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ORIGINAL RESEARCH

CSF Mitochondrial N-Formyl Methionine Peptide as Complementary Diagnostic Tool in Anti-NMDAR Encephalitis and Anti-LGI1 Encephalitis

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Background: Mitochondrial damage is significant in autoimmune diseases, with mitochondrial N-formyl methionine peptide (fMet) being released from damaged mitochondria. However, its potential as a marker for assessing the severity of two kinds of encephalitis - anti-N-methyl-D-aspartate receptor (anti-NMDAR) and anti-leucine-rich glioma-inactivated 1 (LGI1) - remains uncertain. We measured CSF fMet levels in anti-NMDAR encephalitis and anti-LG1 encephalitis patients, assessing its diagnostic and therapeutic potential.

Methods: Twenty-five patients diagnosed with anti-NMDAR encephalitis and nineteen patients with anti-LGI1 encephalitis were included in the study. Their cerebrospinal fluid (CSF) fMet levels were assessed using enzyme-linked immunosorbent assays.

Results: The findings revealed a significant increase in CSF fMet levels, which correlated with modified Rankin Scale (mRS) scores in both anti-NMDAR encephalitis and anti-LGI1 encephalitis patients.

Conclusion: The CSF fMet levels were found to be associated with disease severity in patients diagnosed with both anti-NMDAR encephalitis and anti-LGI1 encephalitis. These findings suggest that preventing mitochondrial damage could serve as an effective treatment strategy for managing these diseases.

Keywords: anti-LGI1 encephalitis, anti-NMDAR encephalitis, mitochondrial damage, mitochondrial N-formyl methionine peptide, modified Rankin scale

Introduction

Autoimmune encephalitis (AE) is an inflammatory disorder characterized by neuropsychiatric symptoms, posing significant challenges globally with regards to disability and mortality rates.[1] The predominant forms of AE include anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis and anti-leucine-rich glioma (anti-LGI1) encephalitis, ranking first and second, respectively.[2] Anti-NMDAR encephalitis manifests due to anti-neuronal autoantibodies, displaying symptoms such as mental disturbances, epilepsy, abnormal movements, behavioral irregularities, hypoventilation, and impaired memory.[3]

Conversely, anti-LGI1 encephalitis manifests clinically with faciobrachial dystonic seizures, cognitive decline, psychiatric ailments, and seizures, and in some cases tumors making a rare occurrence.[4,5] Notably, most instances of anti-LGI1 encephalitis lack a pre-infection history, with the majority of patients being middle-aged to elderly men, typically experiencing onset around 60 years of age. In contrast, anti-NMDAR encephalitis is more prevalent among women and children.[6]

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Several studies propose an association between AE and various circulating anti-neuronal antibodies specific to surface and intracellular antigens, serving as potential biomarkers.[7,8] Despite this, the AE current diagnosis primarily hinges on clinical manifestation, imaging examinations and antibody detection in cerebrospinal fluid (CSF) and/or serum samples. Yet these tests may yield false positive results and are economically burdensome, underscoring the critical need for identifying novel CSF biomarkers for AE.

Damage-associated molecular patterns (DAMPs) released by mitochondria consist of mitochondrial N-formyl peptides (mtNFPs), mitochondrial DNA (mtDNA), reactive oxygen species (ROS), and the structural phospholipid, cardiolipin. These molecules are recognized as alarmins by innate immune system receptors, prompting an inflammatory response.[9,10]

The innate immune response plays a crucial role in detecting and eliminating both infectious and sterile insults. For the innate immune system, mtNFPs are perceived as pathogens, initiating inflammation by activating the formyl peptide receptor (FPR).[11,12] Duvvuri et al reported elevated mtNFP levels (total fMet) in the circulation of rheumatoid arthritis patients, underscoring the significance of mtNFP in sterile inflammatory responses.[13] Thus, evaluating mtNFPs is essential for understanding AE's pathophysiology. In this study, we measured CSF fMet levels in anti-NMDAR encephalitis and anti-LG1 encephalitis patients, assessing its diagnostic and therapeutic potential. Additionally, we explored associations between patient mtNFP profiles and modified Rankin Scale (mRS) scores.[14]

