Online Supplement A: CSF education document

Online Supplement B: Vignette text

Online Supplement A: CSF education document

Amyloid plaques and neurofibrillary tangles are the pathological hallmarks of Alzheimer's disease (AD). Amyloid beta peptide, most commonly the 42 amino acid form ($A\beta_{42}$) is the major component of amyloid plaques; neurofibrillary tangles are made primarily of aggregated tau proteins, including tau phosphorylated at residue 181 ($ptau_{181}$). $A\beta_{42}$, total tau protein and $ptau_{181}$ can be detected in cerebrospinal fluid (CSF). Many studies have shown that AD patients as a group have CSF with lower levels of $A\beta_{42}$ and higher levels of tau and $ptau_{181}$ than cognitively normal people. A ratio of tau/$A\beta_{42}$ or $ptau_{181}$/$A\beta_{42}$ usually provides the best sensitivity and specificity to discriminate Alzheimer's disease from cognitively normal, but there is overlap of values between groups. This may be in large part because about 30% of cognitively normal people over the age of 65 have pathological and CSF changes typical of AD.[1,2] Several studies have shown that cognitively normal people whose CSF shows these changes are five-fold more likely than those without the changes to develop AD in the next 3-4 years.[1] Thus, changes in CSF (reduced levels of $A\beta_{42}$ and increased levels of tau and $ptau_{181}$) may be very specific for the brain *pathology* of AD but can be seen in people who do not have the *symptoms* of AD; these people are at higher risk of having AD in the future and may have "preclinical" or "presymptomatic" AD.

Clinical testing for AD CSF biomarkers is available commercially from Athena Diagnostics. Athena provides values of $A\beta_{42}$, tau and $ptau_{181}$ without reference ranges and provides a normalized ratio of $A\beta_{42}$ to total tau (called the AT index) and level of ptau to discriminate patients with Alzheimer's Disease from those with etiologies for cognitive change. An AT index of less than 1.0 and P-tau concentration of > 61 pg/ml are suggestive of AD. They note that there is some overlap between normal individuals and those with AD (e.g. AT index 0.8-2.0 and ptau 54-68 pg/ml are in a "borderline" range). Athena reports a sensitivity of 85-94% and a specificity of 83-90% for this ratio, citing two studies.[3,4]

For reference, we also provide CSF biomarker values observed in research participants who had a clinical assessment at Washington University (eTable 1) and values observed in a subset of these research participants who had autopsy proven AD (eTable 2).

eTable 1. ***CSF Biomarker Values in Research Participants at the Knight ADRC Comparing Cognitively Normal Individuals (Clinical Dementia Rating (CDR) of 0) to Those Who Have Very Mild or Mild AD (CDR 0.5 or 1).***

	No AD (n=90)		Mild AD (n=33)	
	Mean	**Standard deviation**	**Mean**	**Standard deviation**
$A\beta_{42}$	567	207	434	211
tau	342	175	565	302
$ptau_{181}$	62	26	86	45

Note: All values shown are in pg/ml. The data were aggregated and did not allow calculation of ATI.

eTable 2. ***CSF Biomarker Values in 29 Individuals with Autopsy Proven AD (unpublished data from the Knight ADRC)***

	Mean (Standard Deviation)	**MIN**	**MAX**	**MEDIAN**
$A\beta_{42}$	425 (171)	183	786	360
tau	574 (287)	156	1200	544
$ptau_{181}$	84 (38)	25	192	78
ATI	0.54 (0.3)	0.12	1.58	0.52

Note: All values shown are in pg/ml.

Supplement B: Vignette text

Borderline vignette

A 73-year-old retired pilot comes to your office for routine follow-up with his son who lives nearby and sees him several times per week. His son reports he is concerned about his father's memory. The son reports that his father has always been a little repetitious but now might tell the same story within a day. He is more dependent on his calendar to keep track of appointments, checking it several times per day. He might forget the details of some recent events, but recalls events well "if it interests him." He still drives but has been reluctant to drive to his son's new home. He still goes to church and plays golf with friends. He still does minor home repairs but they take him longer. He is independent in activities of daily living. The patient is not overly concerned about his memory, stating some things just aren't important to him anymore. The patient and his son both report his mood is low sometimes, but he denies having low mood most days for two weeks or more.

AD vignette

A 71-year-old retired real estate agent comes to your office. His wife is also your patient and while you are seeing her she mentions she has some concerns about her husband's memory. She reports he has forgotten several appointments in the past year and often forgets things she has told him. He recalls recent events but is less likely to recall the details. He is still driving, but struggles to find less familiar places. He attends church but stopped serving as a deacon last year because he was having difficulty making decisions; he still meets with retired friends often. She noted that he takes longer to do home repairs and has taken several months to put up shelves in the garage and they are not up to his usual standard. He is independent in his activities of daily living. The patient reports his wife is worried about his memory but that he has not noticed any changes. They both denied low mood.

CSF values accompanying vignettes

Normal CSF: $A\beta_{42}$ = 750 pg/ml

Total tau = 330 pg/ml

$ptau_{181}$ = 40 pg/ml

ATI (Athena) =1.2

Borderline CSF: $A\beta_{42}$ = 502 pg/ml

Total tau = 216 pg/ml

$ptau_{181}$ = 60 pg/ml

ATI (Athena) = 1.0

AD CSF: $A\beta_{42}$ = 300 pg/ml

Total tau = 619 pg/ml

$ptau_{181}$ = 86 pg/ml

ATI (Athena) = 0.31

References

1. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Arch Neurol.* 2007;64(3):343-349.
2. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol.* 1999;45:358-368.
3. Hulstaert F, Blennow K, Ivanoiu A, Schoonderwald HC, Riemenschneider M, De Deyn PP, et al. Improved discrimination of AD patients using β-amyloid$_{(1-42)}$ and tau levels in CSF. *Neurology.* 1999;52(8):1555-1576.
4. Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, et al. Cerebrospinal fluid β-amyloid(1-42) in Alzheimer disease: Differences between early- and late-onset Alzheimer disease and stability during the course of disease. *Arch Neurol.* 1999;56(6):673-680.