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The association between multiple sclerosis and spondylosis: When and why

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ABSTRACT

Objectives: To evaluate risk factors for the development of cervical spine spondylosis (CSS) in patients with multiple sclerosis (MS) and to propose a pathogenetic mechanism.
Methods: Forty-two consecutive patients aged 23–66 years with MS and 42 age and sex matched controls were evaluated retrospectively; Clinical disability was evaluated with the expanded disability status scale (EDSS) and spasticity with the Asworth score. Total brain lesion volume (BLV), total grey matter (GM) volume and deep GM volume were assessed. In the cervical spine CSS indices (disk dehydration, disk protrusion, abnormal posture and osteophytosis) and the spinal cord lesion load (SLL) was evaluated. The association of CSS indices with the presence of MS, the clinical scales and the brain and spinal cord imaging measurements were assessed.
Results: Presence of MS was positively associated with abnormal posture (P = 0.002), disk dehydration at C6–C7 (P = 0.049) and posterior disk protrusion at C5–C6 (P = 0.033) and C6–C7 (P = 0.001). All patients had spasticity. Patients with abnormal posture were younger (37.5 ± 11.1 years) than those with normal (45.4 ± 8.6 years), P = 0.024. Age (P = 0.008), EDSS (P = 0.045) and BLV (P = 0.084) were significant independent predictors of abnormal posture. Younger age combined with worse EDSS and increased BLV predicted abnormal posture.
Conclusions: Patients with MS present more frequently spondylosis which is associated with younger age, more severe disability and extensive lesions in the brain. Spasticity induced by the brain lesions and abnormal expression of extracellular matrix proteins in the brain and the intervertebral disk constitute a possible pathogenetic mechanism.

1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system (CNS) usually first diagnosed in young adults aged 30–40 years, characterized by multiple lesions of the brain and spinal cord disseminated in time and space. The clinical symptoms vary over time and range widely, including sensorimotor impairment, cognitive deficits and behavioral disorders [1]. Spinal cord myelopathy in MS presents with neck and radicular pain, segmental weakness and/or sensory loss, diminution of tendon reflexes and bladder dysfunction [1]. All of these symptoms apart from bladder dysfunction may also appear in myelopathy due to cervical spine stenosis, observed in the context of cervical spondylosis [1,2]. Spondylosis is a degenerative disorder presenting mainly in people aged over 50 years. Vertebral osteophytosis secondary to degenerative disk disease results in spinal canal stenosis, spinal cord compression and myelopathy [2]. Over 60% of people over 50 years have some degree of neurological abnormality related to myelopathy secondary to spondylosis of the cervical spine [2]. A few studies have reported an association of MS with cervical spondylosis [3–7]. In patients with both conditions it is unclear whether the clinical worsening of cervical myelopathy is due to MS or spondylosis. The management is different depending on the cause of the worsening, and patients may benefit from decompressive surgery when spondylosis is responsible and from medical treatment when MS is the underlying cause. The reports on the association of MS with spondylosis cover small series of patients, addressing mainly the value of decompressive surgery and mostly concluding that there is little benefit [3–7]. Brain and colleagues were the first to report in 1957 on

Abbreviations: CSS, cervical spine spondylosis; EDSS, expanded disability status scale; BLV, brain lesion volume; SLL, spinal cord lesion load; WML, white matter lesions; WM, white matter; GM, grey matter; MNI, Montreal Neurological Institute; SPM, statistical parametric mapping; LST, lesion segmentation tool; ADP, anterior disk protrusion; PDP, posterior disk protrusion; $_{SI}$CSS, significant indices of cervical spine spondylosis; ECM, extracellular matrix; MMPs, metalloproteinases

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the association between MS and spondylosis in 17 patients aged 37–61 years [3]. The diagnosis of spondylosis was made with X-rays and myelography and the diagnosis of MS was based on clinical evaluation and cerebrospinal fluid (CSF) analysis. Magnetic resonance imaging (MRI) is now the modality of choice for the evaluation of brain and spinal cord lesions in patients with MS and also for the assessment of myelopathy [1]. Although MRI of the cervical spine was used in three studies, the relationship between the MS lesions in the spinal cord and the degree of spondylosis has never been studied [4–6]. A pathogenetic mechanism leading to the development of spondylosis in patients with MS has never been proposed and the relationship between the brain lesion burden and cervical spondylosis has never been studied.

The purpose of the study was to investigate the relationship of cervical spine spondylosis with the presence and severity of MS indicated by clinical and neuroimaging measurements.

2. Subjects and methods

The MRI of the brain and the cervical spine were evaluated retrospectively in 42 consecutive patients with neurologically proven MS and in 42 age and sex matched controls with normal brain MRI. The study group consisted of 25 females and 17 males with an age range of 23–66 years (mean ± SD 40.1 ± 10.9 years) and MS disease duration 0–22 years (mean ± SD 6.19 ± 5.43 years). The form of MS was relapsing-remitting in 34 patients, while 2 had primary-progressive, 4 secondary progressive and 2 relapsing-progressive MS. Additionally, for each subject, the EDSS and the Asworth score recorded on the same day as MRI examination were retrieved from the clinical records.

