

Characteristics and Outcomes of Autonomic Dysfunction in Anti-NMDAR Encephalitis

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Abstract

Background

To explore the characteristics and prognosis of autonomic dysfunction and paroxysmal sympathetic hyperactivity (PSH), and evaluate the efficacy of drugs used to suppress PSH episode in anti-NMDAR encephalitis patients.

Methods

Patients who met the diagnostic criteria of anti-NMDAR encephalitis were enrolled from January 2012 to August 2018 and followed up. PSH was diagnosed according to the PSH-Assessment Measure. The demographics data, clinical features, main accessory examinations, treatments, and long-term outcomes were prospectively collected and analyzed.

Results

A total of 132 anti-NMDAR encephalitis patients were enrolled, 27.3% of patients experienced autonomic dysfunction, of which cardiac autonomic dysfunction (77.8%) was the most common subdivisions. Of the patients, 9.1% had probable PSH, tachycardia, tachypnea, and hypertonia (100%) were the most common symptoms of PSH. Patients with a higher incidence of ovarian teratoma, mechanical ventilation, intensive care unit admission, and elevated levels of CSF glucose, and higher CSF NMDAR antibody titers were more likely to exhibit autonomic dysfunction or PSH. Diazepam and phenobarbitone were commonly used drugs to control PSH episodes in patients without prior sedative drugs and the overall efficacy was 90.0%. However, the efficacy of monotherapy dropped to 69.6% and approximately half of episodes need a combination of drugs to control symptoms in PSH patients with prior sedative drugs. No significant difference was observed in the prognosis between the autonomic dysfunction group and the non- autonomic dysfunction group or PSH group and non-PSH group after 6 months and during long-term follow-up. However, patients with cardiac autonomic dysfunction had a poor prognosis at 6 months.

Conclusion

PSH is a common clinical condition in patients with anti-NMDAR encephalitis, especially in severe cases, and the clinical management of PSH can be assisted by several acute drug administered therapies. Patients with autonomic dysfunction or PSH do not seem to compromise their neurological recovery despite a longer hospital stay.

Background

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder characterized by generation of autoantibodies against antigenic nerve surfaces or synapses[1]. Although early diagnosis and immunosuppressive therapy can improve outcomes, 7.3–22% of the patients have poor prognosis during follow-up and the mortality rate ranges from 2.7–11.5%[2–5]. Studies show that altered consciousness, intensive care unit (ICU) admission and non-application of immunotherapy are associated with short-term poor prognosis of anti-NMDAR encephalitis[6].

The autonomic nervous system (ANS) controls all unconscious and involuntary functions in response to external stimuli to maintain homeostasis, and any disruption in one or more its branches worsens prognosis of several diseases. Severe dysfunction of the ANS may even lead to disability[7, 8]. Approximately 10–50% of the anti-NMDAR encephalitis patients have autonomic dysfunction[2, 9], including tachycardia/bradycardia, hypertension/hypotension, gastrointestinal dysfunction, urinary dysfunction, abnormal pupil movement etc., which increase patient morbidity and mortality, complicate intensive care and can lead to hemodynamic shock[10]. However, little is known regarding the correlation between autonomic instability and the prognosis of autoimmune encephalitis, and the conclusions are ambiguous[4, 11]. In addition, the prevalence and characteristics of autonomic dysfunction in anti-NMDAR encephalitis have not been systematically evaluated.

Paroxysmal sympathetic hyperactivity (PSH), also known as paroxysmal autonomic instability with dystonia, is characterized by hypertension, tachycardia, tachypnea, diaphoresis, agitation and dystonic posturing. It is caused by severe brain injury and associated with higher morbidity, longer hospital stays and poorer outcomes[12, 13]. PSH is often unrecognized in patients without traumatic brain injury (TBI), which has limited the development of specific PSH management strategies. Only a few case studies have reported an association between anti-NMDAR encephalitis and PSH[14]. To this end, we analyzed the clinical and two-year outcomes of anti-NMDAR encephalitis patients at our center to identify the characteristics, predictors and long-term outcomes of autonomic dysfunction and PSH, and evaluate the efficacy of drugs used to suppress PSH episodes.

Methods

Patient eligibility

The patients were recruited from the Department of Neurology of Xuanwu Hospital, Capital Medical University between January 2012 and August 2018 based on the following inclusion criteria[1]: (1) age ≥ 14 years, (2) acute or subacute onset symptoms of encephalitis (less than three months), (3) exhibiting abnormal behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorder, decreased level of consciousness, autonomic dysfunction or central hypoventilation, or a combination of the above symptoms (4) cerebrospinal fluid (CSF) positive for IgG anti-GluN1 NMDAR antibodies with or without serum positivity, and (5) absence of viral encephalitis, brain tumor, metabolic disease, drug poisoning, etc. The exclusion criteria

were as follows: (1) non-compliance with the treatment, (2) presence of other autoimmune or neurological paraneoplastic antibodies, and (3) not the first onset of anti-NMDAR encephalitis.

