Chapter

Introductory Chapter: AS Times Go by – An Axial Chronicle

Jácome Bruges Armas

1. Introduction

The first description of Ankylosing Spondylitis (AS) is assigned to Bernard Connor, a Medical Doctor, born in Ireland in 1666, who attended the Medical Schools of Paris, Montpellier and Reims. He found a skeleton in a graveyard in which the ilium and sacrum and the 15 lowest vertebral and adjoining ribs formed one continuous bone. This finding was reported in three different languages—French, Latin and English (1691–1695).

The classical description of AS was published by Strumpell (1884) describing two patients with complete ankylosis of the spine and hip joints [1]. This first description was followed by another paper of Strumpell (1897) [2], two papers of von Bechterew (1893 and 1899) [3, 4] and one paper of Pierre Marie (1898) [5]. This last author is agreed to have given the most detailed clinical description together with his pupil, Léri, which gave a detailed pathological description based on two autopsies (1899 and 1926) [6, 7].

During the next years, after Roentgen developed X-rays (1895), many descriptions were written in different languages and countries together with radiological descriptions of the spine. Surprisingly, sacroiliac disease, a hallmark of AS, was not fully recognised until 1930 [8–11].

After the First and Second World Wars, new data were recognised, resulting from the screening and pensionability of young adults. It was found that women were also affected, and that AS was a familial disease, sometimes involving psoriasis, Reiter's disease [12], iritis, ulcerative colitis and Crohn's disease, heart and lung complications, and neurological complications, namely, long tract lesions due to atlanto-occipital and atlanto-axial subluxations and to a cauda equina syndrome associated with arachnoiditis. To investigate AS as a familial disease, with ethnic differences, new tissue antigenic techniques were applied (human leucocyte antigen (HLA) system), and a major breakthrough resulted with a strong association between AS and the allele HLA-B27, published independently in 1973 by Schlosstein et al. [13] and Brewerton et al. [14]. The development of the population survey techniques firmly established familial aggregation [15] and racial differences [16].

During the last years, some modifications in the terminology have been introduced. AS (axial spondyloarthritis (axSpA)) is now included in the Spondyloarthritis (SpA), a group of diseases, which also comprises peripheral SpA (including psoriatic arthritis, reactive arthritis and arthropathy of inflammatory bowel disease), and undifferentiated SpA.

Ankylosing Spondylitis (AS)—the most known and investigated form of SpA—is a chronic, immunomediated arthritis, usually progressive, characterised by inflammation of the axial skeleton, entheses, peripheral joints and extra-articular sites like the eye, bowel and heart. It is also designed as Radiographic axial spondyloarthritis (axSpA). This term comprises the whole group of patients with sacroiliitis (AS or radiographic axSpA) and without radiographic sacroiliitis (non-radiographic axSpA).

Radiographic sacroiliitis has been considered the hallmark of AS but it is a late finding. Patients may complain of back pain for years without any findings in classic X-rays, but MRI shows signs of inflammation much earlier than structural damage. It is known from historical data that patients with end-stage AS were recognised by a stooped posture and by the presence of syndesmophytes on spine X-rays.

The first criteria for use in population surveys to investigate the epidemiology of AS were proposed in Rome in 1961 [17] and revised in New York in 1966 [18]. The Rome criteria were not widely used because the lack of sacroiliitis was considered too greater loss of specificity. These criteria employed new objective clinical methods to measure spinal mobility but sacroiliitis (at least grade 2 bilateral radiographic sacroiliitis) was later introduced in the New York criteria [19]. These diagnostic criteria were modified by van der Linden in 1984 [20], which provided greater specificity and introduced their extension to non-axial spondyloarthropathies.

Because the lone concept of AS was challenged, classification criteria were developed by Amor in 1990 [21], followed by the European Spondyloarthropathy Study Group (ESSG) [22]. More recently in 2004, the Assessment of Spondyloarthritis International Society (ASAS) decided to improve SpA criteria mainly for application in early disease [23]. The ASAS criteria performed better than the Amor and ESSG criteria which were developed in the pre-MRI era, showing that MRI of the axial skeleton was crucial for the characterisation of the SpA. MRI allowed to define two subsets of axial spondyloarthritis (axSpA): non-radiographic axial SpA, and radiographic SpA, considered two stages of the same disease. These new criteria were created to facilitate research in SpA— observational studies and clinical trials, although today they are also used as diagnostic criteria in clinical practice by a large number of rheumatologists.

