Ankylosing Spondylitis: Interaction Between Genes, Joints, Age at Onset, and Disease Expression

SINÉAD BROPHY and ANDREI CALIN

ABSTRACT. ***Objective.*** Ankylosing spondylitis (AS) is a chronic inflammatory disorder with symptom onset generally occurring in the late teens/mid-twenties. In women, a younger age at onset enhances disease susceptibility in the next generation. We examined the influence of age at symptom onset on phenotypic expression.

Methods. Patients were divided into cohorts according to age of symptom onset. The primary outcome measure was radiological progression (by Bath AS Radiology Index, BASRI). Secondary measures were disease activity (Bath AS Disease Activity Index, BASDAI), function (Bath AS Functional Index, BASFI), numbers undergoing AS related surgery, and percentage with secondary disorders.

Results. Age at onset had no significant effect on radiological progression (young onset vs late onset, 8.0, 8.6, respectively) disease activity (young vs late, 4.4, 4.4), need for non-hip surgical intervention (9%, 8%, respectively), or prevalence of secondary disorders (iritis, 40%, 41%; psoriasis, 20%, 19%; inflammatory bowel disease, 7.5%, 8.9%). By contrast, there was a striking increase in prevalence of total hip replacement in those with juvenile onset (18%, 8%, respectively; $p < 0.001$). Regardless of age at onset, spinal progression determined radiologically was greater in those with hip arthritis compared to those without [young onset hip involvement vs non-hip involvement, 9.7 (2.4), 7.2 (3.0) ($p < 0.001$); late onset hip involvement vs non-hip involvement, 10.1 (2.5), 7.1 (3.0), respectively]. Function deteriorates with age (young onset vs late onset, 3.7, 4.5, respectively; $p < 0.01$).

Conclusion. (1) Hip disease (young or late onset) is a major prognostic marker for longterm severe disease (patients with hip disease have a spinal score increased by 2.5–3 points or 35–40% more change). (2) Hip involvement is more prevalent among patients with young age at onset. (3) Young onset patients without hip involvement do not have more severe disease. Thus, age at onset, itself, does not influence disease severity. (4) Since hip involvement and not age at onset is associated with worse outcome, patients with a young age at onset may be assumed to have an increased susceptibility load (i.e., genetic component or environmental trigger) rather than more severity genes. The lack of association between severity and age at onset implies that the determinants of susceptibility and severity are independent. (J Rheumatol 2001;28:2283–8)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SYMPTOM ONSET SEVERITY OUTCOME

Ankylosing spondylitis (AS) is a chronic inflammatory disorder with symptom onset generally occurring in the late teens/mid-twenties. Juvenile age at symptom onset (< 16 yrs) has been found to correlate with increased disease severity[1-3]. In addition, hip involvement (and need for total hip replacement) is more often seen in those with juvenile onset[3,4], and hip involvement itself is a marker for more severe axial involvement[2,5]. However, late onset (after age 55 yrs) has also been reported to affect the clinical pattern of disease. Such patients are said to have more cervical pain, anterior chest wall involvement, aseptic osteitis[6], and shoulder involvement[7]. It can be assumed that the expression of AS results from a combination of severity and susceptibility genes. In women, a younger age at onset enhances disease penetrance in the next generation[8]. Thus patients with a younger age at onset may have an increased number of susceptibility factors and perhaps a different disease expression from those with late onset. Late onset individuals may carry fewer susceptibility and a different array of severity genes.

We examined the influence of age at symptom onset on disease expression as measured by radiological change (by Bath AS Radiology Index, BASRI)[9], disease activity (Bath AS Disease Activity Index, BASDAI)[10], function (Bath AS Functional Index, BASFI)[11], percentage undergoing AS related surgery, and prevalence of secondary disorders [iritis, psoriasis, inflammatory bowel disease (IBD)].

MATERIALS AND METHODS

The Bath Ankylosing Spondylitis Database consists of 4741 patients (2.5:1, M:F). All were outpatients of the Royal National Hospital for Rheumatic Diseases (n = 851) or were members of the National Ankylosing Spondylitis

From the Epidemiology Department, Royal National Hospital for Rheumatic Diseases (RNHRD), Upper Borough Walls, Bath, UK.

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S. Brophy, BSc, Research Assistant; A. Calin, MD, FRCP, Consultant Rheumatologist.

