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CSF Beta-Synuclein, SNAP-25, and Neurogranin in Infectious and Autoimmune Inflammatory Neurologic Diseases

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Abstract

Background and Objectives

Beta-synuclein (beta-syn), synaptosomal-associated protein 25 (SNAP-25), and neurogranin are CSF biomarkers of synaptic damage, which have been poorly investigated in non-neurodegenerative neurologic diseases. In this study, we examined the diagnostic and prognostic role of these markers compared with the neuroaxonal damage marker neurofilament light chain protein (NfL) in infectious and autoimmune inflammatory neurologic diseases (IINDs and AINDs).

Methods

This cohort study included CSF samples from patients with different etiologies of IIND (varicella-zoster virus, herpes simplex virus, tick-borne meningoencephalitis, bacterial meningitis/(meningo)encephalitis, neuroborreliosis, or other/unknown etiology) or AIND (autoimmune encephalitis or other etiology) as well as controls.

Results

A total of 123 patients with IINDs (mean age 55.23 ± 18.04 years, 43.2% female), 22 with AINDs (age 60.41 ± 16.03 years, 81.8% female), and 95 controls (age 52.39 ± 17.94 years, 56.9% female) were enrolled. Compared with the control group, participants with IINDs and AINDs showed higher concentrations of beta-syn ($p < 0.001$ and $p = 0.038$, respectively), neurogranin ($p = 0.039$ and $p = 0.002$, respectively), and NfL ($p < 0.001$ and $p = 0.001$, respectively), with no differences between the 2 latter groups. Overall, synaptic markers and NfL demonstrated poor-to-moderate diagnostic accuracy in discriminating between diagnostic groups (area under the curve 0.366–0.809). All synaptic biomarkers were elevated in participants with IINDs presenting with altered mental status (beta-syn, $p < 0.001$; SNAP-25, $p = 0.002$; and neurogranin, $p = 0.008$), seizures (beta-syn, $p = 0.013$; SNAP-25, $p = 0.005$; and neurogranin, $p = 0.004$), and inflammatory changes on neuroimaging (beta-syn, $p = 0.016$; SNAP-25, $p = 0.029$; and neurogranin, $p = 0.007$). Participants with AINDs requiring intensive care showed higher levels of beta-syn ($p = 0.033$) and NfL ($p = 0.002$). Participants with IINDs with a poor functional status (modified Rankin Scale [mRS] scores of 3–6) exhibited higher concentrations of beta-syn ($p < 0.001$), SNAP-25 ($p = 0.022$), neurogranin ($p = 0.004$), and NfL ($p < 0.001$) compared with those with mRS scores of 0–2. Accordingly, higher levels of synaptic markers were associated with poorer short-term outcomes in patients with IINDs, but not in those with AINDs.

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Supplementary Material

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Glossary

AD = Alzheimer disease; **AE** = autoimmune encephalitis; **AIND** = autoimmune inflammatory neurologic disease; **AUC** = area under the curve; **beta-syn** = beta-synuclein; **CJD** = Creutzfeldt-Jakob disease; **HSV** = herpes simplex virus; **ICU** = intensive care unit; **IIND** = infectious inflammatory neurologic disease; **IQR** = interquartile range; **LP** = lumbar puncture; **mRS** = modified Rankin Scale; **NfL** = neurofilament light chain protein; **SNAP-25** = synaptosomal-associated protein 25; **TBE** = tick-borne encephalitis; **VZV** = varicella-zoster virus.

Discussion

Elevated CSF levels of beta-syn, neurogranin, and NfL may suggest a common pattern of synaptic and neuroaxonal damage in both IINDs and AINDs. Although these biomarkers have limited value in distinguishing between different diseases, they are associated with clinical severity and with short-term outcome, particularly in patients with IINDs.

Introduction

Inflammatory neurologic diseases represent a largely heterogeneous clinical group, with 2 of the most important subgroups being infectious inflammatory and autoimmune inflammatory neurologic diseases (IINDs and AINDs).[1,2] Despite the distinct underlying etiologies, both entities share overlapping pathophysiologic mechanisms (i.e., neuroinflammation, neuroaxonal damage, etc),[3,4] clinical features at presentation, and similar findings on neuroimaging (MRI) and routine CSF investigations, making differential diagnosis often challenging.[1,2,5] Notably, the treatment-responsive and potentially reversible nature of both disease groups has stimulated the development and validation of rapid and comprehensive tests for infectious agents or disease-associated antibodies to improve early diagnosis.[1,2,6] Nevertheless, the disease course of both IINDs and AINDs is highly variable, with some patients showing severe neurologic sequelae and poor outcomes despite receiving anti-infective or immunomodulatory treatment.[1,2,7,8] Moreover, in AINDs and IINDs, therapeutic decisions are still largely based on clinical assessment because disease activity poorly correlates with laboratory parameters such as autoantibody titers and the microbial load.[9,10]

In this context, CSF biomarkers reflecting shared mechanisms such as neuroinflammation and neuronal damage have been extensively investigated, with the aim of improving the diagnostic and prognostic assessment of IINDs and AINDs. Most of the evidence has focused on the neuroaxonal damage marker neurofilament light chain protein (NfL) in CSF or blood, which is elevated in both IINDs and AINDs, as in other neurologic disorders, and has not uniformly demonstrated a relevant prognostic role in previous works on IINDs and AINDs.[6-17]

Thus, there is an urgent need to investigate the role of other candidate biofluid markers possibly reflecting other pathogenetic mechanisms described in IINDs and AINDs, such as synaptic damage/dysfunction.[4,18,19] Among CSF synaptic biomarkers, the presynaptic proteins beta synuclein (beta-syn) and synaptosomal-associated protein 25 (SNAP-25), as well as the postsynaptic protein neurogranin, have been extensively examined in neurodegenerative diseases and have been found to be increased in Alzheimer disease (AD) and Creutzfeldt-Jakob disease (CJD).[15,20-24] However, there are very few studies on CSF SNAP-25 and neurogranin in inflammatory neurologic diseases, examining small cohorts with autoimmune encephalitis (AE), herpes simplex virus (HSV), and tick-borne encephalitis (TBE).[6,7,13,16] Data on beta-syn are also scarce; in the only study to date, we reported increased CSF beta-syn in patients with infectious and autoimmune etiologies in a heterogeneous cohort of patients with rapidly progressive dementia.[15]

In this study, we performed a large multicenter cohort study to investigate the role of the CSF synaptic biomarkers beta-syn, SNAP-25, and neurogranin in comparison with NfL in various forms of IINDs and AINDs and non-neuroinflammatory disease controls. In addition, we investigated possible associations between CSF biomarker concentrations and clinical variables and the results of diagnostic investigations as well as biomarker prognostic value in the 2 disease groups.