PSH was diagnosed according to the PSH-Assessment Measure (PSH-AM) proposed by Baguley et al based on the Clinical Feature Scale (CFS) and Diagnosis Likelihood Tool (DLT). The clinical features were classified as mild (1-6), moderate (7-12), severe (>12) group according to CFS. Both scores were added to determine the likelihood of PSH as unlikely (< 8), possible (8–16) and probable (≥ 17) [15]. The patients were also stratified into the autonomic dysfunction and non-autonomic dysfunction groups, as well as the PSH and non-PSH groups. In addition, the autonomic dysfunction group was further divided into the sympathetic, parasympathetic and both subgroups. Sympathetic hyperactivity may lead to tachycardia, hypertension, bladder and gastrointestinal dysfunction, whereas parasympathetic overactivity may lead to bradycardia, generalized warmth, gastrointestinal hyperactivity and increased glandular secretion. Accordingly, the patients were classified into the cardiac autonomic dysfunction (e.g., tachycardia, bradycardia, malignant arrhythmia, hypertension, hypotension), gastrointestinal dysfunction (e.g., gastrointestinal motility insufficiency, constipation, gastroparesis, nausea, and vomiting), hypersalivation, sudomotor dysfunction (e.g., anhidrosis, hyperhidrosis), fever, bladder dysfunction (e.g., urinary frequency, urgency and nocturia, urinary retention, urinary incontinence), and others (e.g., pupillary abnormalities, priapism) according to clinical symptoms.

Data collection

The following demographic data and ancillary tests results were collected and analyzed: age of onset, sex, prodromal symptoms (including fever, headache, respiratory symptoms, emesis, diarrhea), clinical characteristics, time of admission, medical history, CSF analysis (e.g., pressure of lumbar puncture, white blood cells, and the levels of protein, glucose and chloride), brain magnetic resonance imaging (MRI) and electroencephalography (EEG) findings, treatment details and follow-up data. All serum and CSF antibodies were measured using indirect immunofluorescence test (IIFT) kits that were purchased from EUROIMMUN AG (Lübeck, Germany) and used according to the manufacturer's instructions. Samples were classified as strong positive (titre of 1:100 and above), positive (1:32), weak positive (1:10), and negative according to the antibody titre levels in serum and CSF. EEGs performed during the peak stage of the disease (14–60 days after the onset of symptoms) were analyzed for epileptic discharges, slow activity and other symptoms (including polymorphic delta rhythm and diffuse beta activities).

Treatment

All patients were screened for tumors, symptomatic support and immunotherapy. Patients with cancer, such as ovarian teratoma, were treated with tumor resection. Immunotherapy included intravenous glucocorticoid (1000 or 500mg methylprednisolone for 3 or 5 days followed by a gradual decrease in dosage), intravenous gamma immunoglobulin (IVIG, 0.4g/kg/ day, 5 days per course), plasma exchange (PE, 3-5 times per course) or immunosuppressants (e.g., rituximab, cyclophosphamide, Mofett or azathioprine). For each probable PSH episode requiring intravenous pharmacological treatment, medications (e.g., Midazolam, Propofol, Dexmedetomidine, Diazepam, Phenobarbital) and doses were chosen on the basis of the physician's experience, rather than objective evidence. Each drug administration was classified as fully effective or ineffective (or partially effective) based on whether the PSH episode was suppressed or not within 30 minutes.

End points

The patients were followed-up 6, 12 and 24 months after admission. Treatment efficacy and long-term outcomes were assessed using the modified Rankin Scale (mRS). Recurrence was defined as worsening of previous symptoms or the occurrence of new symptoms after two months of stabilization [5]. Good and poor long-term outcomes were respectively defined as mRS scores 0-2 and 3-6.

Statistical analysis

Statistical analyses were performed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Quantitative data with normal distributions are presented as mean \pm SD, whereas data with non-normal distributions are presented as medians with the interquartile range (IQR). Student's t test was used to compare data with a normal distribution and homogeneous variance, and Mann–Whitney U test was used to evaluate differences in ranked data. Categorical data were summarized as counts (percentages), and compared by Pearson chi-square test or Fisher exact test. P values < 0.05 were considered statistically significant.

Results

A total of 153 patients met the inclusion and exclusion criteria of our study (Figure 1).

The median age at onset was 25 (IQR 19–34) years, and 59 (44.7%) patients were females.

