Early Detection of Alzheimer Disease: Methods, Markers, and Misgivings

R. C. Green, *V. C. Clarke, *N. J. Thompson, J. L. Woodard, and *R. Letz

*Memory Assessment Clinic and Alzheimer's Disease Program, College of Health and Human Sciences, Georgia State University, Atlanta; and *Department of Behavioral Sciences and Health Education, Rollins School of Public Health at Emory University, Atlanta, Georgia, U.S.A.*

Summary: There is at present no reliable predictive test for most forms of Alzheimer disease (AD). Although some information about future risk for disease is available in theory through ApoE genotyping, it is of limited accuracy and utility. Once neuroprotective treatments are available for AD, reliable early detection will become a key component of the treatment strategy. We recently conducted a pilot survey eliciting attitudes and beliefs toward an unspecified and hypothetical predictive test for AD. The survey was completed by a convenience sample of 176 individuals, aged 22–77, which was 75% female, 30% African–American, and of which 33% had a family member with AD. The survey revealed that 69% of this sample would elect to obtain predictive testing for AD if the test were 100% accurate. Individuals were more likely to desire predictive testing if they had an a priori belief that they would develop AD ($p = 0.0001$), had a lower educational level ($p = 0.003$), were worried that they would develop AD ($p = 0.02$), had a self-defined history of depression ($p = 0.04$), and had a family member with AD ($p = 0.04$). However, the desire for predictive testing was not significantly associated with age, gender, ethnicity, or income. The desire to obtain predictive testing for AD decreased as the assumed accuracy of the hypothetical test decreased. A better short-term strategy for early detection of AD may be computer-based neuropsychological screening of at-risk (older aged) individuals to identify very early cognitive impairment. Individuals identified in this manner could be referred for diagnostic evaluation and early cases of AD could be identified and treated. A new self-administered, touch-screen, computer-based, neuropsychological screening instrument called Neurobehavioral Evaluation System-3 is described, which may facilitate this type of screening. **Key Words:** Alzheimer disease—Early detection—Neuropsychological screening—Predictive testing.

Slowing the progression of Alzheimer disease (AD) undoubtedly will be a major focus among the strategies to treat AD over the next decade (Khachaturian, 1992). Successfully slowing the progression of AD would be tantamount to a cure if, and only if, the rate of progression were to be sufficiently slowed by a treatment and if that treatment could be applied early in the course of the

disease, preferably before the development of clinical symptoms. Hence, early detection is vitally important to any discussion of such a treatment.

As we consider the notion of early detection, two fundamental questions must also be considered. First, what is it that we are attempting to detect? Are we referring to the detection of a genetic trait that has been present since conception, a biochemical abnormality in the processing of APP that gradually becomes apparent with age, or a decline in cognitive abilities that heralds the onset of clinical dementia? A second and related question is just

Address correspondence and reprint requests to Dr. R. C. Green at Memory Assessment Clinic and Alzheimer's Disease Program, College of Health and Human Sciences, Georgia State University, 1 Park Place South, Atlanta, GA 30303, U.S.A.

how early should early detection take place? A biologic marker (ApoE genotype determination) that offers a probabilistic measure of risk for AD is already available and could in theory be offered at any time during childhood or adulthood, or even in utero (Farrer, 1997). A recent consensus conference in the United States concluded that ApoE should not currently be used as a predictive test in nondemented individuals (Farrer et al., 1995). However, the likelihood that future tests will be developed with greater accuracy raises interesting questions: Is there a desire for predictive information about the risk for developing AD on the part of unaffected individuals and, if so, what are the benefits and risks of providing this information, both now and once effective neuroprotective treatments become available?

At present there is no effective available treatment to slow the progression of AD. However, there is reason to believe that such treatments will become available in a few years, and at that point the issue of predictive testing, perhaps even with a technique with as limited accuracy as that of ApoE genotyping, will surely become more relevant. Even in a disease such as breast cancer, in which early detection may be indisputably linked to improved clinical outcome, there is considerable controversy about the methodology and ethics of providing genetic testing as a means of assessing the risk for eventual development of this disease. No data are currently available to provide insights into the policies and choices that would be made and the repercussions that might ensue if ApoE testing, or some other measure of the preclinical risk of AD, were to be used in asymptomatic individuals.

