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Massachusetts alzheimer's disease research center: Progress and challenges

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Perspective on: Three decades of progress in addressing challenges of research on Alzheimer's Mass ADRC 30th Anniversary Symposium

On September 19, 2014, the Massachusetts Alzheimer Disease Research Center (ADRC) held a day-long scientific symposium to celebrate 30 years of research productivity. It was a time to reflect on past accomplishments and to anticipate future directions in research and treatment. The presentations summarized in this article point to advances in areas of basic science, neuroimaging, and genetics that hold promise for improving understanding of AD that will lead to effective treatments and possibly prevention. These advances grew out of the large pool of research conducted in the US and throughout the world. Much of this

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research in the US was funded by the National Institute on Aging and by private foundations and philanthropies in response to the epidemic of dementia associated with an aging population. AD is now widely known in the general population and a major focus of research in the medical and scientific communities.

But it was not always so: Thirty years ago, AD was viewed as a relatively rare condition of pre-senile dementia. AD and dementia were generally ignored at the major neurological meetings; there were few scientific publications on AD and only a handful of investigators were interested in the condition. Four things happened in the 1970s that changed perceptions about AD and brought us to our present state of engagement. The first was Robert Katzman's stunning 1976 article (Lijtmaer, Fuld and Katzman, 1976) equating pre-senile and senile dementia, and calling attention to the gathering silent epidemic of dementia. The second was the discovery by several groups that indices of acetylcholine were reduced in brains of AD patients. Having a biochemical abnormality gave hope that it could be corrected pharmacologically, much as levodopa corrected the biochemical deficit in Parkinson disease. Third, Jerry Stone established the Alzheimer's Association in 1979. This private foundation, initially known as ADRDA, raised the profile of AD, promoted education, advocated for patients and raised money to fund research. Finally, the US Congress established the National Institute on Aging, with a focus on AD. Under the leadership of T. Franklin Williams and Zaven Khachaturian, the NIA took the lead in establishing the university-based ADRCs.

In the fall of 1984, Secretary of Health and Human Services Margaret Heckler came to the Harvard Medical School to announce a new federal initiative on AD. She announced that the Massachusetts ADRC, directed initially by John Growdon and now by Bradley Hyman, would receive a 5-year grant from the NIA. The Harvard Gazette covered her announcement in a front page article with an accompanying photograph, and also graciously added a sentence that 4 other centers, in Baltimore, New York, San Diego and Los Angeles, would also be funded. Over subsequent years the number of Alzheimer Centers has expanded; there are currently 29 spread across the US. These Centers are a nidus of excellence in clinical care and research; they have joined together to share data and to conduct a broad range of research activities, including clinical drug trials. Their impact extends beyond the US, as the Centers program has served as a model for AD consortia in European and Asian countries.

Neuroimaging gives a new picture of AD

Nothing has changed the field of Alzheimer's research and clinical work more than the advent of neuroimaging, and the availability of PET ligands to detect amyloid pathology in living people. Imaging of tau pathology has lagged behind, but that is changing, with the development of long-awaited PET ligands for in vivo detection of tau deposition. At the symposium, Keith Johnson described work using a newly developed tau-PET ligand [(18)F]-T807 (Chien et al., 2013; Xia et al., 2013).

According to Johnson, tau deposition detected with T807 follows a similar progression to that documented by post-mortem neuropathology. Johnson sees unmistakable differences between cognitively normal adults and those with AD. In some regions the signal varies by

2.5-fold, which is a large signal for PET, he said. Studies suggest that tau pathology correlates more strongly with neuronal loss and the symptoms of AD than amyloid, and Johnson found that PET signal in the inferior temporal lobe was strongly related to cognitive impairment; correlations with amyloid were much less robust. Tau deposition may also predict incident impairment: Johnson showed data indicating that changes in memory scores over the previous three years correlate with tau levels in the parietal temporal lobe.

