Chapter 30

The Role of Inflammation in Neurodegenerative Disorders: Integrative Approaches to Challenging Neurological Disorders

David Perlmutter, M.D., FACN
Director, Perlmutter Health Center

ABSTRACT

It is now generally accepted that oxidative stress plays a pivotal role in brain degeneration. This paper will focus on the primary role of inflammation in the brain aging and neurodegenerative diseases, the secondary events of elevated signal transduction and increases in oxidative stress, and the ultimate induction of apoptotic neuronal destruction. The therapeutic utility of functional interventions aimed at reducing these inflammatory processes will be explored.

INTRODUCTION

The aim of this paper is to discuss the role of inflammation in neurodegenerative disorders. At present, when dealing with neurodegenerative conditions the treatment is focused upon symptom management. That is definitely the case with Parkinson's and Alzheimer's disease. What we need to do is gain at least some fundamental understanding of what it is that is causing these illnesses. We need to focus on putting out that fire, which is indeed inflammation.

In mainstream medicine, the coin of mint, of medical commerce is the prescription pad. However, inflammation does not respond very well to the use of medications. Yes, there are anti-inflammatory drugs on the market, but our approach in dealing with inflammation as it relates to the brain, and really the rest of the body, needs to focus on the fundamentals of nutrition and lifestyle. Incredible as it may seem, the food that we eat has an impact on our health.

INFLAMMATION AND NEURODEGENERATIVE DISEASE

This whole concept that inflammation is somehow related to dementia and neurodegenerative conditions is not new. We have known about these relationships for years. People have seen elevated levels of inflammatory cytokines in Alzheimer's and Parkinson's patients, things like tumor necrosis factor (TNF), and interleukin-1 beta, have been measured and appear to be elevated in these conditions. One study of interest is one conducted by Schmidt *et al* in which the level of C-reactive protein (CRP) was measured in a group of men, and then 25-years later the men were followed up to see if any had developed Alzheimer's and other forms of dementia. The results showed that there was a profound predictability of these diseases based upon the historical CRP levels. Thus, our levels of an inflammatory marker such as CRP today are an important risk factor for the development of neurodegenerative diseases a quarter of a century from now. What does that mean? It means that this is a very, very powerful tool in terms of prevention.

In his inaugural address, John F Kennedy said that the time to fix the roof is when the sun is shining. Thus, if we want to keep our cognitive prowess into old age it is very, very important that we pay attention to this fundamental role of inflammation, pay attention to these markers, and intervene now proactively.

Alzheimer's Disease

If we look at MRI scans of Alzheimer's patients we see images that are full of light matter, lesions that are not multiple sclerosis (MS) or gluten sensitivity, but are inflammatory lesions. A very interesting study by Cagnin *et al* was published in the Lancet in 2001, this study found via the use of MRI scans that individuals with gluten sensitivity have a significantly increased risk of developing white matter lesions, which, by all intents and purposes could have been diagnosed as a MS plaque. Many of these individuals with gluten sensitivity have focal neurologic deficits that come and go with time. That is to say, lesions separated into space and time. Since that article came out, we have been conducting antigliadin antibody studies on all of our so-called MS patients and lo and behold, we have found that about 20% of these so-called MS patients don't have MS at all – they have gluten sensitivity. Once these individuals were placed

on a celiac type of diet they did not have further flare-ups and they no longer needed daily injections of interferon and steroid treatment.

The cardinal players of inflammation are present in Alzheimer's disease, the usual suspects – the inflammatory cytokines, interleukin-1 beta, and TNF- alpha. The microglia, or the brain's macrophage system is turned on, and the compliment pathway, which is a very, very primitive pathway, seen even in jellyfish, is activated. We have known for some time that individuals who have taken nonsteroidal anti-inflammatory drugs (NSAIDs) substantially reduce their risk of developing Alzheimer's disease.