Methods

Patient Selection

In this retrospective multicenter cohort study, we included CSF samples from patients with IINDs (n = 123), patients with AINDs (n = 22), and non-neuroinflammatory disease controls (n = 95) admitted to 4 different German and Italian Neurology Departments, namely, Halle (Saale), Ulm, Hannover, and Milan. The distribution of diagnostic groups according to the center is as follows: Halle cohort: 14 with IINDs, 14 with AINDs, 42 controls; Ulm cohort: 85 with IINDs, 15 controls; Hannover cohort: 24 with IINDs, 6 with AINDs, 18 controls; Milan cohort: 2 with AINDs, 20 controls. All patients underwent clinical evaluation, neuroimaging (MRI or, when not feasible, CT), and lumbar puncture (LP) as part of the routine diagnostic workup.

The IIND group included patients with meningitis, (meningo)encephalitis, myelitis, cranial nerve affection, vasculitis, polyradiculitis, or a combination thereof as previously described.[25] Encephalitis was defined according to the criteria of the International Encephalitis Consortium.[26] CSF analysis revealed pleocytosis (white blood cell count >5/μL) in all participants with IINDs, as described further. A viral or bacterial etiology was confirmed in 94 patients through PCR, culture/microscopic evidence, or determination of pathogen-specific antibodies in CSF/serum pairs and calculation of antibody indices (AIs). The IIND group encompassed the following etiologies: HSV type 1 and 2 infections (n = 20), varicella-zoster virus infection (VZV; n = 21),[11,27] TBE (n = 16), COVID-19 infection (n = 1), bacterial meningitis/(meningo)encephalitis (BM) (n = 21), bacterial abscess (n = 1), and Lyme neuroborreliosis (LNB; n = 14).[28] Finally, 29 participants with IINDs had meningitis, encephalitis, myelitis, radiculitis, or cranial nerve palsies and presented with the CSF findings described above, but without successful pathogen detection in routine investigations (IINDs caused by unknown pathogens). However, on the basis of clinical findings and CSF laboratory data, viral or atypical pathogens seemed to be the most likely etiology.[25] A total of 95 patients with IINDs were not receiving therapy (antiviral and/or antibiotic) at the time of lumbar puncture (LP).

The AIND group (n = 22) included 19 participants with definite or probable autoimmune encephalitis and 3 with probable neurologic paraneoplastic syndromes according to international consensus criteria.[26,29,30] Fourteen patients with AINDs were not receiving immunomodulatory/immunosuppressive treatment at the time of LP.

Noninflammatory disease controls (n = 95) included patients with no clinical, radiologic, or neurochemical evidence of neurologic inflammatory or neurodegenerative disease (i.e., primary headache disorders, subjective cognitive decline, psychiatric disorders, sleep disorders, or noninflammatory polyneuropathies).

From participants with IINDs and AINDs, we collected the following clinical data and results of diagnostic investigations when available: disease duration at LP (time between symptom onset and LP), major clinical picture with symptoms/signs, CSF basic parameters (presence of CSF pleocytosis and/or oligoclonal bands), brain MRI/CT and EEG data, functional status using the modified Rankin Scale (mRS) score at LP, requirement of admission to the intensive care unit (ICU), duration of hospitalization, and mRS score and/or outcome (complete recovery or not) at discharge. An mRS score of 3–6 was considered a poor outcome, whereas an mRS score of 0–2 was considered a good outcome.[31]

Standard Protocol Approvals, Registrations, and Patient Consents

The study was conducted according to the revised Declaration of Helsinki and Good Clinical Practice guidelines. Informed written consent was obtained from the participants and/or their legal guardians. The study of biosamples and case data was approved by the ethics committees of the following institutions: Martin-Luther University Halle-Wittenberg (approval number 2021-101), Ulm University Hospital (approval number 20/10), Hannover Medical School (No. 7837_BO_K_2018, April 6, 2018, and 2481-2014), and IRCCS Istituto Auxologico Italiano (approval number 2021_05_18_04).

Blood and CSF Biomarker Analyses

CSF samples were obtained through LP, centrifuged in case of blood contamination, divided into aliquots, and stored in polypropylene tubes at −80°C until analysis in each center.

We used an in-house established immunoassay to measure CSF beta-syn as the one used in previous studies.[15,24] Moreover, we measured CSF levels of NfL with a commercially available kit for the ELLA microfluidic system (Bio-Techne, Minneapolis, MN), SNAP-25 with a commercial Simoa kit (Quanterix Inc., Lexington, MA), and neurogranin with a commercial immunoassay (Euroimmun).[24] All biomarker analyses were randomized, and the investigators were blinded to sample allocation and diagnosis. For all biomarker measurements, the coefficients of intra-assay and interassay variability were <10% and <15%, respectively.

Statistical Analysis and Reproducibility

We used IBM SPSS Statistics V.21 (IBM), GraphPad Prism V.7 (GraphPad Software, La Jolla, CA), and R software V.4.0.2 (R Foundation, Vienna, Austria). Depending on the distribution, the data are expressed as percentages, means ± SDs, or medians and interquartile ranges (IQRs). We adopted the χ^2 test for comparisons of categorical variables. For continuous variables, depending on the data distribution and number of groups, we compared groups by applying the Mann-Whitney *U* test, *t* test, Kruskal-Wallis test (followed by the Dunn-Bonferroni post hoc correction) or ANOVA (followed by the Tukey post hoc test). All reported *p* values were adjusted for multiple comparisons. Spearman correlations and univariate or multivariate linear regression analyses were performed to test the possible associations between variables.

