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ORIGINAL ARTICLE

# Neuronal damage and neuroinflammation markers in patients with autoimmune encephalitis and multiple sclerosis

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## Abstract

Inflammatory diseases of the central nervous system (CNS) are a diagnostic challenge to clinicians. Autoimmune encephalitis (AE) is an important diagnostic consideration in patients with CNS inflammatory disorders; despite of a wide range of neuropsychiatric symptoms it should be diagnosed as soon as possible and the patient transferred to the neurologist. We studied a group of AE patients ($n = 24$) as compared to multiple sclerosis (MS, $n = 61$) and control ($n = 19$) groups. Detailed clinical pictures of patients are presented. We focused on relevant cerebrospinal fluid (CSF) tests like protein levels, cytosis and oligoclonal bands, neuroinflammation indices (interleukin-6, soluble receptor of IL-6, neopterin, anti-ribosomal proteins antibodies) and markers of neurodegeneration (phosphorylated neurofilament heavy chain, pNfh). Elevated neopterin level was found in AE group as compared to the MS and control groups, while protein and pNfh were increased in both AE and MS groups. In the MS group, the cytosis and soluble receptor of IL-6 were higher as compared to the control group. Anti-ribosomal proteins antibodies were increased in a single patient with AE. High levels of protein were predictive of mortality in AE patients, while IL-6 and pNfh were elevated in severe AE patients. AE patients with paraneoplastic etiology demonstrated oligoclonal bands positivity. Taken together, our results suggest the neopterin as an additional marker of autoimmune brain inflammation. Though higher levels of protein, IL-6 and pNfh were found in patients with severe disease progression and death, prognostic values of these markers should be validated in larger cohorts of patients.

**Keywords** Autoimmune encephalitis · Multiple sclerosis · Interleukin 6 · Neopterin · Neuroinflammation · Neurodegeneration

## Introduction

Autoimmune encephalitis (AE) is a diverse group of diseases recognized recently; it has a very wide spectrum of clinical syndromes and a variety of etiologies (paraneoplastic, post-infectious or idiopathic) and always becomes a big diagnostic challenge for clinicians: neurologists, intensive care physicians and psychiatrists.

Over the last two decades, the discovery of new forms of encephalitis and antibodies associated with central nervous system (CNS) damage has changed the paradigms for diagnosing and treating previously mischaracterized disorders. The discovery of N-methyl-D-aspartate (NMDA)-encephalitis by Dalmau et al. (Dalmau et al. 2008) stimulated scientific activity and changed the strategy of molecular targets in schizophrenia and other mental diseases (Azuar and Levy 2018) providing new insights in molecular psychiatry (Honnorat and Plazat 2018). Many psychotic episodes, depression- or schizophrenia-like behaviors identified earlier as psychiatric pathology were diagnosed as AE (Fominykh et al. 2018a).

More than thirty antibodies to intracellular neuronal structures and neuronal surface were detected in the last several years (Dalmau 2015), this discovery becoming a remarkable

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link between the immunology and the psychiatry. Psychiatrists proposed a new clinical point of view on patients with first psychosis and suggested that testing antibodies is obligatory in these patients (Pollak and Lennox 2018).

According to recent data, AE has similar prevalence and incidence rate (13.7 /100000 and 0.8/100000, respectively) as infectious encephalitis, though relapse and recurrent hospitalization rates are higher (Dubey et al. 2018). It was reported that 0.6% of patients admitted to intensive care unit with neurological problems are patients with AE, this percentage significantly increasing since 2009 in parallel with the discovery of different antibodies (Harutyunyan et al. 2017). Each year one or two new antibodies presumably associated with novel clinical picture or syndromes are being revealed (Baizabal-Carvallo and Jankovic 2018). Unfortunately, only 50–60% of all AE cases are antibody-known or antibody-positive according to criteria of Grauss et al. (2016).

Since psychiatric symptoms can predominate at the onset or over the course of the disease, the diagnosis is often delayed; one-third of patients with AE have been initially hospitalized in a psychiatric ward, the time between the occurrence of first symptoms and antibody testing being often delayed (Herken and Prüss 2017). This is obviously inappropriate since direct correlations between severity of cognitive impairment and delayed time of treatment were reported in LGI1-encephalitis(Varley et al. 2018) and other antibody-mediated pathology (Hébert et al. 2018; Lascano et al. 2018).

Thus, it is very important to diagnose AE as soon as possible; however, current diagnostic criteria and the range of laboratory markers should be improved. Their sensitivity is very low at early stages of the disease (Wagner et al. 2018) and clearly time-dependent, limiting its validity in acute cases (Li et al. 2017). Additionally, sometimes it is essential to distinguish persistent neurological symptoms due to residual brain injury from new ones due to active ongoing CNS inflammation (Ganesh and Wesley 2018). Currently available work-ups do not have enough sensitivity to detect brain inflammation: magnetic resonance imaging (MRI) is frequently normal in AE, while routine laboratory tests including cytosis and oligoclonal bands (Ogbs) cannot provide sufficient information (Varley et al. 2018). Current problems of AE diagnosis are summarized in Table 1.

The main aim of our study was the search of additional markers for differentiating AE from other inflammatory CNS disorders and evaluation of acute inflammation and neurodegeneration severity in these patients.

Due to the terminology and clinical picture with acute presentation, earlier AE is compared to infection encephalitis (Wilken et al. 2017). However, it is generally historical viewpoint since multidisciplinary impact of autoimmune encephalitis has been expanded recently by revealing patients with overlapping syndromes, including anti-NMDAR encephalitis, neuromyelitis optica or other demyelinating diseases (Leypoldt et al. 2015, Sarigecili et al. 2018). Due to the fact that AE frequently demonstrates slow progressive beginning or a spectrum of symptoms which may be similar to chronic CNS inflammatory diseases with the relapse and remission, it is imperative to use this group of patients as a group of comparison.

According to this standpoint and literature data we used a design including AE comparison with inflammatory CNS disorders (demyelinating disorders in acute stage) but not infectious encephalitis as in some previous studies.

