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Chronic back pain in first-degree relatives (FDRs) of patients with ankylosing spondylitis: predictive value of HLA-B27 and persistence of inflammatory back pain over time

Karim Doughem,[1] Michael H Weisman,[2] Michael M Ward,[3] Lianne S Gensler,[4] Mariko Ishimori,[5] Amirali Tahanan,[6] David C Kung,[7] Laura Diekman,[1] MinJae Lee,[8] Mohammad Hossein Rahbar,[6] John D Reveille[1]

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For numbered affiliations see end of article.

Correspondence to
John D Reveille;
John.D.Reveille@uth.tmc.edu

ABSTRACT

Background/Purpose First-degree relatives (FDRs) of patients with ankylosing spondylitis (AS) may be at high risk of spondyloarthritis. We examined the frequency, characteristics of chronic back pain (CBP), associated features, persistence of symptoms, and HLA-B27 allele frequency in FDRs of AS patients, also comparing those FDRs with participants in NHANES 2009–2010 with CBP.

Methods 399 FDRs of AS probands were divided into: (1) No CBP (subjects >40 years old at study visit without CBP) (n=162); (2) NICBP (non-inflammatory CBP) (n=82), and (3) CIBP (inflammatory CBP) (n=155). White FDRs with CBP were compared with 772 participants in NHANES 2009–2010 with CBP. FDRs were invited to return for reassessment.

Results FDRs with CIBP had earlier onset of CBP than those with NICBP (p<0.001) and had higher frequency of heel pain than those without CBP (p=0.002). HLA-B27 occurred in 57% of FDRs with CIBP vs 39.6% of those without CBP (p=0.005, OR=1.9). Of 23 patients with CIBP at baseline re-evaluated 67.04±31.02 months later, 16 (73%) still had CIBP, whereas 4 (31%) of 13 NICBP patients seen 61.23±31.84 months later remained symptomatic.

Conclusion CIBP in FDRs of AS patients is HLA-B27-associated, has earlier onset and tends to persist compared to NICBP.

Key messages

What is already known about this subject?

- Relatives who did not show radiologic abnormalities of the sacroiliac joints or the spine but had symptoms of chronic inflammatory back pain were more likely to be B27 positive compared to asymptomatic.
- Although HLA-B27 is more prevalent in familial than sporadic cases of AS, previous data did not show that the frequency of other non-major histocompatibility complex susceptibility loci is different between sporadic and familial cases of AS.

What does this study add?

- The study demonstrated that FDRs of AS patients with chronic inflammatory back pain have a younger age at onset, a higher frequency of heel pain compared to those FDRs who do not develop CBP and to the general US population.
- HLA-B27 was more frequently encountered in those with chronic inflammatory back pain compared to those without chronic back pain, and a similar, although nonsignificant trend was seen comparing those with chronic inflammatory back pain to those with noninflammatory chronic back pain.
- Chronic inflammatory back pain in FDRs of AS patients is a stable phenotype that persists over time in most FDRs.

How might this impact on clinical practice or future developments?

- Chronic inflammatory back pain in FDRs of AS patients appears to have a genetic basis, and is likely to be a part of the spectrum of SpA and to persist over time in most, creating a possible need for further longitudinal studies of FDRs for long-term diagnostic and treatment approaches in this group.

INTRODUCTION

Nearly everyone will experience low-back pain (LBP) at some point in their lives.[1] LBP is the second leading cause of disability among adults in USA[2] accounting for 149 million days of work lost and costing 100–200 billion dollars annually.[3] Inflammatory back pain (IBP) was first described as a clinical entity by Calin *et al*,[4] revised in the European Spondyloarthropathy Study Group (ESSG) criteria

for spondyloarthritis (SpA) in 1991,[5] further by Rudwaleit *et al* in 2006[6] and finally as part of the Assessments in Spondyloarthritis International Society Classification Criteria for Axial Spondyloarthritis in 2009.[7]

Given that ankylosing spondylitis (AS) is highly heritable,first-degree relatives (FDRs) of AS patients may represent a group at high risk of disease, particularly in HLA-B27 positive FDRs.[8 9] HLA-B27 is more prevalent in familial than sporadic AS. The frequency of other non-major histocompatibility complex susceptibility loci is not markedly different between sporadic and familial AS.[10]

This study aims to examine clinical features of SpA, HLA-B27 allele and persistence of back pain in FDRs of AS patients with chronic IBP (CIBP), non-inflammatory chronic back pain (NICBP) and no chronic back pain (CBP) as well as to compare clinical features of SpA in FDRs of AS patients with CBP with participants in the National Health and Nutrition Examination Survey (NHANES) 2009–2010 with CBP.[11 12]

METHODS

Patients

FDRs of AS patients enrolled in the Prospective Study of Outcomes in AS (PSOAS) study and the North American Spondylitis Consortium (NASC) study were invited to participate in an examination of SpA features and were administered a questionnaire modified from 2009 to 2010 NHANES study.[11 12] More than half underwent clinical and radiographic evaluation by a study rheumatologist and the rest administered the questionnaire by interview. The research followed the Helsinki Declaration; each institution had the study approved by their respective institutional review boards, and each participant signed an informed consent.

