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Characterisation and outcome of neuropsychiatric symptoms in patients with anti-NMDAR encephalitis

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Original Article

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Abstract

Background: Encephalitis due to anti-N-methyl-D-aspartate receptor antibodies (ANMDARE) is the most frequent immune-mediated encephalitis. It is distinguished by the subacute onset of neuropsychiatric symptoms. *Objective:* To evaluate the characteristic neuropsychiatric symptoms and their outcome in patients diagnosed with ANMDARE. *Methods:* This was a prospective, longitudinal study in patients with a diagnostic suspicion of ANMDARE that presented to the National Institute of Neurology from March 2018 to February 2019. A comparative analysis of two groups (positive N-methyl-D-aspartate receptor [NMDAR] vs. negative NMDAR antibodies in cerebrospinal fluid [CSF]) was done on admission and at discharge. Neuropsychiatric systematic assessments included the Neuropsychiatric Inventory Questionnaire, the Bush Francis Catatonia Rating Scale, the Confusion Assessment Method Severity, the Montreal Cognitive Assessment, and the Overt Agitation Severity Scale. *Results:* 24 individuals were analysed: 14 had positive NMDAR antibodies, and 10 had negative NMDAR antibodies in CSF. On admission, agitation/aggression, euphoria/exaltation, and disinhibition were more common in patients with positive antibodies. Excited catatonia and delirium were diagnosed more frequently in patients with positive antibodies. At discharge, there was an important decrease in neuropsychiatric symptoms, but substantial cognitive impairment remained. The mean hospitalisation length was 41.71 (SD 39.33) days for patients with definitive ANMDARE (p 0.259). *Conclusions:* Neuropsychiatric symptoms profile in ANMDARE was associated with the early onset of euphoria/exaltation and disinhibition, accompanied by marked psychomotor agitation. When ANMDARE was suspected, the presence of excited-type catatonia and delirium showed a tendency to predict definitive ANMDARE. At discharged, most patients recovered from catatonia, delirium, and psychosis, but marked cognitive symptoms, anxiety, and depression persisted at discharge.

Significant outcomes

- Neuropsychiatric symptoms in ANMDARE are characterised by euphoria/exaltation, disinhibition, and psychomotor agitation in the early stages of the disease.
- On admission, excited-type catatonia and delirium are frequent syndromes displayed in ANMDARE and should prompt this diagnostic consideration when present in patients with first episode of psychosis.
- Most patients with ANMDARE recovered from catatonia, delirium, and psychosis, but marked cognitive symptoms, anxiety, and depression persisted.

Limitations

- This study was conducted at a single centre with a relatively small group of subjects.
- The small sample and the descriptive nature of the study prevent estimating the risk of certain factors.
- Other antibodies different from NMDAR known to be related to autoimmune encephalitis were not measured in CSF.

Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (ANMDARE) is a clinical entity recently described (Dalmau *et al.*, 2008). Although it was initially thought to be a rare entity, its frequency

may now be compared to that of any individual infectious forms of encephalitis (Gable *et al.*, 2012). It is characterised by the presence of IgG autoantibodies against the NR1 subunit of the N-methyl-D-aspartate receptor (NMDAR) that leads to the appearance of multiple neuropsychiatric manifestations (Dalmau *et al.*, 2008). During the first month of the disease, approximately 90% of patients experience at least four of the six characteristic clinical manifestations: behavioural disturbances or cognitive dysfunction, speech disorders, epileptic seizures, movement disorders, compromise of the level of consciousness, autonomic symptoms, and hypoventilation (Graus *et al.*, 2016).

