Maternal Age and Family History Are Risk Factors for Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To investigate prevalence and gender distribution in parents of children with ankylosing spondylitis (AS).

Methods. Family history of AS (parents, uncles, and aunts), maternal age at delivery, and consecutive pregnancy number were assessed in the relatives of 40 Mexican Mestizo patients with definite AS (New York Criteria).

Results. We evaluated the family history of AS in 34 families of 40 AS patients; 12 with none, 4 with a paternal history (4 healthy fathers with a brother with AS) (odds ratio, OR, 1.37, p = 0.75), 15 with a maternal history of AS, (15 healthy mothers with a brother with AS) (OR 1.4, p = 0.55), and 3 with both lines (OR 0.84, p = 0.92). In these families AS was more frequent in males (29%) than in females (10%), OR 3.40 (95% confidence interval, CI: 1.43-8.29, p = 0.003). Juvenile onset was more common in the offspring of mothers with family history (72%) (OR 13.0, 95% CI: 1.68-147.48, p = 0.009). The number of first-born children with AS (18%) was similar to the later-born children (23%) (OR 1.37, 95% CI: 0.38-5.31, p = 0.78). The frequency of AS increased when the maternal age at delivery was ≤ 30 years (OR 0.20, 95% CI: 0.04-0.75, p = 0.01).

Conclusion. In Mexican Mestizo patients, there is no correlation between the risk for AS and the gender of the affected parent. However we found an association between juvenile onset and maternal family history with an increased incidence in patients with younger mothers. (J Rheumatol 2003; 30:2182–5)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS GENETICS HLA-B27
JUVENILE ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic, systemic, inflammatory disorder of the axial skeleton that is thought to be genetically determined. It has a trend toward familial aggregation and has been associated with certain antigens from the major histocompatibility complex. Published data indicate that the first child is more frequently affected than the other siblings[1].

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A recent study concluded that a maternal family history of AS was associated with more frequent disease in children of affected mothers[2]. Besides gender of the offspring, maternal age at delivery has been studied in affected mothers, with a major incidence in males and in offspring of younger mothers[1,3].

Our aim was to assess the relationship between family history, consecutive pregnancy number and maternal age at delivery and the development of AS.

MATERIALS AND METHODS

Family history of AS was studied in the relatives of 40 patients seen at the outpatient clinic of the Rheumatology Department, Hospital de Especialidades, CMN S XXI (Mexico City). All patients had definite AS (New York Criteria)[4] and the presence of HLA-B27 had been previously studied in all of them[5].

Evaluation of the relatives. We studied the following relatives of the 40 patients: father, mother, brothers, sisters, uncles, and aunts. For every relative we performed a complete clinical examination; if there was a clinical suspicion of AS, a postero-anterior pelvic radiographic film was taken and subsequently evaluated by an independent observer. If sacroiliitis was present, a peripheral blood sample was taken to determine the presence of HLA-B27. Disease onset was established by the date when the patient was seen by a clinician that confirmed the diagnosis; affected children were classified with either juvenile onset (less than 16 years old) (JOAS) or adult onset disease (AOAS)[6].

Disease-free relatives were recorded as non AS-relatives. Patients were divided into 4 groups: (1) no family history of AS, (2) only paternal family history, (3) only maternal family history, and (4) both parents with a family history.

The sequential history of pregnancy, including miscarriage, was recorded to evaluate the association of AS and birth order. The cut-off points for maternal age at delivery were determined using the traditional format of dividing age by groups of 5 years each, using those closest to the median of our population.

Statistical analysis. Chi-square and Fisher's exact tests were performed and odds ratios (OR) and 95% confidence intervals (CI) were determined. A p value of < 0.05 was considered significant.

RESULTS

We studied 34 families of 40 AS patients with 224 pregnancies; 9 therapeutic and spontaneous abortions were excluded. Of 215 children, 19 who died during childhood, and 5 who were less than 15 years old were excluded from the analysis. One hundred ninety-one children were evaluated; 107 males and 84 females, with a median of 5 children per family (range 1-10). The results of family history, health status of the parents, relatives, and B27 status of patients with AS are specified in Table 1.

Regarding gender, 31/107 (29%) males and 9/84 (10%) females (OR 3.40, 95% CI: 1.43-8.29, p = 0.003) had AS (Table 2).

The mean maternal age at delivery in women with family history of AS was 27.16 ± 3.96 yrs; the 2 different cut-off points were 25 and 30 yrs (Table 3).

The consecutive pregnancy number (both those resulting in live births and those terminating in spontaneous abortion only) did not have any influence on disease prevalence, as shown in Table 3; however we did find a greater proportion of patients with AS in mothers ≤ 30 yrs of age at the time of delivery, 25/86 (29%) compared with mothers ≥ 31 yrs of age 3/39 (8%) (OR 0.20, 95% CI: 0.04-0.75, p = 0.01). The number of children, both male (54) and female (32) borne by mothers ≤ 30 yrs was similar to that of mothers ≥ 31 years: 18 males and 21 females (p = 0.12).

As shown in Table 4, there was no correlation between the risk of AS and the gender of affected family line. However, when family history was on the maternal side, offspring had a younger age at disease onset (16.6 ± 6.99 yrs) than if they had a paternal family history (24.4 ± 10.7 yrs, p = 0.029). As shown in Table 5, JOAS was related to maternal family history of AS (72% JOAS vs 28% AOAS, OR 13, 95% CI: 1.68-147.48, p = 0.009), while AOAS was more frequent when there was either no family history, or a paternal history (83% AOAS vs 17% JOAS and 72% AOAS vs 28% JOAS, respectively).

