Cytokines and Inflammatory Mediators

30. THE LPS STIMULATED PRODUCTION OF INTERLEUKIN-10 IS NOT ASSOCIATED WITH -819C/T AND -592C/A PROMOTER POLYMORPHISMS IN HEALTHY INDIAN SUBJECTS

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Background: Interleukin-10 is a pivotal immunoregulatory cytokine with pleiotropic effects on the immune system. IL-10 promoter polymorphisms have been associated with disease susceptibility and the ability to secrete IL-10 in vitro. We suspected that the association of the widely studied -819C/T and -592C/A polymorphisms with the IL-10 production might vary between ethnic groups. Therefore, we examined the association of -819 C/T and -592 C/A promoter polymorphisms with in vitro LPS stimulated secretion of IL-10 in normal healthy Indian volunteers.

Methods: Peripheral blood was collected from 103 healthy volunteers and diluted whole blood cultures were set up with 100 ng/ml of LPS as stimulant; supernatant was collected at 24 h and IL-10 levels were assayed by ELISA. Genotyping was done for -819C/T polymorphism in 101 individuals and -592C/A polymorphism in 68 individuals by polymerase chain reaction followed by RFLP. The differences in IL-10 production between the genotypes were analysed by ANOVA.

Results: There were 30, 47 and 24 individuals with the CC, CT and TT genotypes with a minor allele (T) frequency of 47% for the -819C/T polymorphism. The CC and TT genotypes at position -819 were strongly associated with CC and AA genotypes at -592 position suggestive of strong linkage disequilibrium. There was no association between the -819 genotype and the in vitro LPS stimulated IL-10 levels.

Conclusions: The -819C/T and the -592 C/A polymorphisms of the IL-10 promoter region are not significantly associated with LPS stimulated IL-10 production healthy Indian subjects.

Disclosure statement: All authors have declared no conflicts of interest.

31. IL-17 PRODUCING CELLS ARE INCREASED IN THE PERIPHERAL BLOOD OF PATIENTS WITH RA AND ARE ENRICHED AT THE SITE OF INFLAMMATION

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Background: Th17 cells are a recently identified CD4+ T cell subset characterized by production of Interleukin-17A (IL-17). IL-17 is a highly pro-inflammatory cytokine with effects on multiple cells and tissues and Th17 cells are likely to have an important role in the pathogenesis of a number of immune-mediated diseases including rheumatoid arthritis (RA). IL-17 recruits other immune cells, induces inflammatory cytokines and is involved in osteoclastogenesis and development of bone erosions. The aim of this study was to identify if Th17 cells are increased in peripheral blood from patients with RA and if these cells are important for disease inflammation.

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from healthy controls or patients with RA and stimulated with PMA and ionomycin for 3 h in the presence of Golgistop. Paired synovial fluid (SF) from inflated knee joints was analysed where available. Synovial tissue was available for five RA patients from arthroscopic biopsies (knee/eltbow). Synovial tissue was digested with collagenase prior to stimulation. Intracellular expression of IL-17, Interferon-γ (IFNγ) and TNFα was determined by multicolour flow cytometry.

Comparisons between patients and healthy controls were made using student t-tests for normally distributed data or Mann-Whitney U tests for non-normal data. Paired data (PB vs. SF) were analysed using paired t tests or Wilcoxon signed rank tests using GraphPad Prism.

Results: Peripheral blood samples were collected from 29 patients with established RA and 23 healthy controls. Th17 cells were present at increased levels in PBMC from RA patients with median (IQR) of 0.56% (1.36) vs. 0.32% (0.36) in healthy controls (P = 0.03). A small percentage of cells positive for both IL-17 and IFNγ were observed, which was higher in RA patients. Paired PB and SF samples were analysed for 14 patients (16 knees). Cytokine producing cells were generally elevated in SF (TNFα, IL-17 or IFNγ—producing CD4+ T cells and TNFα or IL-17-producing CD68+ monocytes). The percentage of total IL-17 producing CD4+ T cells was significantly elevated within SF vs. PB, particularly those with a dual Th17/Th1 phenotype rather than a specific increase in Th17 cells. IL-17 producing T cells were present in synovial tissue (n = 5); with three of five patients showing very high levels (>8%). Interestingly, the two patients with low levels (≤1%) were clinically in remission with DAS28 < 2.6.