The vast majority of ANMDARE cases begin with a subacute onset of neuropsychiatric symptoms before neurological features appear (Warren *et al.*, 2018). In most cases, neuropsychiatric symptoms in ANMDARE can be uncommon in comparison with other psychiatric disorders and occur in the absence of a prior identified psychiatric history (Warren *et al.*, 2018). However, the clinical presentation in ANMDARE can be equivocal and clinical examinations can frequently be biased towards other psychiatric disorders (Barry *et al.*, 2011). Since antibody testing for definite diagnosis of ANMDARE is not readily accessible in many institutions and countries, and/or results take several weeks to obtain, Graus *et al.* (2016) have proposed a practical diagnostic approach based on clinical symptoms and supportive findings in diagnostic tests such as electroencephalogram (EEG) and cerebrospinal fluid (CSF) analysis.

Accordingly, the advent of ANMDARE has meant a change to the diagnostic approach of patients presenting to medical services with psychotic symptoms, behavioural alterations, and catatonic symptoms of acute or subacute instauration. Some authors have recommended the measurement of NMDAR antibodies in patients with atypical psychiatric manifestations (Lennox *et al.*, 2012; Maneta & Garcia, 2014; Restrepo Martínez *et al.*, 2019). However, there is still a limited understanding of how the neuropsychiatric symptoms of ANMDARE differ from those presented in other entities, and when CSF testing should be guaranteed (Al-Diwani *et al.*, 2019). Only a few studies have reported neuropsychiatric outcomes in this population (Bach, 2014; McKeon *et al.*, 2016). Most studies that propose a neuropsychiatric phenotype in patients with ANMDARE have used a retrospective database with limited behavioural descriptions and without a systematic use of psychopathologic measurements, which could lead to an underestimation of some psychiatric syndromes (Warren *et al.*, 2018; Al-Diwani *et al.*, 2019). A prompt diagnosis is necessary, as delayed immunotherapy is associated with poorer prognosis and higher mortality in this population (Titulaer *et al.*, 2013).

Aims of the study

To prospectively characterise the neuropsychiatric symptoms in patients with definitive ANMDARE and to evaluate the outcome at discharge by means of systematic psychopathologic measurements at an adult tertiary neurological referral centre.

Methods

Design

This is a prospective and longitudinal clinical study of patients with definite ANMDARE attended at the National Institute of Neurology and Neurosurgery of Mexico (NINN) whose objective has been to study the overall clinical and paraclinical presentation of the disease as well as the response to treatment and outcome.

Patients

The sample of the current study included all patients admitted from March 2018 to February 2019 to the NINN, who fulfilled the criteria of probable ANMDARE according to Graus *et al.* (2016) or had a first psychotic episode in the presence of key factors to suspect this entity (Maneta & Garcia, 2014; Restrepo Martínez *et al.*, 2019). Among these critical features, we included a history of flu-like prodrome, rapid onset of psychotic symptoms or catatonia, seizures, delirium, severe autonomic dysfunction, aphasia, amnesia, and abnormal movements different from those characteristics of catatonia. Sampling was consecutive according to inclusion criteria. Initially, all patients were selected whenever they displayed the aforementioned features associated to ANMDARE. On admission, a sample of CSF was taken to all patients to look for antibodies against the NR1 subunit of N-methyl-D-aspartate glutamate receptor. These were processed at Labco Nous Diagnostics, Barcelona, Spain with rat brain immunohistochemistry and cell-based assays with N-methyl-D-aspartate (NMDA) expressing cells. Since antibodies against NMDAR were processed abroad, the results were received 4–8 weeks after the samples were taken. Other antibodies known to be related to autoimmune encephalitis were not included as these are not available in Mexico. Tests for HIV, CSF adenosine deaminase, and bacteria (including cultures for *Mycobacterium tuberculosis* and *Cryptococcus neoformans*) and tests for systemic autoimmune diseases (anti-double-stranded DNA, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-beta 2 glycoprotein antibodies, and antiphospholipid antibodies) were negative in all patients. Viral CSF polymerase chain reaction results, for Herpes simplex types 1 and 2, Cytomegalovirus, Epstein-Barr, Varicella zoster, Human herpes types 6, 7, and 8, Enterovirus, Toxoplasma, Parvovirus B19, and Lymphocytic choriomeningitis virus, were also negative in the current episode of all patients, thus reasonably excluding other disorders.

