Ankylosing Spondylitis and Neck Pain: MRI Evidence for Joint and Entheses Inflammation at the Craniocervial Junction

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ABSTRACT: **Background:** Magnetic resonance imaging (MRI), which has recently become the leading imaging modality in the study of ankylosing spondylitis (AS), has not been evaluated in the assessment of disease-specific changes at the craniocervical junction (CCJ) in patients with AS.

Objectives: To describe the spectrum of active inflammatory lesions at the CCJ using MRI in a cohort of patients with AS and neck pain.

Methods: The study included 18 patients with AS presenting with neck pain and a control group of 9 fibromyalgia patients matched for age and levels of neck pain. All patients underwent a focused rheumatologic examination, X-ray of the cervical spine, and a 3T MRI study, which included STIR, CUBE T2, FSE and FSE FAT SAT sequences before and after administration of gadolinium.

Results: The median age of AS patients was 43 years with a median disease duration of 7 years. Fifteen of 18 patients were under biologic treatment. Seven of 18 AS patients had evidence of cervical syndesmophytes on X-ray films. Active inflammatory lesions of atlanto-occipital joints and apical and alar ligaments were detected in MRIs in 2 out of the 18 patients with AS and in none of the patients with fibromyalgia. Both AS patients with active inflammation of CCJ detected on MRI received treatment with biological agents prior to and during the study.

Conclusions: Active inflammation of both entheses and joints of the CCJ can be demonstrated by MRI in patients with AS.

IMAJ 2017; 19: 682–684

KEY WORDS: ankylosing spondylitis (AS), craniocervical junction (CCJ), magnetic resonance imaging (MRI), atlanto-occipital joints, apical ligament, alar ligament

*This study was made possible due to an unrestricted grant from AbbVie

This work was presented at a radiology–rheumatology meeting focusing on the contribution of imaging to the understanding of the pathogenesis and treatment decisions in musculoskeletal rheumatic diseases that took place in December 2016 at the Sheba Medical Center, Tel Hashomer, Israel

Ankylosing spondylitis (AS) is a chronic and progressive inflammatory rheumatologic disorder, which manifests as inflammatory back pain and stiffness that may eventually lead to structural damage and fusion of the spine in some patients. All areas of the spine may be affected in AS, including the cervical spine [1,2].

The craniocervical junction (CCJ) is the region of the spine that includes the occipital bone surrounding the foramen magnum and the first and second vertebrae (atlas and axis, respectively). It is the region of the spine with the most mobility, setting it apart from the rest of the spine with regard to anatomy and biomechanics [3]. Involvement of the CCJ in AS has been previously described using conventional X-rays and computed tomography (CT) [4-6].

Magnetic resonance imaging (MRI), the best imaging modality for detection of active inflammation in the spine, has not been formally evaluated in imaging of joints and entheses of the CCJ in AS.

The goal of this study was to assess the added value of MRI in the study of CCJ structures in a cohort of patients with established AS.

PATIENTS AND METHODS

The study was approved by the Helsinki Committee of the Bnai Zion Medical Center.

The initial patient population of the study consisted of a cohort of 20 patients with AS, all currently being followed by clinicians at the rheumatology department at the Bnai Zion Medical Center. All subjects satisfied the modified 1984 New York classification criteria for AS [6] and complained of persistent neck pain. Demographic and disease-related data were collected for each patient during a medical interview. Visual Analogue Scale (VAS) scores for neck pain were recorded. The rheumatologic examination included range of motion of the cervical spine using a goniometer. The presence of the syndesmophytes was assessed and the cervical Modified

Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [7] was calculated using the analysis of the X-ray films of the cervical spine.

After data collection, AS patients underwent 3T MRI imaging focused on the CCJ at the MRI facility of the Rambam Medical Center. Each MRI study was performed with STIR, CUBE T2, FSE, and FSE FAT SAT sequences before and after administration of gadolinium. Both bony and entheseal structures of the CCJ were systematically assessed.

