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Is surgery beneficial for patients with concurrent multiple sclerosis and degenerative cervical myelopathy? A review of literature

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ABSTRACT

Introduction: Due to an overlap in symptoms, there is significant delay in surgical treatment of patients that have concomitant multiple sclerosis (MS) and degenerative cervical Myelopathy (DCM). The purpose of this review is to evaluate if surgical intervention is beneficial to patients that have concurrent presentations.
Research question: Is surgery beneficial in concurrent MS and DCM?
Materials and methods: A literature search with no date restrictions was conducted on Pubmed and Medline databases. Keywords searched: Degenerative Cervical Myelopathy, Multiple sclerosis, Treatment, Surgery, Quality of Life. Randomised controlled trials, prospective, retrospective, and case series reporting timing of surgery, postoperative outcomes such as improvement in myelopathic symptoms, quality of life, and any serious complications were included.
Results: The literature search yielded a total of 8 studies across all databases. Seven articles were selected for full text review, and all of them were sectioned for inclusion in this review. Seven studies evaluated 160 participants with concurrent multiple sclerosis and degenerative cervical myelopathy. Earlier studies had discouraged performing surgery in this subset of patients, the majority of studies found it worthwhile to perform early surgery for patients with concomitant multiple sclerosis and degenerative cord compression, if the patients had radiculopathy. Quality of life for MS patients did not improve as much as it did for patients that did not have MS.
Discussion and conclusion: Patients with radiculopathy, neck pain and cord compression are most likely to benefit from early surgery. There is no need for delaying to offer surgery unless other medical/anaesthetic contraindications exist.

1. Introduction

Multiple sclerosis is a chronic, predominantly immune-mediated disease of the central nervous system, and one of the most common causes of neurological disability in young adults globally (Oh et al., 2018). Multiple sclerosis (MS), is a chronic disease of the central nervous system (CNS) characterized by loss of motor and sensory function, that results from immune-mediated inflammation, demyelination and subsequent axonal damage (Karussis, 2014; Young, 2000b).

Degenerative cervical myelopathy (DCM) results from compression of the spinal cord due to osteoarthritic changes of the spine, including spondylosis, disk herniation, and facet arthropathy (collectively referred to as cervical Spondylotic myelopathy), pathological changes in the ligaments such as ossification of the posterior longitudinal ligament and hypertrophy of the ligamentum flavum. DCM patients experience a gradual deterioration 20-60% of cases (Tetreault et al., 2015; Young, 2000b).

With similar symptomatology and presentation differential diagnosis between Spondylotic cervical myelopathy and multiple sclerosis or other neurologic conditions may be difficult (Meyer and Sandovss, 1994a) The study aims to examine the evidence available to assist in decision making.

2. Method

The systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review followed the methods

Abbreviations: DCM, Degenerative cervical myelopathy; MS, Multiple sclerosis.

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recommended by the Cochrane Handbook for Systematic Reviews of Interventions.

2.1. Eligibility criteria

Articles were considered for review if they met the following inclusion criteria:

- *Types of studies*: randomised controlled trials, retrospective/prospective studies, case series.
- *Types* of participants: patients with concurrent multiple sclerosis, and degenerative cervical myelopathy
- *Types* of diagnosis: Co-existing multiple sclerosis, and degenerative cervical Myelopathy.
- *Types* of treatments: Surgical treatment
- *Outcomes:* Improvement in myelopathic symptoms, quality of life improvement, MS relapses were noted.

2.2. Search strategy

The electronic databases of Pubmed and Medline, were searched without any date restrictions. A highly sensitive search strategy based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, combined with medical subject headings and keywords to identify potential articles was employed. In addition to the electronic database search, co-authors manually checked the list of references eligible trials and previous reviews.

2.3. Study selection

Titles and abstracts of all records were initially screened by the co-authors after duplicates removed. The full-text article for each potentially eligible article was screened.

2.4. Data extraction

The co-authors independently used a standardised data extraction form to collate first author, year of publication, study design, length of follow-up, number of patients, and main findings.

