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Pathophysiology and Natural History of Cervical Spondylotic Myelopathy

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Study Design. This study is a combination of narrative and systematic review.

Objective. Clinicians who deal with cervical spondylotic myelopathy (CSM) should be up-to-date with the emerging knowledge related to the cascade of pathobiological secondary events that take place under chronic cervical spinal cord compression. Moreover, by performing a systematic review, we aim to (1) describe the natural history and (2) determine potential risk factors that affect the progression of CSM.

Summary of Background Data. The pathophysiology, natural history, as well as the factors associated with clinical deterioration have not been fully described in CSM.

Methods. For the first part of the study, a literature review was performed. To answer key questions 1 and 2 of the second goal, a systematic search was conducted in PubMed and the Cochrane Collaboration Library for articles published between January 1, 1956, and November 7, 2012. We included all articles that described the progression and outcomes of CSM for which no surgical intervention was given.

Results. By performing a narrative literature review, we found that the assumption that acute traumatic spinal cord injury and CSM share a similar series of cellular and molecular secondary injury events was made in the past. However, recent advances in basic research have shown that the chronic mechanical compression results in secondary injury mechanisms that have distinct characteristics regarding the nature and the temporal profile compared with those of spinal cord injury. For the purpose of the systematic review, 10 studies yielding 16 publications met inclusion criteria for key questions 2 and 3. Moderate-strength evidence related to the natural history of CSM suggests that 20% to 60% of patients will deteriorate neurologically over time without surgical intervention. Finally, there is low-strength evidence indicating that the area of circumferential compression is associated with deteriorating neurological symptoms.

Conclusion. CSM has unique pathobiological mechanisms that mainly remain unexplored. Although the natural history of CSM can be mixed, surgical intervention eliminates the chances of the neurological deterioration.

Evidence-Based Clinical Recommendations.

Recommendation. Evidence concerning the natural history of CSM suggests that 20% to 60% of patients will deteriorate neurologically over time without surgical intervention. Therefore, we recommend that patients with mild CSM be counseled regarding the natural history of CSM and have the option of surgical decompression explained.

Overall Strength of Evidence. Moderate

Strength of Recommendation. Strong

Summary Statements. Chronic compression of the spinal cord results in progressive neural cell loss related to secondary mechanisms including apoptosis, neuroinflammation, and vascular disruption.

Key words: spinal cord microvasculature, blood-spinal cord barrier, cervical, conservative treatment, myelopathy, natural history, nonoperative, ossification of the posterior longitudinal ligament, pathophysiology, spondylosis.

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Cervical spondylotic myelopathy (CSM), the most common cause of spinal cord dysfunction in the world, is a degenerative condition that results in a nontraumatic, progressive, and chronic compression of the cervical spinal cord.[1] The disease is more prevalent in males and in the Asian population than in females and Caucasians, respectively.[1] In a recent study, Boogaarts and Bartels[2] reported that the annual

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incidence of patients with CSM treated surgically is 1.6 per 100,000 inhabitants in their referral area, but the actual incidence and prevalence of the disease remain unclear. Recent work has clarified some of the pathophysiological events underlying neural degeneration in CSM; however, much is not yet understood.[1,3] The gaps in knowledge regarding the pathobiology of CSM have limited efforts to develop clinically relevant neuroprotective and neurorestorative therapeutic strategies—although the CSM-Protect trial examining the complementary use of the sodium channel blocker riluzole with surgical decompression (discussed later in the focus issue) is a notable exception. In this article, we seek to summarize recent work relating to the pathobiology of CSM and place this into context by describing the evidence regarding the natural history of this condition. This information should be of value to clinicians in guiding therapeutic decision making.

The natural history of CSM varies greatly and is unpredictable in individual patients. Moreover, uniform recommendations for treatment have been difficult to establish. In the absence of clear guidelines, management is tailored to the specific circumstances of individual patients and decisions are made at the discretion of treating physicians and surgeons. Conservative treatment of physical therapy for gait training and neck immobilization with a firm collar is appropriate for patients with mild myelopathy. Surgery is generally considered if the myelopathy progresses despite conservative treatment.

This study has 2 main goals. The first is to present the emerging knowledge regarding the pathophysiology of CSM. The second is to perform a systematic review to examine the following key questions: (1) What is the natural history of CSM? (2) Which risk factors affect the progression of CSM? Although CSM has been studied for several years, several questions remain regarding disease progression. Specifically, it is not well understood why symptomatic myelopathy develops in certain patients but not in others, despite radiographical evidence of cervical stenosis. It is also poorly understood why certain patients have clinically severe myelopathy and others manifest only mild myelopathy.

MATERIALS AND METHODS

We summarized the current knowledge of the pathophysiology of CSM using primary basic research articles and primary basic research scientific abstracts as well as review articles. For the systematic review, a search was run in PubMed and in the Cochrane Collaboration Library for literature published between January 1956 and November 7, 2012, on the natural history of CSM using key words. The search results were limited to human studies published in the English language. Reference lists of key articles were also systematically checked to identify additional eligible articles. We included studies providing longitudinal data on the progression and outcome of symptomatic CSM or ossification of the posterior longitudinal ligament in those not receiving surgical treatment (Table 1). We also included studies evaluating risk factors for the improvement or deterioration of symptomatic CSM in patients initially treated nonsurgically. We were interested in the following prognostic categories: patient factors such as age, sex, and duration of symptoms; disease severity such as baseline neurological and functional status; and radiographical factors such as C2–C7 alignment, range of motion (ROM), spinal cord diameter, canal stenosis, and local slip. Studies of patients with myelopathy as a result of trauma, tumor, infection, or inflammatory arthritis; studies reporting only surgical outcomes; studies that included less than 10 patients; and animal, cadaver, or biomechanical studies were excluded. The full texts of potential articles meeting the inclusion criteria were then reviewed to obtain the final collection of included studies.

TABLE 1. Inclusion and Exclusion Criteria

Inclusion	Exclusion
Patient	
KQs 2, 3: Untreated or conservatively treated adult patients diagnosed with cervical myelopathy as a result of spondylosis, herniated disc, or ossification of the posterior longitudinal ligament	KQs 2,3: Myelopathy as a result of trauma, tumor, infection, inflammatory arthritis
Prognostic factor	
KQ 2: Incidence or prevalence of outcomes over time	
KQ 3: Risk factors for adverse outcomes	
Outcomes	
Neurological outcomes (JOA, mJOA, Nurick)	Symptomatic ASD with imaging evidence of degeneration
Functional outcomes relating to activities of daily living	Clinical outcomes
Surgery	
Study design	
KQs 2, 3: Longitudinal studies with at least 2-yr follow-up	KQs 2,3: Cross-sectional studies

KQs indicates key questions; JOA, Japanese Orthopaedic Association; mJOA, modified Japanese Orthopaedic Association; ASD, adjacent segment disease.

