Short running head: axSpA in IBD

Full title of manuscript: Identifying Axial Spondyloarthritis in Inflammatory Bowel Disease Patients Utilising Computed Tomography

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Abstract

Objective

The diagnosis of axial spondyloarthritis (axSpA) is hampered by diagnostic delay. Computed Tomography (CT) undertaken for non-musculoskeletal (MSK) indications in patients with inflammatory bowel disease (IBD) offers an opportunity to identify sacroiliitis for prompt rheumatology referral. The study aims to identify what proportion of IBD patients who underwent abdominopelvic CT for non-MSK indications have axSpA and explore the role of a standardised screening tool to prospectively identify axSpA on imaging.

Methods

Abdominopelvic CT scans of verified IBD patients, age range 18-55, performed for non-MSK indications were reviewed by radiology for presence of CT-defined sacroiliitis (CTSI, using criteria from a validated CT screening tool). All patients identified were sent a screening questionnaire and those with self-reported chronic back pain (CBP), duration > 3 months, onset < 45 years were invited for rheumatology review.

Results

CTSI was identified in 60 of 301 patients. Thirty-two (53%) responded to the invitation to participate and 27 were enrolled. Of these, eight had a pre-existing axSpA diagnosis and five did not report CBP. Fourteen patients underwent rheumatology assessment; three of 14 (21.4% [95% CI: 4.7%, 50.8%]) had undiagnosed axSpA. In total, 11 of 27 (40.7% [95% CI: 22.4%, 61.2%]) patients had a rheumatologist verified diagnosis of axSpA.

Conclusions

At least 5.0% of IBD patients (3/60) undergoing abdominopelvic CT for non-MSK indications with CTSI have undiagnosed axSpA, and overall, 18.3% (11/60) have axSpA. This reveals a significant hidden population of axSpA and highlights the need for a streamlined pathway from sacroiliitis detection to rheumatology referral.

Introduction

Extra-musculoskeletal manifestations including acute anterior uveitis (AAU), inflammatory bowel disease (IBD) and psoriasis (PSO) are common among patients with axial spondyloarthritis (axSpA) and referral strategies have been published for AAU in order to reduce delay to diagnosis (1–3). Delayed diagnosis leads to worse outcomes for people with the disease (4,5). To our knowledge, there are no published imaging referral strategies for patients with IBD to assess for concurrent clinically diagnosed axSpA.

IBD patients often undergo imaging to evaluate their gastrointestinal disease, thereby presenting an opportunity to trigger a rheumatology referral in those with sacroiliitis on imaging. Computed Tomography (CT) is one method for identifying sacroiliitis. Recent evidence has shown that the prevalence of sacroiliitis on CT performed in patients with IBD for non-musculoskeletal (non-MSK) indications ranges from 2.2% to 25% (6–9). In parallel, a practical CT screening tool has been developed to differentiate sacroiliitis in (i) axSpA versus controls (10) and (ii) IBD versus controls (9), which could potentially be used to identify axSpA in IBD patients. To our knowledge, there are no studies reporting on the proportion of IBD patients with CT-defined sacroiliitis (CTSI), who have subsequently been diagnosed as axSpA by a rheumatologist, defined here as a rheumatologist-verified diagnosis of axial spondyloarthritis (RVD-axSpA).

This study explores the frequency of undiagnosed and diagnosed axSpA in this population and the utility of a CT screening tool (10) to expedite axSpA diagnosis in the IBD population through the identification of CTSI using scans performed for non-MSK indications.

Material and Methods

Design

The study was a cross-sectional study. IBD patients who were retrospectively identified to have CTSI underwent a prospective clinical assessment, to determine what proportion have RVD-axSpA (see Figure 1).

Identification of the Study Population

The study population was selected from a service evaluation project performed at a large academic teaching hospital. Abdominopelvic CT scans of patients with IBD (Crohn's disease [CD] or Ulcerative Colitis [UC]) were retrospectively identified from the radiology imaging system between January 2010 to December 2017. The diagnosis of gastroenterologist verified IBD was confirmed via clinical records. The study population was limited to ages between 18 and 55 years inclusive at the time of CT, with the most recent CT named the index scan. The scans were reviewed by radiologists trained to identify radiological features of sacroiliitis on CT using the criteria developed by Chan et al (10), after internal reliability testing and clarification (see Supplementary Table S1 for more details).

