, UMR 7225, Paris, France.

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abnormalities in men.[8–23] The aim of this study was to describe the clinical pattern, evolution, and outcome of the disease in male patients from our cohort of NMDAr-Abs encephalitis patients.

METHODS **Patients.** This observational cohort study is based on patients diagnosed after the examination of CSF samples tested for autoimmune encephalitis at the French Paraneoplastic Neurological Syndrome Reference Center from October 2007 to February 2013. CSF has been used rather than serum because of the better quality of results in our experience and because we observed a 3% false-positive rate with serum in healthy patients. To be considered positive, CSF analysis had to fulfill the following previously established criteria[7]: 1) CSF samples must produce a specific pattern of neuropil rat brain hippocampus immunostaining; and 2) CSF samples must yield a positive cell-based assay on HEK293 cells expressing both the NR1 (also named GluN1) and NR2B (also named GluN2B) subunits of the NMDA receptor, using the method previously described.[3] We focused this study on the 13 adult male patients (older than 18 years) from our cohort of 119 subjects, which included 42 children and 77 adult patients. Detailed clinical data on acute disease stages were obtained at the time of biological diagnosis, and data regarding disease clinical course were collected during follow-up examinations.

Standard protocol approvals, registrations, and patient consents. Written consent was obtained from all patients, and this study was approved by the institutional review board of the University Claude Bernard Lyon 1 and Hospices Civils de Lyon. Samples are deposited in the collection of biological samples named "Neurobiotec" registered as the biobank of the Hospices Civils de Lyon.

Definition of clinical events, ancillary tests, treatment, and evolution. Prodromal symptoms were signs or symptoms arising prior to the first neurologic symptoms. They were divided into the following 4 subgroups: 1) headache; 2) gastrointestinal symptoms; 3) infectious signs (upper respiratory tract infection, flu-like symptoms, and fever of unknown origin); and 4) "other," a subgroup that had signs that did not correspond to previously described features or symptoms that developed as the disease progressed. The first neurologic symptoms were considered to be the first clinical signs after the prodromal state, if present, or the first neurologic symptom that did not correspond to any of the prodromal signs described above. These symptoms were observed and reported by the patients' relatives and/or corresponded to the reason that led the patient to be admitted to the hospital. The subsequent symptoms were clinical signs that arose after the first symptoms with a delay interval of at least 24 hours. All symptoms were categorized into the following 7 subgroups: 1) behavioral and psychiatric features; 2) seizure; 3) cognitive dysfunction (which included anterograde amnesia, speech disorder, and alteration of mental status [disorientation, confusion, attention deficit, and dysexecutive features]); 4) movement disorders; 5) fluctuating level of consciousness; 6) dysautonomia; and 7) "other," a subgroup for symptoms that did not correspond to any of the previously described features. The times between the prodromal state and the first neurologic symptoms, between the first and subsequent symptoms, between the first symptoms and the NMDAR-Abs diagnosis, and between the first symptoms and the first immunomodulatory treatment were all calculated. Follow-up information was collected at regular intervals (3, 6, 9, and 12 months) after diagnosis—exceptions were made for patients currently in treatment for whom 12 months of follow-up data were not available. Neurologic disability was assessed using the modified Rankin Scale (mRS). The results from the initial ancillary exams (MRI, CSF analysis, EEG, and tumor screening) were also compiled. Treatment modalities and their sequence were obtained. Recovery was defined as occurring when a patient's mRS score was determined to be 0 or 1, and the time to recovery after onset (measured from the first neurologic symptom) was used to draw the Kaplan-Meier failure function curves. A relapse was diagnosed if there was new encephalitis or a worsening of preexisting symptoms after at least 2 months of stabilization or improvement.

Statistical analysis. The Fisher exact test for contingency tables was used to calculate p values from demographic information and symptoms. Comparisons of medians were drawn using the Wilcoxon rank sum test (Mann-Whitney test). Clinical outcome of female and male patients was obtained after Kaplan-Meier failure function processing using StataSE software (StataCorp, College Station, TX).