**Table 1** Current problems of AE diagnostics

| Clinical criteria | Problem | Differential diagnosis |
|---|---|---|
| Clinical picture<br>MRI data | Very unspecified in many cases<br>• may be positive in only 10–50% of patients; frequently negative (negative in 30% of patients with anti-NMDAR-encephalitis or CASPR2-associated AE; often negative in elderly patients with CASPR2 or LGi1 antibodies) | • IE<br>• tuberculous meningoencephalitis<br>• neurosyphilis and neuroborreliosis<br>• HIV-associated pathology<br>• CNS demyelination and multiple sclerosis<br>• Bickerstaff encephalitis<br>• CNS tumor<br>• epileptic disorders<br>• autoimmune vasculopathy and CNS vasculitis<br>• neurosarcoidosis<br>• Hashimoto's diseases<br>• Creutzfeldt-Jakob disease<br>• B Cell CNS Lymphoma<br>• toxic-metabolic encephalopathy<br>• neurodegenerative dementias<br>• psychosomatic pathology<br>• psychiatric disease |
| Cytosis>5 cells/μl and Ogbs | Ogbs positive in 30–50% of cases; abnormal CSF findings in 20–40% of AE patients with CASPR2- and LGI1-antibodies | |
| Known antibodies | Antibody-known or antibody-positive are 50–60% of all AE:<br>• unknown antibodies<br>• wide spectrum of antibodies<br>• different specificity and selectivity of tests (ELISA, cell-based with live or immobilized cells)<br>• diagnostic procedures need experienced laboratory and skilled staff | |

In addition to the routine tests (CSF protein level, cytosis, Ogbs etc.) and antibodies to neuronal cell surface (the CSF and serum) and intracellular antigens (serum) which were analyzed in all patients, we assessed the following specific target molecules:

1) CSF neopterin, a commonly used CSF biomarker in HIV neurology (x et al. 2016) and a tool for differential diagnostic procedures between AE and viral encephalitis in children (Kothur et al. 2016; Molero-Luis et al. 2013);
2) phosphorylated neurofilament heavy chain (pNfh), a confirmed neurodegenerative marker in amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS);
3) CSF antiribosomal-P antibodies reported to be involved in lupus development: positive associations were found with CSF anti ribosomal-P antibodies in systemic lupus erythematosus (SLE) and neuropsychiatric manifestations (Briani et al. 2009).
4) Interleukin-6 (IL-6) and its soluble receptor (sIL-6R) which are common markers of inflammation.

Based on previous data showing the lack of correlation between IL-6 in the CSF and the serum (Fominykh et al. 2018a; Stelmasiak et al. 2001), we measured IL-6 in the CSF but not in the serum. Higher Il-6 levels were found in AQP-4-associated disorders as compared to MS. The association between CSF Il-6 levels with MOG-antibody was found in acquired demyelination syndrome (Horellou et al. 2015). IL-6 receptor and its blockade with monoclonal antibody was implicated in different demyelinating disorders such as neuromyelitis optica spectrum disorders (NMOSD)(Araki et al. 2014) and may be also involved in AE.

The additional aim of our study was to compare biochemical markers and MRI in different subgroups of AE patients [with or without epileptic seizures, with and without paraneoplastic disorders, with severe course (these patients died during a year of examination) and others] in order to provide deeper insight into the pathophysiology of the diseases and their clinical manifestations.

## Materials and methods

### Patients

One hundred and two patients corresponding inclusion and exclusion criteria (below) visited Bujanov Moscow City Clinical Hospital between September 2015 and April 2017 with suggested AE or acute demyelinating disorders were consecutively reviewed. Study profile is presented in Fig. 1. Minimal follow-up period was 1 year. The research protocol was approved by the local Ethical Committee (IBR number 44).

Inclusion criteria:

1) Possible AE according criteria of Graus et al. 2016(Graus et al. 2016) for AE group. According to this standard AE diagnosis can be made if all three of the following criteria have been met:
   a) subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status or psychiatric symptoms;
   b) at least one of the following: new focal CNS findings, seizures not explained by previously known seizure disorder, CSF pleocytosis (white blood cell count of more than 5 cells per $mm^3$), MRI features suggestive of encephalitis;
   c) reasonable exclusion of alternative causes.
2) definite MS according to the revised new edition of W. McDonald criteria (Thompson et al. 2018a at the time of MS attack for MS group;
3) no immunosuppressive or immunomodulatory therapy at the moment of sampling and during 3 months before.

For all patients lumbar puncture was indicated for medical diagnostic purposes after informed consent and was performed in acute stage.

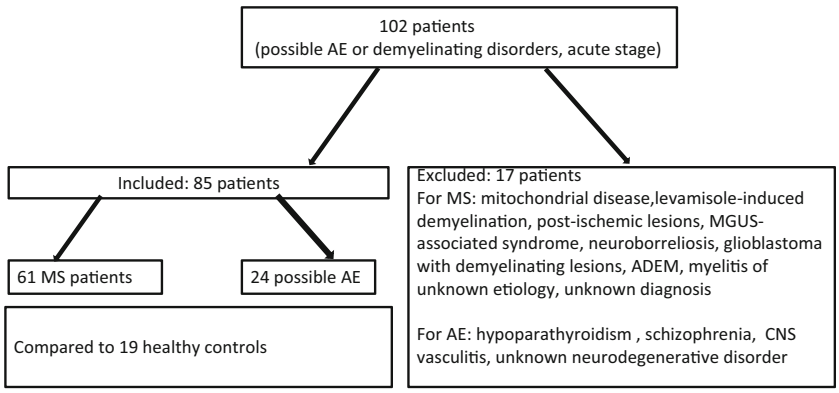


**Fig. 1** Study design

Exclusion criteria:

1) For MS group forms of MS other than relapsing-remitting MS, patients with isolated spinal lesions and aquaporin-4 (AQP-4)-positive profile;
2) Patients with other diagnosis after screening period;
3) Comorbid neurodegenerative pathology, history of alcohol or drug abuse; head trauma; vascular diseases; methylprednisolone pulse-therapy less than 3 months before the study;
4) Acute somatic or infective pathology, positive HCV, HBV, HIV, syphilis reaction.

According to these criteria, 17 patients were excluded (12 from MS group and 5 from AE group).