Univariate and multivariate logistic regression analyses were used to investigate the associations between biomarkers (as continuous variables) and binary prognostic outcomes (i.e., mRS scores 0–2 vs 3–6, full recovery vs incomplete recovery). In this regard, we also tested the contribution of each possible covariate (clinic-demographic variables) using univariate models and then included only those with significant associations to the multivariate logistic model. The diagnostic accuracy of each marker was calculated by receiver operating characteristic analyses. Statistical tests were 2-tailed, and 2-sided *p* values were considered statistically significant at <0.05. The study follows the STROBE guidelines.

Data Availability

Anonymized data will be shared by request from any qualified investigator for the sole purpose of replicating procedures and

results presented in the article and as long as data transfer is in agreement with EU legislation on the General Data Protection Regulation.

Results

CSF Biomarker Distribution in the Diagnostic Groups

The demographic characteristics and CSF biomarker distributions of the diagnostic groups of the whole sample are presented in Table 1 and Figure 1.

The IIND, AIND, and control groups did not differ in age; however, there was a difference in gender distribution ($p = 0.003$). Age was associated with CSF levels of beta-syn (Spearman $r = 0.351$, $p < 0.001$), SNAP-25 ($r = 0.261$, $p < 0.001$), neurogranin ($r = 0.218$, $p = 0.001$), and NfL ($r = 0.401$, $p < 0.001$) in the whole cohort (n = 240) while sex had no effect on biomarker levels. Taking these findings into account, age adjustment was not needed for CSF biomarker comparisons among the main diagnostic groups.

In the whole cohort, patients with IINDs and AINDs had higher CSF beta-syn concentrations than controls did ($p < 0.001$ and $p = 0.038$, respectively), with no difference between the 2 former groups (Table 1, Figure 1A). SNAP-25 levels did not differ among patients with IINDs, patients with AINDs, and controls (Table 1, Figure 1B). CSF neurogranin levels were higher in patients with IINDs ($p = 0.039$) and patients with AINDs ($p = 0.002$) than in controls (Table 1, Figure 1C). CSF NfL was similarly increased in both patients with IINDs ($p < 0.001$) and patients with AINDs ($p = 0.001$) compared with controls (Table 1, Figure 1D).

CSF NfL showed the best diagnostic performance among all biomarkers, with moderate-to-good diagnostic accuracy in the comparisons of AIND (area under the curve [AUC] ± SD 0.809 ± 0.044) or IIND (AUC 0.728 ± 0.034) groups vs controls. CSF neurogranin also showed moderate discriminatory potential in the comparison of IINDs vs controls (AUC 0.734 ± 0.074). The other biomarkers performed worse, as given in eTable 1. The adoption of ratios between CSF synaptic markers did not improve the diagnostic accuracy significantly in distinguishing between IIND, AIND, and control groups (eTable 1). When considering a common clinical scenario, namely, the differential diagnosis between AE and viral (meningo)encephalitis (VZV, HSV, and TBE), we found no difference in any of the CSF biomarkers between the 2 groups.

CSF Biomarker Distribution and Its Associations With Clinical Variables in Infectious and Autoimmune Inflammatory Neurologic Diseases

The clinical data and results of diagnostic investigations of participants with IINDs and AINDs are presented in Table 2. Sex ($p = 0.020$), but not age, differed among patients with distinct etiologies of IIND (eTable 2).

Compared with patients with meningitis, those with (meningo)encephalitis had higher CSF levels of beta-syn ($p = 0.017$) and NfL ($p < 0.001$) (Figure 2a), but not of other markers, regardless of etiology (viral, bacterial, or unknown). The same results (beta-syn, $p = 0.019$; NfL, $p < 0.001$) were confirmed in the subanalysis limited to viral diseases (HSV, VZV, and TBE).

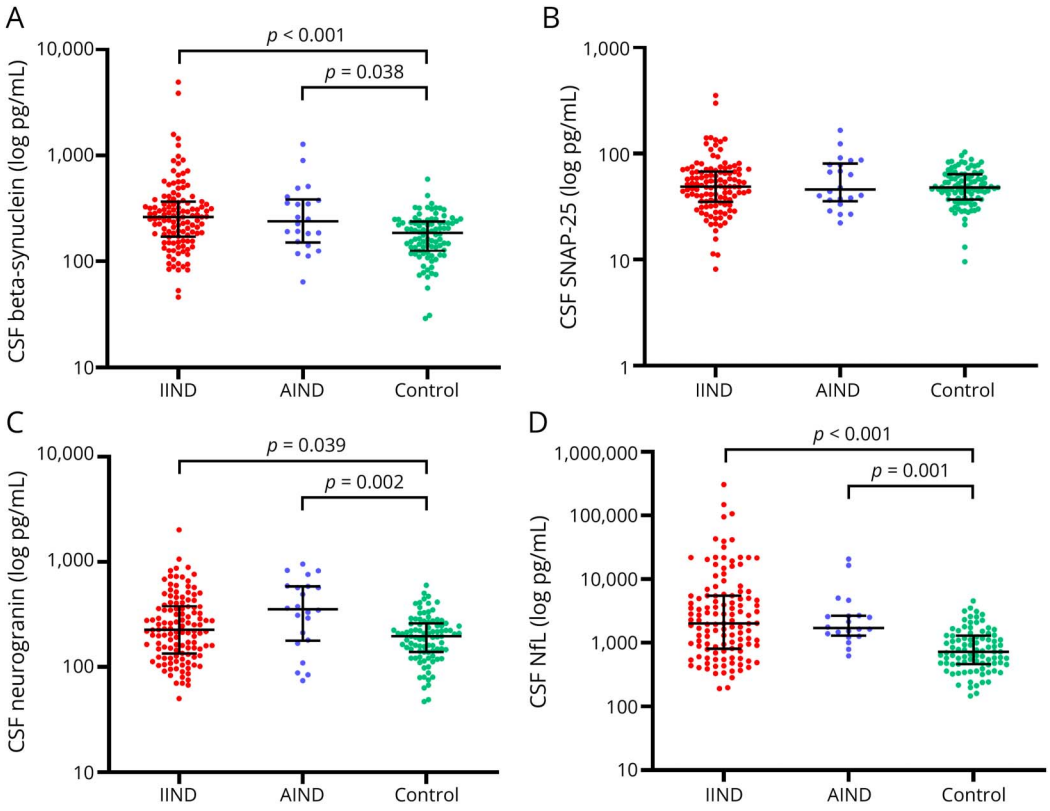
CSF biomarker concentrations did not differ between distinct infectious etiologies, namely HSV, VZV, TBE, LNB, and BM.

