Address correspondence to Dr B. Joy Snider, Washington University, Campus Box 8111 (BT 229), 660 S Euclid Ave, St Louis, MO 63110, *sniderj@neuro.wustl.edu*.

Relationship Disclosure: Dr Snider receives research support from Eli Lilly and Company for a clinical drug trial and anticipates serving as a site principal investigator and coinvestigator on such trials in the future. Dr Buckles reports no disclosure.

Unlabeled Use of Products/Investigational Use Disclosure: Drs Snider and Buckles report no disclosures.

''Will I Get Alzheimer Disease?'' When Cognitively Normal Patients Ask to be Tested for Alzheimer Disease

B. Joy Snider, MD, PhD; Virginia D. Buckles, PhD

ABSTRACT

This article presents the case of a cognitively normal patient who is requesting a procedure (amyloid imaging) recently approved for the diagnosis of Alzheimer disease (AD) in patients with cognitive impairment. The predictive value of this test in unaffected people is not clearly established. Knowing the results of the test will have no effect on therapeutic options, although the patient may make lifestyle decisions based on the results. There is potential risk to the patient in terms of insurability, employability, and psychological consequences. Physicians will face this situation with increasing frequency as the AD biomarker field progresses.

Continuum (Minneap Minn) 2013;19(2):470–474.

Case

Note: This is a hypothetical case.

A 62-year-old insurance agent presents with the complaint that her memory is ''terrible.'' She reports that she can no longer recall the names of her clients, which has led to embarrassing situations on a couple of occasions. The patient's husband accompanies her to the clinic and reports that she has an excellent memory for recent events and remains very active: she runs a successful business, volunteers at the local library, serves on several committees at their church, manages the household finances, planned a recent family vacation, and is an excellent cook. She scores 30/30 on the Mini-Mental State Examination (MMSE), and the results of her neurologic examination are normal. She is able to provide a thorough medical history. After being reassured that her cognition is normal, the patient reports that her mother developed dementia at age 70. She read online about spinal fluid and imaging tests that can detect Alzheimer disease (AD) before symptoms appear and she would like to be tested so she and her husband can plan their retirement.

DISCUSSION

Alzheimer disease (AD) is the most common cause of dementia in older adults; as the population ages, the number of patients who are concerned about AD will increase. The diagnosis of dementia and the determination of whether AD is the likely etiology of dementia is typically based on a careful history to assess intra-individual change in cognition and functional performance, neurologic examination, and if needed, cognitive or neuropsychological testing. More specific diagnostic testing, such as analysis of CSF or positron emission tomography (PET) imaging using amyloid imaging agents, has not been widely used in clinical practice. Online and print media coverage has increased public awareness of this testing,[1] particularly since May 2012, when the US Food and Drug Administration approved florbetapir, an 18F-labeled PET imaging agent that detects amyloid deposition in the brain. Patients and their families will likely request this testing even in cases like this one, in which the patient appears not to have any cognitive impairment.[2]

What is the physician's responsibility in this setting? What ethical issues are raised by this patient's request?

1. Does the principle of autonomy mean that the physician is obligated to order amyloid imaging (florbetapir PET scan) or AD-specific CSF studies because the patient requests them, or can the physician decide whether to order these tests?
2. Given the uncertainty around test interpretation in cognitively normal patients, how do the principles of informed consent apply in counseling the patient about the risks, benefits, and interpretation of this testing?
3. Imaging with florbetapir is indicated for the evaluation of patients with cognitive impairment. How does the physician weigh potential risks versus benefits and apply the principles of beneficence and nonmaleficence for a patient who has no evidence of cognitive impairment?

Clinicians should first determine whether patients have had a decline in cognitive function. In this case, self-reported concerns are limited to mild word-finding difficulty. The patient's husband confirms that her thinking remains good compared to her baseline, and her performance on recall of personal autobiographical events, a sensitive indicator of cognitive change,[3] is excellent. The results of her MMSE, although not a sensitive indicator of cognitive change, are reassuringly normal as well. If further testing were needed, other tests of memory, language, and executive function could be performed in the office or by a neuropsychologist. Repeat testing in 6 to 12 months might also be helpful to document whether the patient's cognitive function is stable or declining.

