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Blood-based biomarkers for Alzheimer's Disease: Plasma A β 40 and A β 42, and Genetic Variants

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Abstract

Identifying a biomarker for Alzheimer's disease that can be obtained from a blood sample has been a goal of researchers for many years. Over the past few years a number of investigators have studied several plasma biomarkers but most frequently plasma amyloid A β 40 and A β 42 while others have explored the use of genetic variants as biomarkers for diagnosis or risk. This review considers the cross sectional and longitudinal data regarding plasma A β 40 and A β 42 as diagnostic biomarkers as well as risk biomarkers. Review of recent genome wide association studies indicates as many as 10 genetic variants have been associated with susceptibility to AD. Further analysis suggests that these factors have modest effects on risk and are thus not helpful, as yet in the diagnosis of disease. Until the function of these genes is understood, their role in risk and diagnosis will remain uncertain. Thus, there are several types of peripheral biomarkers under investigation, but more work is required before that can be deemed clinically useful.

Keywords

plasma amyloid β ; cross-sectional study; prospective study; genome wide association studies

Introduction

Alzheimer's disease (AD) is among the most frequently encountered diseases in aging societies with an estimated five million people in the United States and 17 million people worldwide suffering from the disease. It is expected that these numbers will quadruple by the year 2040, by which 1 out of 45 Americans will be affected, leading to a considerable public health burden.

To date, there are no definitive diagnostic tests or biological risk markers of the disease. The diagnosis of AD during life is based on clinical examination using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRD) Work Group (McKhann, Drachman et al. 1984). Although these criteria have been found to be

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reliable and valid any measure that would increase diagnostic sensitivity and specificity would be highly valuable for improving early detection and intervention.

Plasma A β 40 and A β 42

There have been approximately 26 investigations assessing plasma A β 40 and A β 42 as a diagnostic or as a biological risk factor (Tables 1–3). Studies of high risk populations (Table 1) have been consistent in showing elevated plasma A β 42 levels in individuals from families multiply affected by Alzheimer's disease (AD) (early onset and late onset). Scheuner et al (Scheuner, Eckman et al. 1996) first reported elevated levels among symptomatic carriers of presenilin mutations. Recently Ringman et al (Ringman, Younkin et al. 2008) found that A β 42 and A β 42/A β 40 ratio levels were elevated in unaffected familial AD mutation carriers compared with unaffected individuals with familial AD without mutations. However, A β 42 levels were lower in mutation carriers with incipient AD characterized as having a clinical dementia rating (CDR(Hughes, Berg et al. 1982))= 0.5, supporting the hypothesis that A β 42 decreases prior to overt disease. First degree relatives of patients with LOAD without known mutations or genetic variants have also been found to have increased plasma A β 42 (Ertekin-Taner, Younkin et al. 2008). Adults with Down syndrome who produce more plasma A β 42 due to trisomy and triplication of the gene for APP also show high plasma levels of A β 42 before onset of dementia (Schupf, Patel et al. 2007). Among studies of sporadic LOAD, there has been little consistency in the findings.

Cross sectional studies (Table 2) comparing patients with clinically diagnosed late onset Alzheimer's disease (LOAD) with controls showed no differences in either plasma A β 40 or A β 42. However, two studies that included patients with mild cognitive impairment (MCI) found high plasma A β 42, but not A β 40. Prospective studies (Table 3) have generally shown that higher plasma A β 42 levels are associated with increased risk of LOAD or cognitive decline. Most of the studies cited in table 3 also indicate that the elevation in levels of plasma A β 42 are present before or just at the onset of clinically diagnosed disease. Others have included repeated measurements of plasma A β 42, finding that levels decreased as disease progressed. Not all studies agree. At least two prospective studies examining plasma A β 42 showed no difference in patients with MCI who progressed to LOAD (Hansson, Zetterberg et al. 2006; Hansson, Zetterberg et al. 2007). Two others showed that low plasma A β 42 or a low ratio of plasma A β 42/A β 40 was associated with more rapid cognitive decline or with disease (Graff-Radford, Crook et al. 2007; Locascio, Fukumoto et al. 2008). These findings are consistent with our hypothesis that high plasma A β 42 is an antecedent indicator of risk for LOAD and declines with onset and progression of dementia. One explanation for the differences in the results is the time of sampling. A decline in plasma A β 42 may already have begun when patients develop signs of MCI. Alternatively, the methods used to analyze plasma A β 42 and A β 40 may explain some of the differences in results, though at least two studies used the same methods for measurement of plasma A β with different results (Mayeux, Honig et al. 2003; van Oijen, Hofman et al. 2006). Despite the variability in levels before disease onset, there is a general consensus that plasma A β 42 levels, and perhaps plasma A β 40 levels as well, decrease with disease progression.

