The clinical significance of ubiquitin carboxyl hydrolase L1 and its autoantibody in neuropsychiatric systemic lupus erythematosus

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Abstract

Objective

To identify specific cerebrospinal fluid (CSF) biomarkers for the diagnosis and disease severity evaluation of neuropsychiatric systemic lupus erythematosus (NPSLE).

Methods

Patients presented with neuropsychiatric symptoms were recruited and categorised as 36 NPSLE, 19 SLE controls, 4 other connective tissue disease (CTD) controls and 10 nervous system disorder (NSD) controls. The NPSLE group consisted of severe NPSLE (sNPSLE) and mild NPSLE (mNPSLE). Potential biomarkers were determined by Luminex multiplex assay and enzyme-linked immunosorbent assay.

Results

1) Among a variety of neurological disease-related proteins, only ubiquitin carboxyl hydrolase L1 (UCH-L1) levels were significantly elevated in the CSF samples of sNPSLE patients compared with those of mNPSLE patients (p=0.020) and SLE controls (p=0.037). CSF UCH-L1 levels were significantly positively correlated with SLE disease activity index and overlap number of NPSLE manifestations. 2) CSF anti-UCH-L1 autoantibodies were significantly elevated in patients with NPSLE in comparison to all of the control groups, with a sensitivity of 53% and a specificity of 91% for NPSLE. CSF anti-UCH-L1 levels were associated with organ involvement and were positively correlated with serum anti-UCH-L1 levels in the NPSLE patients (r=0.4551, p=0.0382).

Conclusion

Anti-UCH-L1 is a promising CSF biomarker for NPSLE diagnosis with high specificity, and the elevated levels of CSF UCH-L1 reflect the clinical severity of NPSLE. The elevation of UCH-L1 and its autoantibody in NPSLE patients showed us novel aetiological insights on NPSLE.

Key words

UCH-L1, anti-UCH-L1, neuropsychiatric systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by the dysfunction of immune cells, a broad spectrum of autoantibodies and multiple organ involvement. Neuropsychiatric systemic lupus erythematosus (NPSLE) is a common and fatal complication in severe SLE that includes neurologic and psychiatric syndromes observed in SLE patients in which other causes have been excluded (1). As reported in a 50-year meta-analysis, neuropsychiatric and renal damage negatively affected the overall 5-year survival, whereas neuropsychiatric damage remained the same for 10-year survival (2).

The lack of specific biomarkers has limited the accurate diagnosis of NPSLE in clinical practice. Compared with serum biomarkers, cerebrospinal fluid (CSF) biomarkers showed superior sensitivity and accuracy due to the direct contact of CSF with nerve tissue damage in NPSLE. Studies on CSF biomarkers were initiated in the 1980s, and more than 20 biomarkers have been reported so far, including autoantibodies (anticardiolipin (AcL), anti-rRNP, anti-U1RNP), antigens (β2-GPI), cytokines (IL-1, 2, 6, 8; IFN-α, γ) and other molecules (MMP-9). However, some of these findings lacked consistency and novel biomarkers are still in need to achieve good efficacy for diagnosis or disease severity evaluation (3).

UCH-L1 is a neuronal cytoplasm protein mainly expressed in large neurons such as Purkinje cells, brain stem nuclei neurons and basal ganglia neuron (4), and it has a 50-fold higher concentration in the brain than in other tissues. The most important function of this protein is to regulate the ubiquitin proteasome system and synaptic remodelling (4). It has been reported that the abnormal function of UCH-L1 is involved in the pathogenesis of neurodegenerative diseases, glomerular foot processes injury, tumours and diabetes (4, 5). In this study, we revealed the role of ubiquitin carboxyl hydrolase L1 (UCH-L1) in disease severity evaluation of NPSLE and identified its autoantibody as a promising CSF biomarker in NPSLE diagnosis. By studying the relevance of CSF UCH-L1, anti-UCH-L1 and different NPSLE manifestations, we provided novel clues to understand molecular mechanisms of NPSLE.

