European Spine Journal (2018) 27:1824–1830
https://doi.org/10.1007/s00586-018-5549-5

ORIGINAL ARTICLE

Axonal damage is remarkable in patients with acutely worsening symptoms of compression myelopathy: biomarkers in cerebrospinal fluid samples

Hiroshi Takahashi[1] · Yasuchika Aoki[2] · Arata Nakajima[1] · Masato Sonobe[1] · Fumiaki Terajima[1] · Masahiko Saito[1] · Takuya Miyamoto[1] · Keita Koyama[1] · Keiichiro Yamamoto[1] · Takeo Furuya[3] · Masao Koda[3] · Seiji Ohtori[3] · Masashi Yamazaki[4] · Koichi Nakagawa[1]

Received: 20 February 2017 / Revised: 24 February 2018 / Accepted: 13 March 2018 / Published online: 19 March 2018

Abstract

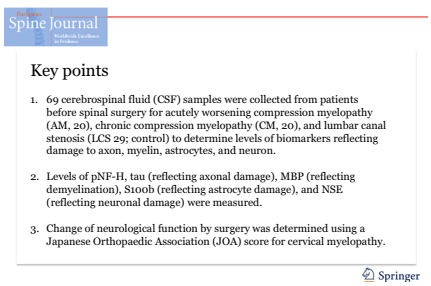
Purpose To determine levels of biomarkers reflecting damage to axon, myelin, astrocytes, and neuron in cerebrospinal fluid (CSF) of patients with cervical compression myelopathy.

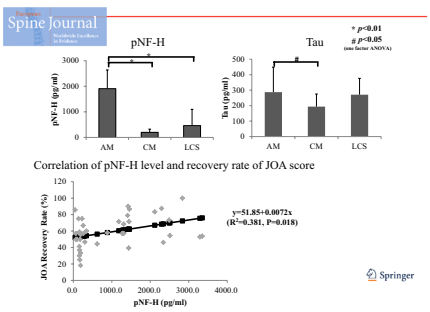
Methods We collected 69 CSF samples from patients before spinal surgery for acutely worsening compression myelopathy (AM, 20), chronic compression myelopathy (CM, 20), and lumbar canal stenosis (LCS 29; control). We measured levels of phosphorylated neurofilament subunit H (pNF-H), tau (reflecting axonal damage), myelin basic protein (MBP) (reflecting demyelination), S100b (reflecting astrocyte damage), and neuron-specific enolase (NSE) (reflecting neuronal damage). Change of neurological function by surgery was determined using a Japanese Orthopaedic Association (JOA) score for cervical myelopathy.

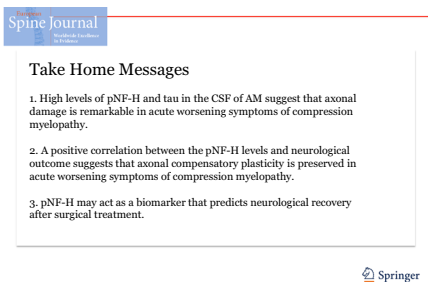
Results Significantly higher levels of pNF-H were detected in AM compared with those in either CM or LCS ($P<0.01$). Significantly higher levels of tau were detected in AM compared with those in CM ($P<0.05$). Levels of MBP were undetectable in almost all the patients. Levels of S100b were equivalent in the three groups. Levels of NSE in AM and CM were significantly lower than those in LCS ($P<0.01$). The recovery rate of JOA score was significantly greater for patients with AM than CM. We found a positive correlation between pNF-H and recovery of JOA score ($r=0.381$, $P=0.018$).

Conclusion The present results suggest that axonal damage is remarkable compared with demyelination, astrocytic, and neuronal damage in AM. Better clinical outcome in AM with high CSF levels of pNF-H indicates that axonal compensatory plasticity in spinal cord is preserved, and pNF-H can be predictive of good surgical outcome for AM.

Graphical abstract These slides can be retrieved under Electronic Supplementary Material.







Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-018-5549-5) contains supplementary material, which is available to authorized users.