Conclusions: Th17 cells are increased in PB from patients with RA relative to healthy donors. Furthermore, we demonstrate an increased percentage of IL-17 producing cells in RA SF, with a shift towards a Th17/Th17 phenotype. Th17 cells are not always increased in ST and higher levels of IL-17 - cells may indicate more active disease. We are now investigating relationships with other measures of disease activity including inflammatory markers and imaging such as power Doppler ultrasound.

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32. BIOMARKER PROFILES ASSOCIATED WITH DISEASE FEATURES IN PATIENTS WITH EARLY RA

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Background: The inflammatory process in RA is associated with excess production of many inflammatory mediators including cytokines and matrix metalloproteinases (MMPs). Numerous studies have shown that individual biomarkers are associated with particular clinical measures of RA. However, the inflammatory process involves a complex network of pro- and anti-inflammatory mediators, so identifying combinations of biomarkers associated with disease features may lead to a better understanding of the molecular pathways involved. The aim of this study was to determine whether disease measures in patients with early RA and at 5-year follow up are associated with particular baseline profiles of circulating cytokines and MMPs.

Methods: Seventy-four DMARD naïve RA patients with a disease duration of < 1 year were investigated. Baseline serum samples were collected and assayed for protein levels of 30 different molecules using bead-based multiplex assays (Luminex) and ELISAs. Principal component analysis (PCA) was used to reduce the number of biomarkers to a smaller set of independent components, which were investigated for their association with disease measures by using regression techniques.

Results: PCA identified 7 components consisting of various combinations of cytokines and MMPs. The strongest association with measures of disease activity and pain was found with a component consisting of MMP-1, MMP-3, PDGF, VEGF and osteopontin (OPN) (see Table). Another component consisting of MMP-1α, IL-9, IL-13 was also associated with markers of inflammation, pain, rheumatoid factor and joint damage. A history of smoking was strongly associated with a profile which included MMP-9, MMP-8, IL-8, OPN and osteoprotegerin (OPG). The MMP-1, MMP-3, VEGF, PDGF and OPN component and MMP-8, IL-9 and IL-13 component were predictive of worse function and damage scores at 5-year follow up.

Conclusions: Our results indicate that different features of the disease are associated with different cytokine/MMP profiles. Our data confirm the importance of molecules involved in angiogenesis and matrix remodelling in the early stages of the disease.
Disclosure statement: All authors have declared no conflicts of interest.

33. MAPPING THE CYTOKINE NETWORK: SIMULTANEOUS ANALYSIS OF CYTOKINE mRNA EXPRESSION PROFILES OF FIVE IMMUNE CELL POPULATIONS ISOLATED FROM SYNOVIAL FLUID AND PERIPHERAL BLOOD OF RA PATIENTS

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Background: Cytokines act as part of a complex network of cells and soluble factors to regulate the processes involved in chronic inflammation and tissue destruction in rheumatoid arthritis. It is important to try to understand the roles of cytokines as components of larger networks rather than isolated pathways. As an initial step towards the characterization of this network, we developed a method that allows simultaneous analysis of cytokine mRNA expression by the five largest cell populations present within the synovial fluid and peripheral blood of rheumatoid arthritis patients. The cells are not cultured or stimulated ex-vivo to reflect their in-vivo cytokine profile as closely as possible.

Methods: Synovial fluid and peripheral blood were obtained from five patients with early or established RA and cells were sorted into five populations. CD3/CD4/CD45RO+ T cells, CD3/CD8/CD45RO- T cells, CD19+ B cells and CD14+ macrophages were sorted with a MoFloTM high-speed cell sorter and neutrophils were isolated using MACS columns. In a series of validation experiments, we confirmed that sample preparation and staining conditions were not affecting the result and that cell numbers were sufficient for analysis.

Results: We have identified patterns of cytokine expression in cytokines expressed by specific cell types or by a range of cell types and have been able to make comparisons between cytokines levels in cell populations within the synovial fluid with those in peripheral blood. T cell cytokines IFN-γ and IL-2 were found only in T cell populations, while cytokines characteristic for myeloid cells such as IL-18 and CCL3 were only found in neutrophils and macrophages; suggesting that we are indeed able to separate the cytokine profiles of the main immune cell populations invading the rheumatoid synovial fluid.

