CLINICAL SCIENCE

Factors predicting axial spondyloarthritis among first-degree relatives of probands with ankylosing spondylitis: a family study spanning 35 years

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ABSTRACT
Objective Factors predicting axial spondyloarthritis (axSpA) among first-degree relatives (FDRs) of ankylosing spondylitis (AS) patients need to be defined. We investigated the predictive value of the probands’ HLA-B27 and radiographic sacroiliitis status on disease occurrence among their FDR. We also assessed the predictive value of features of the clinical history, including chronic inflammatory back pain (CIBP) and acute anterior uveitis (AAU), among the FDR and how they can be used to improve classification and diagnosis of axSpA.

Methods In 1985, we studied 363 AS probands and 806 FDR who underwent rheumatologic examination, completed questionnaires, provided blood samples for HLA-typing and underwent radiography of sacroiliac joints. At follow-up in 2018–2019, 125 patients and 360 FDR were available for study, and completed a postal questionnaire about axSpA features. FDRs were asked to report whether after 1985 they had been diagnosed by Swiss rheumatologists as having axSpA.

Results Among HLA-B27(+)-FDR, axSpA occurred in 25.4%–26.3%, independent of the radiographic sacroiliitis status of the proband. AAU occurred in 13/34 (38.2%) FDR with axSpA vs 29/251 (11.6%) FDR without axSpA (p=0.00004, OR=4.74 95% CI 2.15 to 10.47). The presence of CIBP at baseline did not predict later occurrence of axSpA but combining CIBP and pain/discomfort in the thoracic spine and at anterior chest wall, enhance early clinical suspicion and early diagnosis of axSpA among FDR of axSpA patients.

Conclusion Occurrence of AAU among FDR of axSpA probands should prompt screening for axSpA. Moreover, co-occurrence of CIBP and pain/discomfort in the thoracic spine and anterior chest wall as a three-question tool may further enhance clinical suspicion of axSpA among these FDR.

INTRODUCTION
The high familiality of ankylosing spondylitis (AS) is well established.1–4 The prevalence of AS is considerably higher among HLA-B27(+) first-degree relatives (FDR) of patients with the disease compared with HLA-B27(+) persons from the general population.4,5 This points to an important role of additional MHC genes, such as HLA-B60, and many non-MHC genes in contributing to disease susceptibility.6,7

Nowadays, the notion of AS has changed with increased emphasis on early diagnosis at its non-radiographic phase.8,9 This has led to the concept of axial spondyloarthritis (axSpA), comprising both radiographic axSpA (AS defined by the modified New York (mNY) criteria10 and non-radiographic axSpA (nr-axSpA). Whether the recurrence risk in relatives of axSpA patients varies according to the radiographic status of the proband is unknown. With nr-axSpA reported to be 2–3 times11 more prevalent than AS itself, there is a significant clinical need to determine this risk rate, not the least for counselling and screening purposes.

What is already known about this subject?
⇒ Familial occurrence of ankylosing spondylitis is well known, but factors predicting axial spondyloarthritis (axSpA) occurrence among first-degree relatives (FDR) are less well identified.

What does this study add?
⇒ Occurrence of chronic inflammatory back pain (CIBP) in FDR of axSpA probands is not a reliable predictor of later development of axSpA. However, occurrence of acute anterior uveitis and/or a combined occurrence of CIBP and pain/discomfort in the thoracic spine and at anterior chest wall, enhance early clinical suspicion and early diagnosis of axSpA among FDR of axSpA patients.

⇒ ‘Healthy’ HLA-B27 (+) FDR may have unnoticed ‘hidden’ axSpA, in particular if they have thoracic complaints in the absence of CIBP.

How might this impact on clinical practice or future developments?
⇒ A three-question tool combining pain and discomfort at lumbar spine, thoracic spine and anterior chest wall has high sensitivity (83.1%) and specificity (87.2%). However, this triad needs to be fully validated as a potential diagnostic tool.

