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Genetic Studies on an Alzheimer Clinic Population

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All patients attending the Clinic for Alzheimer Disease and Related Disorders have detailed family histories taken by a geneticist. To date, genetic histories are available for 446 consecutive, unrelated individuals. Of these, 151 (33.9%) are diagnosed as having "probable" (N = 141) or "autopsy-confirmed" (N = 10) Alzheimer disease according to recognized criteria. This data base represents a relatively unselected population with respect to more than one person in the family having dementia.

Seventy-one of these 151 index cases (47.0%) have a positive family history of dementia, of which 8 (5.3%) may represent the familial (autosomal dominant) form of Alzheimer disease (FAD).

Age-corrected empiric recurrence risks for Alzheimer disease/dementia were calculated for first-degree relatives of these 151 index cases using the Kaplan-Meier lifetable method.

Key words: Alzheimer disease, dementia, genetics, recurrence risks

INTRODUCTION

Alzheimer disease is believed to be the most common cause of dementia, accounting for 50–65% of all patients with this diagnosis [Katzman, 1976; Marsden, 1978]. Alzheimer disease is characterized by an insidious onset, a steadily progressive course, and involvement of many areas of cognition in an individual who is otherwise alert, healthy, and free of motor or other neurological signs [Katzman, 1986]. Diagnostic criteria for "possible" and "probable" Alzheimer disease were established in 1984 according to NINCDS-ADRDA Work Group Criteria [McKhann et al., 1984].

The primary cause of Alzheimer disease remains unknown. Both genetic and environmental factors have been implicated. The observation of more than one affected

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member of a family does not necessarily imply that Alzheimer disease is inherited. However, 10–15% of cases are believed to clearly represent autosomal dominant inheritance, but clinical features are identical to those of "sporadic" cases [Friedland, 1988]. Several case reports of families with apparent autosomal dominant transmission of this disorder have been published, including those of Feldman et al. [1963], Heston et al. [1966], Goudsmit et al. [1981], Foncin et al. [1985], Bird et al. [1988,1989], and Sadovnick et al. [1988a]. Familial Alzheimer disease (FAD), as illustrated by these pedigrees, appears to be caused by a genetic defect. However, to date, DNA markers have been mapped to chromosome 21 in only a few such families with early onset dementia [St. George-Hyslop et al., 1987; Marx, 1988; Goate et al., 1989]. Initially, the B-amyloid gene was believed to be a candidate gene for FAD [Goodfellow, 1987; Tanzi et al., 1987a], but further investigation has shown this not to be the case [Tanzi et al., 1987b; Van Broekhoven et al., 1987; Devine-Gage et al., 1988; Schellenberg et al., 1988], although the role of the amyloid precursor protein in plaque formation is still under investigation [Ponte et al., 1988; Tanzi et al., 1988; Kitaguchi et al., 1988]. With respect to clinical, pathological, and biochemical features, the FAD phenotype cannot be clearly distinguished from "sporadic" cases. In fact, it has been hypothesized that there may be no such entity as "sporadic" Alzheimer disease, but rather these cases represent reduced penetrance of an autosomal dominant gene because family members have not lived long enough to express the disease [Editorial, 1986].

The first descriptions of FAD were Flügel [1929] and Schöttky [1932]. Attempts to predict whether a patient with Alzheimer disease has FAD, other than by taking a family history, have been largely unsuccessful [Breitner and Folstein, 1984; Fitch et al., 1988]. Twin studies [Nee et al., 1987] in non-FAD families have shown discordance among monozygotic twins (who are genetically alike), suggesting that non-genetic factors play a role in these families. Multifactorial inheritance has been postulated to explain clustering in some families [Sjögren et al., 1952; Sulkava et al., 1979; Whalley et al., 1982]. The importance of consanguineous matings as a causative factor in familial cases was reported by Lowenberg and Waggoner [1934]. Ethnic or racial differences in Alzheimer disease have been reported, but have not as yet been clearly delineated. Goudsmit et al. [1981] observed a preponderance of affected individuals of Ashkenazi Jewish origin in FAD, and Bird et al. [1988] reported a possible genetic "founder" effect for 7 kindreds of Volga German ancestry.