Differential diagnoses for MS group: mitochondrial disease ($n = 1$), levamisole-induced demyelination ($n = 1$), post-ischemic lesions ($n = 1$), monoclonal gammopathy-associated syndrome ($n = 1$), neuroborreliosis ($n = 1$), glioblastoma with demyelinating lesions ($n = 1$), ADEM ($n = 2$), myelitis of unknown etiology ($n = 3$), unknown diagnosis ($n = 2$);

Differential diagnoses for AE group: hypoparathyroidism ($n = 1$), CNS vasculitis ($n = 2$), neurodegenerative disorder ($n = 1$).

After the screening 85 patients were included into the analysis and two groups of patients were formed:

1) twenty four patients with possible AE (clinical characteristics meeting criteria presented in Table 2);
2) sixty one patients with MS

Neurological assessment, MRI of the brain and spinal cord, serum examination were performed in all patients. Neurological impairment in MS patients was assessed by Kurtzke Expanded Disability Status Scale (EDSS) at the moment of the sampling; additionally, the difference between EDSS at this moment and 1 year later was assessed.

Nineteen neurologically healthy subjects were included into the control group (median value of age was 35, from 19 to 53). Control CSF specimens were sampled during spinal anesthesia in patients with orthopedic surgical pathology. The blood was sampled before surgical procedures. MRI analysis in AE and MS was performed by qualified specialists according to clinical guidelines (Thompson et al. 2018b).

Clinical characteristics of patients and control group are presented in Table 3.

## CSF and blood sampling

Fasted venous blood and CSF samples were collected from all patients and control subjects after an informed consent at acute stage and before the initiation of treatment. Serum and CSF samples were prepared by centrifugation for 20 min at 1500 x g, 4 °C. Supernatants were aliquoted in sterile tubes and stored at −70° C.

In all patients AQP-4 autoantibodies were measured using cell-based AQP4 Assay Kit (Euroimmune, Germany). Antineuronal antibodies in the serum were measured using commercial kit (Euroimmune, Germany). Ogbs, serum Immunoglobulin (Ig) G, IgA, IgM, CSF IgG were measured using test system Hydragel CSF isofocusing (Sebia, France). CSF total protein and cytosis, thyroid function, systemic markers including C-reactive protein, rheumatoid factor, antinuclear antibodies, anti-double strain DNA antibodies, ANCA, ANSA, ssA, ssB, antiphospholipid antibodies were measured routinely in clinical laboratory (Deisenhammer et al. 2006; Buchner et al. 2014; Tkachenko et al. 2017). For AE viruses PCR CSF and CSF microbiological analysis were made (negative).

The levels of biomarkers in CSF samples were measured using commercially available ELISA kits: Anti-ribosomal P (DrFooke Laboratory, GMBH, Germany); IL-6, erythropoietin (Vector-Best, Russia); sIL6-R (Affymetrix, eBioscience, Austria); pNfh (BioVendor, Czech Republic); neopterin (IBL International, Germany). For anti-NMDA, gamma-aminobutyric acid B (GABAb), ionotropic glutamate receptor1 (AMPA1), AMPA2, CASPR2, LGI1 antibodies measurement in paired CSF and serum cell-based kits from Euroimmune, Germany were used. All measurements were performed in duplicate, for calibration curves in triplicate.

## Statistical analysis

Statistica 8.0 (StatSoft Inc., USA) and GraphPad Prism 6 for Windows (USA) were used for statistical analysis. The data are presented as median values (M) with 25 and 75 percentiles (M [25%, 75%]). We used non-parametric Kruskal-Wallis test for multiple comparisons (significant $p$ value <0.05), non-parametric Mann-Whitney U-test with Bonferroni correction for comparison of patients with controls, and confirmed results using ANOVA with post-hoc Newman-Keuls analysis. Spearman correlations between biomarkers levels and clinical data were calculated and logistic regression was performed to determine significant associations of biomarkers levels with outcomes.

The outliers were defined as the values > median value+ 1.5*IQR, where IQR = interquartile range (Aguinis et al. 2013). During data evaluation we performed cluster analysis for the patients and analyzed all data manually point by point. According to this data the majority of all outliers were AE patients who died during our study. Thus, we did not remove outliers but performed further analysis after forming a severe AE group (patients who died); this group was further compared to other AE.

**Table 2** Clinical profile of AE patients

| Case | Age/sex | Initial symptoms | Comorbidity | Abs | Cytosis>5 cells per μl | Ogb | MRI lesion localization | Treatment | Follow-up in 1 year |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 61 m | Cognitive decline, ataxia and seizures | Bladder carcinoma | NMDA (serum and CSF) | yes | type 2 | Brainstem, thalamus, cortical | MP pulse-therapy, PLEX | Very short time of improvement, death |
| 2 | 56f | Cognitive decline, ataxia | No | no | yes | type 4 | Brainstem, cortical | MP pulse-therapy, oral MP | Partial improvement, no relapse |
| 3 | 62 m | Epileptic seizures, cognitive and memory decline | Small cell lung cancer | GABAB (serum and CSF) | no | type 2 | Bilateral hippocampal hyperintesivity | MP pulse-therapy, PLEX | Partial improvement, death |
| 4 | 44 m | Paranoia, depression | Renal cancer | no | no | type 2 | Multifocal lesion | MP pulse-therapy, tumor resection | Improvement, no relapse |
| 5 | 38f | Cognitive decline, stereotyped jerks after viral prodrome | no | no | yes | type 1 | No lesions | MP pulse-therapy, PLEX | Improvement, no relapse |
| 6 | 37f | Depression, aggressive behavior | Fallopian tubes carcinoma | no | no | type 4 | 1 cortical and 1 periventricular lesion | MP pulse-therapy | Improvement, no relapse |
| 7 | 32f | Confusion, coma, tetraparesis (encephalitis letargica) | No | no | yes | type 1 | hypothalamus and basal ganglia | MP pulse-therapy, PLEX | No improvement, death |
| 8 | 47f | Psychosis, cognitive decline, seizures | Breast cancer | no | yes | – | No lesions | MP pulse-therapy | No improvement, death |
| 9 | 69 m | Cognitive decline, confusion, hypoventilation | Arterial hypertension, atherosclerosis | no | yes | – | Multiple lesions with contrast enhancement | MP pulse-therapy, PLEX, IgG | Improvement after two relapse, after third relapse – death |
| 10 | 46f | Drug-resistant epileptic seizures. Psychosis | Obesity | no | no | type 1 | Bilateral hippocampal sclerosis | Decline immunosupressive therapy | Drug-resistant epileptic seizures |
| 11 | 28f | Myoclonus-epilepsy, epileptic status | No | CASPR (serum) | no | type 1 | No lesions | MP pulse therapy, PLEX, oral prednisone, azathioprine | After 2th relapse and azathioprine therapy - remission |
| 12 | 21f | Epileptic status | No | SSa-SSb | no | type 2 | Hyperintensivity in temporal lobe | Decline immunosupressive therapy | Drug-resistant epileptic seizures |
| 13 | 25f | Psychotic episodes, memory decline, drug-resistant epileptic seizures | No | no | no | type 1 | No lesions | MP pulse therapy, PLEX, IVIGs, rituximab | No improvement |
| 14 | 78f | Cognitive and memory decline, tetraparesis, muscle rigidity | Arterial hypertension, atherosclerosis | GAD | no | type 1 | No lesions | MP pulse therapy, PLEX | Total improvement |
| 15 | 28 m | Drug-resistant epileptic seizures, cognitive decline | No | no | no | type 1 | Multiple lesions with contrast enhancement | MP-pulse therapy, IVIGs | Partial improvement |
| 16 | 24f | Catatonia, depression, cognitive decline | No | no | yes | type 1 | no | MP-pulse therapy | Partial improvement |
| 17 | 49 m | Tetraparesis, cognitive decline | No | Anti-Hu | no | type 3 | Brainstem and cortical lesion | MP-pulse therapy, PLEX | Partial improvement |
| 18 | 18f | Epileptic seizures, cognitive and memory decline | No | SSa-SSb | no | type 1 | Lesion in right frontal and left occipital lobe without contrast enhancement | MP-pulse therapy, PLEX, IVIGs | Improvement |
| 19 | 50f | Epileptic seizures, cognitive and memory decline | No | no | yes | type 1 | No lesions | MP-pulse therapy | Improvement |
| 20 | 34f | Drug-resistant epileptic seizures | No | no | yes | type 1 | Hyperintensivity in right temporal lobe | MP-pulse therapy | Improvement |

