INTRODUCTION

Approximately 70% of all patients diagnosed with anti-NMDAR encephalitis exhibit psychiatric symptoms, mainly in the form of acute or subacute onset psychotic episodes characterized by a rapid and serious evolution. Most patients do not have previous history of psychiatric symptoms and are often admitted to psychiatric units. These episodes are usually accompanied by subtle neurological symptoms, which in most patients become more severe during the weeks that follow the initial psychiatric symptoms, including, seizures, abnormal movements, decreased level of consciousness, or...
dysautonomic features. However, there is a small group of patients who only develop psychosis as manifestation of anti-NMDAR encephalitis. Recognition of these patients is important because they also respond to immunotherapy.

Previous studies have described the psychiatric symptoms of patients with anti-NMDAR encephalitis. These studies are often systematic reviews that list the most frequent abnormal features but do not provide a detailed account regarding the appearance, combination, and evolution of these symptoms. Moreover, although some studies suggest a series of warning signs that can help clinicians to identify anti-NMDAR encephalitis in patients with psychotic symptoms, many of these signs are based on the identification of clinical neurological features or abnormal tests (eg EEG, CSF). In order to facilitate an early and accurate diagnosis of patients with isolated psychiatric symptoms, it is crucial to focus in a detail clinical description of the psychiatric phenotype of this illness. Here, we report the psychiatric presentation of three patients with anti-NMDAR encephalitis and discuss the similarity of their symptoms with those in cases of cycloid psychosis.

| PATIENT 1 |

The patient is a 17-year-old Caucasian female without previous history of neurological or psychiatric diseases. She displayed adaptive cluster C personality traits (perfectionism and emotional dependency). In June 2011, she had been subjected to an external stress factor connected with the family. She displayed no prodromal psychiatric symptoms, but she did exhibit nonspecific prodromal somatic symptoms (headaches, general discomfort, and high blood pressure).

She presented with acute onset (within 24 hours) of polysymptomatic psychosis, characterized by feelings of strangeness and delusions of self-reference. Additionally, she showed a high degree of anxiety, distress and confusion, incoherent speech, delusions of guilt, catastrophe and persecutory ideas, and extreme concern with death. She described auditory (noises, imperative voices, and songs) and visual hallucinations (objects and shadows), hypersensitivity to auditory stimuli, and insomnia.

After 72 hours, she was admitted to our Child and Adolescent Psychiatric Unit with an initial diagnostic orientation of an episode of depression with psychotic symptoms. An initial somatic screening including general blood test and head CT scan was normal. For this reason, she was started on fluoxetine 20 mg/day and quetiapine 100 mg/day, which was replaced 3 days later by risperidone 2 mg/day due to features of hypotension (paleness and sedation).

During these first days, the patient showed confusion, disorientation, mood swings (hyporeactivity, irritability, dysphoria, lability, and a feeling of being emotionally overwhelmed) and marked mood fluctuations (euthymia—hypothymia). She experienced changes in thought patterns (disjointed, incoherent, and mental blocks) and in motricity (disorganization, hyperactivity, inhibition, and occasional catatonic posturing). Furthermore, the delusional symptoms, the auditory hallucinations (an expression of perplexity and “listening attitude”), and the global insomnia persisted. At the end of the first week, a number of possible side effects of the psychopharmacological treatment appeared (sedation, a slowing of psychomotricity, and bilateral rigidity). These symptoms evolved toward mutism and catatonia, and some stereotyped movements appeared in the upper extremities, hence complementary examinations were undertaken (see Table 1). Due to the high likelihood of autoimmune encephalitis, the antipsychotic treatment was discontinued and immunosuppressive treatment commenced. In the extension study, an ovarian teratoma was detected and removed. The presence of anti-NMDA receptor antibodies in the patient’s blood and CSF was subsequently confirmed. The patient’s psychiatric and cognitive evolution was good, and she was released from the hospital 70 days after she had been admitted.

| PATIENT 2 |

The patient is a 23-year-old Caucasian woman. She had no history of somatic disorders, and her only psychiatric history was related to her nonadaptive cluster C personality pattern (hyper-responsible, self-demanding, and emotionally dependent). In July 2016, in a context of workplace stress, but with no somatic or psychiatric prodromal symptoms, the patient exhibited an acute episode of psychosis that had occurred fully in a 24-hour period, characterized by suspicion, psycho-physical anxiety, and a feeling of depersonalization and derealization. Additionally, she showed logorrhea, tachypsychia, and incoherent speech with verbalization of persecutory delusions and self-reference, and multiple doubts about past events. Plus, she reported hypersensitivity to auditory stimuli, auditory and synaesthetic hallucinations, false recognitions, psychomotor restlessness, and general insomnia.

