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Alzheimer's disease, oxidative injury, and cytokines

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Abstract. Alzheimer's disease is infrequently a genetically driven disease. Rather it is the product of free radical injury inflicted over decades after an initial insult to the central nervous system (CNS). The brain is uniquely sensitive to oxidative injury. A variety of insults to the CNS are now associated with Alzheimer's disease. These include hypertension, diabetes, and head trauma. These then cause a cytokine cascade and microlocalized inflammation in the CNS, that in time results in clinical Alzheimer's disease. By the ninth decade of life over half of the population manifests Alzheimer's disease. Prevention or reversal of this pathophysiology will lie in administration of effective antioxidant therapy with specific treatments when etiologies are known.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease of aging. Although genetics and amyloid β (Aβ) may play a role, it is a secondary role at best [10,28,31]. The final common pathway to AD appears to be through the aging process to which an insult to the central nervous system (CNS) triggers cytokine dysregulation [8, 11].

Descriptively AD is a progressive unrelenting illness characterized by loss of cognitive function leading to death within eight to twelve years. The cognitive changes include short term and long term memory loss so that the patient ultimately forgets their relatives. Language aphasia becomes so profound that thought is expressed in single words or even a splatter of unintelligible syllables. Judgment is impaired to the degree that hygienic care by caregivers is misinterpreted as an assault. Mood lability from unexplained rage to unexplained tears leads over time to total indifference and apathy. In the end stages the patients are perfectly happy to remain in bed. Apathy extends to loss of interest in food. Weight loss, immunocompromise characteristic of end-stage AD, and inactivity lead to death by complications. These complications are limb flexion posture, decubitus ulcers, and infections (urosepsis, pneumonia, gram negative sepsis, etc).

Current research indicates that AD may actually begin 10–25 years before it is currently diagnosable. Recently, the concept of mild cognitive impairment (MCI) has emerged as a strong predictor of impending dementia [16]. MCI subjects convert to AD at a 10–15% annual rate. MCI is pre-AD.

Aging is a vague and ambiguous term. Here, aging means adverse effects of time on physiologic systems. This constitutes a chronic cumulative insult to the CNS. The most obvious effect of brain aging is the cumulative effect of oxidative free radicals on the CNS.

The brain is uniquely vulnerable to oxidative injury [15]. First, oxygen is highly utilized by neurons. As such the brain receives 20% of cardiac output but is only about one percent of body by weight. Second, neurons have a large cell surface because of the long axons. This means energy production via ATP metabolism in mitochondria is at a high level. This metabolic pathway is a principle generator of free radicals that create oxidative injury to the cell. The normal brain (10^{11}–10^{12} neurons) requires 4×10^{21} molecules of ATP per moment. This is a massive energy requirement also produces large quantities of free radical byproducts. Third, the principle substrate is Glucose (glycolysis and Krebs cycle). Because glycogen is not stored in neurons, any interruption in glucose metabolism creates huge quantities of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Fourth, high calcium ion traffic

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across neuronal membranes causes potential high intracellular free calcium. This leads to productions of ROS and RNS. Fifth, common catecholamine neurotransmitters (dopa, dopamine, serotonin, and noradrenaline) create ROS and RNS when metabolized [15]. Interactions between catecholamines generate the superoxide radical ($O\cdot_2^-$). Metabolism of the amine moiety ($R\text{-}CH_2\text{-}NH_2$) by monoamine oxidases results in reactive hydrogen peroxide (H_2O_2) and reactive ammonia (NH_3). Sixth, some neurotransmitters are by nature excitotoxic. Glutamate, aspartate, and nitric oxide are such neurotransmitters. Excess concentrations of excitotoxins result in intracellular signaling leading to apoptosis [15]. Seventh, metalloproteins are essential components in cytochromes, ferritin tyrosine hydroxylase, tryptophane hydroxylase, and others. In traumatic, anoxic and other brain injuries, these metalloproteins are released into the intracellular space [13,15, 19,20]. The release of the iron, copper and zinc reacts with lipids, free hydroxyl radicals, and hydrogen peroxide. Although Aβ is an efficient antioxidant of iron, copper and zinc, it is membrane bound and when overwhelmed can promote neuron death [23,29]. The result is lipid peroxidation, further free radical production and neuronal apoptosis.