Material and methods

Patients and samples

CSF samples were collected from 36 NPSLE patients, 19 SLE controls, 4 other connective tissue disease (CTD) controls and 10 other nervous system disorder (NSD) controls. All of the controls presented with neuropsychiatric symptoms and were excluded from NPSLE. All patients did not receive glucocorticoid pulse therapy before CSF collection. Bloody CSF samples were excluded. Matched serum samples were collected from 21 NPSLE patients and 6 SLE controls. All of the SLE patients fulfilled the 1997 (6) ACR criteria for SLE, and systemic lupus erythematosus disease activity index 2K (SLEDAI-2K) was calculated to evaluate the severity of SLE (7). All of the NPSLE patients were diagnosed by consultation with rheumatologists, neurologists and psychiatrists and fulfilled the 1999 NPSLE ACR nomenclature and case definitions (1). The NPSLE patients were categorised as severe NPSLE (sNPSLE, patients fulfilled 2001 Ainiala's revised criteria (8)) and mild NPSLE (mNPSLE, patients with only headache or mild depression, excluded by the 2001 criteria but conformed to the 1999 criteria). NPSLE patients combined with other connective tissue diseases (including antiphospholipid syndrome) were excluded. Other CTD controls included one patient who fulfilled the 2002 classification criteria for Sjögren's syndrome proposed by the American-European Consensus Group (9), one patient with necrotising lymphadenitis due to immune disorders, and two patients with undefined CTDs. The study was approved by the Ethics Committee of Peking University People's Hospital (Approval No. 2014PHB087-03). All participants of this study provided informed consent for participation in this study.

Identification of proteins

All candidate proteins were measured using multiplex bead assays (Human

Neurological Disorders Magnetic Beads Panel 1; 96-well plate format; EMD Millipore, Billerica, MA, USA) incorporated in 6 MILLIPLEX MAP panels run on the Luminex 200 (Luminex Corporation, Austin, TX, USA) instrument according to the manufacturer's instructions.

Measurements of UCH-L1 autoantibody

Full-length recombinant human UCH-L1 (233 a.a.) was purchased from Beijing TDY Biotech Co., LTD, Beijing, China. Anti-UCH-L1 levels were measured using indirect ELISA. UCH-L1 was diluted in 0.05 M carbonate buffer, and the final solution concentration was 10 μg/ml. The 96-well plates were coated for 72 h at 4°C with this UCH-L1 solution (1 μg UCH-L1 per well). The plates were blocked with reagent diluent containing 3% BSA in PBS (137 mM NaCl, 2.7 mM KCl, 8.1 mM Na_2HPO4, 1.5 mM KH_2PO4, PH 7.2–7.4, 0.2 μm filtered) for 3.5 hours. The plates were washed 4 times with 0.05% Tween 20 in PBS during each step. A total of 100 μl CSF samples, serum samples (1:50 dilution), and standards were added into wells of the plate, incubated at room temperature for 1 h, and washed 6 times with 0.05% Tween 20 in PBS. The antibody was detected by a biotinylated goat anti-human IgG (R&D Corporation, Minneapolis, MN, USA) and streptavidin conjugated to horseradish-peroxidase (R&D Corporation, Minneapolis, MN, USA). After 0.5 h, Tetramethylbenzidine (Neobioscience, Beijing, China) was added as the substrate solution, and 10 minutes' later, the colour reaction was stopped by the addition of 50 μl 2 M sulphuric acid. Absorbance at 450 nm was measured using a microplate reader (Bio-Rad, model no. 550). The values of OD of anti-UCH-L1 were transformed to arbitary units (AU), calculated as:

$$AU = [OD_{antigen}\text{-}OD_{non\text{-}specific\ background}]_{test\ CSF} / [OD_{antigen}\text{-}OD_{non\text{-}specific\ background}]_{positive\ control\ CSF} \times 100$$

Statistical analysis

The Statistical Package for Social Sciences (SPSS) v. 20.0 was used to analyse the data. Descriptive statistics for continuous variables were expressed as the mean ± SD, and presented using the using the *t*-test (normal distribution), Mann-Whitney U-test (abnormal distribution) and Tukey-Kramer method (multiple comparison) respectively. Pearson's correlation coefficient were applied to detect the correlation between two groups. *p*-values less than 0.05 were considered significant. Receiver operating characteristic (ROC) curves were applied to evaluate the significance of the anti-UCH-L1 in the diagnosis of NPSLE.

