NEUROLOGY UPDATE III: UPDATE ON DEMENTIA

Gregory S. Day, MD, MSc
Washington University in St Louis
St. Louis, MO

The perception that research in dementia moves slowly is pervasive in medicine, and an all-too-present reality for patients and caregivers living with the consequences of dementia. Despite the investment of billions of dollars in drug design and clinical trials, no disease-modifying pharmacotherapies have been approved for the treatment of the most common neurodegenerative dementing illnesses. It is easy to appreciate, therefore, why some may perceive that progress has indeed been too slow. Still, there has been progress: even remarkable progress. This update session will summarize recent advances in the etiologic and biomarker characterization of dementing illnesses, including progress in clinical trials evaluating therapies targeting the molecular pathology of Alzheimer disease (AD). Discussion of research most likely to transform the treatment of patients with dementia will be prioritized.

I. Update on dementia risk and risk factors

Dementia incidence and prevalence

Modification of vascular risk factors has been proposed as an effective strategy to prevent the most common causes of dementia.[1] A recently published analysis of 5205 participants surveilled for incident dementia in the Framingham Heart Study, suggests that overall dementia incidence has declined over the past three decades in individuals with a high school education (or greater). Reduction in the prevalence of vascular risk factors is presumed to contribute to the declining incidence, but did not completely explain the observed decrease, implicating other (unknown) factors.[2] Similar findings were reported within the US population-based Health and Retirement Study,[3] exemplifying the importance of continued efforts to modify vascular risk factors, while promoting healthy life-style interventions known to associate with increased cognitive reserve (e.g., physical exercise,[4] cognitive engagement,[5] and education).

Environmental risk factors for dementia: Traumatic brain injury

β-amyloid aggregates were recently demonstrated on amyloid-PET imaging within the brains of patients recovering from TBI,[9] suggesting that trauma may promote plaque formation, consistent with prior histopathologic findings.[7, 8] However, an increased prevalence of β-amyloid-associated pathology (including AD neuropathologic change) was not found in a pooled analysis including 865 participants with a reported history of TBI and associated clinical-pathologic data. Rather, TBI with loss of consciousness appeared to predict a higher risk of associated brainstem and cortical Lewy body pathology.[10] These findings suggest that further work is needed to understand the potential effect of TBI on the development of the most common neurodegenerative pathologies.

"Other" causes of dementia: Autoimmune dementia

Several autoantibody-mediated syndromes associated with cognitive impairment (due to direct or indirect consequences of autoimmune disease) are now recognized. The recent description of a syndrome associated with antibodies against IgLON5 (a neuron cell adhesion molecule) in patients presenting with slowly-progressive sleep dysfunction and cognitive impairment beginning in the 6th decade of life or later, emphasizes the role that neurologists may play in the identification and characterization of immune-mediated dementias.[11, 12] Additionally, publications documenting the (high) prevalence of long-term cognitive sequelae in patients recovering from the most common forms of antibody-mediated encephalitis (i.e., encephalitis associated with autoantibodies against central nervous system NMDA,[13] LGI1,[14, 15] and CASPR2 cell-surface antigens[16, 17]), articulate the role that neurologists experienced in the assessment and management of cognitive dysfunction will play in the management of these patients.

II. Update on *in vivo* biomarker detection

Advances in the detection of molecular pathology: Neuroimaging

Florbetapir (amyloid) PET imaging was recently reported to improve the differentiation of patients with intracerebral hemorrhage due to hypertension (amyloid "negative") from those with incipient cerebral amyloid angiopathy (amyloid "positive").[18] Despite the growing practical applications of FDA-approved amyloid-PET tracers, clinical access to amyloid-PET remains limited, with most insurers (including the Centers for Medicare and Medicaid Services [CMS]) declining coverage due to the lack of evidence that knowledge of amyloid status will effect disease management and patient outcomes. The results of a recent study enrolling 228 Italian adults may challenge this view. In this nation-wide study, access to amyloid imaging led to a change in clinical diagnosis in 27% of clinically well-characterized patients with cognitive impairment, translating to alterations in recommendations concerning symptomatic therapy in 29% of participants.[19] These findings further emphasize the rationale for the US-based Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study—which aims to complete amyloid imaging in >18 000 Medicare-eligible patients with cognitive impairment, in whom knowledge of amyloid PET status is expected to alter diagnosis and management. The study is jointly funded by CMS under "coverage with evidence development" criteria and the Alzheimer's Association; recruitment is ongoing (IDEAS-Study.org).