Parkinson's Disease

It is pretty well entrenched in neurology that inflammation is fundamental in MS, and we also know that it is involved in Alzheimer's disease, however the whole idea that Parkinson's disease may also represent an inflammatory issue is really relatively new. In 1999 a very interesting literature review was published in *Neurology Reviews.* The article stated that inflammatory markers had been seen in people with Parkinson's disease. This sort of information should say two things to you. Firstly, can we change people's lifestyles to make them less inflammatory and thus possibly prevent Parkinson's disease? Secondly, would anti-inflammatory drugs be of use to a person who has already been diagnosed?

A study by Chen *et al* can help us to answer these questions. Chen looked at the risk of Parkinson's disease in people who had been taking a NSAID for between 14 and 18 years. In fact, many of these individuals had only been taking NSAIDs for a couple of years at a time, however the study results revealed a 45% reduction in the risk of Parkinson's disease in this large study population of 140,000 people. Does this mean that as doctors, we should be prescribing patients Advil or Celebrex or Bextra to prevent Parkinson's disease? No, it does not. What it does mean is that from our perspective, when we understand the fundamentals of inflammatory biochemistry, the role of prostaglandins, and the role of various essential fatty acids in modulating the inflammatory cascade, there is some really important information being given to us. There are 1.4 million Parkinson's disease patients in the US and we know that these patients are declining before our very eyes with the very little that we can do. But the main point here is that it is now entrenched in our most well respected peer review literature that inflammation plays a pivotal role in the risk of developing Parkinson's disease risk and Alzheimer's disease.

What Causes Inflammation?

What causes inflammation? A variety of things we can pay attention to. While we cannot modify our genetic predisposition, we can at least know what our genetic predisposition is. And that is to say that we should check our APOE, or apolipoprotein, status. We know that people who carry the APOE 4 allele as opposed to the 2 or 3, are at substantially higher risk of developing Alzheimer's disease, because that means that they code for the APOE 4 protein, which ultimately lends itself to less antioxidant protection of the brain. It is not that APOE 4 codes for something that is necessarily a detrimental chemical, but that APOE 2 and APOE 3 offer better brain antioxidant protection. APOE 4 puts you at substantially increased risk for Alzheimer's, increases the risk of problems following head injury, is associated with a more rapid decline in people with amyotrophic lateral sclerosis (ALS), and an increased risk and more rapid decline of MS. Thus, APOE 4 is a fairly global issue with reference to the risk for neurodegenerative disease. Other things can increase inflammation, like ischemia, and therefore things like homocysteine come into play. Environment insults, such as toxins and infectious agents also play an important role.

Inflammation does it's dirty work by increasing free radical reactive oxygen and nitrogen species, and ultimately what happens is this cascade leads to the turning on of so-called death genes, for example inducible nitric oxide synthase (iNOS) and cyclooxygenase type 2 (COX-2) enzymes, which we know helps convert arachidonic acid (AA) into inflammatory prostaglandins. We see our patients go from very young to old and we know that levels of reactive oxygen species (ROS) typically increase with age. These inflammatory cytokines bind to the cell membrane and this turns on transduction systems, which actually leads to genetic transcription, gene activation, and the production of iNOS, the rate-limiting enzyme for nitric oxide, and also for COX-2 enzyme and this leads to increased inflammation, which feeds back to cause more cytokine production. So this is a feed forward cycle. We can measure interlukin-1 beta and TNF-alpha in the substantia nigra of the Parkinson's brain and find huge levels compared to normal. Parkinson's disease is an inflammatory disease of the brain. It is a form of encephalitis. And that is what we should be thinking of when we see our Parkinson's patients. That this is an inflamed brain. Sure, we

can give these people dopamine agonistics and L-Dopa to modify their symptoms, but that is a very, very narrow-minded approach. That is clearly treating the smoke, the end-effect, and not treating the fire of inflammation.

