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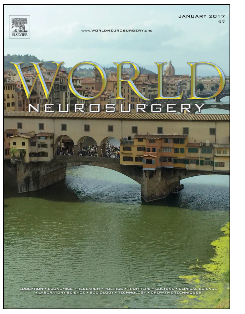

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DEGENERATIVE CERVICAL MYELOPATHY: REVIEW OF SURGICAL OUTCOME PREDICTORS AND NEED FOR MULTIMODAL APPROACH

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INTRODUCTION

Degenerative Cervical Myelopathy (DCM) is a debilitating, progressive, degenerative spine condition, characterized by a neurological dysfunction due to static and dynamic injury of the spinal cord in the cervical spine (1,2). DCM affects quality of life to an extent greater than other chronic debilitating diseases, including hypertension and diabetes, and presents with an incidence of hospitalizations estimated at 4.04/100,000 person-years (3,4).

Since the condition is typically non-painful, and no screening exists, patients are typically diagnosed late once clinical symptoms appear. These include varying degrees of motor and sensory deficits that typically manifest as hand numbness or loss of dexterity in the upper limbs, and loss of coordination, proprioception and imbalance in the lower limbs. Clinically, patients present with hyperreflexia or clonus, and may manifest clinical signs such as the Hoffman or Babinski response (5,6). Symptoms usually appear in an insidious way, however in some patients progression may be slow and yet others may stay stable for a number of years (7,8). Once a clinical suspicion has been raised, imaging confirmation is undertaken with cervical magnetic resonance imaging (MRI) as the modality of choice to assess structural changes of the cervical spinal cord. Besides providing evidence of cord compression, MRI may reveal signs of cord damage on T2-weighted or T1-weighted imaging showing hyperintensity or hypointensity, respectively (9). Other imaging modalities used include conventional radiography with flexion and extension to rule out associated instability and to assess cervical alignment. Computed tomography (CT) scans of the cervical spine may also be useful to assess bone quality and to exclude the presence of ossification of the posterior longitudinal ligament, (OPLL) or ossification of the ligamentum flavum (OLF). Less common, but also useful in the diagnostic process, is the use of electrophysiological exams via sensory evoked potentials (SEPs) and the motor evoked potentials (MEPs) which can evaluate spinal cord tract's conductivity. Changes in conductivity may be useful to assist in the diagnostic process, particularly in patients with mild cord compression, or in whom peripheral neuropathy needs to be excluded.

Once a diagnosis has been established surgical decompression is an effective treatment option for improving both function and quality of life in patients with DCM (10–16). However, it remains challenging to predict the surgical outcome of these patients. Numerous studies on surgical outcome have been performed and some evidence exists that clinical, imaging, and electrophysiological factors can be useful. Indeed, prediction models able to anticipate the surgical outcome have been performed (17–19). However, prediction models comprising imaging and electrophysiological data in addition to clinical data have not yet been formulated. Here we will discuss the predictive capacity of clinical, imaging and electrophysiological data, and discuss the rational for managing patients based on all 3 of these techniques.

CLINICAL PRESENTATION

DCM is essentially a clinical diagnosis (20) and symptoms typically appear in an insidious way, with loss of loss of dexterity (difficulty open and closing buttons, using keys, mobile phones, or writing) or mobility (use of walking aids or frequent falls) (21). The rate of progression and natural history is variable (22,23). In some individuals, symptoms remain mild over extended periods of time, while in others, the disease progresses steadily. Mixed patterns are also described, with long phases of clinical stagnation and sudden aggravation after minor traumatisms (24). In advanced stages of disease, sensory loss, tetraparesis and sphincteric disturbances are common (25,26). Neurological exam is characterized by several signs with different sensitivity and specificity, as hyperreflexia, Hoffmann sign, clonus and Babinski (5,6).

Surgical outcome predictors

Age

The impact of age on surgical outcomes remains the subject of debate. In their systematic review, Tetreault et al. compared significant clinical predictors of outcomes in DCM and evaluated the impact of the age as independent predictor of outcome as well as in association with modified Japanese Orthopedic Association scale (mJOA) and Nurick score (27). The analysis found that age was not clearly predictive of outcome. On the other hand, another systematic review published by Zieli et al. found that the age is a significant clinical variable affecting the outcome, but did not identify a cut-off value (28). Several studies reported that age greater than 65 years should be considered as a negative predictor in DCM (29,30).

