Natural History of Cervical Degenerative Disorders

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Introduction

Cervical spondylosis is a naturally occurring, age-related phenomenon that can be seen radiologically in 95% of males and 70% of females over the age of 70 [13]. It is characterized by degenerative changes affecting the vertebrae, intervertebral discs, facets, and associated ligaments. Starting in the third decade of life, there is a progressive loss of water content of the intervertebral disc that continues with age. This is due to a loss of glycosaminoglycan proteins, which attract molecules of water due to their high molecular weight and overall negative charge, located in the nucleus pulposus. As water molecules leave the nucleus pulposus, this results in a less elastic and more compressible disc that bulges into the spinal canal [7]. At the same time, the vertebral bodies drift toward each other, and the ligamentum flavum and the facet joint capsule fold in dorsally [1]. The combination of these events ultimately decreases the dimensions of the neural foramen and spinal canal. The approximation of the vertebral bodies leads to a reactive process that produces osteophytes around the margins of the disc and at the uncovertebral and facet joints. Radiculopathy in cervical spondylosis is the result of compression either by a hypertrophied facet joint or uncovertebral joints, disc protrusion, spondylotic spurring of the vertebral body, or any combination of these processes [1]. Subacute radiculopathy occurs in patients with pre-existing cervical spondylosis, and these patients often develop symptoms which are polyradicular in nature.

A number of different factors have been implicated in increasing the risk for advanced pathological findings related to cervical spondylosis that include smoking, repetitive trauma (axial loading), Down syndrome, and genetics. Recently, an elevated relative risk of disease in both near and distant relatives of patients with cervical spondylosis has been demonstrated, confirming a genetic predisposition [27]. Additionally, smoking has been associated with disc degeneration and is thus a risk factor for cervical spondylosis [14]. This is particularly true for individuals with collagen IX Trp2 allele, where it is found that smoking amplifies this risk [31]. With disc degeneration, increased mechanical stresses occur at the end plates of the adjacent vertebral body, resulting in subperiosteal bone formation [21]. This bone formation has the potential to ventrally compress the spinal cord, which can result in cervical spondylotic myelopathy (CSM). CSM is the most common acquired cause of spinal cord dysfunction in patients older than 55 years [11]. However, the

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exact prevalence of CSM in the general population is not known [8]. Myelopathy is the end result of three important pathophysiological factors: static mechanical factors, dynamic mechanical factors, and spinal cord ischemia [2]. Unlike typical CSM, ossification of the posterior longitudinal ligament (OPLL) represents a distinct etiological entity with unique natural history [9] that is more commonly seen in certain Asian populations.

The natural history of CSM is very difficult to study due to heterogeneous patient populations, subjective questionnaires used to grade myelopathy and quality of life (QOL) outcomes, and the impossibility of verifying compliance with nonoperative therapy. Although the use of the Japanese Orthopaedic Association (JOA) score is very popular among spine surgeons, the validity of the cutoff JOA score has not been formally tested, and cutoff JOA scores have been seldom used except in some studies. Other commonly used scales include the modified JOA (mJOA), as well as the Nurick scale, which primarily assesses function of the lower extremities. For the Nurick scale, a higher score indicates greater functional impairment (range 0–5). Alternatively, for the mJOA scale, a higher number is associated with normal function (range 1–18). QOL measures have become increasingly important, compared to relying solely on clinical signs/symptoms, in addressing subjective patient concerns when comparing outcomes.

The literature has historically been sparse on studies focusing on comparing outcome measures for patients with CSM. In a recent retrospective study of 119 patients undergoing surgery for CSM by Lubelski et al. [22], the authors compared measured QOL outcomes: health utility (EQ-5D), Patient Health Questionnaire-9 (PHQ-9), and Pain Disability Questionnaire (PDQ) of patients diagnosed with CSM for a 1-year period compared to the CSM-specific measures (mJOA, Nurick scale). The main goal of this study was to examine the convergent validity of QOL outcome measures for CSM, evaluate the responsiveness of each outcome measure, and assess the ability of each measure to predict positive or negative surgical outcomes via EQ-5D index scores [22]. They discovered that all measures demonstrated statistical significance with the EQ-5D and PDQ functional and total scores. The Nurick scale performed the worst in that it did not show significant correlation with either the PHQ-9 or the psychosocial component of the PDQ. Furthermore, the correlation of the Nurick scale was the lowest among those questionnaires with which it did achieve statistical significance. Among the myelopathy scores, the mJOA performed best. The substantially lower correlation between the mJOA and QOL outcomes suggests that these questionnaires are evaluating different aspects of the patient experience. The authors subsequently concluded that the mJOA is best used with the PDQ questionnaire to accurately evaluate the patient's experience following surgery for CSM.