Table 1 Demographic Characteristics and Biomarker Distributions of the Diagnostic Groups

Whole cohort	IIND group	AIND group	Disease controls	*p* Value
N	123	22	95	
Age (y), mean ± SD	55.23 ± 18.04	60.41 ± 16.03	52.39 ± 17.94	n.s.
Female (%)	43.2	81.8	56.9	0.003
CSF beta-syn (pg/mL) Median (IQR)	264 (171–369)	240 (152–386)	187 (127–239)	<0.001
CSF SNAP-25 (pg/mL) Median (IQR)	48.8 (32.7–67.3)	46.1 (35.7–80.7)	47.9 (37.1–63.9)	n.s.
CSF neurogranin (pg/mL) Median (IQR)	225 (132–376)	354 (177–589)	195 (126–258)	0.001
CSF NfL (pg/mL) Median (IQR)	2,015 (807–5,517)	1,688 (1,289–2,638)	740 (466–1,349)	<0.001

Abbreviations: AIND = autoimmune inflammatory neurologic disease; beta-syn = beta synuclein; IIND = infectious inflammatory neurologic disease; IQR = interquartile range; N = number of cases; NfL = neurofilament light chain protein; n.s. = nonsignificant; SNAP-25 = synaptosomal-associated protein 25.
Age, sex, and CSF biomarkers in the 3 diagnostic groups from all cohorts are displayed as the means ± standard deviations (SDs), medians and interquartile ranges (IQRs), or percentages. Depending on the type and distribution of the data, 2-sided *p* values of the Kruskal-Wallis test, ANOVA, or χ^2 test are reported.

Figure 1 Distribution of CSF Beta-Syn, SNAP-25, Neurogranin, and NfL in the Diagnostic Groups



(A) Distribution of CSF beta-syn in the IIND (n = 123), AIND (n = 22), and disease control groups (CTRL, n = 100). (B) Distribution of CSF SNAP-25 in the IIND (n = 123), AIND (n = 22), and disease control groups (CTRL, n = 100). (C) Distribution of CSF neurogranin in the IIND (n = 123), AIND (n = 22), and disease control groups (CTRL, n = 100). (D) Distribution of CSF NfL in the IIND (n = 123), AIND (n = 22), and disease control groups (CTRL, n = 100). Biomarker levels are reported on a logarithmic scale. The dots represent single data points. The horizontal lines represent the median values, the lower and upper lines correspond to the first and third quartiles, and the vertical line represents the interquartile range. Biomarker differences between groups were assessed by the Kruskal-Wallis test, followed by the Dunn post hoc test (adjusted for multiple comparisons). Two-sided *p* values are reported. AIND = autoimmune-inflammatory neurologic disease; beta-syn = beta synuclein; CTRL = control; IIND = infectious inflammatory neurologic disease; NfL = neurofilament light chain protein; n.s. = nonsignificant; SNAP-25 = synaptosomal-associated protein 25.

Similarly, there were no biomarker differences between participants with bacterial (BM and LNB) and viral (HSV, VZV, and TBE) diseases. However, when only patients with a viral etiology were considered, patients with TBE presented higher NfL levels than those with HSV ($p = 0.044$) and VZV ($p = 0.042$) (Figure 2b).

In the IIND group, CSF synaptic biomarkers were strongly intercorrelated and moderately associated with CSF NfL. Specifically, CSF beta-syn was associated with CSF SNAP-25 ($r = 0.694$, $p < 0.001$), neurogranin ($r = 0.809$, $p < 0.001$), and NfL ($r = 0.527$, $p < 0.001$) levels. CSF neurogranin was associated with CSF SNAP-25 ($r = 0.784$, $p < 0.001$) and NfL ($r = 0.321$, $p < 0.001$) levels. CSF SNAP also correlated with CSF NfL ($r = 0.427$, $p < 0.001$).

In patients with IINDs, disease duration at CSF sampling correlated with CSF beta-syn (r = 0.217, $p = 0.016$) and NfL (r = 0.375, $p < 0.001$), but not with other biomarkers.

We analyzed the possible associations between dichotomized clinical variables and CSF biomarkers in the IIND group (Table 3). Owing to the exploratory nature of these analyses and the modest size of the compared groups, analyses were not adjusted for multiple comparisons as in a previous study on the same topic.[13] All CSF synaptic biomarkers were more elevated in participants with altered mental status/consciousness (beta-syn, $p < 0.001$; SNAP-25, $p = 0.002$; and neurogranin, $p = 0.008$), seizures (beta-syn, $p = 0.013$; SNAP-25, $p = 0.005$; and neurogranin, $p = 0.004$), and inflammatory changes on neuroimaging (beta-syn, $p = 0.016$; SNAP-25, $p = 0.029$; and neurogranin, $p = 0.007$). The participants who were admitted to the ICU had higher CSF SNAP-25 concentrations ($p = 0.023$). CSF NfL levels were greater in patients who presented with cognitive deficits ($p = 0.017$), altered mental status/consciousness ($p = 0.020$), and inflammatory changes on neuroimaging ($p = 0.002$) (Table 3). All other investigated associations between clinical variables and CSF biomarkers were not significant.

