Stress is Associated with Severe Anti-NMDA Receptor Encephalitis: A Single-Center Retrospective Cohort Study

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Research

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Abstract

Background: Stress was reported to trigger and exacerbate a lot of autoimmune diseases. The underlying mechanisms include disturbed hormone homeostasis, dysregulated immune function, neuroinflammation by macrophages and microglia, and so on. There have been case reports of stress-induced anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis (anti-NMDARE). To elucidate the association between stress events and anti-NDMARE, we conducted a retrospective single-center cohort study.

Materials and Methods: All severe anti-NMDARE patients admitted to neuro-intensive care unit (NICU) of Nanfang Hospital between September 2013 and July 2020 were screened. The stress events within 1 year before the onset were evaluated by a questionnaire survey using the Chinese Life Event Scale. The demographic information, clinical features, laboratory results and prognosis were collected and compared between patients with and without life stress events (LSE). Patients were further classified based on the existence of teratoma and herpes viruses in cerebrospinal fluid to investigate the association between stress and anti-NMDARE.

Results: Of the 26 severe anti-NMDARE patients, 9 (34.6%) patients reported LSE. Among them, 5 (55.6%) had family stress, 3 (33.3%) had work stress and 1 (11.1%) had both family and work stress. No significant differences were observed in disease severity upon admission, NICU stay time, mechanical ventilation time or other laboratory results. The comorbid rate of teratoma and herpes virus was not significantly different between patients with and without LSE. However, 7 of the patients without teratoma and herpes virus (7/17, 41.2%) experienced LSE before the disease onset. The prognosis of patients with LSE was significantly better than that of patients without LSE (P=0.023).

Conclusions: Up to 34.6% of severe anti-NMDARE patients had LSE within 1 year before the onset, which might even be underestimated. This study suggested that stress might be another risk factor for anti-NMDARE besides teratoma and herpes virus. Neurologists should pay attention to the stress of the patients and provide psychological therapy to the patients.

Introduction

Anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis (anti-NMDARE) was first reported in 2007. Since then, it was widely reported in young women with ovarian teratomas [1]. It is now recognized as a neuro-inflammatory disease mediated by autoantibodies to the NMDAR GluN1 subunit. The antibodies cross-link NMDAR, change its surface dynamics and interaction with other synaptic proteins, inhibit receptor internalization, and lead to severe impairment of synaptic plasticity and NMDAR network function [2]. It is well known that anti-NMDARE may be associated with teratoma and herpes virus infection [3], and also, there are reports in the literature that stress can induce anti-NMDARE [4, 5].

Stress occurs when people's needs exceed their psychosocial resources or adaptability. Some acute life events, such as the death of relatives, long-term work challenges, can be a source of demand or stress [6].

There is now a lot of convincing evidence that acute stress can stimulate plasma inflammatory response. Life stress events (LSE) have widely reported to be associated with the severity and progression of many diseases, including depression, cardiovascular disease, human immunodeficiency virus /acquired immunodeficiency syndrome infection, chronic obstructive pulmonary disease, breast cancer, asthma, toxic diffuse goiter, and autoimmune diseases [7–15].

There has been a case reported that emotional stress-related factors induce anti-NMDARE [4]. To evaluate the correlation between stress and severe anti-NMDARE, and to elucidate the clinical features of severe anti-NMDARE with LSE, we conducted this retrospective single center cohort study.

Materials And Methods

Study design and participants

We screened all patients diagnosed with anti-NMDARE who were admitted to the neuro-intensive care unit (NICU) of Nanfang Hospital, a university-affiliated academic hospital, between September 2013 and July 2020. The diagnostic criteria for anti-NMDARE were as follows: rapid onset (less than 3 months) of one or more of the six major groups of symptoms, including abnormal (psychiatric) behavior or cognitive dysfunction, speech dysfunction (pressured speech, verbal reduction, and mutism), seizures, movement disorders (dyskinesias or rigidity/abnormal postures), decreased level of consciousness, and autonomic dysfunction or central hypoventilation; the presence of anti-NMDAR antibodies in cerebrospinal fluid (CSF); reasonable exclusion of other disorders [16]. Severe anti-NMDARE was defined as fulfilling one or more of following criteria: respiratory failure requiring endotracheal intubation and/or mechanical ventilation (MV); disturbance of consciousness; status epilepticus [17]. Exclusion criteria included: secondary anti-NMDARE; history of psychological or psychiatric illness; loss to follow-up.

