# Diagnosis

# 5

The diagnosis of axSpA is challenging and is usually based on a combination of clinical symptoms (e.g. unexplained inflammatory back pain), patient characteristics (e.g. age <45 years, family history of axSpA, presence of genetic risk factors [human leukocyte antigen allele B27 (HLA-B27) positivity]), and the presence of inflammation on imaging (e.g. sacroiliitis on magnetic resonance imaging [MRI] or X-ray) (Sieper and Poddubnyy 2017; Rudwaleit and Sieper 2012; Rudwaleit et al. 2004). A number of other characteristics of axSpA that may be useful in diagnosis are captured in the ASAS axSpA classification criteria outlined in Fig. 5.1 (Rudwaleit et al. 2011).

Primary healthcare providers often treat patients who suffer from back pain but, as generalists, they can easily miss the signs of axSpA (Seo et al. 2015; Dincer et al. 2008). Early diagnosis and access to effective treatment are critical to reduce the burden of axSpA and prevent disease progression; delays in diagnosis mean that appropriate treatment is also delayed, which could potentially lead to a worse outcome (Seo et al. 2015; Dincer et al. 2008; Mandl et al. 2015). When axSpA is suspected or in all patients with unexplained inflammatory back pain for more than 3 months, referral to a rheumatologist is essential to ensure an accurate diagnosis and appropriate treatment (Rudwaleit and Sieper 2012).

In this chapter, the results from the IMAS European survey relating to diagnosis of axSpA are presented, including the personnel involved, the tests carried out, and the diagnostic delay experienced by participants.
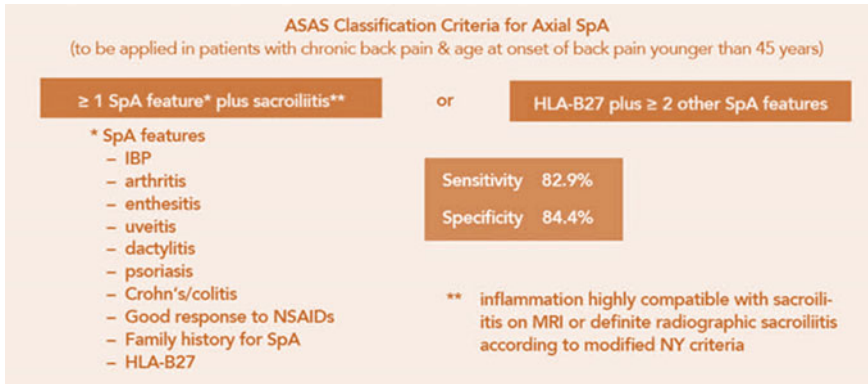
**ASAS Classification Criteria for Axial SpA**
(to be applied in patients with chronic back pain & age at onset of back pain younger than 45 years)

≥ 1 SpA feature* plus sacroiliitis**          or          HLA-B27 plus ≥ 2 other SpA features

* SpA features
 – IBP
 – arthritis
 – enthesitis
 – uveitis
 – dactylitis
 – psoriasis
 – Crohn's/colitis
 – Good response to NSAIDs
 – Family history for SpA
 – HLA-B27

Sensitivity   82.9%
Specificity   84.4%

** inflammation highly compatible with sacroili-
itis on MRI or definite radiographic sacroiliitis
according to modified NY criteria

**Fig. 5.1** ASAS classification criteria for axSpA. *ASAS* Assessment of SpondyloArthritis International Society, *axSpA* axial spondyloarthritis, *HLA-B27* Human leukocyte antigen B27, *IBP* inflammatory back pain, *MRI* magnetic resonance imaging, *NSAID* non-steroidal anti-inflammatory drug, *NY* New York, *SpA* spondyloarthritis

## 5.1 Profile of HCPs Consulted by Patients with axSpA Prior to Receiving Diagnosis

Almost 80% of survey participants reported being diagnosed with axSpA by a rheumatologist (Fig. 5.2).

