RHEUMATOLOGY

Rheumatology 2020;59:iv25–iv37
doi:10.1093/rheumatology/keaa472

Axial spondyloarthritis 10 years on: still looking for the lost tribe

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Abstract

Despite the publication of various recommendations, quality standards and referral strategies to promote early diagnosis in axial SpA (axSpA) over the last decade, there remains a significant delay to diagnosis, leading to a lost tribe of undiagnosed, untreated patients with persistent back pain and axSpA symptoms. This review discusses the various factors contributing to diagnostic delay in axSpA, while providing recommendations to improve the diagnostic pathway, for example use of the online Spondyloarthritis Diagnosis Evaluation (SPADE) tool (http://www.spadetool.co.uk/). Significant shortcomings exist at both the primary and secondary care level, with healthcare professionals often lacking knowledge and awareness of axSpA. Myths regarding the classical signs and symptoms still prevail, including the perception of axSpA as a male disease, only occurring in individuals who are HLA-B27 positive with raised inflammatory markers. Individuals within this lost tribe of undiagnosed patients are likely lacking adequate treatment and are thereby at risk of worse clinical outcomes. It is therefore vital that public health initiatives are implemented to improve education of healthcare professionals and to ensure early specialist referral, to ultimately improve the lives of patients with axSpA.

Key words: axial spondyloarthritis, diagnosis, healthcare professional awareness, early referral, extra-articular manifestations

Rheumatology key messages

- There remains a concerning delay to diagnosis and treatment in axial SpA.
- Significant shortcomings exist at the primary and secondary care level.
- Improved education of healthcare professionals and implementation of early referral strategies is required.

SUPPLEMENT

Introduction

Axial SpA (axSpA) is a chronic, inflammatory, rheumatic disease, characterized by fluctuating periods of flare and remission [1], often resulting in spine fusion and significant disability. The term axSpA encompasses both AS, whereby clear structural changes to the spine and/or SI joints can be observed via X-ray, and non-radiographic axSpA (nr-axSpA), whereby axSpA is instead diagnosed from other clinical features and MRI [2]. Whilst the natural history of axSpA remains unclear, it is evident from follow-up studies that the majority of people with nr-axSpA will not go on to develop structural changes detectable by X-ray [3–5]. Patients more likely to progress radiographically may be smokers, male, HLA-B27 positive, have higher baseline levels of structural changes (e.g. presence of syndesmophytes) or raised CRP and/or ESR[5–8].

AxSpA is estimated to effect ~1 in 200 adults in the UK—twice the prevalence of multiple sclerosis or Parkinson's disease [9, 10]. The primary symptom of axSpA is chronic lower back pain (CLBP), however other symptoms such as fatigue, morning stiffness, sleep disturbance and reduced function and/or mobility are often present [11, 12]; this leads patients with axSpA to experience considerable physical, emotional and economic burden [13–17], with the mean retirement age of people with AS estimated at 36 years [18]. Although primarily affecting the axial skeleton and SI joints, axSpA is frequently associated with a number of peripheral extra-articular manifestations (EAMs), including uveitis, enthesitis, psoriasis, dactylitis and IBDs [19–21].

Increased delay to diagnosis has been associated with worse outcomes in axSpA; a recent systematic review found that individuals with a delayed diagnosis had higher disease activity, worse physical function, increased structural damage, greater likelihood of work

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Submitted 5 March 2020; accepted 14 May 2020

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disability, and higher direct and indirect healthcare costs than those who received earlier diagnosis [13]. Delayed diagnosis is associated with an increased likelihood for worse quality of life and negative psychological consequences [13], in addition to worse treatment outcomes [22, 23], fatigue, difficulty sleeping and prevalence of psychosomatic disorders [24]. Several factors are independently associated with a long diagnostic delay: including female sex, HLA-B27 negativity, presence of psoriasis and young age of symptom onset [25]. Previous misdiagnosis of FM and psychosomatic disorders is suggested to be higher in women compared with men (20.7 *vs* 6.6% and 40.8 *vs* 23.0%, respectively) [24]. Presence of peripheral arthritis and IBD have been associated with earlier diagnosis [26–28]—earlier diagnosis and treatment leading to better outcomes and treatment responses [22, 23].

