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ORIGINAL ARTICLE

Presymptomatic spondylotic cervical myelopathy: an updated predictive model

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Abstract Spondylotic cervical cord compression detected by imaging methods is a prerequisite for the clinical diagnosis of spondylotic cervical myelopathy (SCM). Little is known about the spontaneous course and prognosis of clinically "silent" presymptomatic spondylotic cervical cord compression (P-SCCC). The aim of the present study was to update a previously published model predictive for the development of clinically symptomatic SCM, and to assess the early and late risks of this event in a larger cohort of P-SCCC subjects. A group of 199 patients (94 women, 105 men, median age 51 years) with magnetic resonance signs of spondylotic cervical cord compression, but without clear clinical signs of myelopathy, was followed prospectively for at least 2 years (range 2–12 years). Various demographic, clinical, imaging, and electrophysiological parameters were correlated with the time for the development of symptomatic SCM. Clinical evidence of the first signs and symptoms of SCM within the follow-up period was found in 45 patients (22.6%). The 25th percentile time to clinically manifested myelopathy was 48.4 months, and symptomatic SCM developed within 12 months in 16 patients (35.5%). The presence of symptomatic cervical radiculopathy and electrophysiological abnormalities of cervical cord dysfunction detected by somatosensory or motor-evoked potentials were associated with time-to-SCM development and early development ($\leq$12 months) of SCM, while MRI hyperintensity predicted later (>12 months) progression to symptomatic SCM. The multivariate predictive model based on these variables correctly predicted early progression into SCM in 81.4% of the cases. In conclusion, electrophysiological abnormalities of cervical cord dysfunction together with clinical signs of cervical radiculopathy and MRI hyperintensity are useful predictors of early progression into symptomatic SCM in patients with P-SCCC. Electrophysiological evaluation of cervical cord dysfunction in patients with cervical radiculopathy or back pain is valuable. Meticulous follow-up is justified in high-risk P-SCCC cases.

Keywords Spondylotic cervical cord compression · Evoked potentials · Electromyography · Cervical spondylotic myelopathy

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Introduction

Spondylotic cervical cord compression detected by imaging methods, mostly magnetic resonance imaging (MRI), is a prerequisite for the clinical diagnosis of spondylotic cervical myelopathy (SCM). Previous studies have demonstrated the existence of asymptomatic spinal cord compression detected with MRI [6, 20, 28]. Little is known about the spontaneous course and prognosis of this clinically "silent" presymptomatic spondylotic cervical cord

compression (P-SCCC), and whether progression into symptomatic myelopathy may be predicted. Hypothetically, subclinical functional or structural cervical spinal cord changes detected by electrophysiological or imaging methods, as well as demographic characteristics or type of compression, could serve as potential predictors of an unfavorable course. In a small pilot study, we have previously shown that the presence of these clinically silent changes, detected by both somatosensory-evoked potentials (SEP) and motor-evoked potentials (MEP), could predict the development of clinically symptomatic SCM [2]. In a cohort study of 66 P-SCCC cases, we proposed a predictive model of progression into symptomatic myelopathy based on electrophysiological parameters and the presence of clinically symptomatic radiculopathy [1]. Surprisingly, the imaging parameters, such as increased signal intensities (ISI), decreased cross-sectional spinal cord area (CSA) or Pavlov ratio (PR), were not found to be useful [1, 7, 8, 16, 19, 21–23, 27, 29, 31]. However, some of these papers concluded that some of the imaging parameters could be a predictor of the outcome of surgical or conservative treatment. Moreover, the timing of the progression is yet to be addressed.

The aim of the present study was to confirm and elaborate a predictive model for the development of clinically symptomatic SCM and to assess independently the early and later risks of this event in a larger cohort of P-SCCC subjects followed over a longer time period.

Groups and methods

The study sample consisted of a cohort of 199 subjects (94 women and 105 men; median age 51 years, range 28–82 years) recruited consecutively from patients admitted to the Department of Neurology between January 1993 and 2005 and followed up to July 2007, who completed at least a 2-year follow-up. MRI examination of the cervical spine and spinal cord was performed in all patients with clinical signs and symptoms of cervical radiculopathy or moderate to severe chronic or intermittent axial cervical pain. The main inclusion criteria were:

- MR signs of spondylogenic or discogenic compression of the cervical spinal cord with or without concomitant change in signal intensity from the cervical cord on T2/T1 images (Figs. 1a, b, 2a,b) (see "Imaging");
- axial pain or clinical signs and/or symptoms of radiculopathy that could be controlled by conservative treatment;
- absence of any current clinical signs and symptoms that could be possibly attributed to cervical cord involvement.