Most participants visited a general practitioner (GP) before diagnosis, which reflects the key role that these primary healthcare providers play in identifying possible cases of axSpA (Fig. 5.3). However, participants also reported visiting a
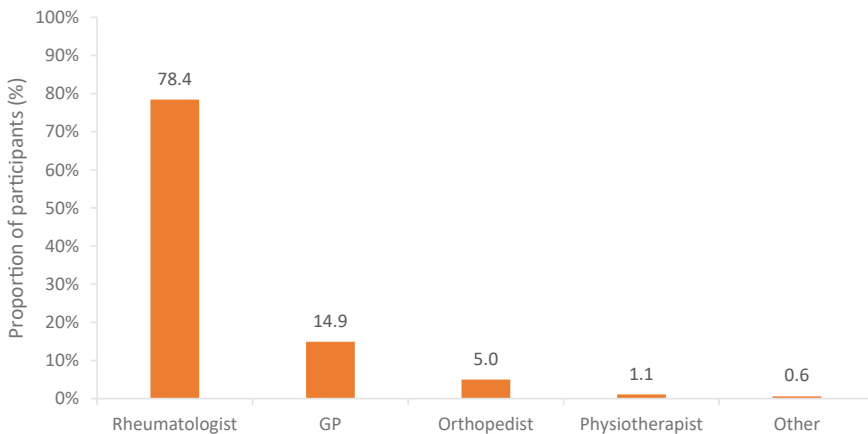


**Fig. 5.2** HCP who diagnosed axSpA (N = 2,635). *axSpA* axial spondyloarthritis, *GP* general practitioner, *HCP* healthcare professional
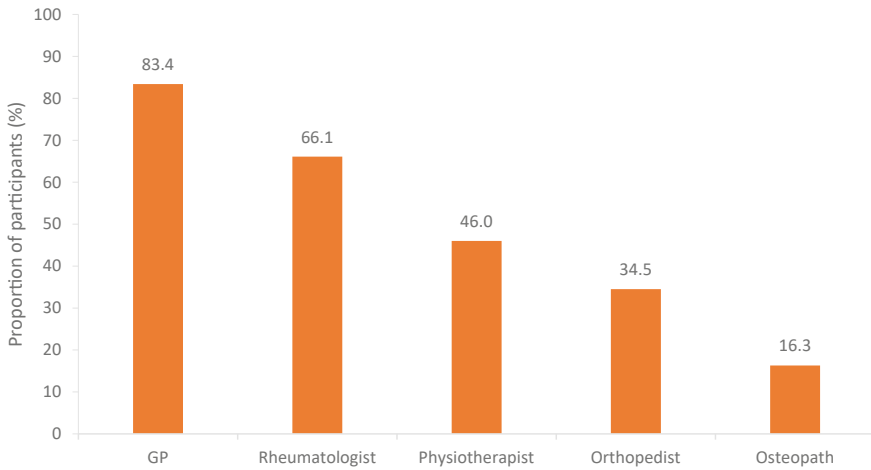
**Fig. 5.3** HCPs visited by participants before diagnosis of axSpA (N = 2,706). *axSpA* axial spondyloarthritis, *GP* general practitioner, *HCP* healthcare professional

number of other specialists prior to diagnosis, including physiotherapists (46%), orthopedists (35%), and osteopaths (16%).

Participants frequently reported visiting more than one specialist prior to diagnosis, indicating that the path to diagnosis and treatment was not optimal. A primary care physician who suspects a high probability of axSpA should always refer patients directly to a rheumatologist for further investigation (Dincer et al. 2008).

## 5.2   Diagnostic Tests

The European League Against Rheumatism (EULAR) recommends that conventional radiography (i.e. X-rays) of the sacroiliac joints and spine should be performed to diagnose inflammation in the spine, sacroiliitis (inflammation of the sacroiliac joints), and assess any structural changes (Mandl et al. 2015). If diagnosis cannot be established based on clinical features and X-rays, MRI is recommended to detect both inflammation and structural changes (Mandl et al. 2015). Genetics plays a major role in susceptibility to axSpA, with inheritance of HLA-B27 being strongly implicated (Sieper and Poddubnyy 2017). Tests to identify the presence or absence of HLA-B27 are therefore also often used in the diagnostic work-up of axSpA (Rudwaleit et al. 2011).