**Table 2** (continued)

| Case | Age/sex | Initial symptoms | Comorbidity | Abs | Cytosis>5 cells per μl | Ogb | MRI lesion localization | Treatment | Follow-up in 1 year |
|---|---|---|---|---|---|---|---|---|---|
| 21 | 52f | Cognitive and memory decline, tetraparesis, muscle rigidity | Arterial hypertension | GAD | no | type 1 | No lesions | MP-pulse therapy, PLEX | No improvement, death |
| 22 | 66 m | Epileptic seizures, cognitive and memory decline | No | LGI1 (serum) | no | type 1 | No lesions | MP-pulse therapy, oral prednisone | Improvement |
| 23 | 50 m | Epileptic seizures, cognitive and memory decline | Thyroid pathology | LGI1 (CSF and serum) antiTPO | no | type 1 | No lesions | MP-pulse therapy, oral prednisone | Partial improvement |
| 24 | 36f | Epileptic seizures, cognitive and memory decline | No | NMDA (CSF and serum) | no | type 1 | Multiple lesions | MP-pulse therapy, PLEX, oral prednisone | Improvement |

Additionally, we used fourfold Chi-square test in specific cases.

## Results

### AE group description (Table 2)

In the group of possible AE, according to Graus et al. criteria (Graus et al. 2016), 24 patients had AE (average age 45, from 18 to 69; 8 men and 16 women). After applying the diagnostic algorithm we recognized 2 NMDA-encephalitis (cell based assay for patients is presented in Fig. 2b), 1 CASPR, 2 LGI1 (Fig. 2c), 1 GABAb (Fig. 3a), 2 glutamic acid decarboxylase (GAD), 1 anti-hu encephalitis and 2 encephalitis with anti SSa-SSb antibodies. According to these data, 9 patients had diagnosis "AE with known antibodies" (37.5%), 2 patients "AE with antibodies with unknown significance" (8.3%), 13 patients "antibody -negative AE, but probable AE" (54.1%).

These results are in conformity with previous reports indicating that about 40–50% of AE have unknown etiology (Yeshokumar et al. 2017, Lee and Lee 2016). We did not have opportunity to analyze some known antibodies (anti-glycine, anti-myelin oligodendrocyte glycoprotein, dipeptidyl-peptidase–like protein 6, Iglon) and this can explain that our results are slightly higher. We found one positive AE patients with anti-Ribosomal-P antibodies in the group of "antibody -negative AE, but probable AE".

In the AE group, Ogbs "type 2" were found in 4 patients (oligoclonal IgG bands in the CSF, but not in the serum), "type 3" in one patient (oligoclonal bands in the CSF plus identical oligoclonal bands in the serum and CSF), "type 4" in 2 patients (identical pattern of oligoclonal bands in the CSF and serum), 15 patients demonstrated "type 1" (no bands in the CSF and serum), and 2 patients - unknown. For Ogbs types we used a recommended classification (Andersson et al. 1994).

Thirteen patients had epileptic seizures (54%); 6 patients (25%) had oncological problems: GABAb encephalitis was found in a patient with small cell lung cancer, NMDA-encephalitis in a patient with prostatic and bladder cancer and no antibodies were found in patients with breast, cervical, renal cancer and fallopian tubes carcinoma. In 2 patients neurological symptoms were presented before cancer diagnosis. Six patients (25%) died during 1 year of follow-up, 3 of them had oncological pathology. For these patients, lifetime value after including in the study was from 2 weeks to 8 months (3.4 ± 2.8 months). Since we included and used in further analysis this group of patients who died, clinical characteristics of these patients were described specifically (summarized in Table 4).