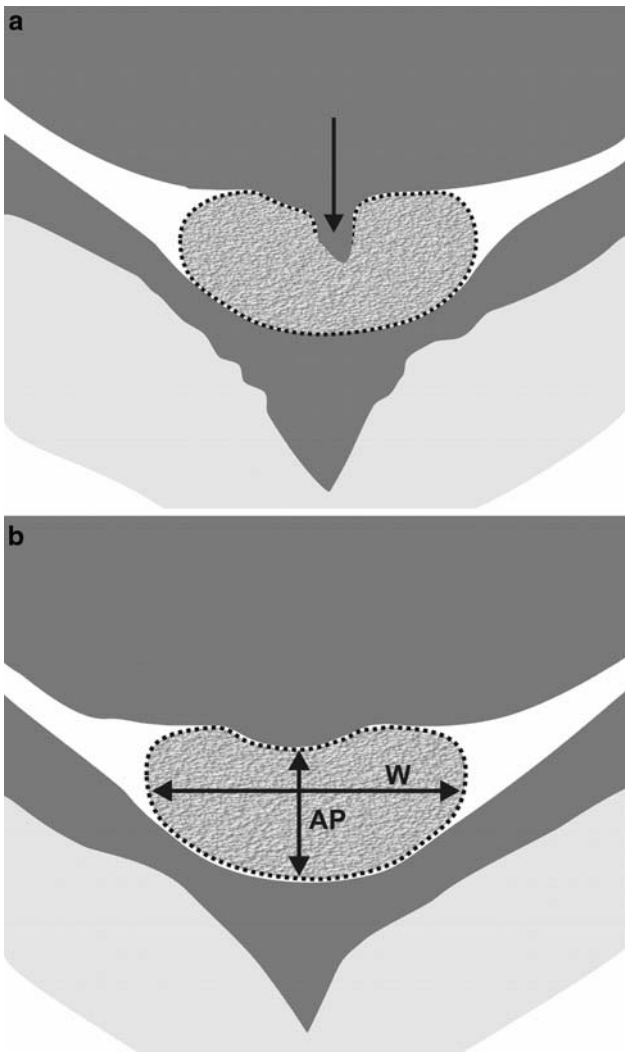

Fig. 1 **a** The scheme of the impingement on the cervical cord (i.e., a concave defect in the spinal cord adjacent to the site of disc bulging or osteophyte). **b** The scheme of the measurement of the compression ratio calculated by division of the smallest anteroposterior diameter of the cervical cord (*AP*) by the broadest transverse diameter at the same level (*W*) as AP/W

Clinical evaluation

A detailed clinical examination was carried out at the beginning of the study, every 6 months for the first 2 years and then annually. Patients were instructed about possible signs and symptoms of newly developed SCM and encouraged to arrange a consultation with a neurologist from our study group whenever they suspected a progression to myelopathy. The minimum follow-up period was 24 months (median 44 months; range 2–12 years). The functional status of the patients was scored with the modified Japanese Orthopaedic Association scale (mJOA; range 3–18 points) [3] and with Nurick's score. At entry, 141

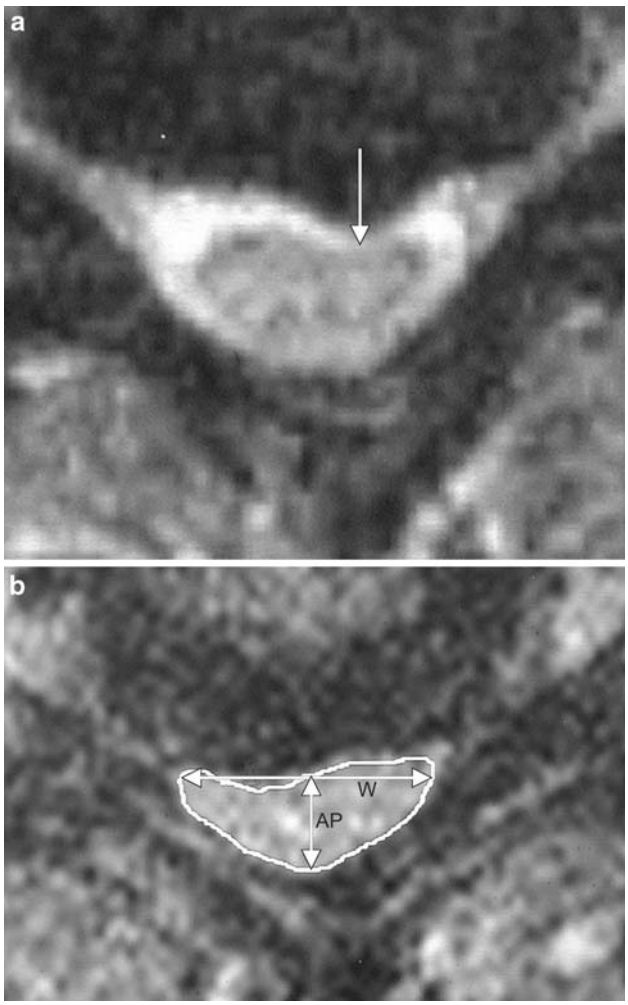

Fig. 2 **a** Axial T2-weighted magnetic resonance image at the C4–C5 level demonstrates ventral impingement (*arrow*) of the spinal cord in the midline as a result of a C4 osteophyte. **b** Axial T2-weighted magnetic resonance image at the C4–C5 level shows ventral compression of the spinal cord with a *banana-like shape* caused by disc herniation and adjacent osteophytes. The compression ratio was 0.37; the cross-sectional area was 71 mm^2

patients had a maximum mJOA score of 18 points; 58 of them had a decreased mJOA score (from 16 to 17) resulting from motor and/or sensory signs of cervical radiculopathy.

The time taken for a standard 10-m walk (as quickly as possible) was evaluated. Clinical symptoms and/or signs were classified as radicular if they fulfilled the following criteria:

- Typical sensory radicular symptoms (pain or paresthesias) always present.
- Motor (weakness and atrophy), sensory (hypoesthesia or dysesthesia), and reflex (diminution or absence of tendon reflexes) symptoms, if present, confined to one dermatome or myotome that corresponded with the pain or paresthesias.
- Clinical symptoms and signs correlated with the level of root compression as a result of disc herniation or spondylotic lateral stenosis.

