Journal of Neuroimmunology 334 (2019) 577005

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Elevated CHI3L1 and OPN levels in patients with anti-*N*-methyl-D-aspartate receptor encephalitis

Jing Zhao, Cancan Wang, Yuanxing Zhang, Ruihua Sun, Huayuan Wang, Gai Li, Jiewen Zhang*

Department of Neurology, People's Hospital of Zhengzhou University, Zhengzhou, China

ARTICLE INFO

Keywords:
Autoimmune encephalitis
Anti-NMDAR encephalitis
Chitinase-3-like 1
Osteopontin

ABSTRACT

Chitinase-3-like 1 (CHI3L1) and osteopontin (OPN) are known biomarkers of neuroinflammation. Herein, we explored the relationship between these inflammatory markers with the disease severity and prognosis in anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. We recruited 36 anti-NMDAR encephalitis patients and 20 controls. Compared to the levels in the controls, the cerebrospinal fluid (CSF) and serum levels of CHI3L1 and OPN were significantly increased in patients with anti-NMDAR encephalitis, and the CSF levels were found to be correlated with the initial and 6-month follow-up modified Rankin Scale (mRS) scores and abnormal brain MRI (suggestive of encephalitis). In addition, the CSF levels of CHI3L1 were associated with age, the CSF white blood cell (WBC) count and the CSF/serum albumin index (CSF-AI). CHI3L1 and OPN might serve as promising biomarkers for anti-NMDAR encephalitis.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is the most frequent form of autoimmune encephalitis, which was first reported in 2007 (Dalmau et al., 2007). It presents with various clinical manifestations, such as altered cognition and behavior, seizures, abnormal movements, autonomic dysfunction, and hypoventilation (Titulaer et al., 2013). The contributing mechanism of anti-NMDAR encephalitis appears to be the reversible internalization of NMDAR, which is mediated by autoantibodies (Hughes et al., 2010). The diagnosis of definitive anti-NMDAR encephalitis relies on a suggestive clinical picture with the detection of anti-NMDAR antibodies (Graus et al., 2016). Antibody titers in the cerebrospinal fluid (CSF) have been suggested to correlate with the disease course and prognosis of anti-NMDAR encephalitis (Gresa-Arribas et al., 2014), while other studies have described the persistence of antibodies in the CSF after clinical recovery (Hansen et al., 2013). Thus, we sought to investigate the levels of two inflammatory markers in anti-NMDAR encephalitis patients to determine whether they could be useful biomarkers for evaluation of the therapy and prognosis of the disease.

Chitinase-3-like 1 (CHI3L1) belongs to the chitinase protein family and is a 40 kDa secreted glycoprotein (Rehli et al., 1997). While the biological function of CHI3L1 is poorly understood, some studies have indicated that it might be involved in neuroinflammation (Baldacci et al., 2017; Bonneh-Barkay et al., 2010; Bonneh-Barkay et al., 2012). Elevated levels of CHI3L1 in the CSF and serum have been reported in some central nervous system (CNS) diseases, such as multiple sclerosis (Comabella et al., 2010; Quintana et al., 2018), stroke (Hjalmarsson et al., 2014), dementia (Hellwig et al., 2015; Zhang et al., 2018; Llorens et al., 2017), narcolepsy (Jennum et al., 2017), and suicidal ideation in older women (Rymo et al., 2017). Chen et al. showed that CSF levels of CHI3L1 were elevated in anti-NMDAR encephalitis and associated with the modified Rankin Scale (mRS) scores (Chen et al., 2018). However, this group did not show serum levels of CHI3L1 in anti-NMDAR encephalitis or correlations between the CHI3L1 levels and the ages of the patients, clinical prodromal symptoms, abnormal brain MRI (suggestive of encephalitis) or other laboratory results.

Osteopontin (OPN) is a phosphorylated matricellular protein that is expressed by various cells (Chiodoni et al., 2010). Its biological function is very complex and plays a role in many pathophysiological processes, including inflammation and the immune response (Rittling and Singh, 2015; Sun et al., 2013). Previous studies have shown that the levels of OPN in either the plasma or CSF are increased in some CNS diseases, such as multiple sclerosis (Comabella et al., 2005; Agah et al., 2018; Tortorella et al., 2018), CNS lymphoma (Strehlow et al., 2016), aneurysmal subarachnoid hemorrhage (Nakatsuka et al., 2018) and dementia (Sun et al., 2013). To the best of our knowledge, we report for the first time an investigation of the OPN levels in anti-NMDAR encephalitis patients.

