Analysis of relapses in anti-NMDAR encephalitis

I. Gabilondo, MD
A. Saiz, MD
L. Galán, MD
V. González, MD
R. Jadraque, MD
L. Sabater, PhD
A. Sans, MD
A. Sempere, MD
A. Vela, MD
F. Villalobos, MD
M. Viñals, MD
P. Villoslada, MD
F. Graus, MD

Address correspondence and reprint requests to Dr. Francesc Graus, Servei de Neurologia, Hospital Clínic, Villarroel 170, Barcelona 08036, Spain
fgraus@clinic.ub.es

ABSTRACT

Objective: The clinical characteristics of patients with relapsing anti–NMDA receptor (NMDAR) encephalitis are not well-defined. In this study, we report the clinical profile and outcome of relapses in a series of anti-NMDAR encephalitis.

Methods: We did a retrospective review of relapses that occurred in 25 patients with anti-NMDAR encephalitis. Relapses were defined as any new psychiatric or neurologic syndrome, not explained by other causes, which improved after immunotherapy or, less frequently, spontaneously.

Results: A total of 13 relapses were identified in 6 patients. Four of them had several, 2 to 4, relapses. There was a median delay of 2 years (range 0.5 to 13 years) for the first relapse. Median relapse rate was 0.52 relapses/patient-year. Relapse risk was higher in patients who did not receive immunotherapy in the first episode ($p = 0.009$). Most cases (53%) presented partial syndromes of the typical anti-NMDAR encephalitis. Main symptoms of relapses were speech dysfunction (61%), psychiatric (54%), consciousness-attention disturbance (38%), and seizures (31%). Three relapses (23%) presented with isolated atypical symptoms suggestive of brainstem-cerebellar involvement. An ovarian teratoma was detected at relapse in only 1 patient (17%). Relapses did not add residual deficit to that caused by the first episode.

Conclusions: Relapses in anti-NMDAR encephalitis are common (24%). They may occur many years after the initial episode. Relapses may present with partial aspects or with isolated symptoms of the full-blown syndrome. Immunotherapy at first episode reduces the risk of relapses.
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GLOSSARY

NMDAR = NMDA receptor.

Anti–NMDA receptor (NMDAR) encephalitis affects children and young women with predominant psychiatric symptoms followed by seizures, decline of consciousness, language dysfunction, and abnormal movements. Patients may develop hypoventilation and autonomic imbalance that requires admission to intensive care units.[1,2] The presence of an underlying ovarian teratoma is highly dependent on age, with incidences ranging from 9% in patients younger than 14 years to 56% in women older than 18 years.[3,4]

Relapses are reported in 15% to 25% of patients.[3,4] However, the clinical features of relapses are not well established. In this study we describe the clinical profile and outcome of relapses in a series of anti-NMDAR encephalitis.

Supplemental data at www.neurology.org

Supplemental Data

CME

METHODS

We retrospectively reviewed the clinical records of all patients with NMDAR-ab detected in our laboratory since 2007 with a minimum follow-up of 6 months. NMDAR-ab were analyzed by immunohistochemistry on sections of rat brain and HEK293 cells transfected with the NR1 subunit of the NMDAR as described.[5] Only one sample was available for each patient. In relapsing patients, all samples were obtained at the time of the relapse.

From the Center for Neuroimmunology (I.G., A.S., L.S., P.V., F.G.), Service of Neurology, Hospital Clinic and Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona; Service of Neurology (L.G., A.V.), Hospital Clínico San Carlos, Madrid; Service of Neuropaediatrics (A. Sans, V.G.), Hospital San Joan de Deu, Barcelona; Service of Neuropaediatrics (R.J., A. Sempere), Hospital General Universitario de Alicante, Alicante; Service of Neurology (A.V.), Hospital Moncloa, Madrid; Service of Neurology (F.V.), Hospital Virgen del Rocío, Sevilla; and Servicio de Neurología (M.V.), Hospital Reina Sofía, Córdoba, Spain.
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We defined the anti-NMDAR encephalitis as "typical" if the syndrome presented at least 3 of the 5 cardinal symptoms of the encephalitis (psychiatric manifestations, speech disorder, seizures, orofacial dyskinesias, and decrease of consciousness).[6] Relapses of anti-NMDAR encephalitis were defined as any new psychiatric or neurologic syndrome, not explained by other causes, that improved after immunotherapy or, less frequently, spontaneously.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Ethic Committee of the Hospital Clinic. Samples are deposited in the collection of biological samples named "neuroinmunologia" registered in the biobank of Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

RESULTS We identified 25 patients with anti-NMDAR encephalitis (table). Twenty-two (88%) developed the typical syndrome. Three patients (12%) presented with epilepsy. Two of them also had other symptoms of encephalitis. However, the third patient, who was diagnosed at relapse, presented with isolated seizures (patient 4, appendix e-1 on the *Neurology*® Web site at www.neurology.org). The clinical outcome was good in 80% of the patients (table). Four patients (16%) were not treated with immunotherapy during their first episode. Although they made an important recovery, 3 of them relapsed.

