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Increased familial risk of the psychotic phenotype of Alzheimer disease

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Abstract—*Background:* Psychotic symptoms in patients with AD (AD with psychosis [AD+P]) define a phenotype characterized by more rapid cognitive and functional decline and a liability to aggressive behaviors. *Objective:* To determine if AD+P aggregates within families. *Methods:* Case-control study of AD+P frequency in 461 siblings of 371 probands diagnosed with AD. All siblings were ascertained as part of a genetic investigation and also were diagnosed with AD. Statistical analysis used Generalized Estimating Equations to adjust for clustering within families. *Results:* AD+P in probands was associated with a significantly increased risk for AD+P in family members (OR, 2.41; 95% CI 1.46–4.0; $p = 0.0006$). The correlation among siblings for AD+P status was modest: 0.16. *Conclusion:* AD+P demonstrates familial aggregation. Further studies are required to investigate a possible genetic basis of AD+P.

NEUROLOGY 2002;58:907–911

Psychotic symptoms such as hallucinations and delusions occur in individuals with AD; most studies report these symptoms occurring in 20% to 40% of patients with AD.[1] A recent report found the cumulative incidence of psychosis in AD (AD with psychosis [AD+P]) to be 51%.[2] AD+P has been associated with more severe cognitive deficits in patients with AD matched on other clinical characteristics.[3,4] The presence of psychotic symptoms also is an independent predictor of aggressive behavior,[5] more rapid functional decline,[6,7] and premature institutionalization.[6,8] Studies conflict regarding whether AD+P is

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Supported in part by research grants AG05133 from the National Institute of Aging and MH01489, MH53459, and MH57881 from the National Institute of Mental Health.

Received May 15, 2001. Accepted in final form December 8, 2001.

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associated with more rapid cognitive deterioration, although most have found an association.[2,6,9,10] When present, more rapid cognitive deterioration is unlikely to be solely an artifact of neuroleptic medication use,[11] as more rapid cognitive deterioration has been found preceding the symptomatic onset of psychosis.[2]

We have hypothesized previously that the presence of psychotic symptoms in patients with AD may identify a phenotype with distinct genetic determinants. Associations of AD+P with several candidate genes have been identified in case-control studies.[12-14] Although these findings support the hypothesis that AD+P may have a genetic basis, positive associations often are observed in case-control studies in the absence of true genetic causality. We are aware of only one prior study addressing the issue of the familial aggregation of AD+P.[15] That report examined 99 sibling pairs concordant for AD and found a concordance rate of 0.21 for AD+P. This rate of concordance was moderately higher than that predicted by the observed prevalence of 0.41 of AD+P in that cohort, although no statistical tests of significance were reported. Therefore, we undertook an examination of the familial risk for AD+P in a larger cohort of 371 AD probands and 461 of their siblings also diagnosed with AD, who were recruited and characterized as part of the National Institutes of Mental Health Genetics Initiative.

Methods. *Subjects.* Descriptions of the ascertainment and characterization of the NIMH Genetics Initiative AD Cohort have been presented elsewhere.[16] The initial identification of probands with AD and the recruitment of family members were designed to maximize ascertainment of families with multiple members affected by AD. Ascertainment did not specifically target the recruitment of AD+P subjects. The current analysis was restricted to families with two or more members diagnosed with definite, probable, or possible AD, who also had been characterized for the presence or absence of psychotic symptoms. Psychotic symptoms in probands and their family members were characterized at the time of initial evaluations and again during follow-up evaluations. The presence of psychotic symptoms was identified by responses to semi-structured interview questions. In a subset of subjects, this assessment was augmented by ratings on the Brief Psychiatric Rating Scale.[17] Subjects were classified as AD+P if they demonstrated either delusions or hallucinations at any time point (initial or follow-up examination).[12] Subjects without delusions or hallucinations were classified as AD without psychosis (AD−P). A more restrictive classification of AD+P, requiring either the presence of more than one psychotic symptom or the presence of psychotic symptoms during more than one assessment, also was generated. In addition, a history of parkinsonian symptoms was obtained, and subjects underwent standardized neurologic examination for evidence of extrapyramidal symptoms (EPS).

