Alzheimer and Related Dementias: The Prevention of Disease, Morbidity and Suffering

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Speakers

I. The Role of Anti-inflammatories and the Inflammatory Hypothesis in the Prevention of Alzheimer Disease
Presented by Patrick McGeer, MD, Vancouver, BC.

II. Decreasing Dementia Risk and Minimizing Cognitive Decline with Participation in Engaging Activities and Memory Rehabilitation
Presented by Angela Troyer, PhD, CPsych, Baycrest Centre for Geriatric Care, Toronto, ON.

III. Pharmacological Strategies for Prevention of Alzheimer Disease
Presented by Serge Gauthier, MD, FRCPC, McGill Centre for Studies in Aging, Montreal, QC.

The goal of research at the Baycrest Centre for Geriatric Care is to provide a scientifically based understanding of diseases and disorders of the elderly. Through various educational methods, staff are trained to implement new practices in assessment, management and rehabilitation. The ultimate goal is to find preventative measures to delay or eliminate the onset of disease. Three of the eight lectures at this conference that touched on how future research, clinicians and care providers may help to achieve these goals in patients with dementia are presented in this report.

I. Inflammatory Hypothesis in the Prevention of AD

Chronic inflammation is the driving force in the most important diseases of our time, including stroke, myocardial infarction and Alzheimer disease (AD). The question of how to control inflammation is far from trivial when you consider that one of these conditions will strike one-quarter of us at some time in our lives.

Two mechanisms of immunity collectively protect and defend the body against foreign proteins or damage. The adaptive immune system is a systemic reaction that relies on the cloning of T- and B-cells to attack the offending foreign protein. Autoimmune diseases occur when cloned products mistakenly attack host tissue. Innate immunity, on the other hand, is the first line of defense in all tissues and can be sustained in the absence of other factors. It does not require cloning of lymphocytes by peripheral immune organs to recognize a target and attack it. In this case, if the target is mistakenly host tissue, the consequence is the same as in classic autoimmunity, but the term autotoxicity has been introduced to explain this phenomenon that is generated local rather than systemic. In some conditions, such as multiple sclerosis, both phenomena are at work.

Inflammation begins as a reaction to the signals produced by the two immune response systems, and many factors may amplify or restrict this initial reaction. Yet nature tends to overdo the inflammation reaction, and we are constantly battling to discourage it. It is important to recognize the point at which inflammation ceases to be a beneficial mechanism and instead becomes harmful.

Basis of Inflammatory Hypothesis in AD

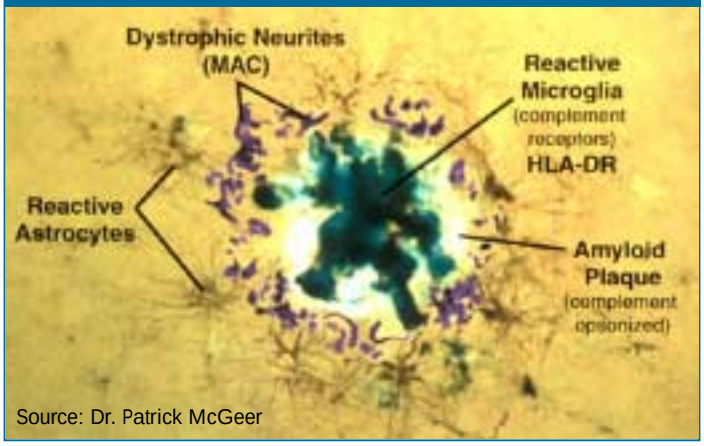
The hypothesis that inflammation of the brain might occur in AD began when activated microglia were identified in association with AD lesions (Figure 1). Microglia, the principal immune element of the brain, possess an extensive arsenal of responses to defend the brain against an assortment of external threats by secreting potentially cytotoxic substances. However, these "little bags of poison" can also attack healthy cells and tissue if they get out of control.