A SURVEY OF ATTITUDES TOWARD PREDICTIVE TESTING FOR AD

We have recently conducted a pilot survey of 176 individuals in which the following questions were asked: What percentage of those surveyed would choose to take a hypothetical predictive test for AD? What characteristics are associated with the desire to obtain predictive testing for AD? How does the accuracy of the predictive test for AD affect one's desire to be tested? How would the availability of a treatment to delay the onset of AD influence the decision to use predictive testing? What characteristics are associated with serious consideration of suicide after a positive predictive test for AD, and how would various degrees of hypothetical test accuracy impact these considerations of suicide?

The subjects in this pilot survey were a convenience sample of cognitively normal individuals drawn in ap-

proximately equal measure from the following groups: (a) family members and caregivers of patients with AD attending a regional symposium sponsored by the Alzheimer Association; (b) subjects participating in a study of past exposures to chemicals in the workplace; and (c) volunteers from a local civic organization. The study was approved by the institutional Human Investigations Committee and all subjects gave informed consent. The response rate and demographics of the study population are shown in Table 1. The first question was: What characteristics are associated with the desire to obtain predictive testing for AD? Using multiple regression, the following subject characteristics were significantly associated with the desire to obtain predictive testing for AD. Such individuals were more likely to believe a priori that they would develop the disease ($p = 0.0001$). They were also more likely to have a lower educational level ($p = 0.003$). This finding is interesting because most studies of people who seek genetic counseling show that more highly educated individuals are more likely to seek genetic testing. The desire to obtain predictive testing for AD in this sample was also associated with being worried that they will develop AD ($p = 0.02$), having a self-defined prior history of depression ($p = 0.04$), and having had a family member with AD ($p = 0.04$). A desire for predictive testing was not significantly associated with age, gender, ethnicity, or income in this sample.

The next question was: How does the accuracy of a hypothetical predictive test affect one's desire to be tested? When the assumed accuracy of the test increased, significantly more individuals in this sample agreed that they would like to be tested. Interestingly, those who already believed that they were going to get the disease were significantly more likely to want to be tested at all levels of hypothetical accuracy than those who did not. This finding appears to provide a clue to at least one underlying reason why individuals may want to be tested: they believe that they are at risk and are seeking evidence to counter this belief. Indeed, we think that this belief is far more pervasive than has been recognized.

TABLE 1. *Response rate and demographics of the study population*

$n = 176$ (54% response rate)
45 ± 12.8 years of age (range 22–77)
75% female
30% African–American, 70% Caucasian
Education
28% ≤ high school
41% with some college
31% with some graduate school
33% (13%) have a family member (parent) with AD

Moreover, there appears to be almost magical thinking that occurs around the question of probabilistic testing for AD.

To illustrate this point, when one women was asked the following question: "If you got a 'yes' answer on a predictive test for AD that was 80% accurate, would you believe that you were surely going to develop the disease?" and she said "Yes." When the same question was asked, substituting 70% accuracy, the answer was "Probably so." Asking the same question using an assumption of 60% accuracy, the answer was "No." So between 60 and 70% accuracy, this individual apparently found room for hope. Indeed, a number of subjects indicated that they were personally convinced that they would develop AD and that they would seek predictive testing to exorcise that belief.

We then asked another question: Would the availability of a treatment to delay the onset of AD influence the decision to seek predictive testing? In this survey, responses indicated that if there were a treatment available to delay onset, significantly more subjects would seek predictive testing. Finally, we asked: What characteristics are associated with serious consideration of suicide after a positive predictive test? Those who anticipated feeling suicidal after a positive result were more likely to be taking the predictive test in order to plan for suicide ($p = 0.0001$), to have had a parent with AD ($p = 0.03$), or to be worried about developing AD ($p = 0.03$). These findings were not significantly associated with age, gender, ethnicity, income, marital status, or prior history of depression.