Upon her arrival, a blood and urine toxic analysis were performed and no alteration was observed. For this reason, she was admitted to the acute care unit for observation with an initial diagnosis impression of brief psychotic disorder. She was prescribed 10 mg/day of olanzapine. In the first days after admission, we observed thymic (hyperthymia—hypothymia) and mood changes (hyperactive and irritable) and abnormal thinking patterns (increased latency, lack of spontaneity, blockages in the course of thought, bradypsychia, and bradyphrenia). She also experienced disinhibition, altered psychomotricity (disorganization, unproductive hyperactivity, inhibition, and slow movements) and cognitive interference (problems with attentional control, short-term memory). During these days,
### Table 1: Patient characteristics and complementary exploration

| Patient | Premorbid personality | Stressor                  | Somatic prodromes                          | Psychiatric prodromes | DUP (hours) | Cycloid Psychosis Criteria | Cranial MRI                                                                 | EEG                                                                 | Serum Ac anti-NMDAR | CSF (num. cells, Ac anti-NMDAR) | Neoplasia test |
|---------|-----------------------|---------------------------|-------------------------------------------|-----------------------|-------------|---------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------|---------------------------------|------------------|
| #1      | Woman, 17             | Cluster C traits          | Family stressor                           | Headaches, general discomfort, high blood pressure | No          | 72 h                       | Yes                                                                            | Hyperintensity from both hippocampus and the lower left temporal lobe | Positive          | 11 cells                        | Ovarian teratoma |
| #2      | Woman, 23             | Cluster C traits          | Workplace stressor                        | No                    | No          | 24 h                       | Yes                                                                            | Normal                                                             | Positive          | 5 cells                         | Ovarian teratoma |
| #3      | Woman, 35             | Cluster C traits          | Workplace and economic stressor           | No                    | No          | 72 h                       | Yes                                                                            | Normal                                                             | Positive          | 11 cells                        | Ovarian teratoma |

Abbreviation: DUP, Duration of Untreated Psychosis.

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This patient is a 35-year-old Caucasian woman. She had no somatic medical history of note. In terms of psychiatric history, she had a mild intensity depressive episode 3 years prior. She was treated with antidepressants (20 mg/day of paroxetine) by her primary care physician and exhibited a good clinical response. In July 2017, she was brought to an emergency psychiatric clinic after exhibiting behavioral alterations over a period of 72 hours. The episode occurred at a time when the patient had been experiencing economic and work-related problems. However, she did not exhibit any psychiatric or somatic prodromes. The initial clinical assessment was characterized by disorganized behavior, intrusive ideas and images, and a belief that something would happen to a family member.

The patient was admitted to the hospital's psychiatric unit. Over the first 24-hour period after her admission, the patient exhibited pronounced clinical fluctuations. She oscillated between periods when she was nearly asymptomatic and others when her symptoms worsened. These showed persistence of temporal trends that were not consistent with the typical course of a mood disorder.

The patient presented with persecutory delusions and self-reference, false recognitions and auditory (music and insults) and synaesthetic hallucinations. After 12 days of hospitalization and still no clinical improvement (and even some deterioration in her psychomotricity), the decision was made to proceed with complementary neuroimaging and lumbar puncture studies. The patient exhibited drowsiness and hypersalivation, so the dose of olanzapine was increased to 20 mg/day. The patient exhibited dysphoria, and the olanzapine was replaced by 4 mg/day of risperidone on day 18 to end this treatment and to begin electroconvulsive therapy.

