Editorial

Novel Concepts of Severity Mechanisms in Ankylosing Spondylitis

In this issue of *The Journal*, a provocative report on ankylosing spondylitis (AS) concludes that, "age at onset, itself, does not influence disease severity"[1]. The inference was based upon findings in patients without hip involvement that showed those with young onset, i.e., less than 22 years, did not have more severe disease by standard criteria than counterparts with late onset, i.e., at age 30 years or older. However, juvenile onset AS, i.e., at less than 16 years, has correlated with increased frequency of hip involvement[2-5], and greater progression of either hip[3] or overall[4] disease, compared to adult onset AS.

A recent report[6] from the same center[1] indicated that juvenile onset AS constituted about 16% of the total patients, whereas those with young onset — less than 22 years — included a full half of the total subjects. Thus, only about one-third of the young patients had juvenile onset AS[1]. In fact, the juvenile onset AS patients had increased surgery in general (Figure 4[1]), and increased total hip replacements in particular (Figure 5[1]), compared to patients who had onset in either teen (17–20 yrs) or late (30+ yrs) ages. Thus, the recent study[1] does not specifically address juvenile onset AS as a phenotypic marker of increased disease severity[4].

Hip disease correlated with greater spinal severity scores in both the young and late onset patients[1]. However, the retrospective analyses were based upon cross sectional data and did not distinguish sequences of occurrences. Early hip involvement in young onset disease is a marker of worse future outcomes in AS[3,4,7]. However, development of hip disease at later ages may itself be a secondary manifestation of more severe AS. The recent report[1] does not address sequential relationships of hip and spinal involvements at different onset ages.

Other conclusions of the recent article[1] were: "The lack of association between severity and age at onset implies that the determinants of susceptibility and severity are independent," and "there are three clearly distinct independent factors: the environment and both susceptibility and severity genes" operating in AS.

Conventionally, complex diseases are believed to result from interactions of multiple susceptibility genes and their modifiers operating via host traits and influenced by environmental factors, without incriminating separate severity genes[1,8]. For example, in rheumatoid arthritis, greater genetic load is associated with: (1) increased risk, (2) younger onset ages, and (3) increased disease severity[9]. However, in AS, essentially all affected Caucasian persons[6,8] and some other ethnic groups[5,10] are HLA-B27 positive. Accordingly, one might logically infer that other genotypes besides HLA-B27 might contribute to severity of AS[1,8]. However, phenotypic markers of juvenile onset[3,4,10] and male sex[11-13] are associated with more progressive AS. Therefore, mechanisms whereby severity genes might operate in AS, either in association with such somatic disease modifiers or independently from them, would be relevant to the proposed hypothesis[1].

The remainder of this commentary addresses: (1) the severity spectrum of AS; (2) the variations in initial symptom patterns and patient subclassifications; (3) methodologic limitations of retrospective study designs; and (4) need for more accurate data on diverse presentation patterns at different onset ages and their conjoint relationships to AS outcomes. Also, a previously proposed hypothesis of intrinsic axial muscular hypertonicity in AS[11] is reviewed as a potential biomechanism contributing to variations in severity of this obscure disease.

A GREAT SPECTRUM OF SEVERITY EXISTS IN AS

Severity of AS can range from chronic low back pain without definite radiological changes[14] to complete ankylosis of the entire vertebral column[11,15]. Nonetheless, the same label, "ankylosing spondylitis," is applied to the entire severity gradient[11,14,15]. The male to female sex ratio tends to increase with severity[11]. Females may predominate in the mildest form of disease[14], whereas males may exceed females in a ratio of 10:1 in the most severe cases[11].

INITIAL SYMPTOM PATTERNS ARE VARIED IN AS

Initial symptom patterns of AS are varied and tend to differ by

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onset age. In juvenile onset AS, the disease often begins in peripheral rather than axial sites[2,10,16]. Peripheral onsets include the syndrome of enthesopathy and arthropathy (SEA), which initially manifests mainly in peripheral lower extremity bones, joints, ligaments, or tendons[10,12,13,16,17]. Within 5 years, many[17] if not most[16] patients with SEA syndrome fulfill criteria for definite AS. However, an axial type of hip or spinal involvement may occur early in juveniles[2-5,7,18]. In adult onset AS, initial symptoms of peripheral joint involvement may also occur[2,10], particularly in overlap with Reiter's disease. However, in adult onset AS, the first manifestation usually affects the sacroiliac joints or low back[2,10]. Except for the hips, axial or spinal onsets are less common in juveniles than adults, and are especially infrequent under age 12, particularly in females[2,10,18]. Juveniles presenting with such central symptoms usually progress to more severe disease[3,4,7,18].