RESULTS **Clinical presentation.** Thirteen adult male patients were observed (median age 25 years, range 18–75 years) (table 1). For one patient (patient 13), data regarding the first symptoms, ancillary tests, and general evolution were missing. Ten of the patients were Caucasian (77%), and the remaining 3 patients were from North or Sub-Saharan Africa. Past medical history was relevant in 4 patients. Patient 3 presented with successive bilateral optic neuritis 4 years prior to the current episode with no identified cause (normal MRI/CSF analysis and no other neurologic symptoms). Patient 5 was diagnosed 9 years ago with a slowly progressive perineal mass (now 20 cm in diameter); a recent biopsy determined it was a schwannoma. This patient was the only male with a tumor. Patient 6 was diagnosed as HIV-positive 6 years prior to the current episode, with a CD4 count stable at approximately 900/mm^3 with no treatment. Patient 9 presented with an episode of acute psychosis 25 years ago and had a favorable outcome after 36 months; we have no other data regarding this episode. Patient 13 suffered from recurrent episodes of anterograde amnesia, behavioral disorders, temporal epilepsy, and dysautonomia for 13 years. Prodromal states were present in 7/13 cases (54%), which consisted mostly of headache (3/7, 43%) or infectious-like diseases (2/7, 29%); 1 patient presented with both symptoms. Other prodromal signs included vertigo (1/7, 15%) and a bilateral fluctuating scintillating scotoma without hemianopsia, headache, or any evident signs of an epileptic origin (1/7, 15%). Based on the first symptoms, male patients can be subdivided into 3 groups: seizure, psychiatric and behavioral disorders, and cognitive dysfunctions (figure 1, tables 1 and 2). Eight patients presented with seizure at onset (8/13, 61.5%); among them, 4 (50%) experienced partial seizures (PS), consisting of unilateral paresthesia in 2 patients and unilateral motor features in the other 2

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Table 1 Description of the 13 adult male patients with NMDAr-Abs encephalitis

	Patient	Age, y	Past medical history	First symptoms	Delay,[a] d	Main subsequent symptoms	ICU	MRI	CSF	EEG	Sequence of immune treatment	Evolution with mRS at 1, 3, 6, 9, and 12 mo, and residual deficits
Seizure	1	25	None	Sensory PS (paresthesia)	15	Hallucinations, SE, orofacial dyskinesia, whole-body dyskinesia, anterograde amnesia	Yes	Normal	WBC: 14/mm^3; prot: <0.4 g/L	SE	Corticoids, IVIg, rituximab	M1: 3; M3: 2; M6: 2; M9: 2; M12: 0
	2	28	Asthma	Sensory PS (right paresthesia)	9	Anxiety, aggressiveness, confusion, mutism, anterograde amnesia	No	Normal	WBC: 30/mm^3; prot: <0.7 g/L; OB	Left temporal discharges	Corticoids, IVIg, rituximab, MM	M1: 5; M3: 3; M6: 1; M9: 1; M12: 1 (attention deficit)
	3	18	Bilateral optic neuritis	Motor PS secondarily generalized	3	Anterograde amnesia	Yes	Left hippocampal FH	WBC: 140/mm^3; prot: 0.76 g/L	Left temporal PLEDs	None	M1: 5; M3: 0
	4	21	None	Motor PS	17	Ataxia, hallucinations, limb dyskinesia, confusion, anterograde amnesia	Yes	Normal	WBC: 8/mm^3; prot: <0.4 g/L	Left temporo-occipital sharp waves	Corticoids, IVIg	M1: 5; M3: 3; M6: 0
	5	75	aHT, perineal schwannoma	Motor PS (left hemiparesia)	2	Hypersexuality, auditory hallucinations, rigidity, confusion, anterograde amnesia	Yes	Bihippocampal FH	WBC: <2/mm^3; prot: <0.4 g/L	Diffuse SW	Corticoids, IVIg, rituximab	M1: 5; M3: 2; M6: 3; M12: 0
	6	32	HIV+	GTCS	NA	Hallucinations, anterograde amnesia, anxiety	No	Left hippocampal FH	WBC: 22/mm^3; prot: 0.5 g/L	Normal	Corticoids, IVIg	M1: 3; M3: 3; M6: 3; M9: 3; M12: 3 (psychosis, amnesia)
	7	24	Tension headache	GTCS	13	Anxiety, catatonia, confusion, SE, limb dyskinesia	Yes	Normal	WBC: 165/mm^3; prot: <0.4 g/L; no OB	SW	IVIg, rituximab, MM	M1: 5; M3: 5; M6: 3; M9: 2; M12: 0
	8	20	None	GTCS	15	Acute aggressiveness, stupor and prostration, visual hallucinations, anterograde amnesia	Yes	Normal	WBC: <2/mm^3; prot: 0.57 g/L; OB	Normal	Corticoids, IVIg, rituximab	M1: 4; M3: 3; M6: 1; M9: 1; M12: 1 (anterograde amnesia)
Abnormal behavior and/or cognitive dysfunction	9	43	Acute delirium at 18	Confusion, aphasia	3	Hallucinations, acute anxiety, orofacial dyskinesia, upper limb dystonia	Yes	Occipital FH	WBC: 7/mm^3; prot: <0.4 g/L	Left lateralized SW	Corticoids, IVIg	M1: 4; M3: 3; M6: 0
	10	66	aHT	Confusion, anterograde amnesia	2	GTCS, confusion, superior limb dyskinesia, anterograde amnesia	Yes	Bihippocampal and putaminal FH	WBC: 40/mm^3; prot: <0.4 g/L	Left temporal discharges	Corticoids, IVIg, rituximab, cyclo	M1: 5; M3: 5; M6: 5; M9: 5; M12: 6 (died from sepsis)
	11	22	None	Incoherent speech, confusion, anterograde amnesia	1	Hallucinations, confusion, orofacial dyskinesia, SE, anterograde amnesia	No	Cerebellar FH	WBC: 76/mm^3; prot: <0.4 g/L	SE	Corticoids, IVIg, cyclo	M1: 5; M3: 2; M6: 2; M9: 2; M12: 1 (attention deficit)
	12	18	None	Psychosis with persecution, suicide attempt, visual hallucinations	10	Confusion, right superior limb chorea, major weight gain, anterograde amnesia	Yes	Normal	WBC: 5/mm^3; prot: <0.4 g/L	Diffuse SW	Corticoids, IVIg, rituximab	M1: 5; M3: 3; M6: 2; M9: 1; M12: 1 (anterograde amnesia and attention deficit)
NA	13	45	Recurrent episodes of temporal epilepsy	NA	NA	Seizure, behavioral changes, anterograde amnesia, dysautonomia	No	NA	NA	NA	Corticoids, IVIg, MM	NA