Asymptomatic Cervical Spondylotic Stenosis

Much of our understanding of the natural history of patients with asymptomatic spondylotic cervical stenosis, and the risk for progression to symptomatic myelopathy, comes from prospective cohort studies performed by Bednarik et al. [3, 4, 5]. In the most recent study [3], the authors investigated 199 patients who received an MRI due to either moderate to severe cervical axial pain or clinical signs and symptoms of cervical radiculopathy. These patients were all admitted to the department of neurology between 1993 and 2005 and completed at least a 2-year follow-up. Inclusion criteria were MRI signs of spondylogenic or discogenic compression of the cervical spinal cord, axial pain and/or clinical signs and symptoms of radiculopathy, and the absence of clinical signs and symptoms that might be attributed to cervical cord involvement. The functional status of the patients was scored according to the modified Japanese Orthopaedic Association (mJOA) scale. 141 patients had a maximum entry score of 18, while 58 had a score of 16–17 resulting from motor and/or sensory signs of cervical radiculopathy. The primary end point was defined as the occurrence of clinical signs and symptoms of

CSM and a decrease in the mJOA scale of at least 1 point. Patients were examined at the beginning of the study, every 6 months for the first 2 years, and then annually.

During the follow-up period, 45 patients (22.6%) displayed clinical evidence of progression to symptomatic CSM with a decrease of at least 1 point in the mJOA scale. Sixteen of these patients (35.5%) progressed within 12 months of entry into the study. The 25th percentile time to clinical manifestation of myelopathy was 48.4 months.

Of the variables studied that might be associated with the development of symptomatic CSM, statistical significance was found for radiculopathy ($P < 0.001$), abnormal EMG ($P < 0.001$), abnormal MEP ($P < 0.001$), abnormal SSEP ($P < 0.001$), and MRI hyperintensity ($P = 0.049$). Male gender had an increased risk that did not reach significance ($P = 0.072$). Other risk factors investigated that were not associated with progression to myelopathy included age >50, type of compression (osteophytes and/or herniation), number of stenotic levels, Pavlov ratio <0.8, compression ratio <0.4, or cross-sectional spinal cord area <70 mm^2. Interestingly, risk of early progression (≤12 months) was predicted by the presence of clinically symptomatic radiculopathy, abnormal SEP, and abnormal MEP. Male gender and EMG abnormality were excluded from the set of independent risk factors and ultimately the multivariate regression model, due to highly significant positive correlation with radiculopathy ($P < 0.001$). Conversely, MRI hyperintensity predicted later (>12 months) development of CSM.

Findings such as these prompted the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) clinical practice guidelines workgroup to recommend that "in patients with cervical stenosis without myelopathy who have either abnormal EMG findings or clinical radiculopathy, decompression should be considered. The presence of EMG abnormalities or clinical radiculopathy is associated with development of symptomatic CSM (quality of evidence, Class I; strength of recommendation, B)" [25].

In an additional study by Bednarik et al. [6], the same 199 patients with asymptomatic spondylotic cervical stenosis as previously followed were analyzed for the risk of the development of symptomatic myelopathy after minor trauma. They concluded that there was no statistically significant association between traumatic events and the subsequent development of symptomatic myelopathy (OR 0.935; 95% CI, 0.247–3.535; $p = 0.921$).

