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ORIGINAL PAPER

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Psychiatric disorders in relatives of subjects with Alzheimer's disease

No evidence for common genetic risk factors

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Abstract *Introduction* The clustering of two or more disorders in the same family might indicate the presence of common genetic risk factors. The prevalence of various psychiatric disorders in relatives of Alzheimer's disease (AD) patients has rarely been investigated. Consequently, family study data were reinvestigated to assess, if there are indications for an overlap of genetic risk factors of AD and other psychiatric disorders. *Method* Family history information on 2964 living and deceased first-degree relatives of 146 AD patients, 168 patients with major depression (MD) and 136 control subjects were obtained by at least one informant. Of the living relatives, 49.2 % could also be interviewed. Best-estimate lifetime diagnoses were made on all available information. Lifetime prevalences of psychiatric disorders were compared in relatives of AD patients, of MD patients and of control subjects using chi^2 statistics. Cox proportional hazards regression analyses were additionally performed to control for the relative's age, gender and source of information (interview vs. family history information). *Results* Relatives of AD patients had no increased risk of other psychiatric disorder compared with relatives of the comparison groups. *Conclusion* AD is genetically distinct from other psychiatric disorders, i. e., schizophrenia, anxiety, obsessive-compulsive, somatoform disorders, alcoholism, substance abuse or dependency.

Key words Alzheimer's disease · major depression · anxiety · somatoform disorder · psychosis · family study · risk factors · familial aggregation

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Introduction

Family studies can provide information on the etiologic classification of psychiatric disorders, especially, if genetic causes are suspected. Assuming that genetic factors increase the risk for a disorder, relatives of subjects with one etiologic entity should show an increased risk for the disorder, but not other conditions. However, when two or more syndromes have common genetic antecedents, their relatives should have an increased risk of all such related syndromes, but not of other disorders (Kendell 1989). On a biological basis, a common example is provided by the apolipoprotein E 4 genotype which is assumed to be a risk factor for AD and vascular dementia (Kalman et al. 1998, Marin et al. 1998, Zhang et al. 2001). The presence of this individual risk factor in family members should increase the expression of both disorders in their families and, thus, should induce the familial co-aggregation of both disorders, i. e., an increased rate of both disorders in these families compared with families from the general population. Even if the relevant genetic risk factors for the individual disorders are not yet known, family studies may provide evidence for such an overlap of genetic risk factors of different disorders by showing familial co-aggregation of disorders.

Such reasoning presupposes significant familial aggregation for the individual disorders in question, such as Alzheimer's disease (AD) and other individual psychiatric disorders. In agreement, family studies have consistently revealed that AD shows a familial aggregation indicating the relevance of genetic risk factors (Heston et al. 1981, Heyman et al. 1983, Breitner and Folstein 1984, Huff et al. 1988, Farrer et al. 1989, Korten et al. 1993, Silverman et al. 1994, Heun et al. 2001). There is also evidence for familial aggregation of various other psychiatric disorders, e. g., affective disorders, anxiety disorders, alcoholism and schizophrenia (Gershon et al. 1982, Weissman et al. 1982, Sadovnick et al. 1994, Varma et al. 1997, Andrew et al. 1998, Bierut et al. 1999,

Kendler et al. 1999, Farmer et al. 2000, Hill et al. 2000, Lichtermann et al. 2000, Scherrer et al. 2000, Kendler et al. 2001, Heun et al. 2001).

Due to the high prevalence of psychiatric symptoms and disorders in AD patients, one might speculate that some of the relevant genetic risk factors might be shared by AD and other psychiatric disorders. In agreement with this, some authors have observed increased frequencies of depressive disorders in relatives of AD patients, especially if they had comorbid depressive syndromes (Pearlson et al. 1990, van Ojen et al. 1995, Strauss and Ogrocki 1996). However, in a comprehensive family study, we could not demonstrate that the prevalence of major depressive disorders (MD) in relatives of AD patients exceeded the rate expected by chance (Heun et al. 2001). Consequently, common genetic risk factors for AD and MD are less likely. Other psychiatric disorders have rarely been investigated for their familial co-aggregation with AD. An increased rate of psychotic disorders in relatives of AD subjects was observed by Li et al. (1992). This was not supported by Kotrla et al. (1995). Thus, no consistent statement about possible overlapping genetic risk factors between AD and these disorders can be made. Consequently, the data set of the above-mentioned comprehensive family study (Heun et al. 2001) were reinvestigated to examine the following hypothesis: Subjects with a genetic risk for AD, i. e. relatives of AD patients, have an increased risk for other psychiatric disorders compared with controls, e. g., bipolar affective disorders, schizophrenia, anxiety disorders, obsessive compulsive disorders, somatoform disorders or alcohol or substance abuse or dependency.

