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EDITORIAL

Axial Spondyloarthritis: A Better Name for an Old Disease: A Step Toward Uniform Reporting

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Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with an average global prevalence rate of 238 per 100,000 in Europe, 319 per 100,000 in North America, and 167 per 100,000 in Asia (1). A very detailed review of its epidemiology was published early this year (2). Skeletal specimens in several museum collections testify that the disease has existed from the earliest times (3). An anatomical description of an ankylosed skeleton most likely resulting from AS was first published by Bernard Connor in 1695 (4). In 1893, Vladimir Bechterev, a Russian neurologist-psychiatrist, described a new disease that, in his opinion, was a neurologic illness characterized by stiffness of the spine, dorsal kyphosis, and symptoms of nerve root irritation, including thoracic girdle pain (3,5). His name has been spelled sometimes as Bechterew, Bechtereff, and Bekhterew. In 1987, Adolph Strümpell from Germany described some patients with gradually progressive ankylosis of the spine and hip joints (3,6). A year later, Pierre Marie from France reported ascending spinal ankylosis with early involvement of the sacroiliac joints (3,7).

NOMENCLATURE

Over the years, this disease was described using many eponyms and synonyms (see Footnote) before the term "ankylosing spondylitis" became a more acceptable descriptor of the disease (3,8). However, in 1941, the American Rheumatism Association (ARA) selected the term "rheumatoid spondylitis," considering it to be a spinal variant of rheumatoid arthritis (RA) (3). But in Europe, the disease was defined as an entity unrelated to RA because of male preponderance, younger age of onset, tendency to spinal ankylosis, no association with subcutaneous nodules and rheumatoid factor (seronegative), and lack of response to treatment with gold salts (3). Finally, in 1963, the ARA formally adopted the name "ankylosing spondylitis" (3,9), accepting it to be a separate entity from RA. Interestingly, in German-speaking countries, AS is still quite widely known as "Morbus Bechterew," even though Bechterew always maintained during his lifetime that the disease he described was different from the one later reported by Strümpell and Marie (5). According to Wright and Moll (10), Marie, not Bechterew, deserves to have his name linked eponymously with the disease.

John Ball, in his 1970 Heberden Oration, reported that enthesitis is a prominent feature in AS, in contrast to RA (11); additionally, in 1971, McEwen et al (12) published a comparative study of AS as well as spondylitis accompanying ulcerative colitis and Crohn disease, psoriasis, and reactive arthritis (previously called Reiter's disease). In 1973, Moll and Wright (13) reported that "familial and clinical interrelationships exist between psoriatic arthritis and other seronegative arthritides," particularly reactive arthritis, idiopathic AS, and enteropathic arthritis. In the same year, a remarkable association of HLA-B27 with AS and these associated rheumatic diseases was discovered (14,15). These advances have supported and validated the proposed grouping of these diseases under the term "spondyloarthropathies," now more appropriately called "spondyloarthritides" (to emphasize their inflammatory aspect) or spondyloarthritis (SpA) (16–18).

EVOLUTION OF ITS CLASSIFICATION CRITERIA

At a symposium in Rome in 1960 that was sponsored by the World Health Organization through the Council for International Organizations of Medical Science, criteria were formulated (subsequently called the Rome criteria) to define AS for epidemiological studies (19). On their subsequent evaluation at a meeting in New York City in 1966, two items—thoracic pain and uveitis—were deleted, resulting in the New York criteria for AS (20,21). Moll and Wright (22) published their critique of the New York criteria in 1973. Four years later, Calin et al (23) proposed a definition for chronic inflammatory back pain (IBP) to help differentiate it from many other causes of chronic back pain. Incorporation of these IBP components in place of the rather nonspecific

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clinical symptom of chronic low back pain that had been used in both the Rome and the New York criteria led to the modified New York (mNY) criteria (24,25).

The presence of radiographic sacroiliitis is an obligatory condition to fulfill the New York and the mNY criteria; therefore, these criteria will perform less well if they are used to classify patients with early disease in whom radiographically detectable damage (meeting the mNY criteria grading of bilateral grade 2 or unilateral grade 3 or 4) may not have yet occurred. Thus, in a study of first-degree relatives of HLA-B27–positive AS probands, presence of "spondylitic disease without radiologic evidence of sacroiliitis" in some of these first-degree relatives, who were quite often females, was reported in 1985 (26). These relatives had some of the clinical features of SpA but did not meet the mNY criteria (26). The use of magnetic resonance imaging (MRI) has now clearly demonstrated that the absence of radiographic sacroiliitis does not imply the absence of inflammation in the sacroiliac joints, whereas its presence implies structural damage that is associated with disease chronicity and/or severity.