Finally, Tetrault et al. analyzed predictors of complications following surgery for DCM and identified age as a significant negative predictor (31). They suggested that this finding is likely due to a combination of factors such as poorer general status, increased number of comorbidities and reduced physiological reserves of the elderly. They also reported that the presence of substantial degenerative pathology in the elderly could require more complex surgery for DCM, with consequential higher rate of complications (32).

While it is unclear if age is a negative predictor of neurological outcome, specific studies on older patients with DCM undergoing surgery have been shown that these patients clearly benefit from surgery, indicating that while older patients may not reach the same neurological recovery and may have more complications due to their age, they can have substantial improvement in neurological function after surgery (29,33).

Duration of symptoms and baseline myelopathy severity

Conceptually, it seems legitimate to think that the longer duration of symptoms, the more consequential and potentially irreversible the spinal cord damage is, thus reducing the possibility of improvement even after surgery. The literature also goes in this direction with recent reviews identifying preoperative myelopathy severity assessment scores (JOA/mJOA and Nurick) and the duration of symptoms as significant predictive factors of surgical outcome (27,28,31,34). Handa et al. retrospectively reviewed a series of 61 patients treated by expensive laminoplasty for DCM and found that patients with a JOA score <12 presented a significant worse neurological recovery rate compared with those with a JOA score >12 (35). Gao et al. retrospectively reviewed 145 patients treated with anterior cervical corpectomy and fusion, to investigate the long term clinical and radiographic outcomes and find out the factors that may affect the long-term clinical outcome (36). They concluded that preoperative duration of symptoms >12 months and mJOA <9 were significant predictors of the fair recovery rate. Machino et al. presented a prospective series of 105 consecutive patients with diabetes and cervical myelopathy who underwent double-door laminoplasty (37). They found that duration of symptoms for 12 months or more were associated with a lower JOA recovery rate. In their retrospective series of 72 patients, Rajshekhar and Kumar found that functional outcomes, calculated by Nurick score, was uniformly correlated with myelopathic symptoms of 12 months' duration or shorter (38). Similar results were reported by Suri et al, who described a lower improvement of Nurick score in patients with longer duration of symptoms (39).

Comorbidities

Comorbidities are known to be a confounding factor on clinical outcomes in many diseases, more particularly diabetes and psychiatric disorders for neurological diseases. The impact of specific comorbidities on DCM prognosis remains a topic not well studied. The most common comorbidities reported in the literature are psychiatric diseases and diabetes, and recently the effect of gastrointestinal comorbidities and anemia have also been investigated.

In a prospective series of 401 patients, Tetreault et al. compared clinical outcomes in patients with and without pre-existing depression or bipolar disorder undergoing surgery for DCM, and concluded that patients with psychiatric comorbidities have smaller functional and quality of life improvements after surgery compared to the control group (40). Similar results were found by Zong et al, who reported that patients with continuous depression showed poorer improvement after posterior decompression with respect to symptom severity, pain intensity, and disability score than patients without depression (41).

The relationship between diabetes and DCM is also debated. Kim et al. compared clinical outcomes in patients with and without diabetes and found that the post-operative recovery rate in the control group was better than that of the diabetic group (42). In their prospective series of 105 patients, Machino et al found that HbA1c levels and duration of diabetes were predictive of achieving a JOA recovery rate (37). In their systematic review, Tetrault et al hypothesized that these results are due to complications associated with diabetes, as macro and microvascular disease, demyelination and peripheral neuropathy (27).

Recently, it has been shown that DCM patients with gastrointestinal comorbidities present with a unique constellation of symptoms different from the general cohort, showing less evidence of neurological dysfunction, but higher neck disability and more frequent psychiatric comorbidity (43). However, no impact on surgical outcome was observed. Multiple studies on anemia in the setting of DCM surgery have also been done. It has been shown that preoperative anemia in general, and also macrocytic anemia are related with a lower preoperative neurological status (44), and that anemia is related with the need for perioperative blood transfusion, return to the operating room, and extended length of stay after cervical surgery (45,46).

Finally, current literature reports a correlation with smoking status and lower postoperative recovery rate (47). In a prediction model developed after evaluating data records, and clinical and radiological data of 278 patients, Tetreault et al. found that patient who smokes is less likely to have a successful outcome compared with a non-smoker (13).

