Heritability of Psychosis in Alzheimer Disease

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Objective: *The authors have previously demonstrated familial clustering of psychotic symptoms in late-onset Alzheimer disease (LOAD + P) and sought to estimate and explore the nature of the heritability of LOAD + P.* **Methods:** *The heritability of LOAD + P, defined by single and multiple psychotic symptoms, was estimated with data from the National Institute of Mental Health AD Genetics Initiative.* **Results:** *The estimated heritability for LOAD + P defined by multiple psychotic symptoms was 61%; for LOAD + P defined by any occurrence of psychotic symptoms, it was 30%.* **Conclusion:** *Multiplicity of symptoms may represent a useful means for defining a genetically determined LOAD + P phenotype.* (Am J Geriatr Psychiatry 2005; 13:624–627)

Psychotic symptoms, such as hallucinations and delusions, have a cumulative incidence of 40%–60% among patients with late-onset Alzheimer disease (LOAD).[1] These symptoms identify a severe phenotype, with greater cognitive deficits, faster cognitive and functional deterioration, tendency to aggressive behavior, and premature institutionalization.[2–7] One strategy in the search for the genetic basis of complex disease such as LOAD is the use of phenotypes with more homogeneous genetic origins.[8] The presence of psychotic symptoms in LOAD (LOAD + P) may define such a critical phenotype.[9] Genetic variation could contribute to accelerated neurodegeneration during LOAD, with more rapid cognitive deterioration and the emergence of psychotic symptoms. Alternatively, genetic variation could underlie a psychosis trait characterized by overt delusions and hallucinations after onset of neurodegeneration. This trait could be etiologically related to psychotic symptoms in the context of other neurodegenerative or neurodevelopmental insults.[9,10]

However, there is remaining uncertainty about how best to use LOAD + P to further genetic analyses of LOAD itself and of psychosis more generally. Most studies have treated psychosis as either present (any occurrence of symptoms) or absent. Because LOAD + P might arise from misclassification of cognitive symptoms or real events as delusional or might result from concurrent medical illnesses or treatments,[9] such an approach may not be best for detecting meaningful associations of psychosis with genetic variation. Our previous analysis of familial aggregation of LOAD + P revealed that, when defined by the presence of at least one psychotic symptom, the odds ratio (95% confidence interval [CI]) of LOAD + P in siblings of LOAD + P probands versus siblings of LOAD probands without psychosis was 2.4 (1.5–4.0). The odds ratio increased to 3.2 (2.2–4.7) when LOAD + P was defined by the presence of multiple psychotic symptoms.[11] These findings led us to hypothesize that number of psychotic symptoms might be useful in differentiating heritable LOAD + P from phenocopies.

METHODS

Subjects

Description of the ascertainment and characterization of the cohort has been presented elsewhere.[11,12] Subjects were ascertained on the basis of the presence of a relative pair afflicted with Alzheimer disease (AD), without additional requirements of family structure or age at onset.[12] Ascertainment did not specifically target the recruitment of AD + P subjects. Diagnoses of AD were made according to criteria of the National Institute of Neurological and Communica-

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tive Disorders and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS–ADRDA).[13] Psychotic symptoms in probands and their affected 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 semistructured interview questions. In a subset of subjects, this assessment was augmented by ratings on the Brief Psychiatric Rating Scale (BPRS).[14] Because of the small number of nonsibling relatives that were phenotyped, we restricted analyses to siblings. Four subjects from our previous report[11] were eliminated because of updated diagnostic and genetic information, and two families were dropped because the affected sibling pairs were monozygotic twins. Subjects without any psychotic symptoms were classified as NP. Those who demonstrated the presence of at least one psychotic symptom at any assessment were classified as Any Psychosis (AP; i.e., the broad definition of our earlier report[11]). Subjects with the presence of more than one psychotic symptom at any assessment or psychotic symptoms during more than one assessment were classified as Multiple Psychosis (MP; i.e., the narrow definition of our earlier report[11]).

Statistical Analysis

The odds ratio for siblings of affected (MP and AP) versus NP probands was determined via Generalized Estimating Equations (GEE),[15] as implemented in Splus' GEE function. We assumed a binomial distribution, a logit link, and an exchangeable correlation structure within families. Proband psychosis status, sex, age, LOAD age at onset and duration, and proband dementia stage, as indicated by the Clinical Dementia Rating Scale score (CDR), were used as covariates.

The heritability of psychosis in LOAD was assessed in the presence of these covariates by use of SOLAR.[16] SOLAR is a software package for genetic-variance-components analysis, including linkage analysis, quantitative genetic analysis, and covariate screening. It performs analyses for marker-specific or multipoint identity-by-descent (IBD) in pedigrees of arbitrary size and complexity, and linkage analysis of traits that may involve multiple loci, dominance effects, epistasis and covariates. SOLAR provides only the p values when testing for significance of heritability and covariate effects. For heritability testing, the p values are internally obtained from statistics that are a ½:½ mixture of a mass at zero and a χ^2_1 random variable[16] (denoted henceforth as *half* χ^2_1). The tests used for covariate effects are standard χ^2_1. This estimate of heritability represents an upper limit, because, by the nature of the data, we must assume: 1) uncorrelated environmental effects; and 2) that the occurrence of psychosis was independent of ascertainment on LOAD. MP and AP were examined as binary traits; that is, compared with NP, assuming a polygenic genetic model for the disease. Covariates were screened by sequentially eliminating covariates with the highest p values, retaining only the significant covariates in the final heritability analysis. As a rough corroboration of the results from SOLAR, we also analyzed the data with a GEE model.[15]