Metrology, like radiology, contributed significantly to AS characterisation and to research on SpA, and also for evaluating improvements in function and activity in patients subjected to treatments in daily practice or in clinical trials. Lumbar flexion measurements had been used since Schober [24]; Macrae and Wright (1969) [25] introduced the modified Schober index that was judged as a reasonably reliable measure of lumbar flexion. Several other measures were proposed like the tragus-to-wall, the chest expansion, hip mobility involving a goniometer, the intermalleolar distance, the finger-to-floor distance, the C7-to-iliac crest line distraction and the lateral finger-to-floor distance. In 1994, Jenkinson evaluated the metrology results from 20 movements and chose five of them that were collectively named BASMI—the Bath Ankylosing Spondylitis Metrology Index [26]. This index proved to be sensitive to changes in patient mobility, although it had a poor relationship with radiology. It has obvious advantages over radiology because it could be repeated as often as required, is able to be quickly performed and did not require expensive equipment, and most importantly, examines parameters that are not irreversible, unlike radiographic changes.

In the early 1980, the concept of self-administered questionnaires became acceptable to investigate rheumatic diseases. One of these—the Health Assessment Questionnaire (HAQ score) [27]—was designed to evaluate the health status of

patients with rheumatoid arthritis, but was modified for use with spondyloarthropathies (HAQ-S) [28]. In 1988, Dougados et al. [29] produced the first functional index designed for patients with AS, followed by Calin A in 1994 with the Bath Ankylosing Spondylitis Functional Index (BASFI) [30], by the validation and development of a Dutch version of the French index (Creemers et al.) [31] and by the Leeds Disability Questionnaire (Abbott et al. 1994) [32]. These questionnaires had all very high Cronbach's alpha scores and were good tools for research on group comparisons and for assessing individual patients in a clinical situation [33]. Another index, designed to evaluate disease activity, was published in 1994 (Garrett et al.) [34]—the Bath Ankylosing Spondylitis Activity Index (BASDAI). This index was considered appropriate as a research tool in group comparisons.

The mechanisms of the pathogenesis of Ankylosing Spondylitis are complex and are not completely recognised. During the last years, several studies established the high heritability of the disease. One of them, the UK Biobank study [35], used the Affymetrix Axiom chip and the hereditability was estimated at 69.1%. The International AS Genetics Consortium Study using the Illumina Immunochip estimated hereditability at 32.7% [36]. Further to genetic factor, there are other factors that may be associated with the disease pathogenesis—environmental factors, altered mucosal immunity, altered gut microbiome, disregulation of the immune system and factors associated with the axial and peripheral skeleton and enthesis. HLA-B*27 is possibly the strongest genetic association with AS and is remarkably polymorphic. To date, at least 271 subtypes have been reported, some of them not disease associated, and the ancestral subtype is suggested to be HLA-B*27:05 that is present in nearly all populations [37]. Several other major histocompatibility complex (MHC) alleles were identified in AS negative HLA-B*27, some of them conferring protection. HLAB*60 was the first to be associated with AS B*27 negative patients [38]. The non-MHC genetic associations were identified through genome-wide association studies (GWAS). The first AS GWAS, the Wellcome Trust Case Control Consortium (WTCCC) and the Australo-Anglo-American Spondylitis Consortium (2007), identified single nucleotide polymorphisms (SNPs) in endoplasmic reticulum aminopeptidase 1 (ERAP1) and interleukin 23 receptor (IL23R) [39]. Other GWAS identified new AS susceptibility loci that can be classified into categories: cytokines and cytokine receptors, mucosal immunity factors, M1-aminopeptidases, transcription factors and intergenic regions. These groups of loci may then be divided mainly into two pathways—the interleukin 23/interleukin 17A (IL-23/IL-17A) and the tumour necrosis factor (TNF) genes [40]. Some of these susceptibility genes identified in these pathways were explored as targets for AS treatment. The successful development of drugs targeting IL-23/Il-17 axis for diseases associated with IL-23/IL-17A illustrates the great value of genetics in drug development.

2. Conclusion

Ankylosing Spondylitis is a fascinating disease that since its first description in 1691–1695 has been the object of an intense research across the world. Several groups focused their research on different aspects of AS: epidemiology, diagnostic criteria, metrology, functional indexes, radiology, genetics and therapy.

All these areas of research gave important contributions to the updated knowledge of AS, although several mechanisms that may help to explain the disease pathogenesis

are still unknown. Relevant breakthroughs were obtained through genome-wide association studies (GWAS) with the identification of genes and pathways involved in susceptibility or protection. These advances on the knowledge of AS were crucial and allowed the development of new treatments which modified significantly the disease prognosis.

Author details

Jácome Bruges Armas[1,2]

1 Epidemiology and Molecular Biology Service (SEEBMO), Hospital de Santo Espirito de Angra do Heroísmo, Terceira Island, The Azores, Portugal

2 Comprehensive Health Research Centre (CHRC), Nova Medical School, University of Lisbon, Lisbon, Portugal

*Address all correspondence to: brugesarmas@gmail.com

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