The clinical data and results of the diagnostic investigations of the participants with AINDs are summarized in Table 2. Among all the considered clinical variables, we detected significantly higher CSF NfL concentrations ($p = 0.001$) in the

Table 2 Clinical Data and Results of Diagnostic Investigations of Participants With IINDs and AINDs

Diagnostic group	IIND group	AIND group
N	123	22
Age (y), mean ± SD	55.23 ± 18.04	60.41 ± 16.03
Female (%)	43.1	81.8
Etiologies, N	21 with VZV, 20 with HSV, 16 with TBE, 21 with BM, 14 with LNB	Antibody status: 6 with CASPR2, 5 with NMDAR, 1 with LGI1, 3 with other antibodies, 7 with seronegative AIND (probable AE or neurologic PNS)
Clinical picture, N (%)	(Meningo)encephalitis: 85 (69.1), meningitis: 32 (26.0), other: 6 (4.9)	Encephalitis: 19 Other: 3
Disease duration at LP (d) **Mean ± SD**	10.40 ± 9.57	307.27 ± 159.05
Presenting symptoms/signs		
Altered mental status/consciousness, N (%)	35 (28.5)	5 (22.7)
Cognitive deficits, N (%)	44 (35.8)	16 (72.7)
Psychiatric symptoms, N (%)	15 (12.2)	10 (45.5)
Seizures, N (%)	27 (22.0)	9 (40.9)
Fever, N (%)	60 (48.8)	—
Headache, N (%)	91 (74.0)	—
Meningism, N (%)	23 (18.7)	—
Focal neurologic signs, N (%)	17 (13.8)	13 (59.1)
Peripheral nervous system signs/symptoms, N (%)	14 (11.4)	1 (4.5)
Autonomic dysfunction, N (%)	9 (7.3)	4 (18.2)
Clinical course		
Requirement for ICU admission, N (%)	25 (20.3)	3 (13.6)
Duration of hospitalization (d) **Mean ± SD**	17.22 ± 13.17	17.00 ± 7.46
Brain MRI/CT: inflammatory changes, N (%)	25 (20.3)	6 (27.3)
CSF: pleocytosis, positive oligoclonal bands, N (%)	123 (100) 45 (36.6)	10 (45.5) 6 (27.3)
EEG: abnormal, N (%)[a]	33 (57.9)	9 (56.3)
Under treatment at time of LP, N (%)	23 (18.7)	5 (22.7)
Tumor association (paraneoplastic), N (%)	—	4 (18.2)
mRS scores at LP[b], N (%)		
0–2	77 (62.6)	11 (73.4)
3–6	46 (37.4)	4 (26.7)
Outcome at discharge[c], N (%)		
Full recovery	79 (65.3)	8 (50.0)
Remaining deficits and/or death	42 (34.7)	8 (50.0)
mRS scores at discharge[d], N (%)		
0–2	92 (76.0)	14 (93.3)

Continued

Table 2 Clinical Data and Results of Diagnostic Investigations of Participants With IINDs and AINDs *(continued)*

Diagnostic group	IIND group	AIND group
3–6	29 (24.0)	1 (6.7)

Abbreviations: AE = autoimmune encephalitis; AIND = autoimmune-inflammatory neurologic disease; beta-syn = beta synuclein; BM = bacterial (meningo) encephalitis; CASPR2 = contactin-associated protein-like 2; CT = computer tomography; HSV = herpes simplex virus; ICU = intensive care unit; IIND = infectious inflammatory neurologic disease; IQR = interquartile range; LGI1 = leucine-rich glioma-inactivated1; LNB = Lyme neuroborreliosis; LP = lumbar puncture; mRS = modified Rankin Scale; N = number of cases; N = number; NMDAR = N-methyl-D-aspartate receptor; n.s. = nonsignificant; PNS = paraneoplastic neurologic syndrome; TBE = tick-borne encephalitis; VZV = varicella-zoster virus.
[a] Available in 57 with NID and 16 with AIND.
[b] Available in all with NID and 15 with AIND.
[c] Available in 121 with NID and 16 with AIND.
[d] Available in 121 with NID and 15 with AIND.

AIND group with altered mental status/consciousness. Furthermore, patients who were admitted to the ICU had higher levels of beta-syn ($p = 0.033$) and NfL ($p = 0.002$) (Table 3).

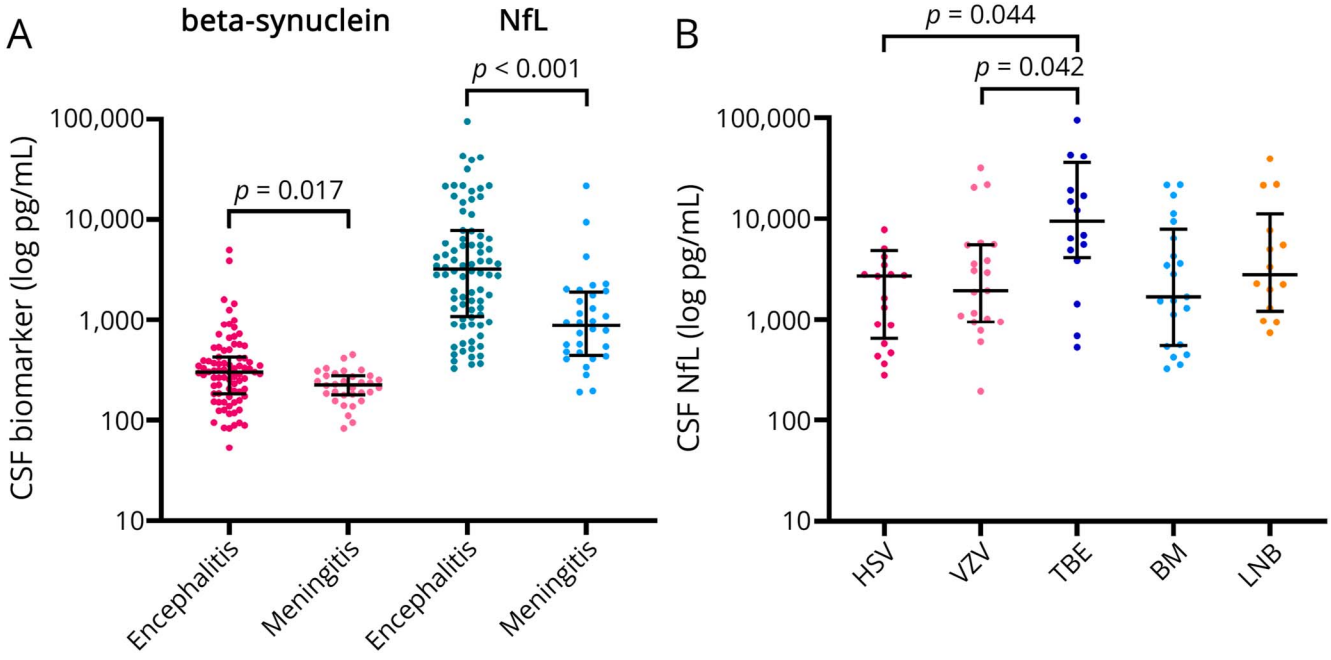
There were also no differences in CSF biomarkers between participants who were treated and those who were not at the time of LP, in both the IIND and NID groups.