Materials and Methods

Patients and Controls

We enrolled 25 patients diagnosed with anti-NMDAR encephalitis, 19 patients diagnosed with anti-LGI1 encephalitis, and 17 controls without inflammatory neurological diseases from two clinical centers into this study. All patients were admitted to the hospital between 2019 and 2021.[15,16] The diagnosis of anti-NMDAR encephalitis was established based on patient symptoms and the detection of anti-NMDAR antibodies in CSF using a cell-based assay. Similarly, the diagnosis of anti-LGI1 encephalitis was based on clinical manifestations in patients and the presence of anti-LGI1 antibodies in plasma. Detailed demographic data of patients with anti-NMDAR encephalitis, patients with anti-LGI1 encephalitis, and controls are presented in Table 1. The revised anti-NMDAR encephalitis diagnosis criteria of 2016 were used as the inclusion criteria for the anti-NMDAR encephalitis group.[15] Patients with confirmed LGI1 antibodies were included irrespective of age or clinical syndrome.[17] Among 25 patients with anti-NMDAR encephalitis, 12 cases were treated with low-dose glucocorticoids to prevent recurrence, 7 cases took AZA orally, and 6 cases took MMF orally. 17 patients with anti-LGI1 encephalitis, 10 cases were treated with low-dose glucocorticoids to prevent recurrence, 4 cases took AZA orally, and 4 cases took MMF orally. This study was approved by the Ethics Committee of The Affiliated Brain Hospital of Guangzhou Medical University, and all participants provided informed consent.

Clinical Evaluation and Follow-Up

Neurological status was evaluated using the mRS for each patient. In the acute stage, all individuals diagnosed with anti-NMDAR encephalitis and anti-LGI1 encephalitis underwent mRS assessment. Patients were followed up with mRS reassessment and CSF resampling six months post-discharge.

Preparation of CSF Samples

CSF samples were obtained via lumbar puncture within three days of admission before initiating treatment, and subsequently at six months after both first and second-line immune therapy. All CSF samples were promptly centrifuged and then divided into aliquots, which were stored in polypropylene tubes at −80°C until further analysis.

Detection of fMet and Proinflammatory Cytokines by Enzyme-Linked Immunosorbent Assays (ELISA)

The levels of fMet were assessed using ELISA kits from My BioSource Inc., San Diego, CA, following the manufacturer's protocols. Additionally, sandwich ELISA kits were utilized to measure levels of inflammatory cytokines IL-6, IL-

Table 1 Clinical Characterization of Anti-NMDAR Encephalitis, Anti-LGI-1 Encephalitis and Control

Items	Anti-NMDAR Encephalitis (n=25)	Anti-LGI-1 Encephalitis (n=19)	Control (n=17)
Gender (male/female)	11/14	15/4	8/9
Age (years, mean ±SD)	37.48±11.84	55.16±7.07	27.53±9.90
Clinic symptoms (n, %)			
Psychiatric symptom	15 (60)	4 (21)	0
Disorders of memory	11 (44)	6 (31.6)	0
Epilepsy	8 (32)	7 (36.8)	0
FDBS	0 (0)	5 (26.3)	0
Status epileptics	5 (20)	3 (15.8)	0
Treatment (n, %)			
Plasma exchange	13 (52)	6 (31.6)	-
Steroids	18 (72)	9 (47.4)	-
MMF	12 (48)	8 (42.1)	-
AZA	10 (40)	5 (26.3)	-
IVIg	17 (68)	12 (63.2)	-
Operation	4 (16)	0 (0)	-
Tumor comorbidity (n, %)	4 (16)	1 (5.2)	0
Anti-NMDAR antibody positive (n, %)			
CSF	25 (100)	-	0
Plasma	19 (76)	-	0
Anti-LGI-1 antibody positive (n, %)			
CSF	-	9 (47.4)	0
Plasma	-	19 (100)	0

Note: - means negative.

10 (Bender MedSystems GmbH, Vienna, Austria), and TNF-α (Cusabio, Wuhan, China), in accordance with the respective manufacturers' instructions.

Statistical Analysis

The analysis was conducted using the R statistical language (version 3.6.3), with visualization conducted using the ggplot2 package. Data are expressed as mean ± standard deviation (SD) for normally distributed data. For non-normally distributed data, mRS scores are presented as medians (min, max). Differences in fMet among groups were assessed using one-way ANOVA. Spearman's test was employed to evaluate correlations between fMet and inflammatory cytokines. All tests were two-sided. $P < 0.05$ was defined as statistically significant (*$P < 0.05$; **$P < 0.01$).

Results

Demographic and Clinical Features

Demographic data from patients with anti-NMDAR (n = 25) and anti-LGI1 (n = 19) encephalitis, as well as controls (n = 17), are outlined in Table 1. Anti-NMDAR encephalitis patients all tested positive for anti-NMDAR autoantibodies in CSF, while those with anti-LGI1 encephalitis had detectable anti-LGI1 autoantibodies in plasma. Predominant symptoms among both AE types included psychiatric manifestations, memory impairment, and epilepsy. Tumor screening revealed concurrent teratomas in four anti-NMDAR encephalitis cases and one anti-LGI1 encephalitis case. Along with tumor resection, all patients received first-line immunotherapy comprising mycophenolate mofetil (MMF), azathioprine (AZA), intravenous immunoglobulin (IVIg), or plasma exchange, either individually or in combination.