When CSF antibody testing was received, patients were separated into two groups depending on the results of NMDAR antibodies testing in CSF: on one side, patients with a definitive diagnosis of ANMDARE given by positive NMDAR antibodies in CSF (NMDAR positive group) and on the other side, patients with suspected ANMDARE or diagnosis of probable ANMDARE with negative antibodies in CSF (NMDAR negative group).

Socio-demographic and clinical variables

We collected socio-demographic data and relevant clinical variables including psychiatric and cognitive symptoms, speech disturbances, motor signs, seizures, altered level of consciousness, autonomic imbalance, hypoventilation, and others that emerged in our subjects during their admission, hospital stay, and at discharge. CSF cytochemical analysis and EEG were obtained in all patients. Magnetic resonance imaging (MRI) was obtained in 13 patients with definitive ANMDARE and all patients with negative NMDAR antibodies. Similarly, an 18-fluorodeoxyglucose positron-emission tomography (PET) scan was performed in 12 patients with definitive ANMDARE and 9 patients with negative antibodies. Trans-vaginal ultrasound was performed in all female patients to screen for ovarian teratomas.

Neuropsychiatric assessment

All patients were systematically assessed employing regular mental status examination, neurological examination, and standardised psychometric evaluations on admission and at discharge. Initial clinical assessments were done before knowing the NMDAR

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antibodies results. Patients were diagnosed as having catatonia if they fulfilled Diagnostic and Statistical Manual of Mental disorders, 5th edition (DSM-5) criteria of catatonic disorder due to a medical condition (excluding item D) (American Psychiatric Association & American Psychiatric Association, 2013) or had the presence of three or more catatonic symptoms on the Bush Francis Catatonia Screening Instrument (BFCSI) and the Bush Francis Catatonia Rating Scale (BFCRS) (Bush *et al.*, 1996). The type of catatonia was classified as excited, stuporous, or mixed if they alternated periods of predominantly stuporous catatonic symptoms with exciting ones. Delirium was diagnosed using the Confusion Assessment Method algorithm (Grover, 2012; Inouye *et al.*, 2014) and DSM-5 criteria (American Psychiatric Association & American Psychiatric Association, 2013). Delirium severity was obtained using Confusion Assessment Method-Severity (CAM-S) short form (Inouye *et al.*, 2014). Agitation was evaluated objectively with the Overt Agitation Severity Scale (OASS) based on vocalisations and orofacial movements, and superior and inferior motor behaviours (Yudofsky *et al.*, 1997). Montreal Cognitive Assessment test (MoCA) was obtained in all patients on admission and at discharge to evaluate cognitive function (Pedraza *et al.*, 2016). Accordingly, the Neuropsychiatric Inventory Questionnaire (NPI-Q) (Cummings, 1997) was given to relatives or caregivers to evaluate neuropsychiatric symptoms presented one month before admission and one week before discharge.

Statistical analysis

Data analysis was performed with the SPSS software (21 version), NY, US. Descriptive statistics and normality tests (Kolmogorov–Smirnov test) were obtained, as well as inferential statistics, using Pearson chi-square or Fisher's test, and *t*-test or Mann–Whitney test, per the distribution of the variables. Bonferroni corrections for multiple comparisons were also obtained.

Results

Socio-demographic and clinical variables

In the period between March 2018 and February 2019, a total of 8692 patients were attended at the emergency department of the NINN: 24 individuals with a diagnostic suspicion of ANMDARE were admitted and included in this study as they fulfilled the inclusion criteria. Of these patients, 14 patients had positive NMDAR antibodies in CSF and fulfilled the current diagnostic criteria for definitive NMDAR encephalitis. Meanwhile, 10 individuals with an initial suspicion of ANMDARE had negative antibodies for this disease. Of the 14 patients with a definitive diagnosis for ANMDARE, 5 (35.7%) were women with a mean age of 24.5 (SD 5.95) years. Patients with negative antibodies had a mean age of 30 (SD 14.68) years, and 50% were women (Table 1). Of the 14 cases diagnosed as definitive ANMDARE, 57.1% had been diagnosed with a psychiatric disorder before admission to our ward. In the group with negative NMDAR antibodies, the following diagnoses were obtained after further evaluation: one patient had multiple sclerosis, one patient was diagnosed with prion disease, four met criteria for probable autoimmune encephalitis but had negative NMDAR antibodies in CSF, and four patients were later diagnosed with psychotic disorder from the schizophrenia spectrum. Mortality was present in one (7.1%) patient with definitive ANMDARE during hospital stay (p 0.583).

