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RESEARCH ARTICLE

Differentiation of viral and autoimmune central nervous system inflammation by kynurenine pathway

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Abstract

Objective: To determine whether the metabolites of Kynurenine pathway (KP) could serve as biomarkers for distinguishing between viral CNS infections and autoimmune neuroinflammatory diseases, especially anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) and herpes virus encephalitis (HSE). **Methods**: This study enrolled CSF samples from 76 patients with viral CNS infections, autoimmune neuroinflammatory, and non-inflammatory neurological diseases. We measured cerebrospinal fluid (CSF) concentrations of tryptophan (Trp) and kynurenine (Kyn) by ELISA. **Results**: Kyn concentrations and Kyn/Trp ratios were highly increased ($p < 0.001$, viral vs. autoimmune) in viral CNS infections, whereas patients with autoimmune neuroinflammatory and non-inflammatory diseases exhibited low concentrations. Furthermore, Kyn concentrations and Kyn/Trp ratio turned out to be excellent biomarkers to distinguish between herpes simplex encephalitis (HSE) and NMDARE (AUC 0.920 and AUC 0.906), whereas Trp concentrations were similar in all three groups. **Interpretation**: The results suggest that elevated CSF Kyn concentrations and Kyn/Trp ratio may serve as biomarkers for distinguishing viral CNS infections from autoimmune neuroinflammatory diseases. In particular, the distinction between HSE and NMDARE is of great clinical relevance. Further studies are warranted to investigate the potential of CSF Kyn levels and Kyn/Trp ratio as routine parameters in patients with CNS diseases.

Introduction

Tryptophan (Trp) is an essential amino acid, which is one of the building blocks for protein synthesis in humans and the only substrate source for the production of several important molecules. Trp is metabolized through two major pathways, the kynurenine pathway (KP) and the methoxyindole pathway, generating a range of metabolites involved in inflammation, immune response, and excitatory neurotransmission.[1–4] The first rate-limiting enzyme of the KP is indolamine 2,3-dioxygenase (IDO), which is expressed in various immune cells and preferentially induced by proinflammatory cytokines.[5–7] In recent years, the regulation of Kynurenine (Kyn) metabolism has been intensely evaluated as it is involved in a variety of CNS disorders.[8–10] We have previously described that the KP is activated in CNS infections and can be measured in cerebrospinal fluid (CSF). Kyn level and Kyn/Trp ratio were highly increased in patients suffering from bacterial and viral CNS infections, but were not changed in autoimmune neuroinflammation, such as anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) or multiple sclerosis (MS).[11] It is especially important to distinguish between CNS diseases which have similar symptoms and CSF findings but require different therapeutic approaches, such as herpes virus encephalitis (HSE) and autoimmune NMDARE.

In this study, we used an ELISA to measure the concentrations of Kyn and Trp in the CSF of patients with viral CNS infections, autoimmune neuroinflammatory,

and non-inflammatory neurological diseases. We also investigated the correlation of these three parameters with routine CSF parameters in the different groups and assessed the potential of Kyn and Kyn/Trp ratio as diagnostic CSF biomarkers particularly to distinguish between HSE and NMDARE.

Methods

Standard protocol approvals, registrations, and patient consents

The study was approved by the institutional Ethics Committee of the Hannover Medical School (file no. 2413-2014) and University hospital Ulm (file no. 20/10). All participants or their legal representative gave their informed consent to participate.

Study design and study participants

The CSF samples were obtained at the Department of Neurology at Hannover Medical School and the Department of Neurology at the University hospital Ulm during a routine lumbar puncture. The study subjects were 76 patients with the following diagnoses: 15 patients with herpes simplex virus meningitis/encephalitis (HSE), 16 patients with varicella-zoster virus meningitis/encephalitis (VZVME), 15 patients with NMDARE, 16 patients with MS, and 14 patients with normal pressure hydrocephalus (NPH) or idiopathic intracranial hypertension (IIH). Diagnostic criteria of the diseases are summarized in Table S1. Patients with HSE and VZVME were subsumed under the term CNS infection group, whereas the autoimmune neuroinflammatory group consisted of NMDARE and MS patients. The patients with NPH and IIH formed the non-inflammatory control group.