TABLE 2. Characteristics of Included Studies

Authors	Study Design	Demographics	Follow-up, Mean (%)	Inclusion Criteria
Barnes and Saunders[31]	Retrospective cohort	N = 76 Mean age = 65 yr Male = 71%	8.2 yr (59%)	1. Myelopathy with evidence of corticospinal tract dysfunction in the legs with or without sensory involvement or radiculopathy 2. Plain radiological changes of cervical spondylosis 3. Myelographic evidence of a complete or partial block to the flow of contrast medium in the cervical spine 4. No other reasonable diagnosis that had manifested itself on follow-up examination
Bednarik *et al*[32]	Randomized controlled trial	N = 33*	†2 yr (NR) ‡3 yr (90%) §10 yr (78%)	1. Clinical signs and symptoms of cervical cord dysfunction
Kadanka *et al*[33–35,43]		Mean age = 54 yr Male = 74%		2. MRI criteria for cervical mono- and multisegmental cord compression and/or myelopathy due to spondylosis (including soft disc herniations) with or without developmentally narrow spinal canal 3. Age <75 yr 4. mJOA score >12 5. Patient's consent to surgery
Lees and Turner[45]	Prospective cohort	N = 44 Mean age = NR (range, 21–80 yr) Male = 68%	5 yr (100%)	1. Radiological and myelographic evidence of cervical spondylosis with signs of cord damage 2. Extensor plantar responses 3. All patients with other neurological diseases such as disseminated sclerosis, even if spondylosis was also present, were excluded
Matsumoto *et al*[36,37]	Retrospective cohort	N = 52¶, N = 27‖ Mean age = 55 yr Male = 75%	3 yr¶ (NR) 4 yr‖ (NR)	1. Diagnosed to have cervical compressive myelopathy on the basis of both the neurological examination and MR findings that showed spinal cord compression 2. Mild paresis 3. JOA ≥10
Nakamura *et al*[33]	Retrospective cohort	N = 64 Mean age = 52 yr (range, 32–73) Male = 72%	6 yr (83%)	Motor function disability in the upper or lower extremity or in both (based on the motor function evaluation of the JOA)
Oshima *et al*[39]	Retrospective cohort	N = 45 Mean age = 59 yr (range, 35–76) Male = 60%	6.5 yr (82%)	1. Motor function JOA scores of ≥3 in both upper and lower extremities 2. Cervical spinal cord compression with ISI on T2-weighted MRI
Roberts[44]	Retrospective cohort	**N = 28 Mean age = 54.2 yr (range, 41–69) Male = 75%	3 yr (86%)**	1. Myelography diagnosis 2. Immobilization of the neck in a plastic or metal frame collar preceded by 2- to 3-wk bed rest in hospital
Sampath *et al*[46]	Prospective cohort	N = 31* Mean age = 48.7 yr (range, 21–75) Male = 48%	1 yr (74%)*	1. Consultation sought for treatment, not second opinion 2. ≥8 wk of symptoms consistent with cervical spondylosis 3. Radiographical evidence of spondylosis 4. ≤1 prior surgical or intradiscal procedures

(*Continued*)

TABLE 2. (*Continued*)

Authors	Study Design	Demographics	Follow-up, Mean (%)	Inclusion Criteria
				5. Able to read English at ≥8th grade level and fluent in spoken English
				6. Age >18 yr
				7. Absence of ailment preventing participation
				8. Legal US residence, no incarceration, signed informed consent
Shimomura *et al*[42]	Prospective cohort	N = 70††, N = 60‡‡	3 yr (80%)††	Mild CSM (mJOA ≥13)
Sumi *et al*[40]		Mean age = 55.1 ± 11.8 yr Male = 70%	6.5 yr (79%)‡‡	
Yoshimatsu *et al*[41]	Retrospective cohort	N = 69* Mean age = 67 yr (range, 42–87) Male = 51%	2.5 yr (NR)	1. CSM based on clinical signs and the presence of compression on the spinal cord by MRI
				2. Patients self-selected to be in the conservative treatment group after treatment opinions were explained to them
				3. All patients except 2 had an initial JOA score ≥13

**Demographics of conservative treatment group.*

†Bednarik et al[32] and Kadanka et al,[43] same study population.

‡Kadanka et al[34] and Kadanka et al,[35] same study population.

§Kadanka et al.[33]

¶Matsumoto et al.[37]

‖Matsumoto et al.[36]

***Denominator determined by the number of people hospitalized for CSM and who did not receive surgical intervention.*

††Shimomura et al.[42]

‡‡Sumi et al.[40]

NR indicates not reported; MRI, magnetic resonance imaging; mJOA, modified Japanese Orthopaedic Association; JOA, Japanese Orthopaedic Association; ISI, increased signal intensity; CSM, cervical spondylotic myelopathy.

Data Extraction

From the included articles, the following data were extracted: study design, patient demographics, follow-up duration and the percentage of follow-up for each treatment group, neurological assessment and outcomes, activities of daily living (ADLs) score results, CSM or ossification of the posterior longitudinal ligament population, risk factors analyzed, risk of and potential risk factors for CSM, and country of origin of each study. We attempted to identify studies with overlapping data and reported only the data from the most complete study (largest sample size) in order to prevent double counting (Table 2).

Study Quality and Overall Strength of Body of Literature

Class of evidence ratings were assigned to each article independently using criteria set by *The Journal of Bone & Joint Surgery*[4] for therapeutic and prognostic studies and modified to delineate criteria associated with methodological quality and risk of bias using recommendations made by the Agency for Healthcare Research and Quality (AHRQ). The appraisal system used in this article accounts for features of methodological quality and important sources of bias by combining epidemiologic principles with characteristics of study design to determine the class of evidence and is consistent with those used in previous focus issues.[5]

After individual article evaluation, the strength of the overall body of evidence with respect to each outcome was determined on the basis of precepts outlined by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group[6,7] and recommendations made by the AHRQ. Qualitative analysis is performed considering AHRQ-required and additional domains.[8]

The initial strength of the overall body of evidence was considered high if the majority of the studies were class I or II and low if the majority of the studies were class III or IV. Criteria for downgrading published evidence 1 or 2 levels included (1) inconsistency of results, (2) indirectness of evidence, (3) imprecision of the effect estimates (*e.g.*, wide confidence intervals [CIs]), or (4) non–*a priori* statement of subgroup analyses. Alternatively, the body of evidence could be upgraded 1 or 2 levels on the basis of the following factors:

(1) large magnitude of effect or (2) dose-response gradient. The final overall strength of the body of literature expresses our confidence that the findings reflect the true course of CSM and the true relationship between risk factors and the course of CSM on the basis of the adequacy or deficiencies in the body of evidence. The final strength of evidence categories were "high," "moderate," "low," or "insufficient."

Data Analysis and Synthesis

For key question 1, we report the proportion (%) of patients having a change in neurological and functional status over time compared with status at diagnosis. When present, mean scores of continuous outcomes and their interval estimate or variance were reported. For key question 2, we report effect measures (adjusted odds ratios and the 95% CIs) if available. Data were summarized in tables and figures but were not pooled between studies because of the limited number of studies and the heterogeneity of study design in terms of outcomes assessed and follow-up periods.