Patients were admitted to the NINN 46.4 (SD 60.4) days after symptoms onset. CSF cytochemical analysis and EEG were obtained on admission, and MRI and PET-CT scans within the first 2 weeks. Table 1 shows the results of MRI, EEG, and PET, as well as CSF analysis. Neither EEG and CSF analysis nor MRI helped differentiate patients with definitive ANMDARE from patients with negative NMDAR antibodies in CSF. However, the presence of bilateral occipital hypometabolism on the fluorodeoxyglucose positron-emission tomography (FDG-PET) occurred in 100% of definitive ANMDARE cases who underwent FDG-PET, as compared to 55% in the group with negative NMDAR antibodies (this difference was significant after Bonferroni correction for multiple comparisons). Only 1 (7.1%) of 14 cases with definite ANMDARE were associated with teratoma. Previous herpes simplex virus was not documented in any case.

Of 14 cases with definitive ANMDARE, 100% received IV steroids (methylprednisolone 1 g/day for 5 days); 60% of patients from the negative antibodies group received this intervention. Plasma exchange was performed in 78.6% of patients with positive NMDAR antibodies. Only four (28.6%) patients with definitive ANMDARE required a second-line intervention in the acute phase of the disease (cyclophosphamide, rituximab, or both). For symptomatic treatment, 14 (100%) patients with definitive ANMDARE received benzodiazepines (lorazepam) and second-generation antipsychotics (quetiapine) due to the presence of psychomotor agitation, catatonia, or both.

On admission, nine (64.3%) patients later diagnosed with definitive ANMDARE fulfilled the diagnostic criteria for probable ANMDARE according to Graus *et al.* (2016). Similarly, patients from the negative antibodies group met these criteria by 60%. In both groups, 100% of the patients had at least one cognitive or behavioural symptom; 78.6% of patients with definitive ANMDARE presented this group of symptoms as the initial manifestation of the disease. Within the criteria proposed by Grauss et al., seizures occurred in 71.4% of patients with definitive ANMDARE. Similarly, within the key features proposed to suspect ANMDARE in the context of a first episode of psychosis, epileptic seizures and delirium were more frequently observed in patients with definitive ANMDARE (p 0.018 and 0.018, respectively). Table 1 summarises demographic and general clinical features of both groups, including Graus criteria for probable ANMDARE and key factors to suspect ANMDARE in patients with a first episode of psychosis.

Neuropsychiatric assessment on admission

In the NPI-Q, the presence of agitation/aggression and euphoria/elation was significantly higher in patients with ANMDARE, occurring in 13 (92.9%) and 11 (78.6%) patients, respectively. Likewise, disinhibition was observed in 11 (78.6%) patients with positive NMDAR antibodies. Additional symptoms evaluated by the NPI-Q did not show significant differences. Table 2 shows a comparative assessment of neuropsychiatric symptoms included in the Neuropsychiatric Inventory Questionnary on admission. Also, 12 (85.7%) patients with definitive ANMDARE fulfilled the diagnostic criteria for catatonia, compared with the negative antibodies group where this syndrome was found in 7 (70%) patients (p 0.320). Importantly, the presence of excited catatonia was significantly higher in patients later diagnosed as definitive ANMDARE [7 (50%) vs. 0 patients] (p 0.010). Delirium was diagnosed in 10 (71.4%) out of 14 patients with definitive ANMDARE, compared with 2 (20%) out of 10 patients in the negative antibodies group (p 0.018).

