

Title: Prevalence of Undiagnosed Axial Spondyloarthritis in Inflammatory Bowel Disease Patients with Chronic Back Pain: Secondary Care Cross-Sectional Study

Authors & Dr Chong Seng Edwin Lim¹

Affiliations: Dr Mark Tremelling²

Dr Louise Hamilton¹

Dr Matthew Kim³

Professor Alexander Macgregor¹

Dr Tom Turmezei³

Professor Karl Gaffney¹

1. Rheumatology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, United Kingdom

2. Gastroenterology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, United Kingdom

3. Radiology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, United Kingdom

Corresponding Dr Chong Seng Edwin Lim

Author: Address: Norfolk and Norwich University Hospitals NHS Foundation Trust, Rheumatology Department, Norfolk & Norwich University Hospital, Colney Lane, Norwich, United Kingdom, NR4 7UY

Primary Email: edwin.lim@nnuh.nhs.uk

Alternate Email: ecslim@gmail.com

Phone: 01603 647835

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Abstract

Objective

To elucidate the prevalence of undiagnosed rheumatologist-verified diagnosis of axial spondyloarthritis (RVD-axSpA) in patients attending routine secondary care IBD clinics with chronic back pain.

Methods

Screening questionnaires were sent to consecutive patients attending IBD clinics in a university teaching hospital. Patients fulfilling the eligibility criteria (gastroenterologist-verified diagnosis, 18 to 80 years old, biologic therapy naïve, no previous diagnosis of axSpA); and a moderate diagnostic probability of axSpA (self-reported chronic back pain [CBP] > 3 months, onset < 45 years) were invited for rheumatology assessment. This included medical review, physical examination, patient reported outcome measures, human leukocyte antigen B27, C-reactive protein, pelvic radiograph and axSpA protocol magnetic resonance imaging. A diagnosis of RVD-axSpA was made by a panel of rheumatologists.

Results

Of the 470 patients approached, 91 had self-reported CBP > 3 months, onset < 45 years, of whom 82 were eligible for clinical assessment. The prevalence of undiagnosed RVD-axSpA in patients attending IBD clinics in a secondary care setting, with self-reported CBP, onset < 45 years is estimated at 5% (95% CI 1.3,12.0) with a mean symptom duration of 12 (S.D. 12.4) years.

Conclusion

There is a significant hidden disease burden of axSpA among IBD patients. Appropriate identification and referral from gastroenterology is needed to potentially shorten the delay to diagnosis and allow access to appropriate therapy.

Keywords

axial spondyloarthritis, inflammatory bowel disease, epidemiology, back pain, magnetic resonance imaging

Key messages

At least 1 in 20 patients attending secondary care IBD clinics with chronic back pain have undiagnosed axial spondyloarthritis.

Asymptomatic and symptomatic sacroiliitis can be present in IBD patients but may not equate to a clinical diagnosis of axSpA.

The high prevalence of chronic back pain in IBD patient does not necessarily indicate an inflammatory aetiology.

Introduction

Axial spondyloarthritis (axSpA) is known to be closely associated with inflammatory bowel disease (IBD). The spectrum of axSpA includes patients with non-radiographic axSpA and radiographic axSpA formerly known as Ankylosing Spondylitis (AS). Due to evolving case definitions of axSpA and methodologies used to identify cases, the reported prevalence of axSpA in IBD is wide. The pooled prevalence of AS in IBD has been estimated as 3% [1] whereas the estimated prevalence of axSpA in IBD is reported to be 7.7% [2]. Contemporary prevalence of undiagnosed axSpA is sparse [3–5].

AxSpA is a physician-verified diagnosis rather than one based on the fulfilment of contemporary classification criteria. Despite advances in imaging technology, improved understanding of the axSpA concept, and awareness campaigns [6–8], delay to diagnosis is still a major problem with an average delay of between 8 – 10 years. Patients often endure intolerable symptoms and worse outcomes (disease activity, function, radiographic), despite the availability of effective new therapies [9,10]. Before we can proceed to develop referral strategies specific for IBD patients, similar to those for the general population and those presenting with acute anterior uveitis [11,12], there is a need to understand the prevalence of this “hidden burden” in daily clinic practice.

