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ORIGINAL ARTICLE

Patients with degenerative cervical myelopathy have signs of blood spinal cord barrier disruption, and its magnitude correlates with myelopathy severity: a prospective comparative cohort study

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Abstract

Purpose The aim of this study is to detect the presence of blood spinal cord barrier (BSCB) disruption in patients with degenerative cervical myelopathy (DCM).

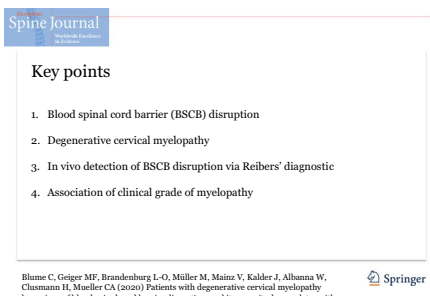
Methods In this prospective non-randomized controlled cohort study, 28 patients with DCM were prospectively included. All patients had indication for neurosurgical decompression. Furthermore, 38 controls with thoracic abdominal aortic aneurysm (TAAA) and indication for surgery were included. All patients underwent neurological examination. Regarding BSCB disruption and intrathecal immunoglobulin (Ig) concentrations, cerebrospinal fluid (CSF) and blood serum were examined for albumin, IgG, IgA and IgM. Quotients (Q) (CSF/serum) were standardized and calculated according to Reibers' diagnostic criteria.

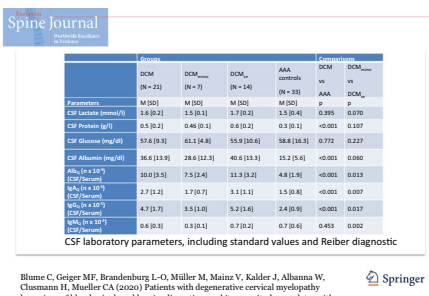
Results Patients and controls distinguished significantly in their clinical status. AlbuminQ, as expression of BSCB disruption, was significantly increased in the DCM patients compared to the controls. Quotients of IgG and IgA differed significantly between the groups as an expression of intrathecal diffusion. In the subgroup analysis of patients with mild/moderate clinical status of myelopathy and patients with severe clinical status, the disruption of the BSCB was significantly increased with clinical severity. Likewise, IgAQ and IgGQ presented increased quotients related to the clinical severity of myelopathy.

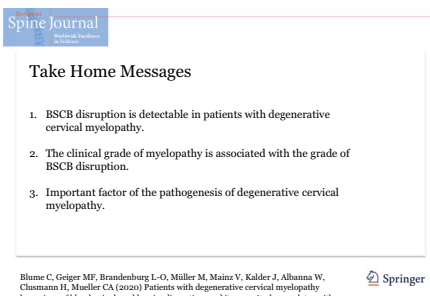
Conclusion In this study, we detected an increased permeability and disruption of the BSCB in DCM patients. The severity of BSCB disruption and the diffusion of Ig are related to the clinical status in our patient cohort. Having documented this particular pathomechanism in patients with DCM, we suggest that this diagnostic tool cloud be an important addition to surgical decision making in the future.

Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.







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Keywords Blood spinal cord barrier disruption · Degenerative cervical myelopathy · Cerebrospinal fluid · Prospective · Non-randomized controlled study

Introduction

The spinal cord is an immunologically privileged compartment. As a boundary layer between the spinal cord and the periphery, the blood spinal cord barrier (BSCB) forms a physical and biochemical barrier between the central nervous system (CNS) and systemic circulation and protects the microenvironment of the spinal cord [1]. Disruption of the BSCB is associated with several acute and neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), peripheral nerve lesion and spinal cord injury [1–4]. To date, the research on BSCB has mainly focused on the association with acute spinal cord injury (SCI). Diseases or injuries of the CNS with increased BSCB permeability promote edema formation into the spinal cord parenchyma and allow the entrance of inflammatory cells derived from the peripheral circulation into the spinal cord parenchyma [5]. The consequences of BSCB dysfunction are the invasion of blood located cells, proteins and molecules in the injured parenchyma [6–9]. These secondary pathophysiological cascades contribute to further spinal cord damage and extend the damage into areas of the spinal cord, which had not been primarily affected [6, 10, 11]. One of these pathophysiological players, of ongoing secondary injury, is the immune-mediated inflammatory response [12]. Therefore, BSCB disruption can be the initiation of endogenous pathways of inflammation, angiogenesis and activation of macrophages, explaining the secondary injury of the spinal cord [13]. Patients with chronic progressive, cervical spinal stenosis suffer from repetitive microtraumas of the spinal cord [14]. Similar to acute SCI, the mechanisms of secondary damage of the spinal cord in patients with degenerative cervical myelopathy (DCM) via proinflammatory cytokines, increased macrophage/microglia expression and Wallerian degeneration have been presented in several studies [5, 15–18].