The overall incidence of autonomic dysfunction was 27.3% (36/132), with more than half of these patients (52.8%, 19/36) exhibiting both sympathetic and parasympathetic dysfunction. The incidence of pure sympathetic and parasympathetic dysfunction were 25% and 22.2%, respectively. Cardiac autonomic dysfunction, gastrointestinal dysfunction and sudomotor dysfunction were most common, with respective incidence rates of 77.8%, 41.7% and 38.9% (Figure 2). As shown in Table 1, patients with autonomic dysfunction or PSH had a higher incidence of ovarian teratoma, involuntary movement, disturbance of consciousness, central hypoventilation, mechanical ventilation and ICU admission compared to patients without ANS involvement. Autonomic dysfunction/PSH was also associated with elevated glucose levels and NMDAR antibody titers in the CSF, as well as a higher rate of IVIG, plasma exchange and immunosuppressor treatments ($P < 0.05$). In addition, patients with autonomic dysfunction were younger ($P = 0.098$), more likely to exhibit prodromal symptoms, and showed higher incidence of insular lobe lesions ($P = 0.078$) and higher WBC counts in the CSF ($P = 0.056$).

Twelve (9.7%) patients were diagnosed with probable PSH based on the PSH-AM criteria, of which 10 were admitted to the ICU. As shown in Table 2, the most common symptoms of PSH were tachycardia (100%), tachypnea (100%) and hypertonia (100%). There were 57 probable PSH episodes requiring intravenous pharmacological treatment. Diazepam and phenobarbitone were commonly administered to control PSH in patients without previous sedative use, and the overall efficacy was 90%. However, the efficacy of monotherapy dropped to 69.6% in patients with previous sedative use, and approximately half of the episodes needed a combination of drugs to control the symptoms (Table 3).

The median duration of hospital stay was longer in patients with autonomic dysfunction or PSH compared to the respective control groups. There was no significant difference in the recurrence and functional outcomes at 6, 12 and 24 months across all groups (Table 2). In addition, cardiac autonomic dysfunction was associated with poor prognosis at 6 months (Figure 3), whereas the other subtypes of autonomic dysfunction were not associated with patient prognosis.

Discussion

To the best of our knowledge, this is the first study to analyze the clinical features and risk factors of autonomic dysfunction and PSH in patients with anti-NMDAR encephalitis. The overall prevalence of autonomic dysfunction and PSH in our cohort was 27.3% and 9.1% respectively, and was associated with a higher incidence of ICU admission, mechanical ventilation, ovarian teratomas, along with elevated NMDAR antibody titers and glucose levels in the CSF. Most PSH episodes can be suppressed by the acute administration of suitable drugs. Although longer hospital stays did not compromise the neurological recovery of patients with autonomic dysfunction/PSH, cardiac autonomic dysfunction was associated with poor outcome at 6 months.

Autonomic dysfunction is common in patients with neurological disorders and predominantly affects the cardiovascular, thermoregulatory, gastrointestinal, urinogenital organs. TBI, cerebrovascular diseases, infectious diseases, immune-mediated diseases and degenerative neurological disorders are some of the common causes of autonomic dysfunction. While PSH is the main clinical manifestation of severe TBI, hypoxic brain injury and stroke, orthostatic hypotension, thermoregulatory disorders and detrusor hyperactivity commonly develop during degenerative neurological disorders[16]. Sinus tachycardia, hypertension and hyperhidrosis were the most common symptoms in anti-NMDAR encephalitis patients, and were observed in two-thirds of those with autonomic dysfunction.

PSH is a relatively common but often unrecognized complication of various acute brain diseases, with estimated prevalence ranging from 7.7 to 32.6% among various cohorts of patients with severe TBI[17, 18]. Raquel et al. reported PSH in 40.7% of the patients with meningoencephalitis and/or encephalitis in the pediatric ICU[19]. In the present study, the overall prevalence of PSH was 9.1%, which increased to 25.6% in the ICU patients. Given the high sensitivity and low specificity of the diagnostic criteria for PSH-AM[20], PSH episodes tend to be confused with or superimposed on central hypoventilation, epileptic seizure or involuntary movements in anti-NMDAR encephalitis. Since only probable PSH was diagnosed in this study, the true incidence of PSH may have been underestimated. It is unclear whether the onset of PSH after anti-NMDAR encephalitis presents with unique features compared to acquired brain injury with other etiologies. The most common symptoms of PSH in our cohort were tachycardia (100%), tachypnea (100%) and hypertonia (100%), which contradicts previous reports indicating that PSH after TBI and ICH mainly manifest as hypertonia (94%) and hyperhidrosis (77%)[21], or hyperthermia (80%) and hyperhidrosis (80%)[22].

Regardless of the type of brain injury, the underlying mechanism of autonomic dysfunction and PSH remains unclear. Impairment of the central autonomic regulatory centers, such as the insular cortex, anterior cingulate and ventral prefrontal regions, as well as lower centers located in the amygdala, hypothalamus, brainstem and spinal cord, have been frequently implicated[12, 23]. Attempts have been made to identify the location of structural lesions that increase the likelihood of autonomic instability or PSH[24]. However, we found no association between structural abnormalities of the brain and autonomic instability or PSH and only patients with autonomic dysfunction have a higher propensity for insular lobe abnormalities, suggesting that those autonomic centers involvement may have occurred at the molecular level without structural MR detection. Besides, the new theory of PSH is help to explain this negative finding, as PSH may not be caused by a single lesion, but rather by disruption of sympathetic circuits, thus explaining the contingency of this condition and its different causes[23, 25].