Laboratory testing

CSF samples were obtained via lumbar puncture using an atraumatic needle. All MS-CSF samples were collected from patients during their first clinical manifestation. Samples from HSE patients were collected during the acute disease stage. All samples were processed and stored according to unified standard operating procedures.[12] After lumbar puncture, the following routine CSF parameters were determined within 2 h: leukocyte count, protein concentration, albumin, and immunoglobulin G (IgG) concentration. Furthermore, serum albumin and serum IgG concentrations were assessed. IgG index was calculated according to the following principle: CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The remainder of the samples was immediately centrifugated, frozen in aliquots, and then stored at −80°C until ELISA analysis.

ELISA analysis

The ELISA was performed according to protocols provided by the kit manufacturer (Immundiagnostik, Bensheim, Germany). Briefly, microtiter Kynurenine plates (96 well, pre-coated with L-Kynurenine derivative) and tryptophan plates (96 well, pre-coated with L-Tryptophan derivative) were prepared to measure the fluorescence of samples, standards, and controls. Afterward, fluorescence was detected by a microplate reader at 260 nm (Sunrise, Grödig, Austria). Concentrations were calculated by the Magellan software (V7.2Sp1) using a four-parametric logistic standard curve derived from the standards provided in the kits. All washes were carried out by Auto mini-Washer AMW-2 (Hydroflex, Grödig, Austria). All samples were tested in duplicate.

Statistical analysis

Continuous data are presented as median (range). Since the data did not follow a normal distribution (Kolmogorov–Smirnow test, $p < 0.001$), non-parametric tests were used to analyze the data. We used the Kruskal–Wallis test followed by multiple comparisons using the Mann–Whitney *U*-test to determine differences among the groups. Bonferroni corrections were used to correct these multiple comparisons and p value was set at 0.005 for significance. Spearman correlation was used to assess correlations between Kyn, Trp concentration, Kyn/Trp ratio, and the routine CSF parameters measured. Receiver operating characteristic (ROC) curve analysis was used to quantify the ability of biomarkers to predict a given diagnosis. p values <0.05 were considered statistically significant. All statistical analyses were performed with SPSS version 24 (IBM, NY, USA) and graphs generated by GraphPad Prism 8 (GraphPad, San Diego, USA).

Results

Patients' characteristics and standard CSF parameters

The demographics and characteristics of standard CSF parameters of all subjects are shown in Table 1. Mean CSF leukocyte count and protein concentrations were significantly increased in the HSE and VZVME group and slightly elevated in MS and NMDARE patients (Table 1). The mean CSF IgG-index was highest in MS, followed by NMDARE, HSE, and VZVME (Table 1). These three

Table 1. Demographic and clinical characteristics of patients.

		CNS infection		Autoimmune neuroinflammatory controls		
	Control[2]	HSE	VZVME	MS	NMDARE	*p* value (all groups)[1]
Age in years	33.5 (21–78)	56 (30–77)	59 (19–104)	35.5 (17–69)	36 (19–81)	0.053
Female sex *n*	9 (14)	6 (15)	7 (16)	13 (16)	10 (15)	0.108
CSF-leukocytes (1/μL)	0.7 (0.3–4.7)	90.7 (6–882)	74 (0.3–900)	5.7 (0.7–42)	2.3 (0.7–172)	1×10^{-3}
CSF-protein (mg/L)	295 (147–594)	895 (518–3800)	912.5 (140–2910)	415 (215–663)	423 (213–878)	1×10^{-3}
CSF-IgG-index	0.4 (0.45–0.56)	0.6 (0.46–1.67)	0.5 (0.41–1.16)	0.77 (0.43–1.7)	0.64 (0.3–2.35)	0.001

CNS, central nervous system, CSF, cerebrospinal fluid, HSE, HSV encephalitis, MS, multiple sclerosis, NMDARE, anti-NMDA-R encephalitis, VZVME, VZV meningitis/encephalitis. Data represent mean value (range).
[1]Kruskal–Wallis test.
[2]Control: non-inflammatory control group consisting of NPH and IIH patients, ***$p < 0.001$.

indicators had significant statistical differences between the groups. Age and sex had no contributory effect in any group. All standard parameters were normal in the control group.