Cytosis moderately correlated with neopterin, protein and IL-6 levels (r = 0.54, 0.55, 0.67, respectively, $p < 0.05$), while protein levels moderately correlated with IL-6 and neopterin levels (0.51 and 0.57, respectively, $p < 0.05$, see Fig. 1

**Table 3** Demographic and clinical characteristics of patients and control groups

| | Possible AE | MS | Control |
|---|---|---|---|
| Patients | 24 | 61 | 19 |
| Age at examination, years | 42.6 (±16.0) | 35.5 (±10.9) | 36.4 (±11.4) |
| Male/Female | 8/16 | 19/42 | 8/11 |
| Epilepsy | 13 | 11 | – |
| Average EDSS score | – | 3.3 (± 1) | – |
| EDSS score after 1 year | – | 3.4 (±1) | – |
| Amount of relapse during 1 year | 0.6 (±0.6) | 0.3 (±0.6) | – |
| Number of patients with relapse | 7 (29%) | 17 (28%) | – |
| Death during 1 year | 6 | 0 | – |
| ICU admission (n)/duration (day) | 9/ from 1 to 14 | 3/from 0 to 1 | – |
| IgG/IgA/IgM serum (Me/ml) | 160/170/215 (±30, 50, 90) | 167/172/210 (±42, 44, 70) | 157/168/205 (±38, 40, 65) |
| IgG CSF (mg/l) | 70.4 (±60) | 57.4 (±44) | 60.2 (±42) |
| CSF cytosis (cell/μl) | 13.0 (±27) | 12.3 (±7) | 3.9 (±1.2) |
| CSF protein level (g/l) | 0.5(±0.3) | 0.4 (±0.2) | 0.3 (0.2) |
| CSF glucose (mM) | 3.2 (±0.8) | 3.6 (±0.7) | 3.9 (0.2) |
| MRI brain abnormal (n) | 14 (58%) | 61 (100%) | – |
| MRI spine abnormal (n) | 0/24 | 44 (72%) | – |

Suppl.). CSF levels of IL-6 and pNfh were higher in patients with mortality within 1 year as compared to survivors 1 year after diagnosis (352 ± 570 vs 16 ± 12 pg/ml, $p < 0.025$; 1153 ± 1111 vs 139 ± 193 pg/ml, $p = 0.04$, respectively).

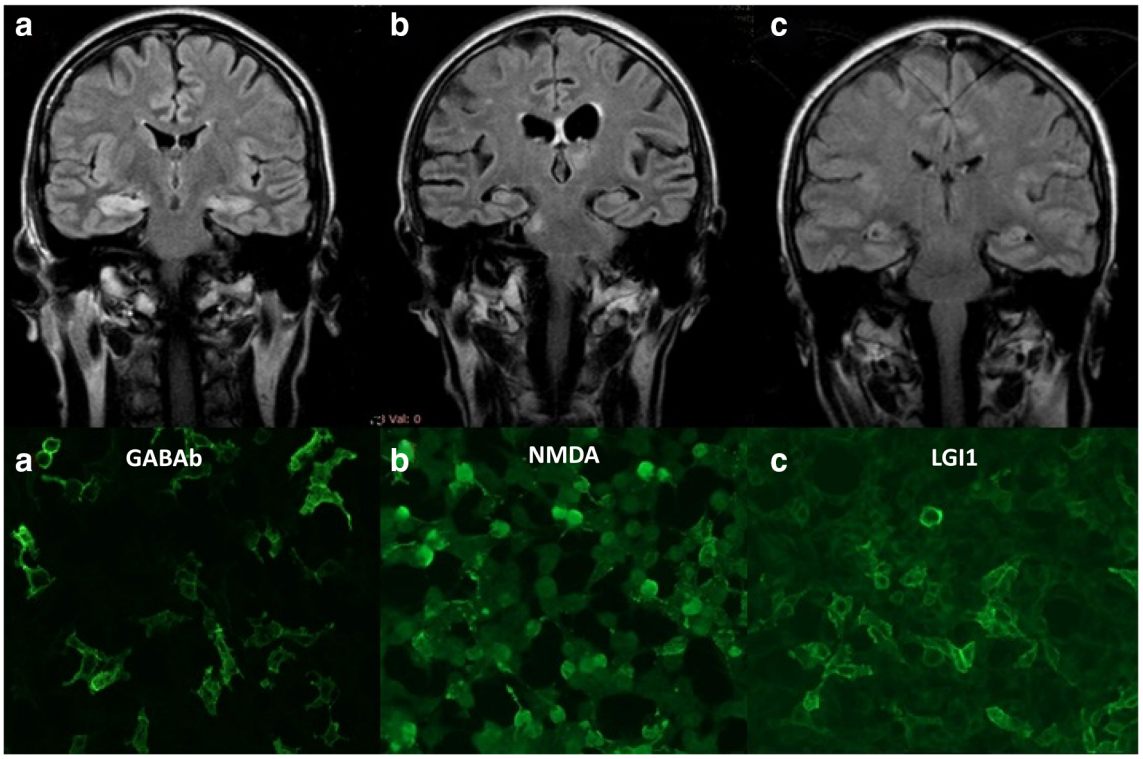


**Fig. 2** Patients MRI (upper panel) and CSF immunoreactivity in biochips with HEK-cells expressing different antigens (Autoimmune encephalitis mosaic 1, Euroimmune, Germany; bottom panel). **a**: case 3: GABAb–limbic encephalitis with bilateral hippocampal MRI hyperintesivity in the patient with small cells lung cancer. **b**: case 1: NMDA – encephalitis with multiple MRI lesions in the patient with epileptic seizures, cognitive decline and bladder carcinoma. **c**: case 22: LGI1- limbic encephalitis with subtle temporal MRI changes in the patient without known cancer pathology