Other molecules which are key mediators in peripheral immune reactions were subsequently found in the brains of AD patients.[1] Thus, the possibility emerged that brain cells, including neurons, microglia and astrocytes, could produce a large number of immune and inflammatory mediators, including complement proteins and their inhibitors, inflammatory cytokines and their receptors and components of the internal and extrernal coagulation pathways. The concept that the brain is able to launch a full-scale innate immune response was established, and continues to undergo investigation.

Complement activation, a defense mechanism that is important in both inflammation and the antibody response, is typically used by the body to ward off infection and usually does not occur in the brain. There has been evidence, however, of activated complement proteins

Figure 1

Activated Microglia in Association with AD Lesions



Source: Dr. Patrick McGeer

near senile plaques—the hallmark of AD—and on damaged neurons in AD, and it appears that β-amyloid triggers this response by its binding to C1q protein. These findings contradicted the classical thought that the only way complement can be activated is by antibodies; complement seems to recognize proteins other than antibodies, one of which is the β-amyloid protein that characterizes AD, and which may start this disease process.

By measuring mRNA levels in AD brains post-mortem, investigators have discovered a huge upregulation of complement in certain areas of the brain that are implicated in AD (i.e., hippocampus), but not in areas unaffected by the AD process. Furthermore, the same sort of inflammatory reaction was found in the affected parts of the brain in Parkinson's disease (PD) patients—in the substantia nigra and in Lewy bodies. So although PD and AD are entirely different diseases with different causes, they seem to share the same consequences.

In cases of atherosclerosis, plaque builds up to cause the same kind of inflammatory reaction as seen in both AD and PD: macrophages (the peripheral nervous system equivalent to microglia) become overly active, releasing collagenase that dissolves the plaque, leading to a myocardial infarction or stroke. Marker studies of various complement proteins have found elevated levels of mRNA in the hippocampus of AD patients, in the heart tissue following myocardial infarction, in the aorta in cases with plaque build-up, and in the joints of patients with arthritis. However, for all these conditions, mRNA levels were normal in the tissues not affected by each disease, i.e., where no inflammation takes place (Figure 2).

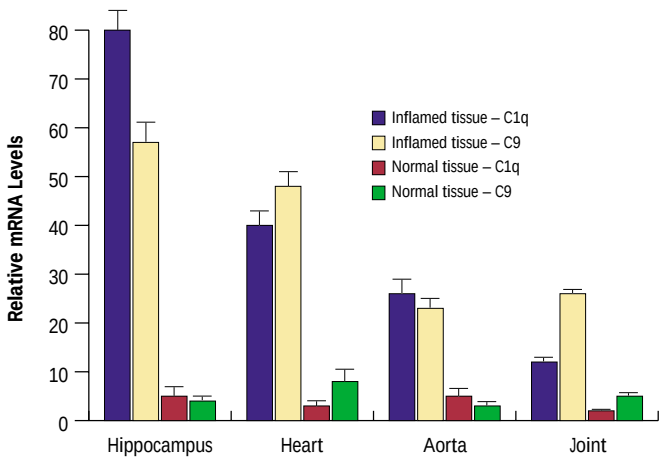
It seems, therefore, that inflammation is the most dangerous when it occurs in areas with no pain perception, such as in the brain and the heart, but not in cases of joint pain, for instance. Perhaps, then, people who are treating painful inflammation that they can feel are inadvertently treating painless inflammation of which they are unaware. At least 25 epidemiological studies have shown that those taking anti-inflammatory agents for a condition in which they are indicated have less incidence of AD. The 15-year Baltimore Longitudinal Study found that people taking non-steroidal anti-inflammatories (NSAIDs) for greater than two years had about 60% sparing of AD (relative risk 0.40; 95% confidence interval: 0.19- 0.84).[2] Results from the 10-year Rotterdam Study indicated 80% sparing of AD with NSAID use for pain-related conditions; in subjects who had more than six months of prescription days, a reduced relative risk for AD was found (RR=0.74; 95% CI: 0.20–2.72).[3] Both of these longitudinal studies emphasize the importance of the duration of NSAID use. In the Rotterdam study, for instance, the liklihood of developing AD was 95% and 83% for those with less than one month's use and with one to 24 months' use, respectively, whereas for those taking an NSAID for 24 months or longer, the likelihood of developing AD was only 20% that of non-users.