The diagnostic test most frequently performed on European IMAS participants was X-ray imaging, followed by HLA-B27 genetic testing and MRI (Fig. 5.4), which is in broad accordance with the current diagnostic recommendations.
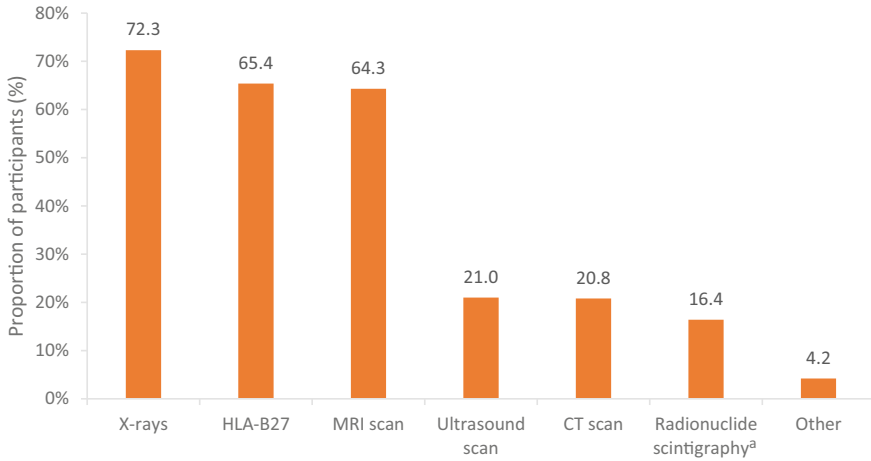
**Fig. 5.4** Medical tests conducted in the diagnosis of axSpA in participants (N = 2,661). *axSpA* axial spondyloarthritis, *HLA-B27* Human leukocyte antigen B27, *MRI* magnetic resonance imaging, *CT* computerized tomography. [a]The number of patients undergoing radionuclide scintigraphy was not collected for participants from Norway

Almost 74% of the 1,735 participants who reported a genetic testing result were HLA-B27 positive, which is within the expected range based on published literature (Salvadorini et al. 2012; Glintborg et al. 2017).

## 5.3   Diagnostic Delay of European IMAS Participants

The mean (±SD) age of participants at symptom onset was 26.6 (±11.1) years, while the mean (±SD) age at diagnosis was 33.7 (±11.5) years. Diagnostic delay was defined, in accordance with previous studies (Masson Behar et al. 2017), as the time interval in years from the age at symptom onset to the age at diagnosis. The mean diagnostic delay of all European IMAS participants was 7.4 years and the median was 4.0 years (Table 5.1) (Garrido-Cumbrera et al. 2021), which is consistent with other European studies that reported an average diagnostic delay of approximately 8–11 years in patients with axSpA (Feldtkeller and Erlendsson 2008; Feldtkeller et al. 2003). In almost one-third of the survey participants, the diagnostic delay was more than 10 years (Table 5.2). A delay of 10 years or more has been associated with an increased probability of spinal structural damage (Haroon et al. 2013).

There was a large disparity in the diagnostic delay across participating countries (Fig. 5.5); this may be due to differences in patient characteristics or healthcare systems between the countries, and may also be influenced by the varying numbers

**Table 5.1** Mean and median diagnostic delay in participants overall and by gender and age (N = 2,652)

|  | Diagnostic delay (years) | | |
| --- | --- | --- | --- |
|  | Mean | SD | Median |
| Overall | 7.4 | 8.4 | 4.0 |
| *Gender* | | | |
| Female | 8.2 | 8.9 | 5.0 |
| Male | 6.1 | 7.4 | 3.0 |
| *Age at time of survey* | | | |
| 18–34 years | 4.4 | 5.5 | 2.0 |
| 35–51 years | 7.9 | 8.2 | 5.0 |
| 52–68 years | 9.5 | 10.2 | 5.0 |
| Over 68 years | 7.3 | 9.7 | 4.0 |

*SD* standard deviation

**Table 5.2** Diagnostic delay of participants classified by year categories (N = 2,652)

| Diagnostic delay (years) | N | % |
| --- | --- | --- |
| 0–1 | 782 | 29.5 |
| 2–4 | 548 | 20.7 |
| 5–7 | 385 | 14.5 |
| 8–10 | 246 | 9.3 |
| 11–15 | 256 | 9.7 |
| Over 15 | 435 | 16.4 |

of participants per country. Countries reporting the highest mean diagnostic delay were Norway (10.6 years), Spain (8.5 years), Slovenia (7.8 years), and Sweden (7.6 years). The lowest values were reported by participants in the UK (2.6 years), Germany (2.7 years), Switzerland (3.5 years), and Belgium (3.6 years). The diagnostic delay observed in the present study in Germany (2.7 years) was shorter than in previous studies such as the PROCLAIR study in which the mean diagnostic delay was 5.7 years (Redeker et al. 2019). This could be due to the larger sample of the PROCLAIR study compared to the IMAS German subgroup.