Conclusions: Complex patterns of cytokine production have been identified and are now allowing us to map which cytokines are identified and are now allowing us to map which cytokines are involved in which cell populations.

Disclosure statement: All authors have declared no conflicts of interest.

34. BLOOD LIPID LEVELS ARE LOWERED BY INCREASED INTERLEUKIN-6 CONCENTRATIONS VIA UP-REGULATION OF THE VERY LOW DENSITY LIPOPROTEIN RECEPTOR

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Background: In patients with rheumatoid arthritis (RA), blockade of interleukin-6 (IL-6) or tumour necrosis factor-α (TNF-α) can increase blood concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides. These changes are inversely correlated to RA disease activity, but the mechanisms by which lipids are altered are unclar. The low-density lipoprotein receptor (LDLR) family, which includes LDLR, LDL receptor-related protein-1 (LRP-1) and very low-density lipoprotein receptor (VLDLR), is involved in lipid uptake and control of blood lipid levels. To investigate the mechanisms of lipid changes induced by blockade of IL-6 and TNF-α, we have investigated the effects of IL-6 and TNF-α on the expression of these scavenger lipid receptors.

Methods: In vitro, vascular skeletal muscle cells (VSMC) were cultured in the presence of IL-6 alone, soluble IL-6 receptor (sIL-6R), IL-6 plus sIL-6R, or TNF-α alone for 24 h. Expression of VLDLR, LDLR and LRP-1 were measured by real-time polymerase chain reaction. In vivo, human IL-6 was injected into mice twice a day for 2 weeks and changes in blood levels of total cholesterol and triglycerides and expression of VLDLR in different tissues were measured. In addition, the effects of anti-IL-6 receptor (IL-6R) antibody injection on blood lipid levels in normal and IL-6-treated mice were investigated.

Results: The expression of VLDLR mRNA in VSMC in vitro was significantly increased by IL-6 plus sIL-6R but not by IL-6, sIL-6R or TNF-α alone. None of the treatments induced LDLR or LRP-1 mRNA expression. In mice, IL-6 treatment significantly reduced blood levels of total cholesterol and triglycerides, although there were no changes in body weight or food intake. VLDLR mRNA expression was increased in all tissues and organs of IL-6-treated mice compared with PBS-treated controls. Administration of anti-IL-6R antibody to IL-6-treated mice increased total cholesterol and triglyceride levels to those of PBS-treated mice and reduced levels of the acute-phase protein serum amyloid A. Administration of anti-IL-6R antibody to normal (non-IL-6-treated) mice did not result in any changes to total cholesterol or triglyceride levels.

Conclusions: Over-produced IL-6 decreased blood lipid levels by increasing VLDLR expression in several tissues. As TNF-α blockers reduce blood IL-6 levels, we conclude that IL-6 and TNF-α blockades normalize reduced lipid levels caused by IL-6 but do not affect normal lipid metabolism.


35. EFFECTS OF ANTI-TUMOUR NECROSIS FACTOR THERAPY ON INSULIN KINETICS IN NORMAL-WEIGHT AND OBSESE PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Anti-tumour necrosis factor alpha (anti-TNF-α) therapies are commonly used in the treatment of rheumatoid arthritis (RA). Apart from their anti-rheumatic effects, anti-TNF-α drugs have been suggested to reduce CVD risk and to improve insulin kinetics. In RA, insulin resistance (IR) is common and it is a potential contributor to the increased risk of cardiovascular disease (CVD) of these patients. Obesity, a potent contributor to IR in the general population, might influence the way anti-TNF-α therapy affects insulin kinetics. The aim of this longitudinal study was to compare the effects of anti-TNF-α therapy on insulin kinetics between normal weight and obese RA patients with and without IR.

Methods: Normal-weight (N-IR) and obese patients with IR (O+IR) embarking on anti-TNF-α treatment were invited to participate. They were assessed for body mass index (BMI), lipids, blood pressure, glucose and insulin and RA disease characteristics, prior to and following 6 months of anti-TNF-α treatment. Their results were compared with age, gender, BMI, disease duration and smoking status matched normal-weight patients without IR (N-IR) and obese without IR (N-IR). IR was defined as HOMA > 2.5, QUICKI < 0.333, presence of diabetes mellitus or use of anti-diabetic medication.

