Immunological Associations in Familial and Non-Familial Alzheimer Patients and Their Families

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Abstract: A number of autoimmune diseases and immune-related conditions were investigated in a series of 100 Alzheimer patients and their families. The group was divided into those who had familial dementia of the Alzheimer type and non-familial dementia of the Alzheimer type. HLA DR3 was associated with the familial dementia of the Alzheimer type patients. Adult exposure to tuberculosis appeared to be a risk factor for familial dementia of the Alzheimer type patients. Autoimmune diseases clustered among the non-familial dementia of the Alzheimer type patients, and also among their relatives. Asthma and infertility were also significantly increased among non-familial dementia of the Alzheimer type relatives. The analysis showed that (1) autoimmunity may be important in the sporadic form of Alzheimer disease; (2) it may be possible to confer a decreased risk for Alzheimer disease among relatives when many autoimmune diseases occur in the family; (3) it may be important to assess environmental risk factors for Alzheimer disease separately in patients with familial and sporadic disease; and (4) the efficacy of drug therapies may be dependent on whether the patients have a familial or sporadic form of Alzheimer disease.

Résumé: Associations immunologiques chez les cas familiaux et non familiaux de la maladie d'Alzheimer et chez leurs familles. Nous avons étudié certaines maladies auto-immunes et certains troubles immunitaires chez une série de 100 patients atteints de la maladie d'Alzheimer et chez leurs familles. Le groupe était divisé en démence familiale de type Alzheimer (DFTA) et démence non familiale de type Alzheimer (DNFTA). Le HLA DR3 était associé à la DFTA. Une exposition à la tuberculose à l'âge adulte semblait être un facteur de risque pour les patients avec DFTA. Il y avait aggrégation de maladies autoimmunes chez les patients avec DNFTA ainsi que dans leurs familles. La fréquence de l'asthme et de l'infertilité étaient également augmentées significativement dans les familles DNFTA. L'analyse a montré que 1) l'auto-immunité est peut-être un facteur important dans les formes sporadiques de la maladie d'Alzheimer; 2) il peut être possible de déterminer qui a un risque plus faible d'être atteint de la maladie d'Alzheimer dans les familles des patients quand plusieurs maladies auto-immunes sont présentes dans la famille; 3) il peut être important d'évaluer séparément les facteurs de risque environnementaux pour la maladie d'Alzheimer chez les patients qui ont une maladie familiale et chez ceux dont la maladie est sporadique; 4) l'efficacité de la thérapie médicamenteuse peut dépendre du fait que les patients ont la forme familiale ou la forme sporadique de la maladie d'Alzheimer.

A role for the immune system in the etiology of Alzheimer disease comes from evidence of immunoglobulins[1] and complement components of the classical pathway[2] in senile plaques, which are a constant neuropathological finding in the disease. Further evidence comes from the presence of T-helper inducer and T-cytotoxic suppressor antigens in diseased brain tissue,[3] of reactive microglia expressing human leukocyte antigen DR (HLA-DR) in complement-rich areas of the diseased brain,[4] and of interleukin-2 receptor expressed by the peripheral blood lymphocytes of patients with Alzheimer disease.[5]

Perhaps the greatest risk factor for Alzheimer disease is the pathological diagnosis of the condition in a first-degree relative. The significance of risk factors in any epidemiological study of

Alzheimer disease may be diminished when patients with a family history of the disease are combined with those among whom the disease occurs sporadically. We therefore approached the problem by dividing a series of Alzheimer patients into two groups; familial dementia of the Alzheimer type (FDAT) and non-familial dementia of the Alzheimer type (NFDAT), and investigating a number of conditions associated with immunity in these two groups.

If the presence of elements associated with activation of the immune system in diseased brain tissue can be interpreted as evidence for a cell-mediated immune response, autoimmunity may be important in our understanding of Alzheimer disease. We therefore investigated the extent of a possible impaired immune repsonse by noting whether there were autoimmune diseases coexisting with a diagnosis of Alzheimer disease, whether patients with autoimmune diseases clustered more frequently in either the FDAT or the NFDAT group, and whether the FDAT and NFDAT groups could be defined by association with any of the human leukocyte antigens (HLA).