Concerning the diagnosis of a BSCB impairment, magnetic resonance imaging (MRI) has been used, to reflect the pathological changes within the spinal cord through changes in signal intensity (SI) in patients with cervical myelopathy [19, 20]. Additionally, contrast gadolinium-diethylene-triamine-penta acetic acid (Gd-DTPA)-enhanced MRI provides information about the integrity of the spinal cord. Several studies have reported contrast Gd-DTPA enhancement in the spinal cord in MR images in patients with cervical myelopathy [21, 22]. However, the mechanism of contrast (Gd-DTPA) enhancement, as a rare phenomenon and sign of BSCB disruption, has not been fully explained in patients with cervical myelopathy [23].

BSCB impairment is a potential promoter of inflammatory and angiogenic reactions and has only been documented in one animal model of DCM in the context of endogenous inflammatory reactions so far [16]. However, there has been no direct proof of BSCB disruption in patients with DCM in molecular condition. The aim of this study was to detect the presence of BSCB disruption in patients with DCM, using the established Reiber diagnostic criteria [24].

Methods

Study procedure and subject characteristics

Study approval was given by the local ethics committee of the Medical Faculty of the XXX University (EK 164/13). Before investigation, all participants of this study gave written informed consent complying with the Declaration of Helsinki (Medical Association 2008). Any participant who showed neurological disorders other than DCM (e.g., neurodegenerative diseases ALS, MS), history of cerebral stroke, cerebral hemorrhage, central nervous infections or spinal trauma) was excluded from study participation.

DCM patients with moderate (mJOA 12-14) and severe (mJOA 11-0) clinical signs of myelopathy and consisting of imaging findings of degenerative cervical spinal stenosis decompressive surgery were offered as first line therapy. Patients with mild (mJOA 14-17) signs of myelopathy surgery or conservative management with structured rehabilitation are possible options. In case of clinical deterioration, surgical intervention was strongly recommended. In general, the management of patients was performed according to the AOSPINE guidelines for DCM [25, 26]. Twenty-eight consecutive patients with DCM and indication for surgical decompression were enrolled. Four patients of the DCM group rejected study associated lumbar puncture; in three patients, lumbar puncture was unsuccessful. These patients were excluded due to missing cerebrospinal fluid (CSF) samples. In the thoracic-abdominal aortic aneurysm (TAAA) group implantation of lumbar drainage failed in five patients, and these patients were excluded as well due to missing CSF samples (Fig. 1).

Twenty-one patients (12 female; 9 male; mean age 63.3 ± 11.6 years) with DCM and indication for cervical decompression and 33 control patients (12 female; 21 male; mean age 62.3 ± 15.2 years) with TAAA were included in the study. All participants underwent surgery. The two groups did not differ with regard to age [$t(52) = .26$; $p = 0.796$] (Table 1).