RESULTS

The 826 subjects had a mean (standard deviation [SD]) age of 80.8 (8.1) years, with a mean age at onset of dementia of 72.0 (8.2) years. Subjects were predominantly female (605; 73.2%). Most, 782 (94.7%) were Caucasian. Definite AD was diagnosed in 256 (31%), probable AD in 520 (63.0%), and possible AD in 50 subjects (6.1%). CDR score was 1 in 113 (13.7%), 2 in 204 (24.7%), 3 in 246 (29.8%), 4 in 183 (22.2%), and 5 in 80 subjects (9.7%). A total of 644 subjects (77.9%) were classified as AP, 366 (44.3%) as MP. The frequency of sibling psychosis status by proband psychosis status is given in Table 1.

The odds ratio (95% CIs) for AP in siblings of similarly affected probands was 2.37 (1.45–3.87). The OR (odds ratio) value for MP was 5.42 (2.62–10.43). The z tests of the log-ORs were 3.37 ($p < 0.001$) and 5.06 ($p < 10^{-6}$) for AP and MP, respectively. Using SOLAR,

TABLE 1. Frequency of Sibling Psychosis Status by Proband Psychosis Status

	Sibling Psychosis Status		
Proband psychosis status	**No Psychosis**	**Single Symptom**	**MP**
No psychosis, N (%)	34 (31.5%)	41 (38%)	33 (30.5%)
Single symptom, N (%)	34 (22.2%)	69 (45.1%)	50 (32.7%)
MP, N (%)	23 (11.9%)	51 (26.2%)	121 (62.0%)

Note: The single-symptom and multiple-symptom (MP) groups combined form the AP group.

the estimated heritability of AP was 29.5% ($p = 0.04$, *half* $\chi^2_1 = 3.25$), the only covariate retained in the model was sex ($p = 0.02$; $\chi^2_1 = 5.18$). For MP, SOLAR estimated the heritability as 60.8% ($p = 0.004$; *half* $\chi^2_1 = 7.03$), with both sex ($p = 0.04$; $\chi^2_1 = 4.31$) and CDR score ($p < 0.1$; $\chi^2_1 = 3.25$) also retained in the model. Similar estimates of heritability were obtained in the GEE analysis; that is, 32.3% (z test: 2.94; $p = 0.003$) and 69.6% (z test: 4.51; $p < 10^{-5}$) for AP and MP, respectively).

DISCUSSION

These findings are consistent with the hypothesis that refining the definition of LOAD + P by consideration of the number of psychotic symptoms may be fruitful for genetic analyses. When we narrowed the definition of LOAD + P from one requiring any occurrence of psychosis (AP) to one requiring multiple or recurrent psychotic symptoms (MP), both the degree of familial aggregation and the estimate of heritability were increased in magnitude. This conclusion needs to be tempered, however, by recognition that the 95% confidence intervals for the AP and MP groups were broad and overlapping. Other limitations of this study also need to be considered. Our estimate of heritability depends in part on the sample being ascertained for LOAD independently of LOAD + P. Although the criteria for ascertainment of families in the NIMH AD Genetics Initiative cohort would meet this assumption, it remains possible that the sources from which subjects were recruited (predominantly academic AD Centers) were biased toward LOAD + P. Moreover, the current estimate of heritability includes both shared environmental and genetic effects. Other approaches, such as twin studies of LOAD + P, are needed to estimate the genetic component more specifically, although no such studies have been conducted to date.

Despite these limitations, defining LOAD + P for genetic analyses by requiring multiple symptoms appears to be a useful strategy. The heritability of the MP group was greater than 60%. This value compares favorably with generally accepted estimates of a heritability of 60%–75% for LOAD[17] and of 70%–85% for schizophrenia.[18] If LOAD + P is more homogenous with regard to genetic etiology than LOAD, then the effect of loci on LOAD + P liability will be larger, making them more likely to be detected by linkage analysis.[19] An initial successful effort using LOAD + P to enhance genetic analysis of LOAD is consistent with this interpretation.[20]

Our model of the relationship of genetic variation to LOAD + P also allows for the possibility that genetic variation contributes to an underlying psychosis trait expressed in the context of neurodegeneration due to LOAD. Although two small studies have not found a family history of psychotic disorders to be more frequent in LOAD + P than in LOAD subjects without psychosis,[21,22] because base rates of idiopathic psychotic disorders are low, the small sample sizes and the lack of structured diagnostic interviews of multiple family members in these studies precludes any firm conclusion that idiopathic psychotic disorders do not co-segregate with LOAD + P. If the relatively high heritability estimates for LOAD + MP reflect loci affecting liability to psychosis, as opposed to liability toward a more genetically homogenous subgroup of LOAD, targeting LOAD + P in linkage analysis would instead contribute to efforts to identify the genetic bases of psychoses. In this regard, it is noteworthy that our linkage analysis of LOAD + P families revealed regions of significant and suggestive linkage on Chromosomes 2p and 6q that are highly overlapping with linkage regions in schizophrenia.[20] Given the success of these initial efforts, as additional cohorts of LOAD families are recruited for linkage analysis, detailed characterization of psychotic symptoms will be critical.

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

This work was supported in part by grants AG05133 and AG16976 from the National Institute on Aging and MH01489, MH53459, and MH57881 from the National Institute of Mental Health. SAB is the recipient of a National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award.

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