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SUICIDAL THOUGHTS AND BEHAVIORS IN ANTI-NMDAR ENCEPHALITIS: PSYCHOPATHOLOGICAL FEATURES AND CLINICAL OUTCOMES

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ABSTRACT

Objective: To describe suicidal thoughts and behaviors in a large cohort of Mexican patients diagnosed with definite Anti-NMDA receptor encephalitis (ANMDARE). Methods: Observational and longitudinal study including patients with definite ANMDARE hospitalized at the National Institute of Neurology and Neurosurgery of Mexico between 2014 and 2021. Suicidal thoughts and behaviors were assessed before and after treatment by means of a clinical interview with relatives and a direct clinical assessment with each patient. Thoughts of engaging in suicide-related behavior were registered, as well as acts of suicidal and non-suicidal self-directed violence, before and during the hospitalization. Results: From a total sample of 120 patients who fulfilled the diagnostic criteria for definite ANMDARE, 15 (13%) had suicidal thoughts and behaviors during the acute phase of the disease. All of these patients suffered from psychosis. Suicidal ideation with intention was present in the 15 patients. Three had preparatory behaviors and seven carried out suicidal self-directed violence. Psychotic depression and impulsivity were more frequent in those patients with suicidal thoughts and behaviors than in those without any form of suicidality. Four patients presented self-directed violence during the hospitalization. There was a sustained remission in 14 patients, and only one patient persisted with suicidal ideation and self-directed violence during follow up. Discussion: Suicidal thoughts and behaviors are not uncommon during the acute phase of ANMDARE. According to our sample, the persistence of these features after immunotherapy is rare but may be observed. A targeted assessment of suicidal risk should be strongly considered in this population.

Key words : Suicide, suicidality, suicidal thoughts and behaviors, anti-NMDAR encephalitis, autoimmune encephalitis, autoimmune psychosis, psychosis.

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor encephalitis (ANMDARE) is a frequent form of autoimmune encephalitis, mediated by autoantibodies against the NR1 subunit of the NMDA receptor and characterized by a prominent and polymorphic neuropsychiatric presentation (1). The clinical course is often characterized by an abrupt onset of behavioral and cognitive symptoms, followed by seizures and movement disorders (2). Due to the predominance of neuropsychiatric symptoms such as psychosis, depression, or impulsivity, patients might be seen first by a psychiatrist(3). In a recent study by Espinola-Nadurille et al. that included 100 patients with definite ANMDARE, the most frequent neuropsychiatric syndromes during the acute phase of the disease were psychosis (81%), delirium (75%), catatonia (69%), anxiety-depression (65%), and mania (27%) (4).

Given the high frequency of neuropsychiatric manifestations, patients with ANMDARE could be at an increased risk of suicidal thoughts and behaviors. Psychiatric disorders such as schizophrenia and depression(5); (6), and neurological diseases, such as epilepsy and multiple sclerosis, are known to be associated with an increased risk of suicide (7); (8). Previous reports described suicidal thoughts and behaviors in about 3.5-7% of patients with ANMDARE (9); (10). However, a recent retrospective study with 133 ANMDARE patients in China found that suicidality symptoms were present in 13% of the sample, including 1.5% who died by suicide (11). Suicidal thoughts and behaviors were related to insomnia, aggressiveness, mania, depression, and delusions in that sample.

Our study aims to describe the frequency and associated features of suicidal thoughts and behaviors in a large cohort of Mexican patients diagnosed with definite ANMDARE, and to describe the outcome of patients with suicidality after immunotherapy. Understanding this aspect of mental health in ANMDARE could improve the safety and quality of care provided to these patients and could impact preventable deaths in the population.

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METHODS

Design. We conducted an observational and longitudinal study which was approved by the Institutional Research Committee (Protocol # 53/16) and by the Ethics Committee of the National Institute of Neurology of Mexico (NINN), according to the Declaration of Helsinki in 1975 (as revised in 2008). Informed consent was obtained from patients. Anonymity was preserved in all patients. All the diagnostic and therapeutic procedures described in this article were necessary to fulfill clinical standards of care.