Abbreviations: aHT = arterial hypertension; cyclo = cyclophosphamide;; FH = MRI fluid-attenuated inversion recovery hyperintensity; GTCS = generalized tonic-clonic seizure; ICU = intensive care unit; IVIg = IV immunoglobulin; MM = mycophenolatemofetil; mRS = modified Rankin Scale; NA = data not available; NMDAr-Abs = NMDA receptor antibodies; OB = oligoclonal bands; PLEDs = periodic lateralized epileptiform discharges; prot = protein; PS = partial seizure; SE = status epilepticus; SW = slow waves; WBC = white blood cell.

[a] Delay refers to the time from first to subsequent symptoms.

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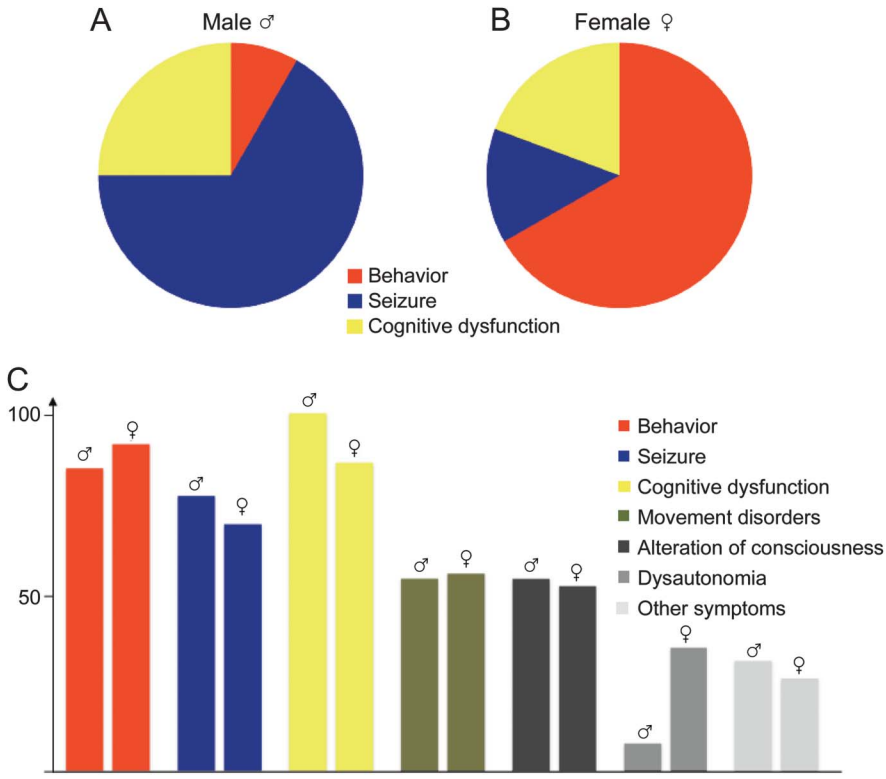
Figure 1 Comparison of clinical patterns between female and male patients



