Alzheimer’s Disease 2012: THE GREAT AMYLOID GAMBLE

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Abstract

Alzheimer’s disease threatens to become the scourge of the 21st century. Hundreds of millions of aging people throughout the world will be at risk, but it is clear that the disease is more than just the natural aging process. Deposits of amyloid abeta peptides in the brains of demented individuals are a defining feature of the disease, yet two decades of intensive investigation, focusing on reducing or removing amyloid deposits, have failed to produce any meaningful therapeutic interventions. Some question whether amyloid is the appropriate target. Others maintain that early, pre-symptomatic intervention would be a more informative test and propose large-scale clinical trials on people who are believed to be in the earliest and potentially reversible stages of the disease. This essay explores the wisdom of that approach.

The past twenty-five years have seen truly impressive gains in our understanding of Alzheimer’s dementia (1,2), yet effective treatments and prevention strategies are still distant goals. Newly developed brain scanning methods, including functional PETs and structural MRI, have pointed to toxic forms of the amyloid abeta peptides as the precipitating cause of brain dysfunction and eventually neuronal cell death, results that appear to confirm the primacy of the amyloid hypothesis. But pursuing amyloid as the most relevant therapeutic target has led to disappointing results, most recently the failure of the high profile gamma secretase inhibitor semagacestat to have any measurable success. Some question whether the failure of anti-amyloid treatments is telling us that amyloid is not the most relevant target. Others suggest that treating patients with advanced disease is not a valid test of any anti-amyloid agent. These conclusions have led to multiple, nationwide, multidisciplinary efforts to focus on people who suffer from mild cognitive impairment (MCI) the earliest detectable stage of Alzheimer’s dementia. Brain damage in these individuals is clearly less advanced and therefore potentially more treatable. This effort, led by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and other consortia, is designed to test the question, whether the amyloid hypothesis is indeed the surest path to the development of new therapies (3).
essay explores the science behind this approach and concludes that this thrust, which will require mega-millions of dollars and countless investigator and patient time, must be considered a gamble, justified by the preliminary findings that support it, but a gamble nevertheless because of so many unknowns that still stalk the Alzheimer’s crusade.

Alzheimer’s dementia is one of the most destructive and feared human maladies that affect aging members of every population in the entire world. First recognized a hundred years ago on the basis of amorphous deposits of unknown material in the brains of affected people, we now know that these deposits are composed in part of small peptide fragments that are generated by proteolytic cleavage of a large trans-membrane protein that resides in the brain and other tissues. The functions of both the parent protein (called APP) and the cleaved peptides (referred to as abeta 40 and 42) are unknown, but there is little doubt that both play critical roles in the workings of the human brain. Moreover, a large body of evidence is consistent with the view that the abeta peptides not only make up the bulk of the plaques that Alzheimer described in 1907, but they are also the primary cause of Alzheimer’s dementia, making them the prime target for therapeutic intervention. The large body of experimental data and clinical observations that support these views is popularly known as the Amyloid Hypothesis.

Background to the Amyloid Hypothesis

It’s always hard in science to decide who did what and when first, but George Glenner, working at the NIH in the mid-60’s, probably provided the first clue as to the chemical nature of the plaques that Alois Alzheimer described in 1907. Glenner extracted a small peptide from the blood vessels of Alzheimer’s brains, and his analysis of this finding led other workers in the field to identify what might be called the “Alzheimer’s protein”. This happened in 1984. More about this protein and the peptide that was derived from it will be described later, but the question readers will be asking is why it took seventy-seven years to make this discovery? Many reasons come to mind.

First it should be realized that enough people had to live beyond early middle life for the disease to develop to the stage where it became clinically evident and the major health problem we now recognize. Moreover, the association of the disease
with advancing age encouraged physicians to assume that it was part of the natural aging process. We now know this was an understandable but incorrect assumption: Alzheimer’s dementia is indeed a disease that accompanies human aging, but it is not an inevitable consequence of it (4). Multiple pathological processes occur as we age, and these we believe explain why human dementia and advanced age are so tightly coupled.

Another obstacle to the study of AD was the limited knowledge we had of the human brain. Encased as it is in a sturdy bony vault it seemed inaccessible to the tools scientists used to study other human tissues. Biopsies were (and still largely are) not feasible, which meant that the tissues of the brain could only be examined by pathologists after death. This led to the widespread view (still shared by many physicians) that a definitive diagnosis of AD could only be made after an autopsy. Autopsy studies are rightly considered the gold standard for determining cause of death and the extent of a disease process, but they have their limitations. For one thing they only tell you what was going on at the time of death, and while they reveal much about the end stage of a complex process such as AD, one can only guess as to what may have happened during the lifetime of the patient. In the case of AD this limitation is glaring, since we now know that AD probably begins, in some form, still to be revealed, years before symptoms appear.