3. Results

Without any restrictions on publication date; English language; main word search in all-fields: “demyelinating disease, multiple sclerosis (MS),

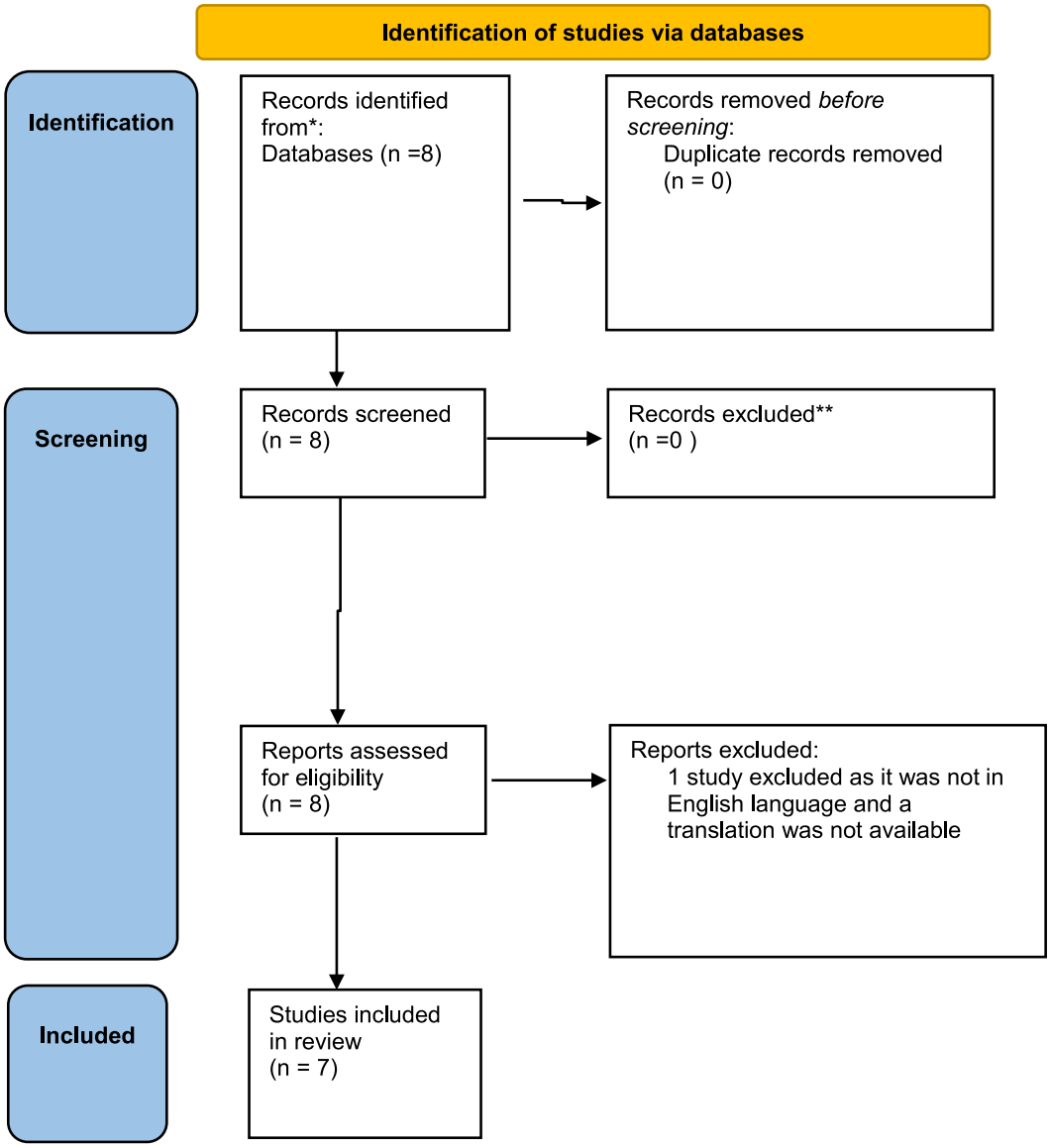

Fig. 1. Prisma flow diagram for review and analysis of surgery in concurrent multiple Sclerosis and cervical Myelopathy.

Table 1
Publications discussing the management of concurrent multiple sclerosis and cervical myelopathy. The table captures the year the publication was made, the number of patients and a summary of key findings.