Study Population

Screening questionnaires (SQ) were sent to all IBD patients with CT performed for non-MSK indications between age 18 - 55 inclusive at the time of CT and identified as having CTSI.

CTSI is defined (see Supplementary Table S2 for more details) as the presence of sacroiliac joint ankylosis, total erosion score (TES) of ≥ 3, > 0.5 cm iliac sclerosis and/or > 0.3 cm sacral sclerosis (as our sampled population was enriched [with IBD diagnosis and age range within the highest diagnostic yield for axSpA], we selected the criteria which were shown to have the highest sensitivity [94%] by Chan et al to identify cases of sacroiliitis suspicious of axSpA, so that all possible cases were included).

Subjects who replied with a valid completed SQ and gave informed consent were enrolled. Those with chronic back pain (CBP) > 3 months, onset < 45 years were invited for rheumatology assessment. Patients with pre-existing confirmed axSpA, verified from their medical records were contacted via telephone to collect clinical characteristics but were not reassessed. This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (252117 19/EE/0125). All participants gave written informed consent before study inclusion.

Clinical Assessment

This included a full medical interview; physical examination (including joint and tender point count, Maastricht Ankylosing Spondylitis Enthesitis Score [MASES], dactylitis count, Bath Ankylosing Spondylitis Metrology Index [BASMI] (11,12)) by a rheumatologist; patient reported outcomes (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Bath Ankylosing Spondylitis Functional Index [BASFI], Bath Ankylosing Spondylitis Global [BASG], Harvey-Bradshaw-Index, Partial-Mayo-Index (11,13,14)); laboratory tests (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], human leukocyte antigen B27 [HLA-B27]); and axSpA protocol magnetic resonance imaging (MRI) (15).

Diagnosis Verification

Each subject was discussed in a virtual meeting: an initial discussion solely based on clinical history and examination findings and a second following the availability of laboratory and imaging results. The panel comprising 3 rheumatologists with a specialist interest in axSpA were blinded to the CT findings. Each made either a positive or negative diagnosis of axSpA. They also indicated their level of diagnostic confidence on a 10-point Likert scale. RVD-axSpA was confirmed when at least two of three rheumatologists agreed. The level of confidence (LoC) was reflected by an average of the three Likert scales. A similar process was undertaken when the results of MRI and laboratory results were available. Any discrepancy between the pre- and post- investigation diagnosis was discussed in a further summary meeting, and a final diagnosis made by a majority consensus vote after a subsequent review of all clinical, laboratory and MRI information.

Definition of CT Screening Tool and retrospective analysis

The *presence of sacroiliac joint ankylosis or total erosion score (TES) ≥3* was defined by Chan et al (9,10) as sufficient to identify patients having sacroiliitis suspicious of axSpA that may warrant a rheumatologist referral (see Supplementary Table S3 for more details). A retrospective exploratory analysis of our study data using the CT Screening Tool definition was done to understand the efficacy of the tool in predicting a final diagnosis of axSpA.

Power calculation and statistical analysis

Estimates of the proportion of RVD-axSpA in those IBD patients with CTSI were unknown. Instead sample size was estimated from symptomatic CTSI (a range of 3% to 45%) (16–18). It was estimated that 21 patients were needed to detect a minimum symptomatic CTSI proportion of 30% (derived from clinical experience at our institution) at a nominal threshold significance of p=0.05. Based on the assumption that 50% would respond to the SQ, and 80% of the respondents would take up an invitation for clinical review, the study aimed to screen an initial sample of 54 IBD patients.

Descriptive statistics were used to summarize the patient characteristics, stratified by symptoms and diagnosis. Inter-clinician diagnostic agreements were calculated using kappa statistic with estimated confidence intervals. Descriptive statistics were used to present the average LoC. For calculation of proportions, the frequency of cases to the base population was used with a calculated confidence interval. The efficacy of the CT Screening Tool in predicting a final diagnosis of axSpA was measured in terms of sensitivity, specificity, positive and negative predictive values. Data analysis was performed using STATA Version 15 (StataCorp, TX, USA) and Microsoft Excel 2016 (Microsoft, WA, USA).