In an analysis of multigenerational kindreds, Bias et al. proposed a genetic model of dominantly-inherited autoimmune genes.[6] To test the hypothesis that Alzheimer disease may have an autoimmune component, we investigated the presence of autoimmune diseases and immune disorders in first- and second-degree relatives of Alzheimer patients to determine whether the "immune" families so defined clustered in either the FDAT or the NFDAT group.

METHODS

Patients were recruited from referrals to neurology, geriatrics and geriatric psychiatry services. The study was approved by the local Human Investigation Committee, and informed consent was given by the patients or a close relative. Individuals who met the criteria of "probable Alzheimer" as outlined in the NINCDS-ADRDA protocol[7] were enrolled in the study. Further inclusion/exclusion criteria[8,9] were used in dealing with coexisting conditions such as a seizure disorder, a stroke, or alcohol abuse, which may be part of the disease process.

A total of 100 patients was evaluated through a standard dementia screen, which included routine laboratory blood tests. A CT scan was carried out in 81% of the patients. Screening included several neurological and psychological tests, the Mini-Mental State Exam,[10] the modified Hachinski Ischemic Score,[11] the Hamilton Rating Scale for Depression,[12] and the Blessed-Roth Dementia Rating Scale.[13] At present, 49 individuals are deceased, 8 of whom had an autopsy. In no case did an autopsy contradict the diagnosis based on the above criteria.

Using a standardized questionnaire, medical histories were obtained on patients and their families from a minimum of two close relatives, usually a spouse and a child, and often a sibling. Aunts and uncles of the proband were not included in second-degree relatives because of the lack of certainty in establishing a definite diagnosis when the informants were children of the proband. Medical records and death certificates were used to corroborate information from the primary source.

The criterion for inclusion in the FDAT group was a history of Alzheimer disease in at least one first-degree relative (parent or sibling). All autoimmune diseases were specifically sought for by name. It was not possible to assign a diagnosis of autoimmune Graves' disease to hyperthyroid patients, since most had had a thyroidectomy as a young adult. For rheumatoid arthritis, patients had to fulfill the 1987 American Rheumatism Association criteria for "definite" disease.[14] Because of the difficulty in differentiating a rheumatoid from an osteoarthritic condition, an analysis of rheumatoid arthritis in relatives was not carried out. Although type 2 diabetes has no association within the HLA complex, it was included because of its increased risk in families with type 1 diabetes.[15]

A statistical analysis of variables was performed using Epi Info software[16] and the results were expressed as odds ratios, comparing the FDAT and the NFDAT groups. Statistical significance was evaluated using 95% confidence intervals for odds ratios and Fisher's exact test.

RESULTS

Family History of Alzheimer Disease

Among the 100 probands, 47 had a first-degree relative with a dementing illness that met the criteria for "possible" or "probable" DAT.[7] In most of these FDAT families there was at least one affected relative; 18 had an affected parent and 14 had an affected sibling. Of the remaining 15 probands with two to five affected relatives, 10 had affected family members in both generations.

Another eight families had second-degree relatives (great-grandparents and greataunts/uncles) with "possible" dementia, but these medical histories were difficult to document. In six of these families the parent was unaffected and had lived beyond the age at onset of the disease in the family. These cases were included in the NFDAT category. For the remaining 45 NFDAT families with no affected close relative, 22 had both parents who lived beyond the age at onset of the disease in that family and could be considered truly non-familial, assuming complete penetrance at the age of onset. An analysis of the variables shown in Tables 2-6 did not indicate a statistical difference between these 22 families and the other NFDAT families and thus the two groups were regarded as a single entity.

Demographics

The demographic characteristics of the two groups are provided in Table 1. From the three sources of ascertainment, those referred from neurology were more likely to be in the NFDAT group (61%), those from geriatrics were more likely to be in the FDAT group (62%), while those from psychiatry were equally represented in both groups. Two-thirds of the patients were female, with less (62%; 29/47) in the FDAT group than in the NFDAT group (74%; 39/53), though not significantly so. Because those in the FDAT group were more often from geriatric sources, they were generally older than those in the NFDAT group; for females the mean ages were 77 and 73 years, respectively; for males, 75 and 73 years, respectively. Similar results were obtained for the ages at onset of symptoms. Further comparison of the two groups indicated that they came from sibships of similar size and that they had a similar number of children. While the total number of relatives did not differ, the first-degree FDAT relatives were slightly older (over 70 years, 30% for FDAT and 25% for NFDAT; OR = 1.26, 95% CI = 0.97-1.64, p = 0.08).