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Keywords Compression myelopathy · Cerebrospinal fluid · Biomarker · Axonal damage

Introduction

Chronic compression of the spinal cord by osteophytes, degenerated discs, hypertrophy of the facet joint, thickened ligamentum flavum, and ossification of the posterior longitudinal ligament are causes of compression myelopathy [3]. Usually, compression myelopathy shows a slow and incremental decline in function. By contrast, acutely worsening symptoms of motor and sensory function with mild or no trauma are observed occasionally. Such acute worsening symptoms of compression myelopathy result in severe neurological deficits with poor functional recovery [21]. To date, the only effective therapy for compression myelopathy is the early surgical treatment, and relatively good functional recovery of JOA score (about 50–70%) is reported [27]. However, in some cases, no sufficient improvement of neurological function is achieved [20]. To date, it is supposed that the pathogenesis of compression myelopathy is similar to secondary injury to the spinal cord in acute spinal cord injury [19]. However, the detailed pathogenesis of compression myelopathy remains unclear and we cannot accurately predict the degree of neurological recovery before surgery.

Phosphorylated neurofilament subunit H (pNF-H) is a structural protein of axon fibers that is not detected in the plasma or cerebrospinal fluid (CSF) of healthy people. The level of pNF-H in plasma and CSF increases in accordance with axonal breakdown [7, 22]. We previously reported that the levels of pNF-H in CSF become elevated in patients with acutely worsening compression myelopathy (AM) [24]. However, to our knowledge, there is no report that analyzes other biomarkers of neuronal damage or the degree of damage to another cells in the CNS such as astrocytes or Schwann cells. Increases in the CSF levels of various proteins occur in accordance with traumatic brain injury or acute spinal cord injury, and reflect the breakdown of various cells in the CNS. Tau is a component of axonal microtubules. Therefore, similar to increases of pNF-H levels, increases of tau levels in the plasma and CSF reflect axonal breakdown [9, 27]. Similarly, increases in the levels of myelin basic protein (MBP) reflect the breakdown of the myelin [27] produced by oligodendrocytes, and increases in S100b levels reflect astrocyte breakdown [8, 18]. Furthermore, increases in neuron-specific enolase (NSE) levels further reflect neuronal damage [11]. Therefore, we sought to determine the CSF levels of proteins that reflect damage to axons, myelin, astrocytes, and neurons in patients with worsening symptoms of cervical compression myelopathy to determine the relationship between the levels of these proteins and clinical outcome.

Methods

Patients and sample selection

The present study was performed to extend our previous study [24]. After approval by Toho University, human ethics committee and informed consent were obtained from all patients; we obtained CSF samples from patients at the time of myelography just before spinal surgery in Toho University Sakura Medical Center from January 2011 to March 2015. All consenting patients who were diagnosed as having cervical compression myelopathy were recommended the surgical treatment and included in this study. Cervical myelopathy was diagnosed from neurological findings, X-ray, and MRI imaging by two orthopaedic spine surgeons. We did not exclude patients because of the severity of their myelopathy. Exclusion criteria included: patients who did not wish to have surgical treatment and chose conservative treatment; patients who had an allergy to the iodinated contrast medium or renal failure complications, because we could not obtain the CSF samples or myelography before surgery; patients who did not undergo myelography for other reasons; patients who were diagnosed as having cervical spondylotic radiculopathy or cervical spondylotic amyotrophy; patients who were diagnosed with spinal cord tumor, infection, and trauma; and patients with a double lesion [cervical compression myelopathy and lumbar canal stenosis (LCS)]. We included 58 patients with cervical myelopathy in the present study and excluded 18 patients for the reasons mentioned above. After informed consent, the CSF samples from the first 37 consecutive patients who underwent surgery for LCS were obtained at the time of myelography as a control group consistent with our previous study [24]. We excluded 8 of the 37 samples, because the sample volume was insufficient for all of the assays. Ultimately, CSF samples from 69 patients were included in this study. The causes of disorder were cervical compression myelopathy in 40 patients and LCS, which was used as a control disorder, in 29 patients. We divided samples from patients with compression myelopathy into two groups: patients with acutely worsening symptoms (AM; 20 patients) and chronic symptoms (CM; 20 patients). We defined AM as that in which the Japanese Orthopaedic Association (JOA) score of patients with cervical myelopathy decreased by two points or more during a recent 1-month period [19]. All the patients were followed up for at least until 1 year after surgery.

Assay of proteins

The assays of pNF-H, Tau, MBP, and S100b were performed using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Human phosphorylated neurofilament H ELISA (BioVendor, Czech Republic) for the pNF-H assay, h-Tau kit (NIPRO, Japan) for the tau assay, myelin basic protein ELISA kit (Cosmic Corporation, Japan) for the MBP assay, and human S100B ELISA (BioVendor, Czech Republic) for the S100b assay were used. The NSE assay was performed using an electro-chemiluminescent immunoassay (ECLIA) kit (Roche Diagnostics, Switzerland). All assays were performed according to the protocols specified by the manufacturers. All samples were tested in duplicate and the average value for each sample was calculated.

