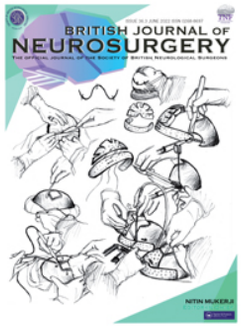

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REVIEW ARTICLE

Tremor as a symptom of degenerative cervical myelopathy: a systematic review

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ABSTRACT

Background: AO Spine RECODE-DCM (Research objectives and common data elements for degenerative cervical myelopathy) has highlighted that the subjective disability reported by people living with DCM is much broader than routinely considered today by most professionals. This includes a description of tremor. The objective of this review was to study the incidence and possible aetiology of tremor in degenerative cervical myelopathy (DCM).

Methods: A systematic review registered in PROSPERO (CRD42020176905) was conducted in Embase and MEDLINE for papers studying tremor and DCM published on or before the 20th of July 2020. All manuscripts describing an association between tremor and DCM in humans were included. Articles relating to non-human animals, and those not available in English were excluded. An analysis was conducted in accordance with PRISMA and SWiM guidelines for systematic reviews.

Results: Out of a total of 4402 screened abstracts, we identified 7 case reports and series describing tremor in 9 DCM patients. Papers were divided into three groups for the discussion. The first group includes DCM correctly identified on presentation, with tremor as a described symptom. The second group includes cases where DCM was misdiagnosed, often as Parkinson's disease. The third group includes a single case with a previous history of DCM, presenting with an otherwise unexplained tremor. This grouping allows for the clustering of cases supporting various arguments for the association between tremor and DCM.

Conclusion: DCM can be associated with tremor. The current evidence is restricted to case series. Further study is warranted to establish tremor prevalence, and its significance to assessment and management.

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Spinal cord diseases; cervical vertebrae; spondylosis; spinal osteophytosis; tremor; dystonic disorders; dyskinesias; movement disorders

Introduction

Degenerative cervical myelopathy (DCM) is a chronic neurological condition of symptomatic cervical spinal cord compression secondary to degenerative spinal pathology.[1,2] Accurate epidemiological data on DCM are scarce, owing to the fact that the condition remains severely under- and misdiagnosed.[3,4]

DCM is often progressive and in extreme circumstances may lead to paralysis.[5] Surgical decompression of the cervical spinal cord is currently the only evidence-based treatment.[6–8] It is able to halt disease progression, and in most cases offer meaningful recovery. However very few patients make a complete or near complete recovery, often being left with life-long disabilities. Consequently, DCM can severely impact quality of life of patients[9] and their carers.[10] Timely management is therefore a critical priority to improving outcomes, as identified by AO Spine RECODE-DCM.[11] However, this requires early identification of DCM patients to facilitate close monitoring,[12] and appropriately timed surgical intervention.[6]

Early identification has proven difficult. Typical DCM symptoms including neck pain and stiffness, limb pain, weakness, stiffness, numbness, paraesthesia, deterioration of manual dexterity, balance and coordination disturbance and autonomic dysfunction such as poor control of the bladder and bowels.[1,13–15] However there is emerging evidence that this description underrepresents the DCM phenotype, a knowledge gap that might be contributing to late detection.[16,17] Amongst the additional symptoms identified in a recent DELPHI survey of 224 people living with DCM, tremor emerged as a symptom reported by around 40% of patients.[16]

The aim was therefore to systematically review the literature for evidence on the incidence, nature and diagnostic utility of tremor in adults with DCM, to further evaluate the association between tremor and DCM.

Methods

Systematic searches were conducted in Embase and MEDLINE via Ovid in accordance with Peer Review of Electronic Research

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Supplemental data for this article can be accessed here.

Strategies (PRESS),[18] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] and Synthesis Without Meta-Analysis (SWiM) guidelines.[20] The review was registered in the international Prospective Register of Systematic Reviews (PROSPERO, CRD42020176905).