Statistical analysis. These data were collected for a genetics study, which had as its goal the discovery of genes affecting liability to AD. Consequently, the data represent "clusters" (families) of individuals affected with AD and therefore cannot be treated as independent for hypothesis tests. To adjust for the clustered aspect of the data, we used Generalized Estimating Equations (GEE),[18,19] as implemented in SAS's Proc Genmod. In GEE, the regression coefficients in the model are estimated assuming that the observations are statistically independent (i.e., not clustered). The standard errors of these coefficients are estimated in such a way that they take into account the correlation of the observations within families and they tend not to be greatly affected if this correlation structure is not specified correctly.

Because most individuals in the data set were either probands or their siblings (92.3%), we restricted our analyses to these family members and used the exchangeable option of Proc Genmod. For analyses involving discrete variables, we assumed a binomial distribution and used the logit link function.[18,19]

Two kinds of analyses were performed: 1) analyses in which the proband's status with respect to diagnosis of psychosis was treated as a predictor variable and the siblings' psychosis status was the outcome variable; and 2) analyses in which both the proband's and siblings' status were outcome variables. For the second analysis, the correlation among siblings' psychosis status was the statistic of interest. Because psychosis prevalence in AD may vary as a function of disease stage, the Clinical Dementia Rating (CDR)[20] score was entered as a covariate.

Results. Probands were predominantly white (350/371, 94.3%) and were predominantly female (269/371, 72.5%). Most (239/371, 64.4%) probands were diagnosed with probable AD, with the remainder (132/371, 35.6%) diagnosed with definite AD. Mean age (SD) of probands was 80.80 (8.26) years (range 46–103 years). Mean age at onset of AD was 72.1 (8.2) years (range 34–93 years). Probands were fairly evenly distributed with regard to severity of dementia with 63 (17%), 83 (22.4%), 111 (29.9%), 79 (21.3%), and 35 (9.4%) having CDR scores of 1, 2, 3, 4, and 5, respectively. Most probands (280/371, 75.5%) were characterized as AD+P.

Demographic and clinical characteristics of the probands' siblings are presented in the table. There was a significant association between proband psychosis status and the occurrence of AD+P in siblings. After fitting a GEE-based logit model, the estimated OR for AD+P in siblings of AD+P probands was 2.4 (95% CI, 1.46–4.0; $p < 0.0006$). In this model only the psychosis status of probands was significant, CDR score did not account for a significant portion of the variance in AD+P. Although proband psychosis status was a significant predictor of sibling psychosis status, the correlation among all siblings (including probands) was not large, 0.16, as estimated by the GEE model.

Similar results were obtained in various supplementary analyses. When sibling age and age-of-onset were entered as covariates in addition to CDR score, none of these covariates had a significant impact, but proband psychosis status remained a predictor with effects similar to those reported for the simpler model (OR, 2.47; CI, 1.49–4.09; $p < 0.001$). When the same model was used to examine the more restrictive definition of AD+P, once again proband psychosis status remained the only predictor (OR, 3.18; CI, 2.17–4.66; $p < 0.0001$). The correlation between siblings

Table *Demographic and clinical characteristics of 461 siblings of AD probands*

Sibling characteristics	Proband psychosis status	
	AD−P, mean (SD) or n (%)	AD+P, mean (SD) or n (%)
Age, y	81.5 (8.2)	80.8 (7.3)
range	55–97	51–105
Age at onset, y	72.5 (8.6)	72.0 (7.8)
range	46–90	42–92
Sex*		
Male	30 (27.8)	93 (26.4)
Female	78 (72.2)	259 (73.6)
Race*		
Black	4 (3.7)	16 (4.5)
White	104 (96.3)	334 (94.9)
Other	0 (0)	2 (0.6)
Diagnosis		
Definite AD	31 (28.7)	94 (26.6)
Probable AD	60 (55.6)	226 (64.0)
Possible AD	17 (15.7)	33 (9.3)
CDR score		
1	19 (17.6)	33 (9.3)
2	22 (20.4)	100 (28.3)
3	25 (23.1)	112 (31.7)
4	30 (27.8)	75 (21.2)
5	12 (11.1)	33 (9.3)
EPS†		
Absent	75 (72.1)	270 (78.3)
Present	29 (27.9)	75 (21.7)
Psychosis status		
AD−P	34 (31.5)	57 (16.1)
AD+P	74 (68.5)	296 (83.9)

* Data missing for one subject.
† Data missing for 12 subjects.