Address reprint requests to Dr. A. Calin, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath BA1 1RL, UK. E-mail: andrei.calin@virgin.net

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Society. Patients referred to the RNHRD had their diagnosis confirmed according to the New York Criteria. NASS members are those who have received a positive diagnosis of AS from a specialist rheumatologist as a result of a radiograph. To validate the diagnosis in those patients recruited through NASS, 146 consecutive subjects were invited to attend an assessment clinic, and all 146 were confirmed as having AS according to the same criteria. In addition, for 240 patients a confirmation was sought from the general practitioner, and confirmed in 229 cases (95.4%) (i.e., AS with radiological evidence of sacroiliitis). We contacted the GPs of 120 psoriasis-AS patients and 139 IBD-AS patients. Of these, 77 (64%) and 112 (81%) replied, confirming the diagnosis of psoriasis in 65 (84%) and IBD in 108 (96%) cases.

Independent samples of patients were divided into cohorts according to age of symptom onset and were controlled for age now and disease duration now (McNemar chi-square). In addition, cohorts of juvenile onset (< 16 yrs), teen onset (17–20 yrs), twenties (21–29 yrs), thirties (30–39), and late onset (40+ yrs) were compared. The primary outcome measure was radiological status, determined by BASRI. Secondary measures were disease activity (BASDAI), function (BASFI), numbers undergoing surgery, and percentage with secondary disorders.

RESULTS

Radiological progression (sacroiliac joints, hips, lumbar spine, cervical spine); BASRI. Age at onset had no significant effect on radiological progression (Table 1, Figure 1]. Radiological change was a factor of disease duration, i.e., those with a young age at onset had more severe disease compared to like-aged late onset patients (young onset vs late onset, 10.0, 8.0, respectively; p = 0.02). However, disease duration-matched pairs were comparable for radiological change (young onset vs late onset, 8.0, 8.6). Patients with hip disease and young onset had comparable spinal disease to those with hip disease and a late onset (Table 1) [young vs late, 9.0, 10.8; p = 0.04 (corrected value not significant)]. Hip disease patients had more spinal change than non-hip patients (Table 2) [young onset — hip disease vs non-hip disease, 9.7, 7.2, respectively (p = 0.0001); late onset — hip disease vs non-hip disease, 10.13, 7.1 (p = 0.0001)].

Secondary outcome measures. Age at onset had no significant effect on disease activity, function, prevalence of secondary disorders, or need for surgery (Tables 3, 4). At comparable age (i.e., age now, Table 3), those with longer disease duration (i.e., young onset) have lower disease activity (young onset vs late onset, 4.0, 4.3, respectively; p < 0.02), more iritis (young onset vs late onset, 50%, 40%; p < 0.01), and more surgical intervention (14%, 7%, respectively; p < 0.01). However,

Table 2. Radiological hip disease vs non-hip disease patients: spinal severity score and age at onset of AS.

	Hip Disease	Non-Hip Disease	p†
Young onset	n = 81	n = 148	
Disease duration, yrs	22.1	22.7	
Mean (SD)	9.7 (2.43)	7.2 (3.0)	< 0.001
Late onset	n = 19	n = 64	
Disease duration, yrs	15.2	14.1	
Means (SD)	10.13 (2.5)	< 0.001	

† Corrected.

Table 3. Influence of age at onset on outcome — age now and sex matched.

	Age of Onset 0–21 (young onset)	Age of Onset 30+ (late onset)	p†
BASDAI			
Whole group (n = 784)	4.0	4.3	< 0.02
Men (n = 543 pairs)	3.7	4.2	< 0.01
Women (n = 241 pairs)	4.5	4.4	NS
BASFI			
Whole group (n = 829)	4.4	4.3	NS
Men (n = 574 pairs)	4.3	4.3	NS
Women (n = 255 pairs)	4.8	4.3	0.03
Secondary disorders			
Iritis (n = 829 pairs)	50%	40%	< 0.01
Psoriasis (n = 807)	20%	20%	NS
IBD (n = 828)	7.5%	7.6%	NS
Surgery			
Total surgery, n = 991	140 (14%)	67 (7%)	< 0.01

† Corrected. IBD: inflammatory bowel disease.

Table 1. Young onset compared to late onset in terms of radiological progression (i.e., total = SI joint, lumbar spine, cervical spine, and hips; spinal = SI joint, lumbar spine, and cervical spine).