Prognostic Value of CSF Biomarkers in Infectious and Autoimmune Inflammatory Neurologic Diseases

In the IIND group, the mRS score at the LP correlated with the CSF concentrations of beta-syn ($r = 0.291$, $p = 0.001$), SNAP-25 ($r = 0.224$, $p = 0.013$), neurogranin ($r = 0.183$, $p = 0.042$), and NfL ($r = 0.298$, $p = 0.001$). Similarly, patients with IINDs with mRS scores of 3–6 at the time of LP presented higher CSF levels of beta-syn ($p < 0.001$), SNAP-25 ($p = 0.022$), neurogranin ($p = 0.004$), and NfL ($p < 0.001$) than did those with mRS scores of 0–2 (Table 3, Figure 3).

According to the logistic univariate regression analysis in eTable 3, higher levels of CSF beta-syn, SNAP-25, and neurogranin, but not NfL, were associated with poor outcomes at discharge (mRS scores 3–6) in participants with IINDs, but the difference was not statistically significant after adjustment for covariables (age, sex, mRS score at LP). Similarly, higher levels of CSF beta-syn and SNAP-25 were associated with incomplete recovery

Figure 2 CSF Biomarkers Among Distinct IIND Forms and Etiologies



(A) CSF levels of beta-syn and NfL were higher in patients with IINDs with (meningo)encephalitis than in those with meningitis. (B) Distribution of CSF NfL levels according to IIND etiology. Biomarker levels are reported on a logarithmic scale. The dots represent single data points. The horizontal lines represent the median values, the lower and upper lines correspond to the first and third quartiles, and the vertical line represents the interquartile range. Biomarker differences between groups were assessed by the Mann-Whitney or Kruskal-Wallis test, followed by the Dunn post hoc test (adjusted for multiple comparisons). Two-sided *p* values are reported. beta-syn = beta synuclein; BM = bacterial meningisitis/(meningo)encephalitis; HSV = herpes simplex virus; IIND = infectious inflammatory neurologic disease; LNB = Lyme neuroborreliosis; LP = lumbar puncture; NfL = neurofilament light chain protein; mRS = modified Rankin Scale; n.s. = nonsignificant; SNAP-25 = synaptosomal-associated protein 25; TBE = tick-borne encephalitis; VZV = varicella-zoster virus.

Table 3 Significant Associations Between Clinical Variables and CSF Biomarkers in IIND and AIND Groups

CSF biomarker		CSF beta-syn (pg/mL) Median (IQR)	CSF SNAP-25 (pg/mL) Median (IQR)	CSF neurogranin (pg/mL) Median (IQR)	CSF NfL (pg/mL) Median (IQR)
IIND					
Presenting symptoms/signs and clinical course					
Altered mental status/consciousness	Yes	328 (253–716)[a]	65.2 (43.0–83.5)[a]	300 (206–545)[a]	4,181 (1,125–14775)[a]
	No	231 (156–323)[a]	45.1 (28.8–61.0)[a]	201 (125–341)[a]	1817 (700–4,834)[a]
Cognitive deficits	Yes	289 (176–408)	49.0 (40.1–72.0)	258 (127–410)	3,391 (1,173–7,490)[a]
	No	244 (158–356)	48.5 (28.0–63.6)	211 (132–368)	1,678 (539–5,448)[a]
Seizures	Yes	328 (225–716)[a]	59.3 (43.0–96.0)[a]	300 (231–617)[a]	2,745 (1,064–4,685)
	No	245 (157–329)[a]	46.0 (31.5–63.6)[a]	204 (124–359)[a]	1899 (734–6,227)
Requirement for ICU admission, N (%)	Yes	301 (127–628)	62.2 (45.4–74.2)[a]	290 (141–530)	2,745 (582–7,575)
	No	251 (173–346)	46.0 (31.4–64.4)[a]	216 (131–361)	1988 (846–5,516)
Brain MRI/CT: inflammatory changes, N (%)	Yes	362 (206–616)[a]	55.0 (43.8–95.6)[a]	300 (206–572)[a]	5,013 (2,154–21761)[a]
	No	251 (158–326)[a]	46.0 (30.4–66.5)[a]	211 (123–358)[a]	1764 (722–4,734)[a]
mRS score at LP	0–2	221 (151–317)[a]	45.9 (28.4–62.1)[a]	201 (121–321)[a]	1,529 (551–3,697)[a]
	3–6	319 (261–602)[a]	54.5 (41.0–72.5)[a]	283 (160–523)[a]	4,052 (1,494–17657)[a]
AIND					
Presenting symptoms/signs and clinical course					
Altered mental status/consciousness	Yes	356 (234–898)	78.4 (47.1–89.3)	573 (391–798)	4,658 (2,545–18490)[b]
	No	192 (142–346)	40.5 (33.4–68.3)	331 (168–587)	1,490 (1,160–1841)[b]
Requirement for ICU admission	Yes	446 (329–1,063)[b]	82.8 (63.4–145.2)	677 (504–1,226)	15,603 (10,516–26352)[b]
	No	190 (130–354)[b]	42.3 (34.4–68.0)	339 (188–584)	1,517 (1,212–2,481)[b]