Abbreviations: CHI3L1, Chitinase-3-like 1; OPN, Osteopontin; CSF, Cerebrospinal fluid; NMDAR, *N*-methyl-D-aspartate receptor; mRS, Modified Rankin Scale; CSF-AI, CSF/serum albumin index; CNS, Central nervous system; FLAIR, Fluid-attenuated inversion recovery; IQR, Interquartile range; ROC, Receiver operator characteristic; AUC, Area under the curve; WBC, White blood cell

* Corresponding author at: Department of Neurology, People's Hospital of Zhengzhou University, No. 7 Weiwu Road, Zhengzhou 450003, China.
E-mail address: zhangjiewen9900@126.com (J. Zhang).

https://doi.org/10.1016/j.jneuroim.2019.577005
Received 14 March 2019; Received in revised form 22 May 2019; Accepted 8 July 2019
0165-5728/

Table 1
Clinical data and laboratory findings of anti-NMDAR encephalitis patients and controls.

	Anti-NMDAR encephalitis	Controls
Age of onset (years, mean ± SD)	32.47 ± 16.54	31.45 ± 18.09
Female/male	17/19	9/11
Clinical features		
Prodromal symptoms	20	–
Psychiatric/behavioral problems	21	–
Amnesia and cognitive disturbance	13	–
Seizures	16	–
Movement disorders	5	–
Speech disorders	4	–
Ataxia	4	
Autonomic dysfunction	12	–
Central hypoventilation	8	–
Loss of consciousness	17	–
Sleep disorders	11	–
Admitted into ICU	9	–
Tumor		
Ovarian teratoma	1	0
Lung cancer	2	0
Relapse	7/36	–
Follow-up (months, median, range)	15 (7–40)	–
CSF pressure (mmH_2O, median, range)	157.50 (60–400)	147.5(52–230)
CSF WBC count ($\times 10^6$, median, range)	17.5 (2–248)	4 (1 − 10)
CSF Protein (g/L, median, range)	0.47 (0.1–6.34)	0.36 (0.19–0.73)
CSF AI ($\times 10^{-3}$)	6.2 ± 4.03	–
Positive oligoclonal bands	7/22	–
Anti-NMDAR antibodies in CSF	36	0
Anti-NMDAR antibodies in Serum	21	0
Abnormal brain MRI	14	–
Initial mRS (mean ± SD)	3 ± 1.12	–
6-months follow-up mRS (mean ± SD)	1.67 ± 0.79	–
CSF CHI3L1 (ng/ml)	250.81(IQR157.89, 472.10)	97.46 ± 61.96
Serum CHI3L1 (ng/ml)	62.97(IQR36.49,89.73)	32.19(IQR23.61,56.42)
CSF OPN (ng/ml)	316.87(IQR100.87,625.29)	84.23 ± 59.39
Serum OPN (ng/ml)	42.99(IQR33.18,62.11)	24.40(IQR15.62,44.90)

2. Materials and methods

2.1. Subjects

In the anti-NMDAR encephalitis group, we examined 46 CSF samples and 26 serum samples that were derived from 36 patients admitted to the People's Hospital of Zhengzhou University from January 2015 to May 2018. Thirty-six CSF samples were obtained during the acute phase prior to immunotherapy, among which 26 had paired serum samples, and 10 CSF samples were obtained during the remission phase following immunotherapy. All recruited patients met the diagnostic criteria of definite anti-NMDAR encephalitis (Graus et al., 2016). The control group comprised 20 noninflammatory neurological disorder patients, which included epilepsy (n = 4), anxiety disorder (n = 4), migraine (n = 3), motor neuron disease (n = 2), cerebral infarction (n = 2), vasovagal syncope (n = 2), idiopathic cranial hypertension (n = 1), myotonic dystrophy (n = 1), and hereditary spastic paraplegia (n = 1).

Clinical and laboratory data were collected from the recruited patients, and only 22 patients with anti-NMDAR encephalitis had CSF/serum albumin index (CSF-AI) data, which was used to assess the integrity of the blood-brain barrier. The mRS was employed to evaluate the neurological status of the patients. Abnormal brain MRI scans, which were suggestive of encephalitis, were identified if there was a hyperintense signal on fluid-attenuated inversion recovery (FLAIR) involving the medial temporal lobes or in multifocal areas involving gray or white matter that was compatible with demyelination or inflammation (Graus et al., 2016).