This study aims to estimate the prevalence of undiagnosed rheumatologist-verified diagnosis of axSpA (RVD-axSpA) in patients attending routine IBD secondary care clinics with chronic back pain.

Patients and Methods

Study Design and Setting

This was an observational cross-sectional study. Screening questionnaires (SQ) were sent prospectively to consecutive patients attending routine IBD clinics between September 2017 and February 2019 at a large university teaching hospital serving approximately 3000 IBD patients. Following this, a structured clinical assessment of a subset of participants (including those with and without chronic back pain) was conducted to determine the proportion with undiagnosed RVD-axSpA (see Figure 1).

Study Population

Patients fulfilling the eligibility criteria (gastroenterologist-verified diagnosis, age range 18 to 80 years old, biologic therapy naïve, no previous diagnosis of axSpA); and a moderate diagnostic probability of axSpA defined as self-reported chronic back pain (CBP) > 3 months and onset < 45 years were invited for rheumatology assessment. Patient on biologics unlike other IBD treatments were excluded because inflammatory lesions may be suppressed and could interfere with objective assessment and diagnostic assignment. Patients with pre-existing confirmed axSpA, were verified from their medical records and contacted via telephone to collect clinical characteristics but were not reassessed.

Screening Questionnaire

This was a self-reported questionnaire [13] which enquired about the presence of a previous axSpA diagnosis, presence of back pain lasting more than 3 months, age of onset of back pain, nature of back pain, personal and family history of associated axSpA conditions, and brief description of their inflammation bowel disease and treatment.

Clinical Assessment

This included a medical review, physical examination (including joint and tender point count, Maastricht Ankylosing Spondylitis Enthesitis Score [MASES], dactylitis count, Bath Ankylosing Spondylitis Metrology Index [BASMI]), 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), laboratory tests (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], human leukocyte antigen B27 [HLA-B27]), pelvic radiograph (X-

ray), axSpA protocol magnetic resonance imaging (MRI) of sacroiliac joints (SIJ) and spine [14], and remote review by a panel of axSpA rheumatologists.

Interpretation of results

The pelvic radiograph and MRI of the sacroiliac joints and spine were performed as per the local axSpA protocol, read and reported by the musculoskeletal radiology team according to routine clinical practice. Any imaging discrepancies were discussed at a weekly radiology multidisciplinary meeting and agreement made by a consensus majority. Furthermore, grading of radiographic sacroiliitis was undertaken by two radiology colleagues with reference to the modified New York criteria [15]. A positive sacroiliac joint MRI for inflammation was determined with reference to the ASAS-OMERACT 2009 definition [16] incorporating recently updated guidance [6]. A positive spinal MRI for inflammation was made with reference to the ASAS-OMERACT 2012 definition [17]. Both imaging modalities were assessed independently from one another.

Rheumatologist-verified diagnosis of axSpA

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 comprised of 3 rheumatologists with a specialist interest in axSpA. 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 imaging 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 imaging information.

Power calculation and statistical analysis

It was estimated that 73 patients were needed to detect a minimum axSpA prevalence of 5% at a nominal threshold significance of $p=0.05$. Based on the assumption that 50% would respond to the SQ, and 50% of the respondents [18–20] would have self-reported CBP (sCBP) of whom 75% would take up an invitation for clinical review, the study aimed to screen an initial sample of 390 consecutive IBD patients.

Descriptive statistics were used for patient characteristics. Inter-clinician diagnostic agreements were calculated using the kappa statistic with estimated confidence intervals. Descriptive statistics were used to present the average LoC. For calculation of prevalence, the frequency of cases (i.e. RVD-axSpA) to the base population (i.e. IBD patients who returned a valid SQ with sCBP and were clinically assessed) was used with a calculated confidence interval when appropriate. Data analysis was performed using STATA Version 15 (StataCorp, TX, USA) and Microsoft Excel 2016 (Microsoft, WA, USA).

Screen Negative Assessment Control (SNAC) Group

A sample of consecutively enrolled IBD patient *without* self-reported CBP (> 3 months and onset < 45 years) were selected (for every two screen-positive patients assessed, matched as closely to gender and age as possible) and assessed as above clinical assessment (except pelvic radiograph due to ethical reasons (see Figure 1)).