Beyond amyloid, marked progress has been made in the development and validation of PET agents capable of visualizing cerebral tau pathology *in vivo* (Table 1). Of these, Flortaucipir (^{18}F-AV1451, T807) has garnered the most attention, due to its reported specificity for paired-helical tau filaments—the primary component of AD neurofibrillary tangle pathology. Early experience in well-characterized clinical populations affirms tracer utility in staging disease severity and differentiating individuals with typical (amnestic) and atypical AD dementia (non-amnestic; i.e., posterior cortical atrophy, logopenic variant primary progressive aphasia, behavioral variant), from cognitively normal controls.[20-22] These findings raise the possibility that tau-PET imaging may serve as a reliable surrogate measure of disease severity (and treatment response), with applications to clinical trials evaluating putative disease-modifying therapies in AD.

Neurodegenerative Tauopathy	PET Tracer	*In vivo* Findings
Alzheimer disease[23]	^{18}F-AV1451	Tracer retention was higher in the temporal lobes and cerebral cortex of participants with AD dementia.
Lewy body disease[24]	^{18}F-AV1451	Cortical retention was highly variable in patients with Lewy body dementia, but higher than that seen in controls.
Progressive supranuclear palsy[25]	^{18}F-AV1451	Retention was increased in the frontal regions, basal ganglia, thalamus, brainstem and dentate nucleus of the cerebellum in participants with PSP.
Corticobasal degeneration[26]	^{18}F-THK5351	Higher retention was observed in the frontal and parietal lobes, and globus pallidus of patients with CBS. Tracer retention was highest contralateral to the side most affected by motor impairment.

Table 1: Tau-PET imaging in common neurodegenerative tauopathies.

Advances in detection of molecular pathology: CSF and blood

Commercial measurement of CSF AD biomarkers (β-amyloid-42/40, total-tau and phosphorylated tau) are increasingly applied in the clinic, owing to the (relative) ease of access, widespread availability, and coverage via most insurers (including CMS). The sensitivity and specificity appears comparable with amyloid-PET measures, suggesting that either biomarker modality may be used to improve confidence when considering a diagnosis of AD dementia.[27] In the research setting, both modalities continue to be applied to identify asymptomatic individuals with AD pathology (so called "preclinical AD").[28] These individuals remain at highest risk of developing dementia, and may benefit the most from enrollment within clinical studies aimed at preventing AD dementia.

Despite great interest and effort, blood-based biomarkers of dementia marker are not (yet) ready for clinical use. A recent report established that a previously described panel of 5 blood-based biomarkers

of neocortical β-amyloid burden (CXCL-13, IgM-1, IL-17, pancreatic polypeptide Y, and VCAM-1) distinguished cognitively normal controls at the greatest risk of progressing to dementia.[29] This finding raises the possibility that blood-based measures may feature prominently in future *Update* sessions.

III. Update on dementia treatment

Disease-modifying treatments for Alzheimer disease dementia

The recent failure of two late-stage clinical trials of anti-AD therapies in patients with mild-severity AD dementia (EXPEDITION3 trial of solanezumab in December 2016, and verubecestat [MK-8931] in February 2017) has intensified interest in clinical trials enrolling patients with AD earlier and earlier in the disease course, when mitigation of β-amyloid is hypothesized to have the greatest effect on AD progression. On this front, early results from the PRIME study (aducanumab) have provided some cause for optimism: reporting dose- and duration-dependent decreases in cerebral β-amyloid deposition (measured with florbetapir PET) in patients randomized to aducanumab versus placebo.[30] Whether this decrease will effect a change in the clinical trajectory of patients with AD dementia remains to be determined in subsequent Phase III follow-up studies (ENGAGE/EMERGE).Table 2 includes a list of active studies currently recruiting patients with AD.