A β 42 as a risk biomarker for LOAD

Compared to asymptomatic individuals with low plasma A β 42 levels at initial assessment, Schupf et al (Schupf, Tang et al. 2008) reported that those with high A β 42 levels had more than a three-fold increased risk of developing LOAD over an average of four and a half years. At the follow-up assessment when blood sampling was repeated, a decrease in plasma A β 42 levels, but not A β 40 levels, was related to the development of LOAD. The likelihood of having converted to LOAD 18 to 24 months before the second blood draw was three

times higher when plasma A β 42 levels had decreased by more than a half a standard deviation or when the plasma A β 42/A β 40 ratio decreased by more than a half a standard deviation. Thus, over time, decreasing levels of plasma A β 42 or a decline in the A β 42/A β 40 ratio are sensitive indicators of recent conversion to LOAD. The authors have posited that the decline in plasma A β 42 reflects compartmentalization and deposition of A β peptides in brain.

These results confirmed and extended previous findings among nondemented individuals who subsequently developed LOAD(Mayeux, Tang et al. 1999; Mayeux, Honig et al. 2003; Schupf, Tang et al. 2008) and are consistent with studies in women with MCI and among asymptomatic first-degree relatives of patients with (Assini, Cammarata et al. 2004; Ertekin-Taner, Younkin et al. 2008), groups at high risk of developing LOAD. However, these results are in distinct contrast to others that report 1) no relation between plasma A β peptide levels and risk of LOAD(Fukumoto, Tennis et al. 2003), 2) an association between low plasma A β 40 and LOAD(van Oijen, Hofman et al. 2006; Sundelof, Giedraitis et al. 2008) or 3) a relation between a low plasma A β 42/A β 40 ratio and subsequent cognitive impairment or LOAD(Graff-Radford, Lucas et al. 2003; Graff-Radford, Crook et al. 2007). A number of factors may account for these inconsistencies. One important factor is likely to be the timing of sample collection in relation to the preclinical period or to stage of disease onset and progression. Few studies have examined risk associated with change in plasma A β peptide levels or change in A β 42/A β 40 ratio over time. In the study by Schupf et al (Schupf, Tang et al. 2008), conversion to LOAD was strongly related to a decline in A β 42 levels and in the A β 42/A β 40 ratio. Similarly, in a study of healthy nondemented elderly individuals, higher initial A β 42 levels and greater reductions in A β 42 levels over an approximately 4 year period were associated with greater cognitive decline(Pomara, Willoughby et al. 2005). In the CSF, low levels of A β 42 and A β 42/A β 40 ratios in patients with MCI are associated with higher brain amyloid load(Fagan, Mintun et al. 2006; Fagan, Roe et al. 2007)and predict conversion to LOAD(Blennow and Hampel 2003; Blennow and Vanmechelen 2003; Hansson, Zetterberg et al. 2006). This suggests that a decline in A β 42 levels and in A β 42/A β 40 ratios can herald the onset of LOAD, possibly reflecting sequestration of A β 42 in senile plaques or the formation of semi-soluble oligomers(Lesne, Koh et al. 2006; Lesne, Kotilinek et al. 2008).

