The Epidemiology of Back Pain, Axial Spondyloarthritis and HLA-B27 in the United States

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Abstract: The concept of inflammatory back pain (IBP) evolved in the 1970s, coincident with the discovery of the HLA-B27 association with ankylosing spondylitis (AS), leading to the development of criteria to determine the presence of IBP. The concept of IBP and it relationship with AS and axial spondyloarthritis (AxSpA) has further evolved, and an instrument developed (the Spondylitis Association of America Back Pain Tool), which was further modified and field tested for use in the 2009 to 2010 National Health and Nutrition Examination Survey (NHANES). This has shown the frequency of chronic back pain to have risen to 19.4%, with nearly one third having IBP. The prevalence of AxSpA has been defined at 1.0% to 1.4% and AS at 0.52% to 0.55%. The national prevalence of HLA-B27 in the United States is 6.1%, and intriguing data from NHANES 2009 suggest a decreasing frequency with increasing age. From this arise new questions and a work agenda ahead.

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Population studies have shown that chronic back pain is among the most common problems that cause patients to seek medical care. Earlier data from the second National Health and Nutrition Examination Survey (NHANES II), conducted between 1976 and 1980, demonstrated that the cumulative lifetime prevalence of low back pain (LBP) lasting at least 2 weeks was 13.8%.[1] LBP is second only to the common cold in frequency among adult ailments and represents the fifth most common reason for an office visit. Recent data from NHANES 2009 to 2010 report the frequency of chronic back pain (defined as being present on most days for at least 3 months) to have risen in frequency to 19.3% of the population between the ages of 20 and 65 years, inclusively.[2]

The high frequency of chronic LBP has engendered a host of diagnostic tests and treatments, many widely used and expensive, not necessarily evidence based and at times associated with significant morbidity in their own right. One recent review reported a 629% increase in Medicare expenditures for epidural steroid injections in the United States, a 423% increase in expenditures for opioids for back pain, a 307% increase in the number of lumbar magnetic resonance imaging (MRI) among Medicare beneficiaries and a 220% increase in spinal fusion surgery rates.[3] The limited studies available suggest that these increases have not been accompanied by population-level improvements in patient outcomes or disability rates.[3]

The awareness of inflammatory back pain (IBP) as a discrete entity in the United states goes back to the 1970s,[4] coinciding with the discovery of the association of HLA-B27 with ankylosing spondylitis (AS),[5,6] for which instruments to gauge it have been refined and validated for use in the clinic as a case-ascertainment tool. Now that such are available the true frequency of IBP and conditions associated with it, including axial spondyloarthritis (AxSpA) and AS, in the United states can be estimated. With the introduction of effective but costly new medications in the treatment of AxSpA and AS, it is clear that more comprehensive ascertainment of these conditions is necessary to plan a health care agenda and to facilitate diagnosis and maximize cost-effectiveness of the treatment of these diseases.[7]

This review will focus on this in the context of how a case-ascertainment tool was converted into a population-based screening instrument of chronic back pain, IBP, AxSpA and AS in the NHANES story. It will further focus on the consequences of carrying out HLA-B27 testing in a population-based sample in NHANES 2009, compare this with other studies in this regard and address unanswered questions left by these new data.

DEVELOPING INSTRUMENTS TO STUDY IBP

In developing the initial instrument characterizing IBP, the Stanford group administered a questionnaire relating to the presence and nature of back pain to all 10,150 employees of an industrial complex.[8] The questionnaire was returned by 2892 subjects (65% men). Of these, 1880 (65% of responders or 19% of total) reported a history of back pain. One hundred twenty-four described their back pain as insidious in onset, persisting for at least 3 months, developing at age less than 40 years, being associated with morning stiffness and showing improvement with exercise. Three hundred sixty-seven subjects scored 4 of these 5 features. Pelvic radiographs of 342 persons were available for blind evaluation. Sixteen patients (12 men) were shown to have definite AS (grades III or IV sacroiliitis or HLA-B27-associated grade II sacroiliitis). Only one of these persons was known to have spondylitis. The majority of these symptomatic patients had been seen by both medical and nonmedical practitioners.

Then, questionnaires containing 17 questions relating to back pain were given to 3 groups of subjects: 42 known HLA-B27–positive subjects with AS by New York criteria, 21 patients from an orthopedic clinic who were B27 negative, with normal X-rays of the sacroiliac joints, and 75 controls, including healthy volunteers or patients attending nonrheumatology clinics.[4] They found that back pain was pretty common in all groups (60% of controls), and the following 5 characteristics distinguished AS from the rest: age less than 40 years, insidious onset, duration at least 3 months, morning stiffness and improvement with exercise.