Much of the data regarding the progression of asymptomatic patients with ossification of the posterior longitudinal ligament (OPLL) comes from two studies by Matsunaga et al. [23, 24]. These were both prospective cohort studies. In the first study, 323 patients did not have myelopathy on initial presentation and were treated conservatively. Of these patients, 55 (17%) developed myelopathic symptoms requiring surgery. Utilizing a Kaplan-Meier estimate of the remaining myelopathy-free patients, 71% remained that way at 30-year follow-up. All patients with OPLL-induced stenosis greater than 60% developed symptoms of myelopathy. Additionally, increased range of motion was found to be a significant risk factor for those patients with myelopathy and less than 60% stenosis. The authors measured the angle between C1 and the inferior margin of C7 on flexion and extension radiographs and found that the group of patients with myelopathy had a cervical ROM of 75.6° ± 18.3. Those patients without myelopathy had a cervical ROM of 36.5° ± 15.9 ($P < 0.05$). Therefore, the authors concluded that in patients with less than 60% stenosis, ROM appears to be an important variable in the development of myelopathy. In a later multicenter prospective cohort study [23], the same authors evaluated 156 patients from 16 institutions over an average 10.3-year period. They did not report on the time interval to the development of myelopathy. Similar to their previous work, all patients with greater than 60% OPLL-induced stenosis had symptoms of myelopathy. 57 (49%) of the remaining 117 with <60% stenosis were myelopathic. Once again, an increased ROM was associated with the development of myelopathy. Additionally, a lateral-deviated-type OPLL

opposed to central OPLL was more commonly seen in patients who developed myelopathy.

With regard to OPLL in asymptomatic patients and their risk for progression after minor trauma, 1 study found that 13/19 (68%) of patients developed myelopathy [19]. This would suggest that asymptomatic patients with underlying OPLL may be at increased risk for the development of myelopathy after minor trauma, as opposed to those patients with CSM *not* caused by OPLL.

Mild CSM

The evidence for how best to manage a patient with mild CSM is weak to moderate at best. This is due to a heterogeneous patient population, inconsistent follow-up, and variation in nonoperative treatments. Additionally, the majority of studies rely on the JOA (Japanese Orthopedic Association), mJOA, motor function JOA, or Nurick scale for use as an objective measure of myelopathy.

Kadanka et al. [15, 16, 17] in a prospective study attempted to look at patients with mild or moderate clinical myelopathy (mJOA score ≥12) by randomizing them into two groups: those treated surgically and those treated conservatively. In their first study of 68 patients, 33 were treated surgically and 35 nonoperatively. Nonoperative treatment consisted of intermittent cervical immobilization with a soft collar, anti-inflammatory medications, intermittent bed rest for patients with pain, and active discouragement of high-risk activities. Inclusion criteria consisted of clinical signs and symptoms of myelopathy, MRI evidence of cord compression caused by spondylosis (with or without congenital narrowing of the spinal canal), age <75, mJOA score ≥12, and consent to surgery. Outcomes evaluated were a patient self-evaluation, mJOA, 10-meter timed walk, and daily activities (evaluated by two independent physicians blinded to the treatment). The results of this study did not show any difference in outcomes between those patients treated nonoperatively and those treated surgically. However, they acknowledged the goal with surgery is not for improvement but to stop progression and/or sudden deterioration. The same study population was assessed again at the 10-year mark [15], and at that time point, no significant difference between the groups was observed. The authors further acknowledged that according to the power analysis, these results could not definitively answer the question as to whether surgical versus nonsurgical treatment was appropriate in this patient population due to the low number of patients available for final evaluation.