(A, B) Pie charts showing the percentage of each first symptom in male and female patients, respectively. (C) Comparison of all symptoms, including first symptoms and subsequent symptoms. There is no significant difference between male and female patients considering all the symptoms.

patients. Over a median time of 12 days (range 2–17 days), these isolated PS were followed by psychiatric features, including hallucinations, psychosis, agitation with hypersexuality, and fluctuating level of consciousness. One subject presented with PS that had unilateral motor features and were immediately complicated by generalization, followed 3 days later by anterograde amnesia. The other 3 patients presented with generalized tonic-clonic seizures (GTCS) at onset, followed by psychiatric features 15 and 17 days later (in one patient the interval was unknown).

Male patients who did not have seizures as the first symptoms instead experienced cognitive dysfunctions (3/13, 23%) or psychiatric symptoms (1/13, 7.7%) as the first symptoms. The 3 patients who experienced cognitive dysfunctions at onset presented with confusion associated with speech disturbances. These cognitive first symptoms were rapidly followed by psychosis or hallucinations 24–72 hours later in one patient, GTCS in another patient, and a fluctuating level of consciousness in the last patient. One patient's first symptom was psychosis with delusions of persecution that led to a suicide attempt, followed 10 days later by a fluctuating level of consciousness.

Ancillary tests, treatment, and outcome. In ancillary tests, no differences were observed between patients who had seizures at onset vs patients who did not (table 1). Initial MRI was abnormal with fluid-attenuated inversion recovery hyperintensity signals in 6/12 patients (50%; no data were available for patient 6) located in the hippocampi (4/6, 67%), the cerebellum (1/6, 17%), or the occipital lobes (1/6, 17%). The initial CSF analysis revealed signs of inflammation in 11/12 patients (92%), which included high white blood cell counts (>3, range 4–165) in 10/11 (90%) and high protein level (>0.45 g/L) and/or oligoclonal bands in 4/11 (36%) patients. Initial EEG showed abnormalities in 10/12 cases (83%): 4 patients had slow waves and 6 had status epilepticus, seizure, or critical activity.

All adult male patients received immunotherapy except patient 11. The first-line treatment for 12 of the 13 patients (92%) was corticoids and/or IV immunoglobulin administration (8 had corticoids alone, 1 had IV immunoglobulin alone, and 3 had a combination of both). No plasma exchanges were performed in these patients. As a second immunomodulatory treatment, 8/13 patients (62%) received rituximab or cyclophosphamide.

The complete clinical pattern was severe in a majority of patients: 9/12 documented male patients (75%) had mRS scores of 5, and 9 patients (all but 2 of the patients who had mRS scores of 5) were admitted to an intensive care unit (75%), mostly for

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Table 2 Comparison of the 13 male patients to the 58 female patients from our study