Pilot data collected in this study suggested that of the 176 individuals surveyed in this convenience sample, 35% would elect to obtain predictive testing for AD even if the hypothetical test were only 60% accurate. When asked to presume that the test were 100% accurate, 69% of respondents indicated that they would elect to obtain such testing. Certainly, individuals who indicate in a survey that they would obtain predictive testing might not actually follow through. However, a remarkably high percentage of this sample appeared to be seriously interested in predictive information.

MARKERS AND METHODS FOR PRECLINICAL DIAGNOSIS

ApoE genotyping is the first example of a genetic marker for the most widespread form of AD that could potentially provide predictive information about risk long before symptoms of the disease begin. However, there are other markers and methods that may aid diagnosis in the very earliest and even preclinical stages of the disease. A full survey of biologic markers in skin and blood is beyond the scope of this presentation, and has been summarized elsewhere (Small and Greenberg, 1988; Blass and Gibson, 1993; Wen et al., 1994). Particular interest in this regard has been directed toward the search for effective cerebrospinal fluid (CSF) markers in AD. Although conventional spinal fluid measures are not helpful in AD (Fishman, 1992), the search for diagnostic CSF markers has been extensive (Wilder-Smith et al., 1994). Spinal fluid from patients with AD has been reported to have increased microglial antibodies (McRae et al., 1993), lowered serotonin, 5-hydroxytryptophan, and 5-hydroxyindoleacetic acid (Volicer et al., 1985), increased levels of AD-associated protein (Bissette et al., 1991), increased norepinephrine (in severely impaired AD patients) (Raskind et al., 1984), increased choline (Elble et al., 1989) and decreased acetylcholinesterase and butyrylcholinesterase (Tune et al., 1985; Kumar et al., 1989; Appleyard and McDonald, 1992), increased ubiquitin (Kudo et al., 1994), increased neuronal thread protein (de la Monte et al., 1992), decreased taurine (Alom et al., 1991), increased glutamate (Pomara et al., 1992), lower levels of monoamine metabolites (Blennow et al., 1991), increased neuron-specific enolase (Blennow et al., 1994), alterations and reductions in soluble derivatives of amyloid β-protein precursor (Palmert et al., 1990; Van Nostrand et al., 1992), increased amyloid β-protein (Nakamura et al., 1994), increased tau (Vandermeeren et al., 1993; Galasko et al., 1996), and decreased $A\beta_{42}$ (Motter et al., 1995). None of these studies has demonstrated clear effectiveness of a marker in a population-based, prospective study.

An interesting possibility was raised in 1994 when it appeared that patients with early AD could be characterized by an exaggerated pupillary mydriatic response after eyedrop exposure to the cholinergic antagonist tropicamide (Scinto et al., 1994). Our own study of this phenomenon was unable to reproduce this finding with sufficient robustness to warrant its consideration as a diagnostic aid (Loupe et al., 1996).

Functional imaging studies have attracted considerable attention as possible diagnostic modalities for the early diagnosis of AD. Although not routinely performed in the evaluation of dementia, these techniques can yield important diagnostic information by providing regional profiles of blood flow or metabolic activity in the brain, particularly when used in conjunction with information derived from structural imaging (Foster, 1994; Osimani et al., 1994). For example, a pattern of bilateral temporoparietal hypoperfusion or hypometabolism is felt to be characteristic of AD. However, this pattern is not appreciated in all cases of early AD (Azari et al., 1993; Pietrini

et al., 1993; Weiner et al., 1993). It has been suggested that, in combination with other information such as ApoE genotyping, positron emission tomography (PET) may eventually be able to detect early cerebral dysfunction in at-risk persons, even before neuropsychological abnormalities appear (Small et al., 1995), and could also prove helpful in predicting the rate of cognitive decline in AD (Wolfe et al., 1995). However, functional imaging is currently of greatest value in less typical dementia cases, such as frontal lobe dementia (Miller et al., 1991) or dementia with combined cognitive and extrapyramidal symptomatology (Tyrrell, 1990), and does not yet appear to warrant routine use in the diagnostic evaluation of a dementing patient (Salmon et al., 1994). In a recent PET study by Reiman and colleagues (1996), individuals homozygous for the ε4 allele, as a group, showed preclinical PET abnormalities that resembled those found in AD. However, PET is expensive and inefficient, and it has not yet been validated as a preclinical measure that would be accurate for individual patients.