Results: Twenty patients (five in each group) participated (aged 56.1 years b=± 6.2). All groups consisted of three females and two males. None had diabetes mellitus at baseline. Anti-TNF-α treatment did not affect BMI in any of the groups (P > 0.05).
Repeated measures ANOVA indicated that inflammation (as indicated by ESR, CRP and DAS) was equally reduced in all groups (P for differences between groups > 0.05 in all cases). However, HOMA (P = 0.0001) and QUICKI (P = 0.026) was reduced significantly in the N+IR group compared with the N-IR group. Similarly, anti-TNFα treatment resulted in greater decreases in systemic BP (P = 0.048) and triglycerides (P = 0.034) in these patients. On the other hand, it marginally improved insulin sensitivity in both O+IR and O-IR individuals; however, no differences in the magnitude of improvements between the two groups were observed (P > 0.05 for both HOMA and QUICKI). Similarly, lipids and blood pressure were marginally improved in obese individuals but not to a significant extent. Finally, the reduction of inflammation (as indicated by CRP) correlated with the reduction in HOMA (r = 0.55, P = 0.000) and QUICKI (r = 0.49, P = 0.000) only in the N-IR group.

Conclusion: Anti-TNFα therapy seems to improve insulin kinetics in normal weight patients with IR but not in obese patients with IR despite the reduction in inflammation. It seems that IR among normal-weight patients with RA is highly dependent on inflammation while IR among obese RA patients possibly depends less on RA-related inflammation and more on obesity.

Disclosure statement: All authors have declared no conflicts of interest.

36. CYTOKINE PROFILE AND FREQUENCY OF IL-17-PRODUCING CD4 T CELLS IN BLOOD, SYNOVIAL FLUID AND SYNOVUM OF PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Th17 cells have recently been implicated in the pathogenesis and persistence of rheumatoid arthritis (RA). The aim of this study was to systematically analyse the phenotype, cytokine profile and frequency of interleukin-17 (IL-17) producing CD4-positive T cells in mononuclear cells isolated from peripheral blood, synovial fluid and synovium of patients with RA and to correlate Th17 cell frequencies with clinical measures of disease activity.

Methods: Flow cytometry was used to analyse the surface phenotype and cytokine production of mononuclear cells isolated from peripheral blood (PBMC) (n = 44), synovial fluid (SFMC) (n = 14) and synovium (SVMC) (n = 10) of patients with RA and PBMC of matched healthy donors (n = 13) following treatment with PMA and ionomycin.

Results: The median proportion of IL-17-producing CD4 T cells in SFMC (1.51% [0.62 - 3.17]) was greater than in PBMC (0.60% [0.33-1.65]) and the same RA patients and PBMC (0.66% [0.71-1.21]) from healthy donors, but was not statistically significant. Conversely, a lower median proportion of IL-17-producing CD4 T cells in cells isolated from RA synovium/SVMC (0.86% [0.48-1.14]) compared with PBMC (1.07% [0.43 - 1.64]) from those individuals was observed.

The frequencies of IFNγ-producing CD4 T cells were significantly higher in RA SFMC (77.75% [82.37 - 85.93]) than paired PBMC (59.97% [31.07-78.27]). The majority of IL-17-producing CD4 T cells coexpressed IFNγ: IL-17-producing CD4 T cells in RA PBMC and SFMC had very little IL-22 coexpression. However, the frequency of IL-22-producing CD4 T cells in the PBMC did show a positive correlation with the frequency of IL-17-producing CD4 T cells (r = 0.5735, P = 0.0004). IL-22-producing CD4 T cells in SFMC had an inverse correlation with the DAS28 (r = -0.6747, P = 0.008). IL-17-producing CD4 T cells had very little coexpression of IL-23R. The percentage of IL-17-producing CD4 T cells coexpressing TNF was significantly increased in SFMC compared with PBMC.

Conclusions: We did not find an enrichment of IL-17-producing CD4 T cells in either RA SFMC or SVMC compared with PBMC, IL-17-producing CD4 T cells in SFMC produced more TNF than their PBMC counterparts, but were not a significant source of IL-22 and did not express IL-23R. Given the data that IL-17 plays a pathogenic role in RA, further work is required to determine whether this cytokine is produced by other cell types in the rheumatoid environment.