Table I. Demographic characteristics and neuropsychiatric manifestations of the 69 patients.

Type of diseases	Number of patients (%)	Age(years ± SD)
sNPSLE	23	33 ± 11
Cerebrovascular disease	12	39 ± 12
Seizure disorders	8	28 ± 6
Acute confusional state	4	41 ± 15
Neuropathy, cranial	4	32 ± 4
Autonomic disorder	3	36 ± 15
Cognitive dysfunction	2	32 ± 3
Aseptic meningitis	1	28
Movement disorder	1	28
Psychosis	1	45
Polyneuropathy	1	35
mNPSLE	13	29 ± 7
Headache	12	30
Mood disorder	1	19
SLE control	19	35 ± 13
Other CTD control	4	39 ± 18
Other NSD control	10	47 ± 5

sNPSLE: severe NPSLE; mNPSLE: mild NPSLE; SLE control: patients with neuropsychiatric manifestations not related to SLE; CTD: connective tissue disease; NSD: nervous system disorder. Descriptive statistics were expressed as mean ± SD.

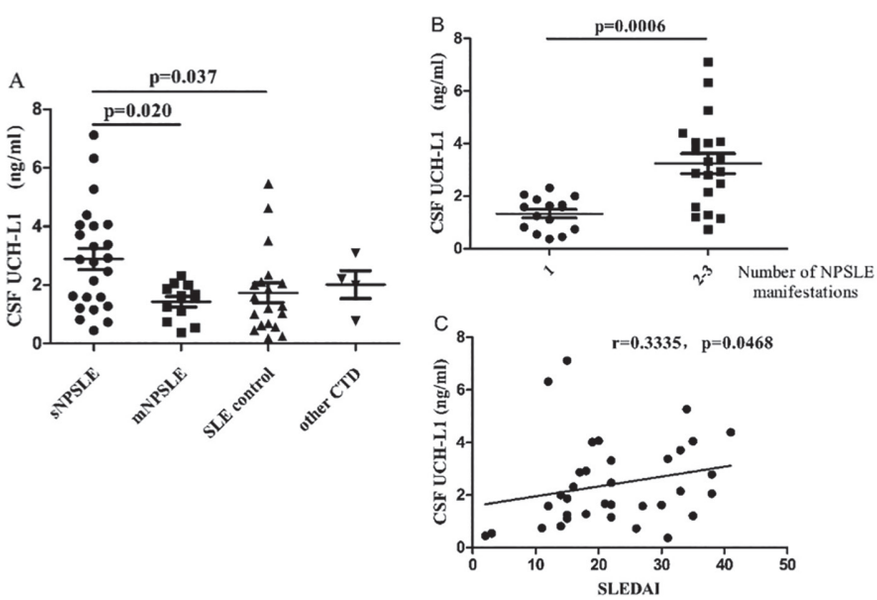

Fig. 1. CSF UCH-L1 in different groups and its association with NPSLE disease severity.
A: The study in the expanded patient groups validated that CSF UCH-L1 levels were significantly elevated in sNPSLE patients as compared to mNPSLE patients, SLE controls and other CTDs. sNPSLE, severe NPSLE; mNPSLE, mild NPSLE; CTD: connective tissue disease.
B: CSF UCH-L1 levels were evidently elevated in the NPSLE patients with 2-3 overlapped neuropsychiatric manifestations as compared to those with only one manifestation.
C: CSF UCH-L1 levels were positively correlated with SLEDAI-2K in the NPSLE patients.

Results

CSF UCH-L1 levels were elevated in severe NPSLE and associated with disease severity

To screen potential biomarkers of NP-

SLE, we determined and compared the concentrations of 6 candidate neurological disease related proteins, including UCH-L1, total Tau protein, phospho-Tau protein, DJ-1 protein, nerve growth factor (NGF) and α-synuclein (α-SYN), in CSF samples from 10 NPSLE patients (6 sNPSLE and 4 mNPSLE) and 6 SLE controls. Elevated CSF UCH-L1 levels were detected in sNPSLE patients (4.79±1.75 ng/ml) compared with those in mNPSLE patients (1.37±0.47 ng/ml, p=0.011) and SLE controls (1.35±0.53 ng/ml, p=0.005). The other candidate proteins did not show significant differences between different disease groups.