AD−P = AD without psychotic symptoms; AD+P = AD with psychotic symptoms; CDR = Clinical Dementia Rating; EPS = extrapyramidal symptoms.

for the more restrictive definition was modestly higher: 0.24. Likewise, the conclusion remained unaltered when the analyses were limited to siblings diagnosed only with definite or probable AD (OR, 2.54; CI, 1.48–4.35; $p < 0.001$), or to siblings with age at onset ≥65 (OR, 2.17; CI, 1.29–3.65; $p = 0.0035$). Entering EPS status and CDR as covariates, there was no significant effect of EPS, and the association of proband psychosis status was unaltered (OR, 2.19; CI, 1.32–3.67; $p < 0.0026$).

Discussion. This is the first study to identify a significantly increased risk for AD+P in the family members of AD+P probands. The odds of AD+P developing in siblings increased by more than twofold when the proband had psychotic symptoms. The increase in risk was not accounted for by stage of illness, nor by sibling age or age at onset. These findings provide additional evidence for AD+P as a distinct phenotype of AD and support the hypothesis that the development of psychosis in AD is determined, in part, by genetic factors.

The finding of familial aggregation of AD+P is an important first step in evaluating the genetics of AD+P, requiring independent replication. Unfortunately, available data sets, like the current study, were not primarily designed to investigate this question. Thus, prospective studies will be needed. Notably, evidence of familial aggregation is not proof of genetic causation. Familial aggregation also may result from environmental influences shared by family members. Although siblings typically are exposed to few shared environmental influences throughout adult life, the possibility that a common environmental influence from earlier in life might render family members vulnerable to the expression of psychotic symptoms after onset of AD cannot be excluded. Nevertheless, our earlier investigations suggest that genetic variation may indeed account for part of the risk for AD+P. We found that homozygosity for either allele of a biallelic *Bal*I polymorphism in the dopamine$_3$ receptor gene (*DRD3*) was associated with an OR (95% CI) of 1.8 (1.0,3.3) for AD+P.[12] An effect of similar magnitude, OR 1.9 (1.1,3.3), was seen for B2/B2 homozygotes for a biallelic *Dde*I polymorphism in the dopamine$_1$ receptor gene (*DRD1*). More recently, we found that homozygosity for long alleles of an insertion/deletion polymorphism in the serotonin transporter (SLC6A4) was associated with an OR of 2.6 (1.4,4.9) for a combined AD+P/aggressive phenotype.[13]

We had previously hypothesized that there may be a set of genes that each contribute a modest risk to psychosis across neurodevelopmental and neurodegenerative conditions.[12] The current finding of familial aggregation of AD+P, in concert with a recent report that identified familial aggregation of psychosis in Huntington disease,[21] suggests that liability to psychosis is heritable in at least these two neurodegenerative disorders. Moreover, the available evidence for AD and Huntington disease indicate that psychotic symptoms are not associated with risk genes for neurodegeneration itself.[21-23] Whether a partly overlapping set of genes contribute to the occurrence of psychosis across these disorders, and to schizophrenic psychosis, remains to be determined. Currently, however, the limited available data do not indicate that AD+P is associated with family history of psychiatric illness[24] or with a family or personal history of psychotic disorders specifically.[25]

Important strengths of the current study are the large number of families and family members evaluated and the rigorous diagnosis of AD. All probands were diagnosed with probable or definite AD, and autopsy confirmation of definite AD in subjects diagnosed during life as having possible or probable AD approached 100%.[16] Notably, even among subjects

with autopsy-confirmed AD, rates of comorbid cortical Lewy body disease can be as high as 60%.[26] This raises the possibility that the familial aggregation of AD+P may in part reflect underlying Lewy body disease. Unlike dementia with Lewy bodies, however, there is less consistent evidence that the presence of cortical Lewy body disease in patients with AD is associated with AD+P.[27-30] Moreover, when EPS, a possible proxy for underlying Lewy body disease, was included as a covariate in the analysis of familial aggregation of AD+P, the results were unchanged.

The major limitation to the interpretation of the results of the study is the high prevalence of psychosis in our subjects. Two possible biases may have contributed to the high AD+P prevalence. First, although AD+P subjects were not specifically targeted for recruitment into this study, it is possible that AD+P probands and siblings were disproportionately ascertained. Because the primary criterion for study entry was the presence of two or more members within the family affected with AD, this raises the possibility that AD+P was over-represented in this sample because AD+P is more prevalent in late-onset familial AD than in sporadic AD. We are not aware of any existing data that directly address this issue.