FDRs were assessed for the presence of CBP. Those who experienced CBP were classified into CIBP (n=155) vs NICBP (n=82) based on Berlin criteria (2006).[11] The third group included 162 FDRs with no CBP and were >40 years of age. FDRs younger than 40 years of age with no CBP were excluded as they may have not yet experienced LBP. Consanguineous relatives within the same group (CIBP, NCIBP, noCBP) were excluded.

FDRs of AS patients in all groups were studied for associated clinical features (including age at onset of back pain, presence of heel pain, presence of acute anterior uveitis, psoriasis, ulcerative colitis, Crohn's disease, effect of pain on sleeping pattern, and the effect of NSAIDs and exercise on the pattern of pain). HLA-B allele typing of FDRs of AS patients was carried out by single-stranded conformation polymorphism analysis of genomic DNA obtained from peripheral blood leukocytes. FDRs previously examined were invited to return for a second visit for repeat clinical evaluation to assess for the persistence of CBP, including some who had been seen much earlier in the study (2006–2011). An arbitrary decision was made to wait until at least two years before scheduling a second visit.

Given that FDRs of AS patients represent a potential spectrum of SpA, we were interested in comparing the frequency, associated clinical features of CBP in FDRs as compared to the general population with CBP. To do that, we compared FDRs of AS patients with CBP aged 20–69 years with 772 white subjects with CBP participating in NHANES 2009–2010, to whom the same questionnaire was administered. Only white subjects were included in this analysis given the scarcity of other ethnic groups in the FDRs examined.

Statistical analysis

Univariable pairwise comparisons were conducted using linear regression for continuous variables (ie, age) and logistic regression for categorical variables to assess the differences in demographic and clinical factors among CBP groups (CIBP, NICBP and no CBP). Nine hundred 78 subjects, including 206 unrelated FDRs of non-Hispanic white PSOAS and NASC AS probands with CBP between 20 and 69 years of age and 772 participants in the 2009–2010 NHANES study were included in the univariable and multivariable logistic regression analyses comparing demographic and clinical factors. Demographic characteristics such as age and gender were adjusted to control confounding effect in multivariable logistic regression models. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) at a statistical significance level of 0.05.

RESULTS

In all, 546 FDRs of AS patients participated in this evaluation, of which 399 were divided into three groups after excluding FDRs with an AS or axial SpA diagnosis at baseline visit. The group without CBP included 162 FDRs who never experienced CBP and were at least 40 years of age (FDRs younger than 40 years were excluded from this group, and CIBP is classically expected to have commenced by age 40 years.[4]) FDRs who could not recall their age of onset of CBP were not included.

FDRs of AS patients who exhibited CIBP (N=155) had earlier onset of CBP than FDRs with NICBP (N=82) (table 1). They were also more likely to be male, in comparison to those with NICBP, and a nonsignificant trend was seen comparing those with CIBP with those without. Overall, those with CBP were more likely to be white than those without CBP (84.6%-p=0.01 overall). HLA-B27 was more frequent in those with CIBP (56.8%) compared to those without CBP, and a similar, although nonsignificant trend was seen comparing those with CIBP to those with NICBP.

FDRs with CIBP reported heel pain more frequently compared to those without CBP. Again, a similar, although nonsignificant trend was seen comparing those with CIBP to those with NICBP. Other features associated with SpA (psoriasis, uveitis, Crohn's disease,

Table 1 Clinical and sociodemographic factors in FDRs with CIBP, NICBP and those without CBP