We further determined CSF UCH-L1 levels in an enlarged NPSLE patient cohort. CSF samples of 23 sNPSLE, 13 mNPSLE and 19 SLE controls were included. The demographic characteristics and neuropsychiatric manifestations of these patients were shown in Table I. Among the 19 neuropsychiatric manifestations defined by 1999 NPSLE criteria, 12 manifestations were present in the NPSLE patients, and 61.1% (22/36) of them showed two or more overlapped neuropsychiatric manifestations. Apart from one patient with mild depression, all of the mNPSLE patients merely presented with lupus headache.

The study in the expanded patient group validated the elevated CSF UCH-L1 levels in sNPSLE patients (2.89±1.73 ng/ml) compared with those in mNPSLE patients (1.43±0.6 ng/ml, p=0.020) and in SLE controls (1.73±1.41 ng/ml, p=0.037, Fig. 1A). Meanwhile, it should be noted that 2 SLE controls also showed elevated UCH-L1 levels. These two patients were diagnosed with severe hyponatremia (5.46 ng/ml) and intracranial tuberculosis infection (4.63 ng/ml), respectively.

According to our study, elevated CSF UCH-L1 levels were associated with overlapped NPSLE manifestations (p=0.0006, Fig. 1B) and SLEDAI-2K (r=0.3335, p=0.0468, Fig. 1C), and were more common in patients with positive AcL (p=0.037, Table II).

Additionally, we determined UCH-L1 levels in the serum of the NPSLE patients and SLE controls, whose CSF samples have been determined. However, it was not detectable in serum samples (<0.11 ng/ml).

Table II. Cerebrospinal fluid UCH-L1 concentrations in the presence or absence of organ involvements and laboratory parameters.

	UCH-L1(ng/ml)		p-value
	presence	absence	
Organ involvements			
Cardiac involvement	3.05 ± 2.14	2.33 ± 1.60	0.587
Lung involvement	2.65 ± 1.90	2.35 ± 1.61	0.756
Lupus nephritis	2.63 ± 1.64	2.13 ± 1.61	0.315
Proteinuria	2.66 ± 1.47	2.22 ± 1.73	0.203
Haematuresis	2.83 ± 1.23	2.14 ± 1.79	0.05*
Elevated Scr	3.99 ± 1.58	2.07 ± 1.46	0.006†
Haematologic involvement	2.92 ± 1.79	1.66 ± 1.02	0.019*
Serological tests			
Increased IgG	2.75 ± 1.74	2.17 ± 1.55	0.267
Increased CRP	3.18 ± 2.16	2.17 ± 1.41	0.284
Increased ESR	2.62 ± 1.69	1.98 ± 1.43	0.27
Decreased C3 or C4	2.34 ± 1.26	2.60 ± 2.81	0.41
Anti-dsDNA	2.21 ± 1.11	2.40 ± 2.04	0.713
ANuA	2.13 ± 1.31	2.74 ± 1.99	0.484
Anti-r-RNP	2.75 ± 2.24	2.31 ± 1.49	0.796
Anti-U1RNP	2.02 ± 1.75	2.66 ± 1.61	0.181
Anti-Sm	2.30 ± 1.08	2.42 ± 1.77	0.668
AcL	3.20 ± 1.91	1.93 ± 1.28	0.037*
β_2-GPI	2.18 ± 1.28	2.60 ± 1.88	0.823
LA	2.62 ± 1.93	2.52 ± 1.53	0.913
Cerebrospinal fluid analysis			
Intracranial pressure ≥200cmH_2O	2.55 ± 2.12	2.11 ± 1.25	0.466
Increased trace protein	3.34 ± 1.57	2.03 ± 1.52	0.014*

ACL: anticardiolipin; AnuA: anti-nucleosome antibody; CRP: C-reactive protein; C3: component 3; C4: component 4; ESR: erythrocyte sedimentation rate; IgG: immunoglobulin G; LA: lupus anticoagulant; r-RNP: ribosomal RNA-protein; Scr: serum creatinine; UCH-L1: ubiquitin carboxyl hydrolase L1; U1RNP: U1 RNA-protein; β2-GPI: β2- glycoprotein I.