Several risk factors of autonomic dysfunction/PSH have been identified in recent years, such as younger[26] or older age [13], tracheostomy[27], lower admission GCS scores[24], higher diffuse axonal injury grade[18, 28] and deep parenchymal lesions[24]. In this study, ICU admission, mechanical ventilation, ovarian teratoma[29] and elevated CSF NMDAR antibody titers[26], all of which are strongly associated with disease severity, were more prevalent in patients with autonomic dysfunction and PSH. Interestingly, the levels of CSF glucose were significantly higher in patients with autonomic instability or PSH, although the exact association remains unclear. The central nervous system regulates glucose homeostasis through ANS-mediated control of metabolic organs such as the liver, pancreas, skeletal muscle, intestine, and brown and white adipose tissues. Autonomic dysregulation leads to excessive sympathetic impulses and reduced parasympathetic function, which impairs metabolic homeostasis and leads to hyperglycemia[30].

ANS abnormalities are usually transient, mildly symptomatic, and recover on their own or with only oral medications. Most PSH episodes are related to various types of stimuli such as turning, back patting, suctioning and emotional excitement. However, the treatment of PSH is not standardized due to poor understanding of its pathophysiology. Identifying triggers can help reduce the occurrence of symptoms, and different classes of drugs such as intravenous anesthetics, β -adrenergic blockers, α 2-agonists and benzodiazepines have been used to treat patients with PSH[12]. However, the efficacy of these drugs have not been compared extensively. A retrospective cohort study quantified the effect of several drugs in 26 PSH patients, and found that the most commonly used analgesic drugs were not very effective whereas benzodiazepine drugs had satisfactory effects[31]. In this study, we compared the efficacy of different intravenous medications, and found that diazepam was frequently administered and highly effective in PSH patients without prior exposure to sedative drugs. However, the efficacy of monotherapy was lower in patients with a history of sedative drug use to control dysphoria, epilepsy or other

conditions, and half of them needed a combination of drugs. This can be attributed to the development of drug tolerance in those patients. Phenobarbitone combined with one anesthetic (dexmedetomidine, midazolam or propofol) is the most commonly used combination drug therapy with relatively high efficacy, and can reduce the use of more than two anesthetics.

The correlation between autonomic instability and prognosis of anti-NMDAR encephalitis is ambiguous. Lim et al found that autonomic instability was associated with worse mRS scores in 32 patients with anti-NMDAR encephalitis[32]. Schubert et al. also confirmed that autonomic dysfunction led to worse neurologic outcomes at discharge in 120 patients with autoimmune encephalitis[33]. In contrast, Dubey et al. found that autonomic dysfunction predicted favorable prognosis in patients with autoimmune epilepsy receiving immunotherapy. It is possible that this cohort included some cases without an autoimmune etiology, and since autonomic dysfunction is associated with true autoimmune epilepsy, these cases likely responded to immunotherapy[34]. Most studies show that PSH is associated with a worse functional outcome compared to patients without PSH symptoms in other diseases[19, 35–37]. In this study, we found that patients with autonomic dysfunction or PSH had a longer ICU stay, although this did not appear to compromise their neurological recovery. Similar results have been reported for disease severity and prognosis of anti-NMDAR encephalitis[26]. Most anti-NMDAR encephalitis patients have good prognosis after active treatment, and the PSH patients in our cohort received active combined immunotherapy. However, cardiac autonomic dysfunction was associated with short-term poor prognosis, which may be related to a greater susceptibility to hemodynamic instability in this group of patients. Consistent with our findings, Byun et al. showed that cardiac autonomic function, specifically sympathetic activity, was reduced and cardiac autonomic dysfunction was associated with poor function at 3 months in 11 patients with anti-NMDAR encephalitis[10].

Our study has some limitations that should be acknowledged. First, asymptomatic autonomic symptoms such as tachycardia, hypertension etc. are easily overlooked, especially in the mildly symptomatic patients, without electrocardiograph monitoring. Furthermore, some parasympathetic excitatory symptoms like hypohidrosis, xerostomia and xerophthalmia can be easily missed. Second, the objective quantification of autonomic dysfunction, such as using heart rate variability and pupillary dynamics, are associated with global patient outcome and other neurophysiological measures[38], while all autonomic symptoms in this study were assessed based on clinical presentation. Third, individual drugs and drug combinations are typically chosen on the basis of the physician's experience rather than objective evidence. The small sample size of patients with PSH episodes and relatively high number of drug subgroups prevented the comparison of the efficacy of different drugs. Further randomized clinical trials are needed to address the above points.