Evidence for heterogeneity is suggested by variability in age of onset, myoclonus, extrapyramidal signs, language deficit, family history, brain cholinergic activity, membrane platelet fluidity, and neuropathological changes [Bird et al., 1983; Mayeux et al., 1985; Chui et al., 1985; Jorm, 1985; Friedland, 1988; Zubenko et al., 1988]. Further evidence for heterogeneity comes from the failure of some groups to show linkage to chromosome 21 in FAD pedigrees [Schellenberg et al., 1988; Pericak-Vance et al., 1988]. This issue of heterogeneity is important and needs further documentation for i) the interpretation of genetic linkage data, especially with regard to the potential of preclinical testing for FAD; ii) practical advice for genetic counselling; and iii) clues to the underlying pathogenesis of Alzheimer disease [Bird et al., 1989].

Lifetable methods [Kaplan and Meier, 1958] can be used to examine age-specific risks for Alzheimer disease. These risks can be combined for estimates of cumulative risk (or morbid risk) of Alzheimer disease among relatives of index cases through any specified age. As long as the study population is sufficiently large, familial risk can be

studied into the 8th and 9th decades of life. If genetic mechanisms are responsible for typical, late-onset Alzheimer disease, it is expected that the cumulative incidence of Alzheimer disease among first-degree relatives of index cases will rise with age to approach 50% (i.e., the risk assuming autosomal dominant inheritance) by some (perhaps *very* late) age. Therefore, assessment of lifetime risk in these relatives is a method for evaluating the degree to which autosomal dominant genes may contribute to the etiology of Alzheimer disease [Mohs et al., 1987, 1988; Breitner et al., 1988; Martin et al., 1988].

Recent studies, using modern clinical research diagnostic criteria for Alzheimer disease, have employed the lifetable approach to determine lifetime risks to relatives of patients [Breitner and Folstein, 1984; Breitner et al., 1988; Martin et al., 1988; Zubenko et al., 1988]. All these studies found a lifetime risk approaching the 50% + figure by approximately age 90, as predicted by genetic models [Breitner et al., 1986]. Heston [1988] pointed out that estimates of Alzheimer disease in the general population by age 90 approach 20–30%; and it may not be appropriate to use specifically "non-demented" elderly controls. Such a control group could introduce a bias if they (and their relatives) are "genetically resistant" to developing dementia. Recently, Farrer et al. [1989] reported a much lower risk among first-degree relatives of patients with Alzheimer disease. In this study, a "weighting" system was used to account for secondary cases in a family for whom the diagnosis of Alzheimer disease was less certain.

All patients attending the Alzheimer Clinic routinely have a detailed family history taken by a geneticist as part of their overall assessment. This avoids many of the biases inherent in studies in which families are identified through genetics clinics or solicitation of volunteers, methods which tend to (understandably) result in overrepresentation of familial cases. Care is taken to identify families referred to the Clinic because of an a priori concern due to multiple members being affected. Such families are excluded from the data base referred to in this paper, even though they are thoroughly assessed. The method of incorporating genetic evaluation directly into a specialized medical clinic has been previously successfully done for multiple sclerosis, another adult-onset disease in which genetic factors are implicated in the etiology, but the exact genetic mechanism(s) is not clearly understood [Sadovnick nd Baird, 1988; Sadovnick et al., 1988b].

METHODOLOGY

Alzheimer Clinic

The mandate of the Alzheimer Clinic is threefold:

1. To provide assessment, often as a second opinion, for individuals referred with memory and other cognitive impairment;
2. To provide initial counselling;
3. To do research in the area of Alzheimer disease and dementing illnesses.

The multidisciplinary Clinic Team consists of an internist/geriatrician, a psychiatrist, a neuropsychologist, a social worker, a geneticist, and a clinical fellow in neurology. All patients are assessed by every member of the Clinic Team. After all the assessment details are evaluated, a diagnosis is assigned. Approximately 50% of patients are

diagnosed as having "probable" or "possible" Alzhimer disease [McKhann et al., 1984]; about 25% as having dementia, but Alzheimer disease is an "unlikely" etiology; and the remaining 25% do not meet the criteria for dementia at the initial assessment. Longitudinal studies of patients diagnosed as having "probable" Alzheimer disease using diagnostic criteria indicate that over 85% of cases have neuropathological findings consistent with a diagnosis of Alzheimer disease [Joachim et al., 1988; Tierney et al., 1988]. The group diagnosed as "not demented" on initial evaluation is followed at regular intervals in the Clinic, with the diagnosis amended as appropriate. All patients and their families attending the Alzheimer Clinic are informed of the importance of neuropathological data to confirm the diagnosis of Alzheimer disease, essential for genetic counselling and for all research [Katzman, 1986; Schellenberg et al., 1988].