This study was approved by the local ethics committee of the People's Hospital of Zhengzhou University, and all participants provided written informed consent.

2.2. CSF and serum CHI3L1 and OPN measurements

The CHI3L1 and OPN concentrations in the CSF and serum were measured by commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions and were measured in duplicate.

2.3. Statistical analysis

The data were analyzed with SPSS version 21.0 software. Continuous variables of normally distributed data were presented as the mean ± standard deviation. If data were not normally distributed, then data were presented as the median and interquartile range (IQR). Group comparisons were analyzed with Student's *t*-test or Mann-Whitney *U* test as appropriate. Correlations between the OPN levels and the clinical data were analyzed by Spearman's correlation, and correlations between the CHI3L1 levels and the clinical data were analyzed by multiple linear regression modeling with age adjustment. Pairwise comparisons of the paired samples were measured by the Wilcoxon signed-rank test. The discriminatory power of the CHI3L1/OPN levels in anti-NMDAR encephalitis was evaluated by receiver operator characteristic (ROC) curves. P values < 0.05 were considered to indicate statistically significant observations.

3. Results

3.1. Clinical features and demographics

The clinical features and CSF laboratory studies of recruited patients are listed in Table 1. The mean age and the male to female ratio of the recruited patients with anti-NMDAR encephalitis were

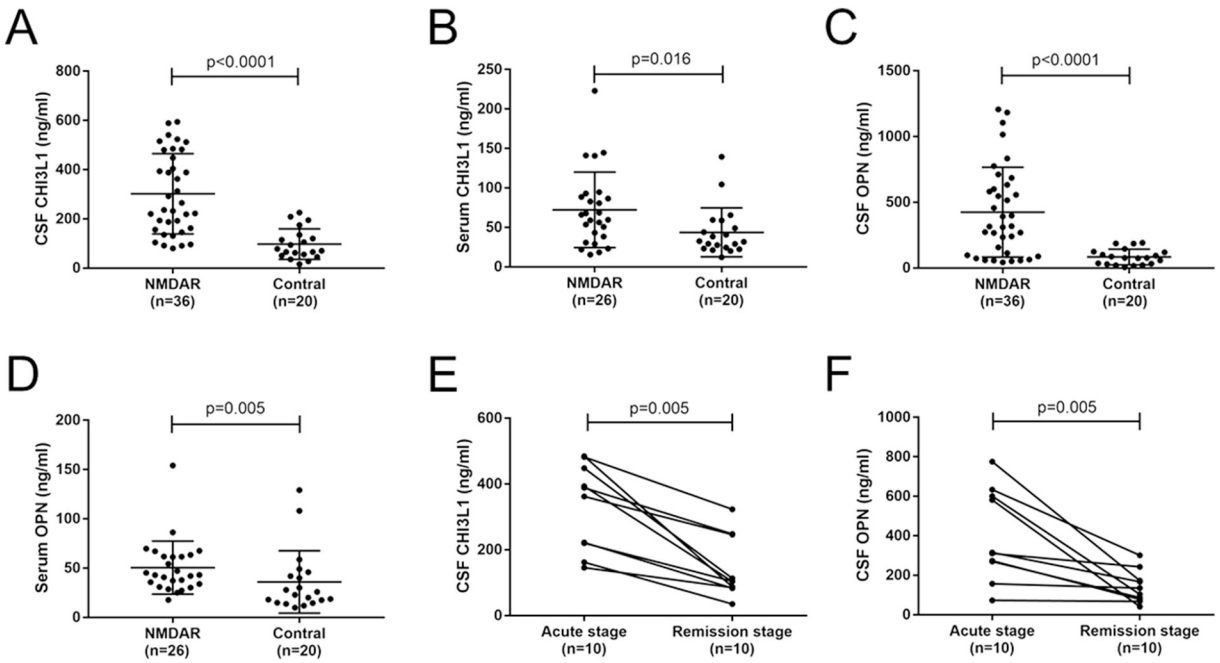

Fig. 1. Levels of CHI3L1 (a, b) and OPN (c, d) in anti-NMDAR encephalitis were higher than were found in controls. In anti-NMDAR encephalitis patients, CSF levels of CHI3L1 (e) and OPN (f) were decreased during remission stage as compared to the acute stage of disease.