The primary end point of the study was the detection of clinical signs and symptoms of compressive cervical myelopathy. Signs and symptoms that appeared at any regular or auxiliary examination had to have no other topical or etiological explanation, i.e., they could unequivocally be attributed to cervical cord dysfunction and had no other compressive etiology. The cases with signs and symptoms that could optionally be attributed to isolated radiculopathy or brain involvement, as well as those with spinal cord dysfunction of the other origin (especially multiple sclerosis), did not meet the end point. MRI of the brain and all the other tests (cerebrospinal fluid, autoantibodies, and so on) were performed when necessary.

Imaging

In all patients, plain anteroposterior, oblique, and lateral radiograms were obtained. The Pavlov ratio at C5 level was calculated from lateral radiograms as the anteroposterior diameter of the spinal canal (measured as the shortest distance between the posterior vertebral wall and the lamina) divided by the anteroposterior diameter of the vertebral body (measured as the shortest horizontal distance passing through its center). Saggital MRI T1 turbo spin echo (TSE) and T2 proton density and TSE-weighted images and axial T2 gradient-echo (GE) images of the cervical spine and the spinal cord were performed for all patients on a Siemens Magnetom Impact 1.0 T system (Siemens AG, Munich, Germany) with a dedicated neck coil [1]. To quantify the stenosis, the cross-sectional area (CSA) of the spinal cord and of the osseous spinal canal (CSAo), and the central compression ratio (CR) were measured from selected GE T2W scans at the level of maximum spinal cord compression [1]. The CSA and CSAo were calculated on the Sun Blade 2000 operating system using Sienet Magic View 1000 software, VE42, Release A (Siemens, Germany). The compression ratio was calculated by division of the smallest anteroposterior diameter of the cervical cord (AP) by the broadest transverse diameter at the same level (W) as AP/W [1]. Spinal cord intensity changes were evaluated, namely the relative increase in signal on T2-weighted sequences and/or decrease in signal on T1-weighted images. The changes were graded according to the system described by Mehalic (range 0–4) [22]. Most of the stenotic levels were visualized by plain computed tomography (CT) scans for the better demonstration of osseous compression. The type of cervical spinal cord compression (herniation, osteophytes or both) and the number of levels with compression were evaluated. All imaging examinations and their evaluation

were performed at the beginning of the study. MRI signs of cervical cord compression were defined as: impingement on the cervical cord (i.e., a concave defect in the spinal cord adjacent to the site of disc bulging or osteophyte; Figs. 1a, 2a [1]) and/or compression of the cervical cord (compression ratio of less than 0.4; Figs. 1b, 2b). Details of the imaging methodology were given in the previous publication [1].

Electrophysiological evaluation

Short-latency SEP from the median (SEP MED) and the tibial nerves (SEP TIB) were elicited at the beginning of the study with electrical stimulation of mixed nerves at the wrist and the ankle and recorded using a Nicolet 4-channel Viking IV unit (Nicolet Biomedical Instruments, Madison, WI, USA). During SEP MED, the brachial plexus N9 response (from the ipsilateral Erb point to the reference electrode at F_z), the segmental dorsal horn medullar N13 response (from the spinous process C VI to an anterior cervical (AC) electrode above the thyroid cartilage), the medial lemniscus P14 response (from the ipsilateral parietal C3/4′-Par_i: 2 cm posterior to the vertex and 7 cm laterally to noncephalic reference at the contralateral Erb point) and cortical parietal response N 20 (from the contralateral parietal C3/4′-Par_c to the ipsilateral parietal C3/4′-Par_i) were recorded. During SEP TIB, the lumbar medullar N 22 response (from the spinous process LI to the reference over the contralateral iliac crest), and the cortical P 40 response (from Cz′ 2 cm behind the vertex to the cephalic reference at Fp_z) were recorded. The absolute peak latencies and peak-to-peak amplitudes of all responses were measured and interpeak latencies between N13, N20 and N22 P40 as "central sensory conduction times" were calculated for each side independently.

Central conduction abnormality attributed to possible cervical spinal cord lesion was defined as follows:

- SEP MED: absent N13, P14, and/or N20 waves; and/or abnormal N13, N20 interpeak latency; and/or abnormal P9/N13 amplitude ratio; and/or abnormal R–L amplitude ratio of N20 wave, all with normal N9 wave.
- SEP TIB: absent P40 wave; and/or abnormal N22-P40 interpeak latency; and/or abnormal R–L amplitude ratio of P40 wave, all with normal N22.

Motor-evoked potentials (MEPs) were elicited using a Magstim 200 magnetic stimulator (Magstim Company Ltd., Spring Gardens, UK) and a circular 90-mm (type 9784) stimulating coil with a peak magnetic field strength of 2.0 T. Online data acquisition was performed using a Dantec Keypoint electromyograph (Dantec, Skovlunde, Denmark). MEPs were elicited by means of transcranial and root magnetic stimulation and recorded from abductor digiti minimi (UMEP) and abductor hallucis muscles (LMEP) on both sides with surface electrodes placed on the belly and tendon of the muscles.