To explore the role of fMet in AE, we assessed CSF fMet levels in patients diagnosed with anti-NMDAR encephalitis (n = 25) or anti-LGI1 encephalitis (n = 19), along with control subjects (n = 17). As illustrated in Figures 1A and 2A, both cohorts of AE patients demonstrated markedly elevated CSF fMet levels compared to the control group (both $p < 0.01$).

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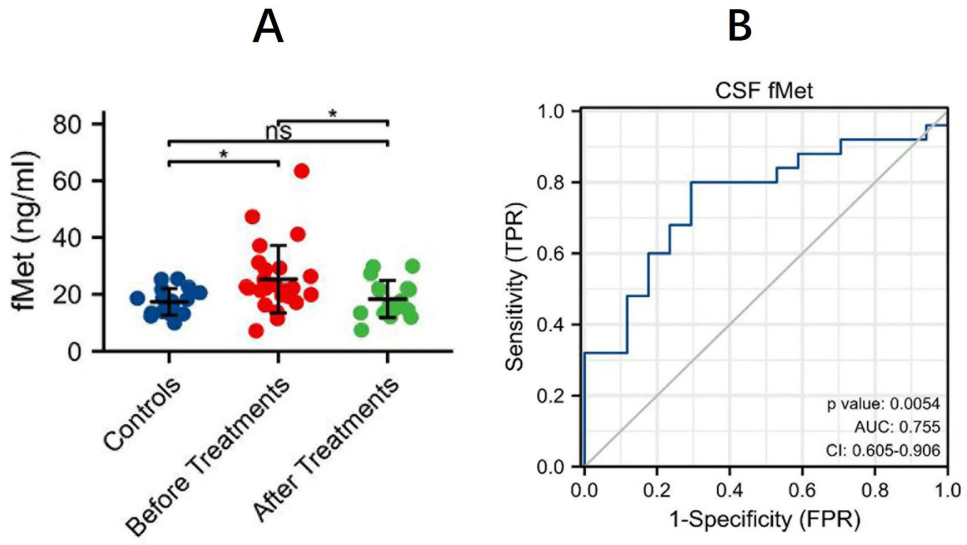

Figure 1 The CSF fMet levels in patients with anti-NMDAR encephalitis and the ROC curve analysis of CSF fMet in anti-NMDAR encephalitis patients to distinguish from controls. The CSF fMet levels were notably increased in patients with anti-NMDAR encephalitis (**A**). Additionally, the ROC curve of CSF fMet was designed to assess its potential diagnostic value in patients with anti-NMDAR encephalitis (**B**). Results are expressed as the mean ± SD, *P < 0.05 versus the indicated group.