Clinical Recommendations and Consensus Statements

Consensus statements were made through a modified Delphi approach by applying the GRADE/AHRQ criteria that impart a deliberate separation between the strength of the evidence (*i.e.*, high, moderate, low, or insufficient) and the strength of the recommendation. When appropriate, recommendations "for" or "against" were given "strong" or "weak" designations on the basis of the quality of the evidence, the balance of benefits/harms, and values and patient preferences. In some instances, costs may have been considered. A more thorough description of this process can be found in the focus issue Methods article.

PATHOGENESIS OF CSM: NARRATIVE LITERATURE REVIEW

Pathophysiological Factors Contributing to the Development of Chronic Compression

Static and dynamic factors are the main contributing components to compression on the cervical spinal cord. The static factors are the structural spondylotic abnormalities that cause canal stenosis and subsequent cord compression. It has been recognized that the disc degeneration is the initiating event of these spondylotic changes. Disc degeneration leads to abnormal cervical spine biomechanics and hypertrophy of the ligamentum flavum as well as laxity of the facet joint, progressive biomechanical stress, and strain on the spinal joints all of which can be compounded by repetitive trauma. A prospective study of 295 patients with symptomatic CSM reported that a narrow spinal canal is an important risk factor for CSM (Morishita *et al*[9]). It might seem obvious that a congenitally narrow spinal canal could predispose a person to potential spinal cord compression particularly in the presence of additional mitigating factors. However, this study was the only one identified that found that a spinal canal with an anteroposterior dimension of less than 13 mm in addition to CSM was associated with an increased risk of disc degeneration disease (DDD).[9] One of the few studies that attempted to determine the genomic determinants of DDD/spondylosis linked genetic anomalies not only with DDD, but also with the severity (not just the propensity to develop) of CSM.[9] Interestingly, the factors that affect the development of DDD with and without progression to CSM remain unclear. It is much more widely accepted that pathological DDD is a distinct condition and not normal "aging" of the spine and that important determinants of the more significant types of DDD rest with pathological changes in the vertebral endplates as well as involving genetic determinants. To identify possible predictive factors with respect to the specific contribution of spondylosis to the development of CSM, appropriate age, sex, and disease-matched studies should be performed. It would be advantageous to include genetic and proteomic studies using human disc and ligamentous tissues from patients receiving surgical treatment with and without CSM in order to resolve some of these issues.

Finally, the dynamic factors are characterized by the repetitive injury placed on the already compressed cord during the flexion or extension movements of the cervical spine.

Pathobiological Mechanisms of Injury Under Chronic Compression

The lack of a reliable animal model of progressive compression of the cervical spinal cord has led to the assumption that acute traumatic spinal cord injury (SCI) and CSM share a similar series of cellular and molecular secondary injury events. Recent advances in basic research into CSM have demonstrated that CSM is a unique progressive disease with clear features, distinct from SCI. Exploiting novel CSM models,[10–12] previously unknown pathophysiological mechanisms of CSM have been elucidated.

Chronic Distortion of the Spinal Cord Microvasculature

Endothelial Cell Loss and Disruption of Vascularization. It has been postulated for many years that chronic interruption of the vascular supply to the spinal cord may be a significant component in the origin and progression of CSM.[1] However, spinal cord microvasculature has only recently been studied in experimental CSM. Specifically, Karadimas *et al*[10] showed that chronic compression of the cervical spinal cord causes loss and dysfunction of endothelial cells as well as flattening, stretching, and consequent loss of vessels.[13] However, the mechanisms of endothelial dysfunction have yet to be fully elucidated in animal models of CSM. Using the same model of progressive and chronic compression, reduced laminin labeling was observed in the cervical spinal cords of late symptomatic rats,[13] further indicating disruption of vascularization architecture. These results indicate that the cervical spinal cord is subjected to chronic hypoxic conditions under the chronic and progressive compression that characterizes CSM.

Compromise of the Blood-Spinal Cord Barrier. The blood spinal cord barrier (BSCB) is a morphological and functional analogue of the blood-brain barrier. It is very well established that the

BSCB is destroyed in traumatic SCI and remains compromised for a long time before being eventually restored.[14,15] Recently, in a novel rat model of CSM that reproduces the chronic and progressive compression nature of human CSM, our group demonstrated that the BSCB remains compromised at chronic stages after the onset of compression.[10,13] These results suggest that the mechanisms underlying the compromised integrity of BSCB are unique to this chronic condition. The persistent disruption of BSCB function over time was strongly associated with the progressive deterioration of the rats' gait pattern. These experimental results were further validated in human CSM tissue.[13] The increased expression of MMP-9 in experimental CSM[16] as well as human spinal cord tissue[13] at the chronic phase of CSM is thought to show that MMP-9 promotes the persistence of BSCB disruption in line with many studies that show increased MMP-9 and subsequent increases in the inflammatory process in SCI. However, the mechanisms of microvascular dysfunction, chronic BSCB disruption, and the associated neuroinflammatory changes have yet to be fully elucidated in animal models of CSM. These complex secondary pathomechanisms are responsible for additional extension of damage into the originally uncompromised segments of the spinal cord.

Neuroinflammation

The slow and progressive compression in CSM generates unique innate and adaptive immune responses that, unfortunately, remain elusive.[17] Evidence stemming from experimental and human CSM studies clearly shows that the chronic compression of the cervical spinal cord induces activation of microglia and the recruitment of macrophages at the site of the compression.[10,18] However, until recently, the pathways that contribute to their recruitment and activation, as well as their role in CSM, were not known. Recent evidence showed increased expression of CX3CR1 in human cervical spinal cords from patients with significant CSM.[19] Exploiting a novel mouse model of acquired CSM,[12] CX3CR1 CSM knockout mice were generated to study the role of microglia/macrophages in CSM. In the healthy central nervous system, fractalkine (CX3CL1) is expressed on the membrane of neurons, whereas its receptor (CX3CR1) is highly expressed on microglia.[20] After neuronal injury such as in CSM, the ligand can be released from the membrane, generating a soluble chemokine. CX3CL1 expression levels are highest in the central nervous system, suggesting an important and unique role for this signaling axis. CX3CL1/R1 signaling is important to (1) neuronal-microglial interactions[21,22] and (2) inflammatory cell recruitment and activation.[23–26] Interestingly, accompanying the arrest of the progression of the disease and improved recovery in CX3CR1-deficient mice was a decrease in microglia/monocyte-derived macrophages accumulation and microglia-related inflammation at the site of compression.[19] Moreover, knockout animals had increased neuronal and oligodendrocyte preservation.[19] However as Drs. Beattie and Manley state "...the role of peripheral innate immune responses versus endogenous immune cells in the early secondary injury cascade remain elusive" in CSM.[17]

The spinal cord, as part of the central nervous system, is an immunologically privileged zone, which is protected from the peripheral nervous system by the BSCB. The persistently disrupted BSCB in CSM, reported previously, renders the spinal cord microenvironment susceptible to peripheral immune cell infiltration that has significant mechanistic implications that contribute to the progression of neural degeneration in CSM. It is clear that the disruption of the BSCB is the start of a vicious cycle. However, the time course of compromise of BSCB function has not yet been fully elucidated and the sequence of events remains unknown. Does the BSCB disruption initiate the neuroinflammatory response or exacerbate the existing one? The enigma remains unsolved.