The shortest latencies of motor responses with brain stimulation [central latency (CL)] and root stimulation [root latency (RL)] and peak-to-peak amplitudes of the largest MEP after cortical stimulation were measured. The difference between CL and RL was defined as central motor conduction time (CMCT). To establish the contribution of the lower motor neuron to the absolute amplitude of MEP, the MEP/CMAP ratio was also calculated. Central conduction abnormality attributed to possible cervical spinal cord lesion was defined as abnormal CMCT and/or abnormal MEP/CMAP ratio.

EMG examination was performed using a Dantec Keypoint electrodiagnostic unit. Motor and sensory conduction studies were performed on six motor nerves (median, ulnar, and tibial nerves bilaterally) and four sensory (ulnar and sural nerves bilaterally) using conventional techniques. Normal limits from the authors' neurophysiological laboratory were used in the assessment. Needle EMG from four muscles (deltoid, biceps brachii, triceps brachii, and first dorsal interosseous) bilaterally was performed with assessment of spontaneous activity, motor unit potential (MUP) parameters, and interference patterns. If necessary, additional muscles were examined for the exact evaluation of the myotome involved. Electromyographic signs of acute motor axonal neuropathy in one myotome (C5–Th1) corresponding with radicular signs and symptoms were classified as radicular. Electromyographic signs of acute, subacute, or chronic motor axonal neuropathy confined to more than one myotome (C5–Th1) unilaterally or bilaterally were classified as signs of anterior horn cell lesion resulting from spondylotic cervical myelopathy. More details on the methodology of electrophysiological examination have been given in a previous publication [1].

The imaging and electrophysiological measurements were performed in a blinded fashion and clinical characteristics of the subjects were not known to the evaluating investigator.

The following variables were recorded at the entry examination and their association with the predefined endpoints (i.e., development of clinically symptomatic SCM and time for this development) were analyzed:

Demographic and clinical data

- Age
- Gender
- Presence of clinical symptoms and signs of cervical radiculopathy (with corresponding CT and/or MR

findings and, in the case of motor deficit with corresponding EMG findings, of motor axonal neuropathy in one myotome)
- mJOA score
- Nurick's score
- 10-m timed walk.

Electrophysiological data

- Abnormal SEP interpreted as either segmental dorsal horn or dorsal column lesion
- Abnormal MEP interpreted as lesion of corticospinal tract
- Abnormal EMG signs of plurisegmental anterior horn cell lesion in cervical lesion.

Imaging data

- Pavlov canal/body ratio $\leq$0.8, indicating congenital stenosis of the cervical spinal canal
- Compression ratio $\leq$0.4 as a sign of spondylogenic or discogenic compression of the cervical spinal cord
- Cross-sectional cervical spinal cord area $\leq$70 mm^2 as a sign of cervical spinal cord atrophy
- Cross-sectional cervical osseous spinal canal area at the level of maximum spinal cord compression <140 mm^2
- Cervical cord MR intensity changes
- Type of every cervical spinal cord compression (classified as herniation, osteophytes, or mixed pattern)
- Number of stenotic levels.

During regular or supplementary visits, the development of clinical signs and/or symptoms of clinically symptomatic SCM (as a primary end point) corresponding with a decrease in the mJOA scale of at least 1 point was sought and registered, and surgical treatment for either cervical radiculopathy that could not be controlled conservatively, or for progressing symptomatic myelopathy, was recorded. To assess the intra/interobserver variability of CSA/CR values, two independent evaluations of 20 randomly selected skin samples were performed blindly by one observer (MK; intraobserver variability) and by two observers (MK and AŠ; interobserver variability), and the reproducibility was evaluated according to the standard methodology proposed by Bland and Altman [4, 5], which is based on the standard deviation of the differences between pairs of repeated measurements (SD_{diff}). The test–retest reproducibility assessed by this method was expressed as confidence limits of differences calculated from SD_{diff} (coefficient of repeatability). The Bland–Altman plot was used to assess a relationship between the differences, to look for systematic bias and to identify possible outliers. Additionally, a standard ANOVA was employed to assess the proportion of total variability of the CSA/CR related to the differences between repeated measurements.

Standard univariate statistical techniques were used to test differences between the chosen subgroups of patients or association between examined parameters: Fisher's exact test in binary outcomes, ML Chi-square test for ordinal categorical variables and Mann–Whitney U test for continuous variables. Based on the Bonferroni correction for multiple testing, the value $\alpha < 0.01$ was taken as the universal limit for significance for any individual statistical test.

Standard Kaplan–Meier product-limit estimate was used to describe the profile of time to clinical manifestation of SCM. The log-rank test was applied to compare Kaplan–Meier curves in stratified survival analysis.

In addition to primary end-point (development of clinically symptomatic SCM), both univariate and multivariate analytical strategies were applied to quantify the predictive power of the variables examined with reference to secondary predefined study end points: a time to clinical manifestation of SCM as a "time-to-event" end point, and probability of early manifestation of myelopathy ($\leq$12 months) as an attempt at an early warning model for a binary coded variable.

Univariate Cox proportional hazard regression (for time-to-myelopathy manifestation) and univariate logistic regression (for binary coded risk of early myelopathy) were employed for each potential risk factor. The relative risk ratio with 95% confidence limits was estimated and tested in the Wald χ^2 test. Parameters with sufficient discrimination power ($P < 0.10$) were then examined for mutual correlation, and interaction terms were coded for significantly correlated pairs of variables. The final set of potential prognostic factors and interaction terms (all in binary code) was subjected to backward stepwise selection algorithm in multivariate Cox proportional regression or in multivariate logistic regression. The potential contribution of predictors to the most stable and significant model was examined and the models achieved were compared with maximum likelihood ratio test. The finally selected model was verified with a calibration data set and quantitative residual analysis was performed.