A questionnaire survey about the patients was conducted on the family members upon admission and a retrospective survey was conducted on the patients themselves after recovery using the Chinese Life Event Scale (LES). LES was compiled by Yang et. al. according to China’s national conditions. There are a total of 50 items, of which 48 are mainly family life items (28), work or study items (13) and social life items (7). These are three common life events in our country. The other two blank items are filled in by the subjects according to their personal circumstances [18] . Each item got one point and the sum of the scores was defined as LSE score. If a patient or family member reported a positive event within one year before the onset of the disease, the patient was defined as LSE+.

This study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University. Informed consent was waived by the review board because this study was observational and retrospective, and all data were fully de-identified.

Data collection

Electrical medical records were carefully reviewed to collect the patients' information including demographic information, teratomas, Glasgow coma scale (GCS) score on admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, laboratory results, immunotherapy protocol (steroids, intravenous immunoglobulins (IVIG), plasma exchange (PE)), LSE scores, length of NICU stay, duration of MV, and the modified Rankin Scale (mRS) score of 6-month after discharge. Information on functional status after discharge was obtained through telephone interview or clinic interview by a trained neurologist blinded to the study data. We defined mRS≤2 as a good prognosis, while mRS ≥3 as a poor prognosis.

Statistical analysis

Student's t-test was used to compare data for continuous variables. Mann-Whitney and Chi-Squared tests were used to compare data for non-continuous and categorical variables between the two groups. A p-value < 0.05 was considered statistically significant. SPSS statistical software v.22 was used for the statistically analysis.

Results

Of 29 patients screened for eligibility, 26 fulfilled the inclusion and exclusion criteria (Fig. 1). In this cohort, 9 patients (9/26, 34.6%) were reported to have experienced LSE within one year before the disease onset. In the LSE+ group, 5 patients reported family stress (55.6%), 3 patients reported work stress (33.3%) and 1 patient reported stress from both family and work (11.1%). Seven patients (77.8%) had an LSE score of 1, one patient (11.1%) had a score of 2, and one patient (11.1%) had a score of 3.

The clinical characteristics were compared between the patients with and without LSE (Table 1). There were no significant differences between the two groups in terms of demographic characteristics, APACHE II score, GCS score, teratoma incidence, NICU stay, mechanical ventilation time and laboratory results of complete blood count (CBC) and CSF results. One LSE+ patient had an extremely long NICU stay [19], and she was excluded from the analysis of NICU stay and MV time to avoid bias.

The association between teratomas, herpes virus and LSE was shown in Table 2. There was no significant difference in the incidence of teratoma between the two groups (P=0.357), though the proportion seemed lower in LSE+ group (1/9, 11.1%) than that (6/17, 35.3%) in LSE- group. And also, the comorbidities of herpes virus detection revealed no significant difference between the two groups (P=1.000). Comorbidities of teratomas or herpes virus revealed no significant difference between the two groups (P=0.418). It is worth noting that among patients without teratoma and herpes virus, 7 (7/17, 41.2%) had LSE.

All the patients received first-line treatment, including teratoma resection if exists, steroids, IVIG, and PE. There was no significant difference in treatment strategies between the two groups. During follow-up, 18 patients (18/26, 69.2%) achieved a good prognosis. In the LSE+ group, all patients (100%) achieved a

good prognosis, while only 52.9% of LSE- patients achieved a good prognosis. The prognosis of LSE+ patients was significantly better than that of patients without LSE (P=0.023).

Discussion

In this retrospective cohort study, we found that in severe anti-NMDARE patients, as high as 34.6% patients had experienced LSE within one year before the disease onset. Since some patients could not provide information by themselves, this incidence could still be underestimated. Patients with LSE seemed to achieve a better prognosis than those without LSE.

