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Olanzapine vs. magnesium valproate vs. lamotrigine in anti-N-methyl-D-aspartic acid receptor encephalitis: a retrospective study

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Abstract

Background This study aimed to compare the impact of olanzapine, magnesium valproate, and lamotrigine as adjunctive treatments for anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. And it is expected to add supporting points related to the rebalance of neurotransmitters in the brain through adjuvant therapy in the clinical management of anti-NMDAR encephalitis.

Methods This retrospective study included patients diagnosed with anti-NMDAR encephalitis who received standardized immunotherapy at Hunan Brain Hospital between January 2018 and December 2020.

Results Compared to the olanzapine group, both the magnesium valproate and lamotrigine groups showed lower scores on the positive and negative symptom scale (PANSS) total score after 3 weeks of treatment (all $P<0.05$). The Montreal Cognitive Assessment Scale (MoCA) scores in the magnesium valproate and lamotrigine groups were significantly higher than in the olanzapine group after 3 weeks and 3 months of treatment (all $P<0.05$). After 3 months of treatment, the proportions of patients with a modified Rankin scale score (mRS) of 0–1 in the magnesium valproate and lamotrigine groups were significantly higher than in the olanzapine group (all $P<0.05$). The electroencephalogram (EEG) abnormality ranks at 3 months were significantly lower in the magnesium valproate and lamotrigine groups compared with the olanzapine group (all $P<0.05$). Furthermore, the Glx/Cr ratio significantly decreased after 3 months of treatment (all $P<0.05$) in the magnesium valproate and lamotrigine groups, while the Glx/Cr ratio in the olanzapine group showed no significant change ($P>0.05$).

Conclusion Compared with olanzapine, the addition of magnesium valproate or lamotrigine to immunotherapy might be associated with a lower PANSS score, higher MoCA score, and lower mRS score. The improvement of neurological functions and cognitive function may be related to the decreased Glx/Cr ratio.

Keywords Autoimmune encephalitis, anti-N-methyl-D-aspartate receptor encephalitis, Adjuvant drug therapy

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a rare autoimmune encephalitis with acute onset neuropsychiatric symptoms due to an autoimmune reaction to the glutamate N receptor (GluN1) subunit of the neuronal NMDAR [1, 2]. The reported annual incidence is about 1.5 per million persons-year [1]. Currently, the recommended treatment for anti-NMDAR encephalitis is the use of first-line immunotherapy that includes glucocorticoids, γ-globulin, plasma exchange, tumor resection, acyclovir (until a viral etiology is ruled out), and symptomatic support [2–4]. Still, only about 53% of patients appear to respond well to first-line immunotherapy, with a fairly high recurrence rate [5–7]. Pathogenically, the autoantibody binds to the extracellular domain of the GluN1 subunit, resulting in NMDAR internalization and glutamatergic hypofunction. The first-line immunotherapies appear to intervene at the antigen/antibody reaction stage, which might underscore the limited effectiveness of this treatment strategy in the context of potentially broader pathophysiological alterations in the brain.

Given the existence of glutamatergic hypofunction in anti-NMDAR encephalitis, it can be hypothesized that an imbalance of excitatory/inhibitory neurotransmission should be present in the brain, contributing to the pathophysiology of the disease. Accordingly, adjuvant therapies that help mitigate this imbalance could be beneficial in the clinical management of patients with anti-NMDAR encephalitis. A case report suggested using adjuvant memantine to manage catatonia in anti-NMDAR encephalitis [8]. Ketamine can also be used in patients with anti-NMDAR encephalitis and refractory persistent epilepsy [9]. Intrathecal methotrexate has been suggested for refractory anti-NMDAR encephalitis [10]. Still, few data are available regarding adjuvant therapies in anti-NMDAR encephalitis.

Therefore, this retrospective study aimed to compare the cognitive and neurological functions of three adjuvant drugs in treating anti-NMDAR encephalitis, and to establish a relationship between these improvements and the balance in neuronal excitation and inhibition through glutamate (Glu) and γ-aminobutyric acid (GABA). Based on this study, we hypothesized that the effects of three adjunctive therapeutics in the treatment of anti-NMDAR encephalitis were determined by relating their clinical efficacy for the improvement of cognitive and neurological functions to their extent of pharmacological modulation of glutamate (Glu) and γ-aminobutyric acid (GABA) transmission in the cerebrum.