	Male (N = 13)	Female (N = 58)	*p* Value
Age, y, median (range)	25 (18–75)	27.5 (18–65)	NS
Caucasian, n (%)	10 (77)	44 (76)	NS
Prodromal symptoms, n (%)	7 (54)	34 of 55 (62)	NS
Infectious diseases	2 of 7 (29)	17 of 34 (50)	NS
Headache	3 of 7 (43)	21 of 34 (62)	NS
Gastrointestinal signs	0 of 7 (0)	9 of 34 (27)	NS
Other[a]	2 of 7 (29)	3 of 34 (9)	NS
Tumor, n (%)	1 (8)[b]	24 (41)	<0.02
Ovarian teratoma	0 (0)	23 of 24 (96)[c]	
First symptoms, n (%)			
Behavior and psychiatric features	1 of 12 (8)	39 (67)	<0.001
Seizure	8 of 12 (67)	8 (14)	<0.001
Cognitive dysfunction	3 of 12 (25)	11 (19)	NS
Anterograde amnesia	0 of 3 (0)	2 of 11 (18)	NS
Speech disorders	0 of 3 (0)	2 of 11 (18)	NS
Alteration of mental status	3 of 3 (100)	6 of 11 (55)	NS
First to subsequent symptoms			
Days, median (range)	10 (1–23)	7 (1–123)	NS
Subsequent symptoms, n (%)			
Behavior and psychiatric features	10 (77)	14 (24)	<0.001
Seizure	2 (15)	32 (55)	<0.01
Cognitive dysfunction	13 (100)	48 (83)	NS
Anterograde amnesia	12 (92)	33 of 48 (69)	NS
Speech disorders	5 (39)	24 of 48 (50)	NS
Alteration of mental status	3 (23)	15 of 48 (31)	NS
Movement disorders	7 (54)	32 (55)	NS
Fluctuating level of consciousness	7 (54)	30 (52)	NS
Dysautonomia	1 (8)	20 (35)	NS
Other symptoms[d]	4 (31)	15 (26)	NS
Paraclinic exams, n (%)			
MRI, abnormal	6 of 12 (50)	19 of 57 (33)	NS
CSF, abnormal	11 of 12 (92)	45 of 55 (82)	NS
EEG, abnormal	9 of 12 (75)	38 of 49 (78)	NS
First symptoms to treatment, d, median (range)	34 (23–361)	25 (6–373)	NS
Treatment, n (%)			
Corticoids	11 (85)	44 (76)	NS
IVIg	12 (92)	49 (85)	NS
Plasma exchange	0 (0)	12 (21)	NS
Rituximab	7 (54)	23 (40)	NS
Cyclophosphamide	2 (15)	5 (9)	NS
Chronic immunosuppression[e]	3 (23)	17 (29)	NS
Follow-up, mo, median (range)	14 (6–44)	11 (1–130)	NS
Evolution, n (%)			
ICU	9 of 12 (75)	38 of 55 (69)	NS

Continued

seizure/status epilepticus and/or a fluctuating level of consciousness that necessitated tracheal intubation. Outcome was favorable (mRS 0–1) in 10/12 patients (83%) 12 months after their first neurologic symptom (figure 2), and complete recovery was achieved in 6/12 patients (50%). Four patients had mRS scores of 1 at 12 months, all due to cognitive dysfunctions, which included anterograde amnesia and attention deficit. Patient 3 died 12 months after the onset of encephalitis from sepsis. Relapse was observed in 3/13 patients (23%). Patient 5 suffered from the reappearance of anterograde amnesia and harbored hypersexuality 6 months after the first neurologic signs and 5 months after immunotherapy was initiated; a favorable outcome was achieved 3 months after treatment using rituximab. Patient 9 suffered from acute psychiatric features 25 years prior to the current episode with no other relapse. In the past 13-year period, patient 13 presented with 4 stereotyped episodes that consisted of behavioral and psychiatric disorders, anterograde amnesia, seizure, and dysautonomia, evoking prior undiagnosed relapses of the disease.

Comparison to female patients. We compared the 13 male patients to 58 female patients identified in our database (table 2). Tumors were present in 24/58 female patients (41%, 23 ovarian teratomas and 1 breast cancer) vs only 1 tumor (schwannoma) in male patients (7.7%, $p = 0.02$). The complete clinical pattern was not different between male and female patients (table 2, figure 1C). However, the first symptoms in male patients were different from female patients. Sixty-seven percent (39/58) of female patients experienced behavioral and psychiatric features as their first symptoms vs 7.7% (1/13) of male patients ($p > 0.01$, figure 1, A–B). Seizure at onset was only observed in 8/58 female patients (13.8%; tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org), whereas it was observed in 8/13 male patients (61.5%, $p < 0.001$, table 2). When seizures were observed as the first neurologic signs in female patients, they were mostly generalized or immediately generalized after a PS. Only one female patient initially experienced only PS. The subsequent neurologic symptoms were observed sooner in female patients than in male patients with seizure at onset (median of 2 days [range 1–7 days] vs 12 days [range 2–17 days], $p < 0.01$). All symptoms, including first and subsequent, are equally encountered within both subsets of patients (figure 1C). Global progression and recovery were similar between both sex-based groups (figure 2).