Table 2. Sex ratio in AS patients and their siblings.

Gender	AS (%)	Healthy (%)	p*	OR	95% CI
Female	9 (10)	75 (90)			
Male	31 (29)	76 (71)	0.003	3.40	(1.43–8.29)

* Chi-square

Table 3. First pregnancy and maternal age as a risk factor for AS in families with B27+ AS history.

Variable	AS (%)	Healthy (%)	p	OR	95% CI
Order of pregnancy (including miscarriage)					
1st	4 (19)	18 (81)			
≥ 2nd	24 (20)	96 (80)	1.0*	1.13	(0.33–4.99)
Order of pregnancy (live births only)					
1st	4 (18)	18 (82)			
≥ 2nd	24 (23)	79 (77)	0.78*	1.37	(0.38–5.31)
Maternal age at delivery					
≤ 25 years	14 (26)	39 (74)			
≥ 26 years	14 (19)	58 (81)	0.47**	0.67	(0.27–1.7)
≤ 30 years	25 (29)	61 (71)			
≥ 31 years	3 (8)	36 (92)	0.01**	0.20	(0.04–0.75)

* Fisher's exact test ** chi-square test

DISCUSSION

The Mexican Mestizo population is the result of a combination of Amerindians (related to the Oriental population) and white Spaniards (European population); the genetic and clinical picture of AS in Mexican Mestizo is different from that of the European population. There is a lower proportion of B27+ (70-75%) AS in Mexican Mestizo[7-10] than B27+ AS in the European population (90-95%)[11]. Additionally, early onset (JOAS < 16 years)[6,7] has been reported probably due to environmental conditions[12]. Both were observed in our

Table 1. Family history, health status of the parents and relatives, and B27 status of patients with AS.

Family History of AS	Number of Families	Health Status of Parents and Relatives	Children with AS, n
None	12	Healthy parents, no family history of AS	12 B27–
Maternal	15	Healthy mothers with a brother with AS	*18 B27+
Paternal	4	Healthy fathers with a brother with AS	**7 B27+
Both lines	3	Two mothers with B27+ AS; one mother with B27+ RA and a brother with AS Two fathers with B27+ AS; one father with B27+ spondyloarthropathy associated with ulcerative colitis	3 B27+

* one family with 4 children with AS; ** 3 families each with 2 children with AS.

Table 4. Number and percentage of children with AS versus affected family line.

Family Line of AS	Number of Families	Male and Female Children With AS (%)	Male and Female Children Healthy (%)	p*	OR	95% CI
None	12	12 (18)	54 (82)			
Paternal	4	7 (23)	23 (77)	0.75	1.37	(0.42–4.39)
Maternal	15	18 (24)	58 (76)	0.55	1.40	(0.57–3.43)
Both	3	3 (16)	16 (84)	0.92	0.84	(0.17–3.83)

* chi-square

Table 5. Juvenile onset AS (JOAS) versus adult onset (AOAS) in relation to gender of affected family line. Each of the inheritance lines was compared to none, i.e. paternal vs none, maternal vs none, and both vs none.

Inheritance Line of AS	JOAS (%)	AOAS (%)	p*	OR	95% CI
None	2 (17)	10 (83)			
Paternal	2 (28)	5 (72)	0.6	2.0	0.14–30.83
Maternal	13 (72)	5 (28)	0.009	13	1.68–147.48
Both	2 (66)	1 (34)	0.15	10	0.37–551.12

* Fisher's exact test.

study: i.e., 28/40 (70%) of our patients were B27+ and 19/40 (47.5%) had JOAS.

Our study was performed at a referral center, which is both a strength and a weakness: those included in our study might have more severe disease, but we were also able to study a large number of cases with familial aggregation.

We focused on the maternal family history of our AS patients because most of the literature highlights the importance of this line in the development of the disease in children[1-3]. We considered it a worthy aim because some experimental studies in B27 transgenic mice showed that the mother's age at time of delivery might exert a higher risk of having AS in the first litter[13]; however, in some human studies it has not been shown that maternal age at delivery implies a risk factor for the disease expression in the child[1–3,14].

Our group of Mexican-Mestizo couples, married between the 1920s and 1960s using no birth control and with a high number of offspring, gave us the opportunity to evaluate family history of disease, birth order, and maternal age at birth as risk factors for AS. We found a disease prevalence of AS of 21% (40/191) in relatives of these families.

Patients with a maternal family history developed the disease earlier than those who had paternal family history, usually in childhood; this suggests that a maternal antecedent of B27+ AS favors early onset of the disease, perhaps through a chronic inflammatory response against some infectious disease.

Our population allowed us to include women whose first pregnancy occurred before the age of 20 and who had several pregnancies; we were therefore able to evaluate the influence of sequential pregnancy order on disease prevalence. This is difficult in other populations with a limited number of pregnancies per family. However we did not find a correlation between the pregnancy order and further disease expression.

Thus we conclude that in the Mexican Mestizo population, there is no correlation between the risk of AS and the gender of the affected parent. In addition, we found the disease predominates in males, that maternal family history of AS is associated with earlier onset of AS, usually as JOAS, and that there are more patients with AS among subjects born from younger mothers.

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