Descriptive statistics for continuous variables were expressed as mean ± SD, and presented using the t-test (normal distribution) or Mann-Whitney U-test (abnormal distribution) respectively. *p≤0.05; †p<0.01.

Anti-UCH-L1 is a promising CSF biomarker in the diagnosis of NPSLE

Considering the elevated levels of UCH-L1 in CSF of NPSLE patients, we detected the existence of CSF anti-UCH-L1 by indirect ELISA to reveal whether UCH-L1 was involved in the autoimmunity of NPSLE as an autoantigen. We determined the CSF levels of anti-UCH-L1 in 30 NPSLE patients, 18 SLE controls, 4 other CTD controls and 10 other NSD controls and demonstrated that anti-UCH-L1 levels were significantly elevated in patients with NPSLE (44.43±21.13 AU) in comparison to SLE controls (30.53±11.56 AU, p=0.042), other CTD (19.9±8.95 AU, p=0.046) and NSD (9.27±9.93 AU, p=0.000) controls (Fig. 2A). The ROC analysis showed a sensitivity of 53% and a specificity of 91% for anti-UCH-L1 in the diagnosis of NPSLE, and the area under curve (AUC) was 0.80 (Fig. 2B).

CSF anti-UCH-L1 levels were associated with SLE organ involvement

We further analysed the clinical significance of CSF anti-UCH-L1 in NPSLE. As shown in Table III, elevated CSF anti-UCH-L1 levels were associated with cardiac involvement (p=0.043), proteinuria (p=0.048) and haematologic involvement (p=0.016). There was a marginally significant positive correlation between CSF anti-UCH-L1 levels and SLEDAI (r=0.3382, p=0.0676, Fig. 2C), while CSF anti-UCH-L1 levels did not differ significantly among patients with overlap of multiple neuropsychiatric manifestations (Fig. 2D).

The correlation between CSF anti-UCH-L1 and UCH-L1 was also studied.