Thus far, both persuasive pathology and compelling epidemiology exist, but these have not been translated into effective treatment. The successful pilot studies to date have included investigations of indomethacin and diclofenac. In a six-month, double-blind, placebo-controlled study, indomethacin appeared to protect AD patients from the degree of cognitive decline exhibited by the placebo-treated group, although the study had limitations.[4] The efficacy of diclofenac was evaluated in 41 patients with mild to moderate AD in a prospective 25-week, randomized, double-blind, placebo-controlled trial. This Australian team found some nonsignificant trends for the placebo group to have deteriorated more than the treated patients. Although this small pilot study did not demonstrate a significant effect of NSAID treatment in AD, the observed trends seem promising.[5]

There has been no success with any of the COX-2 inhibitors. Although COX-2 concentrates in neurons, the areas of the brain in which they concentrate were found to be the wrong target. Any potential treatment of AD must meet the following criteria: the

Figure 2

C1q and C9 mRNA Levels in Inflamed and Normal Tissue



Source: Dr. Patrick McGeer

agent must reach the brain, hit the target and be administered in an adequate dose. In the future, therapeutic targets may include prostaglandins, which are weak inflammatory mediators, inflammatory cytokines (IL-1, IL-6, TNF-α), complement and complement inhibitors and, most importantly, C-reactive protein, amyloid P and amyloid β. We need to develop agents that are more powerful anti-inflammatory mediators and which can be more effective than COX-2 inhibitors. Or, if we are able to develop cognitive inhibitors that identify target proteins—such as C-reactive proteins—a huge spectrum of agents is available to us for investigation, none of which has presently been examined. Further possibilities may also include combinations of agents to give synergistic effects since these inflammatory agents target different areas of the brain.

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II. Cognitive Decline and Engaging Activities

Cognitive engagement involves the participation in activities that make a lot of demands on cognitive skills (e.g., requiring thought, memory, problem solving), as well as involvement in a complex environment at work or at home (e.g., decision making, judgements). The most recent research to explore the potential relationship between cognitive engagement and cognitive ability has shown that people involved in activities that are intellectually demanding tend to have better cognitive ability. These correlational studies administer a battery of cognitive tests to older adults, as well as questionnaires measuring either the complexity of their daily activities (current or past) or the complexity of work duties (current or past; independent thought, complexity of decision making).

Considering that dementia is defined as a decline in cognitive ability, we might expect that those involved in more cognitive activities would have lower rates of dementia. It has, in fact, been established that higher education is associated with a lower risk of Alzheimer disease (AD). One U.S. study found that for every year of formal education, there was a 17% reduction in risk of AD. Furthermore, a handful of literature shows that participation in engaging leisure activities also is associated with lower rates of dementia.

Prospective, longitudinal studies generally follow a group of healthy, older individuals for a number of years. These non-demented subjects are initally given a questionnaire about their current activities, and investigators continue to keep track of who goes on to develop dementia. One such study divided subjects into two groups: those with high levels of participation in leisure activities, and those with lower levels. Although both groups were found to develop dementia, those with higher participation rates developed dementia at a later age (on average about two years later).