Table 1. Demographic characteristics of FDAT and NFDAT patients.

	FDAT (n = 47)	NFDAT (n = 53)	Total (n = 100)
Ascertainment			
Neurology	39% (16)+	61% (25)	100% (41)
Psychiatry	46% (15)	54% (18)	100% (33)
Geriatrics	62% (16)	38% (10)	100% (26)
Sex			
Female	43% (29)	57% (39)	100% (68)
Male	56% (18)	44% (14)	100% (32)
Mean age, yrs			
Females	76.8 ± 7.4	72.5 ± 7.4	74.3 ± 7.7
Males	74.7 ± 10.6	72.5 ± 6.2	73.7 ± 8.8
Mean age at onset, yrs			
Females	71.9 ± 7.8	68.3 ± 7.9	69.8 ± 8.0
Males	68.4 ± 11.3	67.8 ± 8.5	68.2 ± 10.0
Age at onset, ≤ 65 yrs	41% (12)	59% (17)	100% (29)
> 65 yrs	49% (35)	51% (36)	100% (71)
Mean size of sibship	6.6 ±3.3	6.4 ±2.5	
Mean no. of children*	5.0 ±4.1	4.9 ±3.4	
No. of first-degree relatives	576	634	
No. of second-degree relatives	1308	1244	
Total no. of relatives	1884	1878	
No. of first-degree relatives ≥ 70 yrs	30% (173)	25% (161)	

+ Actual numbers are in brackets.
* Excludes unmarried patients and those married post-reproductive years.

Autoimmune Diseases in Patients

The distribution of various autoimmune diseases is shown in Table 2. Among the 12 patients with reported thyroid conditions, 10 were from the NFDAT group (OR = 5.23, 95% CI = 1.01-51.09, p = 0.03). Both of those in the FDAT group had hyperthyroidism; five in the NFDAT group had hyperthyroidism, three had hypothyroidism, and two had euthyroid goitre. All were euthyroid, with five receiving thyroid medication. Both ulcerative colitis and rheumatoid arthritis occurred more often among the NFDAT patients. When the analysis took into account the fact that some patients had more than one condition, the presence of any autoimmune disease was found more frequently among the NFDAT patients (32.1% vs. 14.9%; OR = 2.70, 95% CI = 0.92-8.54, p = 0.06). Removing thyroid disease from the analysis eliminates the significance of having any other autoimmune disease among the NFDAT patients (12.8% and 15.1% for FDAT and NFDAT patients, respectively).

Autoimmune Diseases in Relatives

The distribution of autoimmune diseases among first- and second-degree relatives was not uniform as the NFDAT group of patients had more reported autoimmune diseases among their relatives than had the FDAT group (Table 3). For the thyroid conditions, most relatives in the FDAT group were hyperthyroid (6/7; 3 of these also had "probable" Alzheimer disease). Most of the NFDAT relatives were hypothyroid (8/13). A comparison of the presence of an autoimmune disease in the relatives of the two groups showed that the difference (50.9% vs. 27.7%) was statistically significant (OR = 2.72, 95% CI = 1.09-6.87, p =

Table 2. Distribution of autoimmune diseases in patients from FDAT and NFDAT families.

Autoimmune Disease	FDAT (n = 47)	NFDAT (n = 53)	Odds Ratio NFDAT/ FDAT	95%CI	Fisher's exact p
Thyroid disease	2	10	5.23	1.01-51.09	0.03
Type 1 diabetes	2	2	0.88	0.06-12.65	1.00
Inflammatory bowel disase					
Ulcerative colitis	–	2	–	–	–
Rheumatoid arthritis	1	3	2.76	0.21->100	0.62
Raynaud's phenomenon	1	1	0.88	0.01-70.93	1.00
Pernicious anemia	2	1	0.43	0.01-8.64	0.60
Any autoimmune disease	7(14.9%)	17(32.1%)	2.70	0.92-8.54	0.06

0.02; Table 3). In many families there was a clustering of autoimmune diseases, and this was more evident in the NFDAT families where 18.9% had two or more affected relatives compared with 4.2% in the FDAT families (OR = 5.23, 95% CI = 1.01-51.09, p = 0.03). Of the 13 NFDAT families with thyroid disease among relatives, 6 had only thyroid disease, leaving 21 (39.6%) families with a cluster of autoimmune diseases. Thus, removing thyroid disease from the analysis increased the significance of having any other autoimmune disease among the NFDAT relatives (39.6% vs. 14.9%; OR = 3.75, 95% CI = 1.31-11.66, p = 0.01).

