2012 Year in Review

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Alzheimer’s Disease Clinical Research

This year ushered in the identification of numerous AD susceptibility genes, as multiple genome wide studies began delivering on the promise that sequencing large numbers of individuals will help identify mutations that increase the risk for AD. The Alzheimer’s Disease Genetics Consortium, reported genetic analysis of more than 11,000 people with Alzheimer’s disease and a nearly equal number of elderly people who have no symptoms of dementia. Three other consortia contributed confirming data from additional people, bringing the total number of people analyzed to over 54,000. Until recently, only four genes associated with late-onset Alzheimer's had been confirmed, with the gene for apolipoprotein E-e4, also called APOE4, having the largest effect on risk. The findings here added another five -- MS4A, CD2AP, CD33, ABCA7, and EPHA1, thereby doubling the number of genes known to contribute Alzheimer’s disease. Later in the year, an additional susceptibility gene was identified, TREM2, also using genome wide sequencing. The manner in which these genes contribute to AD are being carefully scrutinized, as each may represent a potential therapeutic target.

Alzheimer's Prevention Initiative

This year also saw the launch of an unprecedented clinical trial, being run by an international collaboration of researchers in academia and industry to prevent dementia due to AD by treating patients with a drug before any cognitive symptoms appear. The trial, called the Alzheimer’s Prevention Initiative (API) is being led by Dr. Eric Reiman at the Banner Alzheimer’s Institute in Phoenix, Arizona, and Dr. Francisco Lopera and his colleagues at the University of Antioquia in Colombia. Over the past two years, these scientists and other colleagues have enrolled members of the world’s largest kindred afflicted with a mutation that leads to early onset AD.

Vaccines

Another notable item from 2012 was the results of the Phase I study of Novartis’ CAD106 vaccine against beta-amyloid. This was only the second vaccine study for AD. The first human vaccination trial in AD, Elan’s AN-1792, which was done almost a decade ago, had too many adverse reactions and was discontinued. However, in contrast, CAD106 was well tolerated, and will hopefully move towards a larger, Phase II study.

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New Gene Resists AD

Perhaps the biggest discovery this year was the identification of a mutation in APP that significantly decreases its cleavage by beta-secretase, leading to 40% less production of beta-amyloid. This mutation also confers resistance to the development of Alzheimer’s disease in patients. That is, people with the mutation make substantially less beta-amyloid and do not get AD. Just to review, all neurons secrete a protein called Amyloid Precursor Protein (APP), and APP is cleaved by two scissor-like proteins, gamma secretase and beta secretase. This leads to the production of beta-amyloid, a toxic protein fragment that accumulates in the brain over time, causing brain cell damage eventually leading to dementia, and deposits into amyloid plaques. Genetic mutations in either APP or either one of the scissor-like secretases that cleave it lead to inherited forms of Early Onset Alzheimer’s disease that strike patients in their 30’s and 40’s.

The gene for APP resides on the 21st chromosome, and in people with Down Syndrome, who are born with an extra copy of the 21st chromosome, each of their brain cells produce 50% more APP and subsequently 50% more beta-amyloid and therefore have a much greater incidence of AD. Intriguingly, individuals with Down Syndrome who have an extra-copy of the 21st chromosome, but lacking the segment that includes the APP gene, do not seem to get AD.

Reports On Phase III Trials

Over the summer, there was a flurry of results from multiple Phase 3 trials for AD. The results of two Phase 3 trials of intravenous bapineuzumab, a monoclonal antibody against beta-amyloid, showed that it failed to meet its primary endpoints in patients with mild to moderate Alzheimer’s disease. However, data from Eli Lilly’s solanezumab study, as well as the independent ADCS analysis of the trial, showed that the drug slowed down the rate of cognitive decline in patients with mild AD by about 34%. Moreover, in looking at subjects who had positive amyloid PET scans, there was a statistically significant change in total beta-amyloid in cerebral spinal fluid (CSF). Both of these findings are quite exciting, and indicate that this anti-beta amyloid drug has a statistically significant effect on cognition, and a biomarker of AD; a first in AD research. A Phase 3 study of solanezumab in mild AD is being planned.

The year also saw the end of the gamma-secretase inhibitor, avagacestat, which followed in the footsteps of another drug in the same class, semagacestat. Both were shown to have trends towards worsening cognition as an adverse effect. Meanwhile beta-secretase inhibitors, as well as gamma-secretase ‘modulators’ move forward in the drug pipeline, and are thought to hold great promise.

Finally, the FDA approval of Amyvid as an amyloid imaging tracer for PET scans represents a major milestone in the clinical evaluation of AD. Other tracers are being developed and may be approved this upcoming year.