Spondyloarthritis

We have recently completed a family study spanning 35 years, the longest longitudinal study in axSpA to date. Here, we report features from patients’ clinical history that best predict presence of axSpA for the large number of FDR who developed the disease during these 35 years. We evaluated whether presence at early age of chronic inflammatory low back pain (CIBP) and occurrence of features of acute anterior uveitis (AAU) are associated with onset of axSpA.

METHODS

Here the term ‘axSpA’ comprises the full spectrum of axSpA, that is, both radiographic (AS defined by the mNY criteria) and nr-axSpA.10

First phase of the study

In 1985, all members of the nation-wide Swiss Ankylosing Spondylitis Patient Society were invited to participate in the family study together with their spouses and FDR. These relatives were invited irrespective of whether they were known to have any rheumatic disease. The study was performed in centres spread all over the country.

A total of 1178 persons consented to participate and completed questionnaires on disease manifestations. They also underwent physical examination of axial and peripheral joints by a rheumatologist. Peripheral blood nucleated cells (PBNCs) were stored for HLA-typing and subsequent genetic analysis. Furthermore, to assess the presence of sacroilitis, consenting non-pregnant participants, aged 18 and over, underwent pelvic radiography unless a recent radiograph was available. Pelvic radiographs were available for 360 of the 363 probands; the three probands with missing pelvic radiographs were excluded in this analysis.

Each sacroiliac (SI) joint on pelvic radiographs (total number 1081) was ‘blindly’ assessed twice by each of 4 experienced readers, that is, 8 (occasionally 9) times. The radiographs of 163/360 probands and 22/713 FDR were only available on-site for a few hours at the time of participant’s physical examination in the local hospital, and therefore, could only be assessed once. Overall, 17.2% of the 1081 radiographs were read once, 0.4% 2–4 times, 3.2% 5–7 times and 79.2% 8–9 times. The sacroilitis score ranged from 0 (normal) to 4 (ankylosis) for each SI joint assessment by a reader as per the mNY scoring system.10 All scores for a single SI joint were added and divided by the number of assessments (range 1–9). Scores below bilateral grade 2.0 or unilateral grade 3.0 were considered not fulfilling the mNY criteria. Interobserver and intraobserver reliability were assessed by evaluating a subset of 243 pelvic films. Observers read films twice in sets of 40–50 radiographs. The interval between both readings was ≥7 days. The interobserver and intraobserver reliability coefficients were 0.865 and 0.903, respectively.

In 1986, all participants were informed by a letter about their individual HLA-B27 test result and radiographic findings of the SI joints.

Follow-up study

The former participants were asked to complete a 157-item postal questionnaire on manifestations of AS. The questionnaire dealt particularly with current or past symptoms at lumbar and gluteal region, thoracic spine and front part of the chest, and also addressed symptoms suggesting episodes of AAU. The next decisive step to perform the follow-up study was to determine whether the former 1178 participants were still alive and, if so, to trace their current postal addresses. Starting in April 2018, up to five mailings to a large number of Swiss city or village administrations were needed to obtain as much as possible up-to-date current addresses.

In the spring of 2019, letters providing detailed information about the follow-up study were sent to supposedly correct addresses. Participants who had provided written informed consent for genetic analysis of PBNCs were mailed the postal questionnaire, and those who did not return the questionnaire were mailed a reminder. The last questionnaires were returned in December 2019. Data were coded and anonymously stored in an Excel database.

Ascertaining of diagnosis

The diagnosis AS in the first phase of the study in 1985 was based on the clinical findings and the evaluation of the pelvic radiographs. Probands were categorised according to the mNY criteria, and their FDR were considered to have AS if they met the mNY criteria.

In the follow-up study (2019), recent imaging of the SI joints was mostly unavailable for us to establish whether the FDR who reported having been diagnosed (between 1986 and 2019) by their Swiss rheumatologists to have axSpA met the mNY criteria or had nr-axSpA. Therefore, we considered all new cases in the follow-up study to be suffering from axSpA, that is, they may have either radiographic axSpA or nr-axSpA.