Among a large series of patients with spondyloarthropathy in North Africa, initial hip involvement was reported in 20% who stated onset of disease under age 18 years, whereas the frequency was 10% in those with symptom onset at age 24 years or older (Figure 2[5]). Subsequent hip involvement was also greater in the younger than older onset subgroup[5].

RELATIONSHIPS OF ONSET AGE AND SYMPTOM PATTERNS TO AS OUTCOMES

Outcome studies of AS should accurately distinguish the different patterns of initial symptoms at different onset ages. For simplicity, onset patterns may be categorized as: (1) spinal, (2) hip, (3) peripheral, and (4) mixed or other. Combination patterns can be assigned to appropriate grouping(s), based upon implied severity risks. Following initial presentation, subsequent rates of occurrences of new or additional manifestations can be analyzed actuarially[5]. Standardized endpoints are now available for outcomes research[1,19]. The recent report[1] correlates severity of AS cross sectionally in relation to hip involvement, but outcomes were not analyzed in the different onset age groups by initial symptoms nor by the sequences of involvements.

LIMITATIONS OF RETROSPECTIVE STUDY DESIGNS

Susceptibility to AS is almost entirely caused by genetic or host related factors[6,8]. Accordingly, observational study designs will likely continue to be the primary methodology to investigate AS in humans for the foreseeable future, rather than by experimental techniques. Numerous types of errors or biases can compromise the quality of available data in observational studies, e.g., inaccuracies of subject's recall, misclassification of unstandardized data, insufficient or inaccurate stratification of subject's categories in analyses, among others. Prospective or longitudinal studies permit improved data gathering compared with retrospective designs[9]. Also, more accurate sequences of occurrences can be determined in prospective or longitudinal observational studies, than from distant retrospective recall[9].

NEED FOR ACCURATE DATA COLLECTION ON VARIED ONSETS OF AS

Reliable data collection is difficult in retrospective studies, due to inaccurate recall of different symptom patterns, their sequences, and even validated onset ages *per se*. To assist in further studies of primary AS onset age frequency distribution patterns[20], a one-page questionnaire was developed with the critical assistance of colleagues experienced in the epidemiology of AS (Table 1). The primary AS onset age questionnaire is not field tested, and will need appropriate modifications, after utilization under different clinical and survey circumstances.

HYPOTHESIS OF INTRINSIC AXIAL MUSCULAR HYPERTONICITY IN AS

A novel physiopathogenetic theory of AS was proposed[11] that may help to explain the varied manifestations and severity observed in AS more parsimoniously than the suggested mechanism of separate severity genes[1,8,21]. Persistently increased axial muscular hypertonicity is hypothesized to contribute to various spinal, hip, and peripheral enthesopathy and arthropathy manifestations of AS. Such constitutional diathesis may also contribute to increased physical (i.e., muscular) energy expenditures, which are suspected to significantly lower blood lipid levels of manual workers with AS versus control diagnoses, i.e., lower serum total cholesterol[22] and triglycerides[23].

The biomechanisms of accelerated hip degeneration in AS are currently unknown. By virtue of increased tension of the spinal kinematic chain, increased pressure may result across hip joints and intraarticularly in AS and may compromise normal joint biomechanics[24]. Increased pressures or tensions may disturb the normal minor incongruencies of articular surfaces and synovial fluid pressure relationships as well as optimal low friction movements[24]. Furthermore, the less flexible and relatively rigid torso in AS (i.e., a decreased spinal spring action) could also transmit increased impacts to the lower extremities via the hips. Chronic microtrauma from increased impacts and transmitted tensional stresses may also contribute to the characteristic lower extremities' peripheral arthropathy and enthesopathy manifestations observed in SEA syndrome[10,12,13,16,17]. Recent high resolution, fat suppressed magnetic resonance imaging studies in spondyloarthropathy show evidences of subchondral osteitis and bone marrow edema at sacroiliac joints and enthesopathy sites[25]. Interpretation of such findings is complex and controversial[25,26], but may be more consistent with chronic microtrauma from increased impacting or tensional stressing mechanisms[26] than from synovial inflammatory and proliferative processes[25].