Searches were conducted for all the studies reporting tremor in the setting of DCM on the 20th of July 2020 using an adapted version of a previously-established search strategy for DCM in MEDLINE.[21] The searches were performed for all entries available up until the date of the search, with no limits imposed. The full search strategies are described in Supplementary Appendix 1.

Title and abstract of each paper were screened independently by two separate investigators (MEK and CP or YH) using the Rayyan web and mobile app for systematic review (Qatar Computing Research Institute, Doha).[22] Two investigators (MEK and AEK) independently reviewed the full text articles. Any instances of disagreement about inclusion of a paper were discussed until a mutual agreement was established. Clinical studies of any design were included if there was a report of tremor in a patient who was diagnosed with DCM. This included abstracts, case reports, and case series. Initially, case reports and series were excluded. However, paucity of on tremor in DCM prompted a revision of the inclusion criteria to include the case reports and conference abstracts before re-screening. Articles were excluded if there was no mention of both tremor and DCM, if the text was not available in English, or if the study investigated cadavers, animals, or tissue samples.

Data from the included papers were extracted by two investigators (MEK and AEK) independently using a pre-established extraction criteria agreed by all authors. Patient demographics, presenting complaint, initial diagnosis, report of tremor, onset (acute/chronic), comorbidities and past medical history, radiological findings, management, and outcomes were extracted. The risk of bias within each study included was assessed used the Evidence Based Spine-Care Journal's definition for class and strength of evidence;[23] no risk of bias across studies was identified, and no methods of additional analysis were used.

Papers were divided into two groups based on whether DCM was initially diagnosed after a patient presented with a tremor, or whether the patients presenting with tremor were initially diagnosed with another entity, and diagnosis revised after imaging investigation. This was to highlight the importance of considering DCM as a differential diagnosis when a patient presents with a tremor and consider whether there were any important differences between the correctly and mis-diagnosed groups.

Statistical analysis

A synthesis without meta-analysis was deemed most appropriate based on characterisation of the extracted data,[20] specifically the absence of any primary research investigating the incidence of tremor in DCM, but the identification of a number of case reports and case series that describe this association.

Results

A total of 4475 manuscripts were identified by the searches; 4402 remained following the removal of duplicates. Overall, 4395 manuscripts were excluded in the initial screen as they did not investigate or report tremor in the context of DCM. A total of 7 papers were further assessed for eligibility; all 7 were included in the qualitative analysis (Figure 1).

The extracted data are summarised in Table 1. All included papers have a high risk of bias, owing to the nature of the publication being a case report[23] (Table 1).

We identified 4 cases where DCM was correctly diagnosed, with tremor as one of the reported symptoms.[24–26] Two of these cases report a complete resolution of the tremor following surgical management of DCM.[25,26] One report describes the development of a right upper limb kinetic tremor 2 weeks following surgical management of DCM.[24] Finally, a case by Perez *et al.* does not directly discuss the progression of the tremor, but reports the resolution of tremor following spinal neurostimulation.[25]

Furthermore, there were 4 patients who were initially diagnosed with a different entity.[27–29] In 3 out of the 4 cases this was believed to be Parkinson's disease.[27,28] In all 4 cases, the diagnosis of DCM was made after radiological evidence of cervical spinal cord compression. Only one case describes outcomes following DCM management, and reports complete resolution of the tremor 8 weeks after cervical discectomy.[28]

One additional case report describes an association between tremor and DCM in a patient with Parkinson's Disease and a history of previous cervical myelopathy.[30] He was treated with a subthalamic nucleus deep brain stimulation,without improvement of PD symptoms. The patient continued to experience residual symptoms, including tremors.

Discussion

DCM is severely underdiagnosed and misdiagnosed.[3] Tremor is not often considered as a symptom of DCM.[1] In our systematic review, a number of cases reporting an association between tremor and DCM were identified, supporting the findings of our recent study that tremor may be a possible presentation of DCM. At present, the quality of evidence is low.