Other plasma biomarkers

Offspring of patients with AD are more likely to have lower mean plasma APOE levels compared with offspring of controls. Individuals with one or more APOE ϵ 4 alleles have lower APOE levels compared to those with other APOE alleles(van Vliet, Westendorp et al. 2009). Blood levels of progranulin are useful as an indicator of progranulin-related frontotemporal lobar degeneration, both null mutations and missense mutations as well as blood levels have also been observed in patients with Alzheimer's disease(Sleegers, Brouwers et al. 2010). Increased plasma concentration of clusterin was predictive of greater fibrillar amyloid-beta burden in the medial temporal lobe at autopsy but has not been investigated as a diagnostic or risk biomarker(Thambisetty, Simmons et al. 2010; Thambisetty, An et al. 2011).

Conclusions and recommendation

There is insufficient evidence to permit a conclusion regarding the use of plasma A β 40, A β 42 or the ratio of A β 42/A β 40 in the diagnosis or assessment of risk of AD using cross-sectional or single measurements. There is suggestive evidence that changes in plasma A β 40, A β 42 or the ratio of A β 42/A β 40 may be associated with -- and therefore useful in identifying -- individuals at risk for developing AD. Standardization of the measurement

A β 40 and A β 42 is required to determine whether or not plasma measurement will be useful in risk assessment of Alzheimer's disease.

There is insufficient data to permit a conclusion regarding the use of plasma or serum levels of APOE, clusterin or progranulin in the assessment of risk or as a diagnostic biomarker in Alzheimer's disease.

Genetic variants as biomarkers of AD and LOAD

Predisposing genetic variants could, in the future, be used to predict who will develop dementia. Individuals genetically predisposed to dementia may benefit from therapeutic interventions in the early stages of the disease. Early intervention could significantly prevent or delay the onset, which in turn would improve quality of life of the patient and their relatives and would significantly reduce the public health burden.

The majority of familial early onset Alzheimer's disease (EOAD) is caused by mutations in *APP*, *PSEN1* and *PSEN2*. These genes have almost complete penetrance (>85%) and a clear autosomal dominant pattern of inheritance. Thus, the presence of a mutation is virtually synonymous with disease. Complicating the wide-spread use of genetic testing for familial EOAD is the relative rarity of cases and the fact that there are multiple mutations in these genes producing the same phenotype. Thus, genetic testing requires full sequencing of the gene.

Current knowledge suggests that a variety of mechanisms underlie the various neuropathological and clinical changes, and that these have different genetic and environmental components. Thus, it is likely that late-onset cognitive impairment is a complex genetic disorder characterized by an interaction of multiple genes and the environment leading to genetic variants that have incomplete penetrance and a low-magnitude associated risk. Consistent with this notion is the fact that to date only *APOE* has been firmly identified as a genetic risk factor, although segregation analyses conducted in families of patients with LOAD support the presence of additional (Daw, Payami et al. 2000). With a population attributable risk that is estimated at 20–50%, the *APOE* ϵ 4 allele increases risk of cognitive impairment, LOAD, and age of onset of cognitive impairment in a dose-dependent fashion: one ϵ 4 allele is associated with a 2–3 fold increased risk, having two copies is associated with a 5–10 fold increase. Similar effect sizes have been observed for progression of cognitive impairment to dementia.

SORL1 was identified as a candidate gene in which two haplotypes in the 3' and 5' regions of the gene (Rogaeva, Meng et al. 2007) found to be associated with LOAD, with effect sizes ranging from odds ratios of 1.4 to 2.2. Subsequent studies have confirmed the association (Reitz, Cheng et al. 2011). Variants in *APOE* and *SORL1* lack sufficient sensitivity and specificity to be used as diagnostics. Variants in both increase risk of cognitive impairment in a non-Mendelian fashion, are not fully penetrant, and that they are neither necessary nor sufficient by themselves to cause impairment. The same is likely to be true for the remaining yet-to-be-identified genetic factors associated with cognitive decline.