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37. OBESITY IS A MAJOR DETERMINANT OF CRP LEVELS IN HEALTHY INDIVIDUALS

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Background: C-reactive protein (CRP) is a sensitive marker of systemic inflammation routinely used in the diagnosis and monitoring of inflammatory conditions. Studies also show links between CRP and the metabolic syndrome, cardiovascular disease (CVD) and obesity where IL6 released from adipose tissue is thought to induce low grade systemic inflammation. Thus a correlation between CRP and obesity would have significant implications in the clinical use and interpretation of CRP. In a previous study, we demonstrated correlation between CRP and body mass index (BMI) in RA patients. In this study, we investigated the correlation between CRP and BMI in healthy individuals.

Methods: Cross-sectional observational study. After obtaining R & D and ethical approval, all hospital employees were invited to participate. Subjects underwent physical examination, fasting blood testing and completed a lifestyle questionnaire. High sensitivity CRP assay was used. Lower detection limit was < 0.2 mg/l (normal range < 8 mg/l). 127 participants had CRP levels lower than this and were assigned the value of 0.1 mg/l. As distribution was highly skewed, statistical analysis was performed using non-parametric methods. Anthropometric and demographic groups were defined according to the World Health Organization criteria: normal BMI < 24.9 kg/m², overweight BMI 25.0-29.9 kg/m², obese BMI > 30 kg/m².

Results: 365 participants (mean age 44.4 years, 82.7% female) completed the study, 8 participants were excluded from analysis due to intercurrent infection. There was a statistically significant association between CRP and BMI. Normal BMI: median CRP 0.15 (IQR: 0.1-0.53 mg/l); overweight BMI: median CRP 1.3 (IQR: 0.1-2.8 mg/l); obese BMI: median CRP 3.7 (IQR: 1.85-10.4 mg/l) (P < 0.0001). The proportion of participants with CRP levels above the normal range (> 6 mg/l) increased with increasing BMI (P = 0.0001). A substantial proportion of obese subjects (40%) had CRP values > 6 mg/l. Only 2 subjects in the obese group had a CRP value of < 0.2 mg/l. There was a significant unadjusted correlation between CRP and BMI, systolic and diastolic blood pressure, HDL, triglycerides, exercise and smoking. The strongest correlation was observed between CRP and BMI (r = 0.44). In the adjusted model BMI and triglycerides remained significantly and independently related to CRP. BMI accounted for 19% of the variability in CRP, triglycerides for 2.6% and age and gender for < 1%.

Conclusions: CRP values increase with increasing BMI in normal weight, overweight and obese individuals independently of other confounding factors. This is particularly important given that 25% of both UK adults are obese. In the diagnosis and monitoring of inflammatory disease CRP should be interpreted in the context of a subjects’ BMI, as raised CRP levels may reflect body habitus rather than systemic inflammation.

Disclosure statement: All authors have declared no conflicts of interest.

38. DETERMINANTS OF MEAN PLATELET VOLUME IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is associated with increased cardiovascular morbidity and mortality. A variety of classic and novel cardiovascular risk factors are believed to enhance atherothrombosis in RA. Mean platelet volume (MPV) is a valuable marker of a prothrombotic state and high MPV values predict cardiovascular events in the general population. The role of MPV and determinants of MPV shifts have not been clarified in RA. We assessed MPV and its determinants in RA.

Methods: 400 well-characterized consecutive RA patients were enrolled. MPV was assessed by flow cytometry. Based on the normal MPV range (7-10.7 fl), patients were divided into two groups: those with low or normal MPV (<10.7 fl - lmMPV) and those with high
Disclosure statement: All authors have declared no conflicts of interest.

Conclusions: For CAPS patients, canakinumab administered every 8 weeks, provided rapid improvement of symptoms and sustained remission in a large cohort of patients across all disease severity phenotypes.