Stress has been reported to trigger and exacerbate a lot of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, Graves' disease as well as other autoimmune conditions [20]. And also patients with stress-related disorders were at increased risk of autoimmune disease [20, 21]. A large number of studies have tried to elucidate the underlying mechanisms of stress and various autoimmune diseases. The suggested hypotheses included disturbed homeostasis, neuroinflammation by macrophages and microglia, and evoked humoral immune response [20, 22].

Rare studies have reported the association between stress and anti-NMDARE, and the mechanism was still unclear [5, 23, 24]. Obi CA and their colleagues suggested that emotional stress triggered immune dysregulation, which ultimately resulted in anti-NMDARE [4]. The other suggested mechanism was the preexisting anti-NMDAR antibody in the peripheral blood [25, 26]. Under some stress inducers, the integrity of blood-brain barrier (BBB) was disrupted and the antibody was passed through the barrier, causing the disease [5]. In animal models, restraint stress mediates time-dependent alterations in the permeability of the BBB [27]. Acute psychosocial stress also has proinflammatory effects mediated by activation of mast cells and is associated with BBB opening [28]. Maladaptation of the BBB to persisting and/or severe stressors may contribute to detrimental health outcomes [29]. In this study, we found that as high as 34.6% of severe anti-NMDARE patients reported LSE before the disease onset, which could still be underestimated. We have no idea whether the disease was attributed to the stress induced immune-dysregulation or stress induced BBB leakage with preexisting serum antibody. However, we did find an association between stress and severe anti-NMDARE clinically, and more research was warranted to investigate the exact mechanism.

There was no significant difference in the comorbidities of teratoma and herpes virus between LSE + and LSE- groups. Nevertheless, 41.2% of the patients without teratoma and herpes virus experienced LSE before disease onset, which indicated that stress might be another risk factor for anti-NMDARE besides teratomas and herpes virus. For anti-NMDARE patients, psychological therapy and stress management should be considered to prevent stress-induced immune dysregulation, as this might help prevent relapse.

Another interesting phenomenon in this study was that patients with LSE revealed a better prognosis although there was no significant difference in disease severity at admission. The underlying reasons were unclear. The relatively low incidence of teratoma in the LSE + group was a possible reason, avoiding

with surgery damage. The second possible reason could be that for most patients, stress was discontinued after the diseases since most patients were unconscious. Another possible reason was that patients with poor prognosis could not provide LSE information by themselves, and the LSE survey was conducted on their family members, which could cause bias. Therefore, this prognosis result should be interpreted with caution and more studies are needed to elucidate the problem.

This study has some limitations. First, this is a single-center retrospective study with a very limited sample size. Secondly, this study only focused on severe patients. Third, the stress assessment was recalled by patients and/or family members, which might introduce bias. Due to all the limitations, some results of the study should be interpreted with caution and more research is required.

Conclusions

In this study, we found that 34.6% of severe anti-NMDARE patients had stress events within one year before the onset of the disease, which might be still underestimated. As high as 41.2% of the patients without teratoma and herpes virus experienced LSE before the disease onset, which suggested that stress might be another risk factor for anti-NMDARE in addition to teratomas and herpes virus. Neurologists should pay attention to the stress events of anti-NMDARE patients, and psychological therapy should be considered during maintenance therapy.

Abbreviations

anti-NMDAR: anti-N-methyl-d-aspartate receptor**; anti-NMDARE:** anti-N-methyl-d-aspartate receptor encephalitis**;** APACHE: Acute Physiology and Chronic Health Evaluation; BBB: blood-brain barrier; CBC: complete blood count; CSF: cerebrospinal fluid; GCS: Glasgow coma scale; IVIG: intravenous immunoglobulins; LES: Life Event Scale; LSE: Life stress events; mRS: modified Rankin Scale; MV: mechanical ventilation; NICU: neuro-intensive care unit; PE: plasma exchange

Declarations

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Authors' contributions:

DW, YW, and SW are responsible for concepts and design. KH, ZL and XZ are are responsible for data collecting. NW and YP are responsible for statistical analysis and result interpretation. All authors contributed to the article and approved the submitted version. All authors acquired, analyzed, and interpreted the data. The manuscript was prepared by DW and NW.

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Availability of data and materials

The data of the study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University. Informed consent was waived by the review board because this study was observational and retrospective, and all data were fully de-identified.