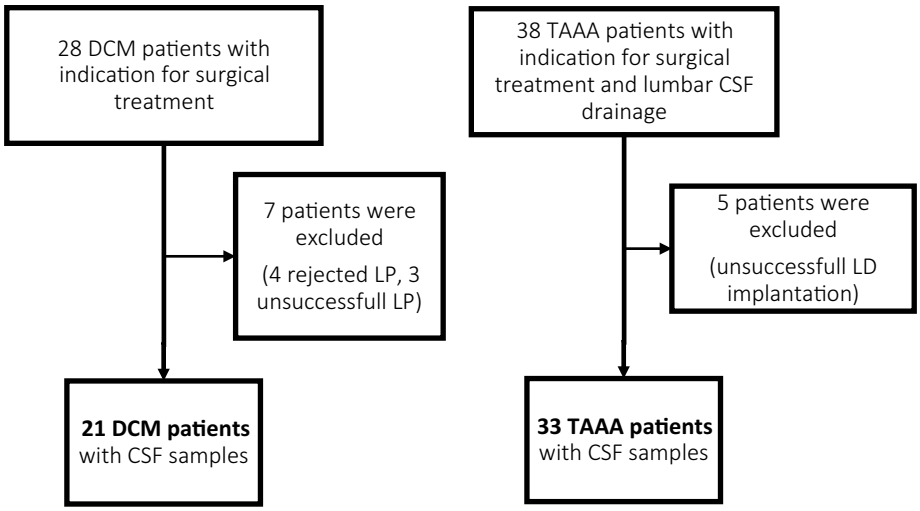

Fig. 1 Flowchart of enrolled patients (DCM) and controls (TAAA) and finally included subjects. *CSF* cerebrospinal fluid, *DCM* degenerative cervical myelopathy, *LD* lumbar drainage, *LP* lumbar puncture, *TAAA* thoracic-abdominal aortic aneurysm

Table 1 Demographics and clinical findings

Parameters	Groups					
	DCM ($N=21$)	DCM_{mimo} ($N=7$, 33.3%)	DCM_{se} ($N=14$, 66.7%)	TAAA controls ($N=33$)	DCM versus TAAA	DCM_{mimo} versus DCM_{se}
	M [SD]	*M* [SD]	*M* [SD]	*M* [SD]	*p*	*p*
Age (years)	63.3 [11.6]	57.3 [7.8]	66.3 [12.2]	62.3 [15.2]	0.131	0.094
mJOA Score	10.1 [3.2]	13.7 [2.0]	8.4 [1.9]	17.2 [1.3]	*< 0.001*	*< 0.001*
Neck Disability Index	46.4 [21.0]	40.3 [17.5]	49.4 [22.5]	6.0 [9.0]	*< 0.001*	0.360
MRI findings	*N* [%]	*N* [%]	*N* [%]			
Positive TW2 signal	16 [84.2] (2 patients myelography)	4 [66.7] (1 patient myelography)	12 [92.3] (1 patient myelography)			
Multisegmental stenosis	15 [71.4]	5 [71.4]	10 [71.4]			
Monosegmental stenosis	6 [28.6]	2 [28.6]	4 [28.6]			

p-value < 0.05 statistically significant

DCM degenerative cervical myelopathy, DCM_{mimo} degenerative cervical myelopathy mild/moderate, DCM_{se} degenerative cervical myelopathy severe, *TAAA* thoracic-abdominal aortic aneurysm, *mJOA* modified Japanese Orthopaedic Association, *M* mean, *SD* standard deviation

In DCM patients, CSF samples were taken preoperatively via lumbar puncture or as part of myelography in accordance with the given indication and contraindication for magnetic resonance imaging (e.g., cardiac pacemakers). The TAAA patients routinely received CSF drainage during surgery for intraoperative intrathecal pressure monitoring. Blood serum samples were taken simultaneously from all patients for calculation of CSF composition and detection of BSCB disruption. In general, a Queckenstedt maneuver was carried out in each DCM patient [27]. Furthermore, each CSF was monitored for an Froin's syndrome [28].

Moreover, all patients underwent neurological examination and the objective functional status was assessed by modified Japanese Orthopaedic Association Score (mJOA) (normal function: 18 points; mild myelopathy: 15–17 points; moderate: 12–14 points; severe: 0–11 points) and Neck Disability Index (NDI) [29–31].

Cerebrospinal fluid analysis/Reiber diagnostic criteria [24]

CSF samples and blood serum samples were taken simultaneously before surgery and directly transferred to the laboratory for examination. Routine laboratory findings of CSF were determined: CSF cell count (/µ), lactate (mmmol/l), protein concentration (g/l). Regarding BSCB and intrathecal immunoglobulin (Ig) concentrations, CSF and blood serum samples were examined via simultaneous nephelometric quantification (BN ProSpec® System, Siemens Healthineers) for albumin, IgG, IgA and IgM (all mg/dl). Quotients (Q)

(CSF/serum) were calculated according to the standardized Reiber diagnostic criteria [24] for IgGQ, IgAQ, IgMQ and AlbuminQ (all quotients: $n \times 10^{-3}$). Individual age-related references of AlbuminQ were calculated: $(4 + \text{age}/15) \times 10^{-3}$ [32, 33] (Table 2).