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39. EFFICACY AND SAFETY OF CANAKINUMAB (ILARIS) IN A LARGE COHORT OF PATIENTS ACROSS DIFFERENT SEVERITY PHENOTYPES OF CRYOPYRIN ASSOCIATED PERIODIC SYNDROME (CAPS)

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Background: CAPS (disease spectrum consisting of FCAS, MWS, NOMID) is a rare hereditary, autosomal dominant, systemic inflammatory disease associated with excessive production of IL-1b. The fully human monoclonal antibody canakinumab provides prolonged selective blockade of IL-1b.

Methods: Patients enrolled in this open-label multi-centre study were canakinumab naïve or rolled over from earlier phase II/III studies. Patients received canakinumab 150 mg s.c. or 2 mg/kg s.c. (≤ 40 kg) every 8 weeks. The primary objective of this ongoing trial is to assess the long-term safety and tolerability of canakinumab in CAPS patients. Secondary objectives included assessment of response (for naïve patients), maintenance of response, percentage of patients requiring dose adjustment and immunogenicity of canakinumab in CAPS patients. The majority of patients (94.9%) had no injection site reactions, 5.1% reported reactions, which were all mild. No anti-canakinumab antibodies were observed.

Conclusions: For CAPS patients, canakinumab administered every 8 weeks, provided rapid improvement of symptoms and sustained remission in a large cohort of patients across all disease severity phenotypes.

Disclosure statement: J.B., Novartis Pharmaceutical Corporation - Funding for clinical studies, honoraria, advisory boards, Centocor, Inc. - Funding for clinical studies, honoraria, advisory boards, Schering-Plough - Funding for clinical studies, honoraria, advisory boards, Schering-Plough - Funding for clinical studies, honoraria, advisory boards, Roche Pharmaceuticals - Funding for clinical studies, honoraria, advisory boards, Amsen - Funding for clinical studies, honoraria, advisory boards, Chugai - Funding for clinical studies, honoraria, advisory boards, Pfizer Inc - Funding for clinical studies, honoraria, advisory boards, BMS - Funding for clinical studies, honoraria, advisory boards, MSD - Funding for clinical studies, honoraria, advisory boards, E.H., Novartis Pharmaceutical Corporation - Consulting fees or other remuneration (payment), P.N.H., Novartis Pharmaceutical Corp - Consulting Fees, I.K.-P., Novartis Pharmaceutical Corporation - Consulting fees or other remuneration (payment), N.P., Novartis Pharmaceutical Corporation - Employment, Stocks, A.W., Novartis Pharmaceutical Corporation - Employment, Stocks. All other authors have declared no conflicts of interest.

Spondyloarthropathies (Including Psoriatic Arthritis)

40. EAGLE’S SYNDROME: AN UNUSUAL ASSOCIATION WITH SERO-NEGATIVE ARTHROPATHY

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Background: Eagle’s syndrome is characterized by recurrent throat pain, foreign body sensations, dysphagia and facial pain as a result of an elongated styloid process or calcified stylohyoid ligaments. It is postulated that the stylohyoid apparatus can be a site of enthesitis in patients with inflammatory spondyloarthopathies, such as ankyllosing spondylitis (AS) and psoriatic arthritis. We present a patient with AS who had symptoms attributable to enthesal attrition and calcification of his stylohyoid ligaments.

Methods: A 48-year-old male, diagnosed as having AS 8 years previously, presented with generalized aches and pains and a 9-month history of discomfort in the right jaw that he said was ‘locking and clenching’ during eating or yawning. He also described strange sensations in vicinity of the right side of his throat, spots in front of his eyes, light headedness and a feeling of being slightly drunk. On examination, he was unable to open the jaw comfortably ≥ 1 cm anteriorly and any further movement produced a loud crepitus at the right temporomandibular joint. Temporomandibular joint dysfunction was excluded.

Results: The orthopantomogram and subsequent CT scan images demonstrated bilateral elongated and calcified stylohyoid ligaments, which were thought to explain his signs and symptoms, resulting in a final diagnosis of Eagle’s syndrome. He has now undergone surgical treatment in the form of tonsillectomies with bilateral removal of 12–14 mm of the calcified stylohyoid ligaments and is showing encouraging results post surgery.

Conclusions: Persistent jaw discomfort in a patient with an underlying spondyloarthropathy should prompt the search for enthesopathy affecting the stylohyoid apparatus. If present, the patient may have Eagle’s syndrome.

Disclosure statement: All authors have declared no conflicts of interest.