Family History Method

Family history information is collected using the "family history" method, which relies on knowledgeable informants to provide information on relatives of the clinic patient or index case. The more elaborate "family study" method, in which all relatives are directly assessed, cannot be used in a study on Alzheimer disease as the majority of the index case's relatives are dead. Comparison of these two methods has shown that although the "family history" method slightly underestimates the number of affected relatives, errors can be greatly reduced by use of *multiple* informants [Andreasen et al., 1977; Silverman et al., 1986]. Multiple informants are used whenever possible; and in fact, to date, over half our families have had at least two informants other than the index case. Spouses and siblings of Clinic patients are preferred co-informants rather than children as they tend to know more about older relatives (parents; siblings).

Verification of the Diagnosis of Dementia/Alzheimer Disease in Relatives of Index Cases

If at all possible, reportedly affected relatives are assessed in a specialized Alzheimer Clinic and arrangements are made for neuropathological examination at a future time. If the relative is deceased, or if assessment cannot be arranged for family reasons, medical/autopsy records are obtained (with consent), and are reviewed with appropriate physicians (geriatrician, neurologist, psychiatrist, neuropathologist) to determine the most likely diagnosis.

Criteria for FAD

It is important to have stringent criteria for accepting a family as representing FAD for research purposes. While these criteria must be relaxed to a certain extent within a clinical setting for counselling purposes, they should be strictly adhered to for research, as was done in the present study. It is of course recognized that these criteria identify a very conservative group of families as FAD. The research criteria used in the present study are as follows:

i. Detailed family history must be available for at least the index case's generation and the previous (parental) generation.

ii. Good clinical documentation of dementia in relatives, preferably from at least 2 separate sibships within the family, must be available; and there must be no other plausible explanation for the dementia such as strokes, alcoholism, head injury, etc.

iii. Neuropathological documentation of Alzheimer disease must be available for at least one member of the family, but preferably for two or more.

iv. Accurate information on ages of death and/or present ages of relatives must be available so that it is possible to assess the "significance" of being clinically unaffected.

Analysis

The Kaplan-Meier lifetable method [Kaplan and Meier, 1958] was used to estimate age-specific cumulative morbid risks for Alzheimer disease in first-degree (parents, siblings) relatives of index cases. Standard errors were calculated using Greenwood's formula [Kaplan and Meier, 1958]. Data were analysed in three ways differing according to how "affected" individuals were included:

i. *Stringent, without FAD:* In this group, relatives were coded as "affected" only if good clinical and/or autopsy records could be obtained and Alzheimer disease seemed the almost certain diagnosis; FAD families were excluded since their inclusion could confound the results if autosomal dominant inheritance does *not* account for all Alzheimer disease.

ii. *Stringent, with FAD:* The criteria are as described in i, but FAD families are included. If all Alzheimer disease is in reality due to autosomal dominant genes, such families should be included in the analyses.

iii. *Relaxed:* This includes all cases in category ii, as well as those relatives for whom the only documentation of dementia is based on the descriptions by family informants, but the descriptions do suggest dementia of unknown etiology; e.g., other causes such as strokes and cardiovascular problems have been eliminated.

RESULTS

Informative genetic histories were available for 446 consecutive, unrelated Clinic cases. Of these, 23.5% were aged less than 65 at the first Clinic visit and 2.3% were aged 85 and above. Table I categorizes all 446 cases presenting at the Clinic according to diagnosis after evaluation. One hundred fifty-one Clinic patients were diagnosed as having "probable" (N = 141) or "autopsy-confirmed" (N = 10) Alzheimer disease as of August 1988. Complete data were available on 705 parents and siblings (45 years of age and over) of these index cases. The number of index cases with a family history (not necessarily a first-degree relative) of dementia meeting the criteria for "possible," "probable," or "autopsy-confirmed" Alzheimer disease is given in Table II. Age-specific morbid risk data for Alzheimer disease/dementia in first-degree relatives of

TABLE I. Diagnoses for 446 Clinic Patients After Evaluation

Clinic diagnosis	No.	% of total
Demented, Alzheimer unlikely	27	6.1
Demented, possible Alzheimer	90	20.2
Demented, probable Alzheimer	141	31.6
Autopsy confirmed Alzheimer	10	2.2
Not demented	108	24.2
Diagnosis pending[a]	70	15.7
Total	446	100.0

[a]This category consists of patients requiring future follow-up prior to assigning a diagnosis as well as those still in the process of assessment.