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disorientation, auditory hallucinations, false recognitions, and incoherent speech. She verbalized demonic possession, megalomaniac and persecutory ideas, all accompanied by significant behavioral alterations (psymchomotor agitation).

At the end of the first week after the patient’s admission, her clinical presentation had deteriorated, as she was exhibiting hyperthymia, megalomania, logorrhea, incoherent speech, and hallucinatory behavior. In response, a decision was taken to increase the dosage of olanzapine to 30 mg/day, and treatment with 600 mg/day of lithium was also prescribed. The patient showed signs of autonomic dysfunction, low-grade fever (37.9º), and orofacial movements on the right side of her face, reaching a state of stupor with generalized rigidity in the second week after admission. In light of the strong suspicion that the patient was suffering from autoimmune encephalitis, a complementary extension study was undertaken (see Table 1) and resulted in the discovery of an ovarian teratoma, which was then removed. Treatment with intravenous immunoglobulins and corticotherapy was begun. The patient’s evolution was slow, and she displayed severe autonomic dysfunction (urinary retention, severe and persistent fever without a source of localized infection, tachycardia, hypertension, and hypoventilation), requiring orotracheal intubation and a transfer to the intensive care unit. Subsequently, test results confirmed the presence of anti-AM DAR antibodies in the patient’s blood and CSF. Despite the initial treatment, the patient’s clinical evolution was poor, and a decision was made to administer weekly treatments with rituximab for a period of one month. A month and a half after her admission, the patient began to display slow and gradual clinical improvement, and she was released from the hospital after 90 days.

5 | DISCUSSION

In the initial phase of the autoimmune process, our three Anti-NMDAR encephalitis patients met Perris and Brockington’s diagnostic criteria for cycloid psychosis (Table 2). To put in a nutshell: acute and polysymptomatic onset, polymorphous psychotic symptomatology, mood swings, and alterations in psychomotor activity which in all cases evolved into catatonia.

Similarly to what usually occurs in cycloid psychosis, three other factors were observed in our three cases: the absence of long-term psychiatric prodromes (cognitive and negative symptoms), the presence of external stress factors preceding symptom onset, and cluster C personality traits (including rumination, perfectionism, and emotional dependency). A context of stress has been connected with the onset and exacerbation of autoimmune diseases such as multiple sclerosis 9,10 and systemic lupus erythematosus.11,12 Prior studies have weighed the possibility that certain personality traits are linked to autoimmune diseases.13-15

Anti-NMDAR encephalitis, likewise cycloid psychosis, tends to appear most frequently in young women and is usually accompanied by general insomnia and slight mood swings starting a few days before the emergence of symptoms.

Related to antipsychotic medication, anti-NMDAR encephalitis patients normally show intolerance to antipsychotic medication. They usually display marked extrapyramidal side effects, especially with those medications with greater antagonist affinity for the receptor D2.16 This is an unusual trend in cycloid psychosis patients.17,18

In anti-NMDAR encephalitis patients, the psychotic symptoms generally evolve into the appearance of serious neurological complications.1 Twenty percent of patients with anti-NMDAR encephalitis experience subsequent relapses,19-21 and often in the months following the acute phase, cognitive interference, and clinical issues related to impulse control appear.22,23 The previous statements make a major difference from cycloid psychosis. Cycloid psychosis is a clinical entity that most frequently follows a recurring pattern, featuring periods of interepisodic ad integrum recovery marked by an overall lack of residual psychotic symptoms (7%-17%).24,25

Unlike the two clinical entities described above, patients who experience a first episode of psychosis in schizophrenia (Table 3) tend to have a long clinical history of prodromal psychiatric features (negative and cognitive symptoms) that affect their basic functioning.26,27 In addition, delusions and hallucinations frequently appear progressively and are latent in these patients, meaning that their psychosis goes untreated for a longer period of time.28
In conclusion, we suggest that patients who initially exhibit an atypical psychotic profile should be subjected to blood analysis (and most importantly, to cerebrospinal fluid analysis) to determine whether antibodies against neuronal cell surface or synaptic receptors are present, so as to be able to rule out a possible diagnosis of autoimmune encephalitis. The markers that should raise suspicion of the presence of autoimmune encephalitis in a first episode of psychosis include (a) a lack of long-term (cognitive and negative) psychiatric prodromes; (b) an atypical psychotic clinical profile; and (c) hypersensitivity to the side effects of antipsychotic medications. These first signs may help arrive at a differential diagnosis. To investigate whether these markers could be useful for detecting anti-NMDAR encephalitis in