What propelled the AD field forward was the development of recombinant DNA technology. Building on the findings of Glenner, it was possible to identify the larger protein from which the peptide was derived, and this led to a watershed of discoveries. These are highlighted in the figure below.
Several points need emphasizing. Once the amyloid peptide was positively identified, the gene for the amyloid precursor protein (APP) was relatively quickly (for that era) deduced and this opened the floodgates to a cascade of discoveries. Within a little more than a decade almost everything we know about the role of amyloid in AD was revealed. Mutant forms of APP and the gamma secretases showed that defective genes could indeed contribute to disease, but their rarity meant that for most AD patients (95%) who lacked these defective genes other causes had to be determined. The APOE4 allele of apolipoprotein E was found to predict earlier onset forms of sporadic AD, but this finding was reported two decades ago, and we still have no clear idea how these protein variants contribute to disease. Recombinant DNA technology allowed investigators to develop animal models that appeared to mirror the human from of AD, but such animals usually generated far more amyloid in their brains than most humans ever have, leading many to question whether they are faithful examples of human AD that can be used to test new forms of therapy.

In 1999 it was discovered that antibodies to the amyloid peptide could be used to flush out amyloid from the brains of genetically engineered mice (5). This was an extraordinarily important discovery that has led to a multitude of clinical trials that are now in progress. Another pivotal advance was the introduction of amyloid-binding dyes that were able to detect amyloid in living people. PIB scans, first described in 2002, provided the ability to monitor the progression of amyloid deposits in individuals who have not yet reached full-blown dementia.

Collectively this huge body of information, both experimental and clinical, supports the idea that abeta peptides contribute in a major way to the pathogenesis of Alzheimer’s disease and its accompanying dementia. That stated, it is still a mystery how the two are causally related. Among the many unknowns are when Alzheimer’s disease first starts, or even how it starts. Nor do we have any idea what the triggering elements are. Two features of the disease are generally agreed upon: AD probably starts years before clinical symptoms are evident, and, because it takes so long to develop into clinical disease, we surmise that it must be a very slow disease process, or more likely, several different processes that act in concert. These two features, its early undetected onset, and the long pathogenic course, have made it
difficult to reproduce the disease in experimental animals. This accounts in part for so much uncertainty about this disease in spite of the vast research effort that has already been expended. This great uncertainty fueled efforts to identify ways to identify people who might be in the early stages of the disease, long before symptoms appear, and hopefully before significant possibly irreversible damage has occurred.

The Search for Biomarkers

Biomarkers are objectively measured ways to detect a disease process or the predisposition to disease in a living person. An elevated white blood cell count signals infection and high serum cholesterol correlates with the predisposition to atherosclerosis. The practice of clinical medicine would grind to a halt without these essential diagnostic tools. Unfortunately there is no simple, reliable and reproducible blood test for any aspect of Alzheimer’s dementia. Many attempts to develop one have been made, but none have succeeded.

While attempts to measure abeta levels in the blood have so far not proven useful, measurements of cerebrospinal fluid (CSF) have produced an unexpected surprise. Levels of abeta 42 are lower in AD patients than matched controls, and when they are correlated with positive PIB a stain for brain amyloid, patients with mild cognitive impairment (MCI) can be identified. By correlating imaging studies with CSF analysis it is therefore possible for the first time to identify MCI patients by objective measurement alone. This was great advance since it offered the possibility of evaluating new therapies using objective measurements alone. Jack and his collaborators further proposed that by correlating five different biomarkers, including three by imaging (PET-amyloid, FDG-PET, and structural MRI) and two by CSF analysis (abeta 42 and P-tau) it might be possible to predict the stage of disease in any given patient (6). This analysis predicts that biomarkers of Aβ deposition become abnormal first, long before neurodegeneration and clinical symptoms appear. In contrast, FDG-PET, CSF Tau, and MRI detectable atrophy become abnormal in the MCI stage, when symptoms of the disease are already evident. These findings and others like them have led to important policy decisions within the AD investigator community.
Should reduction of amyloid deposits in brains of individuals suffering from Mild Cognitive Impairment (MCI) be a high priority goal?

There is a widespread consensus among AD investigators who have participated in the ADNI program that therapies that reduce abeta accumulations either by decreasing production, increasing turnover, or by antibody removal should be tested first on MCI patients in an attempt to arrest the progression of MCI to advanced dementia. This is based on the following assumptions:

(i) Biomarkers and brain scans can be used to identify MCI patients and follow their progression to frank dementia,
(ii) MCI patients will usually progress to clinical dementia over the course of several years
(iii) Amyloid-related peptides accumulate in the brain during the MCI stage and are presumed to be pathogenic

It makes sense to continue to support the expansion of the ADNI program by adding to these studies the testing of new therapies, realizing that existing animal models that focus on amyloid overload have not proven to be reliable ways to test new therapies. Although many recent attempts to treat patients by reducing amyloid levels in the dementia stage of the disease have not succeeded, one assumes that there is a better chance of preserving existing neuronal functions in MCI patients than in those with advanced dementia. An added advantage is the ability to monitor treatment efficacy with objective tests. However while supporting this program, it is useful to acknowledge the imposing number of questions regarding the pathogenesis of AD that if remain unanswered will continue to constrain our ability to design and test the most appropriate therapies and formulate rational guidelines for prevention.