## 5.4   Delay in Diagnosis by Gender

The diagnostic delay was statistically longer in female versus male participants (Table 5.1; mean delay 8.24 years versus 6.14 years; Mann–Whitney p ≤ 0.001) (Garrido-Cumbrera et al. 1865). Similar data were shown in a recent systematic review and meta-analysis, where the mean diagnostic delay was 8.8 years for women and 6.5 years for men (Jovani et al. 2017). Although there are no obvious gender-based differences in the clinical manifestations of axSpA, these differences may be due to a later onset of disease in women, the more widespread pain reported
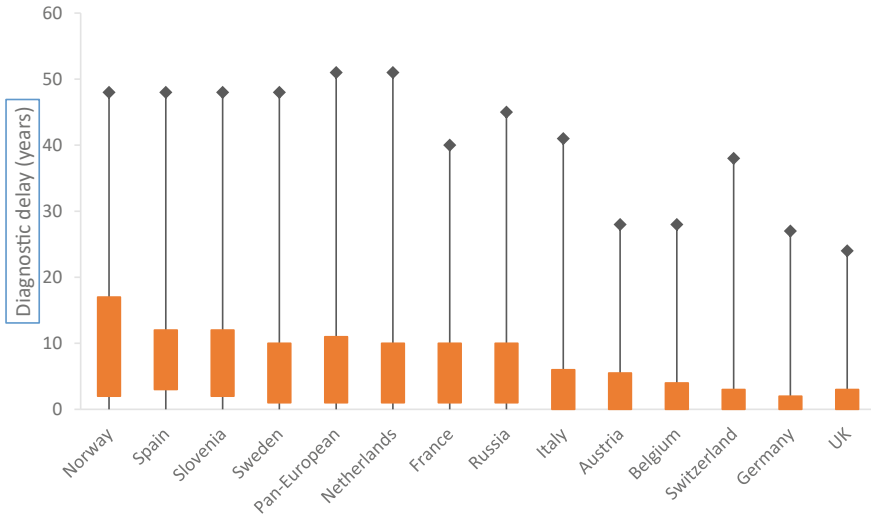
**Fig. 5.5** Quartiles of diagnostic delay by country (N = 2,652)

by female patients with axSpA resulting in delayed diagnosis, or faster disease progression in men (Slobodin et al. 2011; Rusman et al. 2018).

## 5.5   Delay in Diagnosis by Time Since Symptom Onset

Diagnostic delay was significantly longer in older participants than younger ones (Table 5.1; Kruskal–Wallis p $\leq$ 0.001). Furthermore, the delay was longer in participants who experienced symptom onset at a younger age, as indicated by a significant negative relationship between age at onset of symptoms and diagnostic delay (Fig. 5.6; Pearson's correlation −0.377, significant at the 0.01 level [bilateral]). These results may have been partly influenced by data from older participants who were undiagnosed for several years and later received a diagnosis following improvements in axSpA awareness, access to rheumatologists, and advances in imaging techniques (Salvadorini et al. 2012; Glintborg et al. 2017; Sorensen and Hetland 2015). Accordingly, the diagnostic delay was longer in patients diagnosed more recently (Pearson's correlation 0.163, significant at the 0.01 level [bilateral]).

