QUESTION: What is the role of inflammation in Alzheimer’s disease?

For those of you that have been reading my articles, this article is a bit of a tangent. Last month I promised to start talking about the emotional and social aspects of Alzheimer’s disease, but two things happened. Firstly, this question was posed. Secondly, a new study about pathological changes in Alzheimer’s disease was just published in the prestigious New England Journal of Medicine. Because these two items impact on my prior comments, I thought it judicious and timely to address them before continuing.

Part one: Inflammation in Alzheimer’s disease. If one looks up the terms “Alzheimer’s” and “inflammation” in a prominent Internet medical journal search engine [namely PubMed], one will find over 1700 articles have been published on this topic. This robust figure clearly indicates that inflammation plays a role in Alzheimer’s disease and that such a role is complicated and not clearly understood. The question becomes what role inflammation plays and how important is that role. The final current answer is nobody knows for sure.

Inflammation is an important bodily function. As multi-cellular organisms, our cells accumulate waste products, get injured, die, and are replaced. There are the stresses of physical trauma, illness, and infections. Our bodies must be able to repair and replaced injured tissues or we could not survive. The inflammatory response plays a critical role in this maintenance process. Conceptually, it is like a demolition and clean-up crew that helps your body deal with wear-and-tear. It also helps fights off unwelcome intruders. On the other hand, too much inflammation can damage healthy cells and tissues, thereby causing more damage than one would like resulting in excessive scaring and dysfunction. As we get older, studies suggest that our bodies tend to shift to a pro-inflammatory state compared to our youth. This is not good for us. [Alas, people are possibly correct about the issues of age-related toxic accumulations and injuries, natural aging, etc.]

Excessive inflammation causes scarring and other cells to become overly active. In the brain, there are cells called astrocytes and microglia that help support the nerve cells and protect the brain. If these cells are over-active, they may cause local scarring and interfere with the functions of nerve cells, nerve fibers, and nerve-connections. This is
known to occur in multiple sclerosis, brain tumors, brain infections, and strokes. On an internal cellular level, there are chemical inflammatory substances that cause cell dysfunction. There are theories that these cellular metabolic process may contribute to the improper folding of a protein [beta-amyloid] that is thought to play a central role in the pathological findings of Alzheimer’s disease. Improperly folded beta-amyloid is a major component of neurofibrillary tangles and senile plaques that were first described by Dr. Alzheimer over one hundred years ago. There are other potential roles of the inflammatory response in Alzheimer’s disease. There are literally dozens of scientific reviews on the topic – each has its own perspective and overlapping conclusions. [The articles are very good to read on a lazy Sunday afternoon on the patio; they quickly prompt a nap.]

The take-home lesson is that inflammation is a very broad medical concept. It clearly plays a role in all illnesses and general health. In Alzheimer’s disease, the importance of this role is being debated. Clinical trials of anti-inflammatory medications [such as NSAIDS and others] have been unrewarding. In general, these trials have not shown medication benefit over placebo. My personal opinion is that the side-effects and risks outweigh the benefits for most Alzheimer’s patients unless they have other inflammatory conditions.

What does this mean for today’s patient? It means that inflammation is an active area of research toward the basic understanding of the Alzheimer’s disease process and hopefully will bring forward new insights. From a current perspective, the concept of inflammation provides a rationale for the supplements and nutritional advice that was presented in last month’s articles. Many of these supplements may not have a direct affect on the Alzheimer’s disease primary process. On the other hand, many of the supplements and vitamins are known to have a mild anti-inflammatory influence and probably positively act against the “pro-inflammatory” aging effects. If used with common sense, these agents are safe, relatively inexpensive, and will do no harm.

Part two: The New Article. In the May 28, 2009 New England Journal, Savva and others published an article studying the relationship of pathological findings versus age in patients with or without diagnosed Alzheimer’s disease. They found that that this varied with age. Demented patients aged 75 were two times more likely to have moderate or severe neuropathological changes than their normal peers. At 95, demented patients were just slightly more likely to have these changes than their normal peers. Thus, even the fundamental concept of neurofibrillary tangles and senile plaques cannot independently explain the presence or absence of dementia. The article’s discussion was complicated. It basically pointed out that dementia was a multifactorial process and there were multiple components that combined to create the clinical picture. The accompanying editorial mentioned the issues of medications, other diseases and conditions, inflammation, genetics, personality, etc.

What does this article mean for today’s patient? I believe that is becoming increasingly clear that dementia and Alzheimer’s disease are not simple one-factor dominant conditions [like a bacterial lung infections]. I look at the condition like car-accidents.
There are multiple factors that can contribute to the occurrence of car-accidents: the weather, the tires, the brakes, the driver’s experience, the other driver, and others. When these factors add up in a given situation, there will be a collision. Depending on the circumstances, one component may play the dominant role; while in another case, other components may be more important. If one is to reduce the risk and consequences of the accident, then one must think from multiple perspectives.

In my opinion, the same concepts are becoming increasingly true for dementia. Simple “one treatment fits all” approaches are not going to be effective for the foreseeable future. The patient, family, and healthcare providers must take a thorough comprehensive evaluation of the many possible factors at work and adjust them accordingly. With this effort, positive impacts can play big dividends in reducing the consequences of Alzheimer’s disease and related disorders.

With best wishes,

David Ross, M.D.

Post-script. After writing this month’s article, Neurology Today [May 21, 2009] published an article about brain inflammation [brain edema] associated with an Alzheimer’s clinical drug trial. The trial was studying the effects of a new compound bapineuzumab on Alzheimer’s patients. Bapineuzumab is an experimental antibody that might help remove beta amyloid from the brain. It is under development. Many of the patients [10 of 12] receiving the highest dose of the medicine developed MRI evidence of mild cerebral edema. This reversed when the medicine was reduced. The investigators felt that beta amyloid in the blood vessels “bound up all the bapineuzumab and caused inflammation in the vessel walls.” Again, the take home message is that the Alzheimer’s disease story is complex; inflammation is a complicated phenomenon. Inflammation can result whenever you injure or try to treat the body. My overall opinion of the current inflammation theory is one must use common sense and not go overboard. Moderation and good health are the goals.