Retrospective, case-control designs attempt to look even further back at participation in leisure activities in middle life, since the pathology of dementia develops earlier than when symptoms emerge in later life. One trial matched AD subjects to individuals without AD, and all subjects completed a questionnaire about past leisure activities they were involved in over their lifetime. If memory was impaired at baseline, a caregiver who knew the subject that long ago completed the questionnaire on the subject's behalf. Individuals with AD were found to have spent more time in passive activities and less time engaged in intellectual activities compared to controls, but no difference in physical activities between groups was found. In fact, regression analysis showed that the number of hours per month spent on intellectual activities predicted whether an individual was in the AD or control group.

The most optimistic conclusion we can derive from these studies is that cognitive engagement protects from cognitive decline and dementia. However, these are all correlational studies that cannot account for the possibility that early cognitive decline may be preventing people from engaging in more challenging activities. Earlier animal research seems to be consistent with the neuronal reserve hypothesis: individuals who have greater intellectual engagement are more resistant to the effects of AD because of enhanced synaptic complexity (i.e., with richer connections to begin with, intellectually engaged individuals can afford to lose more as the disease progresses).

Memory Rehabilitation

Memory rehabilitation is a type of complex activity, yet the research to date has found that improvements seen with rehabilitation are specifically tied to the task in which the subject was trained. For instance, if a patient is trained in name-face recognition, by the end of rehabilitation improvements will be seen in this particular task, but not necessarily in other cognitive skills.

The goal of cognitive rehabilitation in AD is to minimize the effects of cognitive impairment on the person's functional abilitities, thus improving quality of life and relieving demands on caregivers. Interventions may include space retreival (helping people retrieve information over progressively longer delays), face-name association strategies and the method of vanishing cues (to cue a person on what they need to remember, then gradually remove cue until they recall without any help). Studies have found that these interventions result in improvements in domain-specific knowledge; that is, improvements in the specific task or skill for which the subject was trained.

As for the practical application of these interventions, research on space retrieval training has found that if an individual is able to recall information after three minutes, then they have learned the

skill and can apply it the next day. Space retrieval also is used to help with calender training, in people with anomia (word finding problems) and to prevent repetitive questioning. In the healthy elderly, memory rehabilitation tends to be multifactorial, involving attention training and relaxation as well. Generally, there are not only improvements in the type of memory for which individuals were trained, but also decreased daily memory failures—suggesting the intervention is a practical one—and higher overall satisfaction with memory.

Conclusion

Early intervention is key. To achieve the most benefit from rehabilitation, the time to intervene would be when mild cognitive impairment (mild memory changes, but no global cognitive changes) first begins to develop. Rehabilitation goals are to provide practical interventions in order to improve memory and help delay functional impairment. Since dementia is defined by the presence of cognitive impairment, if we are able to delay this impairment we are, in fact, delaying the development of dementia. Rehabilitation is a way to enhance or maintain cognitive abilities, but if we are able to identify people early and intervene early, rehabilitation may function as a prevention strategy.

III. Pharmacological Strategies for Prevention of AD

The steps in attempting to modify the progression of AD have been to understand its natural history and its pathophysiology, and to develop trials and outcomes appropriate to the stage of disease that is targeted for therapy. Most of us are familiar with the traditional approach of looking at the natural history of AD, with mild, moderate and severe stages. However, now we can broaden these concepts to include people with very early symptoms, such as mild cognitive impairments, as well as those in the presymptomatic stage, including mutation carriers and those carrying a combination of risk factors, such as late-onset depression or post-operative delirium.

Symptomatic Trial Designs

The natural course of AD proceeds down a series of steps, beginning with cognitive complaints, such as memory loss, and continuing to a loss of functional independence and, after two to four years, disturbances in behaviour. On average, death ensues eight years after early diagnosis. Throughout this typical disease progression, certain clinical milestones can be identified. Conversion from mild cognitive impairments (MCI) to dementia is currently being used as a target for treatment in a number of studies. Further milestones include the emergence of neuropsychiatric symptoms, loss of independent activities of daily living (ADL), nursing home placement and loss of self-care ADL.