The Relationship Between Diabetes and Neurodegenerative Diseases

If you have diabetes you dramatically increase your risk of neurodegenerative diseases. Eighteen millions Americans have diabetes. We change proteins in our bodies and in the brain; we modify brain proteins with glucose. Tying glucose onto the amino terminus of amino acids, or glyco-oxidation, makes proteins behave differently and this becomes a huge issue. Why is it important? It is important because glycated proteins produce nearly 50-fold more ROS than non-glycated ones. A Scandinavian study entitled "*Investigations in Oxidative Stress and Therapeutical Implications in Dementia*" looked at the various pharmaceutical approaches available to us to reduce glyco-oxidation, for example advanced glycosylated end products (AGE) inhibitors, antioxidants, and anti-inflammatory substances. And what they did was very interesting. They looked at monocytes that they treated with advanced glycosylated end products. What they found was when this AGE, or advanced or modified protein binds to the RAGE receptor, it leads to a genetic transcription of the enzyme COX-2 messenger RNA, and thus the production of the COX-2 enzyme. This explains the strong relationship between diabetes and elevated inflammation issues throughout the body.

Shanmugam *et al* demonstrated how it is possible to dramatically reduce the production of COX-2 enzyme by using N-acetyl cysteine (NAC). They used a specific ligand for this study – S 100 b. Results showed that when S 100 b bound to the RAGE receptor in the presence of NAC there was a dramatic reduction in the expression of COX-2 messenger RNA, and hence COX-2 production was diminished. So here is a very important role for the supplement NAC, which is available over-the-counter. This is how NAC works, and is why it is so important in neurological conditions, and why it has been shown to be a powerful treatment for Alzheimer's disease. This is treating the fire and treating the smoke.

Diabetes has been shown to have a specific and detrimental effect on the hippocampus, the area of the brain involved in memory processing that is the area that is at risk in Alzheimer's disease. Why is this? Research has revealed that the hippocampus is damaged by glucose. Therefore, we have another advanced glycosylated end product of importance here, and that is beta-amyloid. Beta-amyloid can be modified by glucose, and this enhances its inflammatory predisposition in the brain. Beta-amyloid is one of the hallmarks of Alzheimer's disease. Beta-amyloid is a protein that is actively made in the brain under the influence of specific enzymes, and it is not an inert protein. Beta-amyloid is a very metabolically active protein that dramatically increases inflammation, as it turns on microglia.

A person who takes insulin has a 4.3-fold increased risk of developing Alzheimer's disease. This risk is also at least doubled in people with non-insulin dependant diabetes. And those figures do not take into account other risks, like vascular dementia and stroke. So here are the issues, vascular disease, glycation protein, and beta-amyloid directly link diabetes with an increased risk for Alzheimer's disease. Fundamentally, these are all inflammatory issues.

The Role of Mitochondrial Dysfunction

It is important to take another look at ROS, as ROS themselves are a risk for microglial activation, and therefore for turning on this inflammatory cascade. Thus, we have to consider the concept of excitotoxicity. Simply stated, if we have a neuron that has normal functioning mitochondria, we have adequate ATP, and in the presence of adequate ATP we have a normal electrochemical gradient between the intracellular and extracellular compartments, this maintains the so-called NMDA receptor magnesium block. However, if there are deficiencies of ATP production, then the electrochemical gradient is altered and the magnesium block in the NMDA receptor is relaxed, leading to an influx of calcium. Glutamate is a neurotransmitter that specifically binds to this NMDA receptor. This is why glutamate is of great importance in neurodegenerative conditions. This is why we have become concerned about giving something called monosodium glutamate to people in food. Glutamate binding to the NMDA receptor when there is deficient mitochondrial activity causes the influx of calcium, the influx of calcium damages the mitochondria, which further exacerbates their energy production capabilities and causes again a feed forward cycle.