	Age of Onset 0–21 (young onset)	Age of Onset 30+ (late onset)	p†
Age now (& sex) matched, n = 56 pairs			
BASRI-total* (scale 2–16)	10.0	8.0	0.02 (NS)
BASRI-spine** (scale 2–12)	8.7	7.6	0.02 (NS)
With hip involvement (n = 19, 10)	9.7	10.0	NS
Without hip involvement (n = 37, 46)	8.2	7.1	NS
Disease duration (& sex) matched, n = 68 pairs			
BASRI-total*	8.0	8.6	NS
BASRI-spine**	7.1	8.1	NS
With hip involvement (n = 21, 13)	9.0	10.8	0.04 (NS)
Without hip involvement (n = 47, 55)	6.3	7.5	0.06 (NS)

† Corrected. * Including hips, ** without hips.

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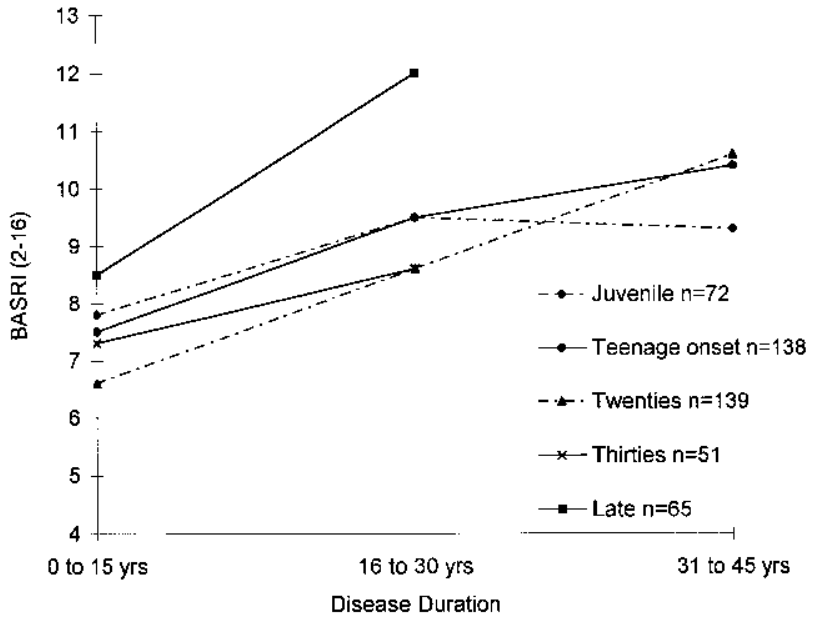

Figure 1. Cohorts of juvenile onset (< 16 yrs), young/teenage onset (17–20 yrs), twenties (21–29 yrs), thirties (30–39 yrs), and late onset (40+ yrs) compared for radiologic change (BASRI). Age at onset has no significant effect on radiological progression. Late onset patients may have asymptomatic radiological changes initially, thus time from first symptoms may be inaccurate.

when matched for disease duration (Table 4), the disease activity (young onset vs late onset, 4.4, 4.4), prevalence of secondary conditions, and need for surgery (9%, 8%) were all comparable for those with young age at onset vs late age onset. When matched for disease duration the function was worse for the delayed onset males (i.e., older aged men) — young onset vs late onset, 3.6, 4.5, respectively ($p < 0.01$). However, at equivalent ages (Table 3) the function was comparable regardless of disease duration (i.e., between young age at onset and delayed onset individuals). Cohorts of juvenile onset (< 16 yrs), young onset (17–20 yrs), twenties (21–29 yrs), thirties (30–39), and late onset (40+ yrs) were comparable for disease activity (Figure 2), function (Figure 3), and surgery (Figure 4).