Selection criteria. This cohort included hospitalized patients with definite anti-NMDAR encephalitis who attended the NINN between 2014 and 2021. Sampling was consecutive and patients were included in the study if they fulfilled the Graus criteria for definite anti-NMDA receptor encephalitis (panel 4), including the presence of one or more of six major groups of symptoms, a positive determination of IgG antibodies against the NR1 subunit of NMDA receptor in cerebrospinal fluid (CSF), and a reasonable exclusion of other disorders (12). CSF anti-NMDA receptor antibodies were processed at Labco Nous Diagnostics (Barcelona, Spain), using rat brain immunohistochemistry and cell-based assays with NMDA expressing cells, to prevent false-positive or false-negative results frequently seen in patient's serum(12); (13). All participants underwent a complete neurological and psychiatric examination, including laboratory tests and brain imaging to rule out other causes of their symptoms, as recommended in the current diagnostic criteria(12). These tests included examinations for systemic autoimmune diseases such as anti-double-stranded DNA, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-beta 2 glycoprotein antibodies, and antiphospholipid antibodies, metabolic/endocrine diseases such as vitamin B12, TSH and T4, and infectious diseases, such as HIV and syphilis. Also, we ruled out viral and bacterial central nervous system infections: CSF PCR 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 negative in the current episode of all patients. Other antibodies known to be related to

autoimmune encephalitis were not included due to financial limitations at the study site (in Mexico).

Measures. All clinical measures were obtained before and after the use of immunotherapy. Clinical data were registered prospectively using a structured format, including a broad scope of neurological and psychiatric variables seen in patients with ANMDARE, as detailed elsewhere. (4) Items for suicidal thoughts and behaviors are part of this instrument. These have been classified according to the Self-Directed Violent Classification System (SDVCS) developed and promulgated by the US Department of Veterans Affairs and Department of Defense (14) Information regarding suicidal ideation and self-directed violence is gathered through clinical interviews with relatives and direct clinical assessment with each patient. Assessments occurred at admission (before receiving pharmacological treatment and immunotherapy), and at discharge. We registered thoughts of engaging in suicide-related behavior if the patient declared those thoughts explicitly and unambiguously. We classified these thoughts as suicidal ideation with suicidal intent, and suicidal ideation without suicidal intent. Suicidal Self-Directed Violence occurring before the hospitalization was registered according to the relative's information, including the description of the specific behavior. As the patients with encephalitis may have erratic behaviors leading to accidental non-suicidal self-directed violence, Suicidal Self-Directed Violence was considered only if the self-harm behavior was accompanied by explicit verbal exchange revealing thoughts of engaging in suicide-related behavior. Acts of Self-Directed Violence were also registered during hospitalization. We used the DSM-5 criteria to diagnose psychiatric disorders such as depression, catatonia, and delirium. The full neuropsychiatric assessment of these patients includes a series of psychometrical scales and inventories, besides cognitive screening tests, (discussed elsewhere)(4). Sociodemographic variables, including socio-economic status, as determined by the social work department (a score of 1 is indicative of a very low socio-economic status, 2 is a low status, 3 is a middle-low status, 4 is a middle status, 5 is a middle-high status, and 6 is indicative of a high socio-economic status), were also registered.

Statistical Analysis. Descriptive statistics and normality tests (Kolmogorov-Smirnov test) were obtained. Wilcoxon tests and chi-square tests were used to compare patients with and without suicidal thoughts and behaviors. Bonferroni corrections for multiple comparisons were used to reduce the probability of type I errors. Data analysis was performed with the SPSS software (21 version).

RESULTS

General features of the sample. We included 120 patients with definite ANMDARE: 15(13%) presented some form of suicidal thoughts and behaviors. This subgroup had a median age was 32 (with a range between 19 and 48) and 53% were female. This subgroup had a median age was 32 (with a range between 19 and 48) and 53.3% were female.

Clinical features of patients with suicidal thoughts and behaviors. As seen in **table 1**, suicidal ideation was present in each of the 15 cases; of these, 12/15 had suicidal ideation with intent; 3/15 patients had preparatory behaviors, and 7/15 engaged in suicidal self-directed violence. All patients had psychotic features: 10/15 had psychotic depression, 14/15 had delusions (9 persecutory, 6 grandiose, 5 nihilistic, and 3 jealousy), and 11/15 reported hallucinations (10 visual and 9 auditory). Delirium and catatonia were observed in 13 and 8 patients, respectively. Interestingly, 5/15 patients were experiencing a relapse of ANMDARE.