There have been approximately 16 genome-wide association studies (GWAS) published to date. Most of these studies have included unrelated patients with LOAD and controls, but there are three studies that used family data (Bertram, Lange et al. 2008; Poduslo, Huang et al. 2009; Wijsman, Pankratz et al. 2011). Most GWAS have confirmed the *APOE* association with LOAD. Two large studies have identified variants in Clusterin (*CLU*), phosphatidylinositol binding clathrin assembly protein (*PICALM*) and complement component (3b/4b) receptor 1 (*CRI*) as being associated with LOAD risk (Harold, Abraham et al. 2009; Lambert, Heath et al. 2009). *CLU*, or apolipoprotein J (*APOJ*), is a lipoprotein

found to be part of amyloid plaques. *CLU* specifically binds soluble A β in cerebrospinal fluid to form complexes able to cross the blood brain barrier. It has also been noted that reduced levels of APOE and increased levels of CLU are correlated with the number of $\epsilon 4$ alleles, suggesting a compensatory induction of CLU in the brain of LOAD individuals with the *APOE* $\epsilon 4$ allele and low brain levels of APOE. *CRI* encodes the complement C3b protein, which is likely to contribute to A β clearance (Wyss-Coray, Yan et al. 2002). *PICALM* is involved in clathrin-mediated endocytosis (CME), an essential step in the intracellular trafficking of proteins and lipids such as nutrients, growth factors and neurotransmitters. Of relevance to LOAD, *PICALM* also appears to be involved in directing the trafficking of VAMP2, which is a soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein that has a prominent role in the fusion of synaptic vesicles to the presynaptic membrane during neurotransmitter release, a process that is crucial to neuronal function. The gene encoding bridging integrator 1 (*BINI*) was also noted initially at a lower threshold of significance (Harold, Abraham et al. 2009) with stronger results in a recent replication analysis (Seshadri, Fitzpatrick et al. 2010). *BINI*, a gene expressed in the central nervous system, and is reported to activate a caspase-independent apoptotic process.

Genome-wide significant results at *MS4A4A* on chromosome 11, *CD2AP* on chromosome 6, *EPHA1* on chromosome 7, and *CD33* on chromosome 19 were observed in independent meta-analyses by the Alzheimer's Disease Genetic Consortium and another European-American Consortium (Hollingworth, Harold et al. 2011; Naj, Jun et al. 2011). The true genetic effector for these genes has not been identified and their roles in the pathogenesis are unknown.

Can any of these genes be used as biomarkers for diagnosis or as measures of disease risk? At this point, only mutations in genes associated with early onset familial Alzheimer's disease could be considered diagnostic. These mutations are virtually 100% penetrant, and therefore those who carry a mutation will develop disease. Of interest, some patients with these mutations also have elevated plasma levels of A $\beta 42$.

Genetic variants associated with late-onset Alzheimer's disease are not useful as diagnostic measures. For example, APOE- $\epsilon 4$ is strongly associated with disease risk, but it has been shown to provide little help in the diagnosis. While there are many candidate genes in which variants are, or may prove to be, associated with increased risk of subsequent disease, none are currently used as biomarkers of risk.

Conclusions and recommendation

There is sufficient direct evidence to support the utility of pathogenic mutations identified in *PSEN1*, *PSEN2* and *APP* in the diagnosis of Alzheimer's disease. There is sufficient evidence to support the use of variation at the APOE locus in the assessment of risk of Alzheimer's disease, but insufficient evidence to permit a conclusion regarding the use of variation at the APOE locus for diagnosis. There is insufficient evidence to permit a conclusion regarding the use of genetic variation in any other gene identified in the assessment of risk or in the diagnosis of Alzheimer's disease.

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Table 1

Studies of Plasma A β 40 and A β 42 in High Risk Populations

Year	Author	Outcome	N (Ca/Co)	Result	Interval	Comment
1996	Scheuner(Scheuner, Eckman et al. 1996)	FAD	12APP/31 control 9 PS1/4 PS2/14 controls	Plasma A β 42 higher in FAD	Cross sectional	FAD with multiple affected members
2007	Schupf(Schupf, Patel et al. 2007)	AD in Down syndrome	44 inc/130control	Elevated A β 42,not A β 40,	3.9 yrs	Prospective
2007	Ertekin-Taner(Ertekin-Taner, Younkin et al. 2008)	LOAD 1 ⁰ relatives	217 relatives 103 controls	High A β 42	Cross sectional	Families with multiple affected members, no known mutations
2008	Ringman(Ringman, Younkin et al. 2008)	FAD mutation carriers (MUC) at risk vs. FAD NC;	9 MUC: 8 NC	A β 42 and A β 42/A β 40 levels higher in MUC vs. NC : A β 42 lower in MUC CDR=0.5	Cross Sectional	Cross sectional. Preclinical stage: A β 42 levels decrease with onset of symptoms prior to overt disease