Kyn and Kyn/Trp ratio is increased in CSF of patients with viral encephalitis

Measured Kyn concentrations and Kyn/Trp ratios were markedly increased in the viral CNS infection group, especially in VZVME (Fig. 1). Kyn concentrations in the VZVME group (0.56 ± 0.44 μmol/L) were 9.3, 7, and 12 times higher compared with MS- (0.06 ± 0.07 μmol/L), NMDARE- (0.08 ± 0.1 μmol/L), and the non-inflammatory control group (0.05 ± 0.07 μmol/L), respectively. The level of Kyn in patients with HSE (0.54 ± 0.39 μmol/L) was 9, 6.8, and 10.8 times higher compared with MS patients, NMDARE patients ($p < 0.001$), and the non-inflammatory control group, respectively. The Kyn/Trp ratio was also significantly ($p < 0.001$) increased in the viral infection group with a mean value of 0.35 in VZVME and 0.26 in HSE patients, compared with MS (0.02), NMDARE (0.03) and non-inflammatory control group (0.02). The Trp concentrations detected in the viral infection group tended to be lower than in the other groups; however, this was not statistically significant. There was no statistical difference in the Kyn and Trp concentrations or the Kyn/Trp ratio between MS, NMDARE, or non-inflammatory control group.

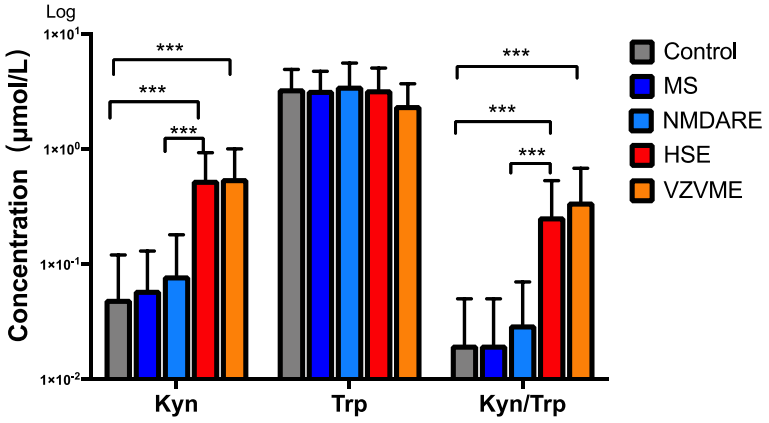

Figure 1. Comparison of CSF kynurenine, CSF tryptophan, and CSF Kyn/Trp ratio between different patient groups. Patients with CNS infections (both HSV encephalitis (HSE) and VZV meningitis/encephalitis (VZVME)) exhibit significantly higher Kyn concentrations and a significantly higher Kyn/Trp ratio compared with the control group consisting of patients with idiopathic intracranial hypertension and normal pressure hydrocephalus. Notably, significantly higher Kyn concentrations and a significantly higher Kyn/Trp ratio are also observed in HSE patients compared to patients with anti-NMDA-R encephalitis (NMDARE). Regarding the CSF Trp concentrations, no difference is found between the individual groups. *Y* axis uses log index. Differences between the two groups were analyzed using Mann–Whitney test. Level of significance: ***$p < 0.001$.

Table 2. Inter-correlations between CSF Kyn concentrations or Kyn/Trp ratio and standard CSF parameters.

	CSF	MS	NMDARE	HSE	VZVME
Kyn	Leukocytes	−0.681** (0.004)	NS	NS	0.736** (0.002)
	Protein	NS	0.591* (0.026)	0.601* (0.023)	0.668** (0.007)
	IgG-index	−0.506* (0.046)	NS	NS	NS
Kyn/Trp	Leukocytes	−0.586* (0.017)	0.535* (0.049)	NS	0.879** (1×10^{-3})
	Protein	NS	0.560* (0.037)	0.557* (0.039)	0.718* (0.003)
	IgG-index	NS	0.604* (0.022)	NS	NS

CSF, cerebrospinal fluid; HSE, HSV encephalitis; Kyn, kynurenine; MS, multiple sclerosis; NMDARE, anti-NMDA-R encephalitis; Trp, tryptophan; VZVME, VZV meningitis/encephalitis; NS, not significant.
*$p < 0.05$.
**$p < 0.01$.