Results

Service evaluation results

Three hundred and one unique scans of verified IBD patients were reviewed by the radiology team (see Figure 1). Twenty percent (60/301) were identified with CTSI. Only 15 (25%) of these cases were reported as showing sacroiliitis with no recommendation made for onward rheumatological evaluation (See Supplementary Table 4 for full results).

Study patient characteristics and axSpA diagnosis

Sixty patients were sent a SQ. Thirty-two (53%) patients responded to the invitation to participate and 27 (84%) were enrolled (see Figure 1). The detailed clinical characteristics of these patients are shown in Supplementary Table S5. Fourteen of 27 (51.9%) patients were invited for rheumatology assessment as 8 (29.6%) had prior diagnosis of axSpA, and 5 (18.5%) did not report CBP. Three of these 14 (21.4% [95% CI: 4.7%, 50.8%]) had undiagnosed RVD-axSpA. The other diagnoses included spondylosis 5/14 (36%), fibromyalgia 5/14 (36%) and non-specific lower back pain 1/14 (7%). In total, 11 of the 27 enrolled (40.7% [95% CI: 22.4%, 61.2%]) patients had RVD-axSpA. See Table 1 for different permutations of various proportions of axSpA/sacroiliitis.

Agreement of RVD-axSpA and LoC

There was moderate agreement (k = 0.42, 95% CI 0.04 - 0.80) with a median LoC of 6 (IQR 2 - 8) of RVD-axSpA based on only clinical information before investigative results. Once presented with investigation results (i.e. CRP, ESR, HLA-B27, MRI findings), the agreement changed to fair (k = 0.30, 95% CI 0.00 - 0.65) with a median LoC of 7 (IQR 3 - 9). The agreement was substantial (k = 0.74, 95% CI 0.10 - 0.98) with a median LoC of 7 (IQR 5 - 8) for discrepant cases after further discussion. For all cases, the final agreement was almost perfect (k = 0.85, 95% CI 0.35 - 0.97) with a median LoC of 8 (IQR 5 - 9).

Performance of the CT Screening Tool

The utility of the CT Screening Tool was explored in different groups for its performance retrospectively. The results from the CT Screening Tool applied to patients that joined the study regardless of having self-reported CBP (Analysis 1: asymptomatic and symptomatic CTSI patients) versus patients with self-reported CBP, duration >3 months, onset < 45 years via the SQ (Analysis 2: symptomatic CTSI patients), are as shown in Table 2. The sensitivity or the ability of the tool to detect patients with RVD-axSpA was similar for both groups at 90.9%, and the specificity or the ability of the tool to correctly reject those without axSpA were 56.3% and 63.6% respectively.

Discussion

AxSpA is a clinical diagnosis (19). Asymptomatic, imaging positive sacroiliitis does not automatically imply a diagnosis of axSpA without physician verification. Sacroiliac joint abnormalities can occur for other reasons including mechanical or degenerative causes, which can manifest as subchondral sclerosis, vacuum phenomenon and osteophytosis (20,21). In addition, targeted therapy should not be given to patients without a clinical diagnosis of axSpA regardless of imaging results. This highlights the importance of understanding what proportion of IBD patients with CTSI have RVD-axSpA. Referral strategies have been published for AAU (3) and questionnaires have been developed to identify spondyloarthritis (using classification criteria) among IBD patients (22,23). However, there are no published data on the utilisation of CT as a referral strategy with subsequent confirmation of a physician-verified diagnosis of axSpA.

We have identified that 60/301 (20%) of IBD patients undergoing CT for non-MSK indications have CTSI and at least 11/60 (20%) of these have RVD-axSpA. Five percent (3/60) were previously undiagnosed, despite a mean interval since the index CT scan of 5.7 years and mean duration of back pain 13.7 years. The validated CT Screening Tool to identify CTSI, has a sensitivity of 90.9% and specificity of 63.6% for a clinical diagnosis of axSpA. Taken together, this suggests that within the age 18-55, IBD cohort with CBP, > 3 months, onset < 45 yrs., the tool would be effective in identifying IBD patients at highest risk of having RVD-axSpA.