Improvements in the diagnosis of axSpA over time are also the likely explanation for the significant relationship observed between year of onset of symptoms and diagnostic delay (Fig. 5.7; Pearson's correlation −0.545, significant at the 0.01 level [bilateral]); diagnostic delay was shorter in patients who experienced symptom onset more recently. More than half of the IMAS European survey sample were diagnosed between the years 2010 and 2017 (Table 5.3), highlighting the improvements in diagnosis that followed publication of the 2009 ASAS guidelines
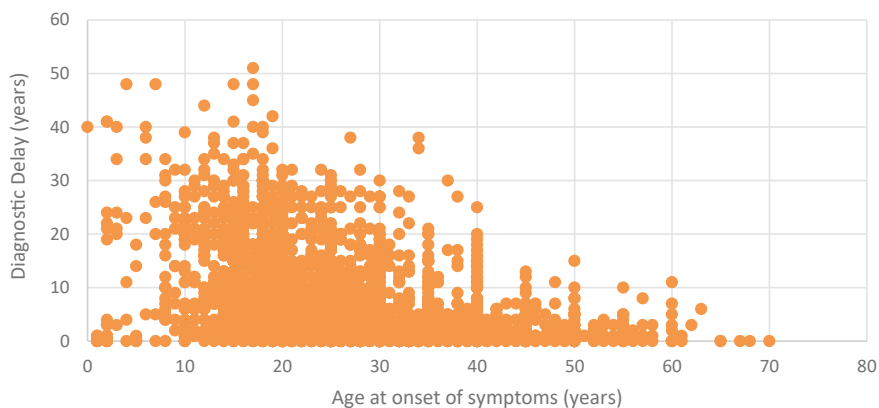
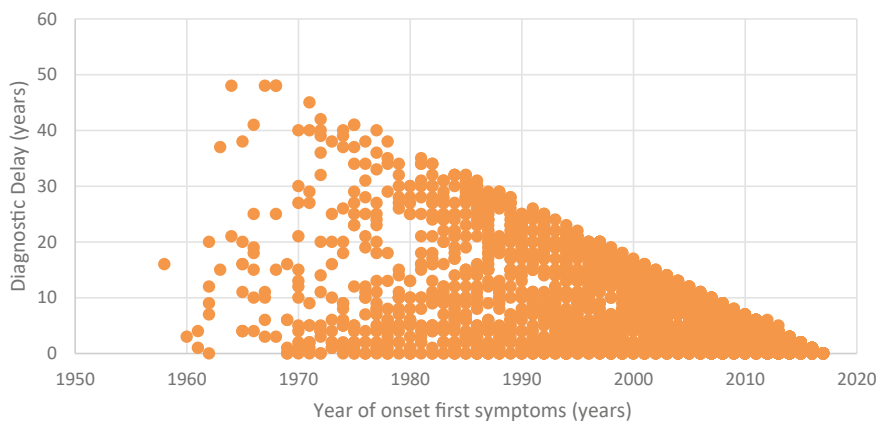**Fig. 5.6**  Scatter diagram of age at onset of symptoms in participants versus diagnostic delay



**Fig. 5.7**  Scatter diagram of year of onset of symptoms in participants versus diagnostic delay

**Table 5.3**  Number of diagnoses of axSpA per decade in IMAS European survey participants (N = 2,649)

| Decade of diagnosis | n | % |
|---|---|---|
| 1960–1969 | 10 | 0.4 |
| 1970–1979 | 66 | 2.5 |
| 1980–1989 | 145 | 5.5 |
| 1990–1999 | 284 | 10.7 |
| 2000–2009 | 647 | 24.4 |
| 2010–2017 | 1,497 | 56.5 |

*axSpA* axial spondyloarthritis, *IMAS* International Map of Axial Spondyloarthritis

for the classification of axSpA (Rudwaleit et al. 2009). It is important to note that the IMAS European survey only included participants who had already been diagnosed with axSpA so does not provide information regarding the current diagnostic pathway/delay for undiagnosed patients with recent onset of symptoms.

## 5.6   Conclusions

- The mean delay in diagnosis reported by participants was 7.4 years, with more than half waiting 5 or more years for a diagnosis.
- Diagnosis was delayed by approximately 2 years longer in female versus male participants.
- The delay was shorter in patients who experienced symptom onset more recently, suggesting that the delay between symptom onset and diagnosis has improved over time.
- Most (83%) European IMAS participants visited a GP prior to receiving a diagnosis, reflecting an important role for primary healthcare providers in identifying possible cases of axSpA.
- Participants also frequently reported visiting other specialists, such as physiotherapists (46%) and orthopedists (35%), prior to diagnosis, suggesting that the preferred pathway to diagnosis (via a rheumatologist) was not followed.
- Although there is evidence that the delay in axSpA diagnosis has improved, it remains a poorly diagnosed disease and further efforts are required to raise awareness amongst patients, HCPs, and the general public to ensure faster diagnosis and treatment.

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