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Therapeutic Advances in Neurological Disorders Original Research

Pathological cerebrospinal fluid protein concentration and albumin quotient at relapse predicts short-term disability progression in multiple sclerosis: a retrospective single center observational study

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Abstract

Background: Blood–brain barrier dysfunction in active multiple sclerosis (MS) lesions leads to pathological changes of cerebrospinal fluid (CSF). Theoretically, CSF analyses could help to predict relapse recovery and the course of disability. In this monocentric study, we investigated the impact of CSF findings assessed during the first relapse of MS on the short-term course of disability.

Methods: We performed a retrospective observational study including MS patients with available CSF data after onset of first MS relapse. Clinical symptoms had to be accompanied by gadolinium-enhanced lesion on magnetic resonance imaging. Expanded Disability Status Scale (EDSS) assessments at timepoint of relapse and after relapse recovery were studied to analyze disability. A two-step multivariate linear regression analysis adjusted for EDSS at spinal tab, duration of symptoms, sex, time until post relapse EDSS assessment, immunotherapy post relapse, and relapse treatment with glucocorticoids/plasma exchange to predict relapse associated disability was run.

Results: In the first step of the regression model, pathological albumin quotient (QAlb) [regression coefficient 0.50, 95% confidence interval (CI) (0.07–0.92), $p = 0.02$, $n = 99$] and CSF protein concentration [regression coefficient 0.84, 95% CI (0.33–1.35), $p = 0.001$, $n = 99$] predicted EDSS after relapse recovery. In the second step, the sum score of both predictors [range 0–2; n per value: 0 ($n = 73$), 1 ($n = 10$), 2 ($n = 15$)] confirmed the negative impact on course of disability after relapse [regression coefficient 0.38, 95% CI (0.13–0.62), $p = 0.003$, $n = 98$]. In this final multivariate linear regression model ($p < 0.001$; R^2 0.34), also EDSS at lumbar puncture [regression coefficient 0.58, 95% CI (0.35–0.81), $p < 0.001$, $n = 98$] and time between symptom onset and CSF evaluation [regression coefficient 0.03, 95% CI (0.006–0.048), $p = 0.01$, $n = 98$] forecast subsequent disability

Discussion: Our study conducted in MS patients during first relapse confirmed that both increased CSF protein concentration and pathological QAlb have a negative impact on EDSS after relapse. As secondary finding, we identified time from symptom onset to lumbar puncture as predictor of disability recovery after relapse.

Keywords: albumin quotient, cerebrospinal fluid, EDSS, progression, protein

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Introduction

Blood–brain barrier (BBB) dysfunction in active multiple sclerosis (MS) lesions leads to pathological changes of cerebrospinal fluid (CSF). Theoretically, CSF analyses could help to predict relapse recovery and the course of disability. Intrathecal IgG synthesis predicted disability after 4 years, independently from immunotherapy and relapse activity.[1] Also albumin quotient (QAlb) and CSF pleocytosis were previously shown to be associated with disease severity.[2,3] In this monocentric study, we investigated the impact of CSF findings assessed during the onset relapse on the short-term course of disability.

Methods

The retrospective observational study (cantonal ethics committee Bern: #2017-01369; Amendment of 18.11.2019) was performed at the Department of Neurology, Bern University Hospital, Switzerland. Diagnosis of relapsing MS was in accordance with McDonald 2017 criteria. Patients ($n=143$) with lumbar puncture within 3 months after onset of first MS relapse accompanied by gadolinium enhanced (Gd+) lesion on MRI and without additional relapses between index relapse and final Expanded Disability Status Scale (EDSS) assessment were identified between 2009 and 2018. Patients without first ($n=3$) or second EDSS assessment ($n=38$) or >1000 erythrocytes/μL CSF ($n=2$) were excluded, leading to a cohort of 100 patients (Figure 1). Continuous variables are compared using Mann–Whitney *U* test/Kruskal–Wallis test for continuous and χ^2-test for categorical variables. Multivariate linear regression analysis (MvReg) with the dependent variable EDSS after relapse recovery was run separately for each dichotomized CSF finding (normal *versus* pathological). MvReg was adjusted for EDSS at lumbar puncture, time between symptoms onset and lumbar puncture, sex, time until post relapse EDSS assessment, immunotherapy post relapse, and relapse treatment with glucocorticoids/plasma exchange (PLEX). The identified significant (defined as $p<0.05$ in the previous model) CSF predictors were used to build a sum score with the range from 0 to number of predictors. This score was integrated in the final MvReg analysis.