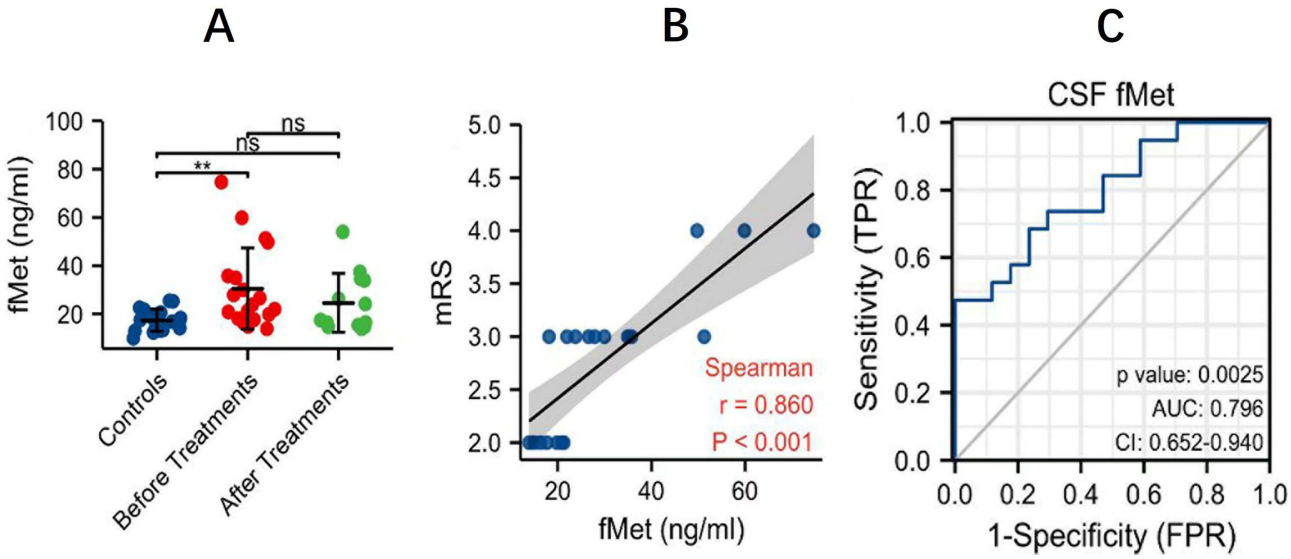

Figure 2 The CSF fMet levels and its correlation with mRS score in anti-LGI1 encephalitis patients and the ROC curve analysis of CSF fMet in anti-LGI1 encephalitis patients to distinguish from controls. The CSF fMet levels showed a significant elevation in patients with anti-LGI1 encephalitis (**A**). Furthermore, a correlation analysis revealed a relationship between the CSF fMet levels and mRS scores of patients (**B**). Additionally, the ROC curve of CSF fMet was designed to assess its potential diagnostic utility in patients with anti-LGI1 encephalitis (**C**). Results are expressed as the mean ± SD, **P < 0.01 versus the indicated group.

Altered CSF Levels of fMet Before and After Treatment

To evaluate the therapeutic efficacy of fMet, we examined alterations in CSF levels of fMet alongside inflammatory cytokines in patients with anti-NMDAR encephalitis and anti-LGI1 encephalitis. Following six months of treatment, a notable reduction in CSF fMet levels was observed in patients with anti-NMDAR encephalitis compared to pre-treatment levels ($p < 0.05$). Conversely, in patients with anti-LGI1 encephalitis, changes in CSF fMet levels did not reach statistical significance ($p > 0.05$); however, a significant positive correlation was noted between CSF fMet levels and mRS scores ($p<0.01$) (Figure 2B).

Receiver Operating Characteristic (ROC) Curve Analysis

We conducted ROC analysis to assess the efficacy of CSF fMet levels in discriminating between patients with anti-NMDAR encephalitis and anti-LGI1 encephalitis compared to control patients. For anti-NMDAR encephalitis patients, the area under the curve (AUC) for CSF fMet levels was 0.755 (95% CI: 0.605–0.906, p = 0.0054), indicating its ability to distinguish patients from controls (Figure 1B). Similarly, for patients with anti-LGI1 encephalitis, the AUC was 0.796 (95% CI: 0.652–0.940, p = 0.0025), underscoring its effectiveness in differentiating patients from controls (Figure 2C). These findings underscore the promising diagnostic potential of CSF fMet levels for both anti-NMDAR encephalitis and anti-LGI1 encephalitis.

Discussion

In our cross-sectional study, we analyzed the CSF of 25 patients with anti-NMDAR encephalitis, 19 patients with anti-LGI1 encephalitis, and 17 controls diagnosed with non-inflammatory neurological diseases. While specific AE types are often characterized by distinctive CSF abnormalities or serum biomarkers — such as the presence of anti-NMDAR antibodies in CSF from anti-NMDAR encephalitis patients and anti-LGI1 antibodies in the serum of anti-LGI1 encephalitis patients — various other cellular and biochemical abnormalities in the CSF can also be manifested.[18,19] According to literature reports, certain treatment methods, such as intravenous immunoglobulin (IVIG) and oophorectomy, can potentially influence the measurement results of biomarkers. Clinical researchers have found that patients with autoimmune encephalitis passively acquire thyroid autoantibodies after intravenous injection of immunoglobulin.[20] In addition, studies have found that the failure to improve after ovarian resection may be a hallmark of recurrent ovarian teratoma in anti-NMDAR encephalitis.[21] Our findings highlight CSF fMet as a promising biomarker of mitochondrial damage in both anti-NMDAR encephalitis and anti-LGI1 encephalitis patients, suggesting a potential link between CSF fMet and the underlying pathogenesis of these diseases. This discovery holds significant promise for facilitating early AE diagnosis and enhancing therapeutic interventions.