Regarding their psychiatric past history, only one patient had received specialized attention due to self-harm and a history of repeated sexual abuse. Three patients had suffered intimate partner violence, and five reported alcohol and/or tobacco abuse. 8/15 had an unstable family situation, and 5/15 had a background of domestic violence.

Routine examinations showed that 7/15 had abnormal CSF inflammatory findings; 8/15 had MRI abnormalities involving the medial temporal lobe; and 15/15 had an abnormal EEG (generalized slowing was present in all patients).

Comparison of patients with and without suicidality. As seen in table 2, patients with suicidality were older and more frequently married (or within a stable relationship) than those without suicidal behaviors. Psychotic depression, insomnia, and impulsivity, as well as being diagnosed with a relapse of the disease, were significantly associated with suicidality. However, after Bonferroni correction for multiple comparisons, only psychotic depression (66.7% vs 10.5%, p <0.001) and impulsivity (86.7% vs 42.9%, p= 0.001) remained significant.

The clinical course of patients with suicidal thoughts and behaviors. During the hospitalization, 4/15 patients presented repetitive acts of self-directed violence, including head banging, cutting their own neck or the forearms, trying to use sheets or towels to hang themselves, and injuring themselves with objects such as pens.13/15 patients received treatment with IV methylprednisolone, 10/15 received plasmapheresis, and 7/15 received immunoglobulin. Regarding psychopharmacological agents, 14/15 patients received an antipsychotic, 12/15 received lorazepam, and 4/15 received dexmedetomidine. At discharge, self-directed violence thoughts and behaviors remitted completely in 14 patients. Long-term follow-up confirmed the absence of suicidal thoughts and behaviors after hospitalization. Follow-up visits were provided within a median of 43 months (with a range between 12 and 92 months). One patient (patient 13) persisted with episodic psychiatric disturbances after hospitalization, including thoughts of engaging in suicide-related behavior, and acts of non-suicidal self-directed violence.

Observations on patient 13. She had a relevant psychosocial and behavioral history, including a repeated sexual abuse in her childhood and non-suicidal self-directed violence (cutting). However, she had never attempted suicide until the onset of the psychotic phase of ANMDARE. She improved significantly after immunotherapy but remained with residual symptoms, including mild anxiety and depression that were exacerbated with interpersonal stress, leading to a chronic, episodic course of psychosis with auditory verbal hallucinations, thoughts of engaging in suicide-related behavior, and non-suicidal self-directed violence.

Only partial response has been observed after psychotherapy and pharmacological therapy (including an antipsychotic and an antidepressant).

DISCUSSION

Our study suggests that suicidal thoughts and behaviors are not uncommon during the acute phase of ANMDARE, mainly in psychotic patients with depression and impulsivity; persistence of suicidality after immunotherapy was rare. These key points require further discussion.

Suicidal thoughts and behaviors are not uncommon in ANMDARE. In our sample, 12.5% of the patients with ANMDARE presented some form of suicidality, which is consistent with the study by Zhang et al. where suicidality was observed in 13% of 133 ANMDARE patients from China: 7 (41%) with suicidal ideation and 8 (46%) with suicidal attempt. Strikingly, 11% of the patients died by suicide in that study (11). No patients died by suicide in our sample. In the Zhang et al. report, patients with suicidality presented initially with more prominent psychiatric symptoms, including delusions, mania, insomnia, aggression, and depression, than those without (11). In our sample, all patients exhibited psychotic symptoms, highlighting the concept of autoimmune psychosis (15), which provides an operational approach to identify patients with psychosis which are in a high risk of having an immunological condition.

In the bivariate analysis, patients with suicidal thoughts and behaviors from our sample were characterized by a later age of onset and a higher frequency of psychotic depression, delusions, insomnia, and impulsivity. After correcting for multiple comparisons, our current hypothesis is that psychotic depression and impulsivity are psychopathological features with a significant relationship with suicidal thoughts and behaviors in patients with ANMDARE.

