The Genetic Risk for Alopecia Areata in First Degree Relatives of Severely Affected Patients

An Estimate

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Substantial evidence indicates that genetic factors may have a role in the etiology of alopecia areata (AA). Most studies, however, provide only general information on the familial incidence but fail to specify family relationships. We therefore obtained information on the incidence of AA in first degree relatives of 348 severely affected patients. In 7% one of the parents was affected. Among the siblings of the patients 3% had developed AA, while AA was present in 2% of the children. Taking into account the age of the children, their lifetime risk was calculated to approach 6%. However, a severe type of AA is to be expected only in about 2% of the children. The degree of involvement observed in the patients did not influence the frequency and type of AA present in their first degree relatives. *Key word: Genetic risk.*

In many studies an increased familial incidence has been found in alopecia areata (AA), indicating that genetic factors may have a causative role (1–10). A high frequency of AA is observed in Down's syndrome (11–14), suggesting the presence of a relevant gene located on chromosome 21. A second locus possibly involved in AA may reside in or close to the major histocompatibility complex on chromosome 6 (15, 16). However, the relationship between HLA and AA is complex and not undisputed (17). Recently, Duvic et al. demonstrated a negative relationship between the HLADRB3 allele and AA (16). From this study it may be inferred that the presence of the DRB3 allele protects individuals against developing AA.

Although having a selection bias for the interesting, case reports of AA in twins provide further evidence for a genetic predisposition to AA (18–23). It is of note that in two reports dealing with monozygotic twins, hair loss occurred simultaneously and in identical areas (18, 19).

Pertinent data, however, concerning the genetic risk of first degree relatives of patients with AA are scarce. Most studies provide only general information on the familial incidence but fail to specify family relationships.

Adult patients often wonder how likely it is that their children will develop the same hair disorder. The aim of the present study was to answer this question by giving an estimate of the genetic risk for AA in first degree relatives.

PATIENTS AND METHODS

Three hundred and forty-eight patients were interviewed by use of a uniform questionnaire at the University Centers of Nijmegen (n=194), and Münster (n=154). All patients suffered from a severe type of AA, with a minimum scalp involvement of 40%, and attended a special outpatient clinic for topical immunotherapy. A detailed family history concerning first degree relatives was taken. Moreover, the age at first presentation, the age at onset of AA, and gender were recorded. The extent of hair loss was classified as patchy, totalis or universalis. Fisher's exact test was used for statistical evaluation.

RESULTS

Of the 348 patients, 208 were female (60%), 140 male (40%); the Nijmegen group had 107 females (55%), whereas the Münster group had 101 females (66%). The median age of the patients was 34 years (Nijmegen: 33 years, Münster: 34 years), the median age at onset of AA was 21 years (Nijmegen: 21 years, Münster: 22 years).

Table I shows the incidence of AA in parents, siblings, and children. In the Nijmegen group, parents were more often affected than in the Münster group ($p<0.03$).

The frequency of AA in first degree relatives of patients with patchy AA was 13%, and for patients with a totalis or universalis type of AA this was 18% (n.s.).

Fifty-six of the 348 patients (16%) had an affected first degree relative, 51 patients having one affected relative, and 5 patients having 2 affected relatives each. Forty-eight out of 61 affected first degree relatives (79%) had a history of patchy AA, 8 (13%) had experienced AA totalis, and 5 (8%) had had AA universalis. In this subgroup no correlation was found between the degree of involvement of the patients and the type of AA observed in their 61 affected relatives.

Fig. 1 shows the distribution of the age at onset of AA in patients having affected first degree relatives versus the distribution of the subgroup without familial occurrence. The two distributions are similar. The median age at onset of AA in the subgroup with affected first degree relatives was 23 years, for patients without familial occurrence 21 years.