**STILL REMAINING UNKNOWNS**

1. When, where, and how do the earliest lesions that lead to MCI develop?
2. How do abeta peptides, in whatever form, damage neurons?
3. What is the physiological function of abeta peptides?
4. How do neurofibrillary tangles contribute to disease?
5. How does oxidative damage contribute to disease onset?
6. Is inflammation a factor?
7. Does blood vessel damage contribute to amyloid dysregulation?
8. What are the most effective preventive measures?

It is hardly surprising that we have yet to determine what the earliest lesions are that eventually lead to neuronal degeneration and clinical dementia. As is the case when studying other chronic diseases, looking solely at the late stages of a disease may be misleading, and this is particularly true if we lack suitable animal models. All the existing mouse models that are routinely studied as AD proxies rely on overproduction of amyloid abeta peptides. Since significant amounts amyloid accumulate late in the human disease, it seems likely that other processes, such as oxidative damage and/or inflammatory reactions may precede amyloid dysregulation, as many AD investigators have previously suggested (see refs in 7). We must also consider the possibility that large-scale amyloid accumulations are a late event in human AD, triggered by as yet unknown processes. In this case anti-amyloid therapies may not be effective ways to treat MCI.

Another perplexing aspect of the AD field is the surprising lack of any consensus as to what form of abeta peptides are toxic to neurons in the living brain. Part of the problem is the quixotic nature of the amyloid abeta peptides themselves. Are they critically involved in synaptic activity and neurotransmission, as recent studies suggest (8), or are they nuisance degradation products prone to clump together and clog up the interstitial spaces? Since elevated levels of abeta production are only found in patients with rare mutations, reduced clearance of abeta rather than overproduction is considered the most likely cause of amyloid accumulation in advanced disease and is the basis for a vigorous effort to reduce their level in the brain. Precisely why they accumulate is still unclear, but reducing them by whatever means is the stated goal, even though we must also consider the possibility that lowering the level of a normal functioning peptide by blocking its synthesis, or by immune-mediated clearance, might in the end impair normal neuronal functions and would therefore be an undesirable side effect. Ideally, targeting the toxic form of abeta makes the most sense, but this still remains an elusive goal. Much has been made of the tendency of abeta peptides to aggregate at high concentrations in vitro. Oligomeric forms, of widely varying sizes, have been identified as putative toxic forms, but their mode of action remains unknown, and
they are technically demanding to study. At this point they don’t seem like promising therapeutic targets.

Neurofibrillary tangles are as omnipresent in AD brains as amyloid plaques, and many have suggested that their presence correlates more faithfully with dementia than the plaques themselves. How and why they develop and how they contribute to the pathogenic cascade is just as mysterious as amyloid’s contribution to neurotoxicity. This is not to deny their importance, only to stress the difficulty we have in evaluating their effects without a suitable animal model.

How does oxidative damage contribute to AD? There is abundant, indeed overwhelming evidence that reactive oxygens and reactive nitrogens have the ability to modify every molecular species in the human brain, and are especially prominent in AD brains. Oxidative changes in membrane lipids are widely recognized, but less attention has been focused on oxidized nucleic acids, which is surprising since modified DNA and RNA have the potential to generate mutant proteins that could play a pathogenic role (9). Inflammatory reactions and damaged small blood vessels were once thought to play major pathogenic roles in early AD, but their significance has been eclipsed by the overwhelming logic of the amyloid cascade. The inability of anti-inflammatory agents to modify advanced disease also diminished enthusiasm for an inflammatory mechanism. However, now that we have discovered that anti-amyloid agents are also unable to modify advanced disease we may have to reconsider anti-inflammatory approaches as therapies for the preclinical stage. Again lacking suitable animal models that reflect inflammatory and vascular damage of the brain hamper our ability to test potential anti-oxidative damage and anti-inflammatory agents.

CONCLUSIONS

It is a good idea and sound public policy to focus on treating individuals who suffer from Mild Cognitive Impairment (MCI). Such individuals can be identified with reliable biomarkers, their progression to frank dementia is predictable, and their response to therapy can be evaluated by objective measurements. But we must be ready for some surprises. While amyloid is likely to contribute to advanced disease, it’s pathogenic potential may rely on as yet unidentified factors which could compromise agents or treatments that act on amyloid alone. While amyloid deposits
are a prominent feature of both MCI and advanced dementia, other pathogenic processes may act in the early stages of the disease, and they may progress to neuronal injury despite the reduction or absence of amyloid. Arresting disease progression is a desirable goal worth pursuing at all costs, but the gold standard will be prevention. This will require answers to the questions stated above.

REFERENCES


