Biomarkers for Alzheimer’s disease (AD) have improved our understanding of the temporal sequence of biological events that lead to AD dementia (Jack et al., 2013). AD is characterized neuropathologically by amyloid plaques comprised of the amyloid-β peptide and neurofibrillary tangles comprised of tau. Brain amyloid deposition, as evidenced by a decline in amyloid-β peptide 42 (Aβ42) in the cerebrospinal fluid (CSF) or by binding of amyloid PET ligands, is thought to be a key initiating event in AD and begins many years prior to the onset of dementia. A rise in CSF tau and phosphorylated tau in the setting of Aβ deposition appears to reflect neurodegeneration and also begins years prior to the onset of dementia but after Aβ deposition has begun to accumulate. Individuals with “preclinical AD,” that is, normal cognition but abnormal AD biomarkers, have a much higher risk for developing AD dementia but may remain cognitively normal for years (Vos et al., 2013). While deposition of amyloid and formation of tau tangles are necessary for AD to occur, it is likely that additional events involving inflammation or other processes contribute to crossing the tipping point from preclinical AD to AD dementia. Current efforts are aimed at defining the biomarker(s) that best predict the transition from cognitive normality to abnormality. A biomarker that is closely associated with the onset of cognitive decline could help us to understand the biological events that connect amyloid deposition and tangle formation to cognitive decline and could have significant practical value in AD diagnosis and clinical trial design.

See also: M Suárez-Calvet et al (May 2016)
evaluate levels of Aβ42, tau, and ptau. The combination of low CSF Aβ42 and high tau/ptau is consistent with the presence of AD pathology, but it is not specific—it may occur either in patients with dementia due to AD or preclinical AD. Addition of sTREM2 to CSF testing may improve our ability to determine whether mild cognitive problems are due to AD or other etiologies. CSF sTREM2 levels could also be helpful in AD drug trials. Biomarkers are being used as endpoints as well as enrollment criteria in some clinical trials. If CSF sTREM2 is reliably associated with the onset of cognitive decline, reduced sTREM2 levels in drug-treated individuals with preclinical AD could indicate a favorable drug effect. Additionally, drugs for AD may be most effective when given at a particular stage of the AD process. Individuals who have abnormal biomarkers for amyloid, tau/ptau but normal CSF sTREM2 may be at an earlier stage of the AD process than individuals with abnormalities in all three biomarkers. If CSF sTREM2 further refines our ability to stage AD, this would allow us to evaluate which drugs are most appropriate for patients at various stages of the AD process. If additional studies confirm the results of Suárez-Calvet et al. (2016), CSF sTREM2 levels may be an important biomarker that represents some of the biological events that connect amyloid deposition and neurofibrillary tangle formation to cognitive decline. A biomarker that marks the transition from preclinical AD to dementia could have a major impact on our ability to understand, diagnose, and treat this formidable disease.

References