A cohort of patients with fibromyalgia, also presenting with neck pain, were selected as a control group. All 10 patients in the control group satisfied the 1980 American College of Rheumatology classification criteria for fibromyalgia [8], were adjusted by age to the AS group, and underwent similar rheumatologic examination and identical MRI imaging.

RESULTS

Twenty patients presenting with AS who met the inclusion criteria were enrolled in the study. Out of these 20 patients, 2 were unable to lie horizontally as required for the duration of the MRI study because of neck deformities, and were therefore excluded. The control group consisted of 10 patients with fibromyalgia. One of these refused gadolinium injection and was therefore excluded from the study. The remaining 18 subjects in the AS group and the remaining 9 patients in the control group followed through to completion of the MRI study.

The average age of patients with AS was 43 years (range 29–62 years), the average disease duration was 12 years (range 2–23 years), and the average VAS for neck pain was 6.6 (range 3–10). Fibromyalgia patients were of similar age (average 41.3 years, range 25–52 years) and had similar levels of neck pain by VAS (average 6.9, range 3.5–9), $P > 0.05$ for all comparisons.

Fifteen of 18 patients with AS were treated with biological treatment during the period of the study, and 7 of them had syndesmophytes of the cervical spine on X-ray films.

MRI revealed active inflammatory changes at the CCJ in two AS patients [Figure1, Figure 2]. One patient's MRI study demonstrated inflammatory changes involving the alar and apical ligaments, while the MRI study of a second patient displayed synovitis of the atlanto-occipital joints. Both patients had been treated with anti-TNF drugs before and during the study. The mSASS scores of both patients with positive MRI of CCJ was 0. No inflammatory changes were seen on MRI imaging of patients with fibromyalgia.

DISCUSSION

Involvement of the sacroiliac joints, located at the lower pole of the spine, is the earliest and most typical feature of AS, as well as a major diagnostic feature. The CCJ, located at the upper pole of the spine, has not received particular attention in the study of AS. It has been known for a long time that AS affects the CCJ in some patients [4-6]; however, studies demonstrating the prevalence, burden, and significance of such involvement are scarce. A recent retrospective CT-based study demonstrated a diversity of structural changes in the CCJ in AS [9]. As has been shown, virtually all structural elements of CCJ, including its entheses and joints, can be affected in the disease course of AS. However, to the best of our knowledge, the presence of active inflammatory changes in the elements of the CCJ has never been previously demonstrated in AS patients. MRI has repeatedly been shown to be a valuable method in depicting active inflammatory lesions in the SIJ and spine of AS patients. This study is the first to demonstrate inflammatory lesions in the structures of the CCJ in AS patients by MRI.

Since the CCJ is a very special area of the cervical spine, which allows for both cervical stability and mobility [3], involvement of this area may lead not only to severe pain and restricted range of motion, but, in more extreme cases, neurological complications. With this in mind, it is imperative that disease-related changes in the CCJ not be missed or ignored. As such, our study, while performed on a limited number of subjects, suggests that MRI may be an important implement

Figure 1. Sagittal **[A]** and coronal **[B]** FSE T1 FAT SAT images after gadolinium injection showing enhancement of apical and alar ligaments

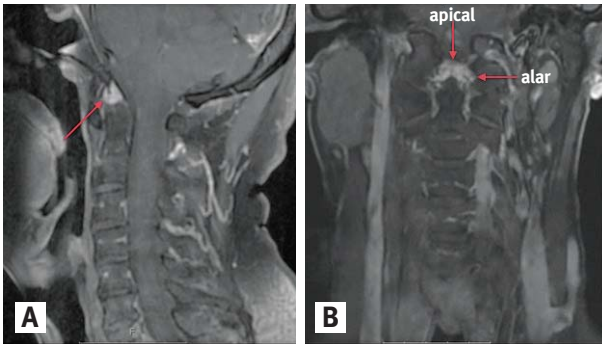
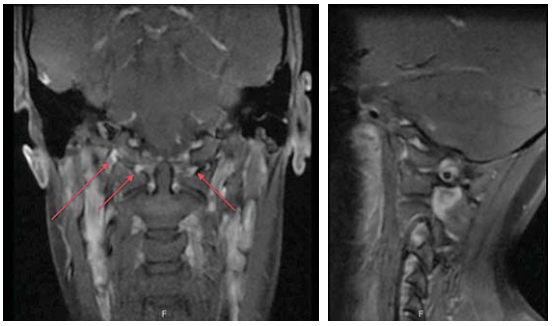