Secondary prevention of Alzheimer disease dementia

Opportunities also exist for the recruitment of asymptomatic cognitively normal older adults within studies aimed at preventing the onset of dementia in individuals with (biomarker-confirmed) AD. The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study is a three-year, placebo-controlled, randomized clinical trial that will randomize 1000 asymptomatic, cognitively normal participants with biomarker evidence of AD to treatment with solanezumab or placebo, with the goal of slowing the rate of cognitive decline in patients at high risk of developing dementia.[31] Follow-up is ongoing, including serial clinical and cognitive assessments, and biomarker measures (CSF and neuroimaging). Borrowing from the A4-model, the EARLY study has recently begun randomizing a similar cohort of participants to treatment with the BACE inhibitor JNJ-54861911 or placebo (clinicaltrials.gov, NCT: 02569398). The launch and operationalization of these innovative and bold studies represents a tangible application of decades of research implicating disrupted β-amyloid metabolism in AD pathophysiology, and the first opportunity to actively participate in treatment trials designed to prevent or delay the onset of dementia in high-risk individuals.

Study Name / *clinicaltrials.gov #*	**Study Drug**	**Study Population**	**Study Duration (months)**
Studies recruiting patients with symptomatic AD dementia			
ENGAGE/EMERGE: *NCT02477800/ NCT02484547*	Aducanumab (monoclonal Aβ antibody)	Patients age 50-85 years with very mild AD dementia (biomarker +ve)	18
CREAD Study: *NCT02670083*	Crenezumab (monoclonal Aβ antibody)	Patients age 50-85 years with very mild or mild AD dementia (biomarker +ve)	23
MissionAD1/2: *NCT02956486/ NCT03036280*	Elenbecestat (BACE inhibitor)	Patients age 50-85 years with very mild AD dementia (biomarker +ve)	24
AMARANTH/ DAYBREAK-ALZ: *NCT02245737/ NCT02783573*	Lanabecestat (BACE inhibitor)	Patients age 55-85 years with very mild or mild AD dementia (biomarker +ve)	24/36
STEADFAST: *NCT02080364*	Azeliragon (RAGE inhibitor)	Patients ≥50 years with very mild or mild AD dementia	18
Studies recruiting asymptomatic cognitively normal patients with biomarker evidence of (preclinical) AD			
A4: *NCT02008357*	Solanezumab (monoclonal Aβ antibody)	Asymptomatic cognitively normal patients age 65-85 (biomarker +ve)	36
EARLY: *NCT02569398*	JNJ-54861911 (BACE inhibitor)	Asymptomatic cognitively normal patients age 60-85 (biomarker +ve)	54

*Tabl*e 2: Summary of active multi-site placebo-controlled phase 3 trials of disease-modifying therapies in AD.