Findings in context

In the cases presented by Perez *et al.* and Magalhães *et al.*, patients reported a tremor as part of their presenting symptoms, which led to a correct initial diagnosis of DCM.[25,26] Following surgical intervention, the tremor in these cases fully resolved. These findings thus support a myelopathic aetiology to the tremor, however the underlying anatomical basis pertaining to tremor aetiology may not necessarily be limited directly to the cervical spinal cord given the emerging evidence for plasticity throughout the brain both in untreated DCM and following decompressive surgery for DCM.[31] Given that tremor is classically associated with basal ganglia and cerebellar networks,[32] it may well be that DCM precipitates plasticity within these networks, indirectly leading to tremor. Future studies on the timing of resolution of tremor following decompressive surgery and its correlation with other symptoms and neuraxial imaging may help delineate the mechanism.

Additionally, one of the papers presented a case of DCM with a new onset of tremor two weeks following C2-C6 posterior laminectomy.[24] The aetiology of this tremor is unclear but may well be a directl result of the spinal cord injury, which constitutes the pathophysiological mechanism of DCM or a knock on effect on the more traditional tremor-generating networks within extrapyramidal structures following decompression. The longevity of this tremor may help with untangling this.

Four cases were identified in the literature where patients presenting with a tremor were initially misdiagnosed. In three of