Results

Intra/interobserver variability of selected MRI parameters

Both applied methods (i.e., standard deviation of pair-wise differences of repeated measurements and analysis of variance) confirmed a sufficient level of reproducibility of both CSA/CR values. The 95% confidence limits for differences

between pairs of measurement (calculated from SD_{diff}) varied intraindividually in the range ± 3.14 mm^2 for CSA and ± 0.015 unit for CR (it means ± 3.9–4.9% of mean of primary values). Similarly, the 95% confidence limits for differences between interindividual pairs of measurement varied in the range ± 4.41 mm^2 for CSA and ± 0.017 unit for CR (± 5.4–5.8% of mean of primary values).

Using one-way ANOVA model, the difference between repeated measurements were thoroughly not significant ($P = 0.967$ for CSA and $P = 0.935$ for CR). The intra-observer differences represented up to 0.03% of the total model sum of squares, and repeated interobserver measurements exhausted up to 0.4% of the total model sum of squares, which again documents a good reproducibility of both the parameters tested (data not shown).

Clinical course

Clinical evidence of the first signs and symptoms of SCM and a decrease in the mJOA scale of at least 1 point within the follow-up period were found in 45 patients (22.6%): the SCM+ subgroup.

Among the first signs and symptoms of SCM were:

- gait disturbance;
- clumsy hand syndrome;
- Lhermitte's sign;
- spastic paresis of any of the extremities (most frequently lower spastic paraparesis);
- flaccid paresis of one or two upper extremities in the plurisegmental distribution;
- sensory involvement in various distributions (always plurisegmental).

In 16 patients (35.5% of the SCM+ subgroup), symptomatic SCM developed within 12 months of entry into the study (early SCM+ subgroup). The 25th percentile time to clinically manifested myelopathy was 48.4 months, i.e., 25% of all P-SCCC cases progressed to symptomatic SCM within this space of time.

A total of 16 patients from this SCM+ subgroup (35.5%) with progressing myelopathic signs and symptoms were operated upon (using various surgical decompression and fusion techniques). Two other patients refused surgical treatment. In the remaining patients, slight neurological deficits were stable or improved during the follow-up period and patients were treated conservatively.

Association between variables concerned (risk factors) and the development of symptomatic SCM

The data for the selected variables and the association between the variables followed and the development of symptomatic SCM are summarized in Table 1 and expressed as relative frequencies. We found a significantly increased occurrence of radiculopathy ($P < 0.001$), EMG signs of anterior horn cell lesion ($P < 0.001$), SEP abnormality ($P < 0.001$), MEP abnormality ($P < 0.001$), MRI hyperintensity ($P = 0.049$), and a tendency to increased risk of SCM in the male gender near to statistical significance ($P = 0.072$). All the other parameters were not recognized as associated with SCM development.

Association between risk factors and time-to-SCM or early (≤12 months) SCM development

The association between the variables under consideration and time-to-SCM development or early (≤12 months) SCM development was calculated independently and expressed in Table 2 (as the 25th percentile time to clinically symptomatic myelopathy, relative risk and 95% confidence limits) and Table 3 (as relative frequencies and odds ratios with 95% confidence limits).

In the time-to-event model, the radiculopathy and electrophysiological parameters (SEP, MEP, EMG) showed a highly significant association with time progression to symptomatic myelopathy, and a trend toward shorter time in males and MRI hyperintensity (Table 2). The same parameters (i.e., radiculopathy, SEP, MEP, and EMG also showed significant association with early development of SCM; Table 3).

All parameters with sufficient discrimination power ($P < 0.10$) were then examined for mutual relationship with the results that follow in Table 4. Male gender and EMG abnormality were excluded from the set of independent risk factors as a result of a highly significant positive correlation with radiculopathy ($P < 0.001$).

Entering all the potentially significant predictors and their interaction terms into the stepwise multivariate Cox proportional regression model revealed that radiculopathy, SEP, and MEP contributed independently to the time to myelopathy and constituted a very significant prediction model for this end point (Table 5a). Similarly, the multivariate logistic regression model also succeeded in terms of an early risk model and showed that, as in Cox regression, radiculopathy, SEP, and MEP significantly contributed to an increased risk of early-manifested myelopathy. However, in addition to these predictors, this model also recognized the influence of MRI hyperintensity as significant, but in the opposite sense. MRI hyperintensity decreased the risk of early manifestation of myelopathy, as it is highly associated with patients with later (>12 months) manifestation (Table 5b). The model reached overall correct classification in 81.4% of cases and only 37 out of 199 cases were misclassified (Table 6). The progression into

Table 1 Initial characteristics in relation to the development of clinically symptomatic SCM