32.47 ± 16.54 years and 19:17 respectively. In the control group, these values were 31.45 ± 18.09 years and 11:9 respectively. There were no significant differences in the age and sex distributions between the groups. The mean initial mRS score of anti-NMDAR encephalitis patients was 3 ± 1.12. The mean 6-month follow-up mRS score for the anti-NMDAR encephalitis patients was 1.67 ± 0.79. In our recruited patients, 14 patients had abnormal brain MRI. Nine patients had hyperintense signals on FLAIR involving the medial temporal lobe. Five patients had hyperintense signals on FLAIR involving multifocal areas such as cerebral cortex, basal ganglia and brainstem.

3.2. Increased CSF and serum levels of CHI3L1 and OPN in anti-NMDAR encephalitis patients

The mean concentrations of CHI3L1 and OPN in the CSF and serum are presented in Table 1. The levels of CHI3L1 in the CSF and serum were significantly higher in patients with anti-NMDAR encephalitis than in controls ($p < 0.0001$ and $p = 0.016$, respectively; Fig. 1). Both the CSF and serum OPN levels were significantly higher in anti-NMDAR encephalitis patients than in controls ($p < 0.0001$ and $p = 0.005$, respectively; Fig. 1).

In anti-NMDAR encephalitis patients, the CSF concentrations of CHI3L1 and OPN were significantly higher than those in the serum ($p < 0.0001$ for all).

We used ROC curves to evaluate the discriminatory power of CHI3L1 and OPN for anti-NMDAR encephalitis. The areas under the curve (AUC) were 0.894 and 0.844 for the CSF levels of CHI3L1 and OPN, respectively (Fig. 3). The AUC for the serum CHI3L1 and OPN levels were 0.710 and 0.746, respectively (Fig. 3).

3.3. Clinical features related to increased CSF and serum CHI3L1 and OPN concentrations in anti-NMDAR encephalitis patients

Spearman's rank correlation analysis showed that the CSF CHI3L1 concentrations were correlated with the age of the patients ($r = 0.405$; $p = 0.014$) but not with their gender ($p > 0.05$) in anti-NMDAR encephalitis patients. Thus, in the remaining analyses, we used multiple linear regression to correct for age, and the results are shown in Table 2. After adjusting for age, we found that the CSF CHI3L1 levels were

Table 2
Correlations between CSF levels of CHI3L1 and clinical data were analyzed by multiple linear regression with age adjustment.

	β	95% CI	p
Initial mRS	0.471	0.168–0.774	0.003
6-months follow-up mRS	0.549	0.255–0.844	0.001
CSF WBC count	0.434	0.140–0.729	0.005
CSF-AI	0.432	0.032–0.832	0.036
Abnormal brain MRI	0.396	0.091–0.702	0.012

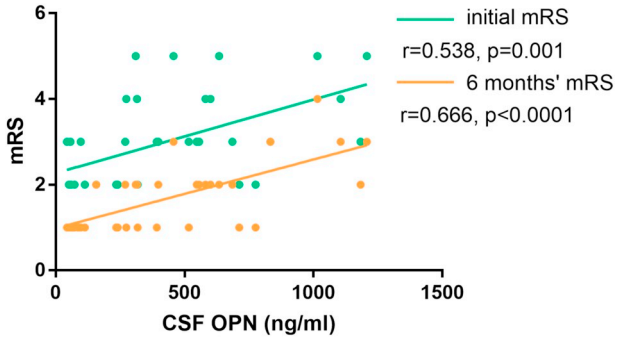

Fig. 2. Correlations between CSF OPN concentrations and the initial, and 6-month follow-up mRS in anti-NMDAR encephalitis patients.

associated with the initial mRS ($\beta = 0.471$; $p = 0.003$), the 6-month follow-up mRS ($\beta = 0.549$; $p = 0.001$), the CSF white blood cell (WBC) count ($\beta = 0.434$; $p = 0.005$), the CSF-AI ($\beta = 0.432$; $p = 0.036$), and the abnormal brain MRI (suggestive of encephalitis) ($\beta = 0.396$; $p = 0.012$) and showed no association between the CSF CHI3L1 levels and prodromal symptoms, relapse, antibody titers.