Statistical analysis

Counts were compared by χ² testing. The test results are expressed as p values. OR were calculated with 95% CI.

Patient and public involvement

Two patients/coauthors were fully involved in the study.

RESULTS

Altogether 1178 persons, including 363 probands, participated in the first (1985) phase of the study of whom 485 consenting persons could be retrieved for the 2018–2019 follow-up study (125 probands and 360 FDR). Altogether 162 former participants (123 probands and 39 FDR) were known to have died; information about causes of death was not available. Demographic data of the 485 participants who were available and consented to participate in the follow-up study are shown in table 1, together with their radiographic and HLA-B27 status (figure 1). At baseline (1985) 84/125 (67.2%) probands met mNY criteria, 41 were categorised as nr-axSpA.

Occurrence of axSpA among FDR

The risk to develop axSpA for HLA-B27(+) FDR of HLA-B27(+) probands is considerable. At follow-up (2018–19) 42/162 HLA-B27(+) FDR had been diagnosed as having the disease, that is, an incidence of 25.9%; 95%CI 19.2% to 32.6%. The sex ratio was about equal: 17/67 (25.4%) HLA-B27(+) males and 25/95 (26.3%) HLA-B27(+) females. In contrast, 1/141 (0.7%) of HLA-B27(-) FDR of HLA-B27(-) probands and 1/29 (3.4%) HLA-B27(-) FDR of HLA-B27(-) probands (a son of a nr-axSpA proband) were diagnosed as having axSpA. The first mentioned HLA-B27(-) axSpA case comprises a sister of an HLA-B27(+) proband with nr-axSpA. The HLA-B27 and radiographic sacroilitic status of the proband of a third HLA-B27(-) case (a female) is unknown. Of the 42 HLA-B27(+) cases, 7 had radiographic sacroilitis in 1985, the remaining 35 either had negative pelvic X-rays or did not undergo radiographic examination of their SI joints at baseline because they were pregnant or <18 years of age at that time. Thus, the diagnosis axSpA of these 35 FDR has
been established at some point in time between 1986 and 2019. For two of these 35 FDR, recent radiographs were available that confirmed AS by mNY criteria, but for the other 33 FDR no recent imaging of the SI joints were available for us to review at follow-up. Of note, based on the responses to the questionnaire, 38 of all 42 (90.5%) HLA-B27(+) FDR with axSpA fulfilled the ASAS classification criteria for axSpA.12 13

Relationship with radiographic status of proband
In total 37 (88.1%) of the 42 HLA-B27(+) axSpA probands of the 42 HLA-B27(+) affected FDR, met the mNY criteria, not significantly different from the HLA-B27(+) proportion observed among axSpA probands who did not have an affected FDR (210/263 (79.8%), p=0.20; OR=1.87, 95% CI (0.70 to 4.98)). Coexistence of both types of the disease (radiographic and non-radiographic) occurred in about 10% of the families.

AAU associated with axSpA
Symptoms suggestive of AAU (one or more episodes of unilateral painful inflamed red eye, and prescription of eye drops containing steroids) occurred significantly more often among FDR who during follow-up developed axSpA than among those who did not: 13/34 (38.2%) vs 29/251 (11.6%), p=0.00004; OR=4.74, 95% CI (2.15 to 10.47). Comparing only HLA-B27(+) FDR, 13/34 (38.2%) HLA-B27(+) FDR who developed axSpA had symptoms suggestive of AAU in contrast to 14/114 (12.3%) HLA-B27(+) FDR without axSpA (p=0.0006, OR=4.42, 95% CI (1.82 to 10.76)). The prevalence of AAU symptoms among FDR with axSpA (38.2%) is similar to the prevalence of AAU among HLA-B27(+) probands: 35/79 (44.3%) for HLA-B27(+) probands, p=0.53. The low prevalence (12.3%) of AAU symptoms in HLA-B27(+) FDR without axSpA does not differ significantly from the 10.9% (15/137) figure for healthy HLA-B27(-) FDR (p=0.74).