Apoptosis

Chronic hypoxic conditions as well as systemic and innate inflammatory processes described previously represent some of the initiators of the apoptotic process in CSM. Indeed, apoptosis in both neurons and oligodendrocytes has been demonstrated to be an important factor in neural degeneration and the progressive nature of CSM.[10] Neuronal and oligodendrocytic apoptoses have been detected in postmortem human CSM spinal cord sections as well as in mice and rats with chronic and progressive compression of the cervical spinal cord.[1,18,27] Interestingly, in a novel rat CSM model, activation of proapoptotic pathways associated with ongoing cell apoptosis was demonstrated during the late stages of cervical spinal cord compression.[10] Surgical decompression improves functional outcomes in CSM rats and decreases levels of cellular apoptosis, indicating a correlation between mechanical compression and ongoing apoptosis.[28] However, the decompressive intervention does not result in elimination of apoptotic cell death,[28] confirming that the chronic mechanical compression initiates a cycle of secondary injury events, which persists even after decompression. Thus, although Fas-ligand,[18] tumor necrosis factor α,[29] and the mitogen-activated protein kinase pathways[30] have been implicated in the initiation of apoptosis, the extracellular and intracellular signaling systems of apoptosis in CSM have yet to be fully elucidated in experimental studies.

RESULTS OF SYSTEMATIC REVIEW

Study Selection

For key questions 1 and 2, we identified 10 studies yielding 16 publications that met the inclusion criteria using our search strategy (Figure 1). Our initial search produced 510 possible publications for review for these 2 key questions. After title and abstract review, we excluded 480 publications, the majority of which did not include conservative or nonoperative treatment of CSM or were review studies. Among the 30 full-text articles subsequently reviewed for key questions 1 and 2, 16 additional publications were found from the references in-text, giving a total of 46 publications for full-text review. After full-text review, 30 were excluded for the following reasons: review articles (n = 16), primary focus was on a surgical population (n = 5), asymptomatic CSM population (n = 3), case reports (n = 4), editorials (n = 1), and an epidemiological study (n = 1). Ten studies (16 publications) met our criteria for inclusion (Table 2).

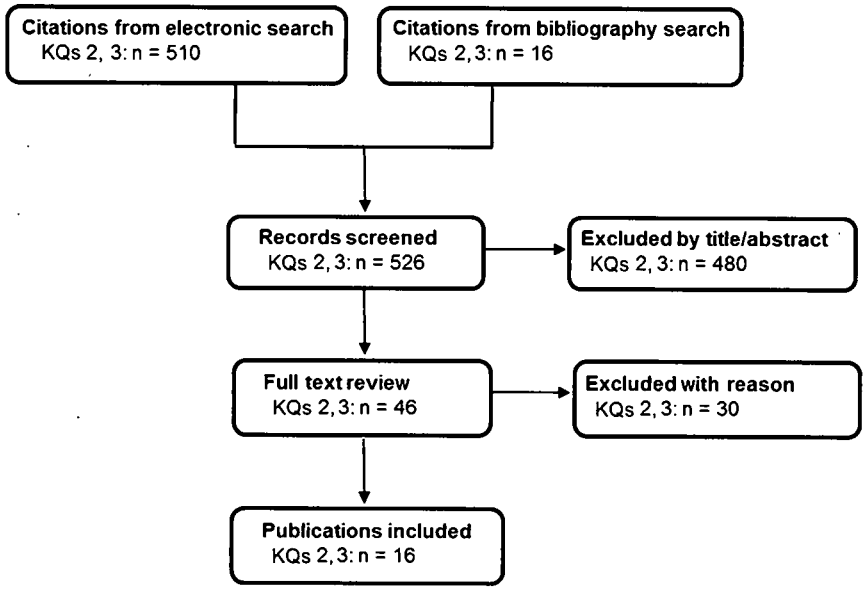

Figure 1. Flowchart showing results of literature search. KQ indicates key question.

The full evidence summary for these included studies can be found in Table 6.

Natural History of CSM

All 10 studies (16 publications) reported on the short-term natural history of neurological deterioration, conversion to surgery, and/or functional outcome in patients with mild symptomatic CSM.

Neurological Outcome

Eight studies (14 publications) examined neurological status among patients with symptomatic CSM treated nonoperatively.[31–44] Six used the Japanese Orthopaedic Association (JOA) score (the modified JOA [mJOA], or the motor portion of the JOA).[32–37,40–43] The proportion of patients with worse JOA scores (≥1-point reduction compared with baseline) at 3- to 6-year follow-up ranged from 20% to 62% (Table 3). Kadanka *et al*[33–35,43] in a prospective study reported that 15% of the patients had deteriorated or remained unchanged at or below a JOA score of 14 at 1-year follow-up, 34% at 2 years, and 27% at 3 years. Two retrospective studies reported deterioration in 31% and 37%, respectively, at 3- and 4-year follow-up,[36,37] and 20% and 26% at 3- and 6.5-year follow-up (Figure 2).[40,42] One retrospective and 2 prospective studies reported slightly different results with respect to the change in mean JOA scores over time compared with baseline (Figure 3). Kadanka *et al* in their prospective study reported a mean JOA score of 15 at the 1-year follow-up and a median JOA score of 15 at the 10-year follow-up. The mean JOA scores slightly decreased in 1 prospective study during a 6.5-year period[42] and slightly increased during a 4-year period in another retrospective study (Table 4).[36]

The Nurick grade was used by Barnes and Saunders[31] to assess neurological change at a mean follow-up of 8.2 years. Thirteen percent of patients deteriorated, 20% improved, and 67% were unchanged after 8 years (Table 3).

Conversion to Surgery

Seven studies reported on the percentage of patients who eventually underwent surgery because of worsening neurological or functional symptoms.[36–42,45] The proportion of patients who converted to surgery after failed nonoperative care ranged from 4% to 40% during a period of 3 of 7 years (Figure 4).

Functional Outcome

Activities of Daily Living. Two studies (5 publications) evaluated the change in ADLs scores over time[32,33,39,43,46] (Table 5). The prospective series by Kadanka *et al*[33–35,43] reported an increasing proportion of patients with worse function over time—6.3% after 1 year, 27.3% after 3 years, and 56% after 10 years of follow-up—compared with baseline. Likewise, a low-quality retrospective study by Sampath *et al*,[46] in 2000, reported worsening ADLs scores after 11 months compared with baseline; the number of activities that worsened patients' symptoms (ranging from 0 to 5) increased from an initial 1.8 to a final 2.5.