The mean diagnostic delay in AS has often been reported as between 8–10 years [23, 29–33]. However, some recent reports suggest this delay may now be <6 years [25, 28, 34–36], although the methodology of one paper has been queried [35]. This reduction is likely multifactorial, but key factors include the recent implementation of MRI in the diagnosis of axSpA and the 2009 publication of updated classification criteria by the Assessment of SpondyloArthritis International Society (ASAS). It is important to note that such criteria are not intended for use in diagnosis—the primary objective of classification criteria is to identify a homogeneous population for clinical trials and research, whereby patients are similar in terms of clinical characteristics. However, the ASAS classification criteria were seminal in that they formally recognized the concept of nr-axSpA, placing emphasis on early disease and use of MRI to identify early inflammatory changes, to allow for earlier detection of patients with the condition and inclusion of patients with nr-axSpA in clinical trials [2, 19]. In addition, in recent years there has been greater education of healthcare professionals (HCPs) through training initiatives introduced by groups such as the National Axial Spondyloarthritis Society and British Society for Spondyloarthritis (BRITSpA) [37].

Despite advances in our understanding of axSpA and improved education initiatives for HCPs, a recent survey of 2846 patients across 13 countries reported that the mean diagnostic delay has remained in the region of ~8 years [38]. While an additional UK study published in 2015 found a stable mean diagnostic delay of 8–9 years and a median delay of 5 years prior to and after the 2009 updated classification criteria [26]. Furthermore, in England, a recent 2019 inquiry led by the All-Party Parliamentary Group for AxSpA found that significant shortcomings remain in axSpA care [39]. For example, just 21% of the 191 clinical commissioning groups and 99 provider Trusts investigated had a specific inflammatory back pain pathway in place. Without such a pathway, rapid referral to specialist care and potential early diagnosis for someone with symptoms of axSpA is unlikely.

Ten years on from the publishing of updated ASAS classification criteria for axSpA, this maintained diagnostic delay has resulted in a 'lost tribe' of undiagnosed, untreated individuals with persistent back pain. The present review will describe some of the key factors contributing to this delay (Fig. 1) and challenges that must be addressed, in addition to outlining some of the policies and recommendations that should be implemented in order to reduce the concerning delay to diagnosis in axSpA.

AxSpA is a relatively uncommon cause of a common symptom

The primary symptom of axSpA is CLBP. Worldwide, 19.6% of individuals in the general population aged 20–59 years are reported to suffer from CLBP [40] and up to 80% of the population experience back pain at some point within their lifetime [41–43]. In contrast, prevalence of AS and axSpA as a whole have been estimated at between 0.01–0.54% and 0.13–1.40%, respectively [44–46]. In primary care, prevalence of axSpA has been estimated at between 5–24% of patients with CLBP [47–49], or 32–71% of CLBP patients in secondary care [50–53], therefore representing a relatively uncommon cause of a common symptom. As such, upon presentation to a primary care setting, the CLBP experienced in axSpA may instead be associated with other, more common or well-known pain disorders, particularly in the absence of 'classical' AS symptoms and obvious radiographic sacroiliitis [13, 54].

Worldwide, individuals often first present with CLBP to their general practitioners (GPs) or other non-rheumatology healthcare providers [53, 55–57], so it is vital that GPs are aware of and able to recognize the hallmark symptoms of axSpA. However, awareness of axSpA among GPs, including knowledge of long-term features, axSpA as a disease spectrum and importance of early diagnosis, is lacking [58, 59]. Due to the high prevalence of CLBP and low awareness among GPs and other non-rheumatology healthcare providers, particularly regarding the differences between mechanical back pain and inflammatory back pain [55, 57–62] (IBP, key for identifying axSpA), it is unsurprising that the delay to diagnosis remains high for axSpA.