Evaluation of the neurological improvement in patients with compression myelopathy

In all patients with compression myelopathy (those in the AM and CM groups), neurological evaluation using a JOA score for cervical myelopathy (cervical myelopathy scores range from 0 to 17) was determined by two orthopaedic spine surgeons [12]. The scores were determined at the time of myelography before surgery and 1 year after surgery. The relationships between the recovery of JOA scores and levels of each protein were evaluated.

Statistical analyses

Results are expressed as mean ± standard deviation (SD). A one factor ANOVA with a post hoc Tukey–Kramer test was used to evaluate differences in the level of each protein between patients with AM, CM, and LCS. A Mann–Whitney *U* test and Spearman's correlation coefficient by rank test were used to evaluate the JOA score and recovery of JOA score. $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS (ver. 21) Software (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

The characteristics of the three types of patients are shown in Table 1. There was no significant difference in the age of the patients between the three groups. There were significantly more women in the LCS group ($P < 0.05$). The JOA score in the group of patients with AM was significantly worse than that in the group of patients with CM ($P < 0.01$). The choice of surgical procedure, laminoplasty (LMP), posterior decompression and fusion (PDF), and anterior decompression and fusion (ADF) was not significantly different between patients with AM and CM.

The levels of proteins

The levels of each protein in the CSF of patients with AM, CM, and LCS are shown in Fig. 1. The levels of pNF-H were 1907.8 ± 730.4 (pg/ml) in the group of patients with AM, whereas the levels were 198.6 ± 124.5 in the group of patients with CM, and 462.9 ± 913.9 in the group of patients with LCS. Significantly higher levels of pNF-H were found in patients with AM than in patients with CM and LCS ($P < 0.01$). The levels of tau were 287.0 ± 161.8 (pg/ml) in the AM group, whereas they were 193.5 ± 81.6 in the CM group and 270.6 ± 105.7 in the LCS group. Significantly higher levels of tau were found in patients with AM than in patients with CM ($P < 0.05$). Levels of MBP were not significantly higher in patients with AM than in those with CM or LCS, expect for slightly higher levels found in CSF samples from two patients with AM (43.5 and 145.0). The levels of S100b were 192.7 ± 104.8 (pg/ml) in the CSF of patients with AM, 144.2 ± 53.0 in the CSF of patients with CM, and 156.3 ± 35.5 in the CSF of patients with LCS. The levels of S100b were not significantly different between the three groups. By contrast, the levels of NSE were 2.02 ± 0.68 (ng/ml) in the

Table 1 Patient characteristics in each group

	Number of cases	Gender (male/female)	Age (years)	JOA score before surgery	Surgical procedure		
					LMP	PDF	ADF
AM	20	11/9	65.4 ± 13.0 (28–86)	8.4 ± 2.9 (0.5–14)	9	5	6
CM	20	15/5	65.6 ± 11.8 (32–79)	11.2 ± 2.3 (7.5–15.5)	9	5	6
LCS	29	11/18	70.4 ± 7.3 (56–86)				
P				0.005			

Data are presented as mean ± standard deviation (range). JOA score before surgery is significantly lower in patients with AM than in patients with CM

AM acutely worsening compression myelopathy, *CM* chronic compression myelopathy, *LCS* lumbar canal stenosis, *JOA* Japanese Orthopaedic Association, *LMP* laminoplasty, *PDF* posterior decompression and fusion, *ADF* anterior decompression and fusion