Tau imaging is in its infancy, and questions remain. But data from an ongoing longitudinal study, which Johnson says will come out in 2015, will help researchers to understand the progression of tauopathy, and evaluate the worth of tau-PET imaging as a biomarker of disease progression or therapeutic efficacy. In addition, the study will reveal more about the relationship of tau and amyloid deposition, and test the hypothesis that tau deposition is accelerated in the presence of amyloid.

Biomarkers for preclinical AD

The ability to image amyloid, and now tau, in vivo has transformed how researchers look at, and think about treating, AD. Amyloid PET scanning, along with animal work and longitudinal human studies have led to the key insight that AD has a decadeslong preclinical phase that precedes the onset of dementia. In those years, amyloid and tau accumulate silently. By the time dementia appears, significant and irreversible damage has occurred in the brain. The long preclinical phase offers a window of opportunity for treatment, if the disease can be detected early.

Much work has been done to develop biomarkers to detect preclinical AD and define its progression, and in 2011, researchers proposed preclinical diagnostic criteria based on imaging and fluid-phase biomarkers for amyloid accumulation, synaptic dysfunction, tau-mediated neuronal injury, and changes in brain structure (Sperling et al., 2011). Validation of these biomarkers in elderly cohorts, and their use to define different stages of preclinical AD, was described by Clifford Jack, (Jack et al., 2012; Knopman et al., 2012). A recent cross sectional study outlined for the first time age-dependent changes in biomarkers (Jack et al., 2014), but prospective studies will be needed to fully validate models of clinical progression, and clarify the relationship between amyloidosis, tauopathy and neurodegeneration.

Genetic studies yield new drug targets

Genetics is another part of the field that has seen enormous changes in the last three decades. The year the Massachusetts ADRC was founded, George Glenner first identified the amyloid peptide Abeta as a major component of Alzheimer’s plaques (Glenner and Wong, 1984), and by 1987 Rudolph Tanzi and colleagues at the Mass ADRC had cloned the amyloid precursor protein (APP) gene and mapped its location near a locus linked to early-onset familial AD (Tanzi et al., 1987; St George-Hyslop et al., 1987). Mutations in APP that cause early-onset AD were identified in 1991, followed by the discoveries of disease-causing mutations in the APP processing enzymes presenilin1 and 2. These discoveries helped focus the field on the amyloid hypothesis that the neurodegenerative cascade in AD began with overproduction and accumulation of Abeta peptides in the brain.

The second genetics revolution in AD began in 2008, with publication of the first genome-wide association study (GWAS) identifying common variants associated with the risk for late-onset or sporadic AD (Bertram et al., 2008). To date, GWAS has pinpointed 22 genes with nucleotide polymorphisms that are significantly associated with AD, and an additional 19 that are highly suggestive. The analysis identified genes involved in innate immunity and inflammation, cholesterol metabolism, and Abeta processing and endocytosis. Tanzi showed two examples of how the data have pointed to new targets CD33 and TREM2 (Griciuc et al., 2012; Hooli et al., 2014; unpublished data).

After GWAS, the challenge is to identify the actual gene variants or mutations that underlie AD susceptibility, and define their function. To uncover functional variants, Tanzi and his group have done whole genome sequencing on 1,510 subjects from 437 families with Alzheimer disease, plus two other large, late-onset AD families and additional elderly subjects with autopsy-confirmed amyloid and tangles, but no dementia.

From nearly one petabyte of sequencing data, the researchers identified 59 loci bearing highly penetrant functional variants tied to AD or other tau-dependent dementias. They are now focusing on 100 variants in those loci that strongly co-segregate with disease and have the highest predicted impact on function. Using the wealth of data to perform pathway and systems analyses, they found many of the variants touch pathways related to innate immunity. An independent analysis of gene expression in 4000 AD cases highlighted similar pathways (Zhang et al., 2013).