Abbreviations: AIND = autoimmune inflammatory neurologic disease; beta-syn = beta synuclein; CT = computer tomography; ICU = intensive care unit; IIND = infectious inflammatory neurologic disease; IQR = interquartile range; LP = lumbar puncture; mRS = modified Rankin Scale; N = number of cases; NfL = neurofilament light chain protein; n.s. = nonsignificant; SNAP-25 = synaptosomal-associated protein 25.
All other investigated associations between clinical variables and CSF biomarkers, which were not significant, are not shown in the table.
[a] Significant associations between clinical variables or results of diagnostic investigations and CSF biomarkers in IIND: altered mental status/consciousness: beta-syn, $p < 0.001$; SNAP-25, $p = 0.002$; neurogranin, $p = 0.008$; NfL, $p = 0.020$; cognitive deficits: NfL, $p = 0.017$; seizures: beta-syn, $p = 0.013$; SNAP-25, $p = 0.005$; neurogranin, $p = 0.004$; headache: NfL, $p < 0.001$; requirement for ICU admission: SNAP-25, $p = 0.023$; inflammatory changes at neuroimaging: beta-syn, $p = 0.016$; SNAP-25, $p = 0.029$; neurogranin, $p = 0.007$; NfL, $p = 0.002$. mRS scores 3–6 vs 0–2 at the time of LP: beta-syn $p < 0.001$, SNAP-25 $p = 0.022$, neurogranin $p = 0.004$, NfL $p < 0.001$.
[b] Significant associations between clinical variables or results of diagnostic investigations and CSF biomarkers in AIND: altered consciousness: CSF NfL $p = 0.001$; requirement for ICU admission: beta-syn $p = 0.033$, NfL, $p = 0.002$.

(remaining deficits or death) at discharge in participants with IINDs according to logistic univariate regression analysis but not after adjustment for covariables, as reported in eTable 3.

In the AIND group, CSF synaptic markers and NfL levels were not associated with prognostic binary outcomes (mRS score at LP, mRS score at discharge, and full recovery at discharge).

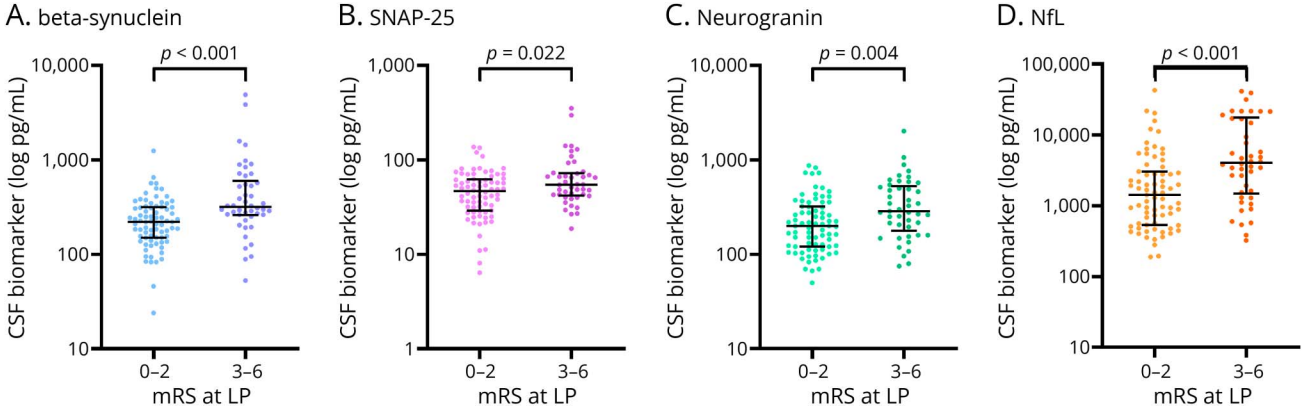
Discussion

This is a comprehensive study which investigated the diagnostic and prognostic role of CSF synaptic biomarkers compared with CSF NfL in a large and heterogeneous cohort of patients with IINDs and AINDs.

For this purpose, we selected synaptic proteins that are involved in different pathways of synaptic physiology; therefore, their alterations in CSF may reflect different aspects of synaptic pathology. Indeed, beta-syn is involved in neurotransmitter metabolism in the presynaptic terminal; the protein SNAP-25 modulates presynaptic vesicle fusion in a calcium-dependent manner, whereas neurogranin regulates the postsynaptic response.[24,32]

In our study, we found that CSF beta-syn and neurogranin were elevated while SNAP-25 was unaltered in IIND and AIND groups compared with controls. Thus, this variable increase in CSF synaptic markers may reflect a common pattern of synaptic damage/dysfunction and involvement of

Figure 3 Associations Between CSF Biomarkers and Functional Status in Participants With IINDs



Patients with IIND with mRS scores of 3–6 at the time of LP had higher CSF levels of beta-syn (A), SNAP-25 (B), neurogranin (C), and NfL (D) than those with mRS scores of 0–2. Biomarker levels are reported on a logarithmic scale. The dots represent single data points. The horizontal lines represent the median values, the lower and upper lines correspond to the first and third quartiles, and the vertical line represents the interquartile range. Biomarker differences between groups were assessed by the Mann-Whitney test. Two-sided *p* values are reported. IIND = infectious inflammatory neurologic disease; mRS = modified Rankin Scale; NfL = neurofilament light chain protein; SNAP-25 = synaptosomal-associated protein 25.

the synaptic compartment in IINDs and AINDs. Synaptic damage is indeed a pathophysiologic hallmark in both IINDs and AINDs and has been related to neuroinflammation through the involvement of phagocytic microglia and complement components.[4,18,19,33] In this regard, previous studies reported on the elimination of synapses by phagocytes after attacks by $CD8^+$ T cells in mouse models of viral encephalitis, human viral encephalitis, as well as in human forms of AE.[4,33] Neuroinflammatory cytokines also seem to play a significant role in synaptic damage and dysfunction by affecting synaptic transmission and plasticity.[19]

Analyzing the distribution of the CSF biomarkers in our cohort, we confirmed our preliminary data on high CSF beta-synuclein levels in a small cohort of patients with IINDs or AINDs presenting with rapidly progressive dementia[15] as well as results of another study on unaltered SNAP-25 in patients with AINDs.[6] While there are no previous data in the literature comparing CSF synaptic markers in patients with IINDs and controls, Day et al.[13] reported reduced CSF levels of neurogranin and SNAP-25 in patients with AINDs as a possible surrogate for depressed neurotransmission and synaptic dysfunction secondary to antibody-mediated internalization of cell surface receptors. The discrepancy between our study and that by Day et al.[13] is quite interesting. This may be due to the differences in proportions of AIND etiologies as well as time points of sample collection in the 2 studies. Nevertheless, the literature on synaptic markers is consistent in showing a variable increase in CSF synaptic biomarkers as a surrogate for synaptic pathology in several neurologic diseases, so the data of Day et al.[13] remain quite exceptional. Indeed, neurodegenerative diseases such as AD and CJD had homogeneously increased CSF beta-syn, SNAP-25, and neurogranin levels, suggesting widespread disruption of different synaptic compartments,[15,20-24] whereas in another autoimmune inflammatory neurologic disease, namely, MS, we previously reported a selective increase in CSF SNAP-25 in patients who experienced relapse within 30 days.[34]