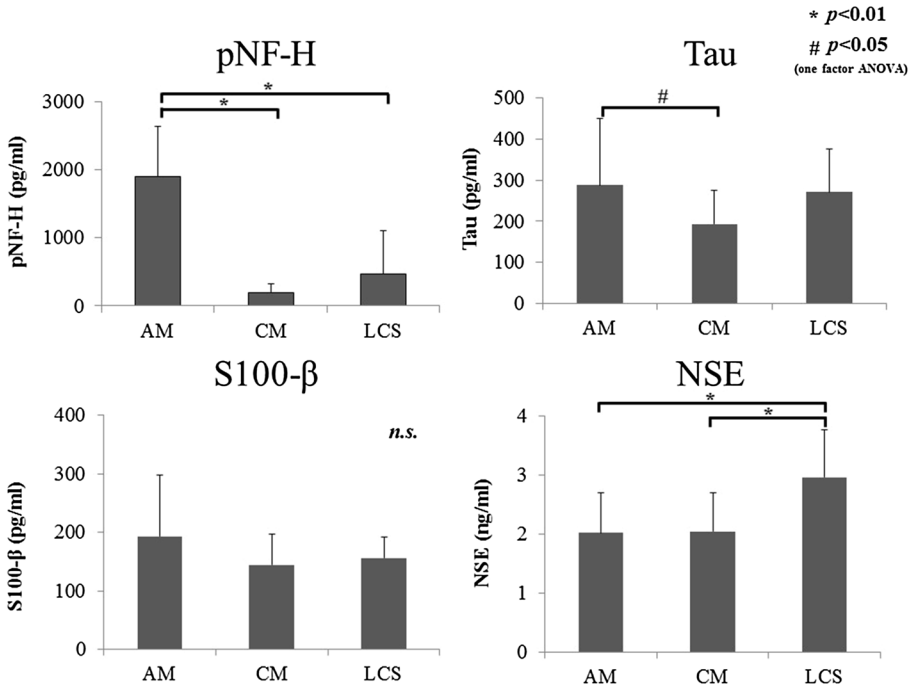

Fig. 1 Levels of proteins. *AM*: acutely worsening compression myelopathy, *CM* chronic compression myelopathy, *LCS* lumbar canal stenosis. $^{*}P < 0.01$, $^{\#}P < 0.05$ by one factor ANOVA

Table 2 Recovery of JOA score

	JOA score before surgery	JOA score 1 year after surgery	Recovery rate of JOA score
AM	8.4 ± 2.9 (0.5–14)	14.0 ± 2.4 (7–17)	68.3 ± 16.9 (46.2–100)
CM	11.2 ± 2.3 (7.5–15.5)	14.2 ± 1.5 (11–16.5)	50.8 ± 17.3 (30–66.7)
P value	0.005	0.848	0.003

Data are presented as mean ± standard deviation (range)

AM acutely worsening compression myelopathy, *CM* chronic compression myelopathy, *LCS* lumbar canal stenosis, *JOA* Japanese Orthopaedic Association

CSF of patients with AM and 2.04 ± 0.66 in patients with CM, whereas they were 2.97 ± 0.81 in patients with LCS. Levels of NSE in the CSF of patients with AM and CM were significantly lower than those in patients with LCS ($P < 0.05$).

Neurological recovery and the levels of proteins

The changes of JOA scores and recovery after surgery are shown in Table 2. The JOA scores before surgery were significantly lower in patients with AM than they were in patients with CM ($P < 0.01$). Although sufficient neurological improvement was obtained in both groups, the recovery of JOA score (%) was significantly higher in patients with AM than in patients with CM ($P < 0.01$). We found a positive correlation between pNF-H levels and the recovery of JOA score after surgery (Fig. 2). There was no significant correlation between other protein levels and the recovery of JOA score after surgery.

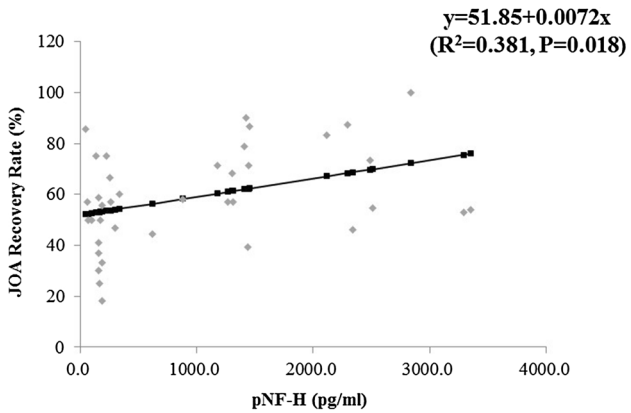

Fig. 2 Correlation of pNF-H level and JOA recovery rate

Discussion

We previously showed that levels of pNF-H that reflect axonal damage are elevated in the CSF of patients with