Table 2

Cross-Sectional Studies of Plasma A β 40 and A β 42

Year	Author	Outcome	N (Ca/Co)	Result	Interval	Comment
2003	Fukutomo(Fukumoto, Tennis et al. 2003)	AD, MCI	146prevAD,37MCI, 96PD, 92co	No diff ca/co	cross-sect	Plasma A β related to age, not disease
2004	Assini(Assini, Cammarata et al. 2004)	Amnesic MCI	88 MCI/72co	High A β 42 vs men and female Co; no diff in A β 40	cross-sect	Preclinical stage, higher incidence of AD in women
2005	Irizarry (Irizarry, Gurol et al. 2005)	AD, MCI, WMH, CAA	54ca/42co	A β 40 associated with WMH in AD/MCI/CAA	cross-sect	Prevalent AD
2005	Sobow(Sobow, Flirski et al. 2005)	AD/MCI	54AD/39mci/35c	High AB42		Highest in MCI
2006	Pesaresi(Pesaresi, Lovati et al. 2006)	AD	146cs/89 MCI/89 NC	Lower A β 42 in AD, not MCI	Repeat 18 mo in 20 Ss	Xsect & repeated no change in levels over Follow up
2010	Lewczuk(Lewczuk, Kornhuber et al. 2010)	AD	243 controls/577 AD	Lower A β 42/A β 40 in cases	Cross-sect	Used CSF to stratify dementia

Table 3

Prospective Studies of Plasma A β 40 and A β 42

Year	Author	Outcome	N (Ca/Co)	Result	Interval	Comment
2003	Mayeux(Mayeux, Honig et al. 2003)	AD	86 inc/365: Repeat in 307	High baseline A β 42, not A β 40, + declining A β 42	3 yrs	Repeat measures: Onset associated with decline in A β 42
2006	Pomara(Pomara, Willoughby et al. 2005)	MMSE; SRT total, delayed recall	34 Nondem (60-74 yrs)	High initial A β 42/ decline A β 42 + decline in MMSE	4.2 yrs	Repeat measures. All cognitively intact
2006	Blasko(Blasko, Jellinger et al. 2008)	NC→MCI→AD	585 nondem, 487 followed;90 AD/ 98 all dem	A β 42 increased with cognitive decline, NC→MCI and NC→AD	2.5 yrs	Repeat measures VITA. 75y+, Vienna
2006	Van Oijen(van Oijen, Hofman et al. 2006)	AD	392inc/1373 co	Low A β 42/A β 40 predicts onset	8.6 years	Case-Cohort
2007	Graff-Radford(Graff-Radford, Crook et al. 2007)	MCI/AD	53 inc/510 NC 379 with 2 evals	Low AB A β 42/A β 40 predicts onset and cog decline	12 mos all 3-7 yrs repeat	Combined MCI/AD outcome (17 AD + 36 MCI)
2008	Sundelof(Sundelof, Giedraitis et al. 2008)	AD/VAD/All dementia	44ca/606 co in 77 years cohort	Low A β 40 and low A β 42 (marginal)	5.3 yrs	Repeat measures (not analyzed). Assoc only in those 77 y
2008	Hansson(Hansson, Zetterberg et al. 2010)	MCI→AD	48 ca/51 stable MCI/38 co	No difference	4-7 yrs	Cohort 1 low A β 42/ A β 40 in those with CSF markers of AD
2008	Hansson	MCI→AD	15 ca/95 MCI/41 Co	No difference	2-4 yrs	Cohort 2
2008	Lopez(Lopez, Kuller et al. 2008)	AD	88i/69mci/117mci	High A β 40 & A β 42		CHS study
2008	Locasio(Locasio, Fukumoto et al. 2008)	Cognitive (BDS) & ADL scores	122 with AD from memory clinic	Earliest: Low A β 40 & A β 42 with more rapid decline	0.2-12 y	retrospective & prospective. Duration of AD at base=3.2 y (0.2-12y)
2008	Schupf(Schupf, Tang et al. 2008)	AD	104i/1021c	High baseline A β 42, decline in A β 42 or A β 42/ A β 40	4.6 yrs	Repeat measures; Onset associated with decline in AB42 and A β 42/ A β 40 ratio
2009	Okereke(Okereke, Xia et al. 2009)	Cognitive(TICS) scores	481 non-demented women	Low A β 42/A β 40 in midlife and decreases over next 10 yrs	10 years	Telephone based interviews
2009	Lambert(Lambert, Schraen-Maschke et al. 2009)	Dementia (AD, VaD, other types)	985 non-demented 233 demented	High A β 42/A β 40 associated with lower risk	4 years	Prospective, clinical assessment Three Cities