Table 3 shows the total scores in NPI-Q, BFCSI, BFCRS, CAM-S, and OASS on admission, comparing patients with definitive ANMDARE and patients in the negative antibodies group.

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Table 1. Comparative socio-demographic and clinical features on admission in patients with definitive ANMDARE and patients with negative NMDAR antibodies in CSF

	NMDAR Positive antibodies ($n = 14$)	NMDAR Negative antibodies ($n = 10$)	p value	Bonferroni corrected p value
Socio-demographic features				
Age (years)	24.5 (SD 5.95)	30 (SD 14.68)	0.049	0.245
Female	5 (35.7%)	5 (50%)	0.398	0.999
Education (years)	12.43 (SD 3.13)	10 (SD 5.47)	0.285	0.999
Days of hospitalisation	41.71 (SD 39.33)	31.30 (SD 32.05)	0.259	0.999
Days from symptoms onset to admission	46.40 (SD 60.40)	94 (SD 114.04)	0.546	0.999
Probable ANMDARE criteria on admission				
Acute onset (less than 3 months)	13 (92.9%)	8 (80%)	0.371	0.999
Abnormal (psychiatric) behaviour or cognitive dysfunction	14 (100%)	10 (100%)	1.00	1.00
Speech disturbances	14 (100%)	9 (90%)	0.417	0.999
Seizures	10 (71.4%)	2 (20%)	**0.018**	0.180
Movement disorder, dyskinesias, or abnormal postures	9 (64.3%)	9 (90%)	0.171	0.999
Decreased level of consciousness	7 (50%)	4 (40%)	0.473	0.999
Autonomic dysfunction or central hypoventilation	5 (35.7%)	2 (20 %)	0.357	0.999
Abnormal electroencephalogram	11 (78%)	6 (60%)	0.296	0.999
Abnormal CSF (inflammatory changes)	5 (35.7%)	3 (30%)	0.561	0.999
Probable anti-NMDAR encephalitis diagnosis	9 (64.3%)	6 (60%)	0.547	0.999
Factors that should prompt consideration of ANMDARE in first-episode psychosis on admission				
Flu-like prodrome	6 (42.9%)	2 (20%)	0.234	0.999
Rapid onset of psychotic or catatonic symptoms	13 (92.9%)	7 (70%)	0.178	0.999
Abnormal movements different from catatonia	1 (7.1%)	2 (20%)	0.371	0.999
History of recent seizures	10 (71.4%)	2 (20%)	**0.018**	0.108
Language abnormalities (aphasia)	4 (28.6%)	1 (10%)	0.283	0.999
Delirium	10 (71.4%)	2 (20%)	**0.018**	0.108
Other diagnostic studies				
Abnormal brain magnetic resonance imaging	5 (35.7%)	4 (40%)	0.940	0.999
Occipital hypometabolism FDG-PET	12 (100%)†	5 (55.6%)†	**0.021**	**0.042**

†FDG-PET was performed in 12 patients with definitive anti-NMDAR encephalitis and 10 with negative antibodies.

None of the results were significantly different between groups after Bonferroni correction.

Neuropsychiatric assessment at discharge

At discharge, psychometric measurements obtained in the ANMDARE group showed a decrease in the number of symptoms and severity, as may be seen in Table 4. The NPI-Q, the BFCRS, and the CAM-S scores decreased significantly compared with those scores on admission in patients with definitive ANMDARE, even after Bonferroni correction for multiple comparisons.

Of the 14 patients with definitive ANMDARE, the presence of delusions, agitation, euphoria, disinhibition, disorganised behaviour, and changes in sleep and appetite had resolved at discharge. However, five (35.7%) and six (42.9%) of patients with definitive ANMDARE reported depressive and anxiety symptoms at discharge. Catatonia, psychomotor agitation, and delirium resolved in most patients; only 2 patients (14.3%) out of 13 presented catatonic symptoms and delirium at the end of their hospitalisation.