Author	Year	*N*	Follow up	Findings
F Meyer [1]	1994	4	N/A	Demyelinating diseases should be excluded prior to surgical management of cervical compression myelopathy because surgical intervention can result in marked worsening of symptoms.
Bashir [32]	2000	14	N/A	Surgical intervention was frequently delayed because the neurological deterioration was initially thought to be attributable to MS. The majority of patients experienced either improvement or stabilization of their preoperative symptoms in the immediate postoperative period. No MS relapses, permanent neurological worsening, or serious complications resulting from surgery or general anaesthesia were noted
Carl Youssef [10]	2021	19	5 years	The average delay for referral to the Spine clinic for these patients was 16.5 months (M=5; SD=25.36). More than 89% of patients experienced significant neurologic improvement postoperatively.
Lee Tan [16]	2014	18		Thirteen of the 14 patients (92.9%) with myelopathy showed either improvement (4/14, 28.6%) or stabilization (9/14, 64.3%) in their symptoms with neck pain and radiculopathy improving in 100% and 80% of patients, respectively. None of the seven patients with urinary dysfunction had improvement in urinary symptoms after surgery
Lubelski [19]	2013	154[a]	49–58 months.	Myelopathic patients with coexisting MS and CS improve after surgery, although at a lower rate and to a lesser degree than those without MS
Arnold [17]	2011	15	47 months	Thirteen patients showed objective improvement in neurologic function, including increased lower and upper extremity strength. Two patients' symptoms stabilized. Thirteen of 15 patients also had improvement in neck and/or upper extremity pain or paresthesias; 2 patients had continuing upper and lower extremity paresthesias. The patient with bladder incontinence had no improvement of this problem.
Lubelski [21]	2014	65[b]	18–22 months	Patients in the control cohort had clinically and statistically significant improvements in QALY outcomes. Those in the MS cohort averaged no change in QALY.

[a] 154 patients. Matched cohort-controlled retrospective review of 77 surgical patients in the MS group and 77 surgical patients in the control group.
[b] *65 patients were reviewed, including 13 in the MS group and 52 in the control group.*

degenerative cervical myelopathy (DCM), cervical spondylitis myelopathy (CSM), demyelination, Surgery and Myelopathy". We obtained eight articles across all databases, Following a full-text review of the remaining 8 studies, the authors selected 7 studies that met the inclusion criteria to draw conclusions (Fig. 1). Out of seven studies, all were case series. Excluded studies included studies published in any language other than English without a translation to English option.

Results are summarised in Table 1.

3.1. Delay in surgery

One study reported excluding patients with concurrent DCM and MS from surgical candidates list, and two studies had surgical intervention delayed for patients.

3.2. Changes in myelopathic symptoms

Although, five studies reported an improvement in symptoms, two comparative studies reported a more significant improvement in patients without concurrent MS and DCM than with. (Youssef et al., 2021; Tan et al., 2014; Arnold et al., 2011; Lubelski et al., 2014a; Bashir et al., 2000).

Quality of Life (Physical Compartment, Mental Compartment Scores).

One study reported higher quality of life in patients without concurrent MS (Lubelski et al., 2014b).

3.3. Serious complications

No serious complications were reported by any study.

4. Discussion

This literature review showed that patients that have multiple sclerosis that is concomitant with degenerative cervical myelopathy will benefit from timely surgery.

Multiple sclerosis is the most common inflammatory neurological disease in young adults. The mean age of diagnosis is approximately 30 years, with most patients presenting with periodic neurological relapse (Reich et al., 2018). There is a clear gender predilection with most of those affected being women (Reich et al., 2018).Over the past five decades, prevalence has been rising across North America and Europe, high incidence has been seen among women and among African Americans, and persistent geographical risk gradients have been documented (Evans et al., 2013; Kingwell et al., 2013). Multiple environmental factors and genetic influences might increase the risk of developing multiple sclerosis, but the underlying cause of the disease is unknown (Dyment et al., 2006).

Common neurological manifestations of multiple sclerosis include optic neuritis, diplopia, sensory loss, limb weakness, gait ataxia, loss of bladder control, and cognitive dysfunction (Karussis, 2014; Kesselring and Beer, 2005). MS causes lesions that can be seen throughout the CNS and these are usually noted to be areas of focal demyelination, inflammation and gliosis (Karussis, 2014). Spinal cord lesions cause a wide range of symptoms and can prove to be debilitating. Spinal cord atrophy results from focal inflammatory demyelination. MRI imaging findings are not reliably correlating to clinical features and findings of MS (Bö et al., 2007; Gilmore et al., 2009). MS is classified into four main types by the National MS Society Advisory Committee on Clinical Trials in MS. The types are based on the phase and severity of disease progression. The four types are: clinically isolated syndrome (CIS); relapsing-remitting MS (RRMS); secondary progressive MS (SPMS), and; primary progressive MS (PPMS). The main modifier in classifying the disease is level of disease activity and MRI changes (Oh et al., 2018; Karussis, 2014; Lublin et al., 2014; Sormani, 2013).