Finally, 50–80% of neurons by weight consist of lipids in membranes. Because a high percent of these lipids are polyunsaturated fatty acids, they are subject to oxygen-dependent deterioration [15]. Lipid oxygenation is called rancidity or lipid peroxidation. The irony of the structure of the brain is that oxygen can result in destruction of cell membranes. Once lipid peroxidation occurs it often propagates in a domino-like effect. Free hydrogen combines with peroxyl radicals to result in lipid hydroperoxide. This precipitates a chain reaction of membrane lipid disruption.

Thus the brain is a dynamic organ, subject to injury related to its structure and metabolism. This injury is called aging and is the foundation for neurodegenerative disorders. Subsequent insults such as diabetes, stroke, head trauma, CNS infections, or toxin exposure then trigger the events that lead to disorders such as AD and Parkinson's disease (Fig. 1). There are numerous means of absorbing free radicals and repairing the brain. Cytokines are one of the responses to cellular injury.

2. Cytokines

Cytokines are regulatory proteins secreted by cells to modulate the organism's immune response to injury. Infection, trauma, and stress trigger cytokines, which initiate and regulate the acute-phase inflammatory response of the organism. They are of low molecular weight and generally constitute less than 200 amino acids. They have very short half lives and often are effective only in close proximity of the cell that produces them. By this loose definition arachidonic acid metabolites PDG2, PGH2, etc. are cytokines as they regulate inflammatory response of the organism on a local level [34]. Cytokines are produced by macrophages, B lymphocytes, T lymphocytes, granulocytes, endothelial cells. Only in the last decade has it been understood cytokines are produced by astrocytes, microglia and neurons [4,6,37]. The number of cytokines is currently about eighty and growing [36].

Cytokines can be loosely thought of as proinflammatory or anti-inflammatory (or neuroprotective). *In vitro*, cytokines work in network groups that have synergistic or antagonistic interactions [36]. One cytokine may either increase (cascade) other cytokines, or decrease (truncate) the production of other cytokines. Cytokine signaling outcomes depend upon a complex network of feedback loops that are not fully understood. What is known is that cytokines have pleiotrophy. That is, a single cytokine can have multiple target cells and multiple actions. In a given inflammatory circumstance, there is redundancy. Several different cytokines will have similar actions.

In the CNS, astrocytes and microglia produce a host of cytokines (Figs 2 and 3) [3,22,24,34–36]. Proinflammatory cytokines include TNF-α, IFN-γ, IL-1α, IL-1β, IL-6, IL-8, MCP-1, MIP-1α, MIP-1β, IP-10, and RANTES. Neuroprotective microglial cytokines which downregulate the inflammatory response or stimulate neuronal repair include BDNF, β-NGF, GDNF, IL-1β, IL-4, IL-10, IL-13, and NT-3, 4/6, 6. The neuroprotective response favors remyelination and trophic support. Doubtless stem cells in the CNS are stimulated as part of this response. The reader is encouraged to study the largely self explanatory Figs 2 and 3 to appreciate the subtle interactions of cytokines. Detail, however, is beyond the scope of this paper. And example of the complexity of the cytokine system is the four GDNF cytokine family have specific two-part receptors on the neuron as follows: GDNF to ret/GFRa1, neurturin to ret/GFRa2; artemin to ret/GFRa3; and persephin to ret/GFRa4 [24]. In general this balanced cytokine system maintains homeostasis in the CNS. The balance is tipped by injury.

Injury begins local microinflammation that can trigger localized self-perpetuating cytokine cascades. In-