HLA Associations

The distribution of the HLA A, B and DR antigens in FDAT and NFDAT families did not differ significantly from Newfoundland controls as reported by Skanes et al.[17] Table 4 shows data from some of the more frequently occurring antigens. Comparing the FDAT and NFDAT patients, HLA DR3 occurred more frequently in the FDAT group (47% vs. 19%; OR = 3.78, 95% CI = 1.29-11.41, p = 0.009). When corrected for bias due to number of antigens compared, p = 0.09. Among the 17 patients with HLA DR3 antigen, two had type 1 diabetes and none had a thyroid disorder. The frequency of HLA B8 was also greater in the FDAT group (35% vs. 19%). There were several differences in the distribution of the antigens by sex. Among the NFDAT patients, significantly more females were positive for HLA A2 (60% vs. 18%; OR = 6.60, 95% CI = 1.09-68.54, p = 0.04). The reduced frequency of HLA A2 in NFDAT males was not statistically different from male controls (18% vs. 52%; OR = 0.21, 95% CI = 0.02-1.08, p = 0.05). With HLA DR4, opposite results were obtained between the two groups of patients; males had a higher frequency in the FDAT group (41% vs. 5%; OR = 12.60, 95% CI = 1.23->100, p = 0.02, and females had a higher frequency in the NFDAT group (42% vs. 18%, OR = 3.21, 95% CI = 0.53-34.02, p = 0.28).

Immune-related Conditions

Type 2 diabetes

Among the 14 patients with type 2 diabetes, 10 (18.9%) were from the NFDAT group and 4 (8.5%) from the FDAT group (OR = 2.50, 95% CI = 0.65-11.68, p = 0.16). Similarly, among the relatives, 15 (28.3%) NFDAT families had persons with type 2 diabetes, as did 10 (21.3%) FDAT families.

Table 3. Distribution of autoimmune diseases in first and second degree relatives from FDAT and NFDAT families.

Autoimmune Disease	FDAT (n = 47)	NFDAT (n = 53)	Odds Ratio NFDAT/FDAT	95%CI	Fisher's exact p
Thyroid	7	13	1.86	0.61-6.07	0.32
Type 1 diabetes	4	8	1.91	0.47-9.26	0.37
Inflammatory bowel disease					
Ulcerative colitis	2	5	2.34	0.36-25.58	0.44
Crohn's disease	1	4	3.76	0.35->100	0.37
Raynaud's phenomenon	1	–	–	–	–
Juvenile rheumatoid arthritis	–	1	–	–	–
Ankylosing spondylitis	–	1	–	–	–
Pernicious anemia	1	2	1.80	0.09->100	1.00
Multiple sclerosis	1	2	1.80	0.09->100	1.00
Systemic lupus erythematosus	–	2	–	–	–
Scleroderma	–	1	–	–	–
Any autoimmune disease	13(27.7%)	27(50.9%)	2.72	1.09-6.87	0.02

Table 4. Frequency distribution (%) of selected HLA antigens in FDAT and NFDAT patients and Newfoundland controls by sex.

HLA	Newfoundland Controls			FDAT			NFDAT		
	T	F	M	T	F	M	T	F	M
	n = 250	n = 138	n = 112	n = 43	n = 25	n = 18	n = 48	n = 37	n = 11
A1	28	31	25	40	32	50	35	35	36
A2	52	51	52	40	40	39	50	60*	18*
B8	24	23	24	35**	28	44	19**	22	9
B12, w44	31	33	28	49	48	50	42	43	36
	n = 253	n = 122	n = 131	n = 36	n = 19	n = 17	n = 47	n = 36	n = 11
DR3	30	30	31	47+	47	47	19+	22	9
DR4	36	37	36	22	5++	41++	36	42++	18++