Variables	P-SCCC studied group ($n = 199$): summary data	Positivity (in %)		
		SCM− subgroup ($n = 154$)	SCM+ subgroup ($n = 45$)	*P* value
Age >50 years	$N = 100$ (50.3%)	49.4	53.3	0.808
Sex (male)	$N = 105$ (52.8%)	49.4	64.4	0.072
Type of compression				
Osteophytes	$N = 67$ (33.7%)	33.1	35.6	0.199
Herniation	$N = 50$ (25.1%)	27.9	15.6	
Herniation + osteophytes	$N = 82$ (41.2%)	39.0	48.8	
No. stenotic levels				
1	$N = 105$ (52.%)	53.3	51.1	0.302
2	$N = 64$ (32.2%)	33.8	26.7	
≥3	$N = 30$ (15.0%)	12.9	22.2	
Lowered PR[a]	$N = 66$ (33.2%)	34.4	28.9	0.485
Lowered CR[b]	$N = 47$ (24.7%)	22.3	33.3	0.153
Lowered CSA[c]	$N = 79$ (39.7%)	39.6	40.0	0.962
MRI hyperintensity	$N = 49$ (24.6%)	21.4	35.6	0.049
Clinically symptomatic radiculopathy	$N = 58$ (29.1%)	20.1	60.0	<0.001
Abnormal EMG[d]	$N = 46$ (23.1%)	17.5	42.2	<0.001
Abnormal MEP	$N = 37$ (18.6%)	12.4	40.0	<0.001
Abnormal SEP	$N = 37$ (18.6%)	12.9	37.8	<0.001

P-SCCC Presymptomatic spondylotic cervical cord compression, *SCM* spondylotic cervical myelopathy, *PR* Pavlov ratio, *CR* compression ratio, *CSA* cross-sectional spinal cord area, *MRI* magnetic resonance imaging, *SEP* median and tibial nerve somatosensory evoked potentials

[a] Pavlov ratio <0.8

[b] Compression ratio <0.4

[c] Cross-sectional spinal cord area <70 m^2

[d] Motor axonal neuropathy in at least two myotomes

early SCM could be correctly predicted in 12 of the 16 patients who developed clinical signs and/or symptoms of early (≤12 months) clinically symptomatic SCM.

Discussion

This long-term study of the natural course of presymptomatic MRI-detected spondylotic cervical cord compression confirmed and elaborated the previously identified and reported list of variables predicting development of clinically symptomatic SCM. One-quarter of presymptomatic compression cases progressed into symptomatic myelopathy within 4 years. Risk of early progression into symptomatic myelopathy (≤12 months), found in 8% of cases, was predicted by the presence of clinically symptomatic radiculopathy, and abnormal SEP and MEP, while MRI hyperintensity predicted the later (>12 months) development of SCM.

In this long-term study of an adequately extensive cohort of 199 P-SCCC cases, we confirmed the presumed value of both SEP and MEP in predicting progression into symptomatic myelopathy based on a previous short-term pilot study [2] and subsequent cohort study [1], with only minor modifications: MEP abnormalities, in addition to SEP, also reached statistical significance (only a trend toward statistical significance appeared in the previous study, $P = 0.112$). Recently, MEP has been shown to correlate closely with the degree of MRI-detected spondylotic cervical cord compression in patients with clinical diagnosis of possible cervical myelopathy [17]. In contrast, EMG abnormalities interpreted as anterior horn cell lesion signs became closely correlated with the presence of symptomatic radiculopathy and were excluded from the final prediction model as a non-independent variable. This is not surprising in view of the fact that differentiation between EMG signs of motor radiculopathy and anterior horn lesion based on distribution (monosegmental vs. plurisegmental) is somewhat arbitrary and there exists inevitably at least a partial overlap between these conditions. These electrophysiological methods could disclose segmental dysfunction of the anterior horns (EMG) as well as the posterior horns (SEP), and dysfunction of the long tracts (SEP, MEP) and are thus highly recommended, not only in patients with MRI-documented asymptomatic cord compression, but also in patients with radiculopathy or back pain before MRI examination. The presence of "central" myelopathic SEP or MEP abnormalities would justify further MRI examination.

Intramedullar MRI hyperintensity was shown to be a significant predictor of the later (>12 months) development of symptomatic myelopathy and the divergence between this "postponed" manifestation and the early progression predicted by SEP, MEP, and the presence of radiculopathy is difficult to explain. Intramedullar ISI changes on T2-weighted MRI images are probably

Table 2 Time to clinically symptomatic SCM as end point related to potential risk factors

Variable	25th percentile time to clinically symptomatic myelopathy (months)	Univariate Cox proportional hazard model[a]		
		Relative risk	95% confidence limits	*P* value
All patients ($N = 199$)	48.4			
Sex (male)	36.8	1.71	(0.96; 3.44)	0.069
Age ≥50 years (category in %)	48.1	1.38	(0.76; 2.49)	0.290
Type of compression				
Osteophytes	48.9	1.57	(0.70; 3.52)	0.270
Others	35.9	0.63	(0.28; 1.43)	
No. of stenotic levels				
1	48.6	0.98	(0.54; 1.75)	0.945
≥2	48.0	1.02	(0.57; 1.84)	
MRI hyperintensity	31.7	1.60	(0.92; 3.42)	0.084
Lowered PR[b]	59.8	0.87	(0.46; 1.66)	0.687
Lowered CR[c]	35.9	1.39	(0.13; 15.3)	0.222
Lowered CSA[d]	36.8	1.09	(0.60; 1.99)	0.759
Clinically symptomatic radiculopathy	23.6	3.68	(2.03; 6.69)	<0.001
Abnormal EMG[e]	23.8	2.95	(1.62; 5.36)	<0.001
Abnormal MEP	23.7	2.91	(1.60; 5.29)	<0.001
Abnormal SEP	22.7	3.21	(1.75; 5.87)	<0.001

