Birth Order and Ankylosing Spondylitis: No Increased Risk of Developing Ankylosing Spondylitis Among First-born Children

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ABSTRACT. ***Objective.*** In the HLA-B27 transgenic mouse model the first litters have been shown to have a higher percentage of diseased offspring than later litters. First-born children (n = 162) have also been shown to have a higher risk of ankylosing spondylitis (AS) than later-born children. We examined this effect of birth order using similar methods but larger numbers.

Methods. Patients from the Bath AS database (n = 4517; M:F = 2.5:1) were examined according to position of birth within the family. Chi-squared analysis was used to examine if AS was more prevalent among first-born than later-born children.

Results. The first-born child was not significantly more likely to have AS than later-born children (p = 0.295). [Observed compared to expected: 1607 (36%) compared to 1641.13 (36%) for first-born children and 2910 (64%) compared to 2876.3 (64%) for later-born children, respectively.] There was no biological gradient (i.e., inverse correlation between birth order and disease risk).

Conclusion. There was no statistically significant effect of birth order based on our data. Findings suggesting a birth order effect may be skewed, as it is possible that those parents who do have AS will be less likely to have a large family and yet it is their offspring who will be at greatest risk of developing disease. This will affect the data, as those children born into a large family (i.e., high birth order children) will be at a lower risk of AS than any child born into a small but family-history-positive unit. (J Rheumatol 2002;29:527–9)

Key Indexing Terms:
BIRTH ORDER ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a systemic disease occurring in genetically predisposed individuals exposed to specific environmental triggers. In the HLA-B27 transgenic mouse the first litters have a higher percentage of diseased offspring than later litters[1]. This could be explained by either: (1) the age of the mother (older maternal age decreases transmission of disease to the next generation), or (2) the birth order of the offspring (i.e., environmental influence) has an influence on susceptibility to disease. Studies have shown that in humans the maternal age does not appear have an effect on inheritance of disease[2]. (Maternal age of onset of symptoms of AS, on the other hand, does influence prevalence of AS among the children of AS women[3].) However, it has been shown by studying 162 patients with AS that the number of first-born children with AS is significantly higher than would be expected[4]. We examined this hypothesis, that birth order of the child may affect the prevalence of disease, using similar methods with 4517 patients.

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MATERIALS AND METHODS

The Bath AS database of 5623 patients was used (M:F, 2.5:1). These patients were either outpatients of the Royal National Hospital for Rheumatic Diseases (RNHRD) or were members of the National Ankylosing Spondylitis Society (NASS). Patients referred to the RNHRD (n = 1874) had their diagnosis confirmed according to the New York criteria. To estimate the validity of the diagnosis of AS among the 3749 patients recruited through NASS, several samplings were performed. First, 146 consecutive patients were invited to attend an assessment clinic. All 146 were confirmed as having AS according to the same criteria. Second, the family physicians of a further 330 NASS members were contacted to check whether their patient's disease had been confirmed radiologically. Of these, 307 (93%) had definite AS, 15 had arthritic diseases other than AS, 3 showed suspicious change on radiograph, and for 5 patients the primary source material was unclear. Thus, of 5623 patients on the database, 264 (4.7%) individuals (i.e., a maximum of 7% of 3764 NASS patients) may not have had definite AS. Third, the radiographs of sacroiliac joints were requested and scored on 90 subjects, all of whom were found to have evidence of sacroiliitis of grade 2 or more. Taken together, the various samplings suggest that about 4% (i.e., 23 of 566 patients sampled using the 3 methods) of NASS recruits may not actually have AS.

All adopted patients were removed from the study (n = 54) and patients from one-child families (n = 1013) were not included.

Chi-square analysis was performed on position of birth compared to family size using SPSS. Patients were grouped as first-born versus not first-

born. After stratification by family size, the number of children with AS who were expected to be first-born on the basis of an equal distribution within birth order was computed.