On admission, only 4 (28.6%) patients with definitive ANMDARE were assessable for cognitive assessment using the MoCA test, while the remaining 10 (71.4%) could not perform this test due to extreme agitation or catatonia MoCa test was obtained in 12 out of 13 patients with definitive ANMDARE at discharge: 6 (42.91%) patients scored 14 or less, 4 (28.42%) scored 15–20, 2 (14.3%) scored 21–25, and only 1 (7.15%) patient had an MoCA score of 26 or more. Most patients had a significant cognitive impairment at the end of their hospitalisation.

Discussion

ANMDARE is an increasingly diagnosed entity worldwide. In Mexico, there are no studies that can inform us about its general epidemiology. However, in the time period of the study at the

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Table 2. Comparative NPI-Q on admission

Neuropsychiatric features NPI-Q	NMDAR Positive antibodies ($n = 14$)	NMDAR Negative antibodies ($n = 10$)	*p* value	Bonferroni corrected *p* value
Delusions	12 (85.7%)	6 (60%)	0.170	0.999
Hallucinations	3 (21.4%)	4 (40%)	0.296	0.999
Agitation/Aggression	13 (92.9%)	2 (20%)	**<0.001**	**0.012**
Depression/Dysphoria	4 (28.6%)	5 (50%)	0.260	0.999
Anxiety	11 (78.6%)	7 (70%)	0.494	0.999
Elation/Euphoria	11 (78.6%)	1 (10%)	**0.001**	**0.012**
Apathy/Indifference	7 (50%)	6 (60%)	0.628	0.999
Disinhibition	11 (78.6%)	3 (30%)	**0.017**	**0.204**
Irritability/Lability	12 (85.7%)	9 (90%)	0.629	0.999
Motor disturbance	12 (85.7%)	6 (60%)	0.170	0.999
Nightime behaviours	11 (78.6%)	8 (80%)	0.668	0.999
Appetite/Eating	12 (85.7%)	9 (90%)	0.629	0.999

Table 3. Comparative medians for total scores in NPI-Q, BFCSI, BFCRS, CAM-S, and OASS on admission

	NMDAR Positive antibodies ($n = 14$)	NMDAR Negative antibodies ($n = 10$)	*p* value	Bonferroni corrected *p* value
NPI-Q	23.50 (8–29)*	15.50 (4–27)	0.074	0.370
BFCSI	6 (0–8)	7 (0–11)	0.508	0.999
BFCRS severity	13.5 (0–29)	17 (0–40)	0.841	0.999
CAM-S	5.5 (1–7)	2 (1–6)	**0.019**	**0.095**
OASS	9 (0–92)	0 (0–6)	**0.013**	**0.065**

*Minimum–maximum.

Table 4. Comparative median scores for NPI-Q, BFCSI, BFCRS, CAM-S, and OASS on admission and at discharge in patients with definitive ANMDARE

	NMDAR Positive antibodies On admission ($n = 14$)	NMDAR Positive antibodies At discharge ($n = 13$)	*p* value	Bonferroni corrected *p* value
NPI-Q	23.50 (8–29)*	4 (0–12)	**0.001**	**0.005**
BFCSI	6 (0–8)	0 (0–5)	**0.001**	**0.005**
BFCRS severity	13.5 (0–29)	0 (0–8)	**0.002**	**0.010**
CAM-S	5.5 (1–7)	2 (0–4)	**0.006**	**0.030**
OASS	9 (0–92)	0 (0–6)	**0.011**	**0.055**

*Minimum–maximum.

NINN, this condition represented a 0.27% of patients who consulted the Emergency Department and 2.1% of admissions to the neurological ward. Even though ANMDARE is considered an autoimmune disease that affects predominantly women, recent reports from other populations have reported a more balanced sex ratio, as our study (Zhang *et al.*, 2017). Another particularity of our sample was the scarce number of patients in whom CSF abnormalities were evidenced. Although the worldwide reports of inflammatory changes in CSF in ANMDARE vary widely (Espinola-Nadurille *et al.*, 2018), a recent Brazilian report also underscored a lower frequency of inflammatory markers in its sample (Nóbrega *et al.*, 2019).