In 2005, Rudwaleit et al (27) highlighted the prevailing difficulties in diagnosing and classifying patients with predominantly axial symptoms of AS but lacking sacroiliitis as defined by the mNY criteria. Such patients had previously been reported as having "spondylitic disease without radiologic evidence of sacroiliitis" (26), and it was emphasized that these patients form part of a wider disease spectrum called axial SpA (axSpA) (27). The patients who show structural damage on plain radiography that meets the mNY criteria definition of radiographic sacroiliitis are classified as having AS, whereas those without such changes were initially classified as having preradiographic axSpA (27). This latter term was subsequently changed to nonradiographic axSpA (nr-axSpA) because not every such patient progresses to AS or what has now been termed radiographic axSpA (r-axSpA) (see Figure 1). The decreasing sizes of the three chevrons from left to right in Figure 1 are meant to emphasize that only a portion of the patients with nr-axSpA will progress to r-axSpA/AS, estimated to be 5% in 5 years and 19% in 10 years (28,29). Others may remain as nr-axSpA, perhaps forever, and some patients can possibly have a self-limiting disease course.

In 2009, the Assessment of Spondyloarthritis International Society (ASAS) proposed a new set of classification criteria to encompass this wider clinical spectrum of axSpA, that has an imaging arm and a clinical arm (30,31). The imaging arm requires the presence of either radiographic sacroiliitis (meeting the mNY criteria grading of bilateral grade 2 or unilateral grade 3 or 4) or active inflammation of the sacroiliac joints detected by MRI, plus at least one other characteristic feature of SpA, whereas the clinical arm requires the presence of HLA–B27 plus at least two other characteristic features of SpA. The patients can be classified as having axSpA if they fulfill the imaging or the clinical arm, but always on the background of having chronic back pain for at least 3 months with an age at onset not exceeding 45 years (30–32).

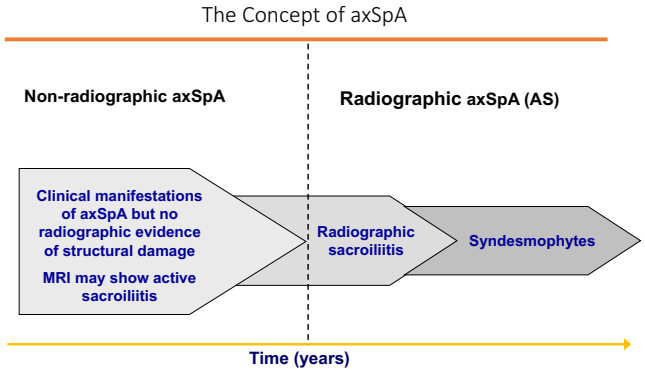

Figure 1. This figure schematically shows a unifying concept of axSpA that has a wide clinical spectrum. Inflammatory back pain is the leading symptom that may be present throughout the disease course without any occurrence of structural damage. As further explained in the text, the decreasing sizes of the three chevrons from the left to the right of this figure are meant to emphasize that only a portion of patients with nr-axSpA will progress to r-axSpA/AS, whereas others may remain as nr-axSpA, perhaps forever or have a self-limiting disease course. This figure also shows that not all patients with radiographic sacroiliitis progress to form syndesmophytes with resulting spinal ankylosis. This figure is adapted from figure 1 from the author's previous publication (17).

Recent studies have shown that nr-axSpA is a more heterogeneous entity than AS. For example, patients with nr-axSpA are female at a relatively higher proportion, confirming the original report (26), have a lower burden of inflammation, and a slower disease course that can sometimes be self-limiting, as compared with patients with AS (32–35). The primary goal of any valid classification criteria for any disease is to provide a homogeneous study population with a common etiopathogenesis, similar prognosis, and similar response to identical treatment (36–38). All criteria are dynamic concepts that need to be updated as our knowledge advances. Thus, there is a need for further research to improve the ASAS criteria, based on better knowledge of the natural history, etiopathogenesis, and response to treatment of patients with axSpA (36–38). Availability of reliable biomarkers are needed to help identify patients with nr-axSpA who are more likely to progress to AS and to facilitate therapeutic drug trials designed to prevent or retard such progression (36–38).