Methods

Subjects

In total 135 patients with late-onset AD (age at onset > 60 years) and 153 patients with MD (DSM-III-R criteria, APA 1987) aged above 60 years were recruited from the inpatient population of the Departments of Psychiatry of the Universities of Mainz (1992–1995) and Bonn (1996–1999), if they had at least one living first-degree relative aged above 50 years. (There were no subjects with familial early-onset AD [age at onset < 60 years] in this sample; consequently, AD patients might be called sporadic, even though their relatives may have had an increased risk for AD.) Recruited from the general population with the help of the city census agencies of both cities were 162 age- and gender-matched control subjects fulfilling identical criteria. Subjects from the general population who suffered either from AD or MD were therefore included in the former samples. The study was approved by the ethics committees of the Universities of Mainz and Bonn.

All subjects were asked for their and their first-degree relatives informed consent, and, if this was the case, provided addresses and contact information of their living relatives. Of the index subjects' first-degree relatives, 52.5 % were still living. These living relatives were contacted by mail and by phone to make an appointment for a personal interview. Of all living first-degree relatives, 49.8 % underwent a comprehensive personal interview and were asked to give family history information on all other first-degree relatives including deceased subjects. Thus, sufficient information for analysis was available on the total of 2964 first-degree relatives. Recruitment strategies were described in detail by Heun et al. (2001). Possible selection bias during recruitment of patients and relatives was carefully examined (Heun et al. 1995, Burkart et al. 1996). The observed reduced recruitment of diseased relatives of control subjects from the general population for personal interview was accounted for by including the above-mentioned second comparison group, i. e., relatives of patients with depression. Relatives of patients with MD as a second control group may also serve to distinguish possible genetic risk factors from other, psychosocial risk factors in families. Relatives of patients with MD who, like the control group from the general population, had no increased genetic risk to develop dementia (Heun et al. 2001), might suffer psychosocial risk factors for particular psychiatric disorders comparable to the relatives of AD patients, e. g., psychological stress caused by a mentally affected family member. Consequently, an increased risk of a disorder genetically related to AD should be observable in relatives of AD subjects in comparison with relatives of MD subjects and that of control subjects from the general population. For description of the study population see Table 1.

Interviews and diagnoses

The clinical examination of the patients consisted of personal and family history, neurological and medical assessment, an extensive laboratory work-up, EEG, computerized tomography or magnetic resonance imaging, and other tests if indicated. The patients, controls and their available first-degree relatives were assessed using the Composite International Diagnostic Interview (CIDI, WHO 1990) to assign

Table 1 Description of the patient and control samples and their first-degree relatives

	Patient diagnosis		
	Alzheimer's disease patients	Patients with major depression	Control subjects
Index subjects			
Number	N = 146	N = 168	N = 136
Male sex	27.4 %	30.4 %	42.9 %**
Female sex	72.6 %	69.6 %	57.1 %**
Age (years, mean ± SD)	75.6 years ± 10.1	69.3 years ± 8.2**	70.6 years ± 10.4**
First-degree relatives			
Number	N = 1055	N = 1069	N = 840
Personally interviewed	24.6 %	29 %*	24.4 %
Male sex	50.1 %	51.8 %	49.8 %
Female sex	49.9 %	48.2 %	50.2 %
Age (years, mean ± SD)	59.8 ± 19.6	57.3 ± 20.1**	57.7 ± 20.0*

* significantly different from the sample of Alzheimer's disease patients with $p < 0.05$ (Student-t test or Fischer's exact test); ** significantly different from the sample of Alzheimer's disease patients with $p < 0.01$ (Student-t test or Fischer's exact test)

lifetime DSM-III-R diagnoses for major psychiatric disorders (APA 1987). To detect and diagnose dementia, we interviewed patients, controls and their relatives over age 50 using the Structured Interview for Diagnosis of Dementia of the Alzheimer Type, Multi-infarct Dementia, and Dementia of other Aetiology (SIDAM, Zaudig et al. 1991). Both instruments include the Mini Mental State Examination (MMSE, Folstein et al. 1975). To detect depression and dementia in living and deceased relatives, we also used the Family History Questionnaire (Andreasen et al. 1977) and the Family Dementia Risk Questionnaire (Breitner and Folstein 1984, Silverman et al. 1986). Final best estimate lifetime diagnoses of all patients and relatives were made by two experienced psychiatrists on the bases of all available information (Leckman et al. 1982). To prevent information bias at this stage, the psychiatrists were kept blind to the diagnoses of the index subjects.