DISCUSSION Our study reveals that the initial presentation of adult male patients who have NMDAr-Abs encephalitis differs from that of female patients. Male patients have mostly PS at onset and delayed

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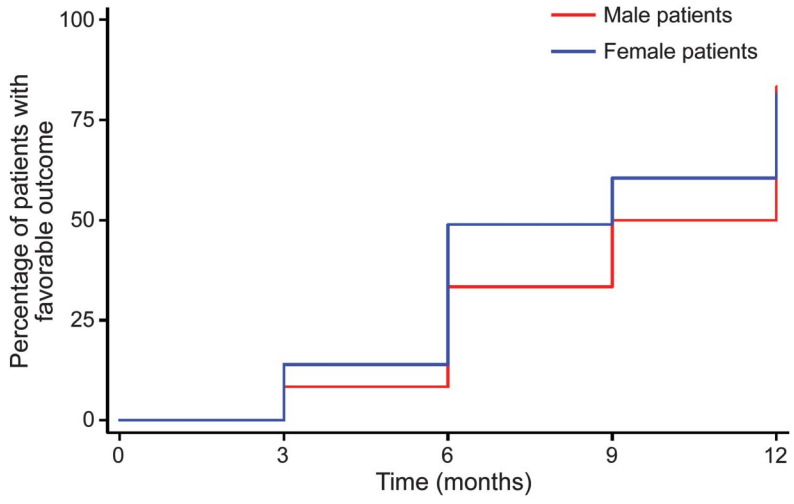
Table 2 Continued

	Male (N = 13)	Female (N = 58)	*p* Value
mRS 5 during illness	9 of 12 (75)	42 of 57 (74)	NS
Death	1 (8)	3 (5)	NS
mRS 0 at 12 mo after onset	6 of 12 (50)	26 of 42 (62)	NS
mRS 0–1 at 12 mo after onset	10 of 12 (83)	35 of 43 (81)	NS
Relapse	3 (23)	8 (14)	NS

Abbreviations: ICU = intensive care unit; IVIg = IV immunoglobulin; mRS = modified Rankin Scale; NS = not significant.
[a] Scintillating scotoma, vertigo.
[b] Perineal schwannoma.
[c] Including one breast cancer.
[d] Ataxia, rigidity and hypertonia, neuroleptic hyperseNSitivity.
[e] Mycophenolatemophetyl, azathioprine.

behavioral and psychiatric symptoms. Despite this major difference, the complete clinical and biological pattern, clinical evolution, and outcome are identical between both sexes. Our findings also confirm the rarity of NMDAr-Abs encephalitis in adult male patients, with an incidence of 18% in our study compared to 8% to 30% in previously published studies. Our study also confirmed the low frequency of paraneoplastic etiology in the male population, accounting for 3% to 15% of cases.[4–7] Different types of tumors, such as testicular germ cell tumors, small cell lung carcinoma, and Hodgkin lymphoma, have been reported.[4–7] We identified only one male (7%) with a tumor, namely a perineal schwannoma. A direct link of causality between this common benign tumor of the peripheral nerve neural sheath and NMDAr-Abs production cannot be clearly established, so this diagnosis is probably coincidental. Schwannomas are exclusively composed of neoplastic Schwann cells without expression of neuronal markers,[24] and NMDAr expression on the tumor has never been reported in the literature. In contrast, ovarian teratomas frequently contain nervous tissue and express NMDA receptors.[25,26]

Figure 2 Clinical outcome of female and male patients



Inverted Kaplan-Meier curves illustrating the clinical progression and favorable outcomes (modified Rankin Scale score 0–1) in female and male patients.