Conclusions

PSH is a common clinical symptom in patients with anti-NMDAR encephalitis, especially in severe cases, and can be suppressed by active treatment. Elevated CSF glucose levels were more common in patients with autonomic instability or PSH. Combined immunotherapy can significantly improve patient prognosis despite longer hospital stays and challenging treatment.

Abbreviations

ANS autonomic nervous system

CSF cerebrospinal fluid

ICU intensive care unit

IQR interquartile range

IVIG IV immunoglobulin

mRS modified Rankin Scale

NMDAR N-methyl-D-aspartate receptor

PSH paroxysmal sympathetic hyperactivity

Declarations

Acknowledgments

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Authors' contributions

Chen Zhongyun carried out the patients enrollment, statistical analysis and drafted the manuscript. Wu xiaowen and Huang huijin carried out the patients enrollment and verification of data. Chen weibi carried out the verification of data and statistical analysis. Zhang yan and Su yingying conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Xuanwu Hospital, Capital Medical University, and was conducted following the latest version of the Declaration of Helsinki. Informed consent was obtained from the patient or their families.

Availability of data and materials

The datasets analyzed in this study are available from the corresponding authors on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Demographics, clinical manifestations, and main accessory examinations, prognosis of patients with anti-NMDAR encephalitis

	Total (n=132)	Non-autonomic dysfunction group (n=96)	Autonomic dysfunction group (n=36)	P values	Non-PSH group (n=120)	PSH group (n=12)	P values
Age, years, median (IQR)	25.0(19.0,34.0)	25.5(19.0,36.0)	23.0(17.3,30.5)	0.098	25.0(19.0,35.8)	23.0(16.8,30.0)	0.199
Female, n (%)	59(44.7)	41(42.7)	18(50.0)	0.453	51(42.5)	8(66.7)	0.193
Ovarian teratoma, n (%)	9(6.8)	3(3.1)	6(16.7)	0.018	5(4.2)	4(33.3)	0.001
Prodromal symptoms, n (%)	69(52.3)	44(45.8)	25(69.4)	0.016	63(52.5)	6(50.0)	0.869
Clinical manifestations, n (%)							
Mental behavior disorder	98(74.2)	66(68.8)	32(88.9)	0.018	87(72.5)	11(91.7)	0.271
Epileptic seizure	88(66.7)	61(63.5)	27(75.0)	0.214	77(64.2)	11(91.7)	0.108
Involuntary movement	62(47.0)	35(36.5)	27(75.0)	0.000	50(41.7)	12(100)	0.000
Language impairment	33(25.0)	25(26.0)	8(22.2)	0.652	30(25.0)	3(25.0)	1.000
Disturbance of consciousness	63(47.7)	34(54.0)	29(80.6)	0.000	52(43.3)	11(91.7)	0.001
Cognitive impairment	42(31.8)	31(32.3)	11(30.6)	0.849	38(31.7)	4(33.3)	1.000
Central hypoventilation	30(22.7)	5(5.2)	25(16.7)	0.000	24(20.0)	6(50.0)	0.045
Electroencephalogram, n=105, n (%)							
Normal	10(9.5)	8(10.7)	2(6.7)	0.528	11(11.7)	1(9.1)	1.000
Epileptic discharges	24(22.9)	14(18.7)	10(33.3)	0.106	20(21.3)	4(36.4)	0.454
Slow activity	57(54.3)	43(57.3)	14(46.7)	0.322	53(56.4)	4(36.4)	0.207
others	14(13.3)	10(13.3)	4(13.3)	1.000	10(9.6)	4(36.4)	0.036
Cranial MRI, n (%)							
Normal	51(38.6)	33(34.4)	18(50.0)	0.101	45(37.5)	6(50.0)	0.591
Temporal lobe	33(25.0)	21(21.9)	12(33.3)	0.176	30(25.0)	3(25.0)	1.000
Limbic lobe	47(35.6)	33(34.4)	14(38.9)	0.630	42(35.0)	5(41.7)	0.886
Frontal lobe	30(22.7)	21(21.9)	9(25.0)	0.703	26(21.7)	4(33.3)	0.577
Parietal lobe	15(11.4)	10(10.4)	5(13.9)	0.576	13(10.8)	2(16.7)	0.896
Occipital lobe	12(9.1)	8(8.3)	4(11.1)	0.621	11(9.2)	1(8.3)	1.000
Insular lobe	18(13.6)	10(10.4)	8(22.2)	0.078	15(12.6)	3(25.0)	0.454
Diencephalon	4(3.0)	3(3.1)	1(2.8)	1.000	4(3.3)	0(0)	1.000
Cerebellum	3(2.3)	3(3.1)	0(0)	0.562	3(2.5)	0(0)	1.000
Brainstem	9(6.8)	6(6.3)	3(8.3)	0.672	9(7.5)	0(0)	0.702
CSF analysis							
Opening pressure, mmH ₂ O, median (IQR)	180.0(140.0,225.0)	180.0(135.0,220.0)	200.0(147.5,240.0)	0.151	180.0(140.0,220.0)	180.0(142.5,260.0)	0.672
WBC, ×10 ⁶ /L, median (IQR)	15.0(5.0,32.0)	13.5(5.0,28.0)	23.0(10.0,37.0)	0.056	14.0(5.0,30.0)	29.0(14.5,35.8)	0.161
Protein, mg/dl, median (IQR)	31.0(20.3,44.0)	31.0(20.5,44.0)	31.0(20.0,44.0)	0.923	31.0(21.0,44.0)	26.0(10.5,41.5)	0.218
Glucose, mg/dl, median (IQR)	60.8(54.5,69.4)	59.4(54.1,66.4)	68.7(56.9,79.8)	0.004	60.0(54.5,68.2)	70.6(64.9,79.2)	0.005