We discovered that the CSF OPN concentrations were associated with the initial mRS ($r = 0.538$; $p = 0.001$; Fig. 2), the 6-month follow-up mRS ($r = 0.666$; $p < 0.0001$; Fig. 2), and the abnormal brain MRI ($r = 0.400$; $p = 0.016$). However, no significant correlations were

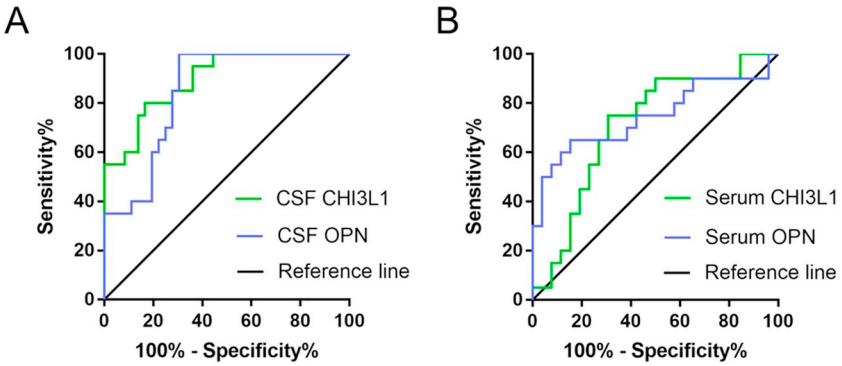

Fig. 3. ROC analyses of CSF and serum CHI3L1/OPN. The AUC were 0.894 and 0.844 for CSF CHI3L1 and OPN respectively (a). The AUC for serum CHI3L1 and OPN were 0.710 and 0.746 respectively (b).

observed between the OPN levels and age, gender, CSF WBC count, prodromal symptoms, relapse, antibody titers, or CSF-AI.

Furthermore, we found a positive association between the CSF and serum levels of CHI3L1 ($\beta = 0.566$; $p = 0.009$) and the CSF and serum levels of OPN ($r = 0.449$; $p = 0.021$) in anti-NMDAR encephalitis patients. No significant correlations were found between the CHI3L1 and OPN levels in serum and the initial mRS, 6-month follow-up mRS, prodromal symptoms, relapse, abnormal brain MRI or other laboratory results.

3.4. Differences in CSF OPN and CHI3L1 concentrations between the acute and remission stages of anti-NMDAR encephalitis

Twenty CSF samples were collected from 10 patients during the acute and remission stages of the disease. The concentrations are shown in Fig. 1. Wilcoxon tests showed that between the acute and remission stages, there were significant differences in the CSF CHI3L1 levels ($p = 0.005$) and the CSF OPN levels ($p = 0.005$).

4. Discussion

At this time, there are no suitable biomarkers for anti-NMDAR encephalitis. Although antibody titers are related to the clinical course of the disease to some extent, the correlation is less perfect. After clinical recovery, antibodies might still be detected in some patients (Gresa-Arribas et al., 2014; Hansen et al., 2013). Both CHI3L1 and OPN are inflammatory biomarkers, and inflammation is an important characteristic of anti-NMDAR encephalitis. Thus, we investigated the CSF and serum levels of these inflammatory factors in anti-NMDAR encephalitis. The results of the present study showed higher CSF and serum levels of CHI3L1 and OPN in patients with anti-NMDAR encephalitis compared with the levels in non-neuroinflammatory patients, and their CSF levels were correlated with both the initial and 6-month follow-up mRS and the abnormal brain MRI. Furthermore, the levels of CSF CHI3L1 were correlated with age, CSF WBC count, and CSF-AI.

Our study confirms previous data demonstrating that the levels of CSF CHI3L1 are correlated with mRS scores in anti-NMDAR encephalitis (Chen et al., 2018). Our study also supports previous research that CHI3L1 levels were correlated with age, which may be explained by the activation of microglia during normal aging, and CHI3L1 is a marker for microglial activation (Schuitemaker et al., 2012; Olsson et al., 2013). After age correction, we found that the CSF levels of CHI3L1 were also correlated with the initial and 6-month follow-up mRS scores. CHI3L1 is a glycoprotein that is secreted by various cell types. Previous studies have shown that IL-6 and IL-1β upregulate CHI3L1 expression via STAT3 and the RelB/p50 complexes (Bhardwaj et al., 2015; Bonneh-Barkay et al., 2012). In anti-NMDAR encephalitis, CSF IL-6 and IL-1β were found to be elevated (Zeng et al., 2018), which might help to explain the increase in the CSF CHI3L1 level in anti-NMDAR encephalitis.

OPN is an extracellular matrix protein. Studies have demonstrated that OPN induces B cell proliferation and antibody production (Wang and Denhardt, 2008). In addition, OPN plays an important role in the differentiation of Th17 cells (Agah et al., 2018; Carecchio and Comi, 2011). The main immunological mechanism in anti-NMDAR encephalitis is intrathecal humoral immunity and B cell activation, which is often helped by Th17 cells (Liba et al., 2016; Tuzun et al., 2009; Zeng et al., 2018; Byun et al., 2016). Therefore, we concluded that elevated OPN levels may be involved in the induction of the immune response in NMDAR encephalitis.