It is also important to note that IBP should not be considered as a mandatory criterion for diagnosis, but as an axSpA feature. In fact, it has been estimated that only 70–80% of patients with axSpA have typical IBP symptoms [52, 63–67]. Although IBP should remain an important characteristic for screening patients in primary care, primary HCPs should bear in mind that absence of IBP does not exclude a diagnosis of axSpA [52]. Indeed, axSpA is a complex disease with heterogeneous presentation, therefore knowledge of all hallmark symptoms is crucial for early referral. While individual symptoms in isolation are insufficient to diagnose or rule out axSpA, identification of a combination of symptoms in an individual with chronic

Fig. 1 Summary figure: source of the axial SpA lost tribe

back pain (CBP) allows for a more confident diagnosis [see Recommendations for improved referrals, with reference to the recently developed Spondyloarthritis Diagnosis Evaluation (SPADE) tool [68] and 2015 ASAS-endorsed recommendations for referral [69]].

Lack of diagnostic criteria

Age at onset (<45 years) and type of back pain (chronic—present for >3 months) are key to screening patients with suspected axSpA. However, after this screening, diagnosis becomes challenging due to lack of validated diagnostic criteria [57].

The aforementioned 2009 ASAS classification criteria for axSpA were developed to facilitate the conduct of clinical trials and observational studies in early axSpA through the identification of uniform patient populations and to help guide a flexible approach to earlier diagnoses [2, 70–72]. While not intended for use as a diagnostic tool, many practitioners may inappropriately use classification criteria as a surrogate for diagnostic criteria [73], potentially leading to over- or under-diagnosing of axSpA. Indeed, discrepancies have been observed between diagnosis by a rheumatologist and satisfaction of the ASAS classification criteria [52, 74].

Imaging difficulties

Assessment of conventional SI joint X-rays is challenging, with high inter- and intra-observer variability [75–80]. Of particular concern, the reproducibility and performance of identification of radiographic sacroiliitis does not significantly improve with training [75].

While MRI has transformed axSpA diagnosis and allowed for much earlier detection of inflammatory and structural changes, there remains some debate around what constitutes a 'positive' MRI suggestive of axSpA [81, 82], potentially leading to over-diagnosis or misclassification if used for diagnostic purposes without context [81, 83–90]. Interpretation of MRI is challenging and will depend on the expertise of the radiologist; inconsistencies have also recently been found regarding its use in clinical practice [91]. Utilizing the survey responses of 269 UK radiologists, Bennett and colleagues found that just 75% of radiologists were aware of the term axSpA; a concerning 31% and 25% were aware of the ASAS definitions of positive MRI for the SI joints and spine, respectively [91]. Furthermore, it has been reported that just one-third of musculoskeletal radiologists perform the recommended MRI protocol for axSpA [92, 93]. Recent efforts by groups such as BRITSpA to provide consensus recommendations for the acquisition and interpretation of MRI in the diagnosis of axSpA should help standardize practice and in future allow for a more consistent, reliable approach to diagnosis [94]. Such efforts should reduce inevitable false-positive and false-negative inference of axSpA from MRI, in part, contributing to the lost tribe of undiagnosed patients with axSpA.