Materials and methods

Study design and patients

This retrospective study collected the clinical data of patients with anti-NMDAR encephalitis admitted to Hunan Brain Hospital between January 2018 and December 2020. All included patients received standard immunotherapy and different adjuvant treatments. The patients were then grouped based on the adjuvant medications they received.

The study was approved by the Medical Ethics Committee of Hunan Brain Hospital (approval #2018K065). The requirement for informed consent was waived by the committee because of the retrospective nature of the study. All data were anonymized after extraction and before analysis.

Inclusion and exclusion criteria

Clinical cases meeting the diagnostic criteria for anti-NMDAR encephalitis according to clinical guidelines [2]. The exclusion criteria included encephalitis with other causes, tumors found, seizures as the first symptom, and incomplete clinical data.

Drug administration

All patients receive standardized first-line immunotherapy after admission, including intravenous immunoglobulin injection (According to the patient's weight, a total of 2 g/kg should be administered intravenously for three to five days.), plasma exchange (with a dose of 1.0 to 1.5 times the total plasma volume, performed 3–6 exchanges within 10–14 days.), glucocorticoids (methylprednisolone 1000 mg/d for 3 consecutive days, 500 mg/d for 3 consecutive days, followed by a reduction of 40-80 mg/d.). According to the 2017 Consensus of Chinese Experts on the Diagnosis and Treatment of Autoimmune Encephalitis, doctors choose different drugs for adjuvant treatment based on the different clinical symptoms of patients.

Outcomes and data collection

The primary outcome was improving the Positive and Negative Syndrome Scale (PANSS), the Montreal Cognitive Assessment Scale (MoCA), and the modified Rankin Scale (mRS). As per routine practice, all patients underwent assessments using the PANSS, the MoCA, and the mRS before initiating any treatment. The PANSS and the MoCA were conducted at 3 weeks and 3 months after the initial treatments. The mRS were assessed at 3 months after the start of treatments. The PANSS quantifies positive symptoms (which refer to excess or distortion of normal functions, e.g., hallucinations and delusions) and negative symptoms (which represent a diminution or loss of normal functions) and is widely used in the study of psychopharmacologic therapy [11]. Each subscale is scored 1–7 points ranging from absent to extreme. The range for the positive and negative scales is 7–49, and the range for the general psychopathology scale is 16–112 [11]. The MoCA is a test used to detect mild cognitive decline and early signs of dementia [12]. It contains

11 tests in eight cognitive areas: attention and concentration, executive function, memory, language, visual structure skills, abstract thinking, computation, and orientation. The total score is 30, and ≥26 is considered normal [12]. The mRS is originally developed to evaluate the state of neurological recovery in patients after stroke [13, 14], and it has been extended used to various neurological conditions, including autoimmune encephalitis [15, 16]. The mRS scores are categorized as follows: 0: no symptoms; 1: no significant disability and able to carry out all usual activities; 2: slight disability; 3: moderate disability; 4: moderately severe disability; 5: severe disability; 6: death. Generally, mRS scores of 0–1 indicate a good functional prognosis [13, 14]. The above experimental scales were evaluated by two residents of the psychiatric department of this hospital.

The secondary outcomes were magnetic resonance imaging (MRI), electroencephalogram (EEG), and antibody titer changes. The above experimental scales were evaluated by two Imaging doctors and electroencephalography doctors.

All patients underwent EEG assessments before initiating any treatment, as well as at 3 weeks and 3 months after the start of the treatments. The EEGs were rated as normal, mild, moderate, or severe [17]. The EEG records from the patients were scored as the frequency (n) of "normal and mild background abnormalities (No+Mi)" or "moderate background and severe background abnormalities (Mo+Se)". The improvement rate of EEG was defined as (No+Mi)/total number of patients ×100%. The patients underwent magnetic resonance spectroscopy (MRS) before treatment and 3 months after treatment. The powers of the neurotransmitters Glu and GABA were determined by brain fluctuation mapping, with the Glx/Cr index measured at the top of the left frontal lobe in each patient [18]. The reference powers of Glu and GABA in the brain were determined by Shenzhen Kangli High Tech Co., Ltd. after testing 10,000 healthy people nationwide and were 38.36±12.91 for Glu and 31.67±13.93 for GABA [19, 20]. In order to further explore the influence of drug treatment on the excitatory/inhibitory homeostasis of the brain, the resonance peaks of Glx (contributed by glutamate, glutamine, and GABA together) and Cr (contributed largely by GABA) were obtained at the top of the left frontal lobe by MRS, with the Glx/Cr ratio calculated for each patient before treatment and three months after treatment.