In 2 studies from this era, AS was found in 20% of healthy HLA-B27–positive blood donors (at Stanford[9] and from

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Chicago[10]) and, with a reported 6% population frequency of HLA-B27, led to the conclusion that AS occurs in 1% of the population.[9,10] A subsequent population-based study, however, suggested this to be an overestimation.[11]

Because back pain was ubiquitous (20%–50% of the population) and genetic testing was expensive, cumbersome (the microcytotoxicity assays for B27 typing in that era required fresh living cells) and reagents were in short supply, the aim was to use a practical alternative to identify patients with AS. Moreover, there were no other laboratory diagnostic tests, and it was recognized then that X-rays were normal in early-stage illness and pelvis X-rays frequently misread. Thus, Calin et al[4] proposed to use the clinical history as a practical screening alternative and emphasize the difference between back pain of an inflammatory nature (AS) from back pain of a nonspecific (mechanical) type. In 1977, their conclusions were as follows: (1) reliance on 4 or more features provided a diagnostic screening test for AS with 95% sensitivity and 85% specificity versus control groups and (2) if affirmative responses for all 5 features were required, sensitivity declined (only 60% of AS patients fulfilled all criteria) but specificity increased. Calin et al[4] felt that they created a simple, cheap, reproducible screening technique compared with HLA-B27 typing, which was felt alone to be 95% sensitive but only 20% specific. Their overall plan, never achieved, eventually was to validate this test in the general population, where AS is less common. However, their results did concentrate the group for subsequent investigation by a factor of between 6 and 30, increasing the efficiency of case-finding.

Since this time, the concept of IBP has been further explored and defined by other groups using largely similar criteria[11–13] (Table 1).

Now, 35 years later, the question is whether this approach is still valid or if we need to do more work? With biologic agents, advanced imaging techniques and recent successes in defining genetic susceptibility, it is even more important to identify disease earlier. Besides, the initial instrument was never used to define how many patients have AS in the population. Even if AS is identified early, important questions remain: Can early intervention change the course of the disease (to the extent to which the natural history of the disease is even known)? Do new drugs make a difference in real outcome effects (bone proliferation, comorbidities) or is there a great deal of health care resources being allocated for nothing that alters the natural history of the disease in return?[7] So, there are plenty of reasons to repeat these studies with a larger sample size and using a more sophisticated analytic approach.

To improve case identification and expand our efforts toward a true population-based survey, the Spondylitis Association of America (SAA) in 2008 initiated the SAA back pain study, ultimately aimed at developed an online screening tool to facilitate the diagnosis of AS.[14] A 3-phase approach was undertaken, beginning with literature review, expert panel and cognitive testing with AS patients followed by initial feasibility testing, and then a case-control study for validation, item reduction and creation of a scoring algorithm. One hundred forty-five AS cases and >300 chronic back pain controls made up the final set.[14] The final model provided a 12-question pool with a sensitivity of 70% and a specificity of 99%. The strongest discriminators were male gender, pain/stiffness in the neck and/or hip, pain/stiffness decreasing with daily physical activity and a history of iritis.[14] This tool performed similar to other case-ascertainment instruments such as mammography, papanicolaou smears and various nuclear cardiology tests for coronary artery disease.

This study employed additional aspects beyond traditional symptom-based questionnaires, including items such as gender, location of pain/stiffness and responsiveness to nonsteroidal anti-inflammatory drugs.[12,13,15] Instead of binary questions, gradations of input were examined. The concept of "exercise" related to pain/stiffness, however, is complex—the differences between intensive physical exercise and activities of daily living should be distinguished. The concept of awakening from sleep is not just in the morning, given people's different sleep patterns. Much more cognitive testing needed to be done for a population-based instrument. The role of diagrams for location of symptoms and signs would be important and provide much more granularity.

The NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States (http://www.cdc.gov/nchs/nhanes.htm). The survey is unique in that it combines interviews, physical examinations and laboratory assessments. Begun in the 1960s, NHANES is a major program of the National Center for Health Statistics (NCHS). The NCHS is part of the Centers for Disease Control and Prevention and has the responsibility for producing vital and health statistics for the nation. The NHANES interview includes demographic, socioeconomic, dietary and health-related questions. The examination component consists of medical, dental and physiological measurements and laboratory tests administered by highly trained medical personnel. Currently, available U.S. population-based data for AS, SpA and IBP from the nationally representative NHANES include both NHANES I (1971–1975)[16] and NHANES II (1976–1980) surveys.[1] The pelvic radiographs obtained in NHANES I provided U.S. prevalence estimates for radiographic sacroiliitis, an important component of the AS case definition. AS and SpA prevalence's cannot readily be calculated from NHANES I survey data; however, IBP prevalence (Rudwaleit et al[13] criteria 7b) can be estimated from NHANES II. The NHANES II estimate for IBP is 0.8% of the adult population aged 25 to 49 years.[2]

TABLE 1. Features of axial pain in NHANES 2009 to 2010

	N	%
Chronic low back pain prevalence[a]	980/5103	19.4
Total axial pain sample	980	100.0
Current pain	873	89.1
No current pain	107	10.9
Age-at-onset of pain (yr)		
<20	164	16.8
20–29	247	25.3
30–44	306	31.4
45+	258	26.5
Duration of pain (yr)		
<1	50	5.2
1–2	154	16.0
3–10	343	35.7
>10	415	43.1
Temporal pattern of pain		
Constant, never goes away	660	67.5
Episodic, no relief >1 mo	178	18.2
Episodic, pain relief >1 mo	123	12.6
1 pain episode only	17	1.7

[a] Chronic back pain is defined as at least 1 episode of neck, upper-, mid- or lower back or buttock pain lasting at least 3 months.