| TABLE 3 | Characteristics of the initial psychotic episode in different entities |
|---------|---------------------------------------------------------------------|
|         | Anti-NMDAR Encephalitis                                           | Cycloid Psychosis                      | Schizophrenia                           |
| Premorbid characteristics | Possible personality cluster C traits. Correlation with neoplasias/viral infections Possible connection with acute stress. | Personality cluster C traits Close family member(s) with epilepsy Possible connection with acute stress. | Cluster A personality disorder (schizotypal). Close family member(s) with psychotic disorder(s). Obstetric and/or perinatal complications. |
| Sex     | Men < Women                                                       | Men < Women                            | Men > Women                              |
| Age     | 5-76 (Mean: 23)                                                  | 15-50 (Mean: 30)                       | Men: 18-25a Women: 25-35a; >40a         |
| Psychiatric prodromes (onset) | Days-Weeks Unnoticed (no functional impairment) | Days-Weeks Unnoticed (no functional impairment) | Months-years (1-5a) Functional deterioration |
| Psychiatric prodromes (phenomenology) | Slight mood swings. Alterations in sleep patterns. | Slight mood swings. Alterations in sleep patterns. | Cognitive symptoms (working memory, verbal memory, and processing speed). Negative symptoms (associability, abulia, anhedonia, affective flattening, and alogia). Diminished (less intense) or brief psychotic symptoms (shorter duration) may appear. |
| Acute phase (presentation) | Acute (hours-days), polysymptomatic, fluctuating | Acute (hours-days), polysymptomatic, fluctuating | Insidious onset, fixed combination of symptoms |
| Acute phase (phenomenology) | Fluctuating consciousness. Mood swings. Paranoid pan-anxiety. Particular concern with death. Polymorphic delusional ideas. Altered thought patterns (forgetfulness/mutism). Hallucinations in all systems (more typically auditory, but more characteristically visual). Alterations in psychomotricity (hyperkinesia-akinisia). | Fluctuating consciousness. Mood swings. Paranoid pan-anxiety. Particular concern with death. Polymorphic delusional ideas. Altered thought patterns (forgetfulness/mutism). Hallucinations in all systems (more typically auditory, but more characteristically visual). Alterations in psychomotricity (hyperkinesia-akinisia). | No alteration in consciousness One or more types of delusional ideas (typically paranoid), generally stable within a single episode. Altered thought patterns. Hallucinations in all systems (most commonly auditory and synesthetic; third-persons auditory hallucinations that make comments or punish, more characteristically; visual hallucinations less common). |
| DUP     | Days- weeks                                                      | Days- weeks                            | Mean: 8.4m/ Median: 3m                   |
| Antipsychotic intolerance | Frequent                                                          | Infrequent                             | Infrequent, varies by sex of patient     |
| ECT response | Variable, it can be partial or transient                          | Good                                   | Variable                                 |
| Evolution | Neurological complications.                                    | Cyclical. Fast resolution of episodes.  | Chronic. Progressive resolution of episodes. |
| Prognosis | Appearance of cognitive interference and decreased impulse control. | Benign in the long term (lesser presence of residual symptoms) | Persistence of negative cognitive symptoms. |

Abbreviations: DUP, Duration of Untreated Psychosis; ECT, Electroconvulsive therapy.
its presentation phase, it would be necessary to undertake prospective comparative studies in which patients presenting a first episode of psychosis are duly evaluated (eg analysis of determination of anti-NMDAR antibodies in the CSF).

**AUTHOR CONTRIBUTIONS**

GS: designed, hypothesized, drafted, and revised the manuscript. BQ: designed and drafted the manuscript. GB: revised the manuscript. CR: revised the manuscript. TR: revised the manuscript. NG: revised the manuscript. D: drafted and revised the manuscript. CP: drafted and revised the manuscript.

**CONFLICT OF INTEREST**

None declared.

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