Results

Main patient characteristics

Four hundred and seventy consecutive IBD patients were approached; 288 (61%) expressed interest, and 191 (66%) returned a completed SQ of which 173 were valid (See Figure 1, which also list the number of patient with known axSpA). Ninety-one (53%) had self-reported CBP > 3 months, onset < 45 years, of whom 82 (90%) were eligible for clinical assessment (See Figure 1, which also list reasons for exclusion). Their detailed clinical characteristics are shown in Table 1 and Table 2.

The salient clinical characteristics of those assessed in the clinical assessment are as follows. The mean age was 52 years, 37% were male, 74% had ulcerative colitis, 26% Crohn's disease, and 66% were in remission. The prevalence of inflammatory back pain (IBP) was 38%, 35% and 29% fulfilling Calin, Berlin and Assessment of SpondyloArthritis international Society (ASAS) expert's IBP criteria, respectively. The frequency of acute anterior uveitis (AAU), psoriasis and other inflammatory peripheral musculoskeletal (MSK) manifestations (i.e. arthritis, enthesitis, dactylitis) were reported to be 5%, 7% and 16% respectively. Twenty-nine (35%) patients had a family history of axSpA-related disorders (of whom 62% IBD, 52% skin psoriasis, 4% axSpA). Mean C-reactive protein (CRP; reference range: 0 – 10) and erythrocyte sedimentation rate (ESR; reference range: 0 – 20) were 4.3mg/L and 14mm/h respectively; 7% were human leukocyte antigen B27 (HLA-B27) positive; 4% fulfilled the ASAS definition of a positive MRI and 6% fulfilled the radiological criteria of the modified New York criteria (mNYC). With respect to the four patients with RVD-axSpA and self-reported CBP, 3 were HLA-B27 positive; there was an average of 2 relevant ASAS axSpA features; 1 fulfilled the ASAS definition of a positive MRI; 2 fulfilled the mNY radiological criteria.

Agreement of RVD-axSpA and LoC

There was fair agreement ($k = 0.25$; 95% CI: 0.07 – 0.51) with a median LoC of 7 (IQR 6 – 8) of RVD-axSpA based on clinical information before investigative results. After considering investigation results (i.e. CRP, ESR, HLA-B27, X-ray, MRI findings) and discussion of discrepant cases, the final agreement was almost perfect ($k = 0.92$; 95% CI: 0.55 – 0.99) with a median LoC of 9 (IQR 8 – 9).

Prevalence of undiagnosed and total axSpA

The prevalence of undiagnosed RVD-axSpA was estimated to be between 1% to 5% in IBD patients. The estimated prevalence of total RVD-axSpA in all patients who were sent a SQ is 2.3%. See Table 3 for different permutations of various prevalence of axSpA/sacroiliitis. The fulfilment of various classification criteria for axSpA were 39% (European Spondyloarthropathy Study Group [ESSG]), 12% (ASAS) and 5% (mNYC) are shown in Table 4.

SNAC group

Forty-one patients were eligible for clinical assessment. The mean age was 63 years, 44% were male, 76% had ulcerative colitis, 24% Crohn's disease, and 68% were in remission. One patient (1/40; 2.5%) had asymptomatic sacroiliitis as shown in Figure 1. A second patient had undiagnosed RVD-axSpA (prevalence was 1/41 or 2.4% [95% CI 0.1 – 12.9]) as shown in Table 3.

Discussion

The link between axSpA and IBD is well established. Despite an improved understanding of the spectrum of axSpA, there continues to be a significant diagnostic delay in axSpA. Referral strategies have been developed to screen the general population and those presenting with acute anterior uveitis [11,12]. Previous studies have reported the prevalence of axSpA spectrum disease in IBD in different care settings, study designs and a range of axSpA case definitions [1]. Few studies [3–5] have explored the burden of undiagnosed axSpA in the IBD population as their main study outcome.

In our observational cross-sectional study, the prevalence of undiagnosed RVD-axSpA in IBD patients seen routinely in a hospital setting with self-reported CBP (> 3 months), onset < 45 years, is estimated at 4/82 (5%). This represents a significant hidden disease burden as it is 4/10 (40%) of the total RVD-axSpA in our sample.