Table 4

Genomewide Association Studies

Study	Year	Population	Platform	# of SNPs	AD Cases		Controls		identified genes/regions
					GWAS	follow-up	GWAS	follow-up	
Reiman(Reiman, Webster et al. 2007)	2007	USA, Netherlands	Affymetrix (500K)	312,316	446	415	290	260	APOE, GAB2
Li (Li, Wetten et al. 2008)	2008	Canada	Affymetrix (500K)	469,438	753	418	736	249	APOE, TOMM40, APOC1, GOLPH2
Poduslo (Poduslo, Huang et al. 2009)	2008	USA	Affymetrix (500K)	489,218	9	199	10	225	APOE, TRPC4AP
Bertram(Bertram, Lange et al. 2008)	2008	USA (NIMH)	Affymetrix (500K)	484,522	941	1767	404	838	APOE, APOC1, ACE, CHRN2, GAB2, TF, GWAS14q31.2
Beecham(Beecham, Martin et al. 2009)	2009	USA (CAP)	Illumina (550K)	532,000	492	238	496	220	APOE, FAM113B
Carrasquillo(Carrasquillo, Zou et al. 2009)	2009	USA (Mayo)	Illumina (300K)	313,504	844	1547	1255	1209	APOE, PCDH11X
Potkin(Potkin, Guffanti et al. 2009)	2009	USA (ADNI)	Illumina (610K)	516,645	172	-	209	-	APOE, TOMM40, EFNA5, CAND1, MAGI2, ARSB, PRUNE2
Lambert(Lambert, Heath et al. 2009)	2009	Europe (EADI1)	Illumina (610K)	537,029	2032	3978	5328	3297	APOE, CLU
Harold(Harold, Abraham et al. 2009)	2009	Europe & USA (GERAD1)	Illumina (various)	529,205	3941	2023	78 48	2340	APOE, CLU, PICALM
Feulner(Feulner, Laws et al. 2010)	2010	Europe	Illumina (550K)	555,000	491	-	479	-	APOE, TOMM40, MAPT, SORL
Seshadri (Seshadri, Fitzpatrick et al. 2010)	2010	Europe+USA (CHARGE, EADI1, GERAD1)	Affymetrix+Illumina	2,540,000 (imputed)	3006	6505	22604	13532	APOE, CLU, PICALM, CR1, EXOC3L2, BIN1
Naj(Naj, Jun et al. 2011)	2011	USA Alzheimer's Disease Genetics Consortium	Affymetrix+Illumina	2,324,889 (imputed)	8,039	3,531	7,366	3,565	MS4A, ABCA7, CD33, EPHA1, CD2AP
Hollinworth(Hollinworth, Harold et al. 2011)	2011	Europe+USA (CHARGE, EADI1, GERAD1)	Affymetrix+Illumina	496,763	6,688	8,286	13,685	21,258	MS4A, ABCA7, CD33, EPHA1, CD2AP