AM [24]. To our knowledge, the present study is the first to determine the levels of proteins that reflect damage to various structures in the spinal cord including axons (pNF-H, Tau), Schwann cells (MBP), astrocytes (S100b), and neurons (NSE) in compression myelopathy. Nevertheless, other studies have reported the levels of inflammatory cytokines in the CSF, such as IL-6, IL-8, and TNF-α [14]. However, there are several reports about protein levels in the CSF of patients with traumatic brain injury or acute spinal cord injury. The levels of breakdown proteins from axons, myelin, astrocytes, and neurons in patients with traumatic brain injury [11, 18, 23] or acute spinal cord injury [1, 4, 6, 17] were about the same. By contrast, we found only increased levels of pNF-H and tau in the CSF of patients with AM. The level of tau is increased in musculoskeletal disorders, and the levels of tau were not as different as levels of pNF-H in the disorders which we examined. Our findings suggest that axonal damage is remarkable in AM. Lower levels of NSE were found in the CSF of patients with AM and CM than the levels found in patients with LCS. By contrast, it is well known that the level of NSE increases by neuronal damage [11]. Importantly, the NSE level was shown to increase significantly in acute spinal cord injury, which reflects the severity of damage to the neuronal cell body [27]. However, the level of NSE in healthy subjects ranges widely from 2.2 to 16 (ng/ml) that indicates that the levels of NSE in the CSF of patients with AM and CM were nearly the same as those in healthy subjects [5, 15, 25]. In any case, the levels of NSE did not increase in AM and CM compared with healthy control different from acute spinal cord injury, which indicates that the damage to the neuronal cell body was not severe despite the remarkable axonal damage in AM. The NSE decrease in cases of compression myelopathy is difficult to explain; however, we hypothesize that the mechanism involves a decrease in the numbers of functional neuronal cell bodies because of chronic spinal cord compression. Nevertheless, the present results suggest the possibility that the pathogenesis of compression myelopathy is distinct from the secondary injury to the spinal cord found in acute spinal cord injury.

In our previous study of pNF-H levels in CSF, we found no significant difference in the recovery rate of JOA score between AM and CM and no significant correlation between the protein level and JOA score recovery after surgery using Spearman's correlation coefficient by rank test because of the small sample size resulting in insufficient power [24]. However, in the present study, the neurological improvement in patients with AM in which the pNF-H value is significantly higher is better than that in patients with CM; and we found a positive correlation between pNF-H levels in the CSF and the recovery of JOA score after surgery, because the larger sample size used provided adequate power. In acute traumatic injury or subarachnoid hemorrhage, higher pNF-H levels reflect poorer functional recovery [2, 22]. However, for compression myelopathy, we found the opposite. This paradoxical finding means that the pathogenesis of compression myelopathy, in which there is chronic compression to the spinal cord, is different to that of traumatic brain injury or acute spinal cord injury, at least in part. The recent report has indicated that delayed decompression exacerbates ischemia–reperfusion injury that result in the better neurological improvement in AM [26]. However, the detail changes of axonal environment are unclear. In general, a direct external force to the brain or spinal cord, as the primary injury, may be reflected by an increase of pNF-H levels and functional recovery in such cases of trauma. This increase is confirmed by observations that peak pNF-H levels found after the onset of traumatic brain injury are at about 24–48 h and the level slowly decreases to baseline over several days [2]. By contrast, in compression myelopathy, there is chronic compression of the spinal cord. This continuous compression probably accounts for the continuous increase of pNF-H. Considering our findings, although we did not follow the time course of pNF-H levels in compression myelopathy, we speculate that the level of pNF-H may increase in the acute phase (AM) and slowly decrease with change to the chronic phase (CM) and that damage to the spinal cord is cumulative. This may result in the good neurological improvement early after surgical treatment in AM when the pNF-H level is significantly high, indicating that axonal compensatory plasticity is preserved in cases of acutely worsening symptoms of compression myelopathy. A clinical study indicated that neuroprotective treatment was effective for acute worsening symptoms of compression myelopathy [19]. In the present study, the neurological improvement in patients with AM was better than that in patients with CM. Furthermore, we found that the higher the level of pNF-H in the CSF, the better the neurological improvement after surgery. The major pathogenesis of better surgical outcome in AM is the ischemia–reperfusion phenomenon [26]. In addition to this phenomenon, our results suggest the possibility that compensatory plasticity is preserved in the axons of AM phase with a higher pNF-H level; and pNF-H may act as a biomarker to predict the outcome of surgical treatment for compression myelopathy. Further investigation is needed to clarify the detailed pathogenesis and mechanism of the pNF-H increase.