Timed 10-m Walk. Kadanka *et al*[33–35,43] evaluated the timed 10-m walk test in conservatively treated patients with CSM during a 10-year follow-up period. They reported no difference in 10-m walk times throughout the 10-year follow-up period. At the 1-, 2-, 3- and 10-year follow-up times, Kadanka *et al*[33] reported times of 7.4, 7.5, 7.5, and 7.1 seconds, respectively, compared with baseline (7.4 s).

Overall Functional Status Rating. Sampath *et al*[46] assessed the overall functional status rating of patients with CSM on the basis of a 4-point scale of usual work and social activities. At a 1-year follow-up, patients had nonsignificant improvements in overall functional status, work, and social activities.

TABLE 3. Proportion of Patients Who Changed Neurological Status Over Time Compared With Status at Diagnosis

Authors	Follow-up (yr)	Deteriorated (% of Patients)	Unchanged (% of Patients)	Improved (% of Patients)	Unchanged or Improved (%)
Neurological assessment by mJOA or JOA					
Kadanka *et al*[35]*	1	†15.1	...	‡84.9	84.9
	2	†34.4	...	‡65.6	65.6
	3	†26.7	...	‡73.3	73.3
Matsumoto *et al*[36,37]	3	31	...	‡69	69
	4	37	...	63	63
Shimomura *et al*[42]	3	19.6	...	...	80.4
Sumi *et al*[40]	6.5	25.5	...	...	74.5
Yoshimatsu *et al*[41]	2.5	62	15	23	38
Neurological assessment by motor JOA					
Nakamura *et al*[38]					
UE	6	0	45	55	100
LE	6	3	39	57	97
Oshima *et al*[39]	6.5	40	...	...	60
Neurological assessment by Nurick					
Barnes and Saunders[31]	8.2	13	67	20	87

*Inclusive of patients from Bednarik et al,[32] Kadanka et al,[43] and Kadanka et al.[34]
†Deteriorated or remained (unchanged) below a JOA score of ≤14.
‡Improved or remained (unchanged) above a JOA score of ≥15.
mJOA indicates modified Japanese Orthopaedic Association score; JOA, Japanese Orthopaedic Association Score; UE, upper extremity; LE, lower extremity.

Prognostic Factors

Seven studies evaluated prognostic factors associated with the change in status over time in patients with CSM who received nonoperative care,[31,35,37–39,41,42] but only 2 used multivariate analyses to control for other potential prognostic factors.[39,42]

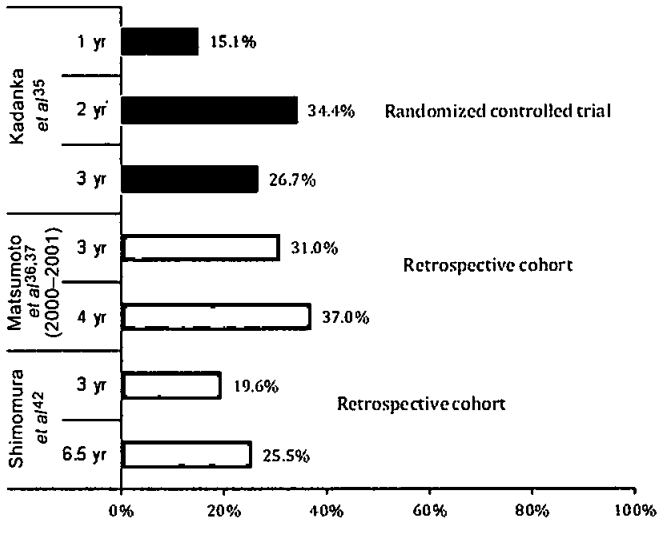

Figure 2. Proportion (%) of patients with worse Japanese Orthopaedic Association scores (≥1-point reduction) compared with baseline evaluation in studies with at least 2 follow-up periods.

Neurological Status

Shimomura *et al*[42] evaluated prognostic factors associated with neurological deterioration in patients with CSM. They found that circumferential cord compression was associated with neurological deterioration (adjusted odds ratio: 26.6; 95% CI: 1.7–421.5). There was no significant association between age, sex, developmental factor, dynamic factor or high T2WI signal intensity, and neurological deterioration (Figure 5). Barnes and Saunders,[31] in 1984, compared patients who did and did not have worse neurological status after a mean follow-up of 8.2 years. Using univariate analysis, they reported that female sex ($P < 0.01$), greater neck ROM ($P < 0.05$), greater head ROM ($P < 0.01$), and total head and neck ROM difference ($P < 0.01$) were associated with a progressively worse neurological condition.

Four studies evaluated factors associated with improved neurological status after conservative care. Kadanka *et al*[33] reported that older age before treatment ($P < 0.05$), larger transverse area of the spinal cord ($P < 0.05$), lower height ($P < 0.05$), higher value of Pavlov Index ($P < 0.05$), and lower entry mJOA score ($P < 0.05$) were predictors of an improved

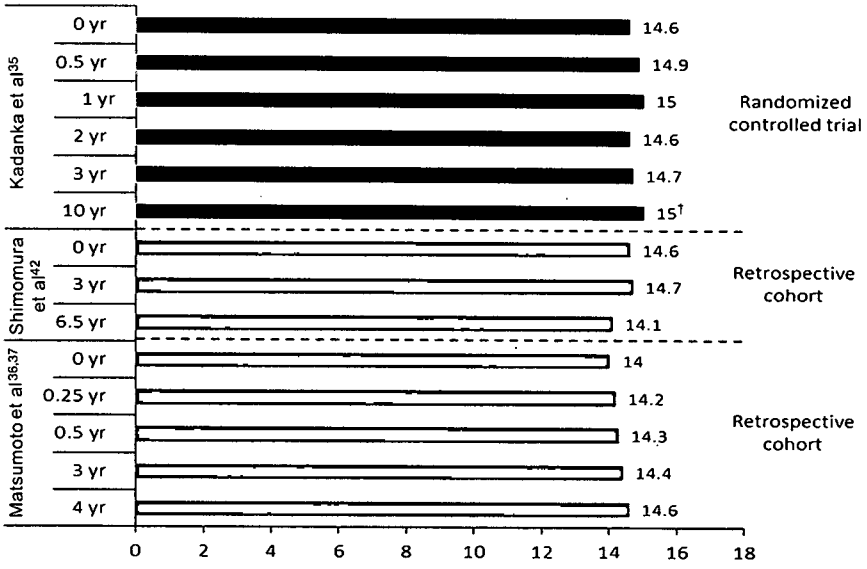

Figure 3. Mean Japanese Orthopaedic Association (17 points) or mJOA (18 points) scores over time in studies with at least 2 follow-up periods. *Modified Japanese Orthopaedic Association. †Median score.