In the present study, interview and family history information was found to be reliable and valid (Heun et al. 1996, 1997, 1998, 2000, Heun and Müller 1998), even though the precision and sensitivity of diagnostic information was limited. Consequently, the individual diagnoses were clustered in diagnostic subgroups, i. e., bipolar affective disorder, dysthymia, schizophrenia, anxiety disorder, obsessive-compulsive disorder, somatoform disorder, alcohol abuse/dependency and substance abuse/dependency (see Table 2). (Unipolar major depression and AD were not included in the present analyses since the data on these disorders in relatives are already published, Heun et al. 2001). The diagnosis of the informant, but not of the index subject influenced the validity of the family history information (Heun et al. 1996, 1997). To prevent this information bias, i. e., more detailed information provided by subjects having personal experience with a psychiatric disorder, proxy information of diseased informants (patients and diseased relatives) was excluded from analysis. To account both for selection and information bias, source of information was also included as a covariate in statistical analysis.

Statistical methods

Chi-square tests were used to compare the prevalence rates of the individual psychiatric disorders between the three groups of relatives, i. e., relatives of AD patients, relatives of patients with MD and relatives of controls. Since the three groups of relatives slightly differed in the portion of interviewed relatives, the gender distribution and the mean age (see Table 1), Cox proportional hazards regression analyses were performed assessing the influence of the diagnosis of the index subjects (AD patient vs. control subject or patient with MD, respectively) controlling for the relative's age, sex (male vs. female) and source of information (personal interview vs. family history information, only) on the risk to develop particular psychiatric disorders.

Results

None of the investigated psychiatric disorders were more prevalent among relatives of AD patients than among relatives of control subjects or among relatives of patients with MD. Accounting for age, gender and the source of information, the Cox regression analysis revealed that anxiety disorders and substance abuse/dependency were significantly less frequent among relatives of AD patients than among relatives of controls (see Table 3).

Table 2 Definition of the diagnostic subgroups used in the study according to DSM-III-R codes

Diagnostic subgroup	DSM-III-R codes
Bipolar affective disorder	296.40–296.70
Dysthymia	300.40
Schizophrenia	295.10–195.94
Anxiety disorder	300–300.02 and 300.21–300.29
Obsessive-compulsive disorder	300.30
Somatoform disorder	300.70–300.81
Alcohol abuse/dependency	303.90 and 305.00
Substance abuse/dependency	304–304.90 and 305.10–305.90

Discussion

In this comprehensive family study, there was no aggregation of any psychiatric disorders in relatives of AD patients compared with relatives of control subjects and with relatives of patients with MD, i. e., the risk for bipolar affective disorders, dysthymia, schizophrenia, anxiety disorders, obsessive-compulsive disorders, somatoform disorders and alcohol or substance abuse or dependency was not increased in relatives of AD patients. Heun et al. (2001) also found no increased risk for major depression among relatives of AD patients compared with controls. Therefore, we concluded that AD is genetically distinct from other psychiatric disorders and has no overlapping risk factors with any of these disorders.

A secondary, unexpected result of the present study was the reduced risk of anxiety disorders and substance abuse in first-degree relatives of AD patients in comparison with relatives of controls. A lower risk of alcoholism in relatives of AD subjects had already been described by Lawlor et al. (1989).

There might be two explanations for this finding: The lower risk for anxiety disorders and substance abuse in relatives of AD patients might be explained by protective factors for anxiety disorders and substance abuse/dependency that were related to the genetic risk factors for dementia. Alternatively, the low risk of anxiety disorders and substance abuse in relatives of AD patients might be explained by a diagnosis-specific information bias: Relatives of AD patients are at increased risk for dementia (Heun et al. 2001); some cognitively impaired elderly relatives might have been insufficient informants on particular psychiatric symptoms, e. g., anxiety and substance abuse. Consequently, the prevalence of anxiety disorders and substance abuse in relatives of AD patients might have been underestimated. However, the general validity of the present data set is supported by the fact that we could clearly replicate the independent familial aggregation of depression and dementia that has been well described in the literature (Heun et al. 2001). In addition, there is no indication for an influence of the diagnosis of the index subjects on the quality of diagnostic information on other psychiatric disorders, even though this issue was only examined for the more frequent disorders, i. e., depression and dementia, in the context of previous analyses of the validity of the family history method (Heun et al. 1995, 1996, 2000, however, this negative finding had not been observed in these papers which focussed on significant variables of influence). Thus, both explanations, diagnosis-specific underreporting by relatives of AD subjects and protec-