SCM Spondylotic cervical myelopathy, *PR* Pavlov ratio, *CR* compression ratio, *CSA* cross-sectional spinal cord area, *MRI* magnetic resonance imaging, *SEP* median and tibial nerve somatosensory evoked potentials

[a] Relative risk supplied with 95% confidence limits and *P* value given by Wald χ^2 test

[b] Pavlov ratio <0.8

[c] Compression ratio <0.4

[d] Cross-sectional spinal cord area <70 mm^2

[e] Motor axonal neuropathy in at least two myotomes

heterogenous [22] and indicate edema, inflammation, vascular ischemia, gliosis, or myelomalacia [14, 22]. It is not usually possible to differentiate between reversible and irreversible lesions underlying MRI hyperintensity. Hyperintensity chiefly indicates lesion in the gray matter, which has an influence predominantly on disability of the upper extremities and less impact on the overall disability of SCM patients and JOA scoring, in contrast to long tract involvement that may be detected by SEP and MEP.

The other imaging parameters have not shown any predictive value in P-SCCC. The cross-sectional area of the spinal cord has been found to be an independent prognosticator for severity of myelopathy, but not for the presence of clinical myelopathy [9]. The values for cross-sectional area overlapped significantly between patients with and without clinical myelopathy and thus cannot serve as a sensitive prognosticator for mild clinical myelopathy.

In a recent study, we found that the critical degree of spinal cord compression needed to induce clinically significant signs was between 50 and 60 mm^2 of cross-sectional transverse area at the level of maximal compression in association with MRI hyperintensities [13]. Only few of our patients, however, exhibited a CSA below 50 mm^2 (5 cases; 2.5%) or below 60 mm^2 (20 cases; 10.1%) and a 70 mm^2 cut-off showed no predictive value.

Penning et al. [24] reported that long tract signs developed only when the cross-sectional area of the spinal cord on CT myelography was reduced by more than 30%. No correlation was found between these imaging parameters and electrophysiological parameters reflecting the extent of cervical cord dysfunction, with the exception of a 1/4 lateral compression ratio [15]. Thus, despite reported correlation between several imaging parameters and severity of clinical symptomatology, disability, and postoperative prognosis [7, 15, 30], these parameters are probably not sensitive indicators of threatening progression into the initial symptomatic stage of myelopathy.

Cervical radiculopathy is one possible clinical manifestation of degenerative cervical spine disease and usually precedes the development of symptomatic SCM [25]. In our material, it appeared to be a powerful predictor for clinical manifestation of P-SCCC. Cervical radiculopathy resulting from cervical disc herniation is frequently managed surgically because of the excellent results reported in some surgical series [10, 12]. Cases with cervical disc extrusion are managed surgically because of the fear of fragment migration or injurious compression of nerve root or spinal cord elements [18]. Many cervical disc herniations can, however, be successfully managed with aggressive non-surgical treatment [26]. In a retrospective study of a cohort of 60 patients with clinical and MR signs of radiculopathy, 35% of them were treated surgically and 65% conservatively [11]. In the practical management of cervical radiculopathy itself, not just the treatment of the symptomatic radiculopathy but also the higher risk of developing early symptomatic myelopathy should be taken

Table 3 Probability of early clinically symptomatic SCM (≤12 months) in relation to potential risk factors

Variable	Positivity (%)		Univariate logistic regression models[a]		
	Early SCM+ cases ($n = 16$)	Early SCM− cases ($n = 183$)	Odds ratio (95% confidence limits)		P value
Sex (male)	43.8	53.6	0.67	(0.23; 1.91)	0.453
Age ≥50 years (%)	62.5	53.0	1.47	(0.51; 4.26)	0.467
Type of compression					
Osteophytes	87.5	73.8	2.48	(0.54; 11.46)	0.239
Others	12.5	26.2	0.40	(0.09; 1.85)	
No. of stenotic levels					
1	37.5	54.1	0.51	(0.18; 1.47)	0.209
≥2	62.5	45.9	1.96	(0.68; 5.67)	
MRI hyperintensity	12.5	25.7	0.41	(0.09; 1.90)	0.254
Lowered PR[b]	25.0	33.9	0.65	(0.19; 2.12)	0.472
Lowered CR[c]	31.3	24.1	1.45	(0.46; 4.53)	0.521
Lowered CSA[d]	43.8	39.3	1.19	(0.42; 3.38)	0.730
Clinically symptomatic radiculopathy	62.5	26.3	4.69	(1.61; 13.7)	0.004
Abnormal EMG[e]	43.8	21.3	2.87	(1.02; 8.25)	0.044
Abnormal MEP	37.5	16.9	2.94	(1.04; 8.75)	0.046
Abnormal SEP	43.8	16.4	3.97	(1.36; 11.6)	0.011

SCM Spondylotic cervical myelopathy, *PR* Pavlov ratio, *CR* compression ratio, *CSA* cross-sectional spinal cord area, *MRI* magnetic resonance imaging, *SEP* median and tibial nerve somatosensory evoked potentials

[a] Estimate of odds ratio supplied with 95% confidence limits and P value given by Wald χ^2 test

[b] Pavlov ratio <0.8

[c] Compression ratio <0.4

[d] Cross-sectional spinal cord area <70 mm^2

[e] Motor axonal neuropathy in at least two myotomes

into consideration when the type and degree of surgical treatment or further conservative treatment and follow-up are being planned.