Demographic data were collected from the medical records of included patients, including age, sex, disease course, time of drug initiation and clinical symptoms.

Statistical analysis

Sample size the retrospective nature of the study predetermines the sample size. A priori sample size calculation was not performed.

All analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA). The continuous data were tested for normal distribution using the Shapiro-Wilk test. Continuous data with a normal distribution were represented as means±standard deviations and analyzed using ANOVA and the LSD-t post hoc test. Continuous data with a non-normal distribution were presented as medians (ranges) and analyzed using the Kruskal-Wallis H-test. Paired sample *t*-test signed rank sum test was used to compare before and after treatment. Categorical data were presented using n (%) and analyzed using the chi-squared test or Fisher's exact test. Two-sided P-values<0.05 were considered statistically significant. The graphs were prepared using GraphPad Prism 7.0 (GraphPad Software Inc., San Diego, CA, USA).

Results

According to the inclusion criteria, 97 patients with anti NMDAR encephalitis were included, 2 patients with concomitant tumors were excluded, and 5 patients with incomplete clinical data were excluded. Finally, 90 patients with anti NMDAR encephalitis were enrolled. Patients were grouped according to the adjuvant medications they received: group A (olanzapine group, $n=36$), group B (magnesium valproate group, $n=30$) and group C (lamotrigine group, $n=24$).

Characteristics of the patients

Ninety patients were included in the study. The olanzapine group consisted of 24 males and 12 females. The patients were 28.50±9.29 years old. The median disease course was 9.5 (4.00, 29.05) days. The time to drug initiation was 0 (0, 1) days. The magnesium valproate group included 17 males and 13 females. The patients were 29.97±11.71 years old. The disease course was 10 (5, 20) days. The time to drug initiation was 0 (0, 2) days. The lamotrigine group included 13 males and 11 females. They were 33.88±9.59 years old. The disease course was 10 (6.25, 17.25) days. The time to drug initiation was 0 (1, 3) days. There were no significant differences in the above indicators among the three groups (all $P>0.05$). There were no significant differences in cognitive impairment, motor impairment, speech impairment, autonomic dysfunction, seizures, and decreased consciousness among the three groups before any treatment (all $P>0.05$) (Table 1).

Psychiatric symptoms

Before treatment, there were no significant differences in total PANSS scores, positive symptom scores,

Table 1 Demographic and clinical data of patients with anti-NMDAR encephalitis

Characteristics	Olanzapine ($n=36$)	Magnesium valproate ($n=30$)	lamotrigine ($n=24$)	*P*
Sex (male/female)	24/12	17/13	13/11	0.564
Age (years)	28.50 (12, 57)	29.97 (13, 53)	33.88 (17, 57)	0.137
Disease course (days)	9.5 (4.00, 29.05)	10 (5, 20)	10 (6.25, 17.25)	0.872
Time of drug initiation (days)	0 (0, 1)	0 (0, 2)	0 (1, 3)	0.076
Clinical symptoms, n (%)				
Cognitive impairment	20 (55.56%)	13 (43.33%)	11 (45.83%)	0.577
Motor impairment	16 (44.44%)	15 (50.00%)	8 (33.33%)	0.463
Speech impairment	4 (11.11%)	5 (16.67%)	4 (16.67%)	0.764
Autonomic dysfunction	17 (47.22%)	12 (40.00%)	11 (45.83%)	0.831
Seizures	19 (52.78%)	21 (70.00%)	12 (50.00%)	0.246
Decreased consciousness	18 (50.00%)	15 (50.00%)	7 (29.17%)	0.213