Suicidality in ANMDARE might improve after immunotherapy: In our study, suicidal thoughts and behaviors remitted completely in 14/15 patients after immunotherapy, after long term follow up. This suggests a causal mechanism of the anti-NMDAR antibodies in most patients from our sample, and it also highlights the need for more research on the relationship between suicidal behavior, inflammation and neurological disease. (16); (17) The activation of the kynurenine pathway and modification of different metabolites (quinolinic and kynurenic acid) with effects on glutamate transmission, has been hypothesized as a biological mechanism related to suicidal behavior. Quinolinic acid, a potent NMDA receptor agonist, is increased in the CNS of suicidal patients, providing a neurobiological hypothesis for the rapid effect of ketamine on suicidal behavior(16). Although the neurobiological mechanism of suicidal behavior in ANMDARE remains to be elucidated, our findings support the hypothesis that antibodies may increase or decrease the biological signaling mediated by NMDAR in the different stages of the disease(18).

Multicausality and complexity of suicidality in ANMDARE. One patient (6%) with a relevant past psychiatric history (repeated sexual abuse in childhood) persisted with suicidal ideation during follow-up. It is worth mentioning that even if our patient had a history of non-suicidal self-directed violence, the psychopathological features of the patient changed significantly after ANMDARE, with the appearance of auditory verbal hallucinations and suicidal thoughts and behaviors, and with a worsening of the self-directed violence. Zhang et al. also reported two patients who presented suicidal thoughts and behaviors after the acute phase of the disease (11), which would be in line with the increased frequency of affective and cognitive symptoms observed following ANMDARE (19); (20). This also calls for an awareness of the potential interactions between the specific neurobiological effects of the anti-NMDAR antibodies and the psychosocial background. A subset of the patients in our sample had relevant personal histories, including repeated sexual abuse (1/15), intimate partner violence (3/15) and domestic violence (5/15). Although the suicidality relapse rate in our sample was low (1/15) and even if ANMDARE is a well-defined neurological disease, we cannot rule out the possibility that there might be biopsychosocial interactions in a subset of patients leading to atypical and unfavorable outcomes.

Strict screening should be recommended across the stages of ANMDARE. Although probably triggered by different pathophysiological mechanisms, suicidality in ANMDARE can occur in different contexts, particularly the acute phase and relapses (11). In our study, 10 (66%) patients presented some form of suicidality as a presentation of the first episode, but 5 (33%) did it during a relapse of the disease. Also, Zhang et al. reported suicidality across different stages of the disease: 10 of 17 presented suicidal thoughts and behaviors prior to admission, 3 during the hospital stay, 2 after discharge, and 2 during relapse. As suicidal thoughts and behaviors represent a potentially lethal risk, clinicians evaluating patients with or suspicion of ANMDARE must strictly and routinely screen and assess suicide risk across the different phases of the disease. Also, staff with mental health experience should be involved whenever necessary.

Suicidality in neurological patients and patients with psychosis. According to our results and previous reports (9)–(11), ANMDARE shares an increased risk of suicidality with other neurological diseases. This is consistent with the research that has been done in patients with neurological diseases leading frequently to cognitive dysfunction and psychotic features. For instance, the risk of suicide is increased in patients with a dementia diagnosis in the first year after diagnosis as compared to the general geriatric population, in a large cohort study(21). A recent Danish study by Erlangsen et al., including more than 7.3 million individuals, found a suicide rate in patients diagnosed with a neurological disorder of 44 per 100 000 person-years compared with 20.1 per 100 000 person-years among individuals not diagnosed with a neurological disorder(17). Importantly, patients with encephalitis demonstrated a higher suicide rate [fully adjusted incidence rate ratio (faIRR) 1.7 (IC 95% 1.3-2.3)] than patients with stroke [faIRR 1.3 (IC 95% 1.2-1.3)] but similar to those with epilepsy [faIRR 1.7 (IC 95% 1.6-1.8)] and Parkinson disease epilepsy [faIRR 1.7 (IC 95% 1.5-1.9)] (17). Interestingly, suicidal thoughts and behaviors have been reported following other forms of encephalitis such as encephalitis due to Herpes Simplex Virus (HSV), encephalitis lethargica, and other forms of autoimmune encephalitis. (22); (23) This

highlights the need to ensure more routine suicide risk screening and assessment by clinicians caring for patients with neurological conditions.

The presence of psychosis in all the patients with suicidal thoughts and behaviors from our sample is consistent with the well-replicated epidemiological relationship between suicide and psychotic disorders(6). Recent studies showed that suicide rate in schizophrenia is 352 per 100 000 person-years; while in bipolar depression, it is 237 per 100 000 person-years(6), highlighting the fact that both affective and nonaffective psychoses are associated with an increased risk of suicide.