Mitochondrial dysfunction reduces ATP production and ultimately leads to calcium influx. It is this mitochondrial dysfunction that ultimately enhances cytokine production, which turns on genes like iNOS,

which in turn increases nitric oxide production, which causes further damage to the mitochondria. So we have to look at all of the factors, that effect mitochondrial function – genetic, xenobiotic, metabolic, viral, endotoxic, drugs – and recognize that mitochondrial oxidative damage ultimately leads to inactivation of the mitochondria. When they are damaged they don't produce enough ATP, and the problem with that is that it feeds back and they are ultimately receive more damage and thus produce less ATP.

Free Radical Activity and Antioxidant Supplementation

It is possible to measure free radical activity by looking at thiobarbituric acid reductase substances (TBARS) or damage to fat in the temporal lobe cortex. Ultimately Parkinson's and Alzheimer's disease are mitochondriopathies. The DNA is damaged in Alzheimer's disease. We can do 8-hydroxydeoxyguanosine (8-OHdG) studies and see that indeed these patients have high levels of 8-OHdG, which is a marker of DNA damage. Levels much higher than those seen in control groups. Mecocci *et al* measured antioxidant levels in Alzheimer's patients, and discovered that they had significantly lower levels of antioxidants compared to control groups and thus lack antioxidant protection. The researchers concluded: "These findings suggest that lymphocyte 8-OHdg levels in patients with Alzheimer's disease reflects a condition of increased oxidative stress related to poor antioxidant status." Which, in simple terms is saying that patients with Alzheimer's disease have poor antioxidant protection. What is our response to that? Probably give them an Alzheimer's drug and see the next patient.

Recent studies have shown that taking supplementary vitamin C and vitamin E could reduce the risk of developing Alzheimer's disease by as much as 78%. If a pharmaceutical company developed a drug that they could claim would reduce the risk of Alzheimer's by 30%, it would make them millions of dollars. This is important information that the world needs to know. But what are we are told to do? We are told to prescribe Aricept, the world's leading so-called Alzheimer's drug. Why? Because it is wonderfully effective, says the literature. However, the manufacturer of this drug has sponsored every study that has shown its effectiveness. In June 2004, the AD 2000 Study by Courtney was published in *The Lancet*. This was the first study of Aricept that was not sponsored by its manufacturer, and the results showed that Aricept produced no measurable reduction in the rate of institutionalization or progression of Alzheimer's – the key determinants of the overall cost effectiveness of treatment. It is not cost effective and the benefits are below minimally relevant thresholds. The AD 2000 study shows the importance of non-commercial research undertaken and reported independently of any commercial interests. The findings of disappointingly little overall benefit from Aricept cannot be taken lightly. The drug doesn't work. We've got to prevent this disease.

The Importance of Homocysteine

Until relatively recently we were unaware of homocysteine's role in terms of vasculopathy, but homocysteine plays another very important role. Homocysteine actually stimulates the NMDA receptor directly. Homocysteine causes this influx of calcium. Which means that homocysteine is basically a mitochondrial toxin. Homocysteine also becomes metabolized to homocysteic acid and homocysteic acid is a direct mitochondrial poison. Thus it is vital to measure homocysteine levels in every patient. Muller *et al* found that the very treatment we use to treat Parkinson's disease - Sinemet, or levodopa – directly elevates homocysteine levels. We have just learnt that homocysteine is a mitochondrial toxin related to increased risk of Parkinson's, so that makes a lot of sense!

Drugs that deplete vitamin B12, drugs that deplete B6 and folic acid, why are all of these important? Because, they have the potential to raise homocysteine levels. If we have patients on these drugs it is vital to be very judicious in monitoring their homocysteine levels. Because it is a mitochondrial toxin homocysteine is a direct risk factor for Alzheimer's disease. A study of the Alzheimer's risk and homocysteine levels by Seshadri *et al* found that having a homocysteine level of 14 of more nearly doubled the risk of developing Alzheimer's disease. Thus, it is vital that homocysteine levels are brought down to eight or lower.