The present study has several limitations. First, there are biases in the degree of severity and surgical procedure. We found that, before surgery, the JOA scores in patients with AM were significantly lower than those in patients with CM. However, usually, the worse the neurological symptom becomes, the lower the recovery of JOA score in patients with compression myelopathy. Therefore, we consider that our findings of neurological improvement do not

produce a bias. Although the surgical procedures to treat compression myelopathy are not standardized, LMP is not recommended for K-line (–) cervical OPLL, and ADF or PDF is recommended [10]. In our procedure, only ADF or PDF was chosen for patients with K-line (–) OPLL and adequate procedures were chosen for all patients. Second, the definition of AM and CM is subjective, because the distinction is only due to the neurological finding. Especially, CM includes both the sub-acute phase and real chronic phase in this definition. That is the reason that we analyzed pNF-H and recovery rate of JOA score in a total of myelopathy patients (AM and CM). In all patients of AM, surgical treatment was performed at the adequate timing. Thus, the recovery rate of JOA score was sufficient in all cases, and no significant correlation between the recovery rate of JOA score and the pNF-H value was observed in the analysis of AM patients. However, the present result of a positive correlation between pNF-H and the recovery rate of JOA score in a total of myelopathy patients (AM and CM that include sub-acute phase) may suggest that the pNF-H level can distinguish the acute and chronic phases, and an objective distinction of AM and CM may become possible. Third, this study lacks assessments using MRI. Plain MRI was performed in almost all cases. However, we found no differences between patients with AM or CM in high T2-signal changes in compressed spinal cords. Diffusion basis spectrum imaging (DBSI), which quantifies axonal loss, shows a strong correlation with neurological outcome [13]. Although DBSI was not performed in the present study, our CSF findings also showed remarkable axonal damage. Furthermore, the high levels of pNF-H in the CSF found correlated with neurological outcome in the present study support the previous imaging-associated outcomes. Fourth, we lack CSF data from healthy controls because of ethical considerations. Based on the previous study, we set the LCS group as the control [24]. The CSF levels of pNF-H were high in patients with LCS [16]. However, the levels of pNF-H in CSF from patients with AM were significantly higher than those in patients with CM or LCS. The levels of S100b and NSE in the CSF of our patients were almost the same as those found in healthy controls [5, 15, 25]. This similarity suggests that the axonal damage is remarkable, and that damage to astrocytes, oligodendrocytes, and neurons is not severe in AM. However, the detailed pathogenesis of compression myelopathy remains unclear. Further studies using rodent models of disease and clinical investigations are required to clarify the pathogenesis. Fifth, the sample size is small and we lack data regarding the change in the CSF levels of proteins over time. In addition, we lack data from patients who chose conservative treatment. For ethical reasons, CSF samples could only be obtained at just one time before myelography in patients who chose the surgical treatment. In the present study, the clinical outcome in conservative treatment for compression myelopathy was excluded. Surgical treatment is recommended to treat compression myelopathy [28]. Furthermore, although CSF usefully contains diagnostic biomarkers, CSF is unsuited for evaluating changes over time because of ethical limitations. Our findings indicate that CSF levels of pNF-H are high in AM. Further investigation using larger sample size would provide greater statistical power. In addition, further investigation of levels in plasma may be useful to evaluate cases of conservative treatment and changes in the levels over time, because the sample can be collected more easily than CSF.

In conclusion, high levels of pNF-H and tau in the CSF suggest that axonal damage is remarkable in AM. The better clinical outcome in AM and a positive correlation between the pNF-H levels and neurological outcome suggest the possibility that axonal compensatory plasticity is preserved in AM. Although pNF-H may act as a biomarker that predicts neurological recovery after surgical treatment, further investigation will be needed to determine its utility.

Acknowledgements This study was supported in part by JSPS KAKENHI Grant Number 25861346.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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Affiliations

Hiroshi Takahashi[1] · Yasuchika Aoki[2] · Arata Nakajima[1] · Masato Sonobe[1] · Fumiaki Terajima[1] · Masahiko Saito[1] · Takuya Miyamoto[1] · Keita Koyama[1] · Keiichiro Yamamoto[1] · Takeo Furuya[3] · Masao Koda[3] · Seiji Ohtori[3] · Masashi Yamazaki[4] · Koichi Nakagawa[1]

✉ Hiroshi Takahashi
hirochann@syd.odn.ne.jp

[1] Department of Orthopaedic Surgery, Toho University Sakura Medical Center, 564-1, Shimoshizu, Sakura, Chiba 285-8741, Japan

[2] Department of Orthopaedic Surgery, Chiba Eastern Medical Center, Togane, Japan

[3] Department of Orthopaedic Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

[4] Department of Orthopaedic Surgery, University of Tsukuba, Tsukuba, Japan