ELECTROPHYSIOLOGY

Current literature reports a growing interest with respect to the role of electrophysiology (MEPs and SEPs) in the management of DCM. Several studies have found that electrophysiological tests offer a good correlation with myelopathy severity and can represent a reliable predictor of surgical outcomes. In their retrospective series, Feng et al. investigated the relationship of progressive myelopathy and SEPs and concluded on a correlation with decline in mJOA and the SEP, reflecting the probability of worsening of myelopathy (48). Nardone et al. evaluated indications and usefulness of various neurophysiological techniques in diagnosis and management of DCM (49). They concluded that SEPs and MEPs recording can usefully supplement clinical examination and neuroimaging findings in assessing the spinal cord injury level and severity.

The value of these tests is not limited to preoperative works up, since the electrophysiology may also help in the differential diagnosis between spinal cord compression and neurodegenerative disorders. Indeed, SEPs and MEPs represent useful tools to evaluate the disease evolution and therefore the efficacy of postoperative rehabilitation. Capone et al. focused on the role of MEPs in the functional assessment of spinal cord before and after surgery to correlate changes in MEPs with clinical findings

(50). They found that, after surgery, the 18-point mJOA score increased significantly from 10.1 to 15.1, and the value of the central motor conduction time for tibialis anterior muscles showed a slight but significant reduction. Therefore, they concluded that beneficial effects of surgery on spinal cord functionality were detected by MEPs. With respect to SEPs, the literature reports the possibility to stratify myelopathic patients in four groups according to the wave configurations (type I, wave configuration was normal; type IV, the waveform was unidentifiable) (51). According to the results, SEPs classification was significantly associated with the JOA, and the recovery rate of patients with identifiable SEPs waves was significantly higher than unidentifiable waves.

Finally, the more interesting advantage of these exams is to identify patients at different stages of disease, mainly at early stages when clinical presentation could be more insidious. Simò et al. analyzed the value of functional assessment of the spinal cord by MEPs and SEPs in the detection of myelopathy, with special emphasis on the correlation of clinical and electrophysiological findings at different moments (52). They found that patients who had no clinical symptoms whatsoever indicating myelopathy (they were referred to MRI examination mostly because of cervical radiculopathy), had in the large majority normal MEPs and SEPs findings, and patients with obvious clinical signs of myelopathy, including pyramidal signs had both abnormal MEPs and SEPs findings. On the other hand, patients with slight, unspecific and non-confirmative symptoms without pyramidal signs had mostly abnormal MEPs but normal SEPs findings. These observations confirmed the superior sensitivity of MEPs over SEPs in detecting myelopathy in its early stages.

IMAGING IN DEGENERATIVE CERVICAL MYELOPATHY

Once there is a suspicion that a patient has myelopathy, an MRI is typically required for confirming the clinical diagnosis. In rare cases, when MRI is contraindicated, a CT myelography may be used. Complementary imaging for surgical planning may be undertaken in the form of standing cervical radiographs, with flexion and extension for assessing alignment, as well CT for assessing bone quality or for confirming the presence of possible ligamentous ossification (OPLL or OLF). As conventional as well as advanced MRI techniques can provide information regarding disease of the spinal cord they

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are frequently used as a supplementary measure to estimate disease severity and to predict surgical outcome.

Conventional and Advanced MRI

Conventional MRI in the setting of DCM is typically performed with T2- and T1-weighted imaging. These are undertaken to identify the cervical levels, and degree of spinal cord compression. However, they can show Modic changes of the bone, as well as demonstrate potential signal intensity changes of the spinal cord. T2 WI hyperintensity signal changes of the spinal cord can appear as fuzzy, not well circumscribed, or sharp with clear borders, with the former typically representing reversible changes such as edema and Wallerian degeneration, whereas the latter typically indicates tissue loss and necrosis (9), (fig.1). Sharp and well circumscribed hyperintensity is often accompanied by T1WI hypointensity changes. Hyperintensity on T2WI is present in most patients, with a range of 58-85% reported in studies (9). The length of T2WI hyperintensity and the presence of T1 hypointensity have been related with worse baseline neurological severity and the presence of clinical signs and symptoms (18). There is also evidence that both T2WI hyperintensity length and T1 hypointensity are predictive of surgical outcome, while the presence or absence of T2 hyperintensity does not seem to discriminate between those that do well versus those that do not (18,21,22,53). This is partially due to its high prevalence. However, the regression of T2WI hyperintensity postoperatively has been correlated with better functional outcomes (21,23). While not routinely undertaken, dynamic MRI also have been shown to have diagnostic importance. Yu et al. evaluated the relationship between signal changes on T2-weighted MRI and cervical dynamics in DCM, and found that increased segmental hyperextension curvature (≥10 degrees) and range of motion are risk factors for high-intensity lesions on T2W in these patients (54). These results are similar to those observed in another study, where the evaluation was performed by flexion-extension MRI. This series showed that patients with DCM are more likely to develop a cord impingement on extension than in flexion (55).