Treatment responses in AD can take one of three hypothetical courses. A complete reversal of symptoms is a response we can not expect in the near future. There may be no improvement, but also no further decline, which would be a beneficial response only if treated in the early stages of disease. Symptoms may improve and reach a peak, to be followed by a loss of initial improvement over time until there is a decline parallel to the disease's natural course (many current treatments follow this hypothetical course).

Therapeutic objectives in AD research include the control of existing symptoms ("symptomatic studies", such as those with cholinesterase inhibitors), the delay of symptoms after diagnosis ("stabilization studies") and the delay of the emergence of symptoms in people at risk ("prevention studies", only one of which is in progress comparing *Gingko biloba* to placebo).

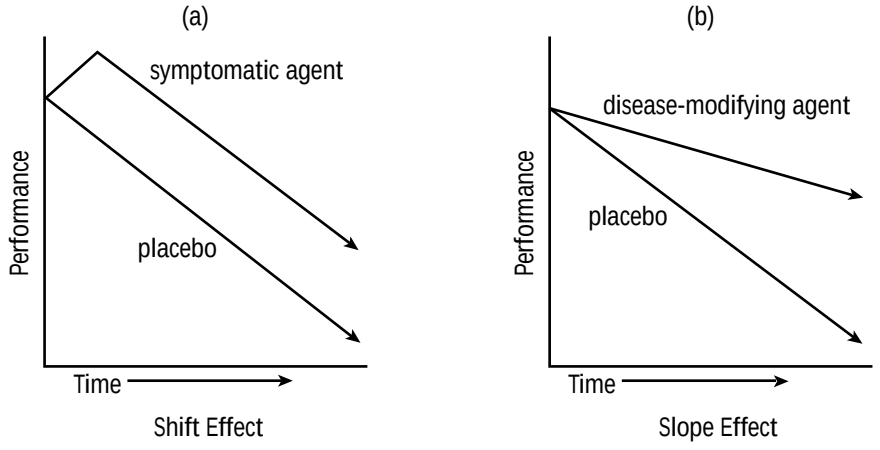
The conceptual framework for a symptomatic trial design is that of shifting symptoms to the right, as illustrated in Figure 3a, which shows a short-term improvement in symptoms without affecting the underlying slope of deterioration (this has been established with cholinesterase inhibitors). What we hope to see with disease-modifying agents is a reduction in the slope of progression; that is, a slowing of disease progression (Figure 3b). Trial designs of a particular agent would interpret parallel groups with a shift to the right as suggestive of symptomatic effects, especially if this effect was reversible in a washout period. Parallel groups with diverging slopes, however, would suggest stablization of the disease, and would be even more convincing if the effect remained on washout—this could be interpreted as "sustained symptomatic benefit", or disease modification.

Trial Designs for Disease Modification Studies

Although no treatment has yet been demonstrated to modify AD progression,

Figure 3

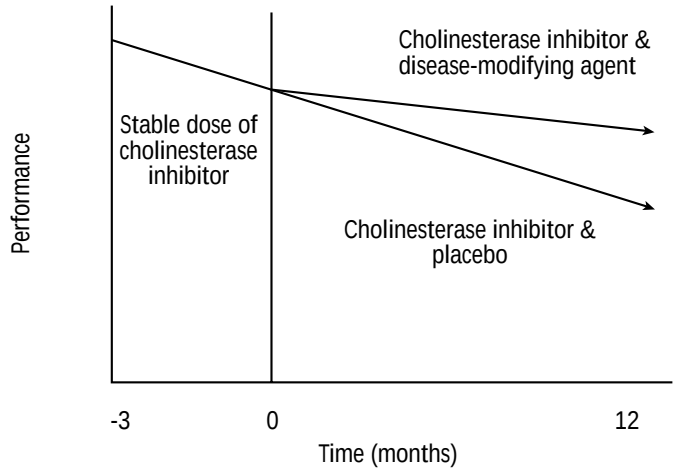
Symptomatic vs. Disease Modification Trials



Source: Dr. Serge Gauthier

Figure 4

Add On Trial Design



Source: Dr. Serge Gauthier

there have been a number of designs proposed and tested in the field. Survival designs look for delays in reaching a clinical milestone, which may be interpreted as sustained symptomatic benefit. However, if the intent is to prove a drug actually modifies the disease and delays its progression, rather than just delaying the symptoms, more evidence than diverging slopes would be necessary. For instance, if MRI studies show a drug is actually slowing brain atrophy, that is convincing evidence of a disease-modifying effect.