Misleading biomarkers

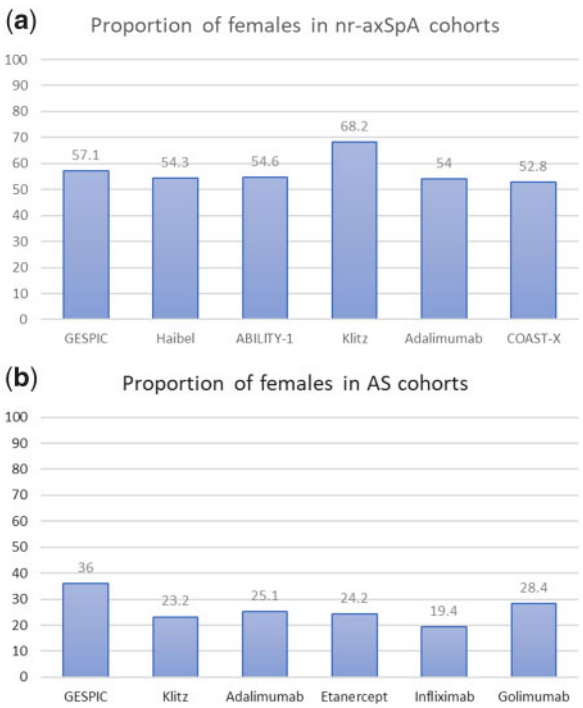
No accurate biomarkers or immune-phenotyping tools currently exist for the identification of axSpA. HLA-B27 and CRP serum biomarkers are commonly used, whereby there is a strong genetic association with HLA-B27 [2]. However, not all axSpA patients are HLA-B27 positive and this often leads to delayed diagnosis in HLA-B27-negative patients [95]. Furthermore, CRP, despite being a widely used laboratory marker for axSpA and used as a criterion for determining treatment, is thought to be lacking in sensitivity and responsiveness, while the natural degree of fluctuation is not well understood. A recent study found frequent fluctuation in CRP levels, whereby 50% of patients with normal CRP at baseline had at least one elevated CRP result within the following 16 weeks [96]. Its use as a one-off diagnostic tool is therefore challenging, and may lead to under-diagnosis of axSpA, particularly in those who have no signs of inflammation on MRI yet experience high disease activity. These factors may have led to a lost tribe of HLA-B27-negative patients with normal inflammatory markers and undiagnosed axSpA.

Myths that need to be dispelled

Historically, X-rays were an important part of diagnosing AS, whereby diagnosis required evidence of significant radiographic changes. This therefore led to long delays from symptom onset to diagnosis. Furthermore, many people with nr-axSpA may never develop the level of radiographic change that would have been previously required for a diagnosis of AS, so these diagnoses would have previously been missed, despite symptoms and disability consistent with AS. Interestingly, radiographic progression is more evident in males, therefore AS was traditionally thought of as a male disease. However, a significant proportion of female patients also suffer from AS or axSpA (Fig. 2) [2, 97–105]. Unfortunately, despite the evidence, common myths prevail; a recent study reported that all interviewed GPs believed AS was almost exclusively diagnosed in men, expressing that practical referral measures would be useful [58].

Another common misconception is that a patient cannot have axSpA if presenting with normal inflammatory markers or if tested as HLA-B27 negative, potentially

Fig. 2 Females prevalent with axial SpA [2, 97–105]



GESPIC: German Spondyloarthritis Inception Cohort [97]; Haibel [98]; ABILITY-1 (Study of Adalimumab in Patients With Axial Spondyloarthritis) [99]; Klitz [100]; Adalimumab [101]; COAST-X [A Study of Ixekizumab (LY2439821) in Participants with Nonradiographic Axial Spondyloarthritis] [105]; Etanercept [102]; Infliximab [103]; Golimumab [104]. GESPIC focusses on patients with primarily axial symptoms but includes patients with peripheral SpA.

leading to missed diagnoses of axSpA (see Misleading biomarkers and Secondary care awareness).