Chloride, mmol/L, median (IQR)	121.0(117.0,124.0)	121.0(117.0,124.0)	121.0(117.0,125.0)	0.984	121.0(117.0,124.0)	120.0(117.3,124.5)	0.662
Serum, Glucose, mmol/L, median (IQR)	5.0(4.5,5.7)	5.0(4.5,5.4)	5.4(4.5,6.1)	0.180	4.5(4.5,5.6)	5.3(4.5,5.9)	0.159
CSF NMDAR antibody titers, n (%)							
+	15(11.4)	13(13.5)	2(5.6)	0.198	15(12.5)	0(0)	0.410
++	74(56.1)	59(61.5)	15(41.7)	0.041	70(58.3)	4(33.3)	0.096
+++	43(32.6)	24(25.0)	19(52.8)	0.002	35(29.2)	8(66.7)	0.020
Serum NMDR antibody titers, n (%)							
-	71(53.8)	56(58.3)	15(41.7)	0.087	68(56.7)	3(25.0)	0.036
+	21(15.9)	14(14.6)	7(19.4)	0.496	18(15.0)	3(25.0)	0.625
++	34(25.8)	24(25.0)	10(27.8)	0.745	29(24.2)	5(41.7)	0.329
+++	6(4.5)	2(2.1)	4(11.1)	0.047	5(4.2)	1(8.3)	1.000
Mechanical ventilation, n (%)	29(22.0)	12(12.5)	17(47.2)	0.000	21(17.5)	8(66.7)	0.000
ICU admission, n (%)	43(32.6)	19(19.8)	24(66.7)	0.000	32(26.7)	11(91.7)	0.000
Immunotherapy, n (%)							
Steroids	113(85.6)	79(82.3)	34(94.4)	0.076	102(85.0)	11(91.7)	0.845
IVIG	77(58.3)	45(46.9)	32(88.9)	0.000	65(54.2)	12(100)	0.002
Plasma exchange	23(17.4)	8(8.3)	15(41.7)	0.000	16(13.3)	7(58.3)	0.000
Immunosuppressor	26(19.7)	13(13.5)	13(36.1)	0.004	21(17.5)	5(41.7)	0.104
Outcome							
Length of ICU length of stay, n=43, days, median (IQR)	38(18.0,73.0)	23.0(13.0,54.0)	39.0(25.8,78.3)	0.106	29.0(16.5,55.0)	61.0(36.0,82.0)	0.079
Hospital length of stay, days, median (IQR)	18.0(13.0,33.5)	16.0(12.0,21.0)	38.5(21.3,72.3)	0.000	18.0(13.0,27.9)	63.5(36.8,81.5)	0.000
Hospital mortality, n (%)	5(3.8)	2(2.1)	3(8.3)	0.125	5(4.2)	0(0)	1.000
Recurrence, n (%)	14(10.6)	11(11.5)	3(8.3)	0.604	13(10.8)	1(8.3)	1.000
mRS>2 after 6 months, n (%)	19(14.4)	11(11.5)	8(22.2)	0.117	17(14.2)	2(16.7)	1.000
mRS>2 after 12 months, n=110, n (%)	21(19.1)	14(18.2)	7(21.2)	0.711	20(20.2)	1(9.1)	0.628
mRS>2 after 24 months, n=105, n (%)	10(9.5)	5(6.8)	5(15.6)	0.159	9(8.5)	11(10.0)	1.000

Abbreviation: CSF = cerebrospinal fluid; ICU = intensive care unit; IQR = interquartile range; IVIG = IV immunoglobulin; mRS = modified Rankin Scale; MRI = magnetic resonance imaging ; NMDAR = N-methyl-D-aspartate receptor; PSH = paroxysmal sympathetic hyperactivity; WBC = white blood cell.

Table 2 Clinical features of patients with PSH (n = 12).