Variable	ALL	No CBP N=162 (40.6%)	NICBP n=82 (20.55%)	CIBP n=155 (38.85%)	*P-value (overall)	NICBP vs no CBP	CIBP vs no CBP	CIBP vs NICBP
Age at study entry, mean (SD) years	54.1 (16.1)	60.7 (11.5)	54.3 (17.2)	47.2 (16.8)	<0.001	<0.01	<0.001	<0.001
Age at Onset of CBP, mean (SD), years	N/A	N/A	40.1 (19.1)	26.2 (11.3)	<0.001	N/A	N/A	<0.001
Male, %	40.6	38.3	32.9	47.1	0.08	0.41	0.11	0.04
B27+, %	47.9	38.9	48.8	56.8	0.01	0.14	0.005	0.24
Heel pain, %	29.4	21.9	27.9	38.2	0.01	0.31	0.002	0.12
Iritis or uveitis, %	4.58	3.38	3.95	6.12	0.52	0.83	0.27	0.50
Crohn's disease, %	0.76	0	0	1.96	0.16	N/A	0.11	0.55
Ulcerative colitis, %	1.28	0	2.50	1.96	0.10	0.11	0.12	1.00
Psoriasis in skin or nail, %	8.72	8.23	5.00	11.2	0.29	0.37	0.38	0.13
Non-Hispanic White, %	90.0	84.6	95.1	92.9	0.01	0.02	0.02	0.50

*p-values based on Fisher exact tests due to zero cells.
All p-values based on linear regressions for continuous variable, logistic regressions for categorical variables *except* Crohn's disease and Ulcerative colitis.

ulcerative colitis) did not show statistically significant variations between the CIBP vs the NICBP groups.

Comparing 206 unrelated white FDRs with 772 white participants in NHANES 2009–2010 with CBP, there were no significant differences in features of IBP (where there might have been two FDRs from the same family included in table 1, one in the CIBP and one in the CIBP group, only the eldest FDR was included in this analysis). In fact, some features (AM stiffness, pain improving as the day progresses, awakening the second half of the night) were less common in FDRs with CBP compared with the general population (table 2). However, other features of SpA (earlier age at CBP onset, uveitis, psoriasis) were more frequent in FDRs of AS patients. These findings from univariable models remained very similar after adjusting for age and gender in multivariable models.

Of 23 patients with CIBP at baseline seen again 67.04 ±31.02 months later, 16 (73%) still had CIBP, whereas only four of 13 NICBP patients (31%) seen 61.23 ±31.84 months later were still symptomatic (p=0.038, OR =5.1 [C.I. 1.2, 22.5]). Of the remaining nine with NICBP, three (23%) developed CIBP and six (46%) had symptoms resolve. Of the 13 without CBP at baseline seen 75.5±29.9 months later, 11(85%) remained asymptomatic (p=0.0045, OR =12.6 [C.I. 2.2, 72.3]), two (15%) developed CIBP and none developed NICBP (15.4% vs 69.7% of those with CIBP at baseline, p=0.0045, OR =12.6 [C.I. 2.2, 72.3]).

DISCUSSION

The study demonstrated that FDRs of AS patients with CIBP have a younger age at onset, a higher frequency of heel pain, and higher frequency of HLA-B27 than those FDRs who do not develop CBP and a younger age of onset and higher frequencies of heel pain, iritis and psoriasis compared to the general US population with CBP (though other features of CIBP were not more frequently seen).

In the NHANES 2009–2010 study, one-third of population with CBP had CIBP.[11] One-quarter of CIBP patients in NHANES 2009–2010 met ESSG classification criteria for axial SpA.[12]

Few studies have investigated FDRs of AS patients. One study of two cohorts of families of HLA-B27 positive probands with AS found relatives who did not show radiologic abnormalities of the sacroiliac joints or the spine but had symptoms of CIBP were more likely to be B27-positive compared to asymptomatic relatives.[8] Another study involving 51 FDRs of HLA-B27 positive AS probands found that several FDRs exhibited clinical and/or radiographic abnormalities suggestive of SpA, with one-third of the FDRs fulfiling either ESSG or ASAS criteria for SpA.[9]

Another concern, raised by the US Food and Drug Administration in its initial consideration of approving biologics for the treatment of AS in 2013, was whether the phenotype of AxSpA or CIBP remitted spontaneously.[13] Our data, despite that relatively few returned for a second visit, suggest that the CIBP phenotype is stable and does not remit over time.

Shortcomings of this study include not being able to compare HLA-B27 typing between AS FDRs and NHANES participants with CBP due to information classification in the latter. Also, our study included mainly Caucasian subjects. Since other ethnicities were underrepresented, the findings of this study may not be generalisable to all ethnicities. Finally, potential participation bias may have occurred in patients who came back later, since patients with persistent CBP are more likely to follow up as compared to those with remitted pain, although we do not believe there would have been any difference in participation among symptomatic patients in the three

Table 2 Clinical factors in FDRs of AS patient compared to the US population with chronic back pain