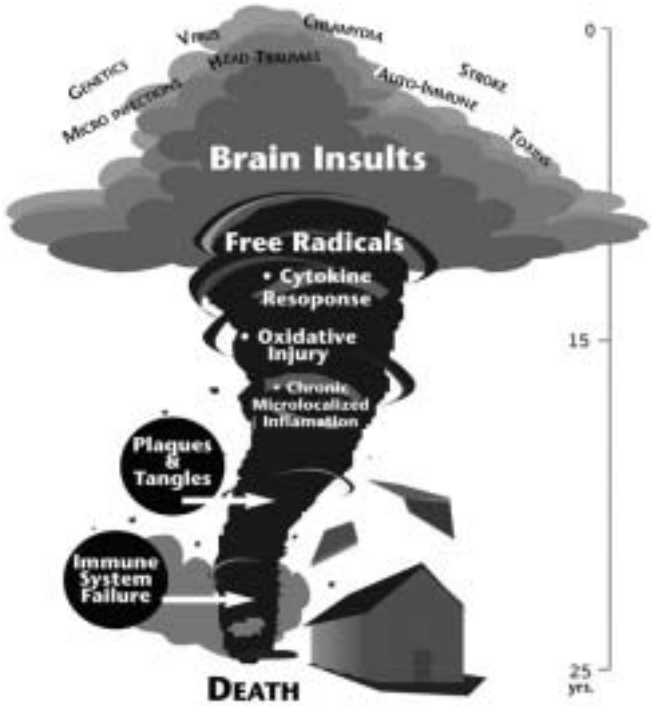

Fig. 1. Pathophysiology of Alzheimer's disease.

jury is imparted on the CNS in numerous ways. Most microinjuries (micro infarcts, diabetes, infections) and macroinjuries (head trauma, stroke) to CNS show association to AD [1,2,14,20,25]. These appear to result in the localized neurolysis with release of intracellular contents into the intracellular space [15,32].

Aβ in soluble physiologic concentrations functions as a cytokine responding to release of metalloproteins containing copper or zinc [29,34]. Copper is required for intracellular enzymes such as superoxide dismutase (SOD), cytochrome oxidase, and dopamine-β-hydroxylase. Zinc is involved in SOD, zinc-finger proteins and matrix metalloproteinases. Both intracellular copper and zinc are found in high concentration in brain [19]. Released into the intracellular space, both metals create ROS. Aβ, in the acidic extracellular matrix is the only known protein that binds copper and zinc.

3. Pathologic protein accumulation

Pathologic protein accumulation next occurs. Excessive Aβ activates microglia. Activated mitochondria release proinflammatory cytokines, of which TNF-α is the most destructive. TNF-α not only acts directly to promote inflammation, but amplifies its signal by recruiting quiescent microglia into activation. This then leads to self-perpetuation by release of more TNF-α and other proinflammatory cytokines such as: TNF-α, IFN-α, IL-1α, IL-1β, IL-6, IL-8, MCP-1, MIP-1α, MIP-1β, IP-10, and RANTES. Activated microglia then are principle sources of free radicals which in turn result in respiratory bursts of myeloid-specific enzyme myeloperoxidases (MPO) [17]. MPO reacts with ROS and RNS to give MPO-H_2O_2 which creates cross linking of molecules of Aβ. This in turn causes Aβ to precipitate into insoluble extracellular masses which are called amyloid plaques. Insoluble Aβ and its subforms Aβ1–40 and Aβ1–42 are neurotoxic and create more self-perpetuating cassettes of cytokine response [5].

Curious that most neurodegenerative disorders have an associated pathologic protein which precipitates in the brain. In the case of AD, it is Aβ. In Parkinson's disease, the protein precipitation is a-synuclein. In Huntington's disease the protein is huntingtin protein. In amyotrophic lateral sclerosis the protein is called oxidatively damaged protein (Ox).

Other accumulations of protein occur in AD. Specifically Tau protein, a member of microtubule-associated proteins (MAPs), spills out of apoptotic cells to form paired helical filament tau which is the basic subunit of neurofibrillary tangles seen in AD.