Data analyses

All data analyses were performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY). Two one-way Analyses of Variances (ANOVAs) were used to compare the DCM with the TAAA patient groups: one investigating the differences between DCM and control group with regard to the routine CSF laboratory parameters lactate, protein, glucose and albumin and the other with regard to the CSF serum quotients (Q) according to the Reiber diagnostic criteria which were IgAQ, IgGQ, IgMQ and AlbuminQ.

In an exploratory analysis, the DCM group was divided into two subgroups, namely patients whom displayed mild to moderate (N DCMmimo = 7) and patients with severe clinical myelopathy (N DCMse = 14). The two DCM groups did not differ with regard to age [$t(19) = -1.76$, $p = 0.09$]. The DCM groups' CSF serum quotients (IgAQ, IgGQ, IgMQ and AlbuminQ) were compared using a one-way ANOVA.

Standardized effect sizes (ES) with the respective confidence intervals (CI, Hedges bias corrected) are reported for all significant comparisons. As a rule of thumb, values of 0.2 indicate a small, values above 0.5 a medium and values above 0.8 a large effect.

Results

Demographics and clinical findings

Mean duration of symptoms in patients with DCM was 15.7 ± 10.7(SD) months. Regarding the clinical severity of clinical myelopathy, seven DCM patients (33.3%) presented a mild to moderate status (mJOA 12–17) and 14 DCM patients (66.7%) a severe (mJOA 0–11) clinical condition. Patients of the TAAA control group had no neurological deficit or history of neurodegenerative disease. The groups differ in their clinical appearance as reflected by significant group differences in a one-way ANOVA regarding the mJOA (DCM mean ± SD: 10.1 ± 3.2; TAAA mean ± SD: 17.2 ± 1.3; $F(1, 52) = 129.22$; $p < 0.001$) and NDI score (DCM mean ± SD: 46.4 ± 21.0; TAAA mean ± SD: 6.0 ± 9.0; $F(1, 52) = 95.61$; $p < 0.001$) (Table 1).

Table 2 Demographics and clinical findings

CSF diagnostics (routine laboratory)	CSF diagnostics criteria (Reiber)
CSF cell count (/µl)	Albumin (mg/dl)
Lactate (mmmol/l)	IgG (mg/dl)
Protein concentration (g/l)	IgA (mg/dl)
	IgM (mg/dl)
	Albumin quotient (individual age related $(4 + \text{age}/15) \times 10^{-3}$)
	IgG quotient ($n \times 10^{-3}$)
	IgA quotient ($n \times 10^{-3}$)
	IgM quotient ($n \times 10^{-3}$)

CSF cerebrospinal fluid, *Ig* immunoglobulin, *µl* microliter, *mmol/l* millimole per liter, *g/l* gram per liter, *mg/dl* milligram per deciliter

Laboratory findings

DCM patients presented a BSCB disruption in regard to the AlbuminQ according to the individual age-related and calculated reference ranges [32, 33]. Ig quotients (IgGQ and IgAQ) were increased in all DCM patients, though all measured Ig values exclusively represented increased permeability of the BSCB and no intrathecal synthesis [32, 33]. Controls neither presented BSCB disruption concerning AlbuminQ nor increased IgQ in CSF/serum quotients. Means and standard deviations (SD) of the routine CSF laboratory findings parameters and the CSF/serum quotients as well as group comparisons are shown in Table 3.

DCM versus TAAA control group

The ANOVA concerning the routine CSF laboratory parameters revealed significant group differences for protein [$F(1,52) = 64.81$, $p < 0.001$; ES = 2.25 (CI 1.56–2.94)] and albumin [$F(1,52) = 62.88$, $p < 0.001$; ES = 2.18 (CI 1.5–2.87)]. Both, protein and albumin were significantly increased in DCM compared to control patients. Groups neither differ with regard to lactate [$F(1,52) = .74$, $p = 0.40$] nor glucose [$F(1,52) = .09$, $p = 0.77$].

The ANOVA concerning the CSF serum quotients revealed significant group differences for IgAQ [$F(1,51) = 19.68$, $p < 0.001$; ES = 1.23 (CI 0.63–1.83)], IgGQ [$F(1,51) = 39.04$, $p < 0.001$; ES = 1.73 (CI 1.09–2.37)] and AlbuminQ [$F(1,51) = 51.73$, $p < 0.001$; ES = 1.98 (CI 1.32–2.64)]. All quotients were significantly increased in DCM as compared to the control patients. Groups did not differ with regard to IgMQ [$F(1,51) = .58$, $p = .453$].