CSF concentrations of Kyn and Kyn/Trp ratio correlate with standard CSF parameters in the different groups

We assessed correlations between different metabolites (Kyn and Kyn/Trp ratio) and CSF leukocyte count, CSF protein, and CSF IgG-index using Spearman correlation tests (Table 2). Regarding the CNS infection group, a correlation between CSF leukocyte count and Kyn concentrations as well as CSF leukocyte count and Kyn/Trp ratio was found in VZVME. Moreover, CSF protein concentrations positively correlated with Kyn concentrations and Kyn/Trp ratio in the CNS infection group (HSE and VZVME). In the NMDARE group, positive correlations existed between Kyn/Trp ratio and CSF leukocyte count, CSF protein concentrations, and IgG-index, respectively. Kyn concentrations of the MS patients negatively correlated with CSF leukocyte count and IgG-index, whereas the Kyn/Trp ratio negatively correlated with CSF leukocyte count as well.

Kyn and Kyn/Trp ratio are biomarkers for the differentiation between viral CNS infections and autoimmune neuroinflammation

We demonstrated that Kyn and Kyn/Trp ratio are significantly higher in viral CNS infections (HSE, VZVME) than in the autoimmune neuroinflammatory or the non-inflammatory control groups. We, therefore, applied ROC analysis to evaluate the potential of these two parameters to serve as a reliable biomarker for the correct diagnosis. Of the two parameters, Kyn demonstrated a higher discriminatory potential for the distinction between HSE versus control, MS, and NMDARE. The ratio of Kyn/Trp showed a higher potential for distinguishing VZVME

Table 3. Diagnostic performance of Kyn and Kyn/Trp.

Group	Biomarker	AUCs	Sensitivity	Specificity	PPV	NPV
HSE versus Control	Kyn	0.952	0.857	0.917	0.917	0.857
	Kyn/Trp	0.946	0.857	0.917	0.917	0.857
HSE versus MS	Kyn	0.960	1.000	0.813	0.834	1.000
	Kyn/Trp	0.915	0.857	0.875	0.865	0.867
HSE versus NMDARE	Kyn	0.920	0.786	0.875	0.847	0.822
	Kyn/Trp	0.906	0.857	0.813	0.802	0.866
VZVME versus Control	Kyn	0.911	0.867	0.833	0.856	0.846
	Kyn/Trp	0.944	0.867	0.917	0.922	0.858
VZVME versus MS	Kyn	0.896	0.867	0.875	0.874	0.868
	Kyn/Trp	0.917	0.867	0.875	0.874	0.868
VZVME versus NMDARE	Kyn	0.858	0.600	1.000	1.000	0.726
	Kyn/Trp	0.888	0.867	0.750	0.766	0.857

AUCs, areas under the ROC curve; HSE, HSV encephalitis; Kyn, kynurenine; MS, multiple sclerosis; NMDARE, anti-NMDA-R encephalitis; NPV, negative predictive value; PPV, positive predictive value. Trp; tryptophan; VZVME, VZV meningitis/encephalitis. Control: non-inflammatory control group consisting of NPH and IIH patients. Data were derived by ROC analysis.

from the autoimmune neuroinflammatory group, MS, and NMDARE (Table 3).

Discussion

The purpose of this study was to compare levels of KP metabolites in patients with viral CNS infections and control patients suffering from autoimmune CNS diseases or non-inflammatory CNS disorders. We especially aimed to investigate their utility as biomarkers for distinguishing viral infections from autoimmune neuroinflammatory CNS diseases since the differentiation between these two conditions may be difficult by clinical, imaging, and basic CSF analysis measures, in particular between HSE and NMDARE. In a previous study using a mass spectrometry-based targeted metabolomic screen, our group already demonstrated that Kyn and Trp are good candidate metabolites for differentiating between viral CNS infections and autoimmune encephalitis.[11]

In the human brain, most Trp is degraded through the KP and converted into a variety of neuroactive substances such as Kyn, kynurenic acid (KYNA), anthranilic acid (AA), 3-hydroxy anthranilic acid (3-HAA), 3-hydroxy-kynurenine (3-HK), and quinolinic acid (QUIN).[2,3,4] The first rate-limiting enzyme of the KP is IDO. IDO-activity is usually calculated using Trp and Kyn concentrations, presented as the Kyn/Trp ratio. IDO activity is preferentially induced by the proinflammatory cytokine interferon-gamma (IFN-γ) and to a lesser degree by interferon beta (IFN-β). Inflammation in the CNS is mostly mediated by invading immune cells including activated T cells and macrophages. Activated T cells produce cytokine mediators of the inflammatory response including the macrophage-activating cytokine IFN-γ, which strongly activates IDO. In our study, the concentrations of Kyn and IDO activity were significantly elevated in the CSF of patients with viral CNS infections compared with autoimmune neuroinflammation or non-inflammatory diseases. In VZVME patients we also observed a positive correlation between Kyn/Trp ratio and the CSF leukocyte count (Table 2). The elevation of KP metabolites in viral encephalitis is consistent with previously reported studies and suggests that increased IDO expression after viral infections may reflect neuronal destruction via an indirect effect of IFNs production from leukocytes, mainly monocytes.[13–17] In the autoimmune neuroinflammation group (MS and NMDARE), we did not detect any change in Trp and Kyn concentrations compared with the control group. The published data on KP metabolites in autoimmune encephalitis like NMDARE are limited. However, our ELISA data confirm our previous findings where Kyn and Trp were measured by liquid chromatography-tandem mass spectrometry in patients with autoimmune encephalitis.[11]