Coenzyme Q10 and Mitochondrial Activity

Is it possible to enhance mitochondrial activity? Yes, we can enhance mitochondrial activity with coenzyme Q10 (CoQ10), which is a very potent antioxidant. Lass and Sohal discovered that there is an inverse relationship between superoxide generation and CoQ10 levels in several animal species, including cows, pigs, and mice. We know that if you look at platelet mitochondria, that Parkinson's

disease patients have very low coQ10 levels. Interestingly, so do their spouses. What might that mean? What do you share with your spouse most of the time? The answer is an environment and a lifestyle. There may be lifestyle factors and environmental factors that deplete CoQ10 levels. Shults *et al* demonstrated that low CoQ10 levels are clearly associated with low levels of Complex I and Complex II/ III of the electron transport system in the mitochondria. So CoQ10 plays a fundamental role in cellular energetics. Low CoQ10 leads to low Complex I activity and causes deficiency of mitochondrial function, and therefore increases ROS formation, which further damages mitochondrial function.

Shults *et al* also showed that it is possible to dramatically increase serum levels of CoQ10 by giving oral CoQ10. Does it help? What is its effect? Results showed that oral CoQ10 up-regulated mitochondrial activity, however there was no change in clinical presentation. In 13 of the 15 patients that Shults studied, there was not much change in their clinical presentation because these patients were also taking a drug that raises homocysteine, and thus damages mitochondrial function. In the Journal *Neurology*, in a summary of the effects of CoQ10, the authors suggest that bioenergetic therapies, such as CoQ10, may have the potential to effect the course of neurologic diseases in which mitochondrial function is impaired and oxidative stress and damage are present. Mitochondrial dysfunction is present in almost any neurologic degenerative condition that you can think of. Additional research into the potential disease modifying effects of such therapies is warranted, particularly at the early or presymptomatic stage of the illnesses.

In yet another study by Shults, 80 people with Parkinson's disease who were not receiving any other treatment were given 1200 milligrams of CoQ10 a day, or a placebo. The subjects were evaluated on the disease rating scale and after 16 months of treatment, a 47% reduction in the rate of decline in the group taking CoQ10 was observed. Every neurologist should be adding CoQ10 and antioxidants to their regimen to treat Parkinson's.

Glutathione

We know that we can challenge rat neurons and specifically look at the effect upon mitochondria when we add vitamin C and iron, which is a very oxidative milieu, and we can see how we can protect those neurons by using specific substances. We can salvage Complex II activity in this hostile environment by using glutathione; vitamin E, CoQ10, and glutathione can salvage Complex III. Is vitamin E effective in slowing down cognitive decline? Sure it is, because it protects mitochondria from free radical damage. In a study by Morris *et al* subjects showed a 36% reduction in cognitive decline amongst people with the highest vitamin E compared with those with the lowest intake. Finally, looking at complex IV, the only thing that seems to work there is glutathione. We know that Parkinson's disease is characterized as a disease of reduced glutathione. Which is why we use glutathione vigorously in our protocols for Parkinson's. What we are doing is we are turning on mitochondria in Parkinson's patients. Why do we do that? Because Parkinson’s disease is a mitochondrial issue.

So we want to enhance glutathione. Giving intravenous glutathione is as safe as safe can be, but what can be done if you don’t wish to give it intravenously? Now we need to go back to the NMDA receptor. What we can do to block the NMDA receptor? This is where this drug Namenda or Memantine comes into play. Namenda has been used in Europe for over 10 years, and was approved in the US for the treatment of Alzheimer’s disease in January 2004. A study by Reisberg *et al* found that patients treated with Namenda showed significantly less functional deterioration than the placebo group, and incredibly, that the drug appears to reduce the risk of death, as significantly more patients in the placebo group died during the study.