DCMmimo versus DCMse

The ANOVA concerning the CSF serum quotients revealed significant group differences for IgAQ [$F(1,19) = 9.08$, $p = .007$; ES = −1.34 (CI −2.33 to −.34)], IgGQ [$F(1,19) = 6.9$, $p < .017$; ES = −1.16 (CI −2.14 to −.19)], IgMQ [$F(1,15) = 14.0$, $p < .002$; ES = −1.99 (CI −3.3 to −.69)] and AlbuminQ [$F(1,19) = 7.5$, $p < .013$; ES = −1.22

Table 3 CSF laboratory parameter

Parameters	Groups				Comparisons	
	DCM ($N=21$)	DCM_{mimo} ($N=7$)	DCM_{se} ($N=14$)	TAAA controls ($N=33$)	DCM versus TAAA	DCM_{mimo} versus DCM_{se}
	M [SD]	*M* [SD]	*M* [SD]	*M* [SD]	*p*	*p*
CSF lactate (mmol/l)	1.6 [0.2]	1.5 [0.1]	1.7 [0.2]	1.5 [0.4]	0.395	0.070
CSF protein (g/l)	0.5 [0.2]	0.46 [0.1]	0.6 [0.2]	0.3 [0.1]	*< 0.001*	0.107
CSF glucose (mg/dl)	57.6 [9.3]	61.1 [4.8]	55.9 [10.6]	58.8 [16.3]	0.772	0.227
CSF albumin (mg/dl)	36.6 [13.9]	28.6 [12.3]	40.6 [13.3]	15.2 [5.6]	*< 0.001*	*0.060*
Alb_Q ($n\times10^{-3}$) (CSF/serum)	10.0 [3.5]	7.5 [2.4]	11.3 [3.2]	4.8 [1.9]	*< 0.001*	*0.013*
IgA_Q ($n\times10^{-3}$) (CSF/serum)	2.7 [1.2]	1.7 [0.7]	3.1 [1.1]	1.5 [0.8]	*< 0.001*	*0.007*
IgG_Q ($n\times10^{-3}$) (CSF/serum)	4.7 [1.7]	3.5 [1.0]	5.2 [1.6]	2.4 [0.9]	*< 0.001*	*0.017*
IgM_Q ($n\times10^{-3}$) (CSF/serum)	0.6 [0.3]	0.3 [0.1]	0.7 [0.2]	0.7 [0.6]	*0.453*	*0.002*

p-value < 0.05 statistically significant

CSF cerebrospinal fluid, *DCM* degenerative cervical myelopathy, DCM_{mimo} degenerative cervical myelopathy mild/moderate, DCM_{se} degenerative cervical myelopathy severe, *Ig* immunglobulin, Ig_Q *IgQuotient*, *TAAA* thoracic-abdominal aortic aneurysm, *M* mean, *SD* standard deviation, *mmol/l* millimole per liter, *g/l* gram per liter, *mg/dl* milligram per deciliter

(CI −2.2 to −.24)]. All quotients were significantly increased in DCMse as compared to the DCMmimo patients.

Discussion

Patients in our cohort presented a reduced BSCB function due to standardized reference values of increased AlbuminQ and diffusion of IgAQ and IgGQ to the intrathecal room according to the Reiber diagnostic criteria [24, 33]. The control group, without any neurological deficits or neurodegenerative diseases, presented a complete absence of BSCB disruption. These results highlight the presence of ongoing and lasting BSCB disruption of patients with DCM.

MRI with Gd-DTPA enhancement provides useful information in the assessment of spinal cord lesions, but the mechanism of intramedullary enhancement in SCI and CSM is not clearly resolved. Terae et al. [34] interpreted the Gd-DTPA enhancement as a disruption of the spinal cord parenchyma and a disturbance of BSCB in the injured spinal cord. In addition, the disturbed venous circulation caused by injury could resulted in local venous hypertension at the affected level [35]. However, Lee et al. described a retrospective series as an incidence of 3% of Gd-DTPA enhancement on MRI in patients with cervical spondylolysis. Terae et al. investigated in their retrospective study eight patients after SCI, and three (37.5%) intramedullary lesions showed a contrast enhancement. Concerning DCM, there are some studies dealing with DCM and Gd-DTPA enhancement on MRI [21, 23, 36]. In these studies, the incidence of detected BSCB disruption (Gd-DTPA enhancement) was between 7.3 and 32%. This is in contrast with our findings. We found in all investigated patients an BSCB impairment, using the Reiber diagnostic criteria. This leads to the consideration that the concept of MRI Gd-DTPA enhancement is not the most sensitive diagnostic tool to assess the status of the BSCB in patients with DCM.