What Does 2013 Hold In Store For The AD World?

We eagerly await the results from the Phase 3 clinical trial of IGIV in mild to moderate AD. In addition, the launch of the Down Syndrome Biomarker Initiative (DSBI) will undoubtedly help us better understand how AD develops in Down Syndrome, and perhaps identify novel biomarkers of AD. Additional data from ADNI and the DIAN studies are expected, focusing on identifying the earliest changes seen in the AD brain. Additional clinical trials in AD and prodromal AD are ongoing, with several new compounds being prepared for launch in mid 2013. One of these includes the intranasal insulin study, which has had positive early results and is being conducted by the ADCS.

We look forward to keeping you updated on what is happening in the world of AD research in the upcoming year, and are optimistic that there will be great developments in the field of AD in 2013. Stay tuned.
It is Possible To Both Have And Not Have Alzheimer’s Disease?

By Jason Karlawish, MD on November 24th, 2012 in Conditions

It is possible to both have and not have Alzheimer’s disease. Contradictory as this statement is, a study reported from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) supports it.

In a paper published in the October issue of the *Annals of Neurology* investigators reported the results of biomarker studies of 53 patients with dementia caused by Alzheimer’s disease. They found a notable proportion of these patients lacked one of the signature pathologies: brain amyloid. This result has notable scientific and policy implications.

Since 2004, ADNI, a longitudinal, NIA-industry funded study, has meticulously followed a cohort of persons with normal cognition, mild cognitive impairment, and dementia caused by Alzheimer’s disease. Key measures are biomarkers, a term that describes a measure that captures a complex pathologic process, such as how low density liproprotein (the LDL or “bad” cholesterol) captures the myriad of events leading to heart disease, and if abnormal, prompts a clinician to prescribe treatment.

In the case of Alzheimer’s disease, one of the most provocative biomarker measures is PET amyloid imaging, a measure of the presence of amyloid plaques in the brain. Amyloid is one of Alzheimer’s disease two pathologic signatures, the other being tangles of dysfunctional tau protein. An amyloid scan of the brain of a person with dementia caused by Alzheimer’s disease is a kind of living biopsy of the brain. An expert clinician, such as those studying the patients in ADNI, would expect to find that a patient with Alzheimer’s disease would have a “positive amyloid scan.”

Which is why the study is so revolutionary. Twelve of the 53 patients that an expert clinician diagnosed as demented because of Alzheimer’s disease had a negative amyloid scan. In short, their virtual brain biopsy was negative.

For clinicians, this result from a small sample of subjects is not enough to change clinical practice for the thousands of older adults diagnosed every year with Alzheimer’s disease dementia. But this may change.

In the Spring of 2012, the Food and Drug Administration approved the use of florbetapir for the imaging of brain amyloid, and Medicare will soon decide what kinds of indications for florbetapir, owned by Lilly, will receive reimbursement. Their decision will, in turn, create precedent for what private insurers will cover. If more studies show the same result as this study, they will challenge whether to expand what is expected to be a fairly narrow set of reimbursable uses.

For researchers and clinicians, this result raises an important question. If one in five of carefully examined older adults with Alzheimer’s disease in fact do not have one of its signature pathologies, what disease do they have? ADNI researchers will undoubtedly hurry to explore the study's vast treasure chest of psychometric, imaging and spinal fluid data answer this question. They may find that what clinicians call Alzheimer’s disease is, in fact, many diseases.

Pharmaceutical companies and clinical trialists should also consider this result. The history of drug development in Alzheimer’s disease has been a serial disappointment. Just this summer, the giants Pfizer and Lilly reported negative results for their drugs—bapineuzamab and solaneuzemab, respectively—that targeted amyloid in persons with Alzheimer’s disease.

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The ADNI results suggest that the drugs may not have been the problem. Instead, the studies may have failed because some of the patients, perhaps as many as one in five, did not in fact have the very pathology the drugs were designed to attack, namely amyloid. Pfizer may want to revisit its decision to shut down a large portion of its once vast Alzheimer’s drug development operation.

For this day forward, it is reasonable to argue that all patients with Alzheimer’s disease recruited for a clinical trial that targets amyloid should have a PET scan for amyloid and that only those who are amyloid positive be enrolled in the trial. The clinical implication of such a design, if it shows the drug is successful, is that prior to initiating treatment, a patient with Alzheimer’s disease will need a PET scan. The future price tag for treating the millions of patients just went up by a few thousand dollars.