There are certain limitations to the present study. First, this study is retrospective, and some of the patients' clinical data were incomplete, such as lacking CSF-AI. Second, the number of patients was relatively small. Third, not all CSF had paired serum samples and due to the relative invasiveness of lumbar puncture, some patients with clinical remission refused to undergo lumbar puncture again during the follow-up, which contributed to the small sample size of the remission period CSF.

5. Conclusions

Our study has shown that the CSF and serum levels of CHI3L1 and OPN are significantly increased in anti-NMDAR encephalitis patients compared with controls. The levels of CHI3L1 and OPN in the CSF were also associated with disease severity and might be useful in predicting the prognosis of patients. However, the role of these inflammatory biomarkers in anti-NMDAR encephalitis remains to be formally explored.

Funding

Not applicable.

Decalaration of Competing Interest

The authors declare there is no conflicts of interest.

Acknowledgements

We thank Dr. Yingying Shi for her great help in sample collection. And thank all the patients who participated in this study.

References

Agah, E., Zardoui, A., Saghazadeh, A., Ahmadi, M., Tafakhori, A., Rezaei, N., 2018. Osteopontin (OPN) as a CSF and blood biomarker for multiple sclerosis: a systematic review and meta-analysis. PLoS ONE 13, e0190252.

Baldacci, F., Lista, S., Cavedo, E., Bonuccelli, U., Hampel, H., 2017. Diagnostic function of