This study is important for several reasons. Firstly, this provides the first estimate of undiagnosed RVD-axSpA in IBD patients based on modern axSpA concepts which mirrors standard daily clinical practice. Previous studies included in a recent systematic review showed that most cross-sectional prevalence studies either collected their data retrospectively or if collected prospectively, the proportion of undiagnosed patients were not specified [1]. It also highlights the absence of adequate contemporary studies that reflect the current population and practice [3,4].

The diagnoses made by the rheumatology panel had good agreement and a high level of confidence. If the diagnosis was based on classification criteria only (see Table 4), our estimates would have aligned with a previously reported pooled prevalence of sacroiliitis (mostly defined with imaging) of 10% [1]. AxSpA remains a clinical diagnosis based on suspicious symptoms supported by laboratory and imaging investigations; the fulfilment of classification criteria does not necessarily equate to a diagnosis of axSpA. In addition, biological therapy should not be given to patients without a clinical diagnosis of axSpA regardless of imaging or classification results.

The study found a low prevalence of sacroiliitis and undiagnosed RVD-axSpA in the asymptomatic sample. AxSpA typically presents with a history of chronic back pain [21]. However, asymptomatic sacroiliitis has been reported in patients with IBD [22] who have MRI findings resembling axSpA [23]. Results from the SNAC group found that only a single case of asymptomatic sacroiliitis. Although, this is lower than the prevalence reported by previous studies [22,24–26], it is most likely due to the varying definition of “asymptomatic” between studies. We used the *absence* of self-reported CBP for > 3 months and onset < 45 years as “asymptomatic” *a priori* because the clinical probability of RVD-axSpA is less likely. This is further substantiated as our results showed that in IBD patients without self-reported CBP, there was only a single case of undiagnosed RVD-axSpA.

In the clinical context, it is extremely important to correlate the clinical phenotype with imaging findings depending on the clinicians’ pre-test probability of axSpA before arriving at a diagnosis of axSpA. This is even more important in IBD as there is a known background prevalence of asymptomatic sacroiliitis as described in the above paragraph. Our study provides more understanding about symptomatic sacroiliitis versus a diagnosis of axSpA (see Figure 1). Previous studies [19,24,25,27,28] have reported symptomatic sacroiliitis, with prevalence ranging from 3% - 45% (due to broad range of definitions). It has to be realised that imaging evidence of sacroiliitis represents supportive evidence of previous or current inflammatory changes at the sacroiliac joints depending on the modality and timing of imaging, but this is not a confirmation of an autoinflammatory or autoimmune cause, without accompanying clinical context/evidence. In this study, 5/82 (6.1%) who have self-reported CBP > 3 months and onset < 45 years have symptomatic sacroiliitis (meeting the radiological criteria of mNYC and/or ASAS) but do not reach a clinical diagnosis of axSpA as shown in Figure 1 and Table 3. Also, it is interesting to note that the prevalence of symptomatic sacroiliitis is higher than undiagnosed RVD-axSpA (6.1% vs 4.9%, see Table 3), this may suggest that it is important to seek expert opinion from specialist rheumatologists in complex cases, as clinical judgement/experience and consensus are needed rather than the application of criteria or reliance on imaging alone when reaching a diagnosis of axSpA in IBD patients.

The presence of back pain alone may not be a reliable indicator of RVD-axSpA in the IBD population. In the study, the prevalence of self-reported CBP (> 3 months, onset <45 years) that might raise the suspicion of axSpA in IBD patients is 91/173 (53%). This is higher than the estimate of CBP in the general population, with an upper limit of 20% in a recent systematic review [29]. When we apply the Calin, Berlin, ASAS inflammatory back pain criteria, this

translates to 31/91 (34%), 29/91 (32%) and 24/91 (26%), respectively. However, in patients that were assessed clinically 82/91 (90%), a majority 78/82 (95%) did not result in a final inflammatory disease diagnosis. The other diagnoses include spondylosis 56/78 (72%), fibromyalgia 1/78 (1%), non-specific lower back pain 6/78 (8%), no specific differential diagnosis 2/78 (3%), and other overlapping non-inflammatory diagnosis 13/78 (17%).