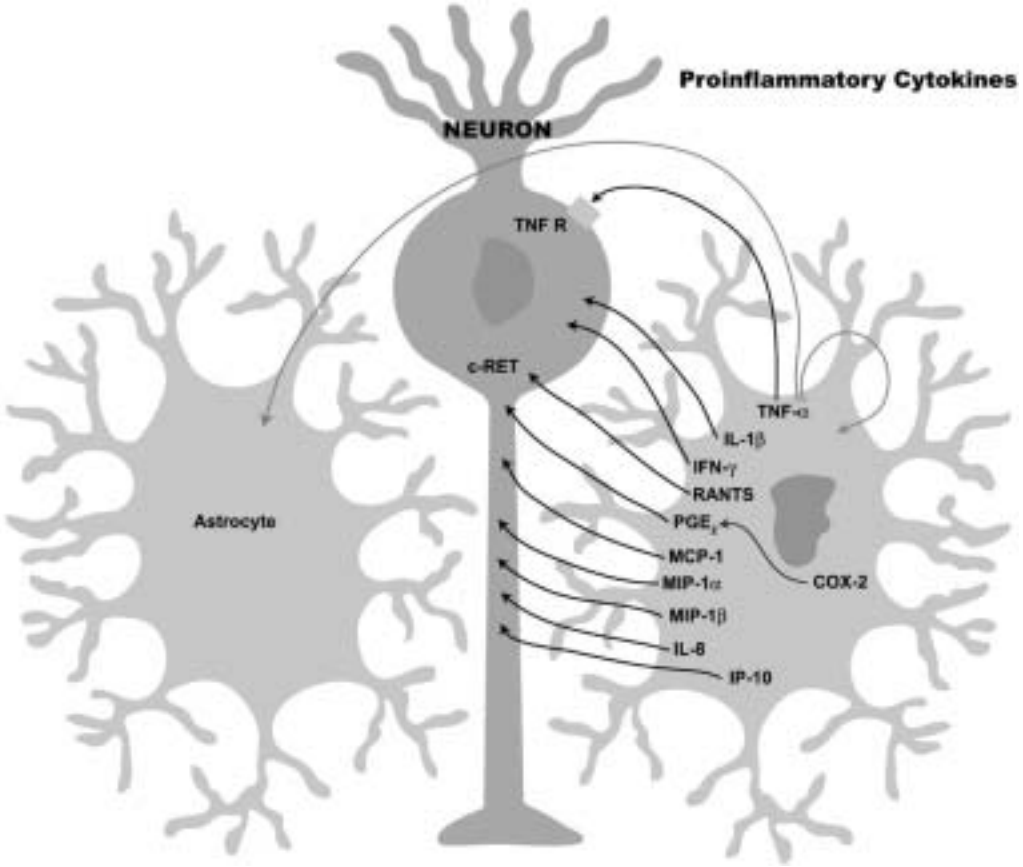

Fig. 2. Proinflammatory cytokines. COX-2 (cyclooxygenase-2), IFN-α (interferon-γ), IL-1β (interleukin-1β), IL-8 (Interleukin-8), IP-10 (interferon-γ inducible protein-10), MCP-1 (monocyte chemotatic protein-1), MIP-1a (macrophage inflammatory protein-1a), MIP-1β (macrophage inflammatory protein-1β), PGE2 (Prostaglandin E2), RANTS (regulated on activation normal T-cell expressed and secreted), TNF-α (tumor necrosis factor-a), TNF-R (tumor necrosis factor- receptor). Cartoons are not intended to accurately portray relative size and location of astrocytes or neurons. Arrows to neurons imply influence on the neuron. Arrows to other astrocytes imply influence on other astrocytes.

4. Widespread apoptosis

Widespread apoptosis and clinical manifestation of AD comes late in the course of illness. Current thought is that AD becomes diagnosable about ten to twenty five years after triggering events. First clinical evidence of pre-AD is called MCI or mild cognitive impairment [27]. At this point in the pathological picture, there are widespread microinflammatory sites with accumulation of amyloid and neurofibrillary tangles. Within and at the margins of these sites there is widespread apoptosis.

Apoptosis is programmed cell death. This is to be distinguished from externally caused cell death which is called necrosis. In an inflammatory environment, there are numerous extracellular ROS and cytokines which trigger apoptosis in the remaining living neurons. Apoptosis is an intracellular mitochondrial event. One such mechanism is the upregulation of BuChE (butyrylcholinesterase) extruded from astrocytes. Elevated BuChE is associated with conversion of soluble Aβ into insoluble Aβ [13]. This contributes to ROS, RNS production; however the elevated BuChE also helps recycle the neurotransmitter acetylcholine (ACh). High BuChE concentrations have the important role of reducing NMDA receptor density on cholinergic neurons [20]. As such BuChE prevents glutamate or other excitotoxic triggering of apoptosis through the NMDA receptor. The major excitatory neurotransmitter affecting the NMDA receptors is glutamate which acts in concert with glycine to activate the NMDA rec eptor [12].