the neuroinflammatory biomarker YKL-40 in Alzheimer's disease and other neurodegenerative diseases. Expert Rev. Proteom. 14, 285–299.
Bhardwaj, R., Yester, J.W., Singh, S.K., Biswas, D.D., Surace, M.J., Waters, M.R., Hauser, K.F., Yao, Z., Boyce, B.F., Kordula, T., 2015. RelB/p50 complexes regulate cytokine-induced YKL-40 expression. J. Immunol. 194, 2862–2870.
Bonneh-Barkay, D., Wang, G., Starkey, A., Hamilton, R.L., Wiley, C.A., 2010. In vivo CHI3L1 (YKL-40) expression in astrocytes in acute and chronic neurological diseases. J. Neuroinflammation 7, 34.
Bonneh-Barkay, D., Bissel, S.J., Kofler, J., Starkey, A., wang, G., Wiley, C.A., 2012. Astrocyte and macrophage regulation of YKL-40 expression and cellular response in neuroinflammation. Brain Pathol. 22, 530–546.
Byun, J.I., Lee, S.T., Moon, J., Jung, K.H., Sunwoo, J.S., Lim, J.A., Kim, T.J., Shin, Y.W., Lee, K.J., Jun, J.S., Lee, H.S., Lee, W.J., Kim, Y.S., Kim, S., Jeon, D., Park, K.I., Jung, K.Y., Kim, M., Chu, K., Lee, S.K., 2016. Distinct intrathecal interleukin-17/interleukin-6 activation in anti-N-methyl-D-aspartate receptor encephalitis. J. Neuroimmunol. 297, 141–147.
Carecchio, M., Comi, C., 2011. The role of osteopontin in neurodegenerative diseases. J. Alzheimers Dis. 25, 179–185.
Chen, J., Ding, Y., Zheng, D., Wang, Z., Pan, S., Ji, T., Shen, H.Y., Wang, H., 2018. Elevation of YKL-40 in the CSF of anti-NMDAR encephalitis patients is associated with poor prognosis. Front. Neurol. 9, 727.
Chiodoni, C., Colombo, M.P., Sangaletti, S., 2010. Matricellular proteins: from homeostasis to inflammation, cancer, and metastasis. Cancer Metastasis Rev. 29, 295–307.
Comabella, M., Pericot, I., Goertsches, R., Nos, C., Castillo, M., Blas Navarro, J., Rio, J., Montalban, X., 2005. Plasma osteopontin levels in multiple sclerosis. J. Neuroimmunol. 158, 231–239.
Comabella, M., Fernandez, M., Martin, R., Rivera-Vallve, S., Borras, E., Chiva, C., Julia, E., Rovira, A., Canto, E., Alvarez-Cermeno, J.C., Villar, L.M., Tintore, M., Montalban, X., 2010. Cerebrospinal fluid chitinase 3-like 1 levels are associated with conversion to multiple sclerosis. Brain 133, 1082–1093.
Dalmau, J., Tuzun, E., Wu, H.Y., Masjuan, J., Rossi, J.E., Voloschin, A., Baehring, J.M., Shimazaki, H., Koide, R., King, D., Mason, W., Sansing, L.H., Dichter, M.A., Rosenfeld, M.R., Lynch, D.R., 2007. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann. Neurol. 61, 25–36.
Graus, F., Titulaer, M.J., Balu, R., Benseler, S., Bien, C.G., Cellucci, T., Cortese, I., Dale, R.C., Gelfand, J.M., Geschwind, M., Glaser, C.A., Honnorat, J., Höftberger, R., Iizuka, T., Irani, S.R., Lancaster, E., Leypoldt, F., Prüss, H., Rae-Grant, A., Reindl, M., Rosenfeld, M.R., Rostásy, K., Saiz, A., Venkatesan, A., Vincent, A., Wandinger, K.-P., Waters, P., Dalmau, J., 2016. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 15, 391–404.
Gresa-Arribas, N., Titulaer, M.J., Torrents, A., Aguilar, E., Mccracken, L., Leypoldt, F., Gleichman, A.J., Balice-Gordon, R., Rosenfeld, M.R., Lynch, D., Graus, F., Dalmau, J., 2014. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol. 13, 167–177.
Hansen, H.C., Klingbeil, C., Dalmau, J., Li, W., Weissbrich, B., Wandinger, K.P., 2013. Persistent intrathecal antibody synthesis 15 years after recovering from anti-N-methyl-D-aspartate receptor encephalitis. JAMA Neurol. 70, 117–119.
Hellwig, K., Kvartsberg, H., Portelius, E., Andreasson, U., Oberstein, T.J., Lewczuk, P., Blennow, K., Kornhuber, J., Maler, J.M., Zetterberg, H., Spitzer, P., 2015. Neurogranin and YKL-40: independent markers of synaptic degeneration and neuroinflammation in Alzheimer's disease. Alzheimers Res. Ther. 7, 74.
Hjalmarsson, C., Bjerke, M., Andersson, B., Blennow, K., Zetterberg, H., Aberg, N.D., Olsson, B., Eckerstrom, C., Bokemark, L., Wallin, A., 2014. Neuronal and glia-related biomarkers in cerebrospinal fluid of patients with acute ischemic stroke. J. Cent. Nerv. Syst. Dis. 6, 51–58.
Hughes, E.G., Peng, X., Gleichman, A.J., Lai, M., Zhou, L., Tsou, R., Parsons, T.D., Lynch, D.R., Dalmau, J., Balice-Gordon, R.J., 2010. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J. Neurosci. 30, 5866–5875.
Jennum, P.J., Ostergaard Pedersen, L., Czarna Bahl, J.M., Modvig, S., Fog, K., Holm, A., Rahbek Kornum, B., Gammeltoft, S., 2017. Cerebrospinal fluid biomarkers of neurodegeneration are decreased or normal in narcolepsy. Sleep 40.