This price tag is just one reason why health care policymakers should ponder the implications of this research. One of the compelling reasons why Alzheimer’s disease is called a “tsunami” is that millions of people have it, and, over the next two decades, millions more. And yet, if perhaps twenty percent of them have some other disease, this prevalence count is unstable. This instability suggests that the value of measuring the size of the problem is the number of persons with dementia, regardless of the cause.

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Eating Lots of Carbs, Sugar May Raise Risk of Cognitive Impairment, Mayo Clinic Study Finds

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Those 70-plus who ate food high in fat and protein fared better cognitively, research showed

ROCHESTER, Minn. — People 70 and older who eat food high in carbohydrates have nearly four times the risk of developing mild cognitive impairment, and the danger also rises with a diet heavy in sugar, Mayo Clinic researchers have found. Those who consume a lot of protein and fat relative to carbohydrates are less likely to become cognitively impaired, the study found. The findings are published in the Journal of Alzheimer's Disease.

The research highlights the importance of a well-rounded diet, says lead author Rosebud Roberts, M.B., Ch.B., a Mayo Clinic epidemiologist.

"We think it’s important that you eat a healthy balance of protein, carbohydrates and fat, because each of these nutrients has an important role in the body," Dr. Roberts says.

Researchers tracked 1,230 people ages 70 to 89 who provided information on what they ate during the previous year. At that time, their cognitive function was evaluated by an expert panel of physicians, nurses and neuropsychologists. Of those participants, only the roughly 940 who showed no signs of cognitive impairment were asked to return for follow-up evaluations of their cognitive function. About four years into the study, 200 of those 940 were beginning to show mild cognitive impairment, problems with memory, language, thinking and judgment that are greater than normal age-related changes.

Those who reported the highest carbohydrate intake at the beginning of the study were 1.9 times likelier to develop mild cognitive impairment than those with the lowest intake of carbohydrates. Participants with the highest sugar intake were 1.5 times likelier to experience mild cognitive impairment than those with the lowest levels.

But those whose diets were highest in fat — compared to the lowest — were 42 percent less likely to face cognitive impairment, and those who had the highest intake of protein had a reduced risk of 21 percent.

When total fat and protein intake were taken into account, people with the highest carbohydrate intake were 3.6 times likelier to develop mild cognitive impairment.

A high carbohydrate intake could be bad for you because carbohydrates impact your glucose and insulin metabolism," Dr. Roberts says. "Sugar fuels the brain — so moderate intake is good. However, high levels of sugar may actually prevent the brain from using the sugar — similar to what we see with type 2 diabetes."

The study was funded by the National Institute on Aging.

For audio and video of Dr. Roberts talking about the study, visit Mayo Clinic News Network.

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For more information, visit MayoClinic.com or MayoClinic.org/news.
Researchers at Johns Hopkins Medicine in November surgically implanted a pacemaker-like device into the brain of a patient in the early stages of Alzheimer’s disease, one of the first such operations in the United States. The device, which provides deep brain stimulation and has been used in thousands of people with Parkinson’s disease, is seen as a possible means of boosting memory and reversing cognitive decline.

The surgery is part of a federally funded, multicenter clinical trial marking a new direction in clinical research designed to slow or halt the ravages of the disease, which slowly robs its mostly elderly victims of a lifetime of memories and the ability to perform the simplest of daily tasks, researchers at Johns Hopkins say. Instead of focusing on drug treatments, many of which have failed in recent clinical trials, the research focuses on the use of the low-voltage electrical charges delivered directly to the brain. There is no cure for Alzheimer’s disease.

As part of a preliminary safety study in 2010, the devices were implanted in six Alzheimer’s disease patients in Canada. Researchers found that patients with mild forms of the disorder showed sustained increases in glucose metabolism, an indicator of neuronal activity, over a 13-month period. Most Alzheimer’s disease patients show decreases in glucose metabolism over the same period.

The first patient in the new trial underwent surgery at The Johns Hopkins Hospital, and a second patient is scheduled for the same procedure in December. The surgeries at Johns Hopkins are being performed by neurosurgeon William S. Anderson, M.D.

"Recent failures in Alzheimer’s disease trials using drugs such as those designed to reduce the buildup of beta amyloid plaques in the brain have sharpened the need for alternative strategies," says Paul B. Rosenberg, M.D., an associate professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine, and site director of the trial’s Johns Hopkins location. "This is a very different approach, whereby we are trying to enhance the function of the brain mechanically. It’s a whole new avenue for potential treatment for a disease becoming all the more common with the aging of the population."