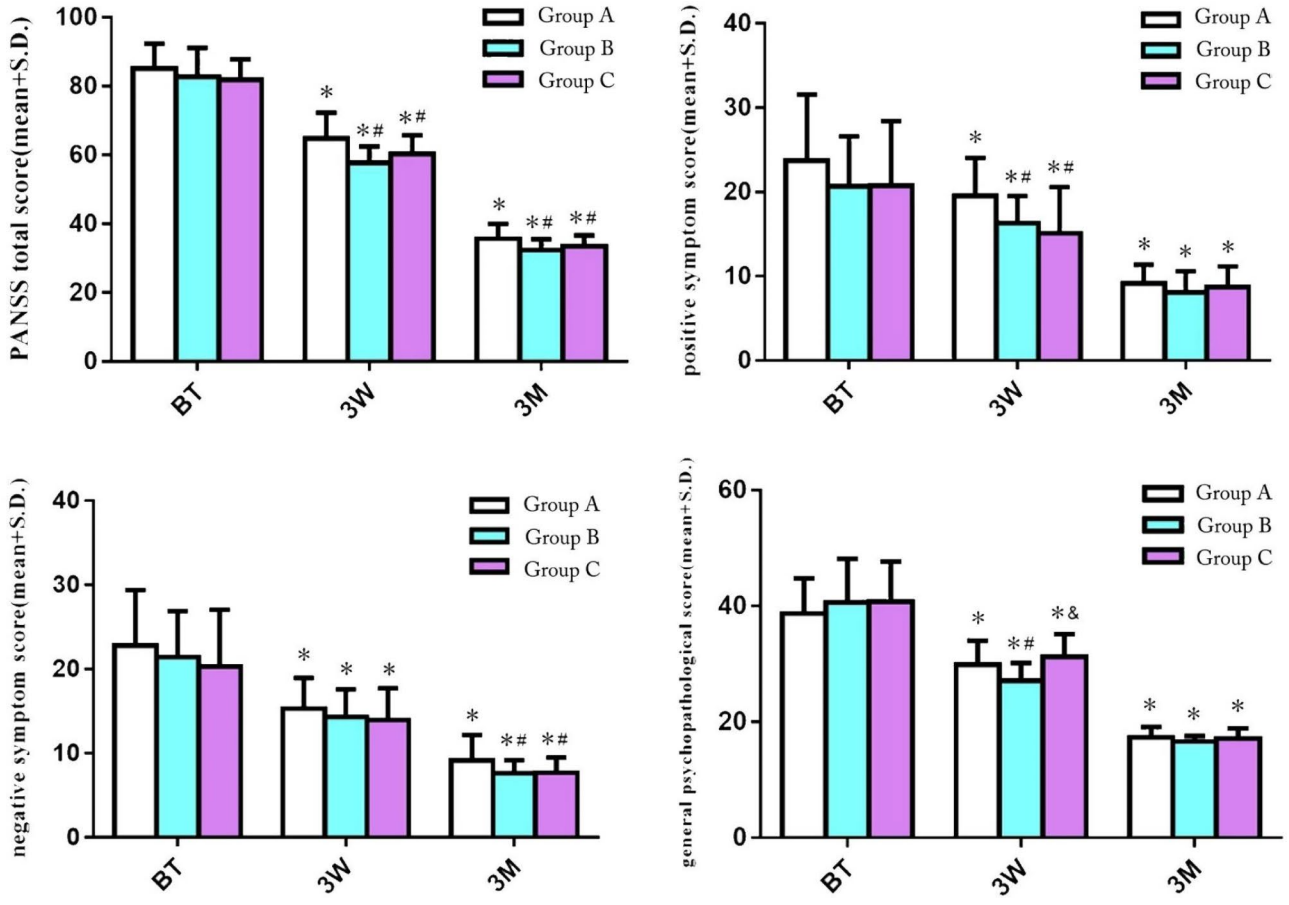

Fig. 1 PANSS score of adjunctive olanzapine (Group A), valproate (Group B) and lamotrigine (Group C) treatments before drug treatment (BT) and at the end of the 3rd week (3 W) and the 3rd month (3 M) after drug intervention

*Statistically significant difference of the means in the same group obtained after relative to before treatment

#Statistically significant different compared with group A at the same time point. &Statistically significant different compared with group B at the same time point

*$P<0.05$, **$P<0.001$, ***$P<0.0001$

negative symptom scores, and general psychopathological scores among the three groups (all $P>0.05$) (Fig. 1). After 3 weeks of treatment, the PANSS total score and positive symptom scores in the magnesium valproate and lamotrigine groups were lower than in the olanzapine group (all $P<0.05$). The general psychopathological scores in the magnesium valproate group were lower than in the olanzapine and lamotrigine groups after 3 weeks of treatment ($P<0.05$) (Fig. 1). After 3 months of treatment, the PANSS total and negative symptom scores

in the magnesium valproate and lamotrigine groups were lower than in the olanzapine group (all $P<0.05$) (Fig. 1).

Cognitive functions

Among the 90 patients, 22 had missing data regarding the MoCA scores, and a total of 68 patients were included in the evaluation of cognitive performance. Among them, 26 patients were in the olanzapine group, 23 were in the magnesium valproate group, and 19 were in the lamotrigine group. Before treatment, the MoCA scores were 21.35±3.76, 22.39±4.30, and 22.26±4.37 in the olanzapine, magnesium valproate, and lamotrigine groups, respectively ($P>0.05$). After 3 months of treatment, the MoCA scores in the olanzapine, magnesium valproate, and lamotrigine groups were improved compared with baseline (all $P<0.05$). Notably, after 3 weeks and 3 months of treatment, the scores in the magnesium valproate and lamotrigine groups were higher than in the olanzapine group (all $P<0.05$) (Fig. 2A).