Liba, Z., Kayserova, J., Elisak, M., Marusic, P., Nohejlova, H., Hanzalova, J., Komarek, V., Sediva, A., 2016. Anti-N-methyl-D-aspartate receptor encephalitis: the clinical course in light of the chemokine and cytokine levels in cerebrospinal fluid. J. Neuroinflammation 13, 55.
Llorens, F., Thune, K., Tahir, W., Kanata, E., Diaz-Lucena, D., Xanthopoulos, K., Kovatsi, E., Pleschka, C., Garcia-Esparcia, P., Schmitz, M., Ozbay, D., Correia, S., Correia, A., Milosevic, I., Andreoletti, O., Fernandez-Borges, N., Vorberg, I.M., Glatzel, M., Sklaviadis, T., Torres, J.M., Krasemann, S., Sanchez-Valle, R., Ferrer, I., Zerr, I., 2017. YKL-40 in the brain and cerebrospinal fluid of neurodegenerative dementias. Mol. Neurodegener. 12, 83.
Nakatsuka, Y., Shiba, M., Nishikawa, H., Terashima, M., Kawakita, F., Fujimoto, M., Suzuki, H., P, S.G., 2018. Acute-phase plasma osteopontin as an independent predictor for poor outcome after aneurysmal subarachnoid hemorrhage. Mol. Neurobiol. 55, 6841–6849.
Olsson, B., Hertze, J., Lautner, R., Zetterberg, H., Nagga, K., Hoglund, K., Basun, H., Annas, P., Lannfelt, L., Andreasen, N., Minthon, L., Blennow, K., Hansson, O., 2013. Microglial markers are elevated in the prodromal phase of Alzheimer's disease and vascular dementia. J. Alzheimers Dis. 33, 45–53.
Quintana, E., Coll, C., Salavedra-Pont, J., Munoz-San Martin, M., Robles-Cedeno, R., TOMAS-ROIG, J., Buxo, M., Matute-Blanch, C., Villar, L.M., Montalban, X., Comabella, M., Perkal, H., Gich, J., Ramio-Torrenta, L., 2018. Cognitive impairment in early stages of multiple sclerosis is associated with high cerebrospinal fluid levels of chitinase 3-like 1 and neurofilament light chain. Eur. J. Neurol. 25, 1189–1191.
Rehli, M., Krause, S.W., Andreesen, R., 1997. Molecular characterization of the gene for human cartilage gp-39 (CHI3L1), a member of the chitinase protein family and marker for late stages of macrophage differentiation. Genomics 43, 221–225.
Rittling, S.R., Singh, R., 2015. Osteopontin in immune-mediated diseases. J. Dent. Res. 94, 1638–1645.
Rymo, I., Kern, S., Bjerke, M., Zetterberg, H., Marlow, T., Blennow, K., Gudmundsson, P., Skoog, I., Waern, M., 2017. CSF YKL-40 and GAP-43 are related to suicidal ideation in older women. Acta Psychiatr. Scand. 135, 351–357.
Schuitemaker, A., van der Doef, T.F., Boellaard, R., van der Flier, W.M., Yaqub, M., Windhorst, A.D., Barkhof, F., Jonker, C., Kloet, R.W., Lammertsma, A.A., Scheltens, P., van Berckel, B.N., 2012. Microglial activation in healthy aging. Neurobiol. Aging 33, 1067–1072.
Strehlow, F., Bauer, S., Martus, P., Weller, M., Roth, P., Schlegel, U., Seidel, S., Scheibenbogen, C., Korfel, A., Kreher, S., 2016. Osteopontin in cerebrospinal fluid as diagnostic biomarker for central nervous system lymphoma. J. Neuro-Oncol. 129, 165–171.
Sun, Y., Yin, X.S., Guo, H., Han, R.K., He, R.D., Chi, L.J., 2013. Elevated osteopontin levels in mild cognitive impairment and Alzheimer's disease. Mediat. Inflamm. 2013, 1–9.
Titulaer, M.J., Mccracken, L., Gabilondo, I., Armangué, T., Glaser, C., Iizuka, T., Honig, L.S., Benseler, S.M., Kawachi, I., Martinez-Hernandez, E., Aguilar, E., Gresa-Arribas, N., Ryan-Florance, N., Torrents, A., Saiz, A., Rosenfeld, M.R., Balice-Gordon, R., Graus, F., Dalmau, J., 2013. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 12, 157–165.
Tortorella, C., Direnzo, V., Ruggieri, M., Zoccolella, S., Mastrapasqua, M., D'onghia, M., Paolicelli, D., Cuonzo, F.D., Gasperini, C., Trojano, M., 2018. Cerebrospinal fluid neurofilament light levels mark grey matter volume in clinically isolated syndrome suggestive of multiple sclerosis. Mult. Scler. 24, 1039–1045.
Tuzun, E., Zhou, L., Baehring, J.M., Bannykh, S., Rosenfeld, M.R., Dalmau, J., 2009. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. Acta Neuropathol. 118, 737–743.
Wang, K.X., Denhardt, D.T., 2008. Osteopontin: role in immune regulation and stress responses. Cytokine Growth Factor Rev. 19, 333–345.
Zeng, C., Chen, L., Chen, B., Cai, Y., Li, P., Yan, L., Zeng, D., 2018. Th17 cells were recruited and accumulated in the cerebrospinal fluid and correlated with the poor prognosis of anti-NMDAR encephalitis. Acta Biochim. Biophys. Sin. Shanghai 50, 1266–1273.
Zhang, H., Ng, K.P., Therriault, J., Kang, M.S., Pascoal, T.A., Rosa-Neto, P., Gauthier, S., Alzheimer's Disease Neuroimaging, I, 2018. Cerebrospinal fluid phosphorylated tau, visinin-like protein-1, and chitinase-3-like protein 1 in mild cognitive impairment and Alzheimer's disease. Transl. Neurodegener. 7, 23.