The progression of the disease in male patients differed from the typical female patient presentation. Indeed, in male patients seizures are the initial symptom rather than behavioral and psychiatric features or cognitive dysfunctions, as in female patients. Curiously, these initial seizures are often partial in our patients, even if they were frequently complicated by progression to generalization. In the literature we identified 21 male patients who had NMDAr-Abs encephalitis with complete clinical descriptions of their disease.[8–23] Due to the low incidence of this disorder in males, we found that most adult male patients described have been pooled together with female patients, and specific symptoms at disease onset could not be easily appreciated. In 14 of these patients the first symptoms described were behavioral and psychiatric features[8–14] or cognitive dysfunction[15,16]; the other 7 patients had seizures.[17–23] Among these 7 patients who had seizures as their first symptoms, 3 had seizures with no precise description,[17–19] 1 had partial complex seizures,[20] and 3 had generalized seizures.[21–23] Because the authors did not specifically study the possibility of PS occurring in male patients at disease onset, it is possible that this symptom was simply not mentioned. However, these data are roughly consistent with our findings, tending to confirm the high prevalence of seizures as initial symptoms in male patients with NMDAr-Abs encephalitis. Seizures at onset are clearly less frequent in female patients; we identified only 8 cases among the 58 in our study (14% vs 61.5%, $p < 0.001$). Interestingly, the nature of the initial seizure seems to be different between female and male patients. Contrary to male patients, female patients who had a seizure as their first symptom mostly had generalized seizures rather than PS; additionally, female patients rapidly developed behavioral and psychiatric symptoms (approximately 2 days after the epileptic onset of the disease, compared to 12 days in male patients).

These sex differences obviously suggest a role for the activity of sexual hormones, not only in the prevalence of this autoimmune disease but also in its clinical presentation, as has been previously related for other autoimmune disorders.[27] Interestingly, a crucial link between seizures, NMDA receptors, and hormonal activity has been experimentally established in various animal models.[28–31] Estrogen has been shown to be directly implicated in the control and modulation of NMDA-induced seizures, with critical

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manifestations being significantly more frequent in ovariectomized rats.[32] Progesterone is generally assumed to have an anticonvulsant effect.[33,34] Testosterone has mixed effects on neuronal excitability, likely depending on the balance of its 2 major metabolites (estradiol, which seems to facilitate NMDA-mediated conductance,[35–37] and dihydrotestosterone, which blocks it).[38] Thus, androgens are generally thought to be proconvulsant in experimental models,[39] but, given that major fluctuations do not occur (except during puberty and progressively with aging), a regulatory influence on seizures is difficult to demonstrate in males.

The role of sexual hormone activity could also explain why epileptic onset is also frequent among prepubertal children.[4,40] A recent study showed that seizures at onset of NMDAr-Abs encephalitis are predominant within a group of prepubertal children.[4] In this cohort, which mostly consisted of female patients (81%), the frequency of seizures at onset progressively decreased with age, suggesting that modification of hormonal activity related to puberty could represent a key factor that explains the progression of the clinical presentation of NMDAr-Abs encephalitis at different ages.

Our retrospective study may have some limitations. The typical clinical pattern of NMDAr-Abs encephalitis in female patients has been extensively described and is nowadays well known and thus better recognized. Low incidence in male patients may be related to the nonrecognition of the disorder, particularly if the clinical pattern, as shown in this study, differs from typical signs. Moreover, first symptoms definition may depend on physician expertise or descriptions from patients' relatives. If symptoms at onset are not characteristic, an interpretative bias may occur. This is particularly the case with patients suffering from seizure (secondary generalized PS or GTCS) or patients with confusion who may eventually have seizure. Further studies will improve our knowledge. However, our study suggests that the clinical presentation of adult male patients who have NMDAr-Abs encephalitis differs from that of female patients; males rarely have associated tumors and frequently have PS at onset, with the development of behavioral and psychiatric features later during the course of the encephalitis. It is uncommon for female patients to have a seizure as a first symptom, and the clinical pattern is characterized by more generalized seizures and the rapid development of behavioral and psychiatric symptoms. Despite these differences, evolution and outcome are not sex-specific. Hormonal activity could partly explain the difference between males and females for these particular first symptoms. Additionally, our study suggests that adult male patients who have partial seizures, normal MRI, and no clear etiology should be tested for NMDAr-Abs to avoid any delay in treatment initiation.

AUTHOR CONTRIBUTIONS

Dr. Aurélien Viaccoz: analysis, interpretation of the data, drafting the manuscript for intellectual content. Dr. Virginie Desestret: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. François Ducray: acquisition of data, critical revision of the manuscript for important intellectual content. Ms. Géraldine Picard: acquisition of data. Ms. Gaëlle Cavillon: acquisition of data. Dr. Véronique Rogemond: acquisition of data. Prof. Jean-Christophe Antoine: acquisition of data, critical revision of the manuscript for important intellectual content. Prof. Jean-Yves Delattre: critical revision of the manuscript for important intellectual content. Prof. Jérôme Honnorat: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

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DISCLOSURE

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