Some 40 patients are expected to receive the deep brain stimulation implant over the next year or so at Johns Hopkins and four other institutions in North America as part of the ADvance Study led by Constantine G. Lyketsos, M.D., M.H.S., a professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine, and Andres Lozano, M.D., Ph.D., chairman of the neurology department at the University of Toronto. Only patients whose cognitive impairment is mild enough that they can decide on their own to participate will be included in the trial.

Other sites performing the operation, supported by the National Institutes of Health’s National Institute on Aging (R01AG042165), are the University of Toronto, the University of Pennsylvania, the University of Florida, and Banner Health System in Phoenix, Ariz. The medical device company, Functional Neuromodulation Ltd., is also supporting the trial.

"We are very excited about the possibilities of this potentially new way to treat Alzheimer’s," says Lyketsos, director of the Johns Hopkins Memory and Alzheimer’s Treatment Center in Baltimore.

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Johns Hopkins Surgeons Implant Brain ‘Pacemaker’ for Alzheimer’s Disease in United States as Part of a Clinical Trial Designed to Slow Memory Loss continued..

While experimental for Alzheimer’s patients, more than 80,000 people with the neurodegenerative disorder Parkinson’s disease have undergone the procedure over the past 15 years, with many reporting fewer tremors and requiring lower doses of medication afterward, Lyketsos says. Other researchers are testing deep brain stimulation to control depression and obsessive-compulsive disorder resistant to other therapies.

The surgery involves drilling holes into the skull to implant wires into the fornix on either side of the brain. The fornix is a brain pathway instrumental in bringing information to the hippocampus, the portion of the brain where learning begins and memories are made, and where the earliest symptoms of Alzheimer’s appear to arise. The wires are attached to a pacemaker-like device, the "stimulator," which generates tiny electrical impulses into the brain 130 times a second. The patients don’t feel the current, Rosenberg says.

For the trial, all of the patients will be implanted with the devices. Half will have their stimulators turned on two weeks after surgery, while the other half will have their stimulators turned on after one year. Neither the patients nor the doctors treating them will know which group gets an early or later start.

"Deep brain stimulation might prove to be a useful mechanism for treating Alzheimer’s disease, or it might help us develop less invasive treatments based on the same mechanism,” Rosenberg says.

By 2050, the number of people age 65 and older with Alzheimer’s disease may triple, experts say, from 5.2 million to a projected 11 million to 16 million, unless effective treatments are found.

For more information, please visit the JHU Alzheimer’s research page

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How the iPhone 5 Can Help Alzheimer's Patients

With the launch of the iPhone 5, we're reminded of all of the old iPhones, iPods, and digital devices sitting around, and the unique ways they can be put to use. Music & Memory is a non-profit organization that puts these discarded devices to use by donating them to those suffering with Alzheimer's and dementia, having found that patients experienced increased socialization after listening to the songs of their youth.


Between 2007 and 2010, more than 50 million iPods were sold annually worldwide, and more than 40 million were sold in 2011. As many of these devices are outdated or replaced by now, Music & Memory encourages donations of new and gently used iPods, iPads, and other Apple music players on an ongoing basis.

Click here to learn how to contribute: http://www.musicandmemory.org/give-an-ipod.html


Music & Memory was recently profiled on 'The Doctors' (CBS) TV show, as part of their "Incredible Medical Stories" episode: http://www.thedoctorstv.com/videolib/init/7206

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Save the date for the 6th edition of Clinical Trials on Alzheimer’s Disease (CtaD) to be held in San Diego, November 14-16, 2013.

After the success of CtaD 2012 with more than 650 participants from all around the world and exciting presentations we are looking forward to making CtaD 2013 scientifically and clinically challenging!

You can find the abstracts of CtaD 2012 as well as articles written on the conference in the press section on our website www.ctad.fr

Alzheimer’s disease is one of the most important health challenges facing aging populations worldwide. The development of the next generation of Alzheimer’s disease drugs is becoming essential to face up to this challenge. We learned in Monte Carlo of new pathways identified with biomarkers, facilitating novel trial designs for studies of tau-based therapies and other disease-modifying drugs including immunotherapy.

However, we still need to overcome hurdles to speed up the development of specific new drug candidates. Again in San Diego we will address methodological issues, follow-up on new therapies and look at novel assessment tools and criteria.

We take this opportunity to wish you a very merry holiday season and we look forward to seeing you in San Diego!

On behalf of the organizing committee

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ADNI II Study

The goal of the Alzheimer's Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer's disease in future generations. Information from the study might, in the future, lead to new treatments. [http://adcs.org/Studies/ImagineADNI.aspx](http://adcs.org/Studies/ImagineADNI.aspx).

Resveratrol for Alzheimer’s is Recruiting

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