Table 1  Demographic data of axSpA probands and relatives participating in the 2019 Swiss Ankylosing Spondylitis Follow-up Family Study by HLA-B27 status and presence of sacroilitis by New York criteria*

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Males</th>
<th>Females</th>
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<th>Age SD</th>
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<tr>
<td>All participants</td>
<td>485</td>
<td>238</td>
<td>247</td>
<td>64.56</td>
<td>9.73</td>
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<td>78†</td>
<td>47§</td>
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<td>7.31</td>
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<td>73</td>
<td>37</td>
<td>72.51</td>
<td>7.16</td>
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<td>54</td>
<td>25</td>
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<td></td>
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<tr>
<td>Sacroiliitis absent (1985)</td>
<td>31</td>
<td>19</td>
<td>12</td>
<td></td>
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<tr>
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<td>4</td>
<td>9</td>
<td>75.54</td>
<td>8.68</td>
</tr>
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<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>10</td>
<td>2</td>
<td>8</td>
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<tr>
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<td>160</td>
<td>200</td>
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<td>8.44</td>
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<td>27</td>
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<td>2</td>
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<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>All healthy relatives</td>
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<td>142</td>
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<td>62.20</td>
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<td>144</td>
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<tr>
<td>HLA-B27 positive relatives</td>
<td>120</td>
<td>50atti</td>
<td>70t†</td>
<td>61.26</td>
<td>8.94</td>
</tr>
<tr>
<td>HLA-B27 negative relatives</td>
<td>140</td>
<td>66tti</td>
<td>74§§</td>
<td>62.87</td>
<td>9.25</td>
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<td>16</td>
<td>13</td>
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<td></td>
<td></td>
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<tr>
<td>HLA-B27 negative relatives</td>
<td>29</td>
<td>16</td>
<td>13</td>
<td>60.76</td>
<td>6.66</td>
</tr>
<tr>
<td>Healthy relatives of HLA-B27? probands</td>
<td>24</td>
<td>8</td>
<td>16</td>
<td>65.34</td>
<td>6.00</td>
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<td>9</td>
<td>4</td>
<td>5</td>
<td>68.12</td>
<td>5.69</td>
</tr>
<tr>
<td>HLA-B27 negative relatives</td>
<td>15</td>
<td>4</td>
<td>11***</td>
<td>63.67</td>
<td>5.39</td>
</tr>
</tbody>
</table>

New York criteria (grade 2 or higher bilaterally, or grade 3 or 4 unilaterally).
* Sacroiliitis: pelvic radiography from 1985 AS Family Study showing sacroiliitis by modified.
† Altogether 84 (67.2%) probands met modified New York criteria, 41 were categorised as nr-axSpA.
‡ Unknown HLA-B27 status of one male proband with sacroilitis.
§ Unknown HLA-B27 status of one female proband with sacroilitis.
¶ No pelvic radiograph available for two FDR unknown (one relative HLA-B27(-); one relative HLA-B27(+)).
** No pelvic radiograph available for five males.
†† No pelvic radiograph available for 11 females.
‡‡ No pelvic radiograph available for four males.
§§ No pelvic radiograph available for five females.
¶¶ No pelvic radiograph available for one male
*** No pelvic radiograph available for two women.
AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; FDR, first-degree relatives.
Back pain as a predictor for axSpA
At baseline (1985) CIBP was reported significantly more often (46/286, or 16.1%) by HLA-B27(+) FDR without radiographic sacroiliitis (mean age ±SD 28.3±8.1 year) than by 27/272 (9.9%) healthy HLA-B27(−) FDR (mean age ±SD 28.4±7.4 year) (OR=1.74, p=0.031). Nonetheless, the onset of CIBP at early age was not a reliable predictor of axSpA. Of the 35 year) (OR=1.74, p=0.031). Nonetheless, the onset of CIBP at young age (mean 28 years) does not reliably predict the long-term development of axSpA.