JOA score at 6-month and 3-year follow-up.[35] Yoshimatsu *et al*[41] reported that shorter duration of disease was associated with improvement in JOA score, $P = 0.001$. They found no other prognostic factors, such as age or radiographical factors, to be statistically significant.

There is low evidence demonstrating that milder disability before treatment as measured by the motor JOA scale was associated with achieving a "no disability" status on the motor JOA scale at 6-year follow-up after conservative treatment.[38] No disability status was significantly influenced by the degree of disability before treatment. Younger patients (<52 yr) and those with a shorter history of symptoms (<6 mo) achieved the level of "no disability" more frequently than their counterparts; however, these trends were not statistically significant. In another retrospective study, there were no statistically significant findings relating T2WI to a poor JOA outcome or severity of myelopathy after conservative treatment in patients with mild CSM.

Conversion to Surgery

One study by Oshima *et al*[39] used multivariate analysis to evaluate risk factors for patients with CSM treated nonoperatively with conversion to surgery. They reported that total cervical ROM (≥50°) (adjusted hazard ratio: 3.3), segmental kyphosis in the maximum compression segment (adjusted hazard ratio: 4.5), or presence of a local slip (adjusted hazard

TABLE 4. Mean Japanese Orthopaedic Association Scores at Diagnosis and Over Time

Authors	Follow-up (yr)	Number of Patients	Mean Scores	95% Confidence Limits/± SD
Kadanka *et al*[35]*	0	35	14.6	14.1–15.2
	0.5	33	14.9	14.3–15.6
	1	33	15.0	14.4–15.6
	2	32	14.6	14.1–15.2
	3	30	14.7	14.0–15.3
	10	25	15.0	12.2–18.0
Shimomura *et al*[42]	0	56	14.6	±1.3
Sumi *et al*[40]	3	56	14.7	±2.0
	6.5	55	14.1	±2.2
Matsumoto *et al*[36,37]	0	52	14.0	±1.4
	0.5	27	14.3	±1.5
	3	52	14.4	±1.9
	4	27	14.6	±1.5

*Inclusive of patients from Bednarik et al,[32] Kadanka et al,[43] Kadanka et al,[34] and Kadanka et al.[33]

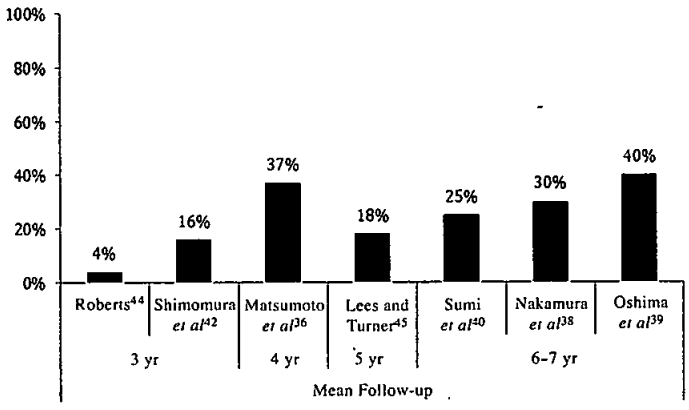

Figure 4. Proportion (%) of patients undergoing surgery at various time intervals after failed nonoperative care.

ratio: 4.7) was independently associated with an increased risk of requiring surgery (Figure 6). Age 60 years and more, sex, C2–C7 alignment, spinal cord diameter less than 50%, developmental canal stenosis, and segmental ROM were not statistically associated with surgery.

Evidence Summary

Although mean scores on the JOA scale tended to remain constant over time, there is moderate evidence that the proportion of patients who deteriorate by at least 1 point 3 to 6 years after the initial diagnosis of CSM ranges between 20% and 62%. Furthermore, the proportion of patients who have difficulty in performing ADLs increases over time and can be as high as 56% 10 years after diagnosis. There is low evidence that circumferential spinal cord compression compared with partial cord compression is associated with a deteriorating JOA score. There is insufficient evidence that age, sex, height, ROM, or other radiological factors influence the rate of progression of CSM (Table 6).

DISCUSSION

Although CSM is the most common cause of spinal cord impairment in adults, the amount and, most importantly, the merit of the clinical studies examining the natural history of this common and unique condition have not been sufficient to provide a clear picture about the natural history of the disease or the risk factors implicated in the progression of the disease.

Moderate evidence coming from mainly small prospective and retrospective studies suggests that the proportion of patients who progressively deteriorate (as defined by at least 1-point decrease in the JOA scale) ranges from 20% to 62%. This large variation could be explained by the different definitions of "deterioration" used in different studies. Moreover, there is moderate evidence showing that patients with CSM experience progressive difficulty in performing ADLs with nonoperative treatment. On the contrary, there is moderate evidence that there is no change in JOA 3 years after the initial assessment. Altogether, it seems that the natural history of CSM varies between patients with some of them exhibiting a slow progressive deterioration and others experiencing long periods of quiescence or slight improvement. Future basic science studies in experimental models that simulate the chronic and progressive nature of the human disease may be most appropriate to elucidate why certain patients remain stable for a long period of time and others progress.

With regard to risk factors that affect the progression of the disease, the available evidence does not suggest age as an associated factor with either the likelihood of deterioration or having surgery. It is worth noting that the available evidence is still insufficient at this point. Furthermore, there is insufficient evidence to indicate that female sex and low body height are associated with a progressively worse neurological condition. Regarding the association of radiographical characteristics, there is insufficient evidence to

TABLE 5. Functional Outcomes at Diagnosis (Baseline) and at Follow-up

Authors	Outcome	Baseline	1-yr	2-yr	3-yr	10-yr
Kadanka *et al*[34]	Daily activities score (% worse *vs.* baseline)*	Referent	6.3	20.9	27.3	56
	Timed 10-m walk (s)	7.4	7.4	7.5	7.5	7.1
Sampath *et al*[46]	Activities of daily living rating assessment	1.84	−0.63†	...	...	...
	Overall functional status rating	1.44	0.27‡	...	...	...

**Patients were evaluated on how they buttoned their shirts, brushed their hair and teeth, performed diadochokinesis, put on their shoes, walked and ran, and went up and downstairs.*

†Positive score indicates improvement, negative score indicates worsening. Patients were asked to indicate which activities of daily living (lifting heavy weights, standing for more than 10 min, sitting for longer than 10 min, driving or riding in a car as a passenger, and lying down) exacerbated their symptoms before and after treatment.

‡Positive score indicates improvement, negative score indicates worsening. Patients used a 4-point scale (none, some, most, all) to indicate how much of their usual work and social activities they were still able to do. Social activities included sexual activity.