References

1. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. The Lancet Neurology 2014;13:788-794.
2. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med 2016;374:523-532.
3. Langa KM, Larson EB, Crimmins EM, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. JAMA Intern Med 2017;177:51-58.
4. Scarmeas N, Luchsinger JA, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA 2009;302:627-637.
5. Krell-Roesch J, Vemuri P, Pink A, et al. Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the APOE epsilon4 Genotype. JAMA Neurol 2017.
6. McKee AC, Cairns NJ, Dickson DW, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathol 2016;131:75-86.
7. Johnson VE, Stewart W, Smith DH. Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. Brain Pathol 2012;22:142-149.
8. Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? Nat Rev Neurol 2013;9:211-221.
9. Scott G, Ramlackhansingh AF, Edison P, et al. Amyloid pathology and axonal injury after brain trauma. Neurology 2016;86:821-828.
10. Crane PK, Gibbons LE, Dams-O'Connor K, et al. Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings. JAMA Neurol 2016;73:1062-1069.
11. Gelpi E, Hoftberger R, Graus F, et al. Neuropathological criteria of anti-IgLON5-related tauopathy. Acta Neuropathol 2016;132:531-543.
12. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. The Lancet Neurology 2014;13:575-586.
13. Finke C, Kopp UA, Pajkert A, et al. Structural Hippocampal Damage Following Anti-N-Methyl-D-Aspartate Receptor Encephalitis. Biol Psychiatry 2016;79:727-734.
14. Arino H, Armangue T, Petit-Pedrol M, et al. Anti-LGI1-associated cognitive impairment: Presentation and long-term outcome. Neurology 2016;87:759-765.
15. Finke C, Pruss H, Heine J, et al. Evaluation of Cognitive Deficits and Structural Hippocampal Damage in Encephalitis With Leucine-Rich, Glioma-Inactivated 1 Antibodies. JAMA Neurol 2017;74:50-59.
16. Joubert B, Saint-Martin M, Noraz N, et al. Characterization of a Subtype of Autoimmune Encephalitis With Anti-Contactin-Associated Protein-like 2 Antibodies in the Cerebrospinal Fluid, Prominent Limbic Symptoms, and Seizures. JAMA Neurol 2016;73:1115-1124.
17. van Sonderen A, Arino H, Petit-Pedrol M, et al. The clincal spectrum of CASPR2 antibody-associated disease. Neurology 2016;87:521-528.
18. Gurol ME, Becker JA, Fotiadis P, et al. Florbetapir-PET to diagnose cerebral amyloid angiopathy: A prospective study. Neurology 2016;87:2043-2049.
19. Boccardi M, Altomare D, Ferrari C, et al. Assessment of the Incremental Diagnostic Value of Florbetapir F 18 Imaging in Patients With Cognitive Impairment: The Incremental Diagnostic Value of Amyloid PET With [18F]-Florbetapir (INDIA-FBP) Study. JAMA Neurol 2016;73:1417-1424.
20. Ossenkoppele R, Schonhaut DR, Scholl M, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 2016;139:1551-1567.
21. Dronse J, Fliessbach K, Bischof GN, et al. In vivo Patterns of Tau Pathology, Amyloid-beta Burden, and Neuronal Dysfunction in Clinical Variants of Alzheimer's Disease. J Alzheimers Dis 2017;55:465-471.
22. Xia C, Makaretz SJ, Caso C, et al. Association of In Vivo [18F]AV-1451 Tau PET Imaging Results With CorticalAtrophy and Symptoms in Typical andAtypical Alzheimer Disease. JAMA Neurol 2017.
23. Brier MR, Gordon B, Friedrichesen K, et al. Tau and A-beta imaging, CSF measures, and cognition in Alzheimer’s disease. Sci Transl Med 2016;8:338ra366.
24. Gomperts SN, Locascio JJ, Makaretz SJ, et al. Tau Positron Emission Tomographic Imaging in the Lewy Body Diseases. JAMA Neurol 2016;73:1334-1341.
25. Whitwell JL, Lowe VJ, Tosakulwong N, et al. [18 F]AV-1451 tau positron emission tomography in progressive supranuclear palsy. Mov Disord 2017;32:124-133.

26. Kikuchi A, Okamura N, Hasegawa T, et al. In vivo visualization of tau deposits in corticobasal syndrome by 18F-THK5351 PET. Neurology 2016;87:2309-2316.
27. Palmqvist S, Zetterberg H, Mattsson N, et al. Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. Neurology 2015;85:1240-1249.
28. Vlassenko AG, McCue L, Jasielec MS, et al. Imaging and cerebrospinal fluid biomarkers in early preclinical alzheimer disease. Ann Neurol 2016;80:379-387.
29. Burnham SC, Rowe CC, Baker D, et al. Predicting Alzheimer disease from a blood-based biomarker profile: A 54-month follow-up. Neurology 2016;87:1093-1101.
30. Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. Nature 2016;537:50-56.
31. Sperling RA, Rentz DM, Johnson KA, et al. The A4 Study: Stopping AD Before Symptoms Begin? Sci Transl Med 2014;6:228fs213.