DISCUSSION

Our data examine young onset compared to late onset AS and were not intended to analyze juvenile AS as a separate entity. However, Figures 1–5 illustrate that findings in young onset patients are applicable to patients with juvenile AS. The data suggest that age at first-symptom onset has no effect on disease severity. However, this must be seen in the context that

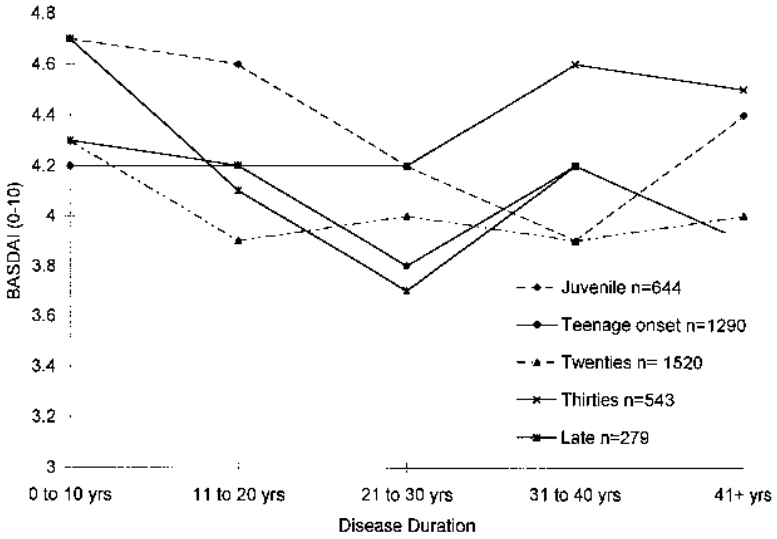

Figure 2. Cohorts by age compared for disease activity (BASDAI). Age at onset had no significant effect on radiological progression.

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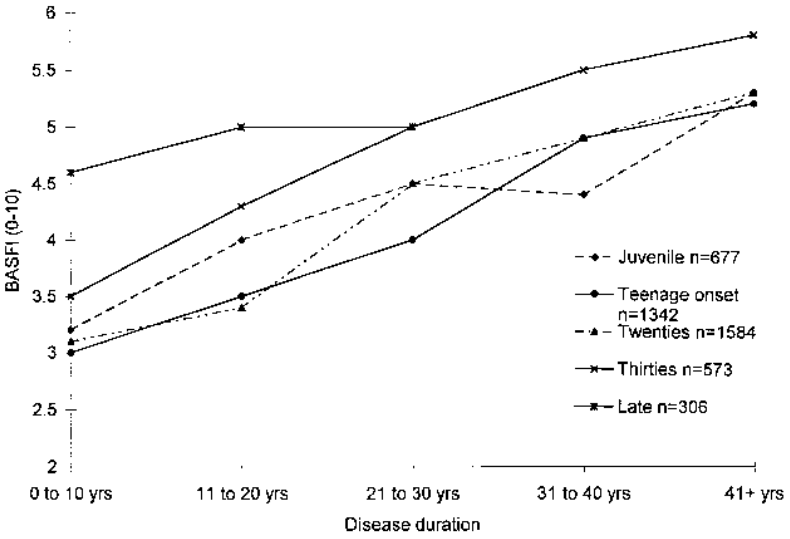

Figure 3. Cohorts by age compared for function (BASFI). Age at onset had no significant effect on function. Older patients (i.e., thirties onset and late onset) have poorer functional score.

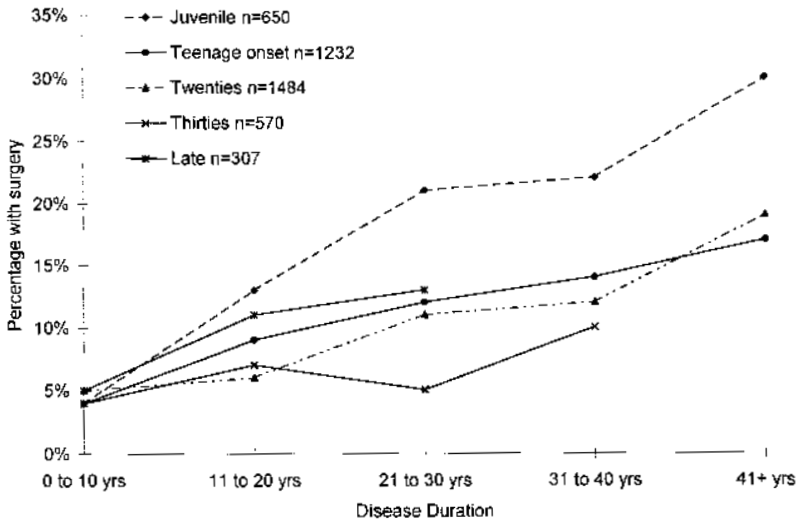

Figure 4. Cohorts by age compared for need for surgery. Age at onset had no significant effect on surgery. Juvenile patients had a trend to more surgery, perhaps due to hip replacements in the cohort with hip disease.