Reducing amyloid production remains a prime target for AD therapies. Inhibitors of the gamma secretase, which cleaves APP and releases pathogenic Abeta peptides, failed in clinical trials because of toxicity due to interference with processing of other, non-amyloid substrates. Tanzi and others are now developing secretase modulators that do not completely block the protease, but shift the balance of production from toxic Abeta peptides to nontoxic species. These modulators do not affect cleavage of other substrates at therapeutic levels, and thus may avoid the side effects of previous gamma secretase inhibitors. Tanzi showed data on one lead compound (Wagner et al., 2014) that dramatically reduced plasma Abeta in rats, and is aimed at beginning a phase I trial in people next year.

Peter St. George-Hyslop described structural studies of the gamma-secretase complex. Solving the molecular structure of the complex has been difficult, because of the size of the multi-protein complex and its membrane location, but structural models are improving, he said. Using electron microscopy, St. George-Hyslop and colleagues have identified the overall shape of the enzyme, and can demonstrate important allosteric conformational shifts during substrate binding and cleavage. The resolution is not yet good enough for drug design, but the group is starting to understand how existing inhibitors work. That could lead to additional selective inhibitors that can block Abeta production while leaving cleavage of other substrates intact.

Other efforts to target Abeta have involved antibodies. In a scheme to develop new and better therapeutic antibodies, Roger Nitsch used healthy centenarians to identify natural human anti-Abeta antibodies with the potential to protect against AD. This immunotherapy

approach has produced one antibody that has gone through phase Ib clinical trials. Based on positive data of amyloid clearance and possible cognitive effects, the antibody will advance to a phase III trial in 2015.

Earlier trials

Despite having reasonable targets and a plethora of inhibitors and antibodies geared at reducing amyloid, the clinical trial landscape in AD is littered with failures. Reisa Sperling pointed to ten Phase III trial failures in mild to moderate AD over the past decade. A likely reason for the failures, says Sperling, is not that the approaches are intrinsically ineffective, but that the treatments are being started too late.

Sperling believes that advances in the ability to identify people believed to be in the preclinical stages of AD "are ripe for translation" to clinical trials aimed at preventing disease progression. These trials are starting now, testing interventions in people with evidence of brain amyloid but no clinical symptoms. Several ongoing trials are recruiting subjects with genetic risk, such the Dominantly Inherited Alzheimer's Network (DIAN) and Alzheimer's Prevention Initiative trials in people with familial AD mutations, and the Tomorrow trial, which is selecting subjects based on risk alleles in ApoE and TOMM40 genes.

In a significant milestone, Sperling is heading up the first trial to base treatment on PET scan evidence of amyloid accumulation in cognitively normal people (the A4 trial, see Sperling et al. 2014). The trial will test the anti-amyloid antibody solanezumab vs. placebo for 168 weeks, with 500 subjects per treatment arm, using novel measures of cognitive function as outcomes. In addition, A4 will be the first to use functional MRI measures at multiple centers, allowing evaluation of this as a biomarker. The trial will also include PET imaging for tau, in a subset of participants. The first participant was enrolled in June 2014.

Going forward, Sperling is working to launch a second trial of a beta-secretase inhibitor in preclinical AD in 2015. After that, she is proposing a combination therapy trial—because the PET data suggest that tau spread starts early, it would be best to combine an amyloid targeted treatment with one that affects tau, if such a treatment can be developed.

With early treatment trials, the field is now in the decisive battle for the amyloid hypothesis, Sperling said. "If it works we'll be in very good shape, but if not we have to switch directions."

New avenues

The final session of the day featured current or past ADRC trainees whose research is aimed towards gaining new understanding of pathological pathways and development of novel biomarkers.

Multiple studies, both imaging and autopsy, highlight the discrepancy between AD pathology and clinical AD: In one study, 12% of elderly nuns with who died with normal cognitive status had enough brain pathology on autopsy to qualify for a diagnosis of AD. Neuroimaging has confirmed this mismatch of pathology and cognitive status, showing both

amyloid and now tau pathology in the brains of healthy people. M. Teresa Gomez-Isla is looking to explain this by comparing in more detail the neuropathology of brains from cognitively normal people with plaques and tangles, to those with dementia (Perez-Nievas et al., 2013). Her results suggest that brain accrual of oligomeric Abeta assemblies and phospho-tau species, as well as glial cell activation may serve as better predictors of anatomical disruptions and dementia than plaques and tangles. Going forward, it will be important to develop PET imaging agents that can differentiae different forms of amyloid and tau, to distinguish the more toxic deposits.