Degenerative cervical myelopathy (DCM) and multiple sclerosis (MS) are two common conditions with distinctive pathophysiology but overlapping clinical manifestations which may include myelopathy, motor/sensory disturbances, and bowel/bladder dysfunctions. The hallmark symptom of DCM is weakness or stiffness in the legs (Youssef et al., 2021; Ghogawala, 2018; Kalsi-Ryan et al., 2013). Patients with DCM may also present with unsteadiness of gait. Weakness or clumsiness of the hands in conjunction with the legs is also characteristic of DCM. Symptoms may be asymmetric particularly in the legs. Loss of sphincter control or frank incontinence is rare; however, some patients may complain of slight hesitancy on urination (Kalsi-Ryan et al., 2013). Myelopathy pathophysiological mechanism is postulated to arise from static compression, spinal misalignment leading to altered cord tension and vascular supply, and dynamic injury mechanisms (Kalsi-Ryan et al., 2013). Factors such as occupational risks and increase in age may accelerate DCM development. There is a small role for genetic factors such as those related to MMP-2 and collagen IX for degenerative disc disease, and collagen VI and XI for ossification of the posterior longitudinal ligament. Congenital anomalies including spinal stenosis, Down syndrome, and Klippel-Feil syndrome may also predispose to the development of DCM (Kalsi-Ryan

et al., 2013; Nouri et al., 2017; Tetreault et al., 2015).

While the pathophysiology of multiple sclerosis (MS) and degenerative cervical myelopathy (DCM) differs—MS via an autoimmune process and DCM by a mechanical compressive process—both are characterized by damage to myelin and have overlapping presentations (Hurwitz, 2009; Young, 2000a; Ulmer et al., 1993; Nouri et al., 2015) Patients with DCM that are candidates for surgery suffer from progressive neurologic changes with signs of severe spinal cord compression or spinal cord swelling (Kalsi-Ryan et al., 2013; Tetreault et al., 2015).

Changes are usually subtle at the onset but usually are progressive, these include limb weakness, clumsiness, loss of balance, gait abnormality (Tetreault et al., 2018; Youssef et al., 2021; Ghogawala, 2018; Kalsi-Ryan et al., 2013).

Typical surgical procedures are anterior cervical discectomy fusion, anterior cervical corpectomy and fusion, laminectomy and laminoplasty (Tetreault et al., 2018; Ghogawala, 2018; Milligan et al., 2019; Badhiwala et al., 2020; Bakhsheshian et al., 2017; Kato et al., 2018).

Significant delay in treatment for surgical findings is noted on treatment of concurrent DCM and MS. Even in cases with radiologically visible impingement of neural elements, significant delay is experienced (Youssef et al., 2021). A retrospective review by Bashir et al. showed that despite the availability of spine imaging showcasing impingement of the neural elements that would warrant a surgical decompression at the time of diagnosis. A delay in referral of an average of 16.5 months was noted. Despite the delay in diagnosis and treatment, the vast majority of the patients in this cohort reported positive outcomes with minimal morbidity following surgery. No additional surgical risks from surgery were identified when compared to the general population. Meyer et al. had concluded that surgery in concurrent DCM and demyelinating diseases would result in marked worsening of symptoms (Meyer and Sandovss, 1994b). This was disputed by Bashir et al. who in two separate studies, showed that Decompression surgery in carefully selected MS patients who have coexistent spinal cord compression is well tolerated and may result in an excellent outcome. (Bashir et al., 2000, 2001). His study further surmised that clinical features in particular; neck pain and cervical radiculopathy together with congruent findings on magnetic resonance imaging may assist clinicians in decision making and help avoid unnecessary delay. In a matched cohort retrospective review by Lubeski et al. in a single centre reviewing patients between January 1996 and July 2011 with concurrent diagnoses of MS and DCM, a total 154 patients were reviewed, including 77 MS patients and 77 control patients, for an average follow-up of 58 months and 49 months. After surgery it was found that a significantly lower rate of postoperative resolution of myelopathic symptoms in both the short-term (39% in the MS group did not improve vs. 23% in the control group; p=.04) and the long-term (44% in the MS group did not improve vs. 19% in the control group; p=.004). (Lubelski et al., 2014a).