Results

Of the 100 patients 66 were female and the mean age was 34.5 years [95% confidence interval (CI) (32.3–36.7); $n=100$]. Relapse symptoms lasted for 4.3 days prior to CSF analysis [mean, 95% CI (2.4–6.1), $n=100$; Table 1]. At lumbar puncture, all patients were untreated, but the majority started disease modifying therapies (DMTs) later (91/100; Table 1). EDSS at relapse was 2.2 [mean, 95% CI (2.1–2.4), $n=100$], which decreased to 1.4 [mean, 95% CI (1.2–1.6), $n=100$] after 0.94 years [mean, 95% CI (0.9–1.0), $n=100$]. Of 100 relapses 94 were treated with glucocorticoids [mean cumulative dose 3726.6 mg; 95% CI (3314.94–4138.25), $n=94$] and 8/100 also with PLEX. Most frequent pathological CSF findings were oligoclonal bands (OCBs; 92/100), pleocytosis (51/100), intrathecal IgG synthesis (46/99), and increased QAlb (25/99; Table 1). Patients with Gd+ lesions in cerebral and spinal magnetic resonance imaging (MRI) had a tendency towards increased CSF IgG quotient and CSF IgG synthesis compared with patients with isolated Gd+ lesions in cerebral or spinal MRI (p-value <0.10; Table 2). CSF findings did not correlate with EDSS assessed at time of sampling (Tables 3 and 4). We used a two-step regression model to predict EDSS after relapse. In the first step, pathological QAlb

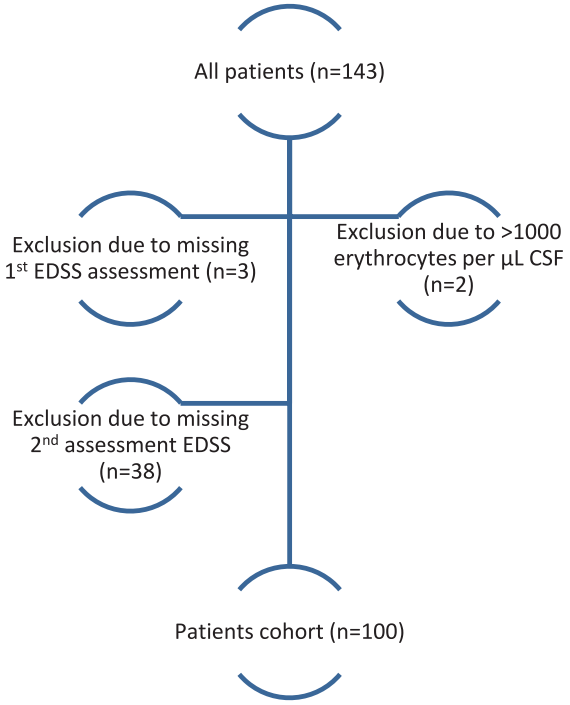

Figure 1. Flow chart demonstrating the generation of the cohort.
CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale.

Table 1. Demographic, clinical, cerebrospinal fluid and MRI characteristics of MS patients at relapse.