DISCUSSION

In the literature familial occurrence of AA is usually not specified in terms of family relationships. The purpose of this study was to estimate the genetic risk of first degree relatives of severely affected patients. Second and third degree kinships

Table I. *Incidence of AA in first degree relatives of patients with severe AA. Figures in parentheses indicate percentages*

	Total group	Nijmegen (n=194)	Münster (n=154)	p value Nijmegen versus Münster
Fathers	12/348 (3.4)	9/194 (4.6)	3/154 (1.9)	n.s.
Mothers	13/348 (3.7)	10/194 (5.2)	3/154 (1.9)	n.s.
Parents	25/348 (7.2)	19/194 (9.8)	6/154 (3.9)	p<0.03
Brothers	16/462 (3.5)	10/289 (3.5)	6/173 (3.5)	n.s.
Sisters	11/438 (2.5)	5/236 (2.1)	6/202 (3.0)	n.s.
Siblings	27/900 (3.0)	15/525 (2.9)	12/375 (3.2)	n.s.
Sons	2/178 (1.1)	1/85 (1.2)	1/93 (1.1)	n.s.
Daughters	7/179 (3.9)	5/95 (5.3)	2/84 (2.4)	n.s.
Children	9/357 (2.5)	6/180 (3.3)	3/177 (1.7)	n.s.

were excluded because we regarded this information as unreliable.

We identified 25 affected parents in the group of 348 patients (7%). We are aware that the ethnic make-up of the two groups is not identical, and this may explain the difference observed. On the other hand, the two populations showed different risk figures only for the parents, and therefore we decided to base our calculations on the joint study.

The median age of the patients was 34 years. As AA rarely becomes manifest after the age of 50 (Fig. 1), a substantial increase of affected parents in the future is not to be expected.

In this study 9 out of 357 children (2%) were already affected. As discussed above, this figure does not reflect the true lifetime incidence of AA due to the age dependency of the disease. The median age of the children was 18 years. It is noteworthy that 42% of the patients had already developed AA before the age of 19. Thus it may be concluded that the lifetime incidence of AA in the children will approach 6% (i.e. $1/42 \times 9/357$). It is of note that the incidence among the parents of the patients (7%) corresponds to the calculated lifetime incidence of the children (6%). This may indicate that first degree relatives run the same genetic risk.
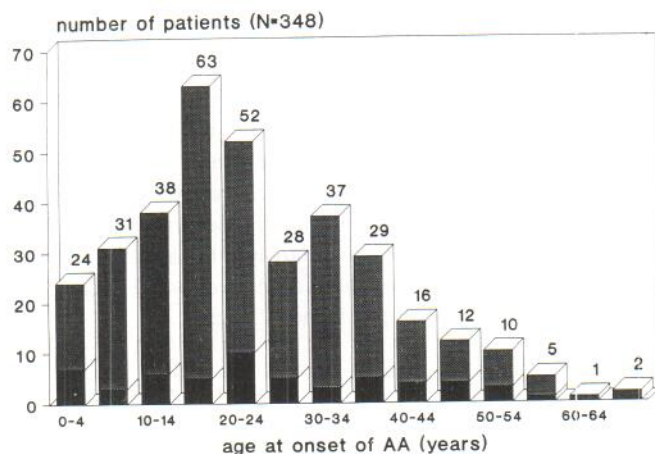
Only 7 of the 25 affected parents (28%) had a history of a severe type of AA. We assume that for children the risk of developing extensive hair loss is in the same range. This means that approximately 2% (i.e. $0.28 \times 6.0 = 2\%$) of all children will eventually develop severe AA.

Neither the number of affected first degree relatives nor their type of AA was influenced by the degree of hair loss in the patients. Immunological and environmental factors may be more important for the clinical course. In the general population the risk for AA is 0.05–0.1% (10). Although there were no mildly affected patients included in the present study, our findings suggest that the genetic risk of developing severe type of AA, even for the offspring of individuals with mild hair loss, is 2%.

The mean age at onset of patients with a positive family history did not differ from those without a familial clustering. This is in contrast with psoriasis vulgaris, where an early onset type showing a high incidence of familial occurrence can be distinguished from a late onset type with predominantly sporadic psoriasis (24). The absence of a separate early and a late onset type in AA may be taken as a further indication that the role of genetic factors is less important in this disease than in psoriasis.

The total number of patients with one or more affected first degree relatives was 56 (16%). This is in agreement with other studies in which the frequency of affected first degree relatives was 10% (2), 12% (4), and 13% (1) but at variance with one report in which the incidence was 6% (3).

Especially those patients who suffer from a severe type of AA are often afraid that their children will develop the same disease. We conclude that, regardless of the type of AA present in a parent, the estimated risk of children for the development of a *severe* type of AA is approximately 2%.

Fig. 1. Age at onset of AA in patients with affected first degree relatives (*dark bars*), and age at onset of AA in the subgroup without familial occurrence (*light bars*). Both subgroups show a similar distribution.

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