The Role of Dietary Fat

Finally I want to look at dietary fat. If you do triceps skin fold measurements on people and then look at their risk for Parkinson's disease 30 years hence, you find a dramatic increase in risk. If you are in the highest quartile of having fat arms, then your risk for Parkinson's disease almost triples. Thus, it is important to tell patients that if they want to reduce their risk of developing Parkinson's disease when they are older, then they should start losing any excess body fat immediately. Fat is a very metabolically active tissue. Fat enhances the production of cytokines. It is not just a storage depot. Body fat acts as a reservoir for toxins, for neurotoxins. Essential fatty acid supplementation, like fish oil helps to reduce inflammation. So dietary choices have a profound effect on our risk for inflammation. Dietary choices have a profound effect for the transcription of genes, such as iNOS and COX-2 enzymes that are

associated with inflammation. A substance called arachidonic acid (AA), is derived from animal fat, is pro-inflammatory. Thus, we should cut down the amount of animal fat in our diet. Why is docosahexaenoic acid (DHA) important? DHA plays a pivotal role in mitochondrial and neuronal membrane fluidity, signal transduction, neurogenesis, gliogenesis, and synaptogenesis. It is also important because DHA reduces COX-2 enzyme at the pivotal point of inflammation. COX-2 up-regulation is seen in a variety of neural conditions, neurological conditions, including Lou Gehrig's disease, Parkinson's disease, stroke and Alzheimer's disease. So we want to do everything we can to think about techniques for reducing COX-2 enzyme.

CONCLUSION

In conclusion, it is vital that we physicians pay as much attention as we can to treating the fire of inflammation and not just treating the smoke. It is vital that we put out that fire of inflammation, and that can be done with the techniques mentioned in this paper.

REFERENCES

Cagnin A, Brooks DJ, Kennedy AM, Gunn RN, Myers R, Turkheimer FE, Jones T, Banati RB. In-vivo measurement of activated microglia in dementia. *Lancet*. 2001;358:461-467. Erratum in: *Lancet.* 2001;358:766.

Chen H, Zhang SM, Hernan MA, Schwarzschild MA, Willett WC, Colditz GA, Speizer FE, Ascherio A. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. *Arch Neurol*. 2003;60:1059-1064.

Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet*. 2004;363:2105-2115.

Lass A, Sohal RS. Effect of coenzyme Q(10) and alpha-tocopherol content of mitochondria on the production of superoxide anion radicals. *FASEB J*. 2000;14:87-94.

Mecocci P, Polidori MC, Ingegni T, Cherubini A, Chionne F, Cecchetti R, Senin U. Oxidative damage to DNA in lymphocytes from AD patients. *Neurology.* 1998;51:1014-1017.

Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Vitamin E and cognitive decline in older persons. *Arch Neurol*. 2002;59:1125-1132

Muller T, Renger K, Kuhn W. Levodopa-associated increase of homocysteine levels and sural axonal neurodegeneration. *Arch Neurol*. 2004;61:657-660.

Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348:1333-1341.

Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol*. 2002;52:168-174.

Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med*. 2002;346:476-483.

Shanmugam N, Kim YS, Lanting L, Natarajan R. Regulation of cyclooxygenase-2 expression in monocytes by ligation of the receptor for advanced glycation end products. *J Biol Chem*. 2003;278:34834-34844.

Shults CW, Haas RH, Passov D, Beal MF. Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. *Ann Neurol*. 1997;42:261-264.

Shults CW, Beal MF, Fontaine D, Nakano K, Haas RH. Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients. *Neurology*. 1998;50:793-795.

ABOUT THE AUTHOR

Dr. David Perlmutter serves as Medical Director of the Perlmutter Health Center (Naples, Florida USA) and the Perlmutter Hyperbaric Center. Dr. Perlmutter also serves as Adjunct Instructor at the Institute for Functional Medicine (Gig Harbor, Washington USA). He is recognized internationally as a leader in the field of nutritional influences in neurological disorders.