Delayed referral to specialist rheumatology care

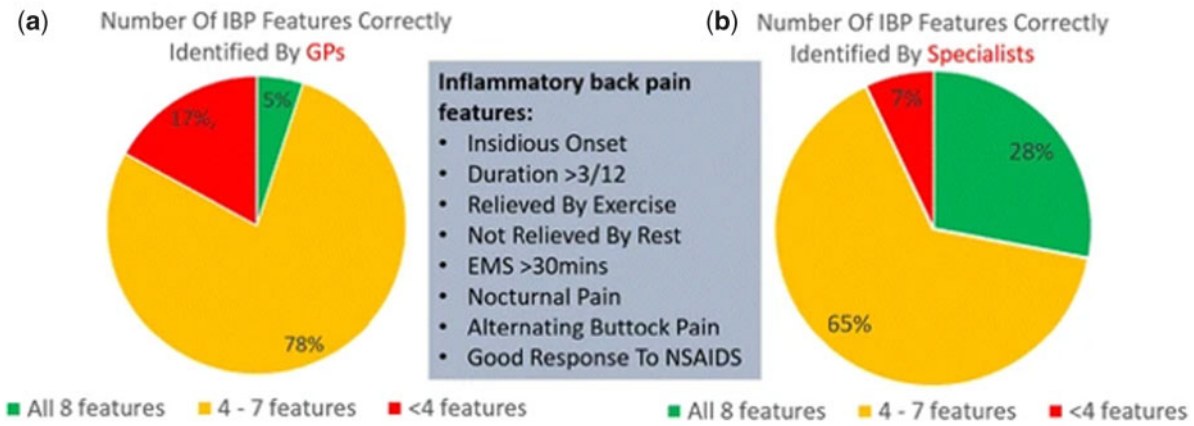
Sixty-two percent of patients report contacting a HCP within 12 months of developing axSpA symptoms [30]. Therefore, one of the significant delays to diagnosis appears to occur after initial presentation to a healthcare provider, with failures both at the primary [39, 59, 61, 106–108] and secondary care [52, 75, 91, 93] level. Evidence suggests that despite various guidelines and recommendations in place relating to referral and investigations of patients with CLBP, there is often a disparity between the guidelines and what is implemented in clinical practice, particularly regarding referral for appropriate imaging when AS or axSpA may be indicated [39, 93, 109–113]. Knowledge, awareness, confidence and clinical assessment for the signs, symptoms and risk factors of suspected axSpA among medical professionals in both primary and secondary care is often poor (Fig. 3) [52, 57, 59, 106, 114], including among musculoskeletal radiologists who often are involved in the interpretation of imaging results during the diagnostic pathway [91–93]. This lack of awareness has a major impact on patients; some report not feeling 'listened to' or 'believed' about their symptoms, with others feeling helpless and withdrawing themselves from care completely, leading to further diagnostic delay (Fig. 4) [115]. A recent 2018 study found that although the interval between initial presentation and diagnosis varied greatly, one-third of patients diagnosed in the past 5 years waited over 10 years from initial presentation to formal diagnosis [93].

Primary care awareness

The majority of patients with CLBP will initially seek care from primary care physicians such as GPs or physiotherapists, orthopaedics, pain clinics, chiropractors, or complementary or alternative medicine practitioners (e.g. osteopaths, massage therapists, acupuncturists [116]), before being referred to rheumatology if displaying musculoskeletal symptoms [55, 60, 117–123]. Although musculoskeletal complaints can account for up to 20% of all consultations in primary care [124], as discussed previously, distinguishing axSpA from other forms of CLBP can be difficult [55, 57–62] (Fig. 3), with a concerning lack of awareness of other axSpA features and EAMs [58, 59, 106]. Collaboration between practitioners is also lacking—in a recent survey of chiropractors and osteopaths, the principal perceived barrier to onward referral was reluctance by the GP to accept their professional opinion [106].

A recent 2019 study found that the majority of HCPs failed to recognize IBP in patients with CLBP, with many of those who did (24.2%) opting to treat the symptoms before referral to a specialist [55, 60]. Forty-one percent of HCPs stated that patients had seen another specialist before consulting them. Upon referral, the top barriers preventing patients from seeing a specialist were the long wait (77%), insurance restrictions (47.1%—will not be applicable in some countries), lack of adequate specialist nearby (35.1%), patient reluctance or resistance (25.2%) and travel distance to specialist (21.5%). Just 7.4% reported no issues with the referral process. Patient reluctance or resistance may be due to denial or perhaps simply other commitments—axSpA frequently presents in the second or third decade of a patient's life, often a critical time for attempting to establish careers and relationships [106]. Patients initially referred for treatment by a physiotherapist to address symptoms

Fig. 3 GPs [59] *vs* specialists[a]—number of correctly identified features of IBP [114]



[a]Secondary care consultants working in the following specialties: orthopaedics ($n = 64$), ophthalmology ($n = 40$), A&E ($n = 35$), gastroenterology ($n = 27$), genitourinary medicine ($n = 16$), spinal surgery ($n = 13$) and dermatology ($n = 10$). IBP: inflammatory back pain; GPs: general practitioners.