Most patients with ANMDARE develop prominent psychiatric symptoms, including anxiety, irritability, aggression, insomnia, paranoia, visual or auditory hallucinations, sexual disinhibition, mania, psychosis, and catatonia (Titulaer *et al.*, 2013; Barry *et al.*, 2015). In our sample, all patients with definitive ANMDARE presented with at least one behavioural or cognitive symptom, and 78.6% did so as the first manifestation in their clinical picture. Similar to the cohort reported by Maat *et al.* (2013), 57.1% of our cases had been referred to psychiatric services before encephalitis was suspected. The presence of psychomotor agitation, euphoria, and disinhibition were the predominant neuropsychiatric manifestations in patients with definitive ANMDARE as rated by the NPI-Q. Previous studies have found similar findings (Warren *et al.*, 2018; Al-Diwani *et al.*, 2019). For example, Warren et al. reported psychomotor agitation as the most common neuropsychiatric sign in patients with ANMDARE. However, different from our study, symptoms of mania were only documented in 4.7% of the sample (Warren *et al.*, 2018). More recently, after a rigorous analysis of 464 published cases of ANMDARE, Al-Diwani *et al.* (2019) proposed a psychiatric phenotype including behaviour (68%), psychosis (67%), mood (47%), catatonia (30%), and sleep disturbance (21%). More specifically, a transdiagnostic cluster of seven clinical features (agitation, aggression, hallucinations, delusions, mutism, irritability or mood instability, and depressed mood) explained 77% of the variance in the data (Al-Diwani *et al.*, 2019).

In our study, the definite ANMDARE patients exhibited high rates of catatonia (85.7%) as recently reported by our group (Espinola-Nadurille *et al.*, 2019), in contrast to other retrospective studies that have reported lower frequencies of approximately 30% (Barry *et al.*, 2015; Espinola-Nadurille *et al.*, 2018). However, this psychomotor syndrome presented also in 70% of patients from the group with negative NMDAR antibodies. Although the presence of catatonia was not significantly different between the two groups, the excited type was significantly more frequent in patients with

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definitive ANMDARE (50%). In the negative NMDAR antibodies group, the stuporous catatonic type predominated. As excited catatonia can be easily mistaken for psychomotor agitation (Fink, 1999), there is a probability that this syndrome has been underestimated in other reports. In accordance of our study, delirious mania, a severe and often unrecognised neuropsychiatric syndrome characterised by the rapid onset of delirium, mania, psychosis, and catatonia (Fink, 1999), has been previously reported in patients with ANMDARE (Restrepo-Martínez *et al.*, 2019)

Regarding key factors to consider ANMDARE in a first episode of psychotic symptoms, we found that seizures and delirium were significantly more frequent in the definite ANMDARE group. These findings are supported by Herken and Prüss who consider epileptic seizures and delirium as warning signs pointing to an autoimmune aetiology in new onset psychosis (Herken & Prüss, 2017). More recently, Gurrera, after a careful analysis of 230 reports of ANMDARE associated with prominent behavioural or psychiatric symptoms, identified seizures as one of the earliest appearing clinical signs that should guide clinicians towards ANMDARE diagnosis when new onset psychiatric symptoms are being approach. Interestingly, although delirium was not reported Gurrera's study, disorientation/confusion was described in 42.6% of the cases (Gurrera, 2018).

Even our sample is small, among the findings of our study, there is the possibility of grouping different neuropsychiatric features that were significantly associated with the diagnosis of definitive ANMDARE. Early neuropsychiatric symptoms of psychomotor agitation, euphoria, and disinhibition followed by excited catatonia and delirium can add up to a more robust suspicion of ANMDARE. The presence of seizures also reinforces the diagnosis. A larger sample is necessary to make a statistical assessment of this hypothetical clinical cluster. Also, an important limitation of the study related to the small sample size is that we cannot make a statistical analysis to find significant differences between patients with ANMDARE and patients with probable autoimmune encephalitis and negative NMDAR antibodies, as there are only four patients classified within this group.