Advanced MRI techniques are increasingly demonstrating clinical utility by investigating structural changes within the spinal cord. Fractional Anisotropy (FA) and Apparent Diffusion Coefficient (ADC) are some of the most commonly done studies, with a lower FA and a higher ADC typically presenting in myelopathy not only at the region of compression (24–26,56). It has also been shown that microstructural changes can be used to evaluate progression of the disease, and outcome (7,26,27). Recent studies suggested that patients with an FAvalue >0.55 represent the best responders to surgery at 1-year (27,53). Additional advanced MRI techniques such as magnetization transfer, T2* and spectroscopy as well as others, are also promising techniques that remain the subject of ongoing investigations (28).

CT and Cervical Radiographs

Standing cervical radiographs are typically obtained in patient with DCM and serve to evaluate the alignment of patient in an upright position. Furthermore, flexion and extension views can be obtained to assess the presence of spondylolisthesis, which is particularly useful to exclude possible dynamic compression in patient with mild compression on MRI that present with clinical symptoms disproportionate to what it would be suspected (29). Other features better evident on radiographs or CT include ossification of the spinal canal ligament such as OPLL and OLF, the presence of Forestier's disease (or DISH), and the presence of congenital cervical fusions (Klippel-Feil Syndrome). While some of these factors do not influence DCM directly, all are important for surgical planning. Of these factors, OPLL is the most important aspect in terms of its potential impact on spinal cord compression. Four types of OPLL are typically described in literature: continuous, mixed, segmental and localized (30). The prevalence of OPLL in the general population has been estimated at 2.2% and prevalence amongst Asians appears to be significantly greater than in other populations (31). The prevalence of OPLL amongst patients with DCM has been estimated at 10.5% (32). Morphological characteristics of OPLL have been also used to predict surgical outcome and it has been suggested that hill-shaped OPLL has worse neurological outcome than that with plateau-shaped ossification (34).

There has been a growing interest in the impact of cervical sagittal alignment in patients with DCM (57,58). Smith et al. showed that cervical sagittal balance (measured via C2-C7 SVA) was related with myelopathy severity with a moderate negative correlation in kyphotic patients of their cord volume and cross-sectional area to mJOA scores (35). On the other hand, they found a positive correlation for

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lordotic patients, suggesting a relationship of cord volume to myelopathy that differs on the basis of sagittal alignment. In their retrospective series, Yuan et al. found that the age combined with C2-C7 SVA could predict the severity of myelopathy, and therefore this parameter should be corrected by surgeons to improve clinical outcomes in DCM patients (59). Similar results were described by Roguski et al., suggesting that preoperative and postoperative sagittal balance measurements predicts clinically significant improvements in patients undergoing decompressive surgery (60). On the other hand, in an analysis of the AO Spine multicenter studies it has been shown that while significant association between cervical deformity and both preoperative disease severity and postoperative outcomes was observed, no impact was seen in patient with deformity correction (36).

RATIONALE FOR A MULTIMODAL APPROACH TO OUTCOME PREDICTION: THE EARLIER THE BETTER

The aim of this review is to highlight diagnostic measures and synthesize the most important predictive factors of surgical outcomes. Indeed, if an early decompressive surgery is considered to be the best treatment option for patients with DCM, the current challenge is to identify patients at early stages of the disease and therefore select the best candidates for surgical treatment. Based on this review, an integration of clinical, radiological and electrophysiological findings should be performed in both preoperative workup and postoperative follow-up. The clinical picture and imaging confirmation remain the first and essential step in diagnosis of DCM. However, our analysis suggests a potential additional benefit from obtaining MEPs and SEPs in the management of this disease. Potential advantages of these investigations include 1) the capacity to early identify patients who present with nonspecific clinical symptoms before the operation; 2) the possibility to use a third parameter to assess postoperative evolution and recovery rate, in addition to the traditional clinical scores and imaging techniques. On the other hand, a possible limitation of these tests could be an overestimation of the disease as well as the risk of “false positives” with additional costs.