Due to the difference of Kyn concentration and Kyn/Trp ratio in the mentioned diseases, we used ROC analysis to prove that CSF levels of Kyn and Kyn/Trp ratio are potential biomarkers that are suitable to differentiate between different diseases, in particular between HSE and NMDARE. Interestingly, Kyn concentrations demonstrated a higher discriminatory potential for the distinction between HSE and NMDARE. With an AUC ranging from 0.92 to 0.96 excellent differentiation could be reached. Kyn/Trp ratio proved to be a better biomarker for distinguishing the VZVME patients from patients with autoimmune CNS diseases and control group patients.

A reliable differentiation between an HSE and NMDARE is of the highest clinical interest. Even though the etiology, pathogenesis, and treatment of both diseases are different, the patients can show similar initial clinical manifestations such as low-grade fever, malaise, headache, respiratory symptoms, fatigue, nausea, vomiting, and diarrhea. The routine examinations of blood and CSF, as well as cerebral magnetic resonance imaging (MRI) may be very similar, which is why the diagnosis requires virological and antibody examinations. Unfortunately, these examinations are time consuming. As the therapeutic approaches for HSE and NMDARE differ considerably, early and rapid diagnosis is crucial for the prognosis of both diseases.[18–22] We can conclude from the results of the ROC analysis that Kyn and Kyn/Trp ratio may be suitable biomarkers for a reliable distinction between HSE and NMDARE which could allow earlier diagnosis.

This study is the first to use a simple immunoassay to detect the concentrations of Kyn and Trp in CSF. Compared with the previously used liquid chromatography-tandem mass spectrometry method,[11] the results are similar, but experimental time is shortened and laboratory requirements are reduced. However, the small number of patients analyzed and the retrospective method are limitations of our work. Additionally, the control samples from NPH or IIH patients do not entirely reflect findings in CSF from a healthy individual. Future studies with a larger prospective cohort are required to confirm the potential of Kyn and Kyn/Trp ratio as reliable biomarkers; however, our results are very reassuring.

In conclusion, measurement of Kyn and Trp using ELISA differentiates between viral CNS infections and autoimmune CNS inflammation. This may be of great importance for the differential diagnosis between viral HSE and autoimmune NMDARE that may present with similar clinical symptoms, cerebral MRI, and CSF findings.

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Conflict of Interest

M. Stangel reports grants from DFG (German Research Foundation) Ecxellence Cluster RESIST EXC2155, during the conduct of the study; personal fees from Bayer Healthcare, Takeda, CSL Behring, Teva, Alexion, Janssen, Celgene/BMS, Grifols, and Roche as well as grants and personal fees from Sanofi-Genzyme, Merck-Serono, Novartis, and Biogen, all outside the submitted work. All other authors declare that they have no competing interests.

Authors' Contributions

YL performed ELISA measurements, analyzed the data, and wrote the first draft of the manuscript. NM interpreted the results and wrote the manuscript. TS reviewed the manuscript and provided important intellectual content. MS and HT provided additional data and gave important intellectual content. FP, KWS, and MS designed the study and interpreted the results. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was approved by the institutional Ethics Committee of the Hannover Medical School (file no. 2413-2014) and University hospital Ulm (file no. 20/10). All participants or their legal representative gave their informed consent to participate.

Consent for Publication

Not applicable.

Data Availability Statement

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

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Diagnostic criteria for HSV encephalitis, VZV meningitis/encephalitis, anti-NMDA-R encephalitis, multiple sclerosis, normal pressure hydrocephalus, and idiopathic intracranial hypertension.