COGNITIVE TESTING: THE CASE FOR COMPUTER-BASED SCREENING

Although there would be some advantages, along with some thorny ethical issues, in having a truly preclinical diagnostic test, one of the most effective short-term strategies may be to develop screening methods that are sensitive and specific for early clinical features of dementia and then to utilize the conventional work-up to establish a precise diagnosis (Corey-Bloom et al., 1995). A number of studies have indicated that careful neuropsychological testing can accurately identify individuals who are experiencing mild (and even unrecognized) cognitive impairment (Rubin et al., 1989; Flicker et al., 1991; Masur et al., 1994; Green et al., 1995; Jacobs et al., 1995; Linn et al., 1995). However, many proposed neuropsychological screening tests are not very practical for widespread use, as they can be time-consuming, may require a technician to administer and score, and have not been validated for population-based screening. In addition, many brief instruments for neuropsychological assessment require that the subject be able to read and sometimes to write, and therefore they may be biased by the subject's level of education.

In response to these needs, one of us (RL) has developed a 15-min computer-based test that uses a stylus-based touch-screen response mode and which presents instructions auditorily and therefore requires no reading or writing (Letz et al., 1996). This system, called the Neurobehavioral Evaluation System-3 (NES-3), is the most recent in a series of very different computer-based but keyboard-mediated neuropsychological tests, NES and NES-2 (Baker et al., 1985; Letz, 1990). NES-3 includes an orientation module, a list-learning task, a test of sequencing ability, forward and reverse visual span, a symbol-digit matching task, and a delayed recall of the words presented in the list-learning task (Letz et al., 1996). Initial validation efforts are under way.

NES-3 may offer a simple, easy-to-administer screening method for early detection of dementia with a minimum of educational bias. NES-3 has the potential to identify individuals to be worked-up for diagnosis and to facilitate the initiation of specific treatments.

CONCLUSIONS

Over the next decade, as we develop treatments that slow the progression of Alzheimer disease, we will have to confront the question of early detection. There is an urgent need to collect data on the ways in which predictive testing and information can be applied in clinical practice effectively, ethically, and compassionately. Until the accuracy of clinical applicability of biologic markers is refined, computer-based neuropsychological screening and early detection of cognitive symptoms may offer the best hope for early identification of individuals with dementia.

REFERENCES

Alom, J, Mahy JN, Brandi N, Tolosa E. Cerebrospinal fluid taurine in Alzheimer disease. *Ann Neurol* 1991;30:735.

Appleyard ME, McDonald B. Acetylcholinesterase and butyrylcholinesterase activities in cerebrospinal fluid from different levels of the neuraxis of patients with dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 1992;55:1074–8.

Azari NP, Pettigrew KD, Schapiro MB, et al. Early detection of Alzheimer disease: a statistical approach using positron emission tomographic data. *J Cereb Blood Flow Metab* 1993;13:438–47.

Baker EL, Letz R, Fidler A. A computer-administered neurobehavioral evaluation system for occupational and environmental epidemiology. Rationale, methodology, and pilot study results. *J Occup Med* 1985;27:206–12.

Bissette G, Smith WH, Dole KC, et al. Alterations in Alzheimer disease-associated protein in Alzheimer disease frontal and temporal cortex. *Arch Gen Psychiatry* 1991;48:1009–12.

Blass JP, Gibson GE. Nonneural markers in Alzheimer disease. *Alzheimer Dis Assoc Disord* 1993;6:205–24.

Blennow K, Wallin A, Ekman R. Neuron specific enolase in cerebrospinal fluid: a biochemical marker for neuronal degeneration in

dementia disorders? *J Neural Transm Park Dis Dement Sect* 1994; 8:183–91.

Blennow K, Wallin A, Gottfries CG, et al. Significance of decreased lumbar CSF levels of HVA and 5-HIAA in Alzheimer disease. *Neurobiol Aging* 1991;13:107–13.