F = Female, M = Male, T = Total
* For NFDAT HLA A2, Odds Ratio F/M = 6.60, 95% CI = 1.09-68.54, p = 0.04.
** For HLA B8, Odds Ratio FDAT/NFDAT = 2.32, 95% CI = 0.81-6.89, p = 0.10.
+ For HLA DR3, Odds Ratio FDAT/NFDAT = 3.78, 95% CI = 1.29-11.41, p = 0.009.
++ For HLA DR4, Odds Ratio FDAT M/F = 12.60, 95% CI = 1.23->100, p = 0.02.
Odds Ratio NFDAT F/M = 3.21, 95% CI = 0.53-34.02, p = 0.28.

Asthma

The presence of an asthmatic condition was identified from general health questions, and not sought for specifically as in the autoimmune diseases. Two FDAT patients had an asthmatic condition confirmed from medical charts; one had been hospitalized for investigation. There were no asthmatic patients in the NFDAT group. Asthma was noted more often among the first-degree relatives in the NFDAT group than among those in the FDAT group (21% of families vs. 6%; OR = 3.84, 95% CI = 0.92-22.65, p = 0.05).

Infertility

Infertility was documented when a patient, sibling or child had been married during his/her reproductive years and had had no children. There were five infertile couples in each of the FDAT and NFDAT group of patients, but among their first-degree relatives, there was a difference (Table 5). There were 21 NFDAT families in which siblings or children had no children compared with 10 FDAT families (40% vs. 21%; OR = 2.43, 95% CI = 0.92-6.63, p = 0.05). There were more (80%; 12/15) infertile female than male relatives in the FDAT group than in the NFDAT group (58%; 15/26).

Tuberculosis Exposure

Lifetime exposure of the patient to tuberculosis was assessed at two levels, within the patient's immediate household and within the household in which the patient was raised (Table 6). Four patients in the FDAT group had a history of tuberculosis in the 1950's; 3 had been hospitalized for periods of 1-2 years with pulmonary disease, while the fourth had tuberculosis with peritonitis. No tuberculosis had occurred among the NFDAT patients. Five spouses of the FDAT patients had had pulmonary tuberculosis while married; three recovered and two had died with tuberculosis confirmed from death certificates. Of the three NFDAT spouses with tuberculosis, one had died from pulmonary tuberculosis, another from tuberculous meningitis, and the third from renal tuberculosis. There were five FDAT families and one NFDAT family containing a child with tuberculosis, and in three FDAT families a parent as well as a child was affected, so that the number of affected households was 11 (23%). This was marginally significantly different from the 4 (8%) NFDAT households with tuberculosis (OR = 3.74, 95% CI = 0.99-17.22, p = 0.05). The presence of tuberculosis in the household in which the proband was raised (in a parent or a sibling living at home) was similar for both FDAT and NFDAT families (19% and 15%).

FDAT and NFDAT Subgroups

The variable and late age at onset of Alzheimer disease makes the separating of families into familial and non-familial groups difficult. One way to overcome this problem is to use more stringent criteria to classify subsets of patients. Thus, the FDAT families were separated into those more likely to have a

genetic form of the disease, namely those with two or more affected relatives (FDAT1; n = 15), and those with a single affected relative (FDAT2; n = 32). Within the NFDAT families, those with no secondary cases and whose parents had died after the age at onset in the family were considered more likely to have a sporadic form of the disease (NFDAT2; n = 22) than the remaining families (NFDAT1; n = 31) who had secondary cases in second- and third-degree relatives or whose parent had died before the age at onset in the family. While recognizing the limitations of such arbitrary criteria, a selection of findings was analysed for a linear trend from the genetic to the sporadic form of the disease in the four subgroups thus defined (Table 7). The results indicated that three attributes were statistically significant, infertility among first-degree relatives, adult exposure to tuberculosis and HLA DR3. When comparisons were made between the genetic (FDAT1) and the sporadic (NFDAT2) groups, only adult exposure to tuberculosis remained significant (OR = 18.38, 95% CI = 1.74->100, p = 0.004).

Table 5. Fertility and infertility in patients and first-degree relatives in FDAT and NFDAT families.