TABLE II. Family History of Dementia

Diagnosis in clinic patient	No. with a family history of dementia	% of total
Demented, Alzheimer's unlikely (N = 27)	3	11.1
Demented, possible Alzheimer's (N = 90)	39[a]	43.3
Demented, probable Alzheimer's (N = 141)	66[b]	46.8
Autopsy confirmed Alzheimer's (N = 10)	5[c]	50.0
Not demented at time of clinic assessment (N = 108)	40[d]	37.0

[a]5/39 (12.8%) have at least one relative with autopsy-confirmed Alzheimer's disease.
[b]14/66 (21.2%) have at least one relative with autopsy-confirmed Alzheimer's disease. This includes 7 families believed to represent FAD.
[c]2/5 (40.0%) have at least one relative with autopsy-confirmed Alzheimer's disease. This includes one familily with documented FAD [Sadovnick et al., 1988a].
[d]6/40 (15.0%) have at least one relative with autopsy-confirmed Alzheimer's disease.

TABLE III. Morbidity Risks for Dementia in First-Degree Relatives of Index Cases With Alzheimer Disease*

Category	No. of index cases	Cumulative risk (%) in first-degree relatives of index cases to age[a] 75	80	90
Stringent, without FAD	143	5.3 ± 1.2	9.9 ± 1.8	11.4 ± 2.5
Stringent, with FAD	151	7.6 ± 1.3	11.4 ± 1.9	14.4 ± 2.6
Relaxed	151	10.0 ± 1.5	14.9 ± 2.2	23.2 ± 3.8

*Dementia in relatives meets the criteria for "possible," "probable," or "autopsy-confirmed" Alzheimer disease.
[a]Percentages given ± standard error.

these 151 index cases are given in Table III. Lifetable adjusted risks for parents and siblings of index cases are presented in Table IV.

Eight out of 151 (5.3%) consecutive, unrelated families in which the Clinic patient has a diagnosis of "probable" or "autopsy-confirmed" Alzheimer disease likely represent FAD. None of these eight indicated a priori concern that they may represent FAD. In all these cases, Clinic referral was specifically to confirm the diagnosis of Alzheimer disease in the index case, and not because of concern about the family history. This relatively low rate of FAD may reflect the strict criteria we used to define FAD. In addition, it is important to note that families presenting at the Alzheimer Clinic specifically because of concern regarding possible FAD (of which there were 8 to date) are excluded from this calculation. If these families were included, the FAD rate would increase to 16/159, or 10.1%.

DISCUSSION

The results from this study are given in Tables III and IV. Risks to age 80 for relatives of index cases are within the range of most other studies [Breitner and Folstein, 1984; Breitner et al., 1988; Martin et al., 1988; Zubenko et al., 1988]. However, after

TABLE IV. Lifetable Age-Adjusted Risks for Parents and Siblings of Index Cases With Alzheimer Disease

	Cumulative risk in affected group (%)		
	Stringent		
Age	Without FAD	With FAD	Relaxed
36	0.00	0.14	0.14
37	0.00	0.14	0.14
38	0.00	0.27	0.27
39	0.00	0.41	0.41
40	0.00	0.55	0.55
41	0.00	0.55	0.55
42	0.00	0.55	0.55
43	0.00	0.55	0.55
44	0.00	0.55	0.55
45	0.00	0.55	0.55
46	0.00	0.55	0.55
47	0.00	0.55	0.55
48	0.00	0.55	0.55
49	0.00	0.55	0.55
50	0.16	0.70	0.70
51	0.16	0.70	0.70
52	0.32	0.85	0.84
53	0.32	0.85	0.84
54	0.32	0.85	0.84
55	0.32	1.00	1.00
56	0.32	1.00	1.00
57	0.32	1.00	1.00
58	0.32	1.00	1.00
59	0.32	1.16	1.33
60	0.50	1.33	1.66
61	0.68	1.51	1.84
62	0.87	1.68	2.01
63	1.06	1.87	2.20
64	1.26	2.24	2.57
65	1.47	2.44	2.77
66	1.47	2.44	2.77
67	1.70	3.09	3.42
68	1.70	3.09	3.42
69	2.21	3.56	3.89
70	2.48	4.33	4.65
71	2.78	4.61	4.93
72	3.10	4.90	5.52
73	3.78	5.86	6.47
74	4.87	6.87	8.49
75	5.27	7.62	9.99
76	6.19	8.47	10.84
77	6.19	8.92	11.29
78	6.19	8.92	11.29
79	6.79	9.48	12.39
80	8.91	11.40	14.92
81	8.91	12.18	15.68
82	9.86	13.04	17.38
83	9.86	13.04	18.31
84	9.86	13.04	19.38