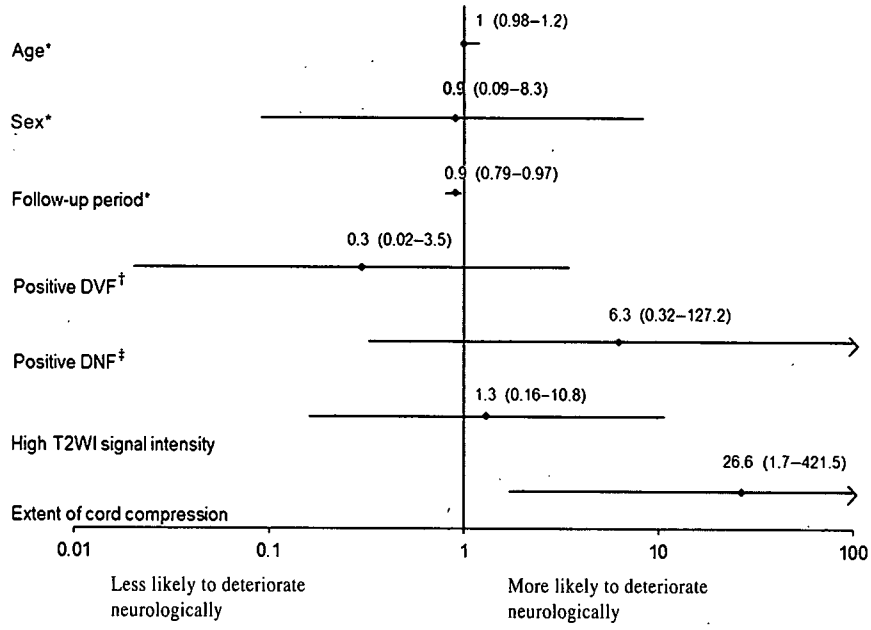

Figure 5. Prognostic factors for neurological deterioration--adjusted odds ratios reported by Shimomura *et al.*[42] *Reference category not mentioned. †Developmental factors on plain lateral radiograph (positive = present). ‡Dynamic factor on plain lateral radiograph (positive = present).

show that a larger transverse area of the spinal cord is associated with neurological improvement. However, low-grade evidence is available showing that circumferential spinal cord compression is associated with deteriorating neurological conditions.

Recent experimental evidence emerging from novel murine models of CSM indicates that chronic and progressive compression of the cervical spinal cord causes microvascular dysfunction, which seems to be critical for the worsening of symptoms in the CSM animals. Because microvascular dysfunction is an important component of diabetes pathophysiology, diabetes may represent an important risk factor affecting the natural history of the disease. Although our literature search revealed few studies[47] that dealt with the surgical outcomes in patients with diabetes experiencing CSM, currently there are no studies examining the interrelation of diabetes with CSM. Thus, exploration of the role of diabetes as a potential risk factor for CSM should be conducted.

Finally, the lack of sensitive outcome measurements to assess the disruption of locomotion, the loss of manual dexterity, and the sensory changes at and below the level of the compression in patients with CSM in a quantitative manner have been considered to be a limiting factor in trying to accurately depict the natural history of CSM. We suggest that there is a need to develop functional outcome measures that will satisfy these conditions and in turn will allow for consistency in the international diagnosis, stratification of severity, and classification of deterioration of CSM. This is covered further in the article by Kalsi-Ryan *et al*[1] in this focus issue.

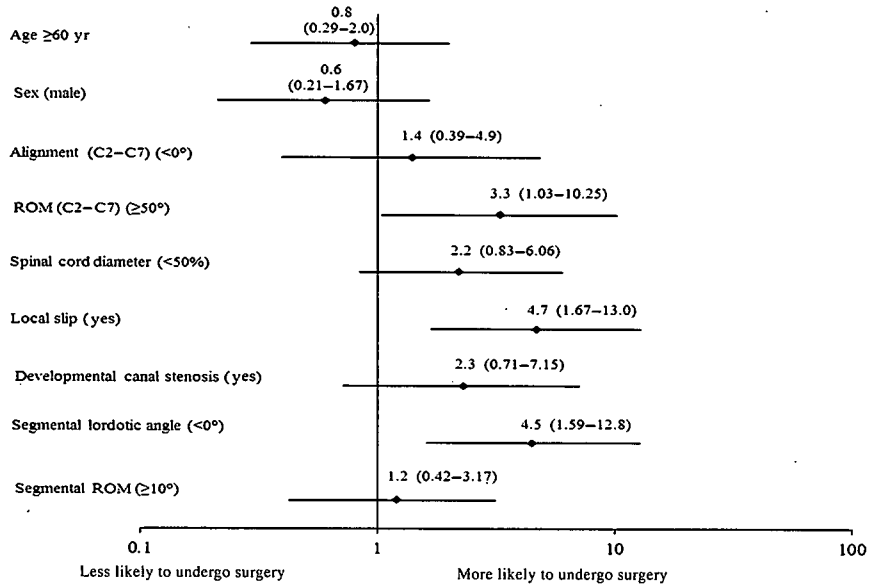

Figure 6. Prognostic factors for surgery--adjusted odds ratios reported by Oshima *et al.*[39] ROM indicates range of motion.

TABLE 6. Evidence Summary

	Strength of Evidence	Conclusions/Comments	Baseline*	Upgrade (Levels)†	Downgrade (Levels)‡
What is the natural history of CSM?					
Neurological outcome					
JOA change compared with baseline	Moderate	Although mean scores tend to remain constant, there is moderate evidence from 2 small prospective and 4 small retrospective observational studies to suggest that the proportion of patients who deteriorate (at least 1 point by JOA) 3–6 yr after initial assessment range from 20% to 62%. Proportion of patients varies by definition of deterioration.	High		Risk of bias (1)
Nurick scale change compared with baseline	Insufficient	There is insufficient evidence from 1 small retrospective observational study (N = 76) to suggest that a majority of CSM patients' status as measured by the Nurick scale will not change over time with nonoperative treatment. Sixty-seven percent of patients were unchanged, 20% improved, and 13% deteriorated after 8 yr.	Low		Inconsistent (1)
Conversion to surgery	Insufficient	There is insufficient evidence from 2 small prospective and 4 small retrospective observational studies to suggest that the proportion of patients undergoing surgery after worsening neurological and/or functional symptoms increases over time. The proportion of patients converting to surgery ranged from 4% to 40% over 3–7 yr, respectively. Severity of disease varied among studies.	Low		Imprecise (1)
Functional outcome					
ADLs	Moderate	There is moderate evidence from 2 small prospective studies (N = 31 and N = 33) that patients with CSM worsen in performing ADLs with nonoperative treatment. One reported 6%, 21%, 28%, and 56% worsening of ADLs at 1-, 2-, 3-, and 10-yr follow-up, respectively, compared with baseline.	High		Risk of bias (1)
Timed 10-m walk	Insufficient	There is insufficient evidence from 1 small prospective study (N = 33) that there is no significant difference in walking times from baseline to 1-, 2-,.3-, and 10-yr follow-up for patients with CSM treated conservatively.	High		Risk of bias (1) Imprecise (1) Inconsistent (1)
Overall functional status	Insufficient	There is insufficient evidence from 1 small prospective observational study (N = 31) to suggest that the overall functional status of conservatively treated patients with CSM improves over time.	Low		Inconsistent (1)
Are there risk factors that affect the progression of CSM?					
Neurological outcome					
Demographic characteristics					
Age	Insufficient	There is insufficient evidence that age at diagnosis is associated with neurological deterioration as measured by JOA. One prospective study reported no association using multivariate analysis, 1 prospective study reported that older age (mean, 58 yr) before treatment was a positive predictor for neurological improvement ($P < 0.05$), and 1 retrospective study using univariate analysis reported that younger age (<52 yr) was a positive predictor for neurological improvement.	Low		Inconsistent (1) Imprecise (1)