The specificity and sensitivity of the ASAS classification criteria for axSpA were found to be 84.4% and 82.9%, respectively, based on the experts' opinions (30–32). However, these performance characteristics were not obtained in an independent set of patients and therefore may be even lower when tested in independent new sets of patients that include non-Europeans. Ideally, the classification criteria should have at least a 90% specificity (in order to decrease their false-positivity) while retaining a sensitivity of at least 80%. It is now generally agreed that a re-evaluation of the ASAS classification criteria is needed. Therefore, ASAS and Spondyloarthritis Research and Treatment Network (SPARTAN)

have embarked on a study named Classification of Axial Spondyloarthritis Inception Cohort (CLASSIC) to validate the current criteria in independent prospective cohorts and plan for its subsequent improvement if its specificity is found to be below 90% (CLASSIC: Background and Introduction. www.spartangroup.org). In the meantime, the mNY criteria for AS continue to be very useful for defining a relatively homogenous group of cases for clinical research and genetic studies (36).

It needs to be emphasized that there are no validated diagnostic criteria for axSpA/AS, and clinicians are inappropriately using the mNY criteria and more recently the ASAS criteria as an aid to clinical diagnosis in daily practice. This also results from a widespread lack of understanding of the differences between diagnostic and the classification criteria (27). We admit that, in hindsight, we had wrongly labeled the mNY criteria as diagnostic criteria in our publications (24,25). This error occurred because, at the time, there was no concept of classification criteria and diagnostic criteria as two distinct entities. For example, Watson Buchanan, a famous rheumatologist, stated in 1980 that the Rome criteria were diagnostic criteria and that the New York criteria should be used in clinical rheumatology practice and in epidemiological surveys (3). Moreover, Alvin Feinstein, a well-known epidemiologist and statistician of his time, discussed the revised Jones criteria for acute rheumatic fever as diagnostic criteria (39).

CONCLUSION

In clinical medicine, use of the term axSpA should be preferred over AS because the word "ankylosing" has a negative prognostic connotation for patients as that degree of structural damage may take a long time to develop or may not occur at all. The introduction of the mNY and the ASAS classification criteria has been very important steps forward for clinical research, earlier disease recognition, and for conducting treatment trials that have led to approval of biologic therapies for patients with axSpA, including AS and nr-axSpA. The performance characteristics of the ASAS criteria are now being re-evaluated in independent prospective cohorts of axSpA patients prior to any decision to further improve them in order to achieve a specificity of at least 90%.

The published studies on the efficacy of the current treatment of patients with axSpA are frequently difficult to compare because some investigators use the term AS and others axSpA or r-axSpA. However, the patients who fulfill the mNY criteria for AS and those who fulfill the ASAS criteria for r-axSpA are not fully comparable (37,38). Therefore, we propose that to promote quality of reporting and comparability of results of future studies of this intriguing disease, authors should clearly indicate important study characteristics, such as age, sex, disease duration, HLA-B27 status, and proportions of patients with AS, nr-axSpA, and r-axSpA.

Lastly, we have a new name—axSpA—for an old disease (32), and to paraphrase William Shakespeare (who had stated in a different context "What we call a rose would smell as sweet by any other name"): What we call a disease is the same by another name.

AUTHOR CONTRIBUTIONS

Drs. Khan and van der Linden drafted the article and critically reviewed it for important intellectual content.

FOOTNOTE

Eponyms of AS: Morbus Bechterew, Bekhterev's syndrome, Bechterew's disease, Bekhterev-Strümpell-Marie disease, Marie's disease, Marie-Strümpell arthritis, (Marie-Strumpell-Bechterew disease, Pierre-Marie's disease (3–8).

Synonyms of AS: Pelvospondylitis, pelvospondylitis ossificans, spondylitis atrophica ligamentosa, rheumatismal ossifying pelvospondylitis, spondylose rhizomélique, spondylosis ankylopoëtica, pelvospondylitis ossificans, spondylitis ossificans ligamentosa, spondylitis ankylopoetica, spondyloarthritis ankylopoëtica, bamboo spine, poker back, atrophic ligamentous spondylitis; ossifying ligamentous spondylitis, rhizomelic spondylosis, spondylitis deformans, rheumatoid ossifying pelvispondylitis, and rheumatoid spondylitis (3–8).

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Correction added after online publication 4 September 2019: the title of reference 26 has been updated.