Corey-Bloom J, Thal LJ, Galasko D, et al. Diagnosis and evaluation of dementia. *Neurology* 1995;45:211–8.

de la Monte SM, Volicer L, Hauser SL, Wands JR. Increased levels of neuronal thread protein in cerebrospinal fluid of patients with Alzheimer disease. *Ann Neurol* 1992;32:733–42.

Elble R, Giacobini E, Higgins C. Choline levels are increased in cerebrospinal fluid of Alzheimer patients. *Neurobiol Aging* 1989;10: 45–50.

Farrer LA. Genetics and the dementia patient. *Neurologist* 1997;3:1–30.

Farrer LA, Brin MF, Elsas L, et al. Statement on use of apolipoprotein E testing for Alzheimer disease. *JAMA* 1995;274:1627–9.

Fishman RA. *Cerebrospinal fluid in diseases of the nervous system.* Philadelphia: WB Saunders, 1992.

Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. *Neurology* 1991;41:1006–9.

Foster NL. PET imaging. In: Terry RD, Katzman R, Bick KL, eds. *Alzheimer disease.* New York: Raven Press, 1994:87–103.

Galasko D, Brown J, Clark C, et al. Assessment of cerebrospinal fluid levels of tau protein in mildly demented patients with Alzheimer disease. *Neurology* 1997;3:632–5.

Green RC, Woodard JL, Green J. Validity of the Mattis Dementia Rating Scale for the detection of cognitive impairment in the elderly. *J Neuropsychiatry Clin Neurosci* 1995;7:357–60.

Jacobs DM, Sano M, Dooneief G, Marder K, Bell KL, Stern Y. Neuropsychological detection and characterization of preclinical Alzheimer disease. *Neurology* 1995;45:957–62.

Khachaturian Z. Editorial: The five-five, ten-ten plan for Alzheimer disease. *Neurobiol Aging* 1992;13:197–8.

Kudo T, Iqbal K, Ravid R, Swaab DF, Grundke-Iqbal I. Alzheimer disease: correlation of cerebro-spinal fluid and brain ubiquitin levels. *Brain Res* 1994;639:1–7.

Kumar V, Giacobini E, Markwell S. CSF choline and acetylcholinesterase in early-onset vs. late-onset Alzheimer disease patients. *Acta Neurol Scand* 1989;80:461–6.

Letz R. The Neurobehavioral Evaluation System (NES): an international effort. In: Johnson BL, Anger WK, Durao A, Xintaras C, eds. *Advances in neurobehavioral toxicology: applications in environmental and occupational health.* Chelsea, MI: Lewis Publishers, 1990:189–201.

Letz RL, Green RC, Woodard JL. Development of a computer-based battery designed to screen adults for neuropsychological impairment. *Neurotoxicol Teratol* 1996;18:365–70.

Linn RT, Wolf PA, Bachman DL, et al. The 'preclinical phase' of probable Alzheimer disease. *Arch Neurol* 1995;52:485–90.

Loupe DN, Newman NJ, Green RC, et al. Pupillary response to tropicamide in patients with Alzheimer disease. *Ophthalmology* 1996; 103:495–503.

Masur DM, Sliwinski M, Lipton RB, Blau AD, Crystal HA. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. *Neurology* 1994;44:1427–32.

McRae A, Dahlström A, Polinsky R, Ling EA. Cerebrospinal fluid microglial antibodies: potential diagnostic markers for immune mechanisms in Alzheimer disease. *Behav Brain Res* 1993;57:225–34.

Miller BL, Cummings JL, Villanueva-Meyer J, et al. Frontal lobe degeneration: clinical, neuropsychological, and SPECT characteristics. *Neurology* 1991;41:1374–82.

Motter R, Vigo-Pelfrey C, Kholodenko D, et al. Reduction of β-amyloid peptide$_{42}$ in the cerebrospinal fluid of patients with Alzheimer disease. *Ann Neurol* 1995;38:643–8.

Nakamura T, Shoji M, Harigaya Y, et al. Amyloid β protein levels in cerebrospinal fluid are elevated in early-onset Alzheimer disease. *Ann Neurol* 1994;36:903–11.