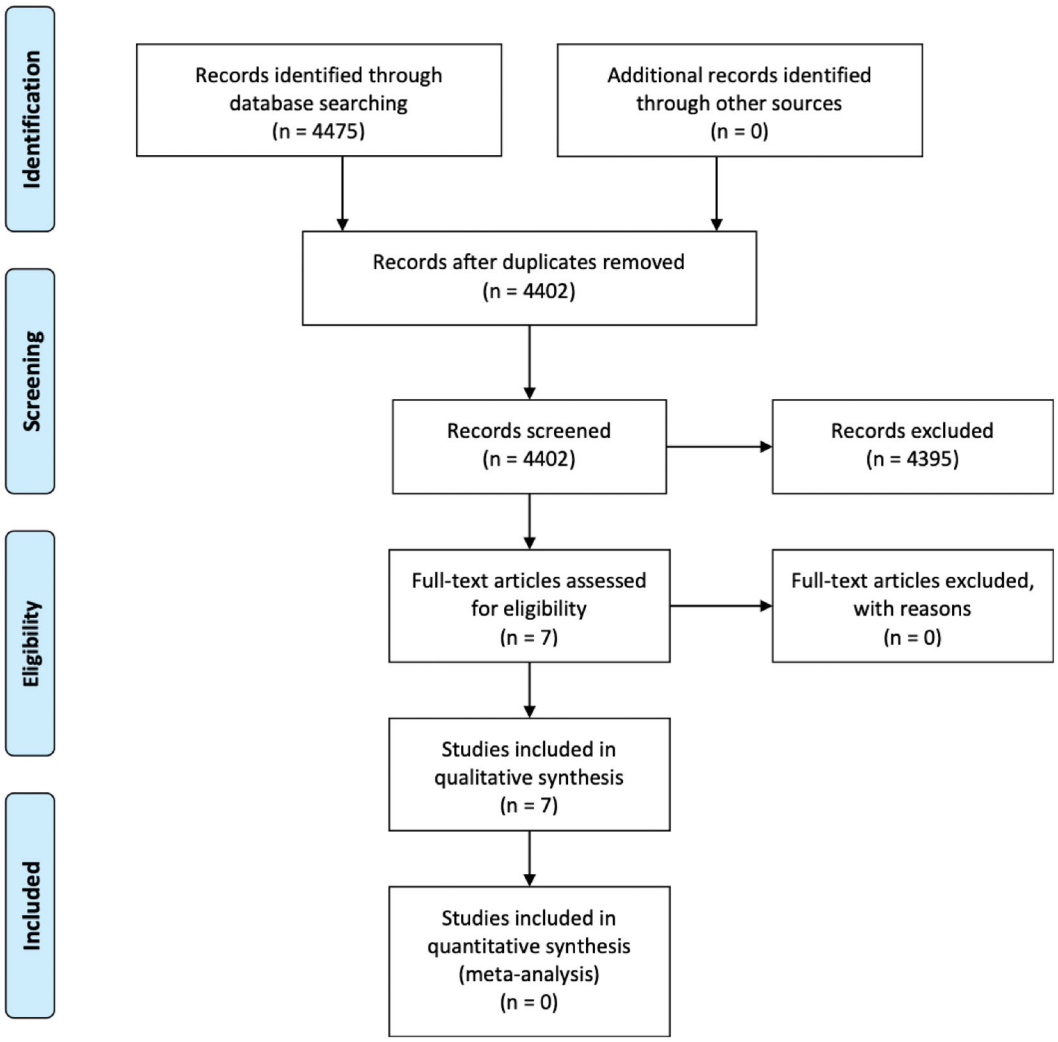

Figure 1. PRISMA flow diagram.

these cases, the patients were initially worked up for Parkinson's disease, with the correct diagnosis of DCM only being reached following spinal imaging. This is likely due to the absence of a well-known association of tremor with DCM, and its classical association with other diseases such as PD. The reports by Ali *et al.* do not specify whether a tremor was detected on presentation; the authors characterise PD as a disease of tremor and bradykinesia, and report missing the diagnosis of DCM in favour of PD.[27]

Furthermore, the case by Farris *et al.* presents a patient with a previous history of DCM who underwent deep brain stimulation of the subthalamic nucleus for parkinsonian tremor. Due to residual tremor following a procedure that normally shows marked improvement of symptoms, it was hypothesised that deep brain stimulation resulted in the unmasking of a DCM-associated tremor.[30]

Diagnostic implications

The diagnostic steps advised would be referral along an agreed local musculoskeletal pathway for an MRI cervical spine if a presentation fits with possible DCM. If Parkinson's disease, or another tremor disorder is a strong differential, referral for a neurology opinion would be advised. Importantly, the message is that tremor can occur in DCM and the presence of tremor should not in itself lead to the dismissal of DCM as a possible differential diagnosis.

DCM Tremor-aetiology

One potential mechanism by which these tremors could arise is through the disruption of supraspinal inhibition of stretch reflex loops in the spinal cord secondary to mechanical compression. Central oscillators in the spinal cord may be disinhibited, resulting in rhythmic muscle contractions. This hypothesis, developed by Dimitrijevic,[33] is further explored in the case report by Fraix *et al.*[24] An alternative hypothesis suggests spinal cord compression precipitates plasticity and reorganisation in cortical and subcortical structures. For example, spinal decompression for the treatment of DCM leads to a significant reduction in activity in the supplementary motor area (SMA).[31] This may well be involved in the resolution of the tremors described in the case reports above, owing to this area's connection with the cerebellum and basal ganglia.[34] A first step in testing these hypotheses requires high-quality primary evidence better characterising the features of tremor in DCM patients, its relationship to other

Table 1. Nine cases relating tremor and DCM from 5 case reports and 2 case series.