	FDAT (n = 47)			NFDAT (n = 53)		
	F	M	T	F	M	T
Fertility						
Mean no. of children+	5.3	4.4	5.0	5.0	4.5	4.9
Infertility						
In patients	2	3	5	5	–	5
In first-degree relatives						
Siblings	10	2	12	11	9	20
Children	2	1	3	4	2	6
Total	12	3	15	15	11	26
Corrected for multiple cases in families			10 (21%)*			21 (40%)*

M = Male, F = Female, T = Total.
+ Excludes unmarried probands and those married post-reproductive years.
* Odds Ratio NFDAT/FDAT = 2.43, 95% CI = 0.92 - 6.63, p = 0.05.

DISCUSSION

The frequency of dementia among first-degree relatives of Alzheimer patients has been reported to range from 25% to 45%.[18-20] When second-degree relatives with dementia are included, the range is higher, 41% to 56%.[21-23] Our finding of 47% of families in which dementia occurred in parents or siblings represented values in the upper range for first-degree relatives. These families with the familial form of Alzheimer disease generally had an early onset of symptoms, as was also shown in the study by Heston et al.[21] of autopsy-documented cases with onset before age 70. This contrasts with the results of the present study in which those with onset of symptoms before age 65 were more likely (59%) to be found in the non-familial group (Table 1). For those with onset of symptoms after age 65, the proportions in the FDAT and NFDAT groups were equal (Table 1). An explanation for the finding of more familial cases in an older group of patients may be that the longer a person lives, the greater is the opportunity to develop a dementing illness.[24] A more likely explanation in this case is that the FDAT group were ascertained more often from geriatrics.

Recent studies examining other illnesses in patients and their relatives as potential risk factors associated with Alzheimer disease have been reviewed by Jorm,[25] and the EURODEM Risk Factors Research Group.[26] The approach has been an epidemiological one, comparing Alzheimer patients with healthy controls. By recognizing the heterogeneity of the disease, the present study analysed several determinants of immunological dysfunction within subgroups of Alzheimer disease, namely those with and without a family history of Alzheimer disease.

Many immunological conditions have been studied, and none more often than thyroid disease. Since the first report[18] of an increase in various thyroid conditions in Alzheimer patients and their relatives, no subsequent study has verified this finding with statistical significance.[25] However, a meta-analysis of risk factors by the EURODEM Research Group showed that a history of hypothyroidism was significant.[27] By separating the Alzheimer patients into familial and non-familial cases, we find a significant increase in thyroid conditions among patients

Table 6. Exposure to tuberculosis as a risk factor for DAT in FDAT and NFDAT families.

Tuberculosis exposure	FDAT (n = 47)			NFDAT (n = 53)		
	History	Death	Total	History	Death	Total
Within patients' immediate household						
in patient	4	–	4	–	–	–
in spouse	3	2	5	1	2	3
in child	–	5	5	1	–	1
Total	7	7	14	1	2	4
Corrected total*	7	4	11(23%)+	1	2	4(8%)+
Within patients' former household						
In parent	2	5	7	1	5	6
In sibling	–	2	2	–	2	2
Total	2	7	9(19%)	1	7	8(15%)

* A correction factor is used to reduce the total in families where both child and patient/spouse had tuberculosis.
+ Odds Ratio FDAT/NFDAT = 3.74, 95% CI = 0.99-17.22, p = 0.05

Table 7. Frequency distribution (%) of selected attributes of DAT subgroups.

Attribute	FDAT1 (n = 15)	FDAT2 (n = 32)	NFDAT1 (n = 31)	NFDAT2 (n = 22)	χ^2	p
Thyroid disease in patients	–	6	23	14	NS	
Autoimmune diseases in patients	–	22	32	32	NS	
Autoimmune diseases in relatives	40	22	55	45	NS	
Autoimmune disease cluster in relatives	7	3	19	18	NS	
Type 2 diabetes	–	13	26	9	NS	
Asthma	13	3	19	23	NS	
Infertility in relatives[1]	13	25	39	41	4.17	0.04
Tuberculosis exposure in household[2]	47	13	10	5	9.59	0.002
	(n = 13)	(n = 30)	(n = 30)	(n = 18)		
HLA A1	31	43	30	44	NS	
A2	38	40	40	67	NS	
	(n = 9)	(n = 27)	(n = 29)	(n = 18)		
HLA DR3[3]	56	44	21	17	7.07	0.008
DR4	–	30	34	39	NS	

[1]Odds Ratio NFDAT2/FDAT1 = 4.50, 95% CI = 0.70-48.85, p = 0.14.
[2]Odds Ratio FDAT1/NFDAT2 = 18.38, 95% CI = 1.74->100, p = 0.004.
[3]Odds Ratio FDAT1/NFDAT2 = 6.25, 95% CI = 0.75-55.74, p = 0.07.