Variable	Mean	95% confidence interval		*n*
		LL	UL	
Age at lumbar puncture (years)	34.5	32.3	36.7	100
Time between symptoms onset and lumbar puncture (days)	4.3	2.4	6.1	100
Duration between first EDSS and lumbar puncture (days)	1.9	0.3	3.6	100
Duration between follow-up EDSS and lumbar puncture (years)	0.9	0.9	1.0	100
Glucocorticoids i.v. (mg)	3726.6	3314.9	4138.3	94
CSF cell count (cells/µL)	8.0	6.4	9.6	99
CSF protein (g/L)	0.4	0.4	0.4	99
CSF IgG (mg/L)	49.6	43.8	55.4	99
CSF IgG quotient	4.9	4.4	5.4	99
CSF IgG synthesis (%)	19.8	15.2	24.4	99
CSF albumin (mg/L)	239.2	216.3	262.2	99
CSF albumin quotient	5.7	5.2	6.2	99
CSF glucose (mmol/L)	3.6	3.5	3.7	100
CSF serum glucose ratio	0.6	0.6	0.7	100
CSF lactate (mmol/L)	1.7	1.7	1.8	97
EDSS at spinal tab	2.2	2.1	2.4	100
Follow-up EDSS	1.4	1.2	1.6	100
Variable	**Absolute numbers**	**Percentage**		***n***
Sex (female)	66	66.0		100
First diagnosis of MS	100	100.0		100
Glucocorticoids i.v.	94	94.0		100
PLEX	8	8.0		100
Presence of Gd enhanced lesion				
Any MRI	100	100		100
Cerebral MRI	80	83.3		96
Spinal MRI	43	58.9		73
Cerebral and spinal MRI	23	33.3		69

(Continued)

Table 1. (Continued)

Variable	Absolute numbers	Percentage	*n*
Immunotherapy			
Prior to lumbar puncture			
No immunotherapy	100	100	100
After lumbar puncture			
No immunotherapy	9	9	100
Interferon	23	23	100
Glatiramer acetate	9	9	100
Teriflunomide	4	4	100
Dimethyl fumarate	36	36	100
Fingolimod	13	13	100
Natalizumab	4	4	100
Rituximab	2	2	100
CSF findings			
CSF cell count ⩾5/μL	51	51	100
CSF/serum glucose index <0.5	8	8	100
CSF lactate ⩾2.1 mmol/L	11	11.3	97
CSF IgG index ⩾0.7	13	13.1	99
CSF IgG synthesis >10%	46	46.5	99
CSF OCB	92	92.0	100
CSF pathological albumin quotient	25	25.3	99
CSF protein >0.5 g/L	15	15.2	99
Main relapse symptom			
Optic neuritis	33	33	100
Sensory	35	35	100
Motor	3	3	100
Sensomotor	10	10	100
Ataxia	4	4	100
Brainstem	14	14	100
Psychomotor	1	1	100

(Continued)

Table 1. (Continued)

Variable	Regression coefficient	95% confidence interval		*n*	*p*-value
		LL	UL		
Step 1: simple models					
CSF cell count ⩾5/µL	−0.002	−0.38	0.38	100	0.99
CSF/serum glucose index <0.5	0.37	−0.32	1.06	100	0.29
CSF lactate ⩾2.1 mmol/L	0.13	−0.47	0.73	97	0.68
CSF IgG index ⩾0.7	0.28	−0.28	0.83	99	0.32
CSF IgG synthesis >10%	0.006	−0.39	0.40	99	0.98
CSF presence of OCBs	−0.25	−0.95	0.45	100	0.48
CSF pathological albumin quotient	0.50	0.07	0.92	99	**0.02**
CSF protein >0.5 g/L	0.84	0.33	1.35	99	**0.001**
Step 2: combined models					
Sum score albumin quotient and CSF protein (range 0–2)	0.38	0.13	0.62	98	**0.003**
EDSS at lumbar puncture	0.58	0.35	0.81	98	**<0.001**
Time between symptom onset and lumbar puncture (days)	0.03	0.006	0.048	98	**0.01**

Statistics: multivariate linear regression (MvReg) to predict EDSS after relapse. MvReg was adjusted for EDSS at spinal tab, time between symptoms onset and lumbar puncture, sex, time until post relapse EDSS assessment, immunotherapy post relapse, and relapse treatment with glucocorticoids/PLEX. A two-step model was performed with first inclusion of single CSF values within the simple model and afterwards a combined model including a sum score of the previously identified significant predictors. Sum score CSF albumin quotient and CSF protein was calculated as follows: Var (pathological albumin quotient) + Var (CSF protein >0.5 g/L) resulting in a variable with a range from 0 to 2; significant findings are shown in **bold**.
CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; Gd, gadolinium; LL, lower limit; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal band; PLEX, plasma exchange therapy; UL, upper limit; Var, variable.