First Author	Year	Patient demographics	Initial diagnosis	Presenting Complaint	Tremor on presentation	Past Medical History	Radiological Findings	Suggestive of DCM?	Diagnosis revised?	Management	Outcome
V Fraix[24]	2008	M, 46	DCM	Paresthesia in 4 limbs	No	Nil	C5-C6 disc protrusion	Yes	No	C2-C6 posterior laminectomy	Right upper limb kinetic tremor developed 2 weeks post-op.
J Perez[25]	2020	M, 39	DCM	Spastic left lower limb and bilateral upper limb paresthesia	Involuntary rhythmic truncal contractions	C5-C6 disc prolapse successfully treated with discectomy and fusion	C5-C6 disc prolapse with cervical myelopathy	Yes	No	C5-C7 ventral fusion with plating	Progression of lower limb symptoms. Resolved with further neurostimulation. No mention of previous symptoms.
J Perez[25]	2020	M, 57	DCM	Left arm tremor	4Hz involuntary movements of left upper limb	C5-C6 disc protrusion, surgically treated	C6-C7 disc prolapse	Yes	No	C6-C7 fusion plating and C7-T1 laminotomy with 16 pole paddle electrodes	Resolution of symptoms.
A Magalhães[26]	2015	M, 81	DCM	Imbalance, clumsy hands	Bilateral upper limb intention tremor	Diabetes	C3-C6 spinal stenosis	Yes	No	C4-C6 decompressive laminectomy	Marked improvement, and resolution of ataxia at 1-month post-op.
R Ali[27]	2009	F	Parkinson's Disease	Fractured wrist	No	Nil	Severe C3-C4 spondylotic myelopathy	Yes	Yes	N/A	N/A
R Ali[27]	2009	F	Parkinson's Disease	Complete paraparesis	No	Nil	C5-C6 spondylotic myelopathy	Yes	Yes	N/A	N/A
M Goh[28]	2019	M, 91	Parkinson's Disease or Stroke	Generalized upper and lower limbs tremor	Four-limb resting and action tremor	Nil	C3-C4 spondylotic myelopathy	Yes	Yes	C3-C4 anterior cervical discectomy	Complete tremor resolution at 8 weeks post-op.
C Cerami[29]	2008	M, 21	Hirayama Disease	Wellness Check	Left hand contraction tremor	Nil	C5-C6 spondylotic myelopathy	Yes	Yes	Referred for corrective spinal surgery	N/A
S M Farris[30]	2008	M, 60s	Parkinson's Disease	Worsening motor function	Right upper limb tremor	C3/C4 spinal cord contusion with residual left leg weakness	N/A	No	No	STN stimulation	Significant improvement

symptoms, association with clinical and radiological disease characteristics and response to surgical management.

Limitations

The findings presented above all constitute case reports and conference abstracts of clinician experiences, and therefore represent low quality of evidence. Nevertheless, these reports, illustrate the difficulty surrounding DCM diagnosis and identify an avenue for research that may improve diagnostic reasoning in DCM.

Initially, case reports and series were excluded in the screening process. However, the absence of any primary literature investigating the association between tremor and DCM prompted a revision of the inclusion criteria to include the case reports and conference abstracts before re-screening the papers that were identified by the search. It is important to note that the absence of primary literature does not necessarily indicate an absence of relation between tremor and DCM, but simply that the association has not yet been investigated.

The significance of these findings should be interpreted in the context of their relevance to patient outcomes. A survey administered by the international DCM charity Myelopathy.org aimed to identify the priorities of patients with DCM and showed a significant prevalence of tremor in DCM patients, with 42% of them reporting hand shaking symptoms, and 38% reporting leg shaking symptoms.[16] In addition, tremor was reported to have a significant impact on the quality of life of patients who were diagnosed with DCM, thus is a potential symptom for which targeting interventions may improve patient quality of life.

Conclusion

Diagnosis of DCM requires a high index of suspicion. This analysis suggests that tremor is a possible presenting symptom for DCM, and its presence should not necessarily direct the focus of clinicians away from DCM towards other neurological conditions that are more classically associated with tremor, such as Parkinson's disease. Clinicians should be particularly wary of worsening tremors in the setting of pre-existing tremor causing conditions. Additional research is required to study tremor in the setting of DCM and to identify targets for medical therapy of such tremors, which could significantly improve the quality of life of people with DCM.

Disclaimers

The authors have no conflicts of interest to report.

Disclosure statement

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