FUTURE CHALLENGES OF DOCUMENTING OUTCOME RELATIONSHIPS IN AS

Further research is needed to determine if axial muscular hypertonicity does occur in AS[11]. If so, young patients with

Table 1. Proposed ankylosing spondylitis age of onset questionnaire.

Interview/Chart Review Questionnaire (II) for Primary AS Onset Age Data

Patient's name: _____ Residence, specify: _____
(Last, First, Middle) (City, State or Region)

Patient's age at interview or review: _____ Years Date of Birth: ___ ___ ___
Day Month Year

Date of interview or chart abstract: ___ ___ ___ Patient ID Number: _____
Day Month Year

Circle body type: thin muscular obese Circle social status: low middle high

	Questions Related to Diagnosis and Onset of Ankylosing Spondylitis (AS):	**Yes**	**No**	**Unk**
1.	Was the diagnosis of ankylosing spondylitis (AS) made by a physician?			
2.	Was the diagnosis of ankylosing spondylitis confirmed by x-ray?			
3.	Specify the type of first symptom believed to be related to onset of AS: (e.g., back or peripheral joint pain, etc.): _____			
4.	At what age did the first symptoms of the back (spine) occur? _____ years. Was this the first symptom related to ankylosing spondylitis?			
5.	Did the patient ever have peripheral joint or tendon inflammation or pain? If yes, was this the very first symptom related to ankylosing spondylitis? At what age did peripheral joint/tendon symptoms first start? _____ years. Which peripheral joint/tendon was first involved? Specify: _____			
6.	Did the patient ever have acute anterior uveitis (irido-cyclitis)? If yes, was this the very first symptom related to ankylosing spondylitis? At what age did acute anterior uveitis start? _____ years.			
7.	Did the patient ever have inflammatory bowel disease (IBD)? If yes, was this the very first symptom related to ankylosing spondylitis? At what age did inflammatory bowel disease first start? _____ years.			
8.	Did the patient ever have psoriasis? If yes, was this the very first symptom related to ankylosing spondylitis? At what age did psoriasis first start? _____ years.			
9.	In summary, specify onset age of first symptom related to AS: ____ years.			
10.	What month and year was the diagnosis of AS first made by a physician? Month (if known) _____, year _____			
11.	At what age was the diagnosis of AS first made? _____ years.			
12.	Does another family member have ankylosing spondylitis? If yes, specify the relationship of all affected members: _____ _____ (Use back, if needed.)			
13.	Specify if the patient is HLA-B27 positive. If yes, what was the subtype (if known)? _____ subtype			
14.	Specify the race or ethnic origin: _____, _____, _____ (patient) (mother) (father)			
	For adult women only:			
15.	Did the AS start during a pregnancy?			
16.	Did the AS start within 6 months after childbirth or miscarriage? If 15. or 16. is yes, specify the pregnancy number (1st, 2nd, etc.): _____			

AS presenting with early hip disease[1-5] may have greater alterations of their axial biomechanical dynamics than their counterparts with initial peripheral manifestations, and greater likelihood of more progressive disease. Increased peripheral joint impacting in SEA syndromes may contribute more to such lower extremity manifestations than the direct consequences of axial muscular hypertonicity, which more likely affects hip and spinal biomechanics.

Hip involvement starting at older ages, particularly if occurring in association with more advanced spinal manifestations, may be a consequence of intrinsically more progressive disease than a predictive marker of severity *per se*. Whether early or late hip involvement is a phenotypic marker of severity genes[1,8,21] or a result of altered axial biomechanics in AS[11] remains to be determined.

Critical analyses of these newly reported findings[1], particularly when focused upon the varied presentation patterns in juvenile onset AS, promise to provide valuable basic knowledge on the physiopathogenesis and course of AS. Further accurate and discriminating data will be needed to support the challenging proposals that the course and outcome of AS are affected by "three clearly distinct independent factors: the environment and both susceptibility and severity genes"[1].