hip disease is more prevalent among patients with juvenile onset (total hip replacement rates, juvenile 18% vs non-juvenile 8%; $p < 0.001$; Figure 5), and this phenomenon is known to be a predictor of more severe spondylitis[2,5]. This paradox [i.e., (1) there is a link between age at onset and hip disease; (2) hip disease is linked to increased severity; but (3) there is no link between age at onset and increased severity] may be explained on the basis that only a subgroup of young onset patients develop hip disease and only this cohort is at risk of more severe spondylitis. [In our study 21/68 (31%) of the young onset and 13/68 (19%) of the late onset patients had hip involvement as assessed by a radiograph, and total hip replacement occurred in 9% and 4%, respectively.]

It is possible that the young developing hip may be more at risk of becoming affected than the adult hip. Thus, patients with young onset are more at risk of hip involvement (because of the juvenile hip). However, patients with hip disease and a young onset do not have more severe disease than subjects with late onset and hip disease (Figure 6). Hip involvement *per se* appears to be the relevant factor contributing to outcome.

The trigger for AS is thought to be a ubiquitous bacterium[12]. If this is so, then the age of onset of disease should be related to the genetic susceptibility load. Yet this enhanced genetic susceptibility in young onset patients does not influence outcome, implying that the contributing genes for sus-

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Table 4. Influence of age at onset on outcome — disease duration and sex matched.

	Age of Onset 0–21 (young onset)	Age of Onset 30+ (late onset)	p†
BASDAI			
Whole group (n = 784)	4.4	4.4	NS
Men (n = 543 pairs)	4.2	4.1	NS
Women (n = 241)	4.6	4.5	NS
BASFI			
Whole group (n = 762)	3.7	4.5	< 0.01
Men (n = 546 pairs)	3.6	4.5	< 0.01
Women (n = 216)	4.1	4.5	NS
Secondary disorders			
Iritis (n = 788 pairs)*	280 (35.5%)	283 (36%)	NS
Psoriasis (n = 777 pairs)**	110 (14.2%)	120 (15.4%)	NS
IBD (n = 810 pairs)***	61 (7.5%)	72 (8.9%)	NS
Surgery			
Total surgery, n = 924	86 (9%)	71 (8%)	NS

† Corrected. * Average age of onset of AS symptoms in iritis vs non-iritis patients: 26.7 vs 26.9 yrs (NS). ** Average age of onset of AS symptoms in psoriasis vs non-psoriasis patients: 27.7 vs 26.9 yrs (NS). *** Average age of onset of AS symptoms in IBD vs non-IBD patients: 28.1 vs 27.0 yrs (NS). IBD: inflammatory bowel disease.

ceptibility and severity are independent of one another. If, by contrast, the age of onset of a patient is governed by the timing of contact with an environmental trigger, the age when this happens appears to have no influence on later disease development. Separate and unrelated severity factors must influence disease progression. This hypothesis is supported by early findings identifying from a genome screen at least one area of significant linkage between severity and genetic factors[13]. In conclusion, there are 3 clearly distinct independent factors: the environment and both susceptibility and severity genes.

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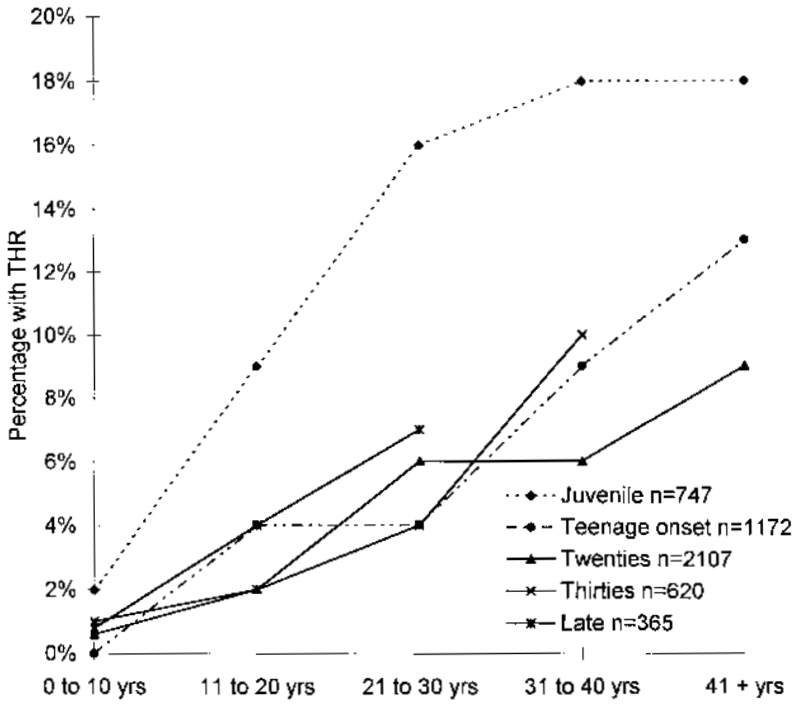