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests.

References

1. Dalmau J, Tüzün E, Wu H-y, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, et al: **Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma.** *Annals of Neurology* 2007, **61:**25-36.
2. Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, Geis C, Lancaster E, Titulaer MJ, Rosenfeld MR, Graus F: **An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models.** *The Lancet Neurology* 2019, **18:**1045-1057.
3. DeSena A, Graves D, Warnack W, Greenberg BM: **Herpes Simplex Encephalitis as a Potential Cause of Anti–N-Methyl-d-Aspartate Receptor Antibody Encephalitis.** *JAMA Neurology* 2014, **71:**344.
4. Obi CA, Thompson E, Mordukhaev L, Khan I, Zhang NJ: **Anti-N-methyl-d-aspartate receptor encephalitis triggered by emotional stress.** *Baylor University Medical Center Proceedings* 2019, **32:**605-606.
5. Vahabi Z, Etesam F, Zandifar A, Badrfam R: **Psychosocial stress, blood brain barrier and the development of anti N-methyl-D-aspartate receptor (NMDAR) encephalitis.** *Multiple Sclerosis and Related Disorders* 2021, **50:**102876.
6. Steptoe A, Kivimäki M: **Stress and cardiovascular disease.** *Nature Reviews Cardiology* 2012, **9:**360-370.
7. Cohen S, Murphy MLM, Prather AA: **Ten Surprising Facts About Stressful Life Events and Disease Risk.** *Annual Review of Psychology* 2019, **70:**577-597.

8. Chilunga FP, Boateng D, Henneman P, Beune E, Requena-Mendez A, Meeks K, Smeeth L, Addo J, Bahendeka S, Danquah I, et al: **Perceived discrimination and stressful life events are associated with cardiovascular risk score in migrant and non-migrant populations: The RODAM study.** *Int J Cardiol* 2019, **286:**169-174.
9. Kendler KS, Karkowski LM, Prescott CA: **Causal relationship between stressful life events and the onset of major depression.** *Am J Psychiatry* 1999, **156:**837-841.
10. Lu Y, Nyunt MS, Gwee X, Feng L, Feng L, Kua EH, Kumar R, Ng TP: **Life event stress and chronic obstructive pulmonary disease (COPD): associations with mental well-being and quality of life in a population-based study.** *BMJ Open* 2012, **2**.
11. Bahri N, Fathi Najafi T, Homaei Shandiz F, Tohidinik HR, Khajavi A: **The relation between stressful life events and breast cancer: a systematic review and meta-analysis of cohort studies.** *Breast Cancer Res Treat* 2019, **176:**53-61.
12. Pence BW, Raper JL, Reif S, Thielman NM, Leserman J, Mugavero MJ: **Incident stressful and traumatic life events and human immunodeficiency virus sexual transmission risk behaviors in a longitudinal, multisite cohort study.** *Psychosom Med* 2010, **72:**720-726.
13. Lietzen R, Virtanen P, Kivimaki M, Sillanmaki L, Vahtera J, Koskenvuo M: **Stressful life events and the onset of asthma.** *Eur Respir J* 2011, **37:**1360-1365.
14. Porcelli B, Pozza A, Bizzaro N, Fagiolini A, Costantini M-C, Terzuoli L, Ferretti F: **Association between stressful life events and autoimmune diseases: A systematic review and meta-analysis of retrospective case–control studies.** *Autoimmunity Reviews* 2016, **15:**325-334.
15. Winsa B, Adami HO, Bergström R, Gamstedt A, Dahlberg PA, Adamson U, Jansson R, Karlsson A: **Stressful life events and Graves' disease.** *Lancet* 1991, **338:**1475-1479.
16. Xu X, Lu Q, Huang Y, Fan S, Zhou L, Yuan J, Yang X, Ren H, Sun D, Dai Y, et al: **Anti-NMDAR encephalitis: A single-center, longitudinal study in China.** *Neurol Neuroimmunol Neuroinflamm* 2020, **7**.
17. Wang D, Su S, Tan M, Wu Y, Wang S: **Paroxysmal Sympathetic Hyperactivity in Severe Anti-N-Methyl-d-Aspartate Receptor Encephalitis: A Single Center Retrospective Observational Study.** *Front Immunol* 2021, **12**.
18. D Y, Y Z: **Life Event Scale.Mental Health Assessment Scale Manual.** *Chin Ment Health J* 1993, **3:**39–41.
19. Wang D, Wu Y, Ji Z, Wang S, Xu Y, Huang K, Peng Y, Zheng H, Wang H, Zhang X, Pan S: **A refractory anti-NMDA receptor encephalitis successfully treated by bilateral salpingo-oophorectomy and intrathecal injection of methotrexate and dexamethasone: a case report.** *Journal of International Medical Research* 2020, **48:**030006052092566.
20. Sharif K, Watad A, Coplan L, Lichtbroun B, Krosser A, Lichtbroun M, Bragazzi NL, Amital H, Afek A, Shoenfeld Y: **The role of stress in the mosaic of autoimmunity: An overlooked association.** *Autoimmunity Reviews* 2018, **17:**967-983.

21. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, Almqvist C, Fall K, Valdimarsdóttir UA: **Association of Stress-Related Disorders With Subsequent Autoimmune Disease.** *Jama* 2018, **319:**2388.
22. Marsland AL, Walsh C, Lockwood K, John-Henderson NA: **The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis.** *Brain, Behavior, and Immunity* 2017, **64:**208-219.
23. Pan H, Oliveira B, Saher G, Dere E, Tapken D, Mitjans M, Seidel J, Wesolowski J, Wakhloo D, Klein-Schmidt C, et al: **Uncoupling the widespread occurrence of anti-NMDAR1 autoantibodies from neuropsychiatric disease in a novel autoimmune model.** *Molecular Psychiatry* 2018, **24:**1489-1501.
24. Pan H, Steixner-Kumar AA, Seelbach A, Deutsch N, Ronnenberg A, Tapken D, von Ahsen N, Mitjans M, Worthmann H, Trippe R, et al: **Multiple inducers and novel roles of autoantibodies against the obligatory NMDAR subunit NR1: a translational study from chronic life stress to brain injury.** *Molecular Psychiatry* 2020.
25. Zerche M, Weissenborn K, Ott C, Dere E, Asif AR, Worthmann H, Hassouna I, Rentzsch K, Tryc AB, Dahm L, et al: **Preexisting Serum Autoantibodies Against the NMDAR Subunit NR1 Modulate Evolution of Lesion Size in Acute Ischemic Stroke.** *Stroke* 2015, **46:**1180-1186.
26. Hammer C, Stepniak B, Schneider A, Papiol S, Tantra M, Begemann M, Sirén AL, Pardo LA, Sperling S, Mohd Jofrry S, et al: **Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood–brain barrier integrity.** *Molecular Psychiatry* 2013, **19:**1143-1149.
27. Xu G, Li Y, Ma C, Wang C, Sun Z, Shen Y, Liu L, Li S, Zhang X, Cong B: **Restraint Stress Induced Hyperpermeability and Damage of the Blood-Brain Barrier in the Amygdala of Adult Rats.** *Frontiers in Molecular Neuroscience* 2019, **12**.
28. Hendriksen E, van Bergeijk D, Oosting RS, Redegeld FA: **Mast cells in neuroinflammation and brain disorders.** *Neuroscience & Biobehavioral Reviews* 2017, **79:**119-133.
29. Segarra M, Aburto MR, Acker-Palmer A: **Blood–Brain Barrier Dynamics to Maintain Brain Homeostasis.** *Trends in Neurosciences* 2021, **44:**393-405.