Fig. 4 Qualitative exploration of patient experience: delay to diagnosis [115]

"I just feel that they should have listened to me more, I should have been listened to... Because they did every test imaginable and couldn't find anything wrong with me, just to be brushed off, you know. As I say ... I knew my body and I knew that this was more than just a back pain." (Julia: Interview)

"A doctor recognizing the symptoms and not assuming it was mechanical: a need to lose weight. Also, I should have persevered. I felt fobbed off and just resigned myself to living with back pain." (Steve: Survey)

"Recognition, awareness, understanding (through education) of the condition fundamentally at primary care level (GP) as well as at Hospital Consultant level, including cross-disciplinary professions. Having ... been diagnosed by a Consultant Ophthalmologist with iritis at the age of 13 (related autoimmune condition) but not for some time mentioned and linked to AS [axSpA]." (Andrew: Survey)

"I think because I was a young woman ... also, as I was still able to work (albeit in great discomfort) it was not deemed chronic enough to warrant further study. Once an initial referral to a physiotherapist ... ran its three-month course and no change for the better I was just signed off with a neural suppressant prescription (this didn't work)." (Amy: Survey)

may also suffer a delay to therapy access; one study reporting problems with access to physiotherapy for 32% of GPs [59].

Following access to physiotherapy, a further diagnostic delay may occur. In 2019, McCrum and colleagues found that the average time from initial physiotherapy visit to diagnosis with SpA was 6.4 years [108]. Forty-four percent of these patients received three or more physiotherapy episodes prior to diagnosis; the number of contacts within each episode ranged from 3 (47 people) to 58 (1 person), a median of 11 contacts per episode (10 people). As in the recently published National Institute for Health and Care Excellence (NICE) guidelines for referral [107, 125], this highlights the importance of physiotherapists for recognition and referral of axSpA, while emphasizing that identification of axSpA is missed at multiple timepoints across a patients journey to diagnosis. Some people have described having to truly fight for their diagnosis, resulting in distress and often feelings of sadness, frustration or anger [126].

Secondary care awareness

Another source of this lost tribe of undiagnosed individuals are those presenting to secondary care with EAMs [52, 127–136]. A 2018 study by Sykes *et al.* [135] explored the prevalence of axSpA among 366 individuals with acute anterior uveitis (AAU). Minimum prevalence was identified as 20.2% of patients with AAU; nearly one-quarter of these patients was previously undiagnosed despite years of back pain, representing a substantial hidden burden of disease. This supports the work of Haroon and colleagues, where 40% of patients presenting with AAU had undiagnosed SpA [134]. HLA-B27 diagnosis is often the trigger for referral of patients with AAU to rheumatology. The Dublin Uveitis Evaluation Tool (DUET) algorithm developed by Haroon and colleagues indeed prompts referral if a patient is HLA-B27 positive, or has co-existing psoriasis or peripheral arthritis—with high sensitivity and specificity (96% and 97% respectively)—potentially implicating HLA-B27 as the 'anchor criterion' for the ASAS classification criteria clinical arm [134, 135]. However, importantly, in the study by Sykes *et al.* nearly half of patients identified as missed diagnoses were HLA-B27 negative. These patients would therefore have remained lost if utilizing the DUET algorithm. Similarly, nearly two-thirds of new diagnoses would have been missed if using IBP rather than CBP as a referral strategy, supporting the presence of IBP as an axSpA feature rather than mandatory criterion for referral [52, 137, 138], in line with ASAS-endorsed recommendations for early referral [69]. Due to the high prevalence of axSpA among individuals presenting with AAU, the authors thereby recommend that all individuals with AAU and CBP with onset before the age of 45 years should be referred to rheumatology regardless of HLA-B27 status [135].

Similar concepts have been recommended for individuals presenting with other EAMs, including IBD and psoriasis [127–130, 136]. SpA may occur in up to 13% of individuals with IBD [128]; a recent review reported that prevalence of sacroiliitis ranged from 2.2 to 68% among IBD patient populations [127]. The latter work has informed a prospective observational study of