Our data on CSF NfL, which is elevated in both IINDs and AINDs, as a nonspecific marker of neuroaxonal damage are in line with previous studies.[6-17,35,36]

On another issue, CSF beta-syn, SNAP-25, and neurogranin did not show relevant diagnostic value in discriminating between patients with IINDs, patients with AINDs, and controls or in the typical clinical scenario of distinguishing between viral and autoimmune encephalitis; thus, their potential applicability for early routine diagnostic assessment is limited, for example, before the results of microbiological and autoimmune diagnostic tests are available.

Of interest, our study provides evidence that CSF beta-syn, SNAP-25, neurogranin, and NfL may play promising roles in tracking disease severity and predicting short-term outcomes in IINDs; indeed, they were generally higher in more severe cases, such as those with altered consciousness, seizures, admission to the ICU, and poor functional status (mRS scores 3–6) at the LP and discharge. Moreover, we found associations between CSF biomarkers and outcomes at discharge; however, these were not maintained after covariate adjustments. These results are consistent with previous findings demonstrating that elevated levels of NfL in the CSF or blood, reflecting severe neuroaxonal damage, were variably associated with disease severity; need for intensive care or mechanical ventilation; and poor functional and/or neurocognitive outcomes in patients with HSV[7,8] or VZV[9] nervous system infection, TBE,[16] and COVID-19.[35-37] Similarly, neuropathologic and animal model data have revealed associations between the presence and/or severity of certain clinical features, such as cognitive impairment, and synaptic degeneration in certain forms of IIND.[18,38,39]

Notably, we did not find significant differences in CSF biomarkers across IIND etiologies, except for higher NfL levels in TBE than in other viral diseases. However, patients with (meningo)encephalitis, whether bacterial or viral, had higher CSF beta-syn and NfL levels than those with meningitis did, expanding preliminary data on NfL in VZV and HSV CNS infections.[8,9,11] These results could easily be interpreted with the notion that brain parenchymal involvement in (meningo) encephalitis is usually associated with more severe synaptic and neuroaxonal damage and a more severe clinical picture.[9,11] Accordingly, we also found that patients with IINDs with longer disease duration and inflammatory changes on MRI had higher levels of CSF biomarkers. Overall, in a large and heterogeneous cohort of patients with IINDs, our study has shown, that, regardless of the etiology, CSF markers of CNS injury (synaptic or neuroaxonal) are very sensitive in reflecting the clinical picture and severity of patients with IINDs.

For AINDs, our findings on the prognostic value of CSF markers were less consistent, showing a significant increase in NfL and beta-syn in patients admitted to the ICU and in NfL in those with altered consciousness but no associations of biomarkers with functional status at LP or at discharge. Even in the literature, data on the prognostic value of NfL in AE are inconsistent, with some studies showing associations between SNAP-25, neurogranin, or NfL concentrations and clinical features, disease severity, and prognosis in patients with AE[13,40] and others revealing no associations.[10,12] It has been speculated that this heterogeneity may be related to the frequent discrepancy between clinical severity and radiologic/CSF findings in patients with AE or to the notion that neuroaxonal damage, and possibly synaptic dysfunction, is not the predominant pathologic feature of AIND,[12] but this issue should be better addressed in future studies.

Our study has several limitations, such as the cross-sectional collection of CSF samples, the short follow-up period as well as the lack of clinical data for a proportion of participants with IINDs and AINDs. Moreover, some laboratory data (i.e., CSF protein levels and albumin quotient, renal function parameters), and clinical validated scales to quantify disease severity were not available in patients with IINDs and AINDs. In addition, we cannot rule out the possibility that drugs (e.g., antibiotics, antivirals, and immunomodulatory therapies) may have affected CSF biomarker levels in the minority of participants with IINDs and AINDs who were receiving treatment at the time of LP. However, we did not find any difference in biomarker concentrations between treated and untreated participants. Furthermore, including different and heterogeneous etiologies of IINDs and AINDs in the study design was advantageous for understanding shared or general mechanisms. However, this may also have contributed to the underestimation or masking of some disease-specific findings. Prospective studies are needed in the future, possibly with longitudinal samples collected at standardized time points for longer follow-up periods, to better investigate the effects of therapies on CSF biomarkers. In addition, it may be interesting to replicate our findings in blood, which is a more easily collected matrix. Indeed, NfL is also a well-established blood marker,[35,36] whereas new digital assays have recently been developed to detect beta-syn in blood; however, these methods are not yet commercially available.[15,23] Moreover, given the median age of our diagnostic groups (50–60 years), it is possible that some of our disease cases may have an underlying AD co-pathology, which could also affect CSF synaptic marker and NfL levels.[24]

In conclusion, the increase in CSF levels of beta-synuclein and neurogranin in patients with IINDs and AINDs suggests that the 2 conditions share a similar pattern of presynaptic and postsynaptic damage, as well as synaptic compartmental involvement. As previously reported, CSF NfL was elevated in both disease groups as an expression of ongoing neuroaxonal damage. However, these CSF biomarkers lack sufficient discriminatory power for routine diagnostic use. CSF synaptic markers, particularly in IINDs, were associated with clinical severity and short-term functional outcomes, indicating their potential utility in prognostic stratification and possibly as surrogate end points in therapeutic trials aimed at preserving synaptic integrity.

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Author Contributions

S. Abu-Rumeileh: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D.K. Erhart: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Barba: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F.F. Konen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Stapf: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Senel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Hudasch: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Steinacker: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Oeckl: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C.M. Weise: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. N. Ticozzi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S.

Halbgebauer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Verde: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K.-W. Sühs: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H. Tumani: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Otto: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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