Tessitore et al. first proposed an approach based on a synthesis of all these three findings (20,53). In their experience, FA in “best responders” were significantly higher than those of the “normal responders”, both preoperatively and 1-year follow-up. Furthermore, they found that preoperative

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abnormal values of MEPs were related to worse mJOA scores. They concluded that these exams are not only part of a complementary diagnostic analysis, but rather crucial tools in order to identify the best candidates to surgery. Indeed, this multidimensional view allows an appropriate screening of patients, with two main advantages in the DCM management: on the one hand, it helps to improve the recovery rate in patients at early stages of the disease, for whom a surgical indication is clear; on the other hand, it allows to plan a close follow up for patients not yet scheduled for surgery. To the best of our knowledge, these remain the only studies performing this multimodal approach according to a standardized model.

This protocol, accepted by the local ethic committee on September 2011, includes clinical, radiological and electrophysiological exams performed at specific timelines, and exclusively for DCM patients. It is routinely adopted in the management of all patients affected by cervical myelopathy. According to the protocol (table 1), patients with age between 30 and 85 years old and clinical signs or symptoms of myelopathy are included. Eligible patients receive cervical MRIs with DTI sequences and cervical dynamic X-Rays. Preoperative neck disability index (NDI) and mJOA scores are calculated. The diagnostic picture is finally completed with MEPs and SEPs, performed by electrophysiologists. The surgical strategy is therefore decided basing on the combination of this preoperative work-up.

After surgery, the patient is systematically followed with cervical X-rays on the first postoperative day. For patients treated by instrumentation (posterior screws or anterior plates) and fusion, we also obtain either an intraoperative or postoperative CT scan.

The same multidisciplinary approach, including all preoperative clinical, radiological and electrophysiological exams, is performed at three, 12 and 24 months follow up.

CONCLUSIONS

DCM is a progressive and debilitating disease. Early decompressive surgery represents the best option of treatment for these patients. Authors propose a standardized and multimodal approach, based on

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clinical, radiological and electrophysiological elements, to early identify this condition and improve surgical outcomes.

FIGURE CAPTIONS

Fig.1. Types of signal changes that can appear in patients with DCM. A-D: Sagittal T2WI. **A**: Type I, diffuse and faint hyperintensity. **B**: Type II, focal and sharp hyperintensity. **C**: Type III, both type I (*higher arrow*) and Type II (*lower arrow*) hyperintensity characteristics are present. **D**: Two discontinuous focal hyperintensities are present. **E**: Sagittal MRI with T1W1 showing focal hypointensity.

Taken from with permission: Nouri A, Martin AR, Mikulis D, Fehlings MG. Magnetic resonance imaging assessment of degenerative cervical myelopathy: a review of structural changes and measurement techniques. Neurosurg Focus. 2016 Jun;40(6):E5

TABLE

Table 1: Multimodal approach in diagnosis and follow up of DCM. Clinical, radiological and electrophysiological exams are performed at specific timelines.

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	Preop	Postop	3 months	12 months	24 months
Neurological exam	X	X	X	X	X
mJOA/NDI	X		X	X	X
Cervical dynamic x-ray	X	X	X	X	X
MEP/SEP	X		X	X	X
DTI MRI	X		X	X	X

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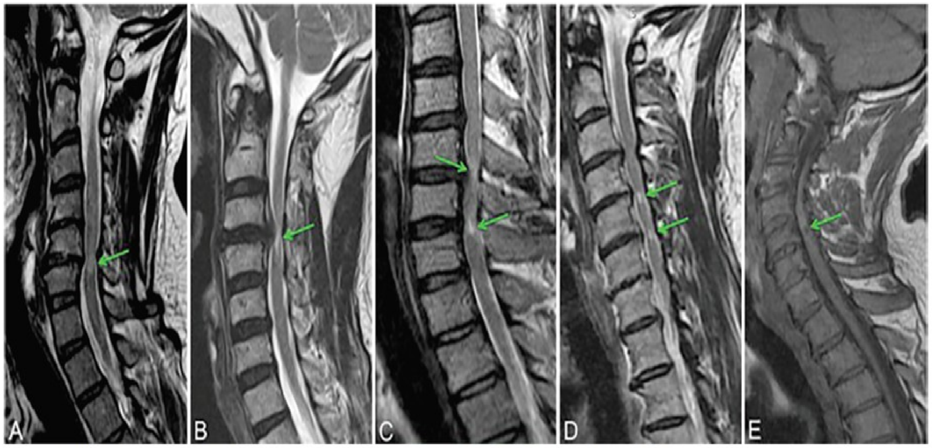
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