This study has several limitations. Firstly, this was a cross sectional design. Secondly, some degree of selection bias may have been introduced as the sample was from a single centre and excluded patients treated with biologic therapy which could have modified the symptoms, laboratory biomarkers, MRI findings and interpretation; and impact on the ability to diagnose AxSpA with confidence. Also, excluding patients treated with biologics for IBD may have excluded patients with concomitant axSpA limiting generalisability. In addition, due to the cut-off age of onset of chronic back pain in the eligibility criteria, axSpA patients with late onset IBD (IBD onset >45 years) may have been excluded. 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. Taken together, the prevalence of undiagnosed RVD-axSpA may be underestimated.

Furthermore, due to ethical and financial constraints, we were unable to sample the whole population (especially those without self-reported back pain). However, a sample in the form of the SNAC group was performed with its limitations. The study assessment protocol for the SNAC group was the same as those in the screen positive group except for pelvic radiography due to ethical concern over radiation exposure. Nonetheless, we had axSpA-protocolled MRI imaging for all 41 patients who attended the clinical assessment (except one who did not complete a full protocol acquisition). In this patient, available imaging was sufficient for clinical reporting but not ASAS criteria reading. It is unlikely that we failed to detect any case of sacroiliitis on imaging due to this process.

Also, as the SNAC group consisted of patients without self-reported CBP (> 3 months and onset < 45 years) it is likely that the mean age will be older than the screen positive group, thus the selection for the SNAC group were matched to the nearest age and sex to ensure that the groups were matched. Due to the small sample to select from (n = 51), this was not entirely possible. Further sub-analysis showed that there was no difference in the percentage of males between the screen positive and SNAC groups (37% vs 44%, p = 0.62), but the mean age of the SNAC group was older despite best attempts at matching (63 vs 52 years, p < 0.0001). A

difference in age may theoretically result in more age-related MRI changes at the sacroiliac joints which may affect the outcome of reported asymptomatic sacroiliitis. Nevertheless, the results are reassuring as there was only one asymptomatic sacroiliitis and one undiagnosed RVD-axSpA.

We believe that we now have a clearer understanding of the magnitude of the hidden burden of axSpA in IBD. Further work will need to focus on reproducing this estimate in other national and international cohorts and developing screening tools to allow early identification and referral of IBD patients for rheumatology assessment. At present, one should still follow the guidance of the ASAS-endorsed recommendation for the early referral of patients with suspected axial spondyloarthritis [30]. This should work in parallel with campaigns and educational strategies to raise awareness of this disease association.

In conclusion, the results of this study have practical implications, as they show that there is undiagnosed RVD-axSpA among patients attending secondary care IBD clinics. To our knowledge, this is the first attempt to estimate the prevalence of undiagnosed RVD-axSpA in IBD patients, based on our current understanding of axSpA in daily clinical practice. The importance of a clinical diagnosis in axSpA is made clearer by understanding the background of asymptomatic and symptomatic sacroiliitis in IBD patients. Appropriate identification of suspected axSpA patients in IBD clinics offers an opportunity to shorten the delay to diagnosis in axSpA.

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Disclosure statement

CL reports grants from AbbVie, outside the conduct of the study. KG reports grants and personal fees from AbbVie, grants and personal fees from Eli Lilly, grants and personal fees from Novartis, grants and personal fees from UCB Pharma, grants from Gilead, during and outside the conduct of the study. MT, LH, MK, AM, TT had nothing to disclose.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (223356 18/EE/0102). All participants gave written informed consent before study inclusion.

Data availability statement

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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Figures – Title & Legend

Figure 1 Flow Chart of Study.

*only 40/41 MRI scan had full protocol acquisition.

+ve: positive; -ve: negative; axSpA: axial spondyloarthritis; dx: diagnosis; CA: clinical assessment; IBD: inflammatory bowel disease; RVD: rheumatologist verified diagnosis; sCBP: self-reported chronic back pain >3 months, age onset <45 years old; SNAC: Screen Negative Assessment Control; SQ: screening questionnaire