Table 3 Prevalence rates of various psychiatric disorders in the first-degree relatives of AD patients, of MD patients and of controls from the general population. χ^2 tests were performed to compare the prevalence rates over the three groups of relatives, i. e., relatives of AD patients, patients with MD and controls, Cox regression analyses were performed to calculate relative risks for the prevalence rates in relatives of AD patients versus the individual comparison groups, and to control for age, gender, age at onset of a disorder, gender, and source of information (family study interview vs. family history, only). (*AD* Alzheimer's disease, *MD* major depression, *Contr* control subjects, *RR* relative risk, *CI* 95 %-confidence interval)

	Relatives of AD patients N = 1055	Relatives of patients with MD N = 1069	Relatives of healthy controls N = 840	Statistical analyses		
					Cox regression analyses	
				χ^2 test	Relative risk AD vs. Contr.	Relative Risk AD vs. MD
Bipolar disorders	3 (0.3 %)	9 (0.8 %)	3 (0.4 %)	$\chi^2 = 3.795$ d. f. = 2 p = 0.150	RR = 0.96 CI = 0.13–6.84	RR = 0.22 CI = 0.05–1.03
Dysthymia	10 (0.9 %)	12 (1.1 %)	6 (0.7 %)	$\chi^2 = 0.838$ d. f. = 2 p = 0.658	RR = 1.42 CI = 0.51–3.96	RR = 0.784 CI = 0.30–2.03
Schizophrenia	6 (0.6 %)	6 (0.6 %)	4 (0.5 %)	$\chi^2 = 0.089$ d. f. = 2 p = 0.957	RR = 1.55 CI = 0.37–6.53	RR = 0.953 CI = 0.29–3.16
Anxiety disorders	28 (2.7 %)	44 (4.1 %)	41 (4.9 %)	**$\chi^2 = 6.745$** **d. f. = 2** **p = 0.034***	**RR = 0.56*** **CI = 0.34–0.92**	RR = 0.74 CI = 0.45–1.22
Obsessive-compulsive disorders	1 (0.1 %)	2 (0.2 %)	0 (0 %)	$\chi^2 = 1.635$ d. f. = 2 p = 0.442	***	***
Somatoform disorders	0 (0 %)	2 (0.2 %)	1 (0.1 %)	$\chi^2 = 1.875$ d. f. = 2 p = 0.392	***	***
Alcohol abuse/dependency	42 (4 %)	39 (3.6 %)	36 (4.3 %)	$\chi^2 = 0.509$ d. f. = 2 p = 0.775	RR = 1.01 CI = 0.63–1.60	RR = 1.29 CI = 0.82–2.04
Substance abuse/dependency	1 (0.1 %)	7 (0.7 %)	14 (1.7 %)	**$\chi^2 = 15.857$** **d. f. = 2** **p = 0.000****	**RR = 0.08*** **CI = 0.01–0.58**	RR = 0.24 CI = 0.03–2.04

* statistically significant with $p < 0.05$; ** statistically significant with $p < 0.001$; *** insufficient numbers of affected cases for calculation of relative risks

tive factors genetically related to AD, remain speculative and could not be discriminated by the present evidence. Therefore, further investigations on this topic are needed before a decision on the relevance of the observations and on their possible explanations can be made.

Conclusion and limitations

In the present study, no increased risk for any psychiatric disorder (except dementia) could be found in relatives of AD patients compared to relatives of MD patients and relatives of control subjects from the general population. Consequently, AD is not likely to be genetically related to affective disorders, schizophrenia, anxiety, obsessive-compulsive disorder, somatoform disorders or alcohol or substance abuse/dependency.

One might argue that the low number of individual psychiatric disorder in relatives may have reduced the chance to detect minor differences in prevalence rates in the different groups of relatives. Consequently, some minor effects of genes, which may influence the expression of different psychiatric disorders in relatives of AD subjects, could not be completely excluded with the present data set. These might be observable in larger samples. However, the necessity to investigate these hypotheses in considerably larger samples will not be easy to fulfill, since the present results were already based on more than 1300 personal interviews and on more than 6000 individual family histories.

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