Variable	AS-FDR (N=206)%	NHANES (N=772)%	Unadjusted OR (95% CI)	*P	Adjusted OR (95% CI)	**p
Male	40.8	45.9	0.81 (0.60, 1.11)	0.19	0.82 (0.60, 1.12)	0.20
If you do not take any medicine when you wake up from sleep how long do or did you have stiffness				0.005		0.004
Less than 10 minutes	13.0	20.0	N/A		N/A	
10 to 30 minutes	20.8	21.2	N/A		N/A	
31 to 60 minutes	14.1	14.5	N/A		N/A	
More than 1 but less than 4 hours	16.2	15.3	N/A		N/A	
More than 4 hours	14.1	18.9	N/A		N/A	
Don't/didn't have morning stiffness	21.4	10.6	N/A		N/A	
If you do not take any medicine and not working or exercising what usually happens to the pain aching or stiffness over the course of the day?				<0.0001		<0.0001
Increases	22.5	26.8	Ref		Ref	
Decreases	19.4	22.7	1.02 (0.63, 1.65)		1.05 (0.64, 1.70)	
Stays the Same	21.9	40.0	0.66 (0.41, 1.04)		0.66 (0.42, 1.04)	
It varies, no pattern	36.2	10.6	4.09 (2.58, 6.47)		4.10 (2.59, 6.51)	
If you do not take any medicine does your pain aching or stiffness often wake you up after you have been sleeping for 4 or more hours?				<0.0001		<0.0001
No	39.2	15.2	Ref		Ref	
Yes	57.2	74.8	0.90 (0.20, 0.45)		0.29 (0.19, 0.45)	
I sleep less than 4 hours	3.61	10.03	0.14 (0.06, 0.34)		0.14 (0.06, 0.33)	
Does your pain aching or stiffness usually get better when you do either walking or stretching for a half hour?				0.59		0.49
No	27.4	30.6	Ref		Ref	
Yes	67.5	65.4	1.15 (0.81, 1.64)		1.2 (0.84, 1.72)	
Do not do these activities	5.08	4.00	1.42 (0.65, 3.09)		1.44 (0.66, 3.14)	
Does the pain aching or stiffness in your buttocks ever switch from one side to the other?	33.5	32.5	1.05 (0.69, 1.59)	0.82	1.04 (0.68, 1.59)	0.87
Besides injuries have you ever had pain that is in one of heel areas every day for at least two weeks?	35.5	19.6	2.26 (1.61, 3.18)	<0.0001	2.30 (1.63, 3.24)	<0.0001

Continued

Table 2 Continued

Variable	AS-FDR (N=206)%	NHANES (N=772)%	Unadjusted OR (95% CI)	*P	Adjusted OR (95% CI)	**p
Iritis or uveitis	4.59	0.65	7.35 (2.44, 22.2)	0.0004	7.22 (2.38, 21.89)	0.0005
Crohn's disease	0.50	0.39	1.28 (0.13, 12.39)	0.83	1.20 (0.12, 11.67)	0.88
Ulcerative colitis	2.51	1.04	2.46 (0.80, 7.61)	0.12	2.33 (0.75, 7.22)	0.14
Psoriasis in skin or nail	9.60	5.31	1.89 (1.07, 3.34)	0.03	1.89 (1.07, 3.34)	0.03
Age (in years; 20–69 only), mean (SD)	45.9 (13.9)	45.1 (13.6)	1.00 (0.99, 1.01)	0.49	1.00 (0.99, 1.01)	0.46
Age of first pain (in years), mean (SD)	29.0 (13.8)	32.7 (14.1)	1.01 (1.01, 1.03)	0.002	1.02 (1.01, 1.03)	0.002

*p-value based on univariable model (unadjusted).
**p-value based on multivariable model (adjusted for age and gender).

groups. Nevertheless, the majority of those recontacted with CIBP had the phenotype persist over time.

Thus, CIBP in FDRs of AS patients is associated with younger age onset and a higher frequency of SpA features such as heel pain, and CBP in FDRs of AS patients is associated with HLA-B27. CIBP in FDRs of AS patients appears to persist over time in most, creating a possible need for further longitudinal studies in this group for long-term diagnostic and treatment approaches.

Author affiliations
[1]Rheumatology, University of Texas McGovern Medical School, Houston, Texas, USA
[2]Cedars-Sinai Medical Center, Los Angeles, California, USA
[3]National Institutes of Health, Bethesda, Maryland, USA
[4]Medicine/ Rheumatology, University of California, San Francisco, San Francisco, California, USA
[5]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, California, USA
[6]Internal Medicine, University of Texas-Health McGovern Medical School, Houston, Texas, USA
[7]Rheumatology, Austin Regional Clinic, Austin, Texas, USA
[8]Department of Population and Data Sciences,University of Texas Southwestern Medical School, Dallas, Texas, USA

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ORCID iD
John D Reveille http://orcid.org/0000-0001-5950-0913

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