Figure 5. Cohorts by age compared for need for surgery. Age at onset had no significant effect on surgery. Juvenile patients had more hip replacement surgery ($p < 0.001$) than the other age at onset cohorts.

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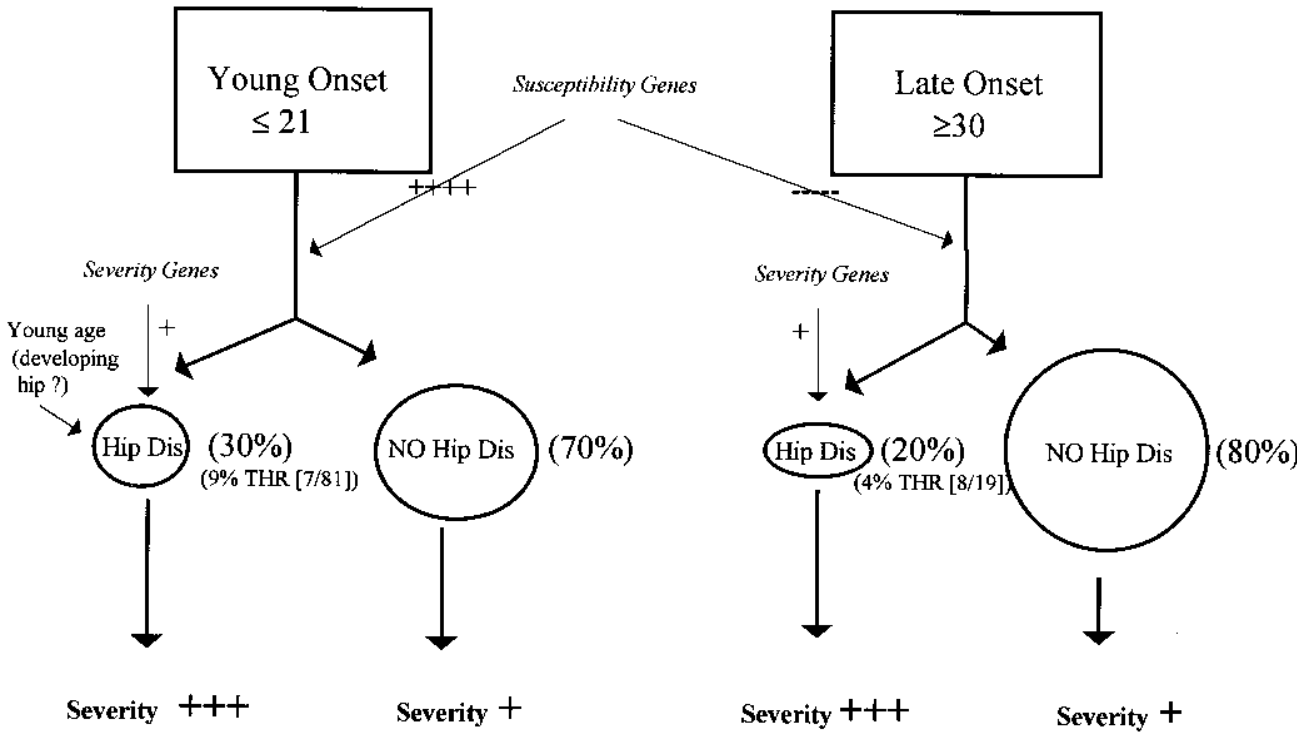

Figure 6. Hip disease and not age of onset affects severity.

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