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ALZHEIMER'S DISEASE BIOMARKERS: THEIR VALUE IN DIAGNOSIS AND CLINICAL TRIALS

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1. ABSTRACT

Biomarkers of Alzheimer's disease may be useful, not only for early diagnosis of the disease, but also for monitoring the progress of drug trials. A number of plasma and cerebrospinal fluid markers are reportedly altered in Alzheimer's disease. So far, no single biomarker can be used to diagnose Alzheimer's disease definitively. Nevertheless, it may eventually be possible to use several markers in combination to obtain sufficient diagnostic accuracy. However, for this to be the case, new specific biomarkers may need to be identified.

2. VALUE OF AD BIOMARKERS

Over the last decade or more, there has been a great deal of progress in understanding the basic biochemical mechanisms that cause Alzheimer's disease (AD). Our improved understanding of the pathogenesis of AD has led to new ideas about therapy. For example, the development of immunization strategies (1) and specific secretase inhibitors (2), which block the production of the β-amyloid protein (Aβ), hold out real prospects for effective treatment. The success of new therapeutic agents will probably depend upon accurate diagnosis. Today, neuropsychological assessment is the major diagnostic approach (3). However, as it is not 100% accurate, more accurate and objective approaches are needed. Genetic tests are of value for early-onset cases (4), but cannot be used for definite diagnosis in cases of sporadic Alzheimer's disease. Imaging techniques may be of value, and there have been some exciting developments recently (5). The potential application of biomarkers both to diagnosis (6) and to the monitoring of drug trials (7) is also of great interest.

A good biomarker should fulfill a number of conditions. First, it should provide a method of detection that is both sensitive and specific. The working group on: "Molecular and biochemical markers of Alzheimer's disease" has proposed a sensitivity and specificity of at least 80% (8). Second, the biomarker should be relatively easy to measure with a procedure that is not too invasive. Third, the marker should detect early (even pre-clinical) stages of Alzheimer's disease so that therapeutic intervention can be started as soon as possible. Finally, it would also be an advantage if the biomarker were to measure disease severity, so that the progression of the disease could be monitored.

A large number of biomarkers of AD have now been reported (Table 1). The value of some of these markers (e.g., cerebrospinal fluid (CSF) tau, phospho-tau or Aβ42) is well known, whereas the value of other biomarkers is unclear, because the studies have not be replicated in more than one laboratory or with large numbers of samples. In many cases, there is often considerable overlap in levels between healthy controls and AD cases. An additional problem is that some biomarkers may not be totally specific as they may be altered in other neurodegenerative diseases.

To date, no single biomarker has achieved the desired level of sensitivity and specificity needed to be used routinely for the diagnosis of Alzheimer's disease (8). However, the expectation that a single biomarker should fulfill criteria of high sensitivity and specificity may be unreasonable, as this expectation is not even met for diagnosis by neuropathologic examination. CERAD criteria (9) require the presence of two histopathologic features, namely *amyloid plaques* and *neurofibrillary tangles*, for a positive diagnosis of Alzheimer's disease. Therefore it may be too much to expect that a single biomarker can provide the basis for a diagnostic assay. However, if two biomarkers are used in combination, they may provide considerably improved specificity and sensitivity. In support of this concept, Kanai et al. (10) have found that when Aβ42 is used in combination with tau, the two markers provide a method that is 91% sensitive.

The concept of using more than one biomarker can be extended even further. There is no reason why only two biomarkers have to be used. By combining the measurement of different biomarkers in a single sample, it

Table 1. Putative CSF and plasma biomarkers of Alzheimer's disease

Body Fluid	Biomarker	Change in AD	Reference
CSF			
	tau (phospho-tau)	Increased	13
	Aβ42	Decreased	14
	APP	Decreased	15
	AD7C-NTP	Increased	16
	Glycoform of AChE	Increased	17
	Glycoform of BuChE	Increased	18
	WGA-reactive glycoprotein	Decreased	19
	ApoE	Increased	20
	Kallikrein-6	Increased	21
	8,12-iso-iPF(2α)-VI	Increased	22
	Lipoprotein oxidation	Increased	23
	Glutamate	Decreased	24
	Interleukin-6	Increased	25
Plasma			
	Aβ42	Increased	26
	p97	Increased	27
	APP (130 kD)	Increased	28
	Homocysteine	Increased	29
	Folate	Decreased	29
	Vitamin B12	Decreased	29
	Kallikrein-6	Increased	21

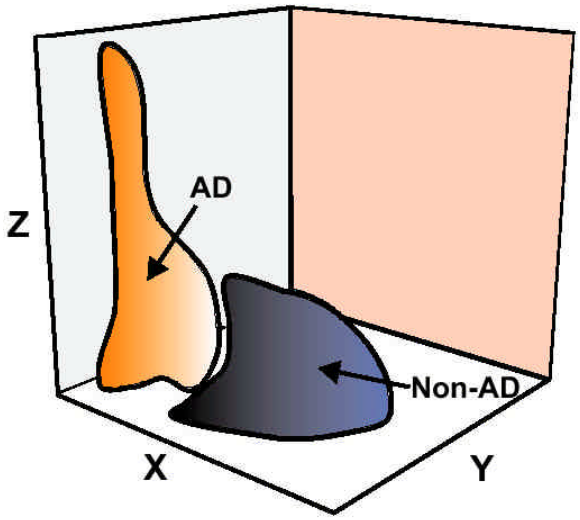

Figure 1. Development of a diagnostic test for Alzheimer's disease may require the use of more than one biomarker. The figure shows a 3-dimensional analysis of three hypothetical biomarkers (X, Y, and Z), each of which adds to the sensitivity and specificity of the total assay method. When all 3 hypothetical biomarkers are used in combination, complete separation of controls from Alzheimer's disease is achieved.

may be possible to improve sensitivity and specificity (Figure 1). So far, there have been few studies that have examined more than one or two biomarkers at a time. Of course, the measurement of three or more biomarkers would be more labor intensive for a diagnostic laboratory.

The availability of effective therapeutic agents will probably also influence the diagnostic methods that are employed. Currently, a number of promising drugs are being tested in clinical trials. However, it is possible that effective compounds may have unwanted toxic side effects. If this is the case, then accurate targeting of the drugs will be essential, and tests that improve confidence in a clinical diagnosis of AD will be of considerable value.

Biomarkers may be of value in helping to distinguish subpopulations of AD patients that may not respond to a specific therapy. For example, it is well known that a subset of patients responds to cholinesterase inhibitors (11). It has been suggested that the response to these drugs may be related to presence of certain allelic forms of apolipoprotein E (12). If this is correct, then analysis of apolipoprotein E alleles may be useful in identifying individuals who can respond to anticholinesterase therapy. Once again, there have been few studies that have examined the relationship between biomarkers and therapeutic efficacy.

3. SUMMARY

More basic research work must be done before biomarkers become part of established clinical practice. In particular, new biochemical markers need to be identified and examined with established markers to determine whether the use of multiple markers in combination can improve diagnostic specificity and sensitivity.

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