All brain images were acquired on a 1.5T scanner (Intera, Philips, Netherlands). From the imaging protocol we used two sequences: (a) three dimensional gradient echo T1w; orientation, 150 contiguous sagittal 1 mm slices; field of view, 240 × 240 mm; voxel size, 1.0 × 1.0 × 1.0 mm^3; TR, 9 ms; TE, 4 ms; and (b) fast spin echo T2 w FLAIR; orientation, 24 contiguous axial 5 mm slices; field of view, 230 × 185 mm; voxel size, 2.0 × 2.0 × 5 mm^3; TR, 104 ms; TE, 140 ms; TI, 2750 ms.

Image analysis was performed using the statistical parametric mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm) software package and the lesion segmentation tool (LST; http://www.applied-statistics.de/lst.html). For each subject LST generated one binary lesion image of the white matter lesions (WML) present, per subject. Next, T1W images were corrected at the lesion voxels with approximating normal white matter (WM) intensity in order to avoid problems during the next steps of grey matter (GM) and WM segmentation and normalization to a standard (MNI) template. The segmentation and normalization steps were further refined using a high-dimensional warping approach ("DARTEL"). The resulting GM and WM images were modulated and smoothed with a Gaussian kernel of 8 mm. Finally the binary lesion images were normalized using the deformation field, derived from the refilled T1 images. Total brain lesion volume (BLV) was calculated by adding all the voxel values of the normalized binary lesion images. Similarly global volumes of GM were calculated by adding the voxel values of the unsmoothed modulated GM images. The same images provided a volume of deep GM volume by applying to them a binary mask of the caudate nucleus, putamen and thalamus using the Wake Forest university atlas (http://fmri.wfubmc.edu/software/PickAtlas).

Sagittal T2W images of the cervical spine were studied for the detection of spondylosis and lesions in the spinal cord. Two radiologists evaluated independently the imaging data with a very good agreement (> 95%). The few conflicting cases were resolved with a consensus meeting between them. A senior radiologist (corresponding author) reevaluated and validated all the measurements. Spondylosis was defined as degenerative disk disease (dehydration, anterior or posterior protrusion), vertebral osteophytosis, and abnormal posture of the spine with loss of normal lordosis [2]. A disk was considered hydrated when the nucleus pulposus appeared with high signal intensity and dehydrated when it appeared with intermediate to low signal intensity (Fig. 1). The presence of anterior or posterior disk protrusion (ADP and PDP respectively) was evaluated separately. The presence of anterior or posterior osteophytes was also noted separately.

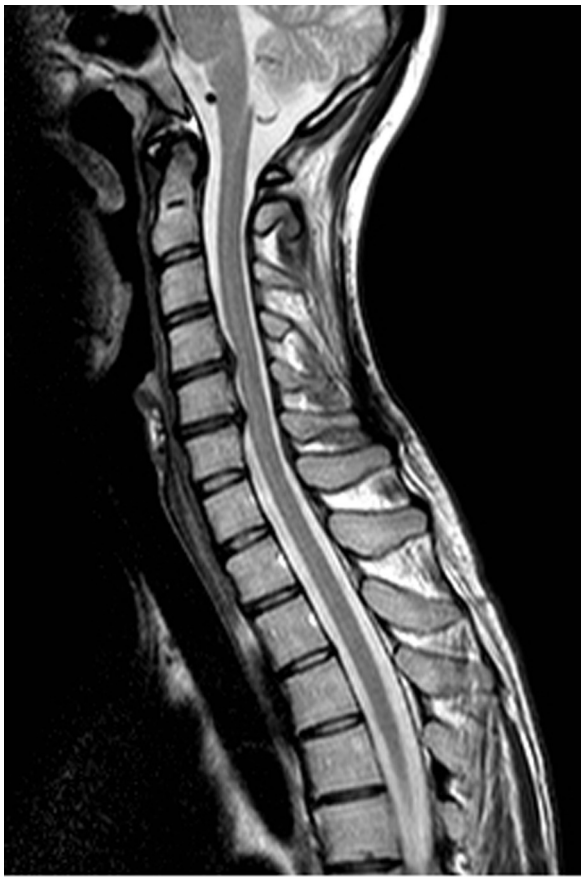

Fig. 1. Evaluation of the disk for the hydration and protrusion state. Thirty seven-year-old female with multiple sclerosis: At C4–C5 and C5–C6 levels the intervertebral disk appears dehydrated along with presence of posterior protrusion. A normally hydrated disk appears at C6–C7 level.

Abnormal posture was defined as either straightening or kyphosis of the cervical spine. Using a midline sagittal scan a line was drawn between the dorsocaudal part of the body of C2 to the dorsocaudal part of the body of C7 [2]. The position of the line in relation to the dorsal parts of C3–C7 vertebral bodies was used to define the posture of the cervical spine. Normal lordosis was associated with a posterior line, straightening was associated with a parallel line and kyphosis with an anterior line (Fig. 2) A binary variable named the spinal cord lesion load (SLL) was used to classify the subjects into two groups: A "low lesion" group with ≤2 lesions and a "high lesion" group with ≥3 lesions.

3. Statistical analysis

The chi square test was used to assess the relationship between the presence of MS and disk dehydration, ADP, PDP, osteophytes and abnormal posture. CSS indices ($_{SI}$CSS) presenting significant difference between patients and controls were identified. *T*-test was used to identify mean differences of total GM volume, deep GM volume, age and disease duration between the group of patients with and those without $_{SI}$CSS. Mann Whitney *U* test was used to assess differences of EDSS and BLV between the same groups. The possible association between $_{SI}$CSS, disease type and SLL was explored using the chi square test. A backward stepwise logistic regression analysis was used to reveal independent predictors of $_{SI}$CSS among all the relevant clinical and CNS