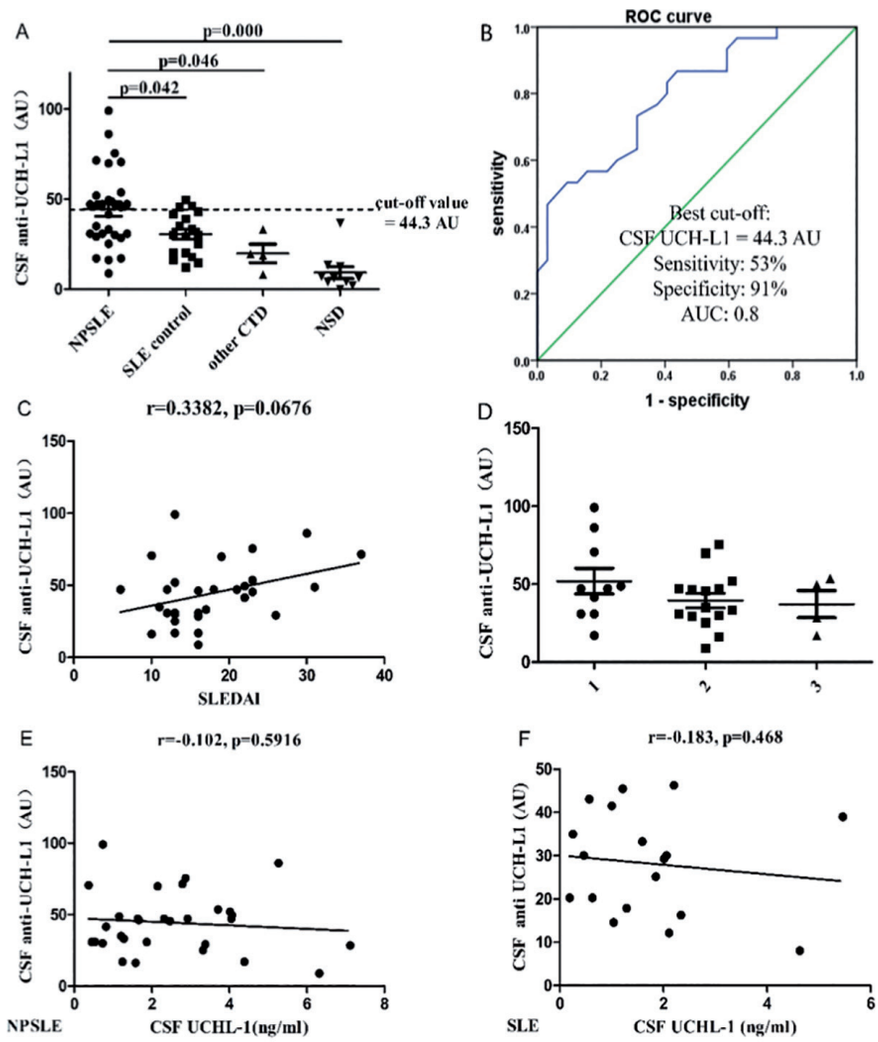

Fig. 2. Elevated CSF anti-UCH-L1 levels in NPSLE and its clinical significance. **(A)** CSF anti-UCH-L1 in the patients with NPSLE and controls. CSF anti-UCH-L1 levels were significantly elevated in NPSLE patients as compared to SLE control, other CTD and NSD patients. SLE control: patients with neuropsychiatric manifestations not related to NPSLE. CTD: connective tissue disease; NSD: nervous system disorder. **(B)** ROC curve of sensitivity versus specificity of CSF anti-UCH-L1 for the diagnosis of NPSLE. The AUC was 0.8 and the cut-off value was 44.3 AU, with 53% sensitivity and 91% specificity for NPSLE diagnosis. **(C-D)** Correlations between CSF anti-UCH-L1 levels and disease activity of NPSLE patients. There was a marginal but not statistically significant positive correlation between CSF anti-UCH-L1 level and SLEDAI-2K, while CSF anti-UCH-L1 levels did not differ among the patients with different numbers of neuropsychiatric manifestations. **(E-F)** Correlations between CSF anti-UCH-L1 and UCH-L1 levels of NPSLE patients or SLE controls. No significant correlation existed between CSF levels of anti-UCH-L1 and UCH-L1 in the NPSLE patients or SLE controls.

As shown in Figure 2E, there was no correlation between CSF anti-UCH-L1 and UCH-L1 levels in the NPSLE patients (r=-0.102, p=0.5916), nor in the SLE control group (r=-0.183, p=0.468, Fig. 2F).

Serum anti-UCH-L1 levels were positively correlated with the matched CSF anti-UCH-L1 levels among the NPSLE patients

The serum levels of anti-UCH-L1 among the NPSLE patients and SLE controls were further investigated. It was demonstrated that serum anti-UCH-L1 levels in the NPSLE group (95.46±32.91 AU) were comparable to those in the SLE controls (96.69±33.93 AU, Fig. 3A). Serum anti-UCH-L1 levels were significantly higher than the matched CSF levels (p<0.0001, Fig. 3B) and were positively correlated with the CSF levels in the NPSLE patients (r=0.4551, p=0.0382, Fig. 3C). Similar trends were not observed in the SLE controls (data not shown).

Discussion

Our study revealed that CSF UCH-L1 and its antibody might be promising biomarkers in NPSLE. According to previous studies, elevated CSF and serum levels of UCH-L1 were detected in brain injury (10-12), neonatal hypoxic ischemic encephalopathy (13), epilepsy (14) and toxic encephalopathy (15), which might be caused by mechanical damage or the ischaemic necrosis of neurons, and dynamic changes in UCH-L1 levels have been observed in the progress of cerebrovascular diseases and epilepsy (10-12, 14, 15). Our study showed that CSF UCH-L1 levels were significantly increased in the sNPSLE patients, patients with overlapping neuropsychiatric manifestations, and two patients with severe cranial injury in the SLE control group as well, which suggested that elevated UCH-L1 could be the consequence of non-specific neuron damage caused by severe nervous system disorders, rather than specific autoimmune conditions in NPSLE. Our study also showed that elevated CSF UCH-L1 levels were associated with overlapped NPSLE manifestations and increased disease activity, and further studies might help us better understand the neuron damage in NPSLE and the role of UCH-L1 in this process.