PSH	Value
Clinical features, n(%)	
Tachycardia	12(100)
Tachypnea	12(100)
Hypertension	5(41.7)
Hyperthermia	6(50.0)
Hyperhidrosis	9(75.0)
Hypertonia	12(100)
Severity of clinical features, n(%)	
Moderate	8(66.7)
Severe	4(33.3)
CFS maximum score, median (IQR)	12(10,13.5)
DLT score, median (IQR)	8(7,8.75)
PSH-AM probability, n (%)	
Probable	0(0)
Probable	12(100)
PSH duration, day, median (range)	17(4,123)

Abbreviation: CFS = Clinical Feature Scale; DLT = Diagnosis Likelihood Tool; PSH = paroxysmal sympathetic hyperactivity

Table 3 Efficacy of drugs used to suppress PSH episodes

Drug treatment	Dose range	Efficacy, %
Without Prior Sedative drugs		
Monotherapy		
Overall		9/10(90.0)
Diazepam	5-10 mg	7/8(87.5)
Phenobarbitone	0.2 mg	2/2(100)
With Prior Sedative drugs		
Monotherapy		
Overall		16/23(69.6)
Propofol	30-60 mg/h	4/6(66.7)
Phenobarbitone	0.2 mg	4/5(80.0)
Midazolam	2-6 mg/h	4/6(66.7)
Diazepam	10 mg	3/4(75.0)
Dexmedetomidine	16-20ug/h	1/2(50)
Combination drug therapy		
Overall		17/24(70.8)
Midazolam + Phenobarbitone	3-6mg/h + 0.2mg	4/6(66.7)
Propofol + Phenobarbitone	30-60mg/h + 0.2mg	4/5(80.0)
Dexmedetomidine+ Phenobarbitone	16-20ug/h + 0.2mg	3/4(75.0)
Propofol + Midazolam	40-60mg/h +2-4mg/h	3/4(75.0)
Midazolam + Dexmedetomidine	2-5mg/h + 16-20ug/h	2/3(66.7)
Dexmedetomidine+ Propofol	12-20ug/h +40-60mg/h	1/2(50.0)

Figures

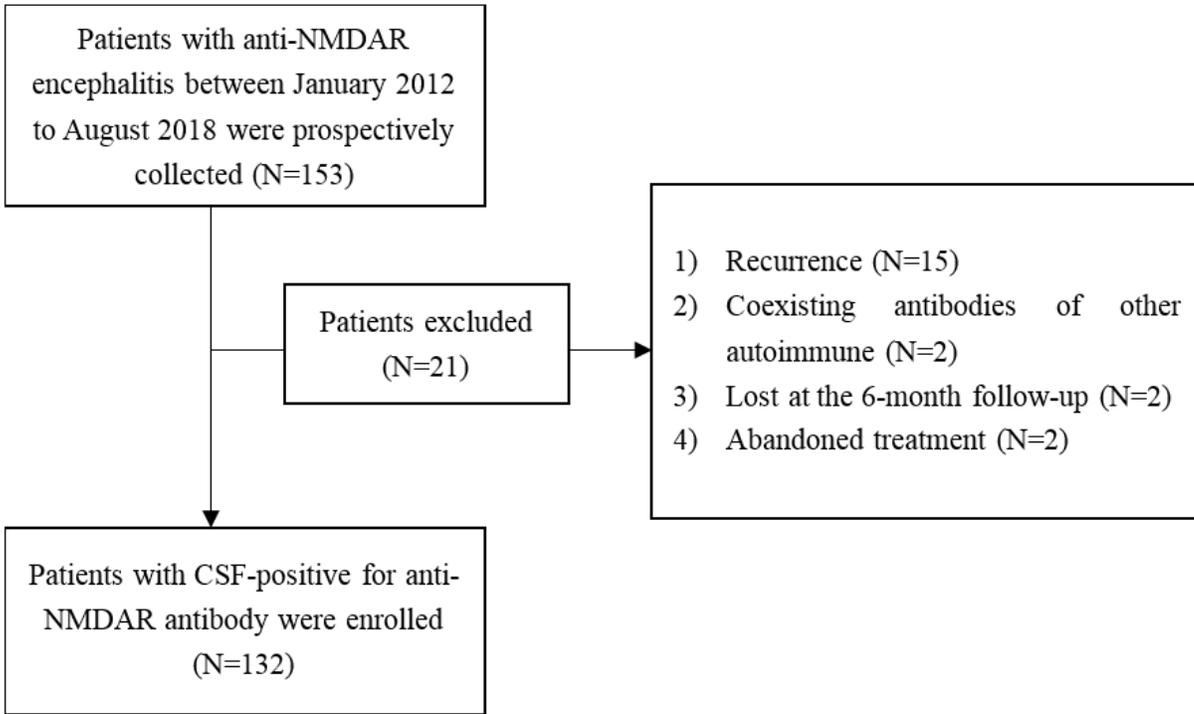


Figure 1

Patient inclusion/exclusion flowchart.