In the future, the add-on design will be used by Canadian investigators in AD research (Figure 4). Patients are put on stable doses of a cholinesterase inhibitor (ChEI) for a minimum of three months, after which a placebo or a new disease-modifying agent is added for one year. At the end of the year, all patients on the new agent will be switched to placebo (so a washout is built into the study design). With the add-on design, if the effects of the combination of a potentially disease-modifying drug and a ChEI are irreversible on washout, and less atrophy on serial brain volumetry by MRI is seen, this can be interpreted as stabilization of disease.

There is a rapid turnover of candidate drugs for AD prevention, based on the safety and tolerability in phase I and II and efficacy in phase II and III (Table 1). The latter are often done in mild to moderate AD when the pathology has likely reached an irreversible state, and potentially effective drug classes or individual agents are discounted prematurely. The long duration of randomized, controlled trials to establish disease prevention or modification with the associated costs will also limit such evidence of candidate drugs to the most promising based on best available evidence.

From a clinical point of view, we need to ask when a disease-modifying drug should be used. A possible preventive approach in asymptomatic people at risk of AD might develop in the future. In those with minimal risk, simple prevention strategies include maintaining a good diet, keeping the mind busy and controlling vascular risk factors, especially between the ages of 40 and 60. For those with a mild risk (i.e., a family history), an antioxidant may come forth in the future or perhaps estrogen replacement will prove beneficial. In people with moderate risk (already have symptoms or have whatever may be determined as high genetic risk), non-steroidal anti-inflammatories may be prescribed. In the future, we can hope for a system whereby preventive strategies are well matched to an individual's level of risk.

Impact on Health Care System

Of course the question of who is going to pay for this risk assessment will arise. One cost-effective possibility would be to have patients self-screen on the web or on paper while in waiting rooms. Other health care professionals including occupational therapists, neuropsychologists and nurses can be further trained to help screen people. In those with mild complaints, there may be two or three genes we can assess. And what about the costs of treatment? In the next year or so, if the results on ChEIs in those with MCI prove beneficial, how will we recoup the cost of prescribing ChEIs in people who are still functional two years earlier than previously done? Unfortunately, the newer agents in development are not to be any less expensive than the current drugs. However, these costs need to be weighed against the benefits of delaying symptoms and delaying progression to severe stages.

We are at the turning point in hypothesis testing towards delaying the progression from very early AD to its later stages. Success in these studies could lead to a delay in the onset of symptoms for people at risk, and we now have time to begin planning for care costs and delivery. ◆

Table 1

Candidate Drugs for Prevention Studies

Hypothesis	Clinical trial status
Anti-amyloid	
– Immunotherapy	Stopped in phase II because of meningoencephalitis
– Inhibition of gamma secretase	Phase I underway
– Prevention of fibrillogenesis	Phase II underway
Antioxidants (alpha tocopherol)	One positive study (Sano *et al.* 1997) Study underway in MCI
Anti-inflammatory drugs (NSAIDs, COX-II inhibitors, dapsone)	Negative studies in AD (Aisen *et al.* 2000; Aisen *et al.* 2002) Study underway in MCI
Estrogens	Negative studies in AD (Henderson *et al.* 2000; Mulnard *et al.* 2000; Wang *et al.* 2000)
Statins	Studies underway in AD
Vascular	One positive study (Forette *et al.* 1998)