In this study, we also investigated the diagnostic value of the anti-UCH-L1 autoantibody in the CSF of NPSLE patients, SLE patients, other CTD and NSD controls that presented with similar neuropsychiatric manifestations. Although the levels of CSF UCH-L1 were elevated in all of the conditions with neuron damage, its autoantibody levels were specifically elevated in NPSLE, especially when compared with other CTDs and other NSDs, indicating that specific autoimmune responses have been induced by UCH-L1 in NPSLE patients. According to our study, anti-UCH-L1 showed promising diagnostic significance (53% sensitivity and 91% specificity). Due to the lack of diagnostic methods in NPSLE with complex clinical conditions, anti-UCH-L1 may help the clinicians to make the diagnosis of NPSLE more precisely.

The mechanism of anti-UCH-L1 production in NPSLE is elusive. One pos-

Table III. Cerebrospinal fluid anti-UCH-L1 levels in the presence or absence of organ involvements and laboratory parameters.

	Anti-UCH-L1 (AU)		*p*-value
	presence	absence	
Organ involvements			
Cardiac involvement	64.45 ± 19.49	41.35 ± 20.39	0.043*
Lung involvement	44.88 ± 28.09	44.34 ± 20.65	0.96
Lupus nephritis	44.16 ± 21.06	44.73 ± 22.76	0.944
Proteinuria	51.04 ± 17.56	39.37 ± 23.30	0.048*
Haematuresis	49.08 ± 17.42	41.73 ± 23.55	0.376
Elevated Scr	40.25 ± 28.29	45.07 ± 20.89	0.684
Haematologic involvement	59.76 ± 26.32	38.85 ± 16.87	0.016*
Serological tests			
Increased IgG	42.65 ± 23.13	45.78 ± 20.76	0.7
Increased CRP	49.92 ± 28.86	43.33 ± 20.29	0.541
Increased ESR	43.34 ± 20.84	46.60 ± 23.73	0.779
Decreased C3 or C4	44.92 ± 20.31	41.96 ± 29.37	0.784
Anti-dsDNA	45.76 ± 22.27	42.23 ± 21.05	0.686
ANuA	40.66 ± 16.68	56.80 ± 31.29	0.082
Anti-r-RNP	47.66 ± 31.02	43.78 ± 19.87	0.719
Anti-U1RNP	39.77 ± 14.36	47.12 ± 24.67	0.376
Anti-Sm	45.8 ± 14.94	44.08 ± 23.09	0.865
AcL	40.22 ± 19.40	47.65 ± 23.00	0.357
β2-GPI	41.60 ± 18.41	45.13 ± 22.49	0.725
LA	34.26 ± 21.63	48.12 ± 20.69	0.385
Cerebrospinal fluid analysis			
Intracranial pressure ≥ 200cmH_2O	51.77 ± 28.21	42.59 ± 19.79	0.359
Increased trace protein	50.32 ± 25.61	41.9 ± 19.61	0.263

ACL: anticardiolipin; AnuA: anti-nucleosome antibody; CRP: C-reactive protein; C3: component 3; C4: component 4; ESR erythrocyte sedimentation rate; IgG: immunoglobulin G; LA: lupus anticoagulant; r-RNP: ribosomal RNA-protein; Scr: serum creatinine; UCH-L1: Ubiquitin Carboxyl Hydrolase L1; U1RNP: U1 RNA-protein; β2-GPI: β2- glycoprotein I.
Descriptive statistics for continuous variables were expressed as mean ± SD, and presented using the *t*-test (normal distribution) or Mann-Whitney U-test (abnormal distribution) respectively. *p<0.05.