magnetic resonance enterography as a screening tool for axSpA, initiated in March 2019 (ClinicalTrials.gov NCT03817983) [139]. Similarly, the recent ADIPSA [Axial Disease In PSoriatic Arthritis (PsA)] study found that 49/201 (23.9%) PsA patients fulfilled Modified New York criteria for AS [140]. Although due to lack of MRI, fulfilment of the full ASAS criteria could not be assessed, 85/118 (72%) psoriatic SpA cases and 9/127 (7%) peripheral PsA cases fulfilled ASAS clinical or radiographic imaging criteria. In the multicentre SASPIC (Screening for AxSpA in Psoriasis, Iritis, and Colitis) cohort, 47.6% of patients with psoriasis, AAU or colitis $\leq$45 years of age with $\geq$3 months of undiagnosed back pain were diagnosed with axSpA when utilizing a proposed three-stage evaluation approach [clinical evaluation; labs (HLA-B27, CRP) and radiography; MRI] [141], while as many as 68.7% were diagnosed after the clinical evaluation alone [142]. These studies suggest a significant lost tribe of undiagnosed axSpA patients among people with AAU, psoriasis and IBD.

It has even been suggested that a lost tribe of axSpA patients could exist within a population of young people undergoing hip arthroplasty; a publication by Waters and colleagues in 2015 identified structural abnormality in 24/92 patients (26.1%) and known inflammatory arthropathy in 3/92 (3.3%) [143]. Inflammatory markers were investigated for 41 patients, 10 (24%) of which had elevated CRP and/or ESR. Eighty-three individuals had radiographs available for investigation; SI joint abnormality observed in nine individuals (10.8%), five (6%) having bilateral grade 2 sacroiliitis. None of these patients was previously diagnosed with axSpA.

Recommendations for improved referrals

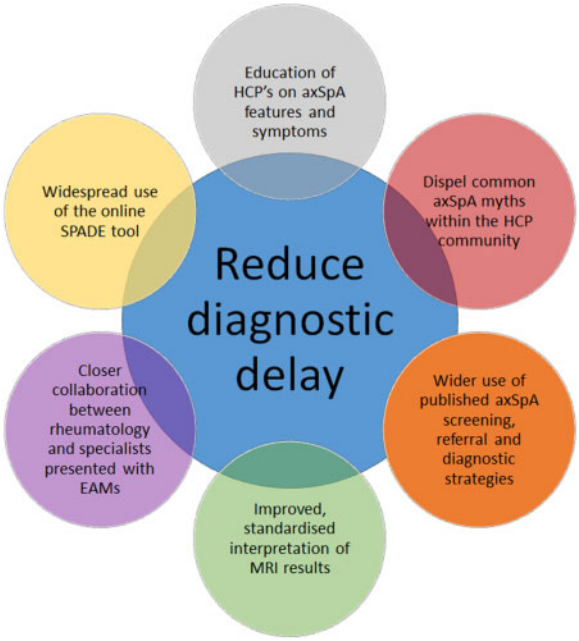
Following recommendations from earlier studies, amid growing concerns regarding delay to diagnosis and consequences for the patient, over the past decade we have seen the development, publication and evaluation of multiple early referral and screening strategies, recommendations, quality standards and algorithms for identifying and referring suspected axSpA and/or CLBP [67, 69, 123, 125, 136, 139, 142, 144–149], in addition to the development, introduction and testing of various educational tools for HCPs.

Indeed, education of HCPs in primary and secondary care and the wider use of diagnostic algorithms may improve early recognition and referral of axSpA, thereby improving patient outcomes. Education has been found to substantially improve the recognition and referral of patients with suspected axSpA by GPs [150, 151]—one recent prospective, multicentre study demonstrated over 40% improvement in referral after receiving SpA education or training [150]. In physiotherapists, good awareness of the NICE 2017 guidance on SpA and continuing professional development was associated with better awareness and knowledge of axSpA features [61]. Furthermore, the delay to diagnosis is shortened in individuals with peripheral disease [26–28], likely due to the fact that GPs have been consistently prompted via the early arthritis initiative about the importance of early referral for patients with swollen joints [26]. A recent study of two large UK centres found a 51% increase in new axSpA diagnoses between 2009 and 2013, following the introduction of the ASAS 2009 classification criteria [2], *vs* the prior 5 years [26].