Mitochondria play an active role in regulating innate immune responses against both infectious and sterile insults. The innate immune system identifies endogenous DAMPs and exogenous pathogen-associated molecular pattern molecules (PAMPs), initiating either a non-infectious or pathogen-induced inflammatory response, respectively.[9,22] DAMPs encompass circular mtDNA and mtNFPs. The measurement of mitochondrial DAMPs is promising when it comes to predicting disease severity and outcomes. In a previous study, we identified cell-free mtDNA as a potential biomarker of mitochondrial damage in anti-NMDAR encephalitis, revealing significantly elevated levels of CSF cell-free mtDNA in affected patients.[23] mtNFPs act as potent neutrophil chemotactic peptides and innate immune system activators. Through signaling via FPR1, they can prompt the release of ROS from neutrophils, potentially leading to tissue damage upon sustained neutrophil activation.[24,25]

FPR is expressed in various cell types, including phagocytes, leukocytes, endothelial cells, and microglia, and mtNFPs are capable of activating FPR in the lung and cardiovascular system.[11,12] Wang et al demonstrated that CSF TNF-α and IL-6 exacerbate memory impairment in animals treated with anti-NMDAR antibodies, underscoring the pivotal role of inflammatory factors in chronic neuroinflammation-induced neuronal dysfunction.[26] In our study, we observed increased levels of CSF IL-6, IL-10, and TNF-α in both anti-NMDAR encephalitis and anti-LGI1 encephalitis patients during the acute stage, although this data was not provided. Additionally, mtNFP levels were found to be correlated with CRP and ESR, which are commonly included in disease activity indexes.[13] Our team has previously established that elevated levels of inflammatory cytokines are associated with disease activity in anti-NMDAR encephalitis patients.[23,27] We hypothesize that N-formyl peptides/FPR play an active role in local brain inflammation, contributing to the accumulation of inflammatory factors in the CSF, thus promoting brain dysfunction and a spectrum of clinical symptoms. However, further investigations are warranted to validate this hypothesis.

Both groups of AE patients underwent either first-line or second-line immunotherapy for a duration of 6 months. Following treatment, anti-NMDAR encephalitis patients exhibited a significant reduction in CSF fMet levels, whereas such a decrease was not observed in anti-LGI1 encephalitis patients. Furthermore, in anti-LGI1 encephalitis patients, there was a positive correlation between mRS scores and CSF fMet levels, unlike in anti-NMDAR encephalitis patients.

However, it's important to acknowledge that our study has limitations, with regard to the use of mRS only for evaluating neurological manifestations. As the mRS primarily assesses physical disability, its utility in capturing the full spectrum of neurological outcomes, such as mental symptoms, epilepsy, or cognitive impairment, in AE patients may be limited.[28] To address this limitation, future studies may benefit from employing the Clinical Assessment Scale in Autoimmune Encephalitis (CASE).[29]

When analyzing NMDAR antibodies solely in serum, there's a potential for false negative outcomes among patients with anti-NMDAR encephalitis. Similarly, antibodies targeting LGI1 may not always be detectable in the CSF.[30,31] Consequently, the absence of autoantibodies does not preclude an AE diagnosis, underscoring the necessity for additional biochemical markers to corroborate suspicions of AE. Our discoveries suggest that fMet holds promise as a novel diagnostic biomarker. In future, our research aims to elucidate the mechanisms through which fMet induces tissue damage and cellular loss, as well as identify pertinent targets for the treatment of patients with AE. This article did not include results on cytokines, which is a limitation of the study. The abnormal elevation of cytokines such as IL-6 has been confirmed in previous studies, and mitochondrial damage is an important manifestation of neuroinflammation. In the future, our team will continue to study the correlation between changes in inflammatory factors and mitochondrial damage in anti-NMDAR encephalitis.

Conclusion

In our investigation, we observed a correlation between CSF levels of fMet and disease severity among patients afflicted with anti-NMDAR encephalitis and anti-LGI1 encephalitis. Moreover, safeguarding against mitochondrial damage could emerge as a promising therapeutic approach for these conditions. Our results underscore the potential utility of fMet as a novel diagnostic biomarker in AE disorders.

Abbreviations

AE, Autoimmune encephalitis; anti-NMDAR, anti-N-methyl-D-aspartate receptor; anti-LGI1, anti-leucine-rich glioma; CSF, cerebrospinal fluid; DAMPs, Damage-associated molecular patterns; mtNFPs, mitochondrial N-formyl peptides; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; FPR, formyl peptide receptor; mRS, modified Rankin Scale; ELISA, Enzyme-Linked Immunosorbent Assays; SD, standard deviation; MMF, mycophenolate mofetil; AZA, azathioprine; IVIg, intravenous immunoglobulin; AUC, area under the curve; PAMPs, pathogen-associated molecular pattern molecules; CASE, Clinical Assessment Scale in Autoimmune Encephalitis.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University (No. 2021-032). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Disclosure

The authors declare that they have no competing interests.

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