Department of Trauma & Orthopaedic Surgery,
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May 4, 2015

Dear Sir/Madam,

I wish to thank the reviewers for their constructive critique of my review article entitled 'The Mechanical and Cellular Processes Driving Cervical Myelopathy'. I have attempted to address the concerns raised by each reviewer and have highlighted the respective changes in the resubmitted manuscript.

Please find enclosed the edited manuscript in Word format (file name: Ortho review revisions 1).

Title: The Mechanical and Cellular Processes Driving Cervical Myelopathy

Authors: RT Dolan, JS Butler, JM O'Byrne, AR Poynton.

Name of Journal: *World Journal of Orthopedics*

ESPS Manuscript NO: 22406

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1:
The authors tried to review the significant pathophysiological processes involved in the development of cervical myelopathy comprehensively. This manuscript was well written; however this reviewer can find several typing errors, unfortunately. The authors should revise them in the revision process.

The typing errors have been corrected and language changed from British English to American English throughout the manuscript.

Reviewer 2:
Authors nicely reviewed underlying mechanism, anatomy and pathology of CSM. Unfortunately, no description was made regarding recent advancement in neuro-radiology of spinal cord. MR findings, such as high signal on T2-image, low signal on T1-weighted image, and findings on diffusion weighted image (ADC maps) may contribute to understand degenerative changes in the cord. Please review MR findings and, if possible, correlate between these MR findings and pathology.

Following a comprehensive literature review a further 14 references relating to neuro-radiology of the spinal cord have been incorporated to the manuscript. Specifically, we have attempted to review recent MR imaging advances in the early detection of cervical spondylotic myelopathy and use of MRI as a prognostic tool following surgical intervention for cervical spondylotic myelopathy.

The following paragraphs and references have been added to the manuscript:

Introduction

1. This sentence has been amended in the final paragraph.
Despite advances in the surgical management of cervical myelopathy in addition to timely diagnosis facilitated by advances in diffusion tensor magnetic resonance imaging (MRI) and kinetic MRI, a significant proportion of patients suffer residual neurological disability related to underlying irreversible structural injury to the spinal cord[13-17].

Static mechanical factors

1. Under the sub-section entitled 'spondylosis and disc degeneration' the following two passages have been added.
MRI studies which take into account soft tissue structures, weight-bearing, and dynamic imaging have suggested that a congenital sagittal spinal canal diameter of <13mm is a significant risk factor for the development of CSM [18, 40].

Radiological assessment is key, as it assists the clinician in differentiating discogenic neck pain, radiculopathy, and myelopathy, in addition to localization of the site and level of the disease for preoperative planning when surgical intervention is required [26]. *Compared with other radiological studies magnetic resonance imaging (MRI) provides an accurate morphological assessment of both osseous and soft tissue structures including intervertebral discs, spinal ligaments, and the neural elements. Dynamic weight bearing (kinetic) MRI has recently been championed as the preferred technique for pathology-specific diagnosis* [15, 27]. *Myelopathy is seen as increased signal within the cord on T2-weighted and a decreased signal on T1-weighted MRI. However, these signal changes are not reciprocal and are likely to represent different underlying pathology* [28]. *Diffusion tensor imaging (DTI) improves pathologic specificity through the quantitative directional diffusivities, which measure water diffusion parallel and perpendicular to the white matter tracts* [16, 29]. *A recent study of the role of DTI in cervical spondylotic myelopathy suggested that DTI may reveal abnormalities of the spinal cord before the development of T2 hyperintensity on conventional sequences and thus may be a superior imaging modality in the future*[13].

Under the sub-section entitled 'congenital cervical canal stenosis'
The most accurate measurement of spinal canal diameter is obtained using MRI which assesses both osseous and soft tissue structures when calculating canal diameter. This is important as central stenosis is often due to a combination of degenerative hypertrophy of the facet joints, osteophytic spurring, ligamentum flavum thickening, ossification of the posterior longitudinal ligament, posterior disc protrusion and translation of one anatomical segment on the next [44, 45]. *Spinal MRI should include imaging sets obtained in the axial and saggital planes using T1-weighted, proton-density, and T2-weighted techniques. In addition pulse sequences that provide high signal from cerebrospinal fluid (myelographic effect) using three-dimensional fast spin-echo MR imaging, help delineate epidural pathological*

processes such as disc fragments and osteophytes [46].

Cellular mechanisms involved in cervical myelopathy

Under the sub-section entitled 'Ischemic injury' the following sentence has been added:
The role of ischemic injury has also been proposed with evidence of edema and gliosis as high-intensity signal change on T2-weighted MRI, and myelomalacia and necrosis as a low-intensity signal change on T1-weighted MRI [68]*. This is an important distinction as it suggests that changes seen with increased intensity on T2 images are reversible whereas those seen as low signal on T1 are irreversible. However, it has been proposed that all increased signals in the spinal cord represent diffuse neuronal cell loss, replacement by glial cells in the stroma, and axonal and spongy degeneration in the white matter, indicating advanced spinal cord damage* [69].

Future innovations

1. This paragraph has been added which addresses future technological advancements in neuro-imaging specifically the potential for FDG-PET image analysis.
Regarding technological advancements, innovations in neuro-imaging will continue to play a key role by facilitating timely diagnosis of soft tissue and osseous pathology in CSM, assist in optimal patient selection for surgical intervention and provide prognostic information in the post-operative period. In addition to advances in kinetic magnetic resonance imaging (kMRI) and diffusion tensor imaging (DTI), metabolic neuroimaging specifically high-resolution 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), have been compared with clinical scores and findings on magnetic resonance imaging in patients undergoing surgery for myelopathy. FDG-PET findings correlated highly with preoperative scores, postoperative scores, and the rate of postoperative improvement[89, 90]*. The major limitation of this technology is the poor resolution of PET scans. Future technological advancements in PET scanning may facilitate evaluation of early spinal cord damage and provide indications for surgical intervention.*

Thank you again for considering publishing our manuscript in the *World Journal of Orthopedics*.

Sincerely yours,

Dr Roisin T. Dolan MA MD MRCSI

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Ireland.

September 8, 2015

Dear Sir/Madam,

I wish to thank the reviewers for their constructive critique of my review article entitled 'The Mechanical and Cellular Processes Driving Cervical Myelopathy'. I have attempted to address the concerns raised by each reviewer and have highlighted the respective changes in the resubmitted manuscript.

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The manuscript has been improved according to the suggestions of reviewers and the following changes have been made.

1. Conflict of interest statement has been uploaded
2. Audio core tip has been uploaded
3. City of author added
4. Title of author added

Thank you for your time.

Yours Sincerely,

Roisin Dolan