After a median follow-up of 20 months (range 6–170) since the first event, relapses were diagnosed in 6 patients (24%). The median relapse rate was 0.52 relapses/patient-year. A total of 13 relapses were

Table Clinical characteristics of the first episode in the whole series, relapsing, and nonrelapsing patients with anti-NMDAR encephalitis

Variables	All patients (n = 25)	Relapsing (n = 6)	No relapsing (n = 19)	*p* Value
Age, y, median (range)	23 (0.7–53)	20 (8–35)	23 (0.7–53)	NS
Female	22	6	16	NS
Ovarian teratoma, n (%)	5 (20)	1 (17)	4 (21)	NS
Clinical syndrome, n (%)				
Typical encephalitis[a]	22 (88)	5 (83)	17 (89)	NS
Epilepsy	3 (12)	1 (17)	2 (11)	NS
Ancillary tests, n (%)				
CSF pleocytosis (>5 cells/mm^3)	20 (80)	4 (67)	16 (84)	NS
Brain MRI, abnormal	15 (60)	3 (50)	12 (63)	NS
EEG, abnormal	20 of 22 (91)	5 of 6 (83)	15 of 16 (94)	NS
Treatment, n (%)				
No IT	4 (16)	3 (50)	1 (5)	0.009[b]
First-line IT[c]	15 (60)	3 (50)	12 (63)	NS
IV CS	5 (20)	1 (17)	4 (21)	NS
IV CS + IVIg	10 (40)	2 (33)	8 (42)	NS
Second-line IT[c]	6 (24)	0	6 (32)	NS
Plasma exchange	3 (12)	0	3 (16)	NS
Rituximab	1 (4)	0	1 (5)	NS
Cyclophosphamide	3 (12)	0	3 (16)	NS
Tumor removal	4 of 5 (80)	1 of 1 (100)	3 of 4 (75)	NS
Clinical outcome, n (%)				
Follow-up, mo, median (range)	20 (6–170)	81 (48–170)	15 (6–71)	0.014[b]
Complete recovery (mRS 0–1)	12 (48)	2 (33)	10 (52)	NS
Mild disability (mRS 2–3)	8 (32)	3 (50)	5 (26)	NS
Severe disability or death (mRS >3)	5 (20)	1 (17)	4 (20)	NS

Abbreviations: CS = corticosteroids; IT = immunotherapy; IVIg = IV immunoglobulin; mRS = modified Rankin Scale; NMDAR = NMDA receptor.
[a] Typical encephalitis: presence of ≥3 of the cardinal symptoms of anti-NMDAR encephalitis (psychiatric manifestations, speech disorder, seizures, abnormal movements, and decrease of consciousness).
[b] *p* Values were calculated by Fisher exact test.
[c] First-line IT: patients who were treated exclusively with IV corticosteroids or IV corticosteroids and immunoglobulins. Second line-IT: patients who in addition to first-line IT required further treatments like plasma exchange, rituximab, or cyclophosphamide.

identified (2 patients had 1 relapse, 2 had 2 relapses, 1 had 3 relapses, and 1 had 4 relapses) with a median delay of 2 years (range 0.5–13 years) for the first relapse and 5.8 years (range 2.5–14 years) for the last relapse.

At relapses, the typical syndrome was usually lacking. Only 4 relapses (31%) presented as typical anti-NMDAR encephalitis (see Methods). Relapses were usually less severe than the first episodes: only 2 relapses (15%) needed admission to the intensive care unit whereas 17 (68%) of the 25 patients were admitted in the intensive care unit at the first episode of the encephalitis (Fisher exact test, $p = 0.002$).

For a detailed clinical description of relapsing patients, see appendix e-1. Main clinical features of relapses were speech disorder (61%), psychiatric symptoms (54%), consciousness-attention disturbance (38%), and seizures (31%). Three relapses (23%) presented with isolated atypical symptoms suggestive of brainstem-cerebellar involvement (ataxia, diplopia, dysphagia, tremor).

In general, no significant clinical differences were observed between the first episode of relapsing and nonrelapsing patients (table). The only remarkable finding corresponded to the use of immunotherapy: 3 of the 4 patients who were not treated with immunotherapy subsequently relapsed (50% of relapsing patients) (Fisher exact test: $p = 0.009$). All but one relapse were treated with immunotherapy and no additional relapse-attributable disability occurred.