continued

TABLE IV. Lifetable Age-Adjusted Risks for Parents and Siblings of Index Cases With Alzheimer Disease (continued)

	Cumulative risk in affected group (%)		
	Stringent		
Age	Without FAD	With FAD	Relaxed
85	11.39	14.43	20.77
86	11.39	14.43	20.77
87	11.39	14.43	23.25
88	11.39	14.43	23.25
89	11.39	14.43	23.25
90	11.39	14.43	23.25

age 80, even using "relaxed" criteria for inclusion of relatives as "affected," the cumulative risk does not approach 50% + as reported by these groups. There are several possible explanations for this difference.

The data presented here are for a comparatively large group (705 relatives of 151 index cases). Breitner et al. [1988] reported on 379 relatives (age 45 and over) of 79 index cases; Martin et al. [1988] reviewed 130 relatives of 22 index cases, the paper by Zubenko et al. [1988] included 211 relatives (age 45 and over) of 50 index cases, and Huff et al. [1988] studied 250 relatives of 50 index cases. At the older ages, sample size may be a factor. For example, at age 85, the risk group for the present study numbers 58, 2.8 × the size of the risk group of 21 in the study by Breitner et al. [1988].

It is possible that our study group may be different from those in the other studies [Breitner and Folstein, 1984; Breitner et al., 1988; Martin et al., 1988; Zubenko et al., 1988], especially since our data are for Canada, a country in which there is a universal medical insurance program. However, sufficient data are not available in the literature to allow detailed comparison of demographics (e.g., ethnic breakdown, age distribution) with the present study to determine whether any of these factors may contribute to the conflicting results.

Martin et al. [1988] raised an interesting point in conducting lifetable analyses, namely, that divergent thresholds for disease onset (the early observed symptom) and "caseness" (sufficient dementia for acceptance as affected) exist. Criteria used for determining onset can therefore influence the estimation of familial risk [Breitner and Magruder-Habib, 1989]. In the present study, onset was defined as the "first detectable symptoms of cognitive embarrassment" rather than the stricter definitions of either "first definite symptoms of dementia" or "evidence of progressive dementia" [Breitner and Magruder-Habib, 1989]. The definition of onset may alter calculated risks.

Another factor which could alter risk values is that even the "relaxed" criteria used in this study for accepting a relative as affected are designed only to include cases for whom the family information suggests no other etiology for the dementia. This is a different situation from accepting all reportedly demented or senile relatives as affected in the absence of *any* additional descriptive information. The term "relaxed" is in reference to accepting a case as affected in the absence of good clinical and/or autopsy records but still requires descriptions from family members and the completion of a dementia questionnaire [Silverman et al., 1986] whenever possible.

The question has been raised about whether the risk to relatives varies with age of onset in the index case. Since there is increasing evidence that Alzheimer disease rep-

resents a heterogeneous disorder, this may very well be a factor. Heston et al. [1981] found that relatives of index cases with their onset of Alzheimer disease under age 70 had the greatest risk, but this is not a universal finding [Larsson et al., 1963; Whalley et al., 1982; Heyman et al., 1983; Breitner and Folstein, 1984]. Although Bird et al. [1989] and Nee et al. [1987] reported variable age of onset within families, others have found significant correlations in age of onset between affected relatives [Sjögren et al., 1952; Larsson et al., 1963; Heston and Mastri, 1977; Heston et al., 1981; Heyman et al., 1983; Breitner and Folstein, 1984; Powell and Folstein, 1984; Sadovnick et al., 1988a]. This topic is currently being addressed for the study population as part of another series of analyses.

In conclusion, our data, as analysed for the present study, do not appear to indicate lifetable age-adjusted risks for parents and siblings of index cases approach 50% by age 90, even using "relaxed" criteria for accepting a relative as affected.

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