(Table 2) and a non-significant increase among relatives (Table 3), but only in the NFDAT group.

With the exception of the study by Graves et al.[28] no case-control study[20,29] has separated autoimmune rheumatoid arthritis (OR = 1.18, 95% CI = 0.35-3.91) from the more common form, osteoarthritis. Kokmen et al. report pernicious anemia as a non-significant increased risk factor.[30] Other autoimmune diseases such as inflammatory bowel disease, lupus and multiple sclerosis have not previously been investigated in epidemiological studies of Alzheimer disease.

Allowing for the occurrence of more than one autoimmune disease in an individual, the presence of any autoimmune disease was observed more often among the NFDAT patients (Table 2). Similarly, more families with any of the autoimmune diseases were found in the NFDAT group (Table 3). This was particularly true for those families with multiple autoimmune diseases. Compared to the FDAT group, the NFDAT patients are younger and have younger relatives, so it is surprising that they have more immune-related conditions, which are age-related. However, there were proportionately more females (74% vs. 62%) in the NFDAT patient group and this may, in part, account for the increased immune-related response in this group. A similar reason does not explain the increase in autoimmune diseases in families since the proportion of females among NFDAT relatives is not higher (49%; 308/634) than that in FDAT relatives (51%; 293/576), as is the proportion of females over age 70 years (13% vs. 17%).

Most reports on the association of HLA antigens with Alzheimer disease have disregarded the heterogeneity of the disorder.[31-37] Some studies attempted to distinguish between patients with early and late age at onset of symptoms,[38-40] while others reported on patients with early-onset disease.[41,42] Two studies examined the HLA associations by age at onset and sex; both reported an increase in HLA A2 in males with early-onset disease.[43,44] The latter report further defined the group to include the sporadic occurrence of early-onset disease in males. With the exception of the last finding in a subset of patients, the only other study which examined data for differences in sporadic and familial Alzheimer disease was that of Reisner et al. who found a non-significant increase in HLA B7 in familial Alzheimer disease.[40] No such increase was found in the present study (16% vs. 27% for FDAT and NFDAT groups, respectively).

Our finding of an increased frequency of HLA A2 in NFDAT females (Table 4) disagrees with two previous studies citing an increased susceptibility in males.[43,44] This greater frequency is observed in the absence of any difference between FDAT and NFDAT groups, or between Alzheimer disease and controls. However, to postulate a disease susceptibility among females without a family history of Alzheimer disease is speculative on the basis of a single study.

A previous report on the Newfoundland population indicates that HLA DR3 occurs more frequently in patients with Graves' disease, and that both HLA DR3 and DR4 are increased in those with type 1 diabetes.[17] The association of the familial type of Alzheimer disease with HLA DR3 (Table 4) occurs in the absence of thyroid disease, while the two patients with type 1 diabetes expressed DR3. Even in the NFDAT group in which thyroid conditions were increased, there was no association with HLA DR3 (2 of the 10 patients).

It has been suggested that the association of HLA DR3 with late-onset autoimmune diseases reflects a failure in function resulting in an amplification of autoantibody production, and is in response to ageing factors.[6] Our data suggest that the HLA DR3 association is associated with ageing in the genetic form of Alzheimer disease and is not associated with coexistent autoimmune diseases in the sporadic form of Alzheimer disease. It

should be noted that the HLA DR3 association was observed in both sexes, although Bias et al. suggested an increased penetrance of the autoimmunity trait in females.[6]

Diabetes has not been shown to be a significant risk factor for Alzheimer disease.[25] A protective effect of diabetes mellitus in Alzheimer patients has been suggested,[45] but this was questioned by others.[46] This study showed that the frequency of type 1 and 2 diabetes is high in the FDAT group (13%; 6/47) and considerably higher in the NFDAT group (23%; 12/53, see Table 2), when compared with both patients (5.9%) and controls (5.6%) in the study of Small and Rosenthal.[46] No studies distinguish between autoimmune type 1 diabetes and non-autoimmune type 2 diabetes. We have shown a high frequency (19%; 10/53) of type 2 diabetic patients in the NFDAT group.