A later study by Lubeski et al. reviewed the quality of life (QOL) and quality of life adjusted years (QALY) for two cohorts. Sixty-five patients were reviewed, including 13 in the concurrent MS/DCM group and 52 in the control group that were followed for an average of 22 and 18 months, respectively. Whereas patients in the concurrent MS/CCM cohort remained at a Quality-Adjusted Life-Year (QALY) gain of 0.51 both pre- and post-operatively ($p = 0.96$), patients in the matched control cohort improved from a preoperative QALY of 0.50 to a postoperative QALY of 0.64 ($p < 0.0001$). The control cohort represents an improvement that exceeds the minimum clinically important difference. Overall, 70% of patients in the control group experienced an improvement in QALY, compared to only 54% in the MS group ($p = 0.4$). Though patients in the control cohort had clinically significant improvements in QALY outcomes. Those in the MS cohort averaged no change in QALY. However, only a minority of MS/CS patients had worsening QALY following surgery, and as such surgery may still be considered for these patients. The possibility of minimal improvement must be discussed with these patients. [21]

A retrospective cohort review by Tan et al. of eighteen patients with coexistent DCM and MS who had undergone cervical spine decompression showed a low rate of surgical complications. This did show that spinal surgery is safe in concomitant CS and MS. It also enables the clinical team eliminate DCM as a confounding factor in the management of MS patients (Tan et al., 2014). It is worthwhile to note that none of the patients with urinary dysfunction in his cohort had improvement in urinary symptoms after surgery. Urinary symptoms, bladder incontinence to be specific, did not recover after surgery in another long term follow up of 15 patients with concurrent DCM and MS (Arnold et al., 2011).

Due to a suspicion that areas of demyelination attributable to multiple sclerosis (MS) might occur more commonly in regions of pre-existing cervical stenosis (CS); a retrospective study was done by Gratch et al. In this study they looked at 100 concurrent MS/DCM patients and 100 MS-only controls over a period spanning 10 years. In this study an association was found to exist between segments of spinal cord with at least moderate DCM and segments with MS lesions. Clinical significance of this association has not been established (Gratch et al., 2020). However, despite the biological feasibility of this idea, it remains quite controversial due to a lack of definitive epidemiological evidence and the difficulty of proving such a broad connection. Though larger multi centre studies are required to assess if cervical stenosis is a causative or aggravating factor in multiple sclerosis, it might seem intuitive to perform decompressive surgery in this context.

5. Limitations of the review

There were no randomised control studies or prospective studies identified for this literature review and thus this limits the strength of recommendations that can be made from this literature review.

6. Conclusion

Cervical spine decompression and fusion can improve or stabilize myelopathy, and significantly relieve neck pain and radiculopathy in the majority of patients with coexistent DCM and MS. Urinary dysfunctions appear unlikely to improve after surgery. Early surgery is recommended for radiologically visible spinal cord compression in patients that have neck pain and/or radiculopathy. In patients with radiologically visible cervical myelopathy and radiculopathy that is concurrent with MS, surgery helps eliminate DCM as a confounding factor or factor contributing for deterioration in future presentations and treatment of the patient. Due to an overlap in symptoms, the potential for significant delay in treatment is a potential pitfall. Patients with concurrent MS and DCM might have a lower rate of symptom resolution as compared to CSM patients without MS but this should not be a deterrent for performing surgery. We find it useful to recommend early surgery unless there are other medical or patient related factors that would necessitate a delay. Surgery remains safe and provides clinical improvement. There is a possibility that the change in quality of life might not be significant after surgery for patients with concurrent MS and CSM and we therefore urge an honest discussion aimed at balancing patient expectations. There are very few prospective trials for spinal surgery in the context of concurrent MS with cervical myelopathy and as such we propose that regional/local consensus based guidelines be used to assist in decision making.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: No other relationships or conflicts of interest to declare

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