Sensitivity and specificity of clinical features
The clinical history serves as a useful tool in discriminating people with and without axSpA. Items with sensitivity or specificity above 70% for the presence of axSpA are provided in table 2. It shows that, overall sensitivity decreases as specificity increases, and vice versa. Sensitivity was assessed among all AS probands who met the mNY criteria, whereas specificity was appraised in the group of HLA-B27(+) FDR who never developed the disease (18/126, 14.3%) (OR=1.15, p=0.8). Thus, for FDR of AS probands, the presence of CIBP at young age (mean 28 years) does not reliably predict the long-term development of axSpA.

In the whole group of 45 FDR who had been diagnosed as having axSpA at some point in time between 1985 and 2019, 21/44 (47.7%) FDR fulfilled criteria for CIBP; 28/40 (70.0%) reported thoracic complaints; 21/42 (50%) had complaints at the frontal chest wall. The proportion reporting positive answers to ≥2 questions of the three-item composite index among these ‘new’ axSpA patients was 61.0% (25/41). The specificity of this composite index is 86.3% (101/117) among the HLA-B27(+) healthy FDR.

AxSpA symptoms in ‘healthy’ relatives
For this analysis, we define ‘healthy’ to mean never having been diagnosed as suffering from axSpA. Feelings of pain, stiffness or discomfort at the frontal chest wall, the lumbar or thoracic spine occurred in up to 25% of ‘healthy’ HLA-B27(+) FDR, significantly more than in the HLA-B27(−) healthy relatives (who reported such features in less than 9%) (table 3). These symptoms suggest an inflammatory component for their discomfort. These symptoms tend to cluster in individuals in one anatomical region; in particular complaints at the thoracic spine (last 4 items of table 3) occurred in 9/117 (7.7%) ‘healthy’ HLA-B27(+) FDR vs only 2/138 (1.4%) of HLA-B27(−) FDR (p=0.015). This suggests possible ‘hidden’ (undiagnosed) axSpA clinical features, mainly at the thoracic spine and mostly without the well-known CIBP, among genetically predisposed relatives.

DISCUSSION
AS occurs commonly among FDR of HLA-B27(+) probands when they share this susceptibility allele. In this family study spanning 33 years, we observed that ~25% of HLA-B27(+) FDR developed axSpA irrespective of their proband’s radiographic status (ie, presence or absence of sacroiliitis), but very rarely among the HLA-B27(−) FDR (3% in this study). Moreover, we observed that AS and nr-axSpA may run in one and the same family. This supports the view of genetic homogeneous propensity of both expressions (radiographic and non-radiographic forms) of the disease, at least where the family involved carries HLA-B27. It illustrates a major role of the family history and
putative additional familial factors as predictor of development of axSpA.5 15 16

One might wonder whether the cumulative axSpA incidence of ~25% for HLA-B27(+) FDR might be inflated by selection bias or case-ascertainment (clinical examination at baseline and patient reported information at follow-up).

Selection bias would have occurred if symptomatic HLA-B27(+) FDR who had developed axSpA after baseline would have preferentially volunteered to participate in the follow-up study. In fact, the proportion participating HLA-B27(+) FDR was even slightly lower compared with baseline: in 1985 360/668 (53.9%) FDR of HLA-B27(+) probands were HLA-B27(+) compared with 162/329 (49.2%) at follow-up.

Ascertainment of diagnosis at baseline (clinical diagnosis at the study centre) differed from ascertainment at follow-up (patient reported diagnosis by a Swiss rheumatologist). Moreover, the concept of disease has broaden in the last two decades. This may have impacted (inflated) our axSpA incidence ~25% figure. However, as our findings illustrate, ‘AS without sacroiliitis’ was somewhat higher prevalence figure than the earlier reported 21% figure5 seems sensible.