A trend toward reduced fertility has been reported in several studies comparing the number of offspring in female probands with their unaffected siblings or controls.[25] Increased fertility has also been reported for male probands,[47] and for both sexes.[22] Comparing our FDAT and NFDAT group of patients, there was no difference in fertility as measured by the mean number of offspring per patient (Table 5). The suggestion of reduced fertility noted in males, contrary to previous studies, was similar for both groups (Table 5). Infertility in Alzheimer patients was reported to be lower (14%) than in their normal siblings (19%).[47] Although infertility did not differ between our two groups of patients, a significant increase (Table 5) was noted among the first-degree relatives of the NFDAT group, among whom autoimmunity appears to be enhanced, as shown by the prevalence of autoimmune diseases.

The absence of dementia in spouses shows that a shared adult environment is not a sole risk factor for Alzheimer disease. Genetic predisposing factors may explain this finding, or the causative factor may be some childhood environmental exposure. Both adult and childhood exposure to tuberculosis were analysed as possible risk factors for Alzheimer disease (Table 6). In Newfoundland, tuberculosis was the leading cause of death in the first half of the century, and most elderly Newfoundlanders would have been exposed to the disease.[48] While our results do not show that tuberculosis is a risk factor for Alzheimer disease, the presence of tuberculosis in the patients' immediate household was found more often in the FDAT group. This correlation suggests that exposure to tuberculosis may increase the risk in the familial form of Alzheimer disease. Since HLA DR3 was also found to be increased in this group, an analysis showed there was no additive effect for the presence of DR3 and tuberculosis; only 29% were HLA-DR3 (2 of 7; 1 was not DR typed; and 3 could not be successfully DR typed after two attempts). A history of tuberculosis was not a risk factor for patients in an Australian study.[20] The role of tuberculosis in immunity is unclear, but some mycobacterial protein antigens have DNA sequences homologous to stress proteins which may be the immune targets formed as a response to an infectious agent.[49] As well, there are several microbial superantigens which can trigger an autoimmune response by binding to MHC class II molecules.[50]

By separating Alzheimer patients into familial and non-familial cases, it was possible to characterize the two groups with respect to possible risk factors. HLA DR3 and adult exposure to tuberculosis were features of the FDAT group, while a clustering of autoimmune diseases, asthma and infertility among

relatives were features of the NFDAT group. Further classification of FDAT and NFDAT into subgroups did suggest that adult exposure to tuberculosis may be of further relevance. However, this test for linear trend has its limitations in the assumption that the divisions between groups are quantitative. There is an apparent contradiction inferred from these findings which is difficult to explain. On one hand, HLA DR3 is associated with FDAT patients; they are older (30% over age 70, Table 1) and thus should have had more time to develop age-related autoimmune diseases. On the other hand, familial autoimmunity with known DR3 susceptibility occurs more frequently in the younger (25% over age 70) NFDAT patients. This suggests heterogeneity of Alzheimer disease based on different forms of disordered immunity.

There are two inferences which this analysis brings to light. First, it may be possible to confer a decreased risk for Alzheimer disease among first-degree relatives when many autoimmune diseases occur in the family. Second, the results suggest the relevance of environmental risk factors for Alzheimer disease as assessed after removing patients with the genetic form of the disease from the analysis.

Recent studies have addressed the efficacy of anti-inflammatory drugs, such as indomethacin[51] in the treatment of Alzheimer disease. As the basis for this treatment is to inhibit an inflammatory process, it may be suggested that Alzheimer patients with impaired immune function might have a different response to drug therapies. It may be important to define such a subgroup of Alzheimer patients. However, predicting that a group of patients from autoimmune families, such as in this study, would have a beneficial response to anti-inflammatory drugs is difficult, since the mechanism by which beta-amyloid provokes the immune system is not the same as in the conventional autoimmune response.[52]

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