DISCUSSION Anti-NMDAR encephalitis is the most common and best characterized antibody-defined autoimmune neuronal disorder.[2] Unlike the clinical presentation, relapses have not been well described. Similar to previous series, we observed relapses in 24% of patients after a minimal follow-up of 6 months.[3,4] Relapses may present with partial aspects or with isolated symptoms of the full-blown syndrome, they may occur many years after the initial event, and treatment seems to prevent accumulated disability. Relapse risk was higher in patients who did not receive immunotherapy at the onset of the disease.

Patients may have more than one relapse and the typical syndrome was present only in 31% of relapses. In 2 relapses only one cardinal symptom was present. One of them consisted of a progressive predominant speech dysfunction in which repeated EEGs did not show epileptic activity. Two patients presented at least one relapse characterized by isolated cerebellar and brainstem symptoms. Patients with anti-NMDAR encephalitis frequently develop central hypoventilation due to dysfunction of respiratory centers in the medulla.[6] However, symptoms like cerebellar ataxia, diplopia, or dysphagia are not described as part of the disorder except in one of the patients included in the initial study of 2007 (patient 11) who presented 2 relapses characterized by diplopia, facial numbness, dysphagia, and ataxia.[7]

We found that patients who were not treated with immunotherapy at the first event had a higher risk for relapse. Absence of tumor has also been identified as a risk factor for relapse in larger series.[2] No or suboptimal immunotherapy was also reported in 8 of 10 relapsing patients of a series of 44 anti-NMDAR encephalitis.[4] The beneficial effect of early immunosuppressive treatment to prevent disease progression or relapses has also been suggested in other antibody-mediated autoimmune disorders.[8] However, while early aggressive immunotherapy (and tumor removal, if detected) seems to prevent disability and relapses in anti-NMDAR encephalitis, the role of chronic immunotherapy is unclear. Nevertheless, treatment with mycophenolate mofetil or azathioprine for at least 1 year has been recently recommended.[2]

Relapses of anti-NMDAR encephalitis may lead to definitive diagnosis, as happened in all of our relapsing patients. Presentation of the disease as partial syndromes, the fact that brain MRI is frequently normal, and that some patients improve without immunotherapy may favor this situation. In our relapsing patients, anti-NMDAR antibodies were not analyzed during the first event to unambiguously prove that the episodes were the first symptom of an anti-NMDAR encephalitis. In fact, most of them had the initial episode before anti-NMDAR antibodies were discovered[1] and they were misdiagnosed as unspecific encephalitis or encephalitis lethargica.[9] However, the review of the first event in our relapsing patients strongly suggests they were typical cases of anti-NMDAR encephalitis except in one patient who was initially diagnosed with cryptogenic epilepsy.[10]

This study has several limitations. The follow-up is relatively short and we cannot rule out that patients in the nonrelapsing group present a relapse in the future and increase the frequency of this complication. Similarly, the retrospective recollection of the clinical data may favor the description of partial or isolated symptoms of the disease because we could miss subtle signs or symptoms associated with the predominant manifestation. Finally, we did not have serial samples of the patients to correlate the antibody levels with the clinical course.

Our study emphasizes that 1 out of 4 patients with anti-NMDAR encephalitis is at risk to have a relapse that may occur several years later. It is important to identify early symptoms of the disease to start treatment without delay and to prevent disability and further relapses. Whether changes in serum anti-

NMDAR levels serve to predict relapses is presently unclear. However, serial determinations of antibody levels may be impractical considering the long delay between relapses and the first event and the fact that in some relapses antibodies may be only detectable in the CSF.[2]

AUTHOR CONTRIBUTIONS

Dr. Gabilondo: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Dr. Saiz: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Galán: drafting/revising the manuscript, acquisition of data. Dr. González: drafting/revising the manuscript, acquisition of data. Dr. Jadraque: drafting/revising the manuscript, acquisition of data. Dr. Sabater: drafting/revising the manuscript, technical work. Dr. Sans: drafting/revising the manuscript, contribution of vital reagents/tools/patients. Dr. Sempere: drafting/revising the manuscript, acquisition of data. Dr. Vela: drafting/revising the manuscript, contribution of vital reagents/tools/patients, acquisition of data, study supervision. Dr. Villalobos: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Dr. Viñals: analysis or interpretation of data. Dr. Villoslada: drafting/revising the manuscript, analysis or interpretation of data. Dr. Graus: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision.

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DISCLOSURE

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