Overall, this study provides important insights into the mental health of those in the acute stage of ANMDARE. Raising awareness and encouraging risk assessments in these patients among diagnosing and treating clinicians can help reduce morbidity and mortality in this patient group. The impact on families, friends and communities following suicide is devastating and far-reaching. The WHO also outlines the importance of suicide -prevention not only for individuals and families directly affected but also for the benefit and well-being of communities, our health-care systems and society at large(24).

Limitations of the study. Cognitive dysfunction and catatonic states interfered with our capacity to make in-depth interviews to provide a better understanding of the patients' motivations for suicidal and non-suicidal self-directed violence. After the acute episode of encephalitis, most patients were unable to provide a clear recollection of the mental state during the psychiatric episodes in which suicidal thoughts and behaviors appeared. The observational nature of the design is not appropriate to make strong inferences regarding the neurobiological mechanisms related to suicidality, or about the efficacy of immunotherapy in this population, and the small sample size limits the generalizability of the results.

Conclusions. According to our study, suicidality is not uncommon during the acute phase of ANMDARE, including both first episodes and relapses. Clinicians must be aware of this potentially lethal risk, particularly in those presenting with symptoms of psychotic depression. Although the persistence of suicidal thoughts and behaviors after immunotherapy is rare, we

encourage a long-term risk assessment for suicidal and no-suicidal self-directed violence throughout the different stages of the disease.

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Table 1. Clinical features of the patients with suicidal thoughts and behaviors in a Mexican cohort of anti-NMDAR encephalitis.

Demographics	Suicidal ideation	Suicidal Attempt	Self-Directed Violence during hospitalization	Follow up
Patient 1	Suicidal ideation, with intent, and preparatory behavior	Absent	Present	Remitted
Patient 2	Suicidal ideation, with intent, and preparatory behavior	Present. Medication overdose.	Absent	Remitted
Patient 3	Suicidal ideation, with intent	Present	Absent	Remitted
Patient 4	Suicidal ideation, with intent	Absent	Absent	Remitted
Patient 5	Suicidal ideation, with intent	Absent	Absent	Remitted
Patient 6	Suicidal ideation, with intent	Absent	Absent	Remitted
Patient 7	Suicidal ideation, with intent	Absent	Absent	Remitted
Patient 8	Suicidal ideation, with intent	Absent	Absent	Remitted
Patient 9	Suicidal ideation, with intent	Present. Went up to the roof of her house and tried to jump	Absent	Remitted
Patient 10	Suicidal ideation, with intent	Absent	Absent	Remitted
Patient 11	Suicidal ideation, with intent	Absent	Absent	Remitted
Patient 12	Suicidal ideation, with intent	Present	Present	Remitted
Patient 13	Suicidal ideation, with intent	Present. Tried to cut her wrists with a razor	Present	Persisted
Patient 14	Suicidal ideation, with intent, and preparatory behavior	Present. He crossed avenues with heavy traffic and tried to shoot himself with a gun	Present	Remitted
Patient 15	Suicidal ideation, with intent	Tried to throw herself off the roof	Absent	Remitted

Table 2. Comparison of ANMDARE patients with and without suicidal behavior

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Variable	Patients with suicidality (n= 15)		Patients without suicidality (n= 105)		P
Age, median (range)	32	19-48	25	15-73	0.005
Female sex, n (%)	8	53 %	51	48 %	0.730
Stable couple, n (%)	9	60 %	34	32 %	0.037
Socioeconomic status, median (range)	2	1-4	2	1-5	0.435
Currently unemployed, n (%)	3	20 %	7	6 %	0.081
Psychotic syndrome, n (%)	15	100 %	84	80 %	0.057
Depressive syndrome, n (%)	10	66 %	11	10 %	<0.001 *
Delirium, n (%)	13	86 %	79	75 %	0.328
Catatonia, n (%)	8	53 %	70	66 %	0.311
Impulsivity, n (%)	13	86 %	45	42 %	0.001 *
Insomnia, n (%)	15	100 %	66	62 %	0.004
Seizures, n (%)	6	40 %	65	61 %	0.106
Dyskinesia, n (%)	6	40 %	67	63 %	0.077
Relapse, n (%)	5	33 %	12	11 %	0.023

424 * Significant after Bonferroni correction for multiple comparisons (0.05/14 = 0.003)

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