Until now, few studies have measured neuropsychiatric outcomes in patients with ANMDARE (Bach, 2014). Most studies that refer to outcomes in this populations have done it in terms of improvement of Modified Rankin Scores and cognitive function (Finke *et al.*, 2012; Titulaer *et al.*, 2013; McKeon *et al.*, 2018); only one study has evaluated outcomes in social cognition (McKeon *et al.*, 2016). Bach et al., in a case report study of three different patients with ANMDARE, reported that emotional distress and behavioural difficulties were prominent and had a deep impact on rehabilitation (Bach, 2014). On a screening self-report measure of mood (hospital anxiety and depression scale), two patients out of three reported symptoms of anxiety and depression (Bach, 2014). In terms of neuropsychiatric outcomes, we observed that at discharge most patients with definitive ANMDARE had recovered from psychotic, manic, and catatonic symptoms, as well as delirium. However, similar to the previous observations (Bach, 2014; McKeon *et al.*, 2016), depressive and anxious symptoms were reported by 35.7% and 42.9% of patients, respectively. On the other hand, our results add to the accumulating evidence that neurocognitive deficits can persist during recovery from ANMDARE. Cognitive deficits are prominent at the onset and throughout the disease. In a large percentage of patients (71%), cognition was not assessable on admission by means of Moca instrument because psychotic, catatonic, or delirium symptoms prevented the evaluation. At discharge, only one patient with definitive ANMDARE had an MoCA score of 26 or more. Meanwhile, 42.9% of them had severe cognitive impairments, with scores of 14 or less. Finke *et al.* (2012) found substantial cognitive impairments in eight out of nine patients who mainly consisted of deficits in executive functions and memory. A systematic review found neuropsychological dysfunction in more than 75% of patients recovering from ANMDARE and associated its severity in patients in whom immunotherapy is ineffective or when initial treatment is delayed (McKeon *et al.*, 2018).

About treatment, the decision to receive immunotherapy was done by a multidisciplinary clinical team and was usually started when patients added symptoms or paraclinical investigations that strengthened the possibility of the disease (even before a positive result of NMDAR antibodies). That is, there is a different threshold to (a) suspect ANMDARE and perform anti-NMDAR antibodies testing and (b) to start immunotherapy. In the cases with negative antibodies where immunotherapy was withhold, the reasons were (a) that even when they presented with complex neuropsychiatric presentations resembling ANMDARE, paraclinical investigations did not support the diagnosis and/or clinical symptoms did not progress to a clearer clinical picture of the disease and/or (b) if, over the days of hospitalisation they displayed symptoms and/or paraclinical results more consistent with other nosological entities (e.g. myoclonus in the case of Creutzfeldt–Jakob disease). No adverse reactions were observed in patients who received immunotherapy.

In summary, through the findings obtained in this study, it is possible to consider that there is a difference in the profile of neuropsychiatric symptoms of patients with definitive ANMDARE when compared to other entities that resemble the disease. The presence of psychomotor agitation, euphoria, disinhibition, delirium, and excited catatonia appear to be associated with a higher probability of detecting positive antibodies in the CSF when ANMDARE is suspected. After immunotherapy, most patients recover from neuropsychiatric syndromes including mania, psychosis, catatonia, and delirium. However, marked cognitive deficits, depression, and anxiety can still be present at discharge: neuropsychiatric follow-up must be guaranteed in these patients. Further prospective studies with larger samples sizes are necessary to validate our findings.

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Ethical considerations. The Institutional Research Committee revised and approved the protocol before sampling. The research project of this study was approved by the Ethics Committee of the National Institute of Neurology of Mexico, and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Patient anonymity has been preserved in all cases. Those patients competent to consent received and signed an informed consent. If this was not possible, relatives or caregivers signed it. No patient refused to participate.

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