(Continued)

TABLE 6. (Continued)

	Strength of Evidence	Conclusions/Comments	Baseline*	Upgrade (Levels)†	Downgrade (Levels)‡
Sex	Insufficient	There is insufficient evidence that sex is associated with neurological progression of CSM (JOA); 1 prospective study found no association using multivariate analysis and 1 retrospective study reported that female sex was associated with a progressively worse neurological condition ($P < 0.05$).	Low		Inconsistent (1)
Height	Insufficient	There is insufficient evidence that lower body height (mean, 170 cm) is a positive predictor for JOA neurological improvement ($P < 0.05$) as reported by 1 prospective study.	High		Risk of bias (1) Imprecise (1) Inconsistent (1)
Radiographical characteristics					
Circumferential spinal cord compression	Low	There is low evidence that circumferential spinal cord compression (compared with only partial cord compression) is associated with deteriorating neurological conditions (JOA) (adjusted odds ratio: 26.6; 95% CI, 1.7–421.5), reported by 1 prospective study using multivariate analysis.	High	Large effect (1)	Risk of bias (1) Imprecise (1) Inconsistent (1)
Transverse area of the spinal cord; Pavlov Index	Insufficient	There is insufficient evidence that a larger transverse area of the spinal cord (mean, 76 mm^2) ($P < 0.05$) and a higher value of Pavlov Index (mean, 0.9) ($P < 0.05$) are associated with improved neurological status (JOA), reported by 1 prospective observational study.	High		Risk of bias (1) Imprecise (1) Inconsistent (1)
Other radiological factors	Insufficient	No significant association between developmental and dynamic canal factors of cervical spine, nor high T2WI signal intensity and neurological deterioration (JOA), reported by 1 prospective study using multivariate analysis.	High		Risk of bias (1) Imprecise (1) Inconsistent (1)
Clinical characteristics					
Initial level of disability	Insufficient	There is insufficient evidence that milder disability before treatment (lower JOA score) is associated with achieving greater neurological improvement ($P < 0.05$), reported by 1 prospective and 1 retrospective observational study.	Low		Imprecise (1)
Duration of disease	Insufficient	There is insufficient evidence that shorter duration of disease is associated with neurological improvement (JOA) ($P = 0.001$), reported by 2 retrospective observational studies.	Low		Inconsistent (1)
Range of motion	Insufficient	There is insufficient evidence that greater neck ROM ($P < 0.05$), greater head ROM ($P < 0.01$), and total head and neck ROM difference ($P < 0.01$) are associated with progressively worse neurological condition (JOA), as reported by 1 retrospective study.	Low		Inconsistent (1) Imprecise (1)
Conversion to surgery					
Demographic characteristics					
Age; sex	Insufficient	There is insufficient evidence that there is no association between age ≥60 yr or sex and conversion to surgery in 1 retrospective study using multivariate analysis.	Low		Inconsistent (1) Imprecise (1)

(*Continued*)

TABLE 6. (Continued)

	Strength of Evidence	Conclusions/Comments	Baseline*	Upgrade (Levels)†	Downgrade (Levels)‡
Radiographical characteristics					
Cervical range of motion	Insufficient	There is insufficient evidence from 1 small retrospective study (N = 45) using multivariate analysis that there is an association between increased risk of surgery and the following 3 factors:	Low	Large effect (1)	Imprecise (1) Inconsistent (1)
Segmental lordotic angle		Total cervical ROM (≥50°) (adjust HR: 3.3; 95% CI, 1.03–10.25)			
Local slip		Segmental lordotic angle (<0°) (adjusted HR: 4.5; 95% CI, 1.59–12.8)			
		Presence of a local slip (adjusted HR: 4.7; 95% CI, 1.67–13.0)			
Other radiographical factors	Insufficient	There is insufficient evidence from 1 small retrospective study (N = 45) using multivariate analysis that there is no association with C2–C7 alignment (<0°), spinal cord diameter (<50%), presence of developmental canal stenosis, and segmental ROM (≥10°)	Low		Imprecise (1) Inconsistent (1)

*Baseline quality: High = majority of article level I/II. Low = majority of articles level III/IV.
†Upgrade: Large magnitude of effect (1 or 2 levels); dose response gradient (1 level); and plausible confounding decrease magnitude of effect (1 level).
‡Downgrade: Inconsistency of results (1 or 2 levels), indirectness of evidence (1 or 2 levels), imprecision of effect estimates (1 or 2 levels), risk of bias (1 or 2 levels), failure to specify subgroup analysis a priori (1 level), and reporting bias (1 level.)
CSM indicates cervical spondylotic myelopathy; JOA, Japanese Orthopaedic Association; ADLs, activities of daily living; CI, confidence interval; ROM, range of motion; HR hazard ratio.

CONCLUSION

With an aging population, the frequency of CSM will continue to increase. Surprisingly, the narrative review we conducted indicates that the natural history of the disease remains to be fully clarified. Thus, the elucidation of the pathobiology and molecular mechanisms of neural degeneration of this unique disease is of crucial importance. Experimental research studies will serve to better direct the clinical studies toward the risk factors responsible for the progression of the disease that will lead to elucidation of the natural history of CSM. We anticipate that preclinical translational research in CSM will enable clinical trials of therapeutic modalities that will complement existing surgical treatments. In addition, careful multicenter clinical registries are needed to define the incidence and prevalence of CSM more accurately and to track the natural history of this common, debilitating condition.

Evidence-Based Clinical Recommendations.

Recommendation. Evidence concerning the natural history of CSM suggests that 20 to 60% of patients will deteriorate neurologically over time without surgical intervention. Therefore, we recommend that patients with mild CSM be counseled regarding the natural history of CSM and have the option of surgical decompression explained.

Overall Strength of Evidence. Moderate

Strength of Recommendation. Strong

Summary Statements. Chronic compression of the spinal cord results in progressive neural cell loss related to secondary mechanisms including apoptosis, neuro-inflammation, and vascular disruption.

➢ Key Points

- ❑ CSM has a unique series of pathobiological mechanisms related to chronic, progressive, spinal cord compression that distinguished this condition from traumatic SCI.
- ❑ Chronic neuroinflammation, cellular apoptosis, and microvascular compromise contribute to the pathobiology of neural degeneration in CSM.
- ❑ The neurological status of 20% to 60% of patients with mild CSM deteriorates over time without surgical intervention.

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