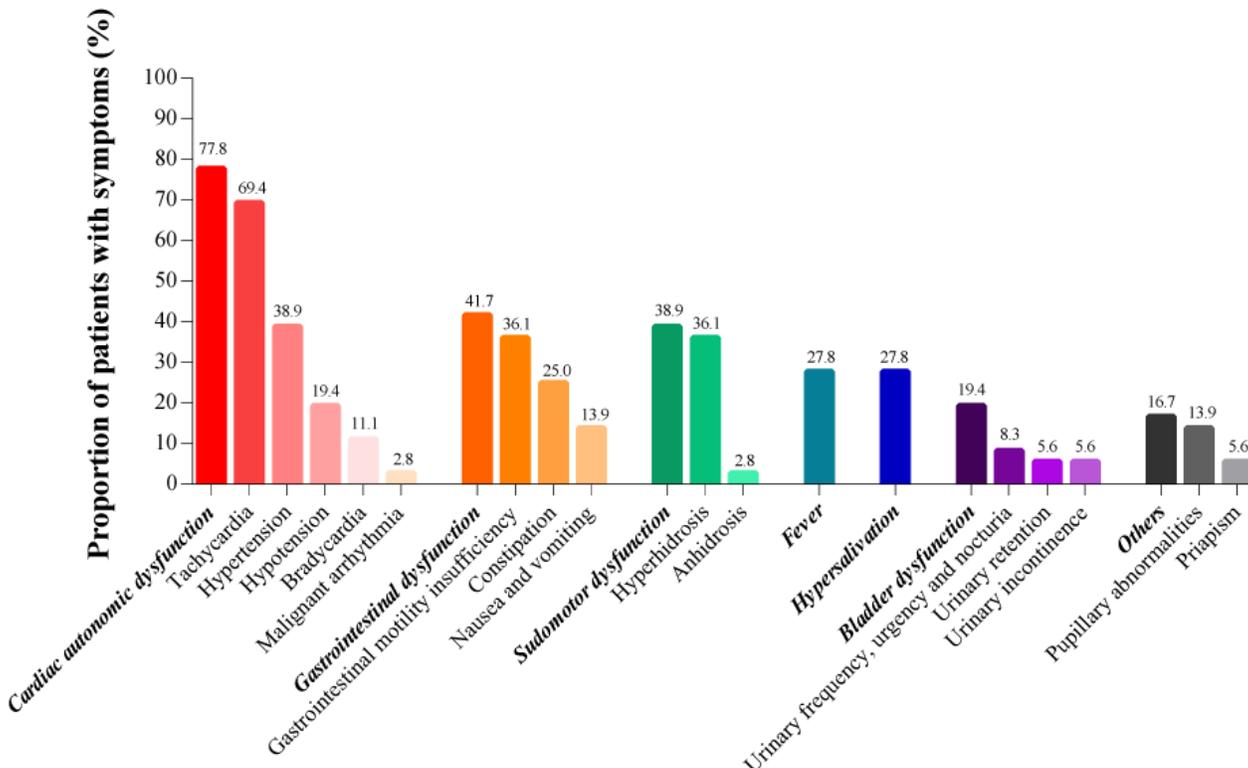


Figure 2

The incidence of autonomic dysfunction subdivisions

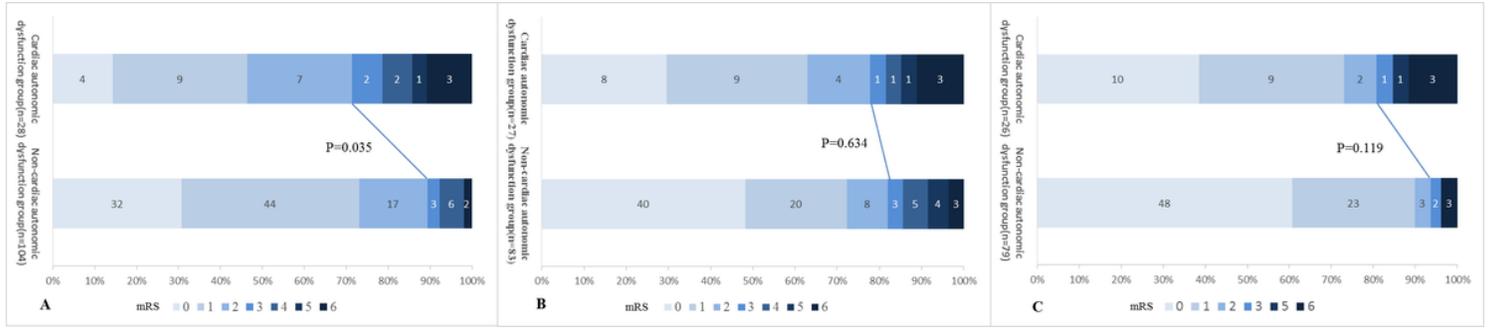


Figure 3

The relationship between cardiac autonomic dysfunction and prognosis A Relationship between cardiac autonomic dysfunction and outcome 6 months, B Relationship between cardiac autonomic dysfunction and outcome 12 months, C Relationship between cardiac autonomic dysfunction and outcome 24 months