[regression coefficient 0.50, 95% CI (0.07–0.92), $p=0.02$, $n=99$] and CSF protein concentration [regression coefficient 0.84, 95% CI (0.33–1.35), $p=0.001$, $n=99$] predicted EDSS after relapse (Table 1). In the second step, the sum score of both predictors [range 0–2; n per value: 0 ($n=73$), 1 ($n=10$), 2 ($n=15$)] confirmed the negative impact of these parameters on EDSS after relapse [regression coefficient 0.38, 95% CI (0.13–0.62), $p=0.003$, $n=98$]. In this final MvReg model ($p<0.001$; R^2 0.34), also EDSS at lumbar puncture [regression coefficient 0.58, 95% CI (0.35–0.81), $p<0.001$, $n=98$] and time between symptom onset and CSF evaluation [regression coefficient 0.03, 95% CI (0.006–0.048), $p=0.01$, $n=98$] forecast subsequent disability (Table 1).

Discussion

Our study conducted in MS patients during first relapse confirmed that both increased CSF protein concentration and pathological QAlb have a negative impact on EDSS after relapse whereas immune cell count or presence of OCBs did not predict disability levels in our model. Increased BBB permeability is considered a key factor of the inflammatory process as demonstrated in MS pathology studies, supporting our findings.[6]

As secondary finding, we identified time from symptom onset to lumbar puncture as predictor of disability recovery after relapse. This time interval is possibly indicative for the start of relapse treatment,

Table 2. Correlation between CSF findings and gadolinium enhancement on cerebral (cMRI) and spinal (sMRI) magnetic resonance imaging.

Variable	cMRI: gadolinium (+)				sMRI: gadolinium (+)				cMRI and sMRI: gadolinium (+)				*p*-value
	Mean	95% CI		*n*	Mean	95% CI		*n*	Mean	95% CI		*n*	
		LL	UL			LL	UL			LL	UL		
CSF cell count (cells/μL)	7.14	5.06	9.22	57	8.00	3.95	12.05	20	10.17	6.42	13.93	23	0.20
CSF protein (g/L)	0.37	0.33	0.41	56	0.38	0.32	0.43	20	0.40	0.34	0.47	23	0.60
CSF IgG (mg/L)	42.76	37.31	48.21	57	45.22	36.34	54.09	19	70.33	51.81	88.84	23	**0.02**
CSF IgG quotient	4.45	3.91	4.99	57	4.48	3.63	5.34	19	6.40	4.92	7.88	23	0.06
IgG synthesis (%)	16.20	10.83	21.58	57	18.38	7.13	29.64	19	29.95	18.25	41.65	23	0.10
CSF albumin (mg/L)	236.82	203.59	270.06	57	234.95	188.18	281.71	19	248.78	202.96	294.61	23	0.67
Albumin quotient	5.68	4.96	6.41	57	5.54	4.51	6.57	19	5.70	4.65	6.74	23	1.0
CSF glucose (mmol/L)	3.54	3.43	3.65	57	3.70	3.41	3.99	20	3.58	3.38	3.7	23	0.53
CSF serum glucose ratio	0.63	0.60	0.66	57	0.66	0.60	0.72	20	0.64	0.59	0.68	23	0.67
CSF lactate (mmol/L)	1.74	1.65	1.82	55	1.72	1.57	1.86	20	1.70	1.60	1.79	22	0.93

Statistics: Kruskal–Wallis test; significant findings are shown in **bold**.
CI, confidence interval; CSF, cerebrospinal fluid; LL, lower limit; UL, upper limit.

Table 3. Correlation between CSF findings and Expanded Disability Status Scale at time point of sampling.