Sumi et al. [30] added to the work of Kadanka with a prospective study of nonoperatively treated patients with mild CSM (JOA ≥13). Sixty patients with mild CSM (42 males and 18 females, average age 57.2 years) were initially treated conservatively. Patients with OPLL were excluded from the study. Follow-up records were available for 55. The mean overall follow-up period was 78.9 ± 39.0 months (range 5–147 months), with those that did not deteriorate being followed for more than 5 years. Surgery was offered with deterioration of myelopathy, defined as a decline in JOA score to less than 13 with a decrease of at least 2 points. Deterioration occurred in 14 of 55 (25.5%) cases between 5 and 96 months after the initial visit. There was not a significant difference seen in mean JOA score between the initial visit (14.5 ± 1.3) and the end point (14.1 ± 2.2; $p = 0.227$). Those patients that deteriorated had a decrease in JOA from 14.3 ± 1.0 to 10.9 ± 1.0 at the end point ($p = 0.001$). No statistical difference was seen between sex, age, or JOA score at the initial visit between the groups that deteriorated and those that remained clinically stable. 74.5% of mild CSM cases maintained the same level of symptoms without deterioration over more than 5 years, with a tolerance rate of 70%. The major prognostic factor in this study that predicted deterioration was the presence of angular-edged deformity, opposed to an ovoid deformity on T1-weighted axial MR imaging. Of those patients with ovoid deformity, only 1/19 (5.3%) deteriorated. This is in stark contrast to those with angular-edged deformity, of which 13/14 (92.9%) deteriorated and 23/41 (56.1%) remained stable during the follow-up period ($p = 0.006$).

Oshima et al. [26] performed a retrospective review of patients with mild myelopathy, as defined by a motor JOA score of 3 or more in both upper and lower extremities, in addition to cervical spinal cord compression with ISI (increased signal intensity) on T2-weighted MRI. They did not include patients with OPLL or disc herniation. The mean follow-up period was 78 months (range, 24–208 mo), and the end point was conversion to surgery. Of the 45 patients at the beginning of the study, 16 deteriorated and underwent surgery, while 27 remained neurologically stable. Two of the patients worsened after minor trauma and consequently received surgery. Kaplan-Meier survival analysis indicated that 82% of the patients continued to be followed without surgery at 5 years and 56% at 10 years. Prognostic factors of the 16 patients that gradually deteriorated were compared to the 27 patients who were followed without surgery, and significance was found for local slip, as well as the segmental lordotic angle at the maximum compression segment. Cox proportional hazard analysis revealed that total ROM between C2 and C7 larger than 50°, segmental kyphosis in the maximum compression segment, and existence of a local slip were all risk factors for surgery. The authors concluded that even in the presence of ISI on MRI, mild CSM is well tolerated in most patients. However, patients should be counseled on the possibility of acute spinal cord injury after minor trauma.

Similarly, Shimomura et al. [29] prospectively analyzed prognostic factors for deterioration in patients with mild CSM. The prognostic factors analyzed included age, gender, follow-up period, developmental or dynamic canal factors of the cervical spine on lateral radiographs, presence or absence of ISI, and the extent of cord compression at the maximum compression segment. The extent of cord compression was further divided into that of partial and circumferential. The mean follow-up period was 35.6 ± 25.2 months. Seventy patients with mild CSM were included in the analysis. Fifty-six of these 70 were observed for the duration of the study, of which 11 deteriorated (moderate or severe forms of myelopathy). The only factor that had a significant effect was circumferential spinal cord compression on axial MRI. Indeed, 10/11 patients with this finding deteriorated. Nonsurgical treatment is generally well tolerated as the first choice of treatment in mild CSM; however, the authors concluded that surgery can be considered for those patients with circumferential compression on axial MRI.

One of the most informative studies in the patient population with mild CSM (JOA ≥13) was performed by Kong et al. [20]. In this study, 78 patients were followed prospectively, and initial management was conservative (traction for 8 h/day for 2 weeks). After discharge, these patients were followed every 3 months and instructed to present earlier should myelopathic symptoms progress. Surgery was subsequently performed when JOA became <13 or a decrease of ≥2 points was observed. All surgeries were performed within 1 month of deterioration, and all surgically treated patients were followed for ≥1 year postoperatively. Twenty-one patients were ultimately treated surgically with a mean reduction in JOA score of 2.9 points (range 2–5) at the time of treatment. The remaining 57 patients had an average JOA score at presentation of 14.2 ± 1.0, compared to 14.0 ± 1.1 in the surgically treated group with a nonsignificant *p*-value of 0.62. The mean JOA score of the surgically treated group decreased to 11.1 ± 0.8 at the time of surgical treatment but improved to 13.4 ± 2.5 following timely surgical intervention. This work and the recent systematic review by Karadimas et al. [18] suggest that patients with mild CSM can be safely managed conservatively with close follow-up and surgical intervention performed acutely once progression of myelopathy is observed, since these patients can generally be expected to return to a level of neurological function similar to those patients who did not experience a decline in JOA scores.

