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Large enthesophytes in teenage skulls: Mechanical, inflammatory and genetic considerations

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ABSTRACT

Background: The literature implies that large enthesophytes are exclusive to genetically predisposed individuals and to Spondyloarthropathies sufferers. Accordingly, the aim of this investigation and report was to assess the involvement of genetic predisposition, inflammatory and/or mechanical influences in the development of large enthesophytes in a sample population of teenagers presenting with large enthesophytes emanating from the external occipital protuberance.

Methods: Analysis was based on four teenage males (13–16 year-old) possessing 14.5–30.5 mm enthesophytes projecting from the external occipital protuberance. This study included assessment of radiographs, MRI scans, blood-work, history, the SF-36 health survey, and the comparison of these data with the relevant literature to describe the interrelationships between the presence of enlarged external occipital protuberance, forward head protraction, active inflammation and/or genetic factors.

Findings: Known genetic markers (e.g. HLA-B27) were not detected by allele-specific primers and both ESR and CRP tests were negative. Additionally, MRI analyses failed to detect active localised inflammation at the external occipital protuberance and surrounding structures. The health survey yielded normal parameters for all participants. All participants displayed significantly large Forward Head Protraction values (> 40 mm), and interviews with participants and their parents indicated that concerns related to posture were prevalent since early childhood.

Interpretation: This report suggests that mechanical load has an important role in enthesophyte development, irrespective the involvement of inflammatory or genetic factors.

1. Introduction

Enthesophytes (bone spurs) often materialize as jagged projections emanating from the bone cortex into the ligament/tendon at the enthesis (insertion) (Benjamin et al., 2000; Rogers et al., 1997). Enthesophyte formation and enthesitis may be observed on both the axial and appendicular skeleton (D'Agostino and Olivieri, 2006; Jacques and McGonagle, 2014; McGonagle et al., 2001), including the site of muscular attachment on the external occipital protuberance (EOP) (D'Agostino and Olivieri, 2006; Olivieri et al., 1998). The presence of enthesophytes has been linked to genetic, inflammatory and biomechanical factors (Claudepierre and Voisin, 2005; Hardcastle et al., 2014; McGonagle et al., 1998; McGonagle et al., 2001; Shaibani et al., 1993), although these factors do not bear an equal weight on entheseal development and the progression of related disorders throughout life (Jacques et al., 2014; Thomopoulos et al., 2007).

Previously we have presented data from a retrospective radiographic investigation on the prevalence of an enlarged EOP (EEOP) in a young adult population (18–30 year-old) (Shahar and Sayers, 2016). In that study we classified the EOP as enlarged if it exceeded 10 mm. Alarmingly, EEOP was identified in over 40% of our sample, with 10% presenting with an EOP ≥ 20 mm. The implications that excessive enthesophyte growth occurs in predisposed individuals (Marshall et al., 2015) and that large enthesophytes are exclusive to SpA sufferers (McGonagle et al., 2008) are concerning, as tissue remodelling associated with SpA leads to a largely irreversible structural damage, which has clear functional repercussions (Rudwaleit et al., 2009a). Importantly, early diagnosis and effective treatment to limit structural damage persist to be a primary challenge in the management of Spondyloarthritis (SpA) (Maksymowych, 2009).

Enthesophytes are seen rarely in the young population (Boden et al., 1990; Matsumoto et al., 2010). Accordingly, our previous findings of highly prevalent and unusually large enthesophytes emanating from the EOP in a young population were surprising. In the attempt to better

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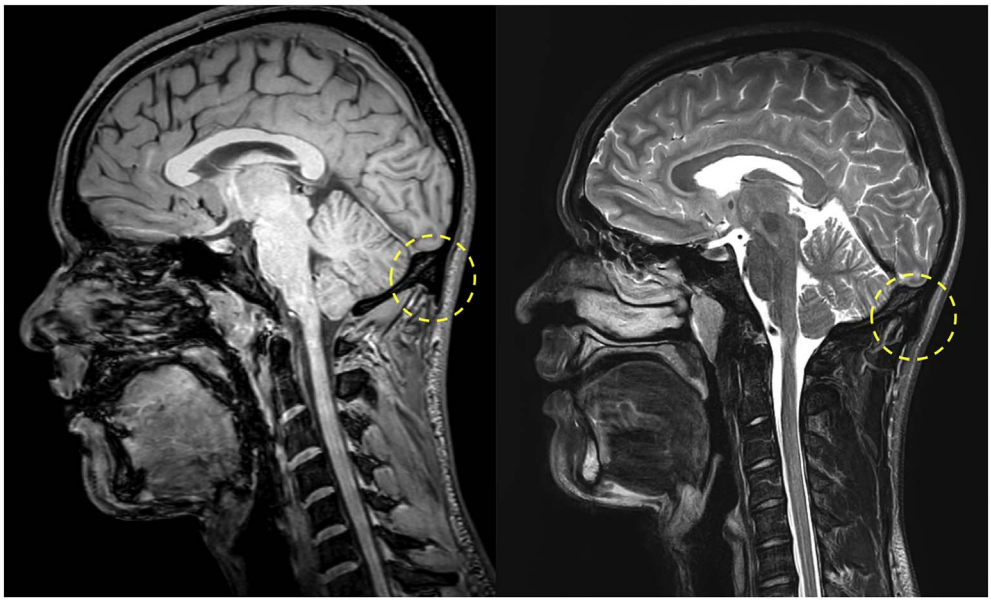