An enduring mystery in AD is the relationship between amyloid and tau, the proteins that make up plagues and tangles. In the amyloid hypothesis, the build of up abeta leads to amyloid plague deposition, which is followed by tau neurofibrillary tangle deposition and cell death. But testing this hypothesis in animals or cells has been impossible, because cells don't make plaques, and animal models make abundant plaques, but don't show tau tangles. Doo Kim recently developed an in vitro cell system that recapitulates both plaque and tangle pathology (Choi et al., 2014), and his results support the hypothesis that accumulation of Abeta drives tau. His "plaques in a dish" provide a unique system for understanding the amyloid cascade hypothesis and testing new therapeutics.

On the biomarker front, Mark Albers is looking at whether changes in the ability to remember odors can serve as a novel specific biomarker for early AD. Ninety percent of people with AD dementia have deficits in their ability to identify odors, which correlates with neuropathological changes such as atrophy of the hippocampus and tau deposition. Albers has found that in the percepts of odor episodic memory (POEM) test, AD patients perform no better than chance, and perform much worse than cognitively normal age-matched subjects. Among clinically normal subjects, those with poor POEM performance relative to their odor discrimination and identification abilities had lower hippocampal volumes, entorhinal cortical thinning, and were more likely to carry APOE4 alleles. Albers concluded that the POEM test might be an affordable means to detect preclinical disease.

The future of AD research and role of the ADRCs

Without doubt we are all optimistic that the future of AD research is pointed towards therapeutics. Yet key questions remain for which having a large, well characterized cohort of patients and biosamples, including brain tissue, will be critical. Understanding the natural history of AD patients – from the preclinical phase through the final devastating illness – is critical to be able to think clearly about disease modifying trials and eventually treatments. It is likely that the types of approaches needed to slow progression in the earliest, presymptomatic phase of disease will be different than the approaches necessary to impact neurodegenerative changes in which neuroinflammation, deafferentation, and vascular alterations all contribute. The Alzheimer Disease Center (ADC) program provides this kind of longitudinal information that will be so important.

A challenge for the future remains attempts to better phenotype patients with neuroimaging and fluid based biomarkers – discovery work that is thriving in the ADCs. Fundamental neuroscience questions directly related to clinical issues abound as well: is the clinical syndrome "Alzheimer disease" or "Alzheimer diseases"? How do we interpret cases with

relatively few plaques as observed on PET imaging? What is the role of neuroinflammation, or even of the very well established genetic risk factors including apoE? The ADC programs have long been pivotal in facilitating studies that combine the clinically important issues such as these questions of disease heterogeneity with the basic science of current genetics, epigenetics, proteomics, etc. The next decade will only hold more – and more sophisticated --omics approaches, but the deep phenotyping of patients remains the cornerstone of the understandings that will emerge. The same logic holds for the advances in neuroimaging that are occurring at increasing speed. One only has to look at the impact of amyloid PET scans, which developed and grew from ADCs, to the recent explosion of tau PET scans, and new MRI based tools including fMRI and connectome studies, to see the power of these approaches when developed in the setting of programs focused on understanding Alzheimer's disease.

The ADC programs are also a natural place to focus efforts on new clinical trials – both in terms of having infrastructure and well-characterized patient populations, but also in terms of innovations in neuropsychology and biological methods to advance the science of clinical trials. Cross disciplinary by nature, the ADCs are in a perfect position to push this science forward, which will have the benefit of being able to run smaller, more predictive trials on our way to cures. Finally, the ADCs are the training ground for the next generation of scientists who will be trained in a multidisciplinary environment, with access to tissues and biofluids and neuroimaging data, who will take advantage of "big data" approaches and who knows what else – to continue the tradition of learning about Alzheimer disease and moving towards sensitive diagnosis, effective treatments, and cures.

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