Alternatively, the reliance on a semi-structured interview assessment of psychotic symptoms rather than using behavioral rating scales designed and validated for the assessment of psychosis in AD may have led to an overestimate of the frequency of psychosis in these subjects. Studies using validated behavioral rating instruments for the identification of psychosis typically have found lower AD+P prevalences when examining unrelated individuals with AD, recruited from similar community settings.[9,12,31] Therefore, it is possible that use of a standardized instrument to classify AD+P might have led to a different estimate of the familial risk. Mitigating against this possibility, however, when we used a more restrictive definition of psychosis, requiring the presence of multiple symptoms or the persistence of symptoms across multiple assessments, the evidence of familial risk for AD+P persisted and even strengthened. Similarly, the one prior report[15] to examine the concordance of sibling pairs for AD+P used a dementia-specific rating scale to assess behavioral symptoms, the Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia (MOUSEPAD),[32] and also found evidence congruent with a moderately increased familial risk for AD+P.

Despite the concurrence of these findings, the dependence of AD+P rate on the method of behavioral assessment used highlights the difficulties in treating AD+P as a dichotomous phenotype. Future studies of AD+P heritability and genetic causation should give consideration to alternate approaches to AD+P, including use of persistence and number of psychotic symptoms to define a quantitative trait.

Appendix

Data and biomaterials were collected in three projects that participated in the National Institute of Mental Health (NIMH) Alzheimer Disease Genetics Initiative. *Principal investigators and co-investigators (1991–1998)*: Massachusetts General Hospital, Boston, MA, U01 MH46281, Marilyn S. Albert, PhD, and Deborah Blacker, MD, ScD; Johns Hopkins University, Baltimore, MD, U01 MH46290, Susan S. Bassett, PhD, Gary A. Chase, PhD, and Marshal F. Folstein, MD; University of Alabama, Birmingham, AL, U01 MH46373, Rodney C.P. Go, PhD, and Lindy E. Harrell, MD.

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CME

Prevalence and clinical importance of sleep apnea in the first night after cerebral infarction

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Abstract—*Objective:* To determine the prevalence of sleep apnea (SA) during the first night after hemispheric ischemic stroke and its influence on clinical presentation, course, and functional outcome at 6 months. *Methods:* The first night after cerebral infarction onset, 50 patients underwent polysomnography (PSG) followed by oximetry during the next 24 hours. Neurologic severity and early worsening were assessed by the Scandinavian Stroke Scale and outcome by the Barthel Index. Patients were evaluated on admission, on the third day, at discharge, and at 1, 3, and 6 months. *Results:* There were 30 males and 20 females with a mean age of 66.8 ± 9.5 years. Latency between stroke onset and PSG was 11.6 ± 5.3 hours. Thirty-one (62%) subjects had SA (apnea–hypopnea index [AHI] ≥ 10). Of these, 23 (46%) had an AHI ≥20 and 21 (42%) an AHI ≥25. Sleep-related stroke onset occurred in 24 (48%) patients and was predicted only by an AHI ≥25 on logistic regression analysis. SA was related to early neurologic worsening and oxyhemoglobin desaturations but not to sleep history before stroke onset, infarct topography and size, neurologic severity, or functional outcome. Early neurologic worsening was found in 15 (30%) patients, and logistic regression analysis identified SA and serum glucose as its independent predictors. *Conclusions:* SA is frequent during the first night after cerebral infarction (62%) and is associated with early neurologic worsening but not with functional outcome at 6 months. Cerebral infarction onset during sleep is associated with the presence of moderate to severe SA (AHI ≥ 25).

NEUROLOGY 2002;58:911–916

Sleep apnea (SA) is characterized by recurrent cessation of airflow, oxyhemoglobin desaturation, and sleep fragmentation and affects 2 to 5% of the population.[1] Several risk factors for ischemic stroke, such as arterial hypertension, coronary heart disease, cardiac arrhythmias, obesity, and habitual snoring, are common among patients with SA.[1,2] Conversely, SA is frequent in patients with recent cerebral infarction,[3-12] and it has been suggested that hemodynamic disturbances such as decline in cerebral

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Supported by a grant from Carburos Metalicos ($35,000) and the Fondo de Investigaciones Sanitarias of Spain (FISS 97-1088).

Received June 25, 2001. Accepted in final form December 1, 2001.

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