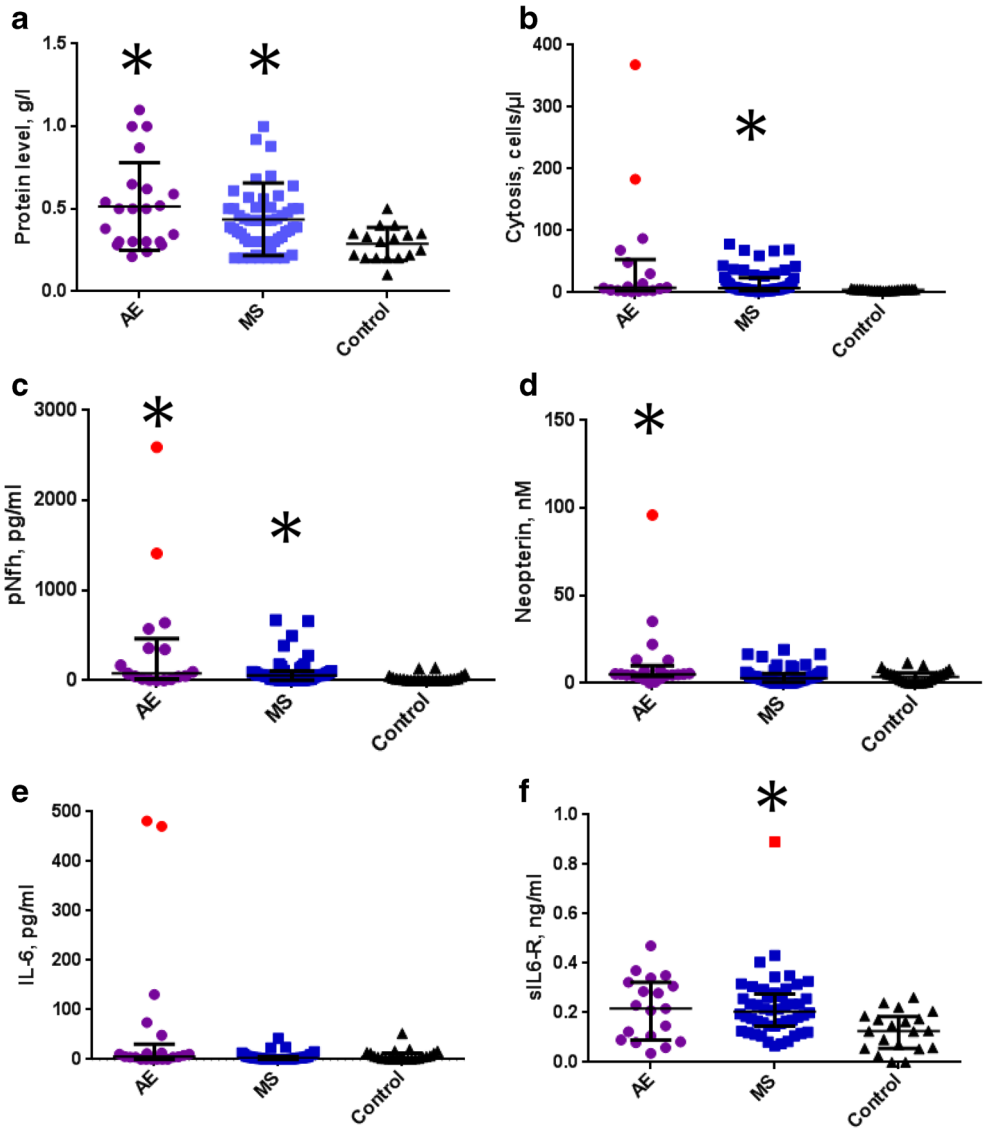


**Fig. 3** CSF protein, cytosis, pNfh, neopterin, IL-6 and sIL-6R levels in different groups of patients. Asteriks indicate significant statistical differences versus control group ($p < 0.017$, Mann-Whitney U-test with Bonferroni correction after significant results in Kruskal–Wallis test for multiple comparisons). Red marks are used for outliers. **a**: CSF protein levels in AE, MS and control groups; **b**: CSF cytosis in AE, MS and control groups; **c**: CSF pNfh in AE, MS and control groups; **d**: CSF neopterin in AE, MS and control groups; **e**: CSF IL-6 in AE, MS and control groups; **f**: CSF sIL-6R in AE, MS and control groups.

**Table 4** Demographic and clinical characteristics of patients from "Severe AE" and "Other AE" groups

| | Severe AE | Other AE |
|---|---|---|
| Patients | 6 | 16 |
| Age at examination, years | 53.8 (±13.2) | 39.9 (±14.9) |
| Male/Female | 3/3 | 6/12 |
| Epilepsy | 3 | 10 |
| Death during 1 year | 6 | 0 |
| ICU admission (n)/duration (day) | 6/ from 1 to 14 | 3/from 0 to 3 |
| Oncology (n) | 3 | 3 |
| Antibodies profile | 1 GABAb, | 2 SSA-SSB |
| | 1 NMDA, | 1 CASPR, 1 GAD, |
| | 1 GAD | 2 LGI1, 1 NMDA, 1 hu |
| CSF cytosis (cell/µl) | 15.0 (±29) | 10.0 (±9) |
| CSF protein level (g/l) | 0.7 (±0.3) | 0.5 (±0.3) |
| CSF glucose (mM) | 2.4 (±0.8) | 3.4 (±0.5) |
| MRI brain abnormal (n) | 4 (67%) | 10 (56%) |

All patients with oncology had Ogbs, while in other patients only 14% were Ogbs positive ($P = 0.0004$, fourfold Chi-square test).

Cytosis, protein levels, neopterin, IL-6, sIl-6R, pNfh did not differ in patients with and without epileptic seizures, with and without known Abs, with and without cancer, with and without Ogbs ($p > 0.05$).

## Characteristics of MS group (Table 3)

From 61 MS patients; 11 had epilepsy. Screening for anti-neuronal surface antibodies in these patients did not give positive results in either the CSF, or the serum. CSF anti-Ribosomal-P antibodies screening provided single positive patient with MS and epilepsy, while all other patients were negative. In this group, positive correlation of age with EDSS was revealed ($r = 0.38$, $p < 0.05$). A weak correlation between EDSS and CSF IL-6 was found ($r = 0.32$, $p = 0.008$, see Fig. 2 Suppl.).

## Analysis

The data from AE, MS and control groups were compared. Using non-parametricKruskal–Wallis test for multiple comparisons, we found differences in CSF protein levels ($p = 0.005$), cytosis ($p = 0.048$), IL-6 and sIL-6R levels ($p = 0.04$ and 0.01, respectively), pNFh and neopterin levels ($p = 0.02$ and 0.04, respectively).

Next we compared AE group with MS and control group, and MS with control group using Mann-Whitney U-test with Bonferroni correction ($p < 0.017$). We did not find differences in IL-6 levels. In AE group higher protein, pNfh and neopterin levels were revealed as compared to control group ($0.5 \pm 0.3$ vs $0.3 \pm 0.1$ g/l; $378 \pm 675$ vs $23.9 \pm 35.0$ ng/ml; $11.8 \pm 2.0$ vs $3.5 \pm 3.3$ nM, respectively). The comparison of MS with control group showed significantly higher cytosis ($16.3 \pm 19.8$ vs $3.9 \pm 1.2$ cells/μl), protein ($0.4 \pm 0.2$ vs $0.3 \pm 0.1$ g/l), pNfh levels ($98.4 \pm 100$ vs $23,9 \pm 35.0$ ng/ml) and sIL6-R levels ($0.2 \pm 0.1$ vs $0.1 \pm 0.1$ ng/ml) (Fig. 3). In AE with MS group, protein and pNfh levels were similar; however, neopterin levels were significantly higher in AE group ($11.8 \pm 2$ vs $4.3 \pm 2.1$ nM).