We did not examine and follow patients without any symptoms or signs (i.e., back pain or radiculopathy) that would justify MRI and other tests. Our conclusions therefore have restricted applicability to such cases. In clinical practice, for patients in whom MRI was done for other reasons, one would only rarely encounter such cases with asymptomatic spondylotic cervical cord compression (as in the study by Teresi et al. [28]).

It is obvious from the data presented that P-SCCC is generally a benign condition and preventive surgical treatment is probably not justified. Only about a quarter of patients progress into clinically symptomatic myelopathy within 4 years, and in only some of them does the symptomatology further progress and require surgical decompression. Furthermore, clinical management could

Table 4 Mutual relationships of significant SCM predictors: association matrix based on two-sample Fisher exact test

	MEP	Male sex	MR hyperintensity	Radiculopathy	EMG
SEP	DN: 67.8%	DN: 38.7%	DN: 63.8%	DN: 59.3%	DN: 63.8%
	DP: 5.0%	DP: 10.1%	DP: 7.0%	DP: 7.0%	DP: 5.5%
	$P = 0.164$	$P = 0.816$	*$P = 0.034$*	$P = 0.222$	$P = 0.287$
EMG	DN: 64.8%	DN: 407 %	DN: 59.3%	DN: 59.8%	
	DP: 6.5%	DP: 16.6%	DPP: 7.0%	DP: 12.1%	
	P = 0.081	*$P = 0.004$*	$P = 0.331$	*$P = 0.002$*	
Radiculopathy	DN: 59.8%	DN: 38.7%	DN: 53.3%		
	DP: 7.5%	DP: 20.6%	DP: 7.0%		
	$P = 0.109$	*$P = 0.002$*	$P = 0.536$		
MR Hyperintensity	DN: 64.3%	DN: 34.1%			
	DP: 7.5%	DP: 11.6%			
	$P = 0.019$	$P = 0.411$			
Male sex	DN: 39.2%				
	DP: 10.6%				
	$P = 0.716$				

DP double positive values, *DN* double negative values, *P* significance value (Fisher exact test)

Only parameters with univariate predictive test of $P < 0.10$ were included in the analysis

Table 5 Multivariate predictive models generated on the basis of univariate results

Parameters included in model	Coefficient (SE; *P* level)	Model log-likelihood	Log-likelihood ratio Test
(A) Cox proportional hazard regression model for time to clinically symptomatic myelopathy[a]			
Null model		−214.1	
Step 1. [Radiculopathy; R]	1.19 (0.31; $P < 0.001$)	−203.8	<0.001
Step 2. + [SEP]	1.10 (0.31; $P = 0.004$)	−196.7	<0.001
Step 3. + [MEP]	0.77 (0.31; $P = 0.012$)	−190.9	<0.001
(B) Multivariate logistic regression model for the probability of early clinical manifestation of myelopathy[a, b]			
Null model		−111.3	
Constant b_0	−1.35 (0.24; $p < 0.001$)		
Step 1. [Radiculopathy; R]	1.67 (0.61; $P = 0.007$)	−104.4	0.014
Step 2. + [SEP]	1.27 (0.55; $P = 0.007$)	−98.1	0.008
Step 3. + [MEP]	1.35 (0.63; $P = 0.033$)	−94.0	0.002
Step 4 + [MR hyperintensity; H]	−1.63 (0.82; $P = 0.036$)	−90.3	<0.001

[a] Multivariate stepwise procedures driven only by statistical measures (log-likelihood function)

[b] Dependent variable Y = probability of clinical manifestation of myelopathy ≤12 months

Table 6 Multivariate predictive models generated on the basis of univariate results: model validation

Model equation[a]	$Y = e^Z/(1 + e^Z)$
Linear predictor Z	$Z = -1.35 + 1.67 \times [R] + 1.27 \times [SEP] + 1.35 \times [MEP] - 1.63 \times [H]$
Cross validation[b]	
Correctly classified patients with early myelopathy	81.3%
Correctly classified patients without early myelopathy	77.1%
Model residuals[c]	
Correctly classified patients with early myelopathy ($n = 12$)	Mean 0.72; Median 0.83; MIN/MAX 0.57/0.89
Correctly classified patients without early myelopathy ($n = 150$)	Mean 0.24; Median 0.21; MIN/MAX 0.04/0.47

[a] Dependent variable Y = probability of clinical manifestation of myelopathy ≤12 months

[b] Cross validation performed retrospectively on calibration data set ($n = 199$)

[c] Quantitative residual summary in absolute values

be tailored to patient's individual risk. In high-risk individuals, meticulous follow-up together with measures to prevent further deterioration (reduction of risk activities, intermittent application of soft collar) may be recommended, while in low-risk, asymptomatic compression cases, less frequent clinical observation at 1–2-year intervals is probably sufficient.

Conclusions

Presymptomatic spondylotic cervical cord compression detected by MRI is generally a benign condition, as only a few patients progress into symptomatic myelopathy within 4 years. Electrophysiological evaluation of cervical cord dysfunction in patients with cervical radiculopathy or back pain is valuable, as electrophysiological abnormalities of cervical cord dysfunction together with clinical signs of cervical radiculopathy and MRI hyperintensity are useful predictors of early progression into symptomatic SCM in patients with P-SCCC.

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