Figure 2. Coronal and sagittal FSE T1 FAT SAT images after gadolinium injection showing areas of synovitis in both atlanto-occipital joints



to reveal active craniocervical arthritis and enthesopathy and should be considered the imaging modality of choice in AS patients presenting with neck pain.

Active inflammation was appreciated on MRI of the CCJ in only 2 patients out of 18 in our study group. This small number may be explained by the fact that the majority of our AS patients had received biological treatment prior to and during the study, presumably decreasing the incidence of active inflammation. Accordingly, it was impossible to examine correlation of clinical characteristics of neck pain with specific MRI features because of the small number of positive findings. Therefore, more aspects of CCJ involvement may remain be uncovered, necessitating further research on this topic.

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Capsule

Glucose-regulated protein 78 autoantibodies associate with blood-brain barrier disruption in neuromyelitis optica

Neuromyelitis optica (NMO) is an inflammatory disorder mediated by antibodies to aquaporin-4 (AQP4) with prominent blood-brain barrier (BBB) breakdown in the acute phase of the disease. Anti-AQP4 antibodies are produced mainly in the periphery, yet they target the astrocyte perivascular end feet behind the BBB. Shimizu and colleagues reasoned that an endothelial cell–targeted autoantibody might promote BBB transit of AQP4 antibodies and facilitate NMO attacks. Using monoclonal recombinant antibodies (rAbs) from patients with NMO, the authors identified two that strongly bound to the brain microvascular endothelial cells (BMECs). Exposure of BMECs to these rAbs resulted in nuclear translocation of nuclear factor κB p65, decreased claudin-5 protein expression, and enhanced transit of macromolecules. Unbiased membrane proteomics identified glucose-regulated protein 78 (GRP78) as the rAb target. Using immobilized GRP78 to deplete GRP78 antibodies from pooled total immunoglobulin G (IgG) of 50 NMO patients (NMO-IgG) reduced the biological effect of NMO-IgG on BMECs. GRP78 was expressed on the surface of murine BMECs in vivo, and repeated administration of a GRP78-specific rAb caused extravasation of serum albumin, IgG, and fibrinogen into mouse brains. These results identify GRP78 antibodies as a potential component of NMO pathogenesis and GRP78 as a candidate target for promoting central nervous system transit of therapeutic antibodies.

Sci Transl Med 2017; 9: eaai9111
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Capsule

Inflammation and cardiac reprogramming

Tissue repair after a heart attack is a balance between inflammation to remove cell debris and active cell regeneration. Intervening in cell replacement and reprogramming thus offers therapeutic options to promote healing with minimal scar formation by fibroblasts. However, reprogramming of adult fibroblasts into pulsatile cardiomyocytes is not straightforward. To improve the reprogramming protocol, Zhou et al. performed an unbiased screen of 786 transcription factors, epigenetic regulators, cytokines, and nuclear receptors. The screen identified a transcription factor (ZNF281) that associates with the essential cardiac development transcription factor GATA4 to stimulate cardiac reprogramming and suppress inflammatory signaling. Anti-inflammatory drugs also stimulate cardiac gene expression. ZNF281 appears to act at a nexus between cardiac and inflammatory gene programs that exert opposite influences on fibroblast reprogramming.

Genes Dev 2017; 10.1101/gad.305482.117
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