Using epilepsy as a factor in factorial ANOVA we did not find a difference between patients with and without epilepsy. The comparison of biochemical data in patients with known antibodies to neuronal antigens and antibody-negative AE did not reveal differences between groups. Using death as a grouping factor, higher protein ($0.7 \pm 0.7$ vs $0.4 \pm 0.2$ g/l), pNfh ($1153 \pm 1011$ vs $84 \pm 72$ ng/ml), and IL-6 ($377 \pm 228$ vs $8.3 \pm 11.0$ pg/ml) were found in the group of AE patients with mortality (Fig. 4). Using univariate logistic regression we established protein level as a significant factor for death (odds ratio 21.2 for 1 g/l, CL 1.1 to 684, $p = 0.04$). It was not possible to perform univariate logistic regression for pNfh and IL-6 CSF levels due to small number of patients. Obviously, larger cohorts of patients should be used to accurately evaluate predictive values for these markers.

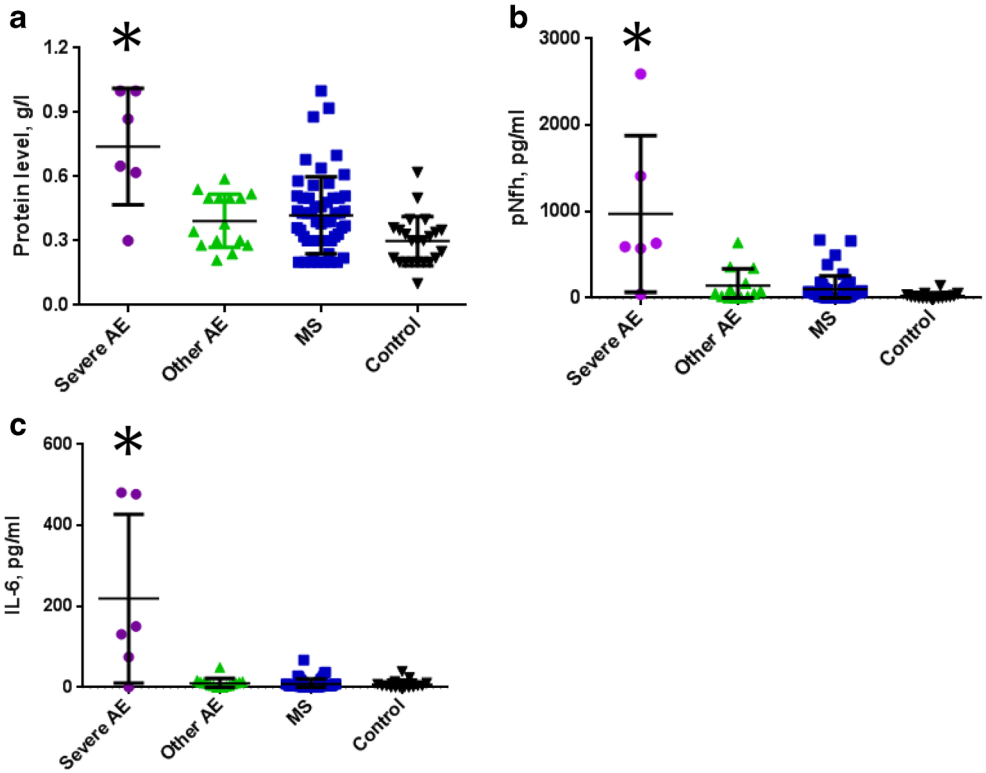


**Fig. 4** The level of AE markers in patients with severe disease course and other patients. Asteriks indicate significant statistical difference versus control group ($p < 0.017$, Mann-Whitney U-test with Bonferroni correction after significant results in Kruskal–Wallis test for multiple comparisons). **a**: CSF protein levels were higher in severe AE; **b**: CSF pNfh levels were higher in severe AE; **c**: CSF IL-6 levels were higher in severe AE

## Discussion

The differential diagnosis of AE is exceptionally difficult; particularly at an early stage. The clinical presentation of AE is variable and often not specific enough to make diagnosis easily. However, early recognizing of AE is critical: it is a treatable condition and early cure is associated with better prognosis (Thompson et al. 2018b). Therefore, the aim of our analysis was to define CSF markers in order to facilitate diagnostic procedures. Only a few publications with comparisons of AE with other disorders are available. Investigators prefer to use IE as a group of comparison (Kothur et al. 2016), and in some cases they compare AE to MS patients (Hottenrott et al. 2015). However, comparison with CNS inflammatory disorders like demyelinating disorders is extremely important due to recent data indicating expanding AE spectrum with overlapping syndromes, including anti-NMDAR encephalitis and neuromyelitis optica or other demyelinating diseases (Leypoldt et al. 2015; Sarigecili et al. 2018).

In accordance with the data previously reported in children (Kothur et al. 2016), we found higher neopterin levels in AE patients as compared to other groups (controls and MS group).

Neopterin is a biochemical product of guanosine triphosphate pathway that is both cell-restricted and inducible by immune-inflammatory stimuli (Fig. 3, Suppl.). Neopterin induces the expression of pro-inflammatory nuclear factor-κB, intercellular adhesion molecule-1, cytokines and inflammatory mediators (Hagberg et al. 2010). It has a short half-life and can be used for monitoring inflammatory activity in patients with acute inflammation or relapsing-remitting encephalitis in contrast to chronic inflammation. Historically, neopterin was described as well-established early marker of intrathecal immune response, and particularly of macrophage activation in HIV neurology (Motta et al. 2017; Edén et al. 2016). It was also promoted in pediatric neurology as a CSF marker of active CNS inflammation and intrathecal immune activation (Dale et al. 2009). These authors suggested that CSF neopterin is a useful and sensitive marker of inflammation in a broad range of acute and chronic CNS disorders. We confirm this showing that CSF neopterin is more useful and sensitive marker of neuroinflammation than CSF pleocytosis, however, obviously larger cohort of AE patients should be used to appropriately validate this marker. Kothur et al. (2016) defined neopterin cut-off value of 29 nM to differentiate AE and viral encephalitis from ADEM in children, but in our study only two AE patients had values higher than this cut-off. This difference may be due to different neopterin levels in children and adults and different groups included into the study. However, for HIV-neurology an upper normal reference value was defined as 5.8 nmol/l (Hagberg et al. 2010) and in our AE and control group we received analogous results ($11.8 \pm 2.0$ for AE vs $3.5 \pm 3.3$ nM for control group), though we did not find correlation with neurofilament levels.