Fig. 1. Images representing MRI scans of a 16-year old male participant, showing a T1 weighted mid-sagittal image (left) demonstrating the enlarged external occipital protuberance (EOP). This image separates bone from soft tissues. The right image shows T2 weighted mid-sagittal image, with these T2 fat suppressed images highly sensitive for the detection of edema. The lack of signal demonstrates no inflammation at the EOP and surrounding structures. The linear high signal structures adjacent to the EOP are normal blood vessels.

isolate the main cause of this phenomenon, we turned our focus to an even younger age-group (13–16 year-old) and subjected those participants to a more thorough investigation. Our current analysis evaluated the possible influence of genetic predisposition, inflammation and mechanical factors in the development of large enthesophytes in our sample.

2. Methods

This assessment was based on criteria extracted from current reports on SpA detection and classification (Rudwaleit et al., 2005; Rudwaleit et al., 2009a; van der Heijde et al., 2010) and was provided full ethics approval by the institutional Human Research Ethics Committee. Our recent analysis (Shahar and Sayers, 2016) revealed an EEOP (> 10 mm) in four teenage males (three 16-years old and one 13-years old). The young age of these individuals meant that these data were excluded from the previous analysis, but they are now the subject of this report.

To evaluate the potential influence of genetic predisposition and inflammatory factors, blood analysis took place (rheumatoid master panel e.g. HLA-B27, C-reactive protein, ESR). Furthermore, T1 and T2 weighted MRI scans (Fig. 1) were performed and analysed by an experienced radiologist, for the purpose of identifying the presence of active inflammation at the EOP and its surrounding structures (Akgul and Ozgocmen, 2011; Oostveen et al., 1999; Rudwaleit et al., 2009a; Rudwaleit et al., 2009b; Sieper, 2009). MRI studies have been shown to be effective in the early diagnosis of SpA as they can provide visual confirmation of active inflammation at an early stage of the development of the disease (Akgul and Ozgocmen, 2011; Oostveen et al., 1999; Rudwaleit et al., 2009b; Sieper, 2009; Tse and Laxer, 2012).

Potential aberrant mechanical influences were considered by investigating the participants' medical histories through an oral interview with participant and their parents. All participants also completed the SF-36 Health Survey. Additionally, using a lateral cervical radiographs, analysis to quantify the degree of forward head protraction (FHP) was carried out by recording the length (in millimeters) of a horizontal line (labelled a in Fig. 2) drawn from the margin of the posterior-superior corner of the body of C2, to a vertical line (labelled b in Fig. 2) drawn up from the margin of the posterior-inferior corner of the body of C7 (Harrison et al., 1996). The size of the EOP was defined as the distance in millimeters from the most superior point of the EOP to a point on the EOP that is most distal from the skull (labelled c in Fig. 2) (Shahar and Sayers, 2016).

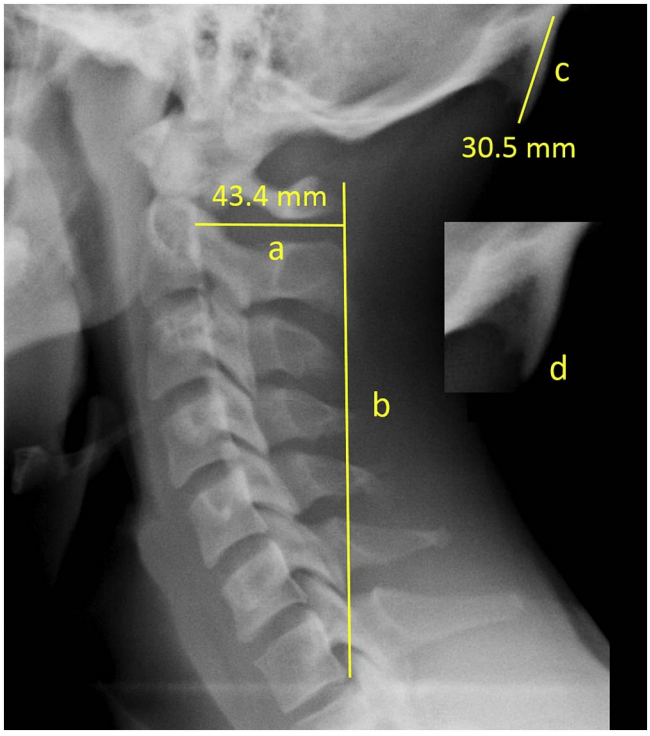

Fig. 2. Lateral cervical radiograph of the same participant demonstrating the two lines (a and b) that were used to determine forward head protraction. This image includes a measurement line "c" indicating the origin, tip and length of the enlarged EOP. Labelled "d" in this image is a magnified representation of an enlarged EOP.

2.1. Technical data

Lateral cervical radiographs were obtained using digital capturing equipment with participants instructed to stand in their normal posture looking straight ahead and with their right shoulder in contact with the wall-mounted 'bucky'. The tube-to-bucky distance was kept constant at 1.5 m. An experienced clinician conducted all radiographic analyses using standard software (Genesis OmniVue® Genesis Digital Imaging, Los Angeles, CA, USA).

MRI images were acquired using a 3 T MR Imager (Ingenia; Philips Healthcare, Veenpluis, Best, Netherlands). In all cases, imaging was