Furthermore, the subgroup analysis of clinical neurological severity of DCM (DCMmimo vs DCMse) presented a significant association between the clinical severity (mJOA) and the AlbuminQ, as well as the IgQ. AlbuminQ, as key marker, provides the most valuable information concerning possible BSCB impairment. IgQs, depending on concentration levels, are indicators for either diffusion in the intrathecal space (BSCB disruption) or primary synthesis of immunoglobulins in the intrathecal space (e.g., CNS infections). DCM patients in our study presented concentration levels of IgQ which were only based on diffusion in the intrathecal space caused by an impairment of the BSCB. Only IgMQ revealed contrary results. There were no differences between DCM patients and controls, but significant lower concentrations in DCM_{mimo} patients. With the highest molecular mass, changes in concentrations of IgM, because of diffusion, may be expected to be detected less [37]. However, these results of IgM remain unclear in the setting of DCM and BSCB.

Regarding our patient's cohort, the degree of BSCB disruption could have considerable influence on the clinical manifestation of cervical myelopathy. Especially the chronic setting of this disease and continous impairment of the BSCB, could be responsible for the secondary harm to the spinal cord. In this context, the pathological decrease of CSF flow rate, i.e., the blood–CSF barrier dysfunction with an up to 100-fold increase in protein concentrations in CSF, has different causes [32, 38, 39]: like a reduced passage of

CSF through the arachnoid villi in inflammatory diseases or a blockade of the subarachnoid space (Froin's syndrome) by a tumor or a complete lumbar stenosis [28, 32]. In our study, we also identified an increase in protein concentrations in CSF, although in our study we excluded patients with lumbar stenosis and trauma. Furthermore, while lumbar puncture, (I) a Queckenstedt's maneuver in each patient was carried out, (II) a Froin's syndrome was never found and (III) via MRI imaging a complete spinal block could be excluded. However, in the subgroup analysis we could detect significant differences of the AlbuminQ and clinical signs of myelopathy, measured by mJOA-Score [27]. In other words: Patients with a mild or moderate DCM had lower AlbuminQ compared to patients with a severe DCM. This observation was independent in grade of spinal stenosis in MRI.

The time course of BSCB disruption in SCI has been described previously [4, 11, 40, 41]. Dysfunction of the BSCB has been documented almost immediately (5 min) after trauma [4]. Findings on the re-establishment of BSCB vary between the studies. Noble et al. reported about a re-establishment after 14 days; in other studies the range was between 28 and 56 days [6, 42]. To record the condition of the BSCB in patients with DCM over time does not seem to be feasible due to the chronic character of this disease and a lack of sudden onset. In our patients with longer duration of clinical symptoms (> 6 months), BSCB impairment was still detectable. Based on this finding, we assume that the BSCB disruption is a long-lasting process in DCM and this might maintain mechanisms of secondary injury of the spinal cord. This BSCB-triggered process of secondary injury culminates in apoptosis of neuronal structures with a reduced chance of clinical recovery [15]. For this reason, the diagnostic tool of BSCB evaluation could be a valuable addition in the decision making on surgical intervention. This applies especially to patients with mild clinical signs of myelopathy, where surgical treatment is not directly obvious. But these patients may already have ongoing chronic and potentially irreversible endogenous harm to the spinal cord. Therefore, the detection of BSCB disruption could provide important information to find the right therapy for the patients. Future work needs to address whether the CSF/serum ratios improve or stabilize after surgical decompression.

Conclusion

Patients with DCM in our cohort presented BSCB disruption. Values of BSCB impairment (AlbuminQ and IgQ) presented significant differences in relation to the clinical neurological status (DCMmimo vs DCMse) of the patients. Patients with higher values of BSCB disruption presented with a more severe degree of clinical myelopathy in our subgroup analysis.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Christian Blume, Christian Andreas Mueller, Walid Albanna, Lars-Ove Branadenburg, Johannes Kalder and Matthias Geiger. Data analysis was performed by Verena Mainz. The first draft of the manuscript was written by Christian Blume, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee [local ethics committee of the Medical Faculty of the RWTH Aachen University, Germany (EK 164/13)] and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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