We found that levels of neuronal damage markers (pNfh) and protein levels were augmented in both AE and MS groups. CSF pNfh and light chain, indicative of axonal and neuronal injury, were non-specifically increased in patients with various brain disorders including autoimmune encephalitis (Constantinescu et al. 2017; Vorobyeva et al. 2014). Thus, higher levels of neuronal damage markers due to active neuroinflammation in the CSF of AE patients were expected. We did not find significant difference of pNfh in AE as compared to MS patients; however, pNfh levels were higher in patients with severe disease course and unfavorable prognosis. Similar results were previously reported by Constantinescu et al. in Constantinescu et al. 2017 for neurofilament light chain: its levels measured soon after disease onset correlated with long-term outcome in autoimmune neurological syndromes. Neurofilament markers are used as prognostic in different neurological disorders such as ALS and MS in relapse (Gendron et al. 2017). Obviously, these markers should be investigated in larger cohorts of AE patients. Recent article by Körtvelyessy et al. (2018) reported neurofilament light chain elevation in different types of encephalitis with neuronal surface antibodies. Unfortunately, levels of biomarkers were compared with a non-inflammatory control group only.

In our study higher protein level appeared a significant factor for death (odds ratio 21.2 for 1 g/l), these results corresponding to those of Harutyunyan et al. 2017 who revealed higher protein concentration in intensive care unit admitted AE patients (Harutyunyan et al. 2017). The elevation of CSF protein levels was associated with increased risk of death in tuberculosis meningitis patients (Yasar et al. 2010) and other bacterial meningitis (Lin et al. 2016).Though these results were not confirmed in a study on AE patients (Liao et al. 2017), the authors tried to correlate CSF markers with different Modified Rankin Scale scores as outcome measure, comparing AE with good outcome and severe AE (Modified Rankin Scale >3) without using death as a factor.

In our cohort positive oligoclonal synthesis (type 2–5) in paraneoplastic patients was revealed as compared to non-paraneoplastic encephalitis. It could be indicated in diagnostic procedures and suggests more thorough oncological screening of AE patients with oligoclonal synthesis, though Constantinescu et al. (2017) reported that Ogbs were similar in paraneoplastic and non-paraneoplastic cases. We found higher IL-6 levels in AE patients with unfavorable prognosis but did not find differences between groups as in previous studies (Byun et al. 2016); it should be noted, however, that the data on CSF cytokines in AE are limited.

The comparison of MS with control group revealed significantly higher cytosis, protein, pNfh and sIL6-R levels confirming neuroinflammatory activity and the neurodegeneration in these patients. Recently we demonstrated that levels of soluble sIL-6R binding with IL-6 were higher in MS patients as compared to other demyelinating disorders (Fominykh et al.

2018b). In the present study we have shown increased sIL-6R level confirming other studies (Padberg et al. 1999).

High level of sIL-6R may reflect the involvement of soluble IL-6 receptor-associated pathways in MS, similar to other demyelinating disorders with active IL-6R dependent pathway. Surprisingly, we did not find correlation between inflammatory markers and pNfh levels; this may be related to different time course of neuroinflammation processes and the neurodegeneration during the development of the disease.

We measured CSF anti-ribosomal P antibodies level basing on the data about the involvement of this protein in lupus development. Positive associations were found with CSF anti ribosomal P antibodies in systemic lupus erythematosus (SLE) and neuropsychiatric manifestation (Briani et al. 2009). In the present study, only two positive cases were found among all patients: one patient with suggested AE and one patient with MS and epilepsy. These patients had epileptic seizures but due to small number of positive results we cannot come to a definite conclusion about the significance of these antibodies in disease pathophysiology.

Relatively small sample size is a major limitation of our study; however, this fact is due to the low occurrence of AE patients in the population. Another limitation is heterogeneous AE group with inclusion of antibodies-negative patients; however, this is compatible with the aim of our study - searching additional biochemical markers for AE in clinical settings to accelerate diagnostic procedure. A larger study should be performed for further evaluation of these markers and their contribution to therapeutic decisions.

## Conclusion

Taken together, this study showed evidently higher levels of neopterin in the CSF of patients with AE as compared to control group and MS group suggesting that it may be reasonable to evaluate this marker for additional confirmation of CNS inflammation in AE. Using univariate regression model, protein level was revealed as possible negative prognostic factors for severe AE, while IL-6 and pNfh levels were higher in severe AE course; however, a larger study should be performed. Protein levels and pNfh levels were higher in AE and MS group as compared to control, while cytosis and sIL-6R levels were higher in MS.

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## Compliance with ethical standards

**Conflict of interest** No conflict of interest.

**Abbreviations** *ADEM,* acute disseminated encephalomyelitis; *AE,* autoimmune encephalitis; *ALS,* amyotrophic lateral sclerosis; *AMPA ,* ionotropic glutamate receptor; *AQP4,* aquaporin-4; *CASPR2,* contactin-associated protein-2; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *EDSS,* Kurtzke Expanded Disability Status Scale; *GABA,* gamma-aminobutyric acid; *GAD,* glutamic acid decarboxylase; *Ig,* immunoglobulin; *IL-6,* Interleukin-6; *LGI1,* Leucine-rich glioma-inactivated 1; *MP,* methylprednisolone; *MRI,* magnetic resonance imaging; *MS,* multiple sclerosis; *NMDA,* N-methyl-D-aspartate; *NMOSD,* neuromyelitisoptica spectrum disorders; *Ogbs,* oligoclonal bands; *PLEX,* plasmapheresis; *pNfh,* phosphorylated neurofilament heavy chain; *sIL-6R,* soluble Interleukin-6 Receptor; *SLE,* systemic lupus erythematosus

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