In the first analyses only confirmed cases of AS (i.e., patients at RNHRD) were analyzed. Of 1874 subjects, 670 were not included due to adoption/only child/incomplete data.

In the second analysis, all confirmed or possible cases of AS (i.e., 4% of the sample may not have definite AS) were included. Thus, of 5623 subjects, 1013 were single-child families/56 incomplete data/37 adopted.

RESULTS

Demographic data. The children with AS born into family sizes of 2–9 children were comparable for sex ratio and disease duration. (Table 1). AS patients from families of 7 or 8 children were older than those from 2, 3, or 4-child families (50 vs 45 yrs, respectively; p = 0.001) and they therefore had the disease for longer (22.5 vs 21 yrs, respectively; p = 0.001; Table 1). Of the 4517 patients studied, 741 (16.4%) had a sibling with AS.

Birth order. Chi-squared test on first-born compared to later-born children: when observed values of confirmed AS patients who were first-born were compared to those observed for later-born children, the first-born child was not more likely to develop disease (p = 0.9; Table 2).

When all patients were included (confirmed AS and not confirmed) there still was no effect of birth order (p = 0.3; Table 3).

DISCUSSION

Considering the AS population as a whole, we found no significant effect of birth order. Factors that may have an influence on birth order would obviously include abortion, miscarriage, and stillbirth. Only live births are included in this analysis. It is possible that families of 4 or 5 children have more miscarriages and the children may be of a much later birth order (i.e., 6th or 7th) than recorded. In addition, this study did not attempt to validate the absence of AS in apparently unaffected siblings, and it is possible that asymptomatic AS is present among some of the sample. However, it is unlikely to affect the results of the study unless a first-born child were more likely to have milder (asymptomatic) disease.

Recent research by Baudoin, *et al*[4] shows an increased risk of AS among first-born children. In 40 families with 2 children, 26 of children with AS were first-born, whereas the number expected was 20, a surplus of 30%. This study does not substantiate these findings. It is possible that the discrepancy between the Baudoin findings and those presented here are due to the difference in numbers. The

Table 1. Demographic data (n = 4511).

	Family Size								
	Family of 2, n = 1785	Family of 3, n = 1330	Family of 4, n = 706	Family of 5, n = 492	Family of 6, n = 106	Family of 7, n = 46	Family of 8 n = 32	Family of 9, n = 14	p
Age of AS child (SD), yrs	45 (13)	45 (13)	45 (13)	47 (12)	45 (10)	51 (11)	49 (11)	45 (9)	0.001
Sex ratio of child, M:F	2.3:1	2.3:1	2.3:1	2.3:1	2.0:1	3.0:1	1.5:1	1.8:1	NS
Disease duration of child (SD), yrs	21 (14)	21 (13)	20 (13)	21 (13)	20 (11)	23 (13)	22 (13)	23 (12)	NS
Average age of disease onset in child, yrs (SD)	24 (11)	24 (11)	25 (11)	25 (10)	25 (9)	27 (10)	27 (10)	22 (10)	0.001

Table 2. Birth order of confirmed individuals with AS within the family. Data in parentheses are percentages.

	Family Size							Total	
Birth Order	2	3	4	5	6	7	8	Observed	Expected
1	215 (48)	127 (36)	54 (27)	30 (18)	2 (6)	1(11)	1 (20)	430	429.23
2	232 (52)	110 (32)	55 (28)	27 (17)	9 (27)	2 (22)	0	435	429.23
3		112 (32)	40 (20)	32 (20)	5 (15)	2 (22)	0	191	205.73
4			48 (24)	41 (25)	10 (30)	1 (11)	0	100	89.43
5				34 (21)	4 (12)	0 (0)	2 (40)	40	40.18
6					3 (9)	1 (11)	1 (20)	5	7.38
7						2 (22)	1 (20)	3	1.88
8							0	0	0.6
Total	447	349	197	164	33	9	5	1204	1203.66
AS child first-born	215	127	54	30	2	1	1	430 (35.7)	429.23 (35.6)
AS child not first-born	232	222	143	134	31	8	4	774 (64.3)	774.43 (64.4)
								Chi-square = 0.006* p = 0.967	

* First-born child compared to later-born children.