The occurrence at baseline of ‘AS without radiographic sacroiliitis’ among axSpA probands, shown in table 1, illustrates that this entity is nowadays widely known as nr-axSpA. Selection bias would have occurred if symptomatic HLA-B27(+) FDR who had developed axSpA after baseline would have preferentially volunteered to participate in the follow-up study. In fact, the proportion participating HLA-B27(+) FDR was even slightly lower compared with baseline: in 1985 360/668 (53.9%) FDR of HLA-B27(+) probands were HLA-B27(+) compared with 162/329 (49.2%) at follow-up.

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Uveitis as a predictor for axSpA
AAU is a common, usually unilateral, HLA-B27 associated, intraocular inflammatory disease, concomitantly occurring in patients with axSpA. The prevalence of AAU in AS increases with disease duration, and may exceed 50%, particularly in HLA-B27(+) patients with longstanding disease.18–23 We accepted
participants’ reply of having used corticosteroid containing eye drops as the most important proxy for a diagnosis of AAU. Although this might have face validity, it is not a firm proof. With this limitation in mind, AAU was significantly associated with development of axSpA, whereas there was no difference in occurrence of AAU between healthy HLA-B27(+) and HLA-B27(-) FDR. This is compatible with the reported 45% association of HLA-B27 with AAU in the general population, that is, about equally in HLA-B27(+) and HLA-B27(-) individuals.24

The stronger association of AAU with axSpA than with HLA-B27 might, at least partly, be due to diagnostic suspicion bias, that is, an established diagnosis (say axSpA) might increase the likelihood that an associated disease (say AAU) will be diagnosed appropriately. Nonetheless, our findings are strongly supported by recent genome-wide association studies revealing that the association of AAU and axSpA is primarily with the full genetic overlap (HLA and non-MHC genes) of both conditions rather than with the HLA-B27 allele alone.15 23 One may conclude that AAU is more closely related to the rheumatologic disease than to the HLA-B27 allele, and therefore, may predict future axSpA. Literature indicates that among HLA-B27(+) AAU patients the prevalence of concomitant axSpA may rise to about 80%, indicating that occurrence of AAU among relatives warrants screening for axSpA.19

**Chronic back pain as a predictor for axSpA**

CIBP at young age failed to predict future development of axSpA in our study. Reveille et al21 reported that FDR of AS patients had earlier onset of CIBP than those with non-IBP, and that their CIBP persisted longer (73% of the FDR still had CIBP after a mean of 5.5 years). On the other hand, Wang et al22 found that a minority of patients with new onset IBP progressed to SpA, while IBP resolved in many. They suggest that the finding that IBP often resolved may explain the difference between the prevalence of IBP (3%-6%) and the prevalence of SpA (0.4%-1.3%). Of note, at baseline 16.1% (46/268) of our HLA-B27(+) FDR had CIBP without sacroiliitis vs 9.9% (27/272) of the HLA-B27(-) FDR (p=0.03), but there was no difference observed at follow-up 35 years Later. This supports the view that CIBP might be a potentially resolving manifestation of axSpA, that is, a favorable outcome of the disease. This view is also supported by recently published findings from the pre-SpA cohort study. IBP was reported by 19% of seemingly healthy FDR (of HLA-B27(+)) axSpA patients) with an equal distribution between HLA-B27(+) and HLA-B27(-) FDR. Progression from subclinical inflammation to clinical axSpA within 1 year of follow-up occurred in 6%, and was mainly (86%) observed in HLA-B27(+) FDR.20