Functional status of the patients

There were no significant differences in the mRS score among the olanzapine group (0/36, mRS score 0–1/mRS score≥2), the magnesium valproate group (0/30), and the lamotrigine group (0/24) before treatment (all $P>0.05$). After 3 months of treatment, the proportions of patients with an mRS score 0–1 in the magnesium valproate and lamotrigine groups were significantly higher than in the olanzapine group (all $P<0.05$) (Fig. 2B).

EEG characteristics

Before treatment, the EEG ranks were 7/29 (No+Mi/Mo+Se) in the olanzapine group, 7/23 in the magnesium valproate group, and 5/19 in the lamotrigine group.

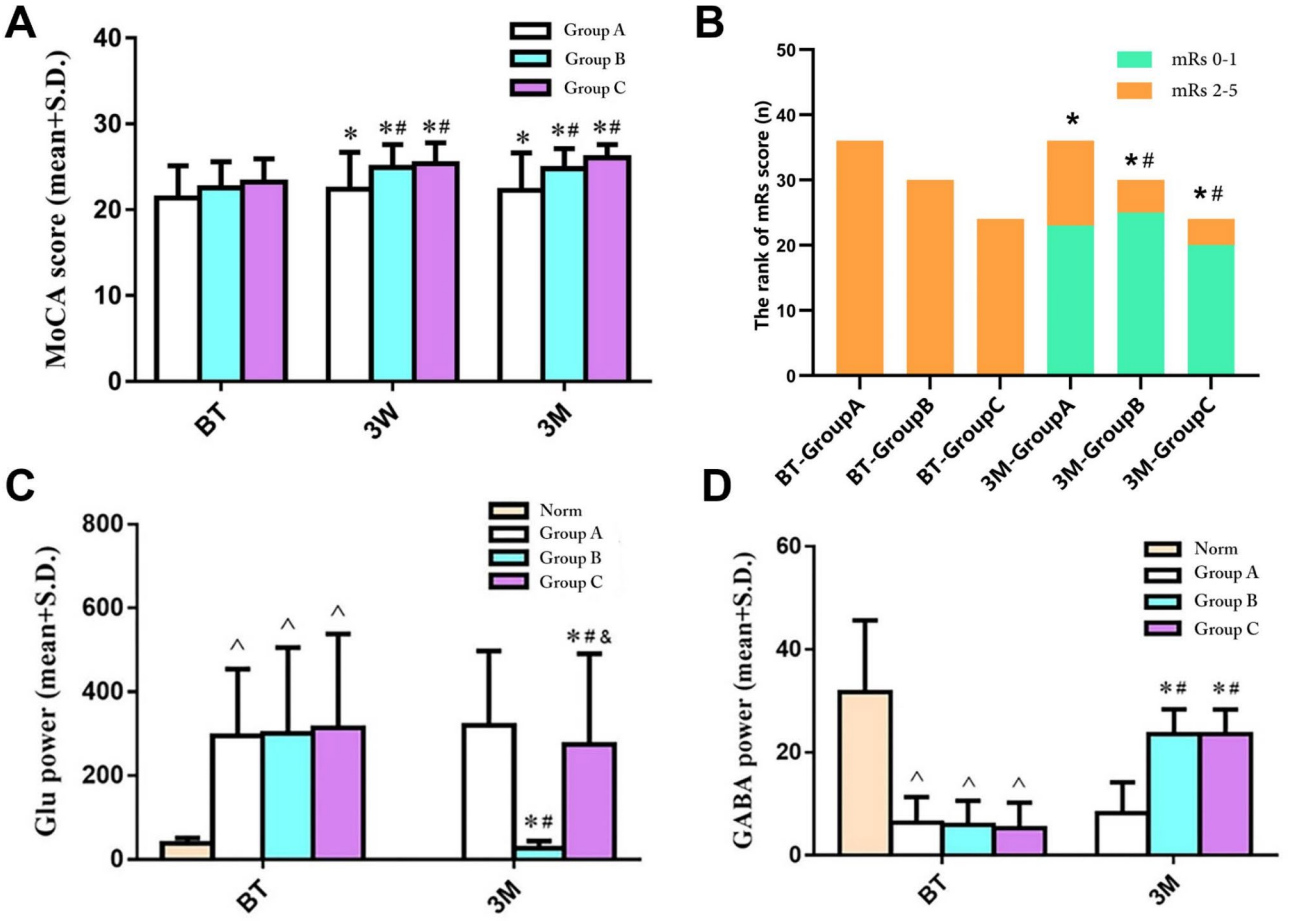

Fig. 2 **A** MoCA score of adjunctive olanzapine (Group A), valproate (Group B) and lamotrigine (Group C) treatments before drug treatment (BT) and at the end of the 3rd week (3 W) and the 3rd month (3 M) after drug intervention. **B** The mRS scores of three groups before drug treatment and the 3rd month after drug intervention. **C** Glu power of three groups before drug treatment and the 3rd month after drug intervention. **D** GABA power of three groups before drug treatment and the 3rd month after drug intervention

*Statistically significant difference of the means in the same group obtained after relative to before treatment

#Statistically significant different compared with group A at the same time point. &Statistically significant different compared with group B at the same time point

*$P<0.05$, **$P<0.001$, ***$P<0.0001$

There were no significant differences among the three groups ($P>0.05$). After 3 weeks and 3 months of treatment, the EEG ranks were as follows: 10/26 after 3 weeks and 18/18 after 3 months in the olanzapine group, 11/19 after 3 weeks, and 24/6 after 3 months in the magnesium valproate group, 12/12 after 3 weeks and 21/3 after 3 months in the olanzapine group. There was a significant improvement in the EEG characteristics after 3 weeks and 3 months of treatment (all $P<0.05$). The abnormality EEG ranks at 3 months were significantly lower in the magnesium valproate and lamotrigine groups compared with the olanzapine group (all $P<0.05$) (Fig. 3A).

Excitatory/inhibitory rebalance