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REFERENCES

1. Brophy S, Calin A. Ankylosing spondylitis: Interaction between genes, joints, age at onset and disease expression. J Rheumatol 2001;28:2283-8.
2. Marks SH, Barnett M, Calin A. A case-control study of juvenile- and adult-onset ankylosing spondylitis. J Rheumatol 1982; 9:739-41.
3. Calin A, Elswood J. The natural history of juvenile-onset ankylosing spondylitis: a 24-year retrospective case-control study. Br J Rheumatol 1988;27:91-3.
4. Amor B, Santos RS, Nahal R, Listrat V, Dougados M. Predictive factors for the longterm outcome of spondyloarthropathies. J Rheumatol 1994;21:1883-7.
5. Claudepiere P, Gueguen A, Ladjouze A, et al. Predictive factors of spondyloarthropathy in North Africa. Br J Rheumatol 1995;34:1139-45.
6. Calin A, Brophy S, Blake D. Impact of sex on inheritance of ankylosing spondylitis: a cohort study. Lancet 1999;354:1687-90.
7. Schaller JG. Ankylosing spondylitis of childhood onset. Arthritis Rheum 1977;20 Suppl:398-401.
8. Hamersma J, Cardon LR, Bradbury L, et al. Is disease severity in ankylosing spondylitis genetically determined? Arthritis Rheum 2001;44:1396-400.
9. Masi AT. Hormonal and immunologic risk factors for the development of rheumatoid arthritis: an integrative physiopathogenetic perspective. Rheum Dis Clin N Am 2000;26:775-803.
10. Burgos-Vargas R, Naranjo A, Castillo J, Katona G. Ankylosing spondylitis in the Mexican Mestizo: patterns of disease according to age at onset. J Rheumatol 1989;16:186-91.
11. Masi AT. Do sex hormones play a role in ankylosing spondylitis? Rheum Dis Clin N Am 1992;18:153-76.
12. Burgos-Vargas R, Vázquez-Mellado J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. Arthritis Rheum 1995;38:835-44.
13. Burgos-Vargas R, Pacheco-Tena C, Vázquez-Mellado J. Juvenile-onset spondyloarthropathies. Rheum Dis Clin North Am 1997;23:569-98.
14. Khan MA, van der Linden SM, Kushner I, Valkenburg HA, Cats A. Spondylitic disease without radiologic evidence of sacroiliitis in relatives of HLA-B27 positive ankylosing spondylitis patients. Arthritis Rheum 1985;28:40-3.
15. Calin A, Elswood J. The relationship between pelvic, spinal and hip involvement in ankylosing spondylitis — one disease process or several? Br J Rheumatol 1988;27:393-5.
16. Burgos-Vargas R, Clark P. Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progression to ankylosing spondylitis. J Rheumatol 1989;16:192-7.
17. Cabral DA, Oen KG, Petty RE. SEA syndrome revisited: a longterm followup of children with a syndrome of seronegative enthesopathy and arthropathy. J Rheumatol 1992;19:1282-5.
18. Burgos-Vargas R, Vázquez-Mellado J, Cassis N, et al. Genuine ankylosing spondylitis in children: A case control study of patients with early definite disease according to adult onset criteria. J Rheumatol 1996;23:2140-7.
19. van der Heijde D, Bellamy N, Calin A, Dougados M, Khan MA, van der Linden S. Preliminary core sets for endpoints in ankylosing spondylitis. Assessments in Ankylosing Spondylitis Working Group. J Rheumatol 1997;24:2225-9.
20. Masi AT, Wilkins WR, Dong CH, et al. Mathematical modeling of primary ankylosing spondylitis onset age (PASOA) data: utility in critical analyses of patient series [abstract]. Arthritis Rheum 1997;40 Suppl:S214.
21. Brophy S, Hamersma J, Bradbury L, et al. Towards defining the genetic determinants of disease severity in ankylosing spondylitis. Rheumatology 2001;40:17.
22. Masi AT, Aldag JC, Mohan PC, Murugan TSR. Determinants of significantly lower serum total cholesterol levels in ankylosing spondylitis patients (PTS) than age-, gender-, and medical service-matched control PTS: results of multivariate analyses [abstract]. Arthritis Rheum 1999;42 Suppl:S300.
23. Masi AT, Aldag JC, Mohan PC, Murugan TSR. Significantly lower serum triglyceride levels in ankylosing spondylitis patients than age-, gender-, and medical service-matched controls: results of multivariate analyses [abstract]. Arthritis Rheum 2000;43 Suppl:S104.
24. Mankin HJ, Radin EL. Structure and function of joints. In: WJ Koopman, editor. Arthritis and allied conditions: A textbook of rheumatology. 13th ed. Baltimore: Williams & Wilkins; 1997:175-91.
25. Maksymowych WP. Ankylosing spondylitis — At the interface of bone and cartilage. J Rheumatol 2000;27:2295-301.
26. McGonagle D, Emery P. Enthesitis, osteitis, microbes, biomechanics, and immune reactivity in ankylosing spondylitis. J Rheumatol 2000;27:2302-4.