Variable	Correlation coefficient	*p*-value	*n*
CSF cell count (cells/μL)	−0.11	0.27	100
CSF protein (g/L)	0.04	0.68	99
CSF IgG (mg/L)	0.02	0.82	99
CSF IgG quotient	0.02	0.88	99
IgG synthesis (%)	−0.08	0.42	99
CSF albumin (mg/L)	0.004	0.97	99
Albumin quotient	0.05	0.60	99
CSF glucose (mmol/L)	−0.06	0.53	100
CSF serum glucose ratio	−0.16	0.10	100
CSF lactate (mmol/L)	0.17	0.09	97

Statistic: Spearman-rho test.
CSF, cerebrospinal fluid; *n*, number of observations.

arguing towards an early termination of inflammatory processes with glucocorticoids as performed in 94/100 patients. However, this remains speculative as we were not able to calculate the time interval from symptom onset to first glucocorticoid infusion. Limitations of our work are the retrospective and monocentric design as well as the cohort inclusion criteria, which focused only on those patients with MRI confirmed relapse defined as presence of Gd+ lesion on MRI. Thus our findings cannot be transferred to patients without focal disease activity on MRI. Since the therapy groups were heterogeneous, we conducted further analysis and decided to group the first line treatments of the European Medicines Agency (EMA) label (interferon, glatiramer acetate, dimethyl fumarate and teriflunomide) together. Running the analysis confirmed the predictive effect of our sum score variable (regression coefficient 0.39, 95% CI 0.081–0.706, $p=0.01$, $n=71$). Further grouping on untreated patients or those with second line EMA label was, due to low sample size, not possible and should therefore be considered as a limitation of our retrospective study.

Table 4. Magnetic resonance (MR) imaging protocol and CSF methods/pathological values.

CSF methods/pathological values	
CSF cell count	Sysmex Flow Cytometry (Sysmex, Horgen, Switzerland)
CSF protein (g/L)	Turbidimetric method with benzethonium chloride TPUC3; Roche Cobas8000 (Roche, Basel, Switzerland)
CSF IgG (mg/L)	Nephelometry IgG Siemens BNII (Siemens, Munich, Germany)
CSF albumin (mg/L)	Nephelometry ALBT auf Siemens BNII (Siemens, Munich, Germany)
CSF glucose (mmol/L)	Enzymatic, hexokinase method, GLUC3 (Glucose HK Gen.3) Roche Cobas8000 (Roche, Basel, Switzerland)
CSF lactate (mmol/L)	ABL825 Radiometer (Radiometer Medical ApS Åkandevej Brønshøj, Denmark)

CSF analysis was performed in the ISO 17025 accredited Center of Laboratory Medicine (ZLM) of the Inselspital – Bern University Hospital (see table above). The following previously described cut offs were used to define pathological CSF findings: Cell Count ≥5 per ul, Protein Concentration >0.5 g/L, CSF/Serum Glucose Quotient < 0.5, Lactate concentration in CSF ≥ 2.1 mmol/l, (5) IGG Index ≥ 0.7 and IgG Synthesis > 10%. Further the age adjusted upper reference value of the albumin quotient (QAlb) was calculated as suggested by Reiber et al.: QAlb= (4 + Age / 15) * 10^{-3}. Positivity of oligoclonal bands was defined as presence of CSF specific OCB referring to type II and III (6).
Magnetic resonance (MR) imaging protocol
MR images are acquired on 3 Tesla (T) and 1.5T MR scanners (Magnetom Verio 3T, Magnetom Trio 3T, Magnetom Avanto 1.5T and Magnetom 1.5T Aera, Siemens Healthcare, Erlangen, Germany) with a standardized MS protocol containing: (i) diffusion weighted imaging, (ii) 3D T1-weighted MPRAGE pre- and postgadobutrol i.v., (iii) dual echo T2/PD weighted imaging, (iv) 3D FLAIR imaging and (v) 2D T1-weighted imaging post gadobutrol i.v. All patients receive gadobutrol (Gadovist (Bayer: Leverkusen, Germany)) 0.1mL·kg^{-1} body weight.
CSF, cerebrospinal fluid.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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