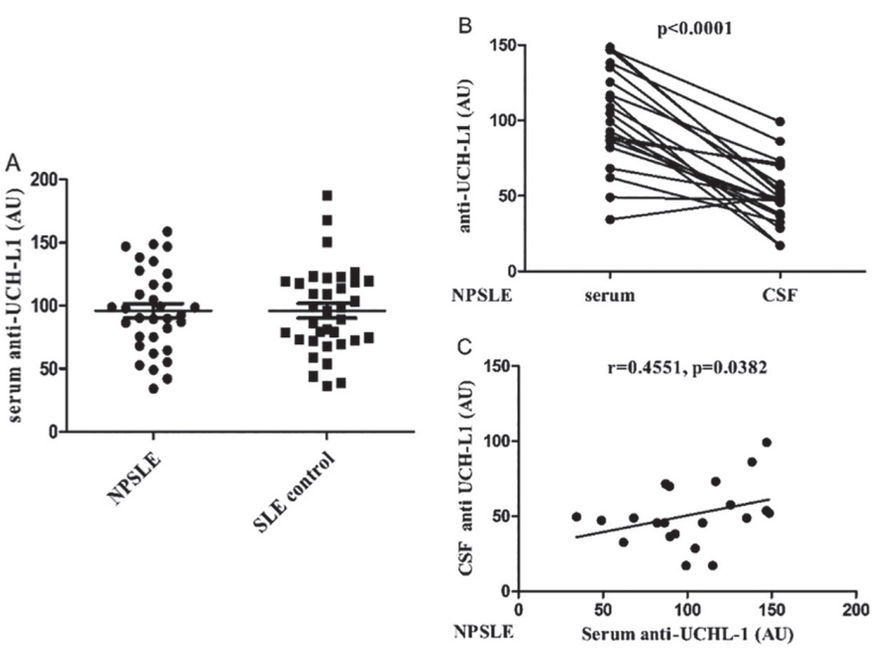

Fig. 3. Serum anti-UCH-L1 and its correlation with CSF anti-UCH-L1. (**A**) No difference of serum anti-UCH-L1 levels were detected between NPSLE patients and SLE controls. SLE control: patients with neuropsychiatric manifestations not related to NPSLE. (**B-C**) Serum anti-UCH-L1 levels were significantly higher, and positively correlated with the matched CSF levels in the NPSLE patients. Paired *t*-test was applied to compare the matched continuous variables.

sible explanation is the increased transudation from the systemic circulation due to the damage of blood-brain barrier in NPSLE (16). Our study showed that the levels of anti-UCH-L1 in CSF were positively correlated with those in serum, and the serum levels of anti-UCH-L1 were significantly higher than those in CSF, which supported this possibility. It should be noted that comparable serum anti-UCH-L1 levels existed in NPSLE patients and SLE controls, which indicated that anti-UCH-L1 might be induced in the peripheral tissues, as UCH-L1 was also expressed in the kidneys, large intestine, ovaries, and testes (4). These results suggested that circulating anti-UCH-L1 may enter central nervous tissues due to an impaired blood-brain barrier, and this might be pathogenic in NPSLE, considering anti-UCH-L1's possible reaction with neurons that expressed UCH-L1 at the highest level. Intrathecal expression of autoantibodies in CNS by B-lymphocytes that infiltrate and mature locally is another possible mechanism behind anti-UCH-L1 elevation (17). However, no correlation between CSF UCH-L1 and its autoantibody was observed in our study.

Some limitations exist in this study. Due to the limited availability of CSF samples, the relatively small sample size restricted the statistical power in our study, therefore, an enlarged sample size is needed in future studies to more precisely clarify the clinical relevance of UCH-L1 and its autoantibodies; Nevertheless, NPSLE patients overlapped with other autoimmune diseases (including antiphospholipid syndrome) or had received glucocorticoid pulse-dose therapy were excluded from our study, which added to the reliability of our conclusion. Another limitation is the lack of control CSF samples from people without neuropsychiatric symptoms. However, UCH-L1 and anti-UCH-L1 were actually identified by their differential levels between NPSLE patients and control patients with neuropsychiatric symptoms similar to NPSLE, which guaranteed the specificity of anti-UCH-L1 in distinguishing NPSLE from other neurologic manifestations or diseases.

In conclusion, this study revealed the clinical significance of CSF UCH-L1 and its autoantibodies in NPSLE. CSF anti-UCH-L1 is a promising biomarker for NPSLE diagnosis with a relatively high specificity. CSF UCH-L1, which may be indicative of neuron damage, is associated with disease severity of NPSLE. Further studies are needed to determine the pathological mechanism behind the involvement of UCH-L1 and its autoantibodies in NPSLE.

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