Ultimately, treatment decision-making in mild CSM requires a balancing in understanding the above evidence base, clinician expertise, and patient choice. This is largely why the AANS/CNS spine section clinical practice guidelines recommend that "patients with mild CSM (aged younger than 75 years with a mJOA scale score

>12) be offered both operative and nonoperative management options (quality of evidence: Class I; strength of recommendation, B) [25]. Furthermore, evidence suggests that clinical gains after nonoperative treatment in this patient population are maintained over 3 years in 70% of cases (quality of evidence, Class III; strength of recommendation, D)" [25].

Spinal Cord Injury and CSM

Estimating the risk of acute spinal cord injury (SCI) or central cord syndrome from even minor trauma in patients with cervical stenosis is impossible due to the unknown prevalence of asymptomatic stenosis in the population. Some attempts at estimating this risk through administrative database reviews have been performed. In cases of mild CSM, Wu et al. [33] found a worst-case incidence of SCI of 13.9/1000 person-years for nonoperative care vs 9.4/1000 person-years for operative care. However, this study suffers from the typical problems associated with administrative database studies including lack of clinical granularity and likely incorrect coding issues. In patients with OPLL, however, some data suggests that the risk of SCI is higher than in typical CSM [10, 32], and so clinicians may have a lower threshold for surgical intervention in cases of mild myelopathy with OPLL.

Although patients with asymptomatic or minimally symptomatic CSM should be counseled regarding the possible risk of SCI in the absence of operative treatment, they should also be aware that this risk is very small [9]. Similarly, when contrasting the risks and benefits of treatment for asymptomatic/mild CSM, the clinician need also acknowledge the risks of operative intervention. Total complication rates (early and late) for CSM surgery in one prospective multicenter study [12] have been calculated to be 20%. Though a true "number needed to treat" when considering surgery to prevent a SCI cannot be accurately calculated, perhaps a true "number needed to harm" can be when analyzing surgical complications. Regardless, as mentioned earlier, the decision for or against surgery for asymptomatic or mild CSM should derive from a nuanced discussion between patient and surgeon that is driven by the limited evidence available, rational consideration of the risks, surgeon judgment, and patient preferences.

Moderate to Severe CSM

There is a consensus that patients with moderate to severe CSM should undergo surgical decompression [28]. These patients have a low likelihood of improvement with nonoperative measures [25].

Conclusions, Key Recommendations, and Guidelines

- For asymptomatic patients with evidence of cervical cord compression (without evidence of radiculopathy), prophylactic surgery should not be offered. These patients should be closely followed clinically and understand the relevant signs and symptoms for which to watch. For patients with clinical evidence of a radiculopathy or abnormal findings on EMG, SEP, or MEP, a surgical discussion is appropriate once the patient has failed conservative measures. Class I evidence shows that electromyographic abnormalities (as well as presence of radiculopathy) are predictive of the development of myelopathy in minimally symptomatic patients with cervical stenosis and spinal cord compression [11]. Class II evidence suggests that somatosensory evoked potentials have prognostic value in patients with CSM [11].
- For patients with mild CSM, 20–60% will progress over time without surgical intervention [18]. A supervised trial of nonoperative management may be appropriate in this group. Class II evidence suggests that in patients with mild to moderate CSM (mJOA ≥12), the clinical condition remains stable when observed over a 3-year period in patients younger than 75 [11]. If, however, they fail to improve or demonstrate subsequent neuro-

logical deterioration, prompt operative intervention is warranted.

- The presence of low signal on T1-weighted images and high signal on T2-weighted images and the presence of cord atrophy on preoperative MRI in CSM are indicators of poorer outcome as well as lack of improvement after surgical intervention [11].
- Class III evidence suggests that the duration of symptoms and possibly advancing age negatively affect outcome in patients with CSM [11].
- All patients with moderate and severe CSM should undergo surgical intervention [25].

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