Osimani A, Ichise M, Chung D-G, Pogue JM, Freedman M. SPECT for differential diagnosis of dementia and correlation of rCBF with cognitive impairment. *Can J Neurol Sci* 1994;21:104–11.

Palmert MR, Usiak M, Mayeux R, Raskind M, Tourtellotte WW, Younkin SG. Soluble derivatives of the beta-amyloid protein precursor in cerebrospinal fluid: alterations in normal aging and in Alzheimer disease. *Neurology* 1990;40:1028–34.

Pietrini P, Azari NP, Grady CL, et al. Pattern of cerebral metabolic interactions in a subject with isolated amnesia at risk for Alzheimer disease: a longitudinal evaluation. *Dementia* 1993;4:94–101.

Pomara N, Singh R, Deptula D, Chou JC-Y, Schwartz MB, LeWitt PA. Glutamate and other CSF amino acids in Alzheimer disease. *Am J Psychiatry* 1992;149:251–4.

Raskind MA, Peskind ER, Halter JB, Jimerson DC. Norepinephrine and MHPG levels in CSF and plasma in Alzheimer disease. *Arch Gen Psychiatry* 1984;41:343–6.

Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med* 1996;334:792–4.

Rubin EH, Morris JC, Grant EA, Vendegna T. Very mild senile dementia of the Alzheimer type. I. Clinical assessment. *Arch Neurol* 1989;46:379–82.

Salmon E, Sadzot B, Maquet P, et al. Differential diagnosis of Alzheimer disease with PET. *J Nucl Med* 1994;35:391–8.

Scinto LFM, Daffner KR, Dressler D, et al. A potential noninvasive neurobiological test for Alzheimer disease. *Science* 1994;266: 1051–4.

Small GW, Greenberg DA. Biologic markers, genetics, and Alzheimer disease. *Arch Gen Psychiatry* 1988;45:945–7.

Small GW, Mazziotta JC, Collins MT, et al. Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. *JAMA* 1995;273:942–7.

Tune L, Gucker S, Folstein M, Oshida L, Coyle JT. Cerebrospinal fluid acetylcholinesterase activity in senile dementia of the Alzheimer type. *Ann Neurol* 1985;17:46–8.

Tyrrell PJ. Clinical and positron emission tomographic studies in the 'extrapyramidal syndrome' of dementia of the Alzheimer type. *Arch Neurol* 1990;47:1318–23.

Vandermeeren M, Mercken M, Vanmechelen E, et al. Detection of tau proteins in normal and Alzheimer disease cerebrospinal fluid with a sensitive sandwich ELISA. *J Neurochem* 1993;61:1828–34.

Van Nostrand WE, Wagner SL, Shankle RW, et al. Decreased levels of soluble amyloid β-protein precursor in CSF of live Alzheimer disease patients. *Proc Natl Acad Sci* 1992;89:2551–5.

Volicer L, Langlais PJ, Matson WR, Mark KA, Gamache PH. Serotonin system in dementia of the Alzheimer type: abnormal forms of 5-hydroxytryptophan and serotonin in cerebrospinal fluid. *Arch Neurol* 1985;42:1158–61.

Weiner MF, Wighton-Benn WH, Risser R, et al. Xenon-133 SPECT-determined regional cerebral blood flow in Alzheimer disease: what is typical? *J Neuropsychiatry Clin Neurosci* 1993;5:415–8.

Wen GY, Wisniewski HM, Blondal H, et al. Presence of non-fibrillar amyloid β protein in skin biopsies of Alzheimer disease (AD), Down's syndrome and non-AD normal persons. *Acta Neuropathol (Berl)* 1994;88:201–6.

Wilder-Smith E, McConnell H, Wilder-Smith A. CSF in neurological illness. In: McConnell H, Biancine J, eds. *Cerebrospinal fluid in neurology and psychiatry.* London: Chapman & Hall Medical, 1994:127–9.

Wolfe N, Reed BR, Eberling JL, Jagust WJ. Temporal lobe perfusion on single photon emission computed tomography predicts the rate of cognitive decline in Alzheimer disease. *Arch Neurol* 1995;52: 257–62.