Supporting Patient Autonomy and Providing Information Needed for the Patient to Participate in Decision Making

It is important to understand why patients have concerns about their memory. In this case, the patient is nearing the age when her mother developed dementia, and she may have symptoms of anxiety or depression that merit further investigation or treatment. She requests information about her future risk of developing dementia in order to guide decisions regarding retirement and long-term care. She may simply want more certainty about the future and better insight about when she might experience cognitive decline. To address

these issues, the physician should determine whether the testing offers prognostic value for a patient with no apparent cognitive impairment. In patients with cognitive changes, even those with mild cognitive impairment, CSF biomarkers and PET amyloid imaging ligands may play a role in differential diagnosis.[4–6] In cognitively normal participants, however, the diagnostic and prognostic value of these tests are not established. Patients with biomarker evidence and possibly pathologic changes of AD are more likely to have brain atrophy and lower cognitive test scores and are at higher risk of developing cognitive changes in the future.[7–10] The only study to date looking at the predictive value of positive florbetapir imaging included 10 cognitively normal participants with a florbetapir scan interpreted as positive for amyloid deposition. This group had slightly more decline than those with a negative scan on two out of seven cognitive tests over an 18-month period.[11]

Clearly, the presence of brain amyloid is not benign, but there has not been sufficient longitudinal research to know whether it predicts risk of disease or time to disease onset. The few longitudinal studies published find that the risk of developing cognitive changes in the near future (1.5 to 4.0 years) is around fivefold greater when CSF or amyloid imaging biomarkers (eg, Pittsburgh Compound B or florbetapir) are positive.[7,11] Perhaps more importantly to the patient in this case, many to most participants (one-third to two-thirds) with positive biomarkers remained cognitively normal throughout the follow-up period. The lifetime risk for developing AD in a 65-year-old woman is about 20%[12]; what, if any, additional prognostic information a positive CSF or amyloid imaging biomarker study provides in an asymptomatic person remains unknown. The physician could address the patient's concerns by recommending repeat cognitive testing in 3 to 6 months or formal neuropsychological testing to monitor for mild cognitive changes.

The process of informed consent presumes that information is shared in such a way that the patient can understand it to make an informed decision. However, relative risk and statistical significance are concepts that may not easily be understood by patients. For example, 64% of participants who were counseled about the risk of developing AD associated with their *APOE* status could correctly (ie, with a 5% margin of error) recall their risk 6 weeks later, but almost half of these participants perceived their personal risk for AD as different from the accurately recalled risk.[13] Despite such challenges, physicians must make the best effort possible to explain the implications of the test results and what they might mean for the individual patient.

Balancing Benefit and Harm

Results of florbetapir testing in a cognitively normal patient could have both beneficial and harmful effects, so the principles of beneficence and nonmaleficence apply. Although a negative test might be reassuring, it does not preclude development of AD in the future. Furthermore, because no medications have been shown to prevent the onset of AD, a positive test would not change treatment. Arguably, a patient with a positive test could be more strongly encouraged to undertake measures such as prevention or control of cerebrovascular risk factors (eg, blood pressure and lipid control) and to make other potentially beneficial changes in lifestyle (eg, diet, exercise, intellectual and social engagement) that are thought to play a significant role in the development of

dementia, but these risk-reduction strategies are appropriate for all patients. Even in people with cognitive impairment, from mild impairment to frank dementia, test results often do not change treatment, although they do provide more diagnostic certainty (eg, AD dementia versus a frontotemporal dementia) and can offer prognostic information.

Physicians are obligated to minimize harm, which includes anticipating and mitigating the potential for negative psychological effects of learning that one is more likely to develop a progressive and potentially fatal disease. Dementia diagnosis disclosure has not received significant research attention, but in a controlled study, Carpenter and colleagues[14] found little evidence of catastrophic reaction even in patients with mild dementia, and some evidence of relief that an explanation for symptoms was provided. However, the situation in this case study may be more similar to disclosure of susceptibility or deterministic genetic test results in asymptomatic patients. When paired with genetic counseling, two studies found no negative psychological reactions after deterministic disclosure[15] and no difference in test-specific distress between patients receiving susceptibility (*APOE*E4*-positive) versus deterministic (*PSEN1*) results.[16] Studies in people tested for dominantly inherited forms of dementia including AD and Huntington disease suggest that, with appropriate screening and counseling, disclosure of test results may produce anxiety and depression in some participants, but these reactions are not severe.[17–19] Health care reform in the United States regarding ''preexisting conditions'' may negate the threat a positive test might hold toward future insurability for long-term care and health insurance. Ramifications for employability could be moot if retirement is imminent. Were the patient to receive results positive for brain amyloid, the physician could consider referring the patient for subsequent counseling and follow-up.