Closer collaboration is recommended between rheumatology and specialists presented with EAMs (e.g. ophthalmology [134, 135], gastroenterology [127–130, 136], dermatology [131]). As outlined by Sykes and colleagues regarding patients presenting with AAU and CBP [135], there does not appear to be a straightforward mechanism for screening patients. Therefore, specialists should be made aware of axSpA referral guidelines, which should be implemented appropriately based on their existing healthcare infrastructure, perhaps utilizing a referral strategy of all patients with EAMs + CBP with onset at age <45 years old. Knowledge of axSpA and EAMs is advancing all the time, therefore specialists should remain aware of such updates—for example, the recent suggestion of hidradenitis suppurativa (acne inversa) as a possible new EAM [132, 133]. Other secondary healthcare providers such as rheumatologists and radiologists should also work more closely to improve and standardize interpretation of MRI on the pathway to diagnosis, as outlined in recommendations by the BRITSpA collaborators [91, 94]. This also calls for better training of rheumatologists and radiologists in the interpretation of MRI in the context of suspected axSpA [152]. Closer collaboration is also recommended between primary healthcare providers, including GPs, physiotherapists, osteopaths and chiropractors [106].

To summarize Poddubnyy and Sieper (2019) [152]: any screening or referral strategy for SpA is useful, with no existing strategy illustrating outstanding performance (applied referral strategy increases probability of axSpA from 5 to 40–50%) and complex/simple strategies performing equally as well. Importantly, the starting point for referral should be CBP starting at a young age, usually suggested at <45 years. The formal ASAS-endorsed recommendation for early referral of patients with suspected axSpA suggests that patients with CBP (duration $\geq$3 months) with onset before the age of 45 years should be referred to a rheumatologist if at least one of the following parameters is present: IBP; HLA-B27 positive; sacroiliitis on imaging if available (X-rays or MRI); peripheral manifestations (arthritis, enthesitis, dactylitis); EAMs (psoriasis, IBD, uveitis); positive family history for SpA; good response to NSAIDs; elevated acute-phase reactant (e.g. CRP) [69]. This recommendation may thereby be used in clinical practice by GPs and other primary care HCPs or non-rheumatology specialists as a flexible, universal strategy for referral of patients with suspected axSpA. However, the ideal referral strategy will likely vary depending on the clinical setting and country, due to potential differences in healthcare structure and prevalence of referral parameters (e.g. availability/use of HLA-B27 testing) [144].

Fig. 5 Summary figure: implementable steps to reduce diagnostic delay in axial SpA



Importantly, individual symptoms in isolation are insufficient to either diagnose or rule out axSpA. As outlined in Rudwaleit's early work on likelihood ratios for diagnosis, it is the identification of a combination of axSpA symptoms that should lead to diagnosis [153]. The online SPADE tool (http://www.spadetool.co.uk/) was recently developed to aid HCPs in their diagnosis of axSpA, whereby probability of axSpA is displayed on a chart based on symptoms entered into the tool, with clear instructions on how to then proceed (e.g. further tests needed, assessment by a rheumatologist is recommended) [68]. Future implementation of such strategies, education tools and quality standards will be paramount for reducing the delay to diagnosis in axSpA, in order to uncover the lost tribe of undiagnosed, untreated individuals with persistent back pain (Fig. 5).

Conclusions—the future of axSpA care

Lack of knowledge, awareness and confidence diagnosing axSpA in both primary and secondary care has led to a lost tribe of undiagnosed patients experiencing persistent back pain and ongoing axSpA symptoms (Fig. 1). These individuals may reside within existing patient populations, including those with IBD, psoriasis/PsA, AAU and early hip arthroplasty, or may not exhibit the outdated, preconceived 'classic' symptoms of AS if HLA-B27 negative, female or not displaying raised inflammatory markers. Importantly, these individuals are likely lacking optimal treatment and are thereby at risk of worse outcomes and potential complications. It is therefore of the utmost importance that this lost tribe is uncovered, through better education of HCPs and implementation of existing referral strategies, recommendations and quality standards.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article. This paper was published as part of a supplement funded by Novartis.

Disclosure statement: R.S. has received grants and honoraria from Abbvie, Biogen, Lilly, Novartis, Celgene and Union Chimique Belge. The other authors have declared no conflicts of interest.

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