Compared with the reference range for healthy people, the Glu powers (294.41±160.09, 300.55±205.34, and 314.46±224.11 for the olanzapine, magnesium valproate, and lamotrigine groups, respectively) were increased significantly (Fig. 2C), and the GABA powers (6.31±5.04, 5.92±4.68, and 5.26±4.98 for the olanzapine, magnesium valproate, and lamotrigine groups, respectively) were decreased significantly in all three groups before treatment, while no intergroup difference existed at this point (Fig. 2D). The olanzapine group showed no significant alterations in Glu (319.67±177.71) and GABA (8.18±6.01) power after 3 months of treatment. Compared with the olanzapine group, the power of Glu (27.24±16.74) was significantly decreased after treatment, whereas the power of GABA (23.59±4.76) was significantly elevated after treatment in the magnesium valproate group. Similarly, compared with the olanzapine group, the power of Glu (274.66±216.39) was decreased, and the power of GABA (23.55±4.78) was increased after treatment in the lamotrigine group.

Cerebral Glx/Cr ratio measured by MRS

The Glx/Cr ratios before treatment were 0.35±0.24, 0.30±0.10, and 0.28±0.20 for the olanzapine, magnesium valproate, and lamotrigine groups, respectively ($P>0.05$). After 3 months of treatment, the Glx/Cr ratio in the olanzapine group (0.33±0.24) remained comparable to the pre-treatment levels ($P>0.05$). However, in the magnesium valproate group, the Glx/Cr ratio significantly decreased to 0.17±0.09, and in the lamotrigine group, it decreased to 0.14±0.13 compared to the pre-treatment levels (all $P<0.05$). Furthermore, the Glx/Cr ratios obtained after 3 months of treatment were significantly lower in the magnesium valproate and lamotrigine groups compared to the olanzapine group (all $P<0.05$) (Fig. 3B).

Discussion

The findings of this study indicate that the addition of magnesium valproate or lamotrigine to immunotherapy might be associated with lower PANSS scores and higher MoCA scores compared to olanzapine. It has been observed that patients with anti-NMDAR encephalitis show an imbalance between glutamatergic and GABAergic neurotransmission in the brain. The beneficial effects of magnesium valproate and lamotrigine appear to be associated with restoring the balance between excitatory and inhibitory neurotransmission in the brain.