CONCLUSION

While the patient might argue that results of this testing could provide information useful in making decisions about her future, the principle of autonomy does not give the patient the right to demand a test, particularly one that is not approved for that indication (predicting risk of dementia in cognitively normal patients) and has no known diagnostic or prognostic value given the patient's current condition. However, the physician does have an obligation to address the patient's concerns and can do so by offering appropriate evaluation and follow-up (ie, repeat cognitive testing and neuropsychological evaluation) and reassuring her that the observed changes are not suggestive of the beginnings of a dementia. Some patients may not be reassured and may continue to request testing; the physician must then weigh the potential benefit of testing (eg, relief or reduced anxiety if the result is negative; planning for long-term care, estate planning, or other lifestyle changes if the result is positive) versus potential harms of a positive test (eg, emotional harm of patients concluding they will certainly develop AD). If a physician decided to agree with testing in this setting, counseling before and after testing (similar to that done for patients with genetic forms of dementia) should be strongly considered.

NOTE

New guidelines by the Amyloid Imaging Taskforce of the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging have

recently been published recommending that amyloid imaging is inappropriate in asymptomatic individuals (*www.alz.org/research/downloads/appropriate_use_criteria_for_amyloid_pet_alz_and_dem_january_2013.pdf*).

REFERENCES

1. Doraiswamy PM. Answers about Alzheimer's, part 1. The New York Times. November 12, 2012. *www.nytimes.com/2012/11/14/booming/answers-about-alzheimers-part-1.html?pagewanted=all&_r=0.* Accessed January 2, 2013.
2. Hauser SL, Josephson SA, Johnston SC. Florbetapir: knowing one's future. Ann Neurol 2012; 71(6):A6.
3. Dreyfus DM, Roe CM, Morris JC. Autobiographical memory task in assessing dementia. Arch Neurol 2010;67(7):862–866.
4. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011;305(3):275–283.
5. Holtzman DM. CSF biomarkers for Alzheimer's disease: current utility and potential future use. Neurobiol Aging 2011;32(suppl 1):S4–S9.
6. Matsuda H, Imabayashi E. Molecular neuroimaging in Alzheimer's disease. Neuroimaging Clin N Am 2012;22(1):57–65, viii.
7. Fagan AM, Roe CM, Xiong C, et al. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. Arch Neurol 2007;64(3):343–349.
8. Stomrud E, Hansson O, Blennow K, et al. Cerebrospinal fluid biomarkers predict decline in subjective cognitive function over 3 years in healthy elderly. Dement Geriatr Cogn Disord 2007; 24:118–124.
9. Fagan AM, Head D, Shah AR, et al. Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly. Ann Neurol 2009;65(2):176–183.
10. Fagan AM, Mintun MA, Shah AR, et al. Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease. EMBO Mol Med 2009;1(8–9):371–380.
11. Doraiswamy PM, Sperling RA, Coleman RE, et al. Amyloid-β assessed by florbetapir F 18 PET and 18-month cognitive decline: a multicenter study. Neurology 2012;79(16):1636–1644.
12. Weinstein G, Wolf PA, Beiser AS, et al. Risk estimations, risk factors, and genetic variants associated with Alzheimer's disease in selected publications from the Framingham Heart Study. J Alzheimers Dis 2012;Epub ahead of print.
13. Linnenbringer E, Roberts JS, Hiraki S, et al. ''I know what you told me, but this is what I think:'' perceived risk of Alzheimer disease among individuals who accurately recall their genetics-based risk estimate. Genet Med 2010;12(4):219–227.
14. Carpenter BD, Xiong C, Porensky EK, et al. Reaction to a dementia diagnosis in individuals with Alzheimer's disease and mild cognitive impairment. J Am Geriatr Soc 2008;56(3):405–412.
15. Molinuevo JL, Pintor L, Peri JM, et al. Emotional reactions to predictive testing in Alzheimer's disease and other inherited dementias. Am J Alzheimers Dis Other Demen 2005;20(4):233–238.
16. Cassidy MR, Roberts JS, Bird TD, et al. Comparing test-specific distress of susceptibility versus deterministic genetic testing for Alzheimer's disease. Alzheimers Dement 2008;4(6):406–413.
17. Meiser B, Dunn S. Psychological impact of genetic testing for Huntington's disease: an update of the literature. J Neurol Neurosurg Psychiatry 2000;69(5):574–578.
18. Steinbart EJ, Smith CO, Poorkaj P, Bird TD. Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. Arch Neurol 2001;58(11):1828–1831.
19. Dufrasne S, Roy M, Galvez M, Rosenblatt DS. Experience over fifteen years with a protocol for predictive testing for Huntington disease. Mol Genet Metab 2011;102(4):494–504.