Table 3. Birth order of individuals with AS (confirmed and suspected) within the family. Data in parentheses are percentages.

	Family Size										Total	
Birth Order	2	3	4	5	6	7	8	9	10	11	Observed	Expected
1	865 (49)	447 (34)	186 (26)	92 (19)	7 (7)	4 (9)	5 (16)	1 (7)	0	0	1607	1641.13
2	920 (52)	462 (35)	176 (25)	84 (17)	20 (19)	9 (20)	1 (3)	1 (7)	1 (33)	0	1674	1641.13
3		421 (32)	190 (27)	86 (18)	16 (15)	9 (20)	5 (16)	2 (14)	0	1 (33)	730	748.63
4			154 (22)	104 (21)	26 (25)	10 (22)	2 (6)	2 (14)	0	0	298	305.33
5				126 (26)	21 (20)	7 (15)	5 (16)	0	1 (33)	0	160	128.83
6					16 (15)	5 (11)	3 (9)	1 (7)	0	0	25	30.43
7						2 (4)	5 (16)	4 (29)	1 (33)	1 (33)	13	12.77
8							6 (19)	2 (14)	0	0	8	6.17
9								1 (7)	0	0	1	2.17
10									0	1 (33)	1	0.57
11										0	0	0.27
Total	1785	1330	706	492	106	46	32	14	3	3	4517	4517.43
AS child first–born	865	447	186	92	7	4	5	1	0	0	1607 (36)	1641.13 (36)
AS child not first–born	920	883	520	400	99	42	27	13	3	3	2910 (64)	2876.3 (64)
											Chi- squared 1.09* p = 0.295	

* First-born child compared to later-born children.

difference of 6 children in the expected compared to the observed translates to 3.7% of the total patient sample being first-born instead of later-born. This difference seems to disappear with a larger number. In addition, many factors make comparisons between families difficult. For example, we know that genetic susceptibility is required to develop AS and that women with early onset AS are more likely to pass on the disease to their children[3]. Logically, women with symptoms of AS would be less likely to have a large family. Therefore, only women with no family history of AS will be likely to have families of 4–5 children. Thus, any child born into a large family is automatically at a lower risk of AS than any child born into a small family. This means that children born 4th or 5th (higher birth order) may appear to have a lower risk when compared to the population. However, compared to first-born children in a larger family they do not actually have a lower risk (Tables 2 and 3).

Both this study and Baudoin, *et al* examined only multi-sibling families. Future work may examine if AS is more prevalent in "only" children (by definition first-born, with no siblings) than expected. This could be done by estimating how many only children with HLA-B27 there are in the population (i.e., HLA frequency × only child frequency) and then compare the prevalence of AS in this group with the prevalence of AS in the entire HLA-B27 positive population.

In summary, previous work using a mouse model and examining 162 patients suggested a birth order effect in AS. However, using similar methods on 4517 patients we were not able to substantiate these findings. Thus, there does not appear to be a birth order effect operable in AS.

REFERENCES

1. Weinreich S, Hoebe D, Ivanyi P. Maternal age influences risk for HLA-B27 associated ankylosing enthesopathy in transgenic mice. Ann Rheum Dis 1995;54:754-6.
2. Raza K, Kennedy G, Calin A. Maternal age and the risk of developing ankylosing spondylitis. Ann Rheum Dis 1997; 56:209-10.
3. Calin A, Brophy S, Blake D. Impact of sex on inheritance of ankylosing spondylitis: a cohort study. Lancet 1999;354:1687-90.
4. Baudoin P, van der Horst-Bruinsma E, Dekker-Saeys A, Weinreich S, Bezemer P, Dijkmans B. Increased risk of developing ankylosing spondylitis among first born children. Arthritis Rheum 2000;43:2818-22.