In patients with anti NMDAR encephalitis, the incidence of epileptic seizures is second only to mental

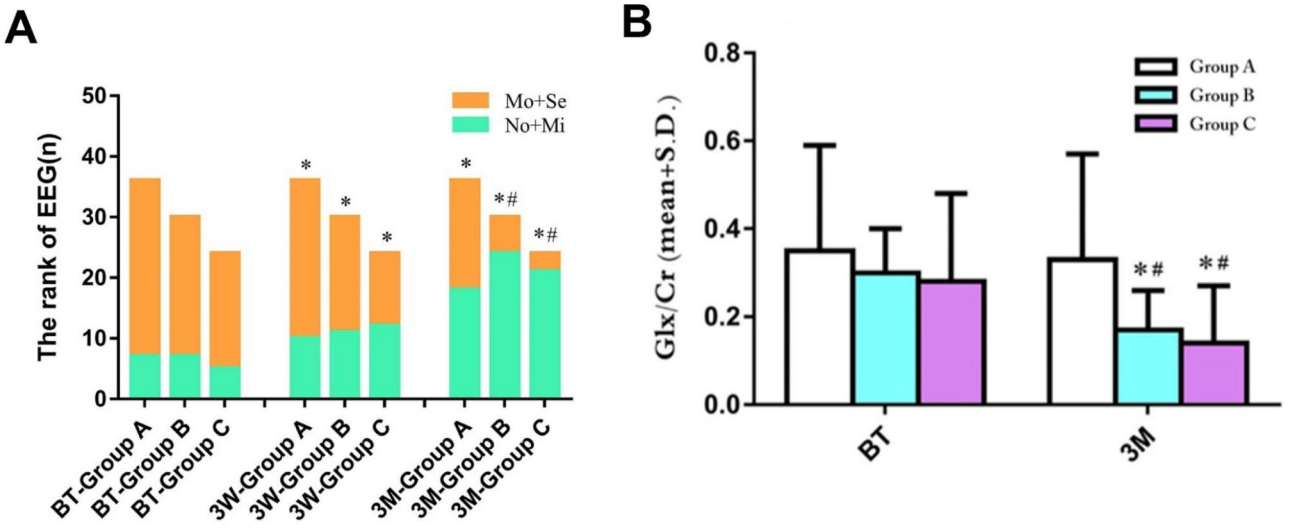

Fig. 3 **A** EEG grading of adjunctive olanzapine (Group A), valproate (Group B) and lamotrigine (Group C) treatments before drug treatment, at the end of the 3rd week and the 3rd month after drug intervention. **B** Frontal lobe Glx/Cr ratio of three groups before drug treatment (BT) and at the 3rd month (3 M) after drug intervention. *Statistically significant different compared with the same group before treatment; #Statistically significant different compared with group A at the same treatment time point

*$P<0.05$, **$P<0.001$, ***$P<0.0001$

disorders, consistent with previous reports. [14, 21]. Other clinical symptoms in the present study included cognitive impairment, autonomic nerve dysfunction, decreased level of consciousness, dyskinesia, and speech disorder, also Consistent with clinical characteristics reported in previous studies [22].

Immunotherapy is the gold standard in the clinical management of anti-NMDAR encephalitis [2, 3]. Because the disease often presents with broad and complex neurological and psychiatric symptoms, other central nervous system medicines can be used for anti-NMDAR encephalitis. Along with the mainstay immunotherapy, adjuvant pharmacological intervention to facilitate the homeostasis of neurotransmission in the brain could be beneficial in the clinical management of anti-NMDAR encephalitis by managing specific symptoms related to the imbalance described above.

Olanzapine, magnesium valproate, and lamotrigine are commonly used antipsychotics in the treatment of schizophrenia, epilepsy, bipolar disorder, and other psychiatric diseases. Although their specific use in anti-NMDAR encephalitis carries little evidence, they can be used to manage psychiatric symptoms. Compared with olanzapine, magnesium valproate and lamotrigine led to lower scores on the PANSS total score and positive symptom scores after 3 weeks of treatment. The MoCA scores were significantly higher with magnesium valproate and lamotrigine than with olanzapine. The proportions of patients with good clinical outcomes of mRS scores in the magnesium valproate and lamotrigine groups were greater than in the olanzapine group after 3 months of treatment.