**Clinical history as an aid to diagnosis**

For axSpA the diagnostic yield and accuracy might improve by paying close attention not only to the well-known inflammatory symptoms at the lumbar spine,18,27 but also to complaints of pain and discomfort at the thoracic spinal and the frontal chest wall region. Combining features at these three anatomical regions into a *trip* yielded high (87%) specificity. While our study requires independent validation, this finding compares quite well with Rudwaleit’s refined set of criteria for CIBP that have a sensitivity of 70.3% and specificity of 81.2% if at least two of the four parameters (morning stiffness of >30 min’ duration, age at onset of back pain, no improvement in back pain with rest, awakening because of back pain during the second half of the night only, alternating buttock pain and time period of the onset of back pain) were fulfilled.25 It would be worthwhile to combine and evaluate the refined CIBP criteria with complaints of pain and discomfort at the thoracic spine and the chest wall. If such studies would also demonstrate high specificity and sufficient sensitivity, then the composite triad index of complaints of pain and discomfort at lumbar spine, thoracic spine and chest wall might also provide the needed improvement of the specificity of the current classification criteria for axSpA that is being addressed in the ongoing CLASSIC study.28 29

In summary, about 25% of FDR of HLA-B27(+) probands with axSpA also develop the disease. Occurrence of AAU among FDR of patients with axSpA calls for screening for the disease, but presence of CIBP among young FDR has no long-term predictive value for the diagnosis axSpA. Paying attention to prevailing symptoms of pain and discomfort at the thoracic spine and frontal chest wall in addition to CIBP may improve the diagnostic yield and classification of axSpA. ‘Healthy’ HLA-B27(+)-FDR with such symptoms may have unnoticed ‘hidden’ axSpA, that may not be captured by the current sets of criteria or fall short of being diagnosed properly.

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**Table 3** Prevalence of symptoms suggesting ‘hidden’ axial SpA among HLA-B27 positive FDR compared with HLA-B27 negative FDR

<table>
<thead>
<tr>
<th>Question</th>
<th>Relatives HLA-B27 positive no. positive/total and percentage</th>
<th>Relatives HLA-B27 negative no. positive/total and percentage</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change of body position causes exacerbation of complaints at the ventral chest wall</td>
<td>6/114 (5.3%)</td>
<td>1/138 (0.7%)</td>
<td>7.61</td>
<td>0.90 to 64.18</td>
<td>0.029</td>
</tr>
<tr>
<td>Worsening of low back pain during the early morning before getting up</td>
<td>28/111 (25.2%)</td>
<td>12/137 (8.8%)</td>
<td>3.51</td>
<td>1.69 to 7.20</td>
<td>0.00046</td>
</tr>
<tr>
<td>Persisting low back pain after getting up</td>
<td>19/117 (16.2%)</td>
<td>11/137 (8.0%)</td>
<td>2.22</td>
<td>1.01 to 4.88</td>
<td>0.043</td>
</tr>
<tr>
<td>Waking up regularly after 14:00 hour because of pain or discomfort at the thoracic spine</td>
<td>7/116 (6.0%)</td>
<td>1/137 (0.7%)</td>
<td>8.73</td>
<td>1.06 to 72.07</td>
<td>0.016</td>
</tr>
<tr>
<td>Morning stiffness at the thoracic spinal region</td>
<td>11/117 (9.4%)</td>
<td>5/137 (3.6%)</td>
<td>2.74</td>
<td>0.92 to 8.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Morning stiffness at the thoracic spinal region for at least 15 to 60 min</td>
<td>8/117 (6.8%)</td>
<td>2/138 (1.4%)</td>
<td>4.99</td>
<td>1.04 to 23.99</td>
<td>0.027</td>
</tr>
<tr>
<td>Improvement of stiffness at the thoracic spinal region through exercises</td>
<td>12/112 (10.7%)</td>
<td>5/137 (3.7%)</td>
<td>3.10</td>
<td>1.06 to 9.08</td>
<td>0.032</td>
</tr>
<tr>
<td>Exercising improves thoracic complaints due to sustained body position</td>
<td>17/116 (14.7%)</td>
<td>9/137 (6.6%)</td>
<td>2.42</td>
<td>1.04 to 5.67</td>
<td>0.037</td>
</tr>
</tbody>
</table>

None of these FDR of HLA-B27 positive axSpA probands had ever been diagnosed as axSpA. axSpA, axial spondyloarthritis; FDR, first-degree relatives.