Previous clinical studies have shown that 3% to 45% of IBD patients have symptomatic sacroiliitis seen on plain radiograph and/or CT utilising a broad range of definitions for sacroiliitis (16–18). These authors also showed that the proportion of asymptomatic sacroiliitis (i.e. IBD patients with sacroiliitis but no back pain) ranged from 13.6% to 32% (16,18,24). On the other hand, radiology-based studies found that the proportion of incidental/coincidental sacroiliitis on CT in IBD patients is 2.2% to 25% (6–9). In our study, 22/27 (81.5%) of IBD patients had symptomatic CTSI {11/27 [40.7%] had RVD-axSpA (3/11 were undiagnosed and 8/11 had known diagnosis); 11/27 [40.7%] had symptoms but no RVD-axSpA} and 5/27 (18.5%) were asymptomatic CTSI (see Table 1 and Figure 1 for details).

This study is important for several reasons. Firstly, the design of the study is novel. It involves a cross-sectional postal survey of patients with CTSI, supplemented by a structured clinical assessment of a subset of participants to establish the proportion with RVD-axSpA. This is designed to mirror the real-world scenario, whereby if an IBD patient undergoing CT scan is found to have suspicious sacroiliac changes on imaging, the responsible clinician (the SQ is the surrogate here) will review the patient before onward referral to rheumatology.

Secondly, the diagnosis was made by an experienced panel of rheumatologists with a special interest in axSpA with good agreement and high level of confidence. Given there is no gold standard diagnostic biomarker; the current gold standard is expert opinion. When approaching patients with multisystem complex disease, it can be difficult to make a diagnosis (25). There is a need to distinguish if the aetiology of sacroiliitis (and back pain) is due to underlying mechanical/degenerative (and/or psychological pain overlay of a chronic disease), undiagnosed active inflammatory axial disease, or a combination of both. In this cohort (See Supplementary Table S5), where the mean disease duration is more than 10 years, only 4/9 (44%) patients with RVD-axSpA and CTSI have active sacroiliac joint inflammatory lesions on MRI. On the other hand, in patients with a mean disease duration of 17 years, those with symptomatic CTSI but

no diagnosis of RVD-axSpA, none (0/11, 0%) had active sacroiliac joint inflammatory lesions. This could reflect the nature history of inflammatory lesions and highlights the challenges around reliance on structural/inflammatory imaging lesions in making a clinical diagnosis of axSpA in this population.

Thirdly, our study was able to explore the usefulness of a validated imaging tool which may prompt earlier referral to rheumatology, potentially expediting a diagnosis of axSpA. This study shows that by utilising an objective tool and a self-reported screening questionnaire, it is feasible to filter the large numbers of IBD patients having CT scans to those with a high pre-test probability of axSpA and arrive at a manageable proportion of patients for clinical assessment. This will ensure that rheumatology services are not overwhelmed and yet be able to identify some undiagnosed axSpA.

This study has several limitations. This was a cross sectional design. The sample size is small, and this is a single centre study. We focused our sample on the population with the highest probability of axSpA, therefore it is possible that we have missed other cases due to selection bias. Also, 33/60 patients (55% of patients with CTSI) did not complete the SQ or declined to participate (see Figure 1 for details), thus their data have not been captured. This means that the results may not be generalisable and the prevalence of undiagnosed RVD-axSpA may have been underestimated. Our design did not allow for evaluation of those without CBP, some of whom may have axSpA, however it is likely that such patients would have a lower symptom burden and not require targeted therapy. Finally, we did not clinically re-evaluate those with a pre-existing diagnosis of axSpA, so it is theoretically possible that some of these could have been misdiagnosed.

In conclusion, the results of this study may have practical implications, as they show that there is still undiagnosed axSpA in established IBD patients attending a secondary care institution. It also explores the possibility of using a pragmatic CT Screening Tool to improve disease awareness among radiologists, aid axSpA identification and reduce the delay to diagnosis in this population. The practicalities of implementing this strategy on a wider scale in routine practise will need further research.

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Figures Legends

Figure 1. Flow chart of study. -ve: negative; +ve: positive; axSpA: axial spondyloarthritis; CT: Computed Tomography; CTSI: CT-defined sacroiliitis; MSK: musculoskeletal; IBD: Inflammatory Bowel Disease; sCBP: self-reported chronic back pain >3 months, age onset <45 years old; SQ: screening questionnaire; w/o: without