Olanzapine is a second-generation antipsychotic agent and exhibits high affinity to many neuroactive receptors, such as serotonin, dopamine α-adrenaline, and histamine [23], with limited influence on the glutamatergic pathway [24]. Limited evidence (mostly case reports) supports using olanzapine in anti-NMDAR encephalitis, with some effectiveness [25, 26]. Valproate is approved for manic or mixed episodes associated with bipolar disorder or for the prevention of migraine headaches; it can competitively inhibit GABA transferase and reduce its metabolism to increase the content of GABA in the brain, which may, in turn, inhibit glutamatergic neurons and reduce glutamate release [27, 28]. The evidence for valproate using in anti-NMDAR encephalitis is also limited but appears favorable [29, 30], but the use of valproate before an anti-NMDAR encephalitis diagnosis could possibly interfere with the diagnosis [31]. Lamotrigine mainly blocks glutamate release from the presynaptic membrane [21], inhibiting the excitatory action potential mediated by glutamate and managing seizures. Although lamotrigine has been reported to control the seizures associated with anti-NMDAR encephalitis, the evidence is limited [9, 22, 32]. Previous evidence [33] suggested that the dysfunction of the glutamatergic pathway is related to the epileptic symptoms of anti-NMDAR encephalitis.

However, the mechanism by which NMDAR down-regulation causes complex clinical symptoms in patients with anti-NMDAR encephalitis remains incompletely understood. Some studies have proposed that besides NMDAR down-regulation and resulting glutamatergic hypofunction, an imbalance of excitatory/inhibitory neurotransmission may be involved in the pathogenesis and clinical manifestations among patients with anti-NMDAR encephalitis [5, 34, 35]. Accordingly, the present study showed that such imbalances exist based on the Glu, GABA, and Glx/Cr ratio obtained by MRS and compared with reference values obtained from 10,000 healthy individuals in China [19, 20].

Based on their neuropharmacological characteristics, this study evaluated the clinical benefits of adjuvant administration of olanzapine, magnesium valproate, and lamotrigine in anti-NMDAR encephalitis, particularly about their capability of facilitating the rebalance of excitatory/inhibitory neurotransmission in the brain. Olanzapine treatment did not alter the Glu and GABA powers in the brain, nor the cortical Glx/Cr ratio, which is consistent with the notion that this drug does not modulate the glutamate system in the brain [36]. On the contrary, adjuvant magnesium valproate lowered the Glu power and the Glx/Cr ratio and elevated GABA power in the cerebrum. Similarly, lamotrigine treatment reduced the power of Glu and Glx/Cr ratio but increased the power of GABA in the brain. Importantly, these above differential neurochemical modulations by the three drugs are associated with measurable differences regarding neurological recovery. Thus, compared with olanzapine, magnesium valproate, and lamotrigine showed better therapeutical effects, as indicated by the assessments on the extent of mitigation of mental symptoms, improvement of cognitive function, better functional outcome, and normalization of EEG features in patients with anti-NMDAR encephalitis.

This study had limitations. It was performed at a single hospital and included patients diagnosed over a limited period, resulting in a relatively small sample size. The retrospective nature of the study limited the data that could be analyzed to the ones available in the patient charts. No control group of patients treated with immunotherapy could be included because most patients received adjuvant treatments during the study period. Additional studies with other adjuvant drugs, such as memantine [8], ketamine [9], and intrathecal methotrexate, should be carried out to determine the most optimal adjuvant treatments and determine whether specific subgroups of patients could benefit more from a given drug.

Conclusion

This study shows that based on standard immunotherapy, adjuvant therapeutics aiming to correct the cerebral Glu/GABA or excitatory/inhibitory imbalance, such as valproate and lamotrigine, can improve the clinical outcome among patients with anti-NMDAR encephalitis.

Abbreviations

3M	The 3rd month
3W	The 3rd week
BT	Before drug treatment
Cr	Creatine, contributed largely by GABA
EEG	Electroencephalogram
GABA	Glutamate (Glu) and γ-aminobutyric acid
Glx	Glutamate, contributed by glutamate, glutamine, and GABA together
Mo + Se	Moderate background and severe background abnormalities.
MoCA	Montreal Cognitive Assessment Scale
MRS	Magnetic resonance spectroscopy
mRS	Modified Rankin scale score
NMDAR	N-methyl-D-aspartate receptor
No + Mi	Normal and mild background abnormalities
PANSS	Positive and negative symptom scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-03811-z.

Supplementary Material 1

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Y.H.Y., C.X.Y., B.Z, Z.Y.Y., M.T., Q.L., and J.H.X. The first draft of the manuscript was written by Y.H.Y. and C.X.Y. All authors commented on previous versions of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

I confirm that all methods were performed in accordance with the relevant guidelines. This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study has been approved by the Medical Ethics Committee of Hunan Brain Hospital (approval #2018K065). The requirement for informed consent was waived by the committee because of the retrospective nature of the study. All data were anonymized after extraction and before analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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