Tables

Table 1 The clinical features of the patients

	LSE+ (n=9)	LSE- (n=17)	*p*
Gender (female), n (%)	6 (66.7%)	12 (70.6%)	1.0[c]
Age (years), mean±SD	28.67±11.09	26.35±10.40	0.603 [a]
*Time of NICU stay (days), median (IQR)	23.5 (0.75, 36.25)	25 (7.5, 68.5)	0.771 [b]
*Mechanical ventilation time (hours), median (IQR)	26 (0,336)	17 (0,432)	0.734 [b]
6-month mRS≤2, n (%)	9 (100%)	9 (52.9%)	0.023 [c]
Teratoma, n (%)	1 (11.1%)	6 (35.3%)	0.357 [c]
First-line therapy, n (%)			
Steroids	7 (77.7%)	11 (64.7%)	0.667 [c]
IVIG	7 (77.7%)	16 (94.1%)	0.268 [c]
PE	7 (77.7%)	14 (82.4%)	1.0 [c]
CSF results			
WBC (cells/μL), median (IQR)	2 (0, 36.5)	4 (0, 45)	0.442 [b]
Total protein (g/L), median (IQR)	0.21 (0.15, 0.28)	0.23 (0.17, 0.295)	0.787 [b]
Glucose (mmol/L), median (IQR)	3.43 (3.01, 4.22)	3.9 (3.60, 4.39)	0.235 [b]
CSF herpes virus detection, n (%)	1 (11.1%)	2 (11.8%)	1.0 [c]
CBC results			
WBC (G/L), mean±SD	10.4±3.57	10.0±3.82	0.800 [a]
Lymphocytes (G/L), mean±SD	1.39±0.52	1.53±0.77	0.621 [a]
Neutrophils (G/L), mean±SD	8.37±3.25	7.62±4.06	0.639 [a]

[a], Student's t-test; [b], Mann-Whitney test; [c]: Chi-square test.

* Exclude one patient for her extremely long hospital stay and NICU stay.

Abbreviations: CBC, complete blood count; CSF, cerebrospinal fluid; IQR, interquartile range; IVIG, intravenous immunoglobulins; LSE, life stress events; mRS, modified Rankin Scale; PE, plasma exchange;

WBC, white blood cell.

Table 2: The association between teratomas, CSF herpes virus and LSE in the patients

		LSE, n		P*
		Yes	No	
Teratomas	Yes	1	6	0.357
	No	8	11	
CSF herpes virus	Yes	1	2	1.000
	No	8	15	
Teratomas or CSF herpes virus	Yes	2	7	0.418
	No	7	10	

*, Chi-square test;

Abbreviations: CSF, cerebrospinal fluid; LSE, life stress events.

Figures

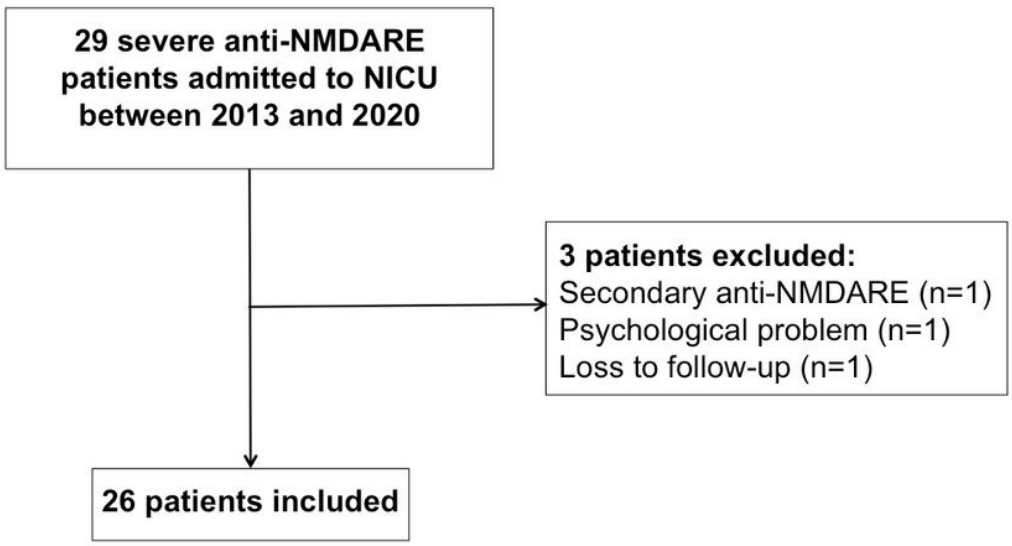

Figure 1

Flow chart of enrolled patients. anti-NMDARE, anti-N-methyl-d-aspartate receptor encephalitis; NICU, neuro-intensive care unit.