Although all details of the process are not worked out, it is apparent that apoptosis is triggered by a sophisticated interplay between Bcl-2/BAX proteins on the mitochondrial membrane, the endoplasmic reticu-

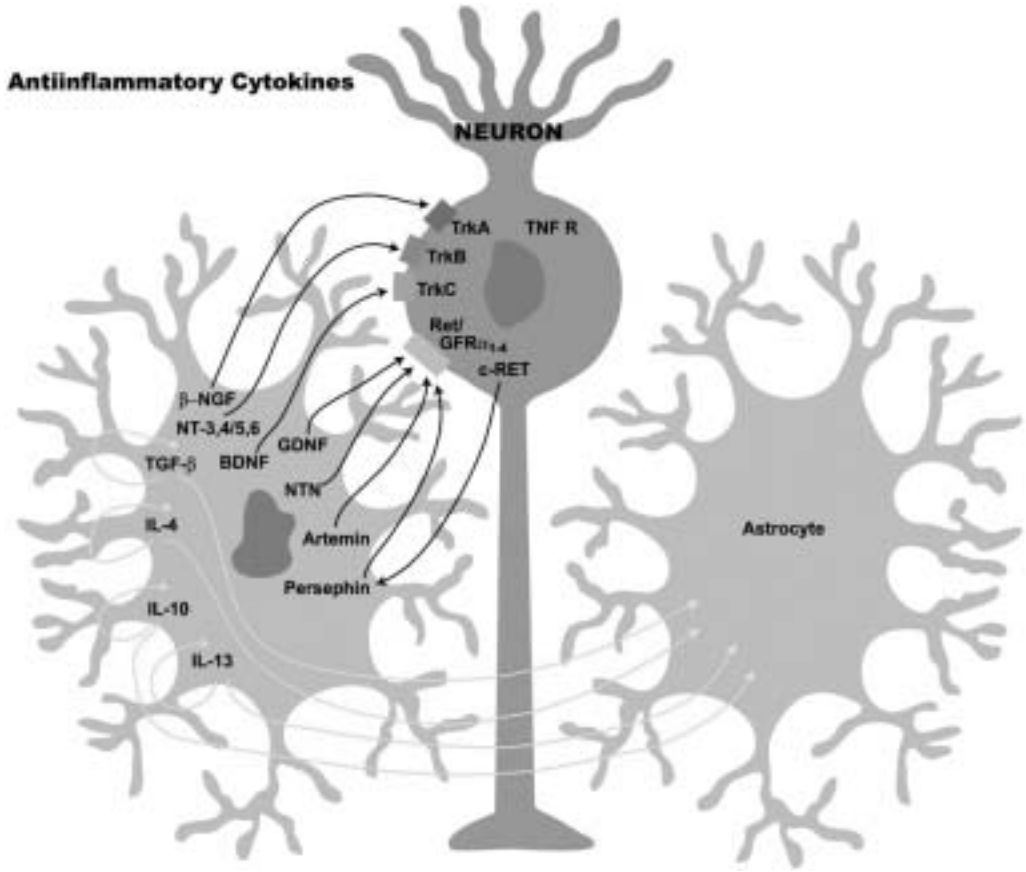

Fig. 3. Neuroprotective and anti-inflammatory microglial cytokines. Artemin, BDNF (brain derived neurotrophic factor), β-NGF (β-nerve growth factor), c-RET (cholinergic receptor tyrosine kinase), GDNF (glial derived neurotrophic factor), GFRα_{-4} (GDNF receptor a_{1-4}), IL-4 (interleukin-4), IL-10 (interleukin-10), IL-13 (interleukin-13), NT-3/NT-4/NT-5/NT-6 (neurotactin-3), NTN (neurturin), Persephin, Ret (receptor tyrosine kinase), TGF-β (tumor transforming growth factor-β), TrkA (tyrosine kinase A), TrKB (tyrosine kinase B), TrKC (tyrosine kinase C). Cartoons are not intended to accurately portray relative size and location of astrocytes or neurons. Arrows to neurons imply influence on the neuron. Arrows to other astrocytes imply influence on other astrocytes.

lum and calcium ion concentrations [30]. The actual execution of the cell death is accomplished by release of caustic mitochondrial enzymes such as cytochrome c which activate executioner caspase proteases.

Once microlocalized CNS inflammation is sufficient, there is a systemic response. Chronic simple anemia (CSA), so prevalent in the elderly that it may represent a biological marker of early AD. Recent research has established that CSA is related to high levels of circulating IL-6, a 26-kilodalton proinflammatory cytokine [8]. Injections of human IL-6 result in bone marrow suppression and anemia. IL-6 appears to oppose a hematopoietic growth cytokine, known as erythropoietin. This may explain why erythrocyte progenitor cells do not respond as robustly to endogenous erythropoietin in the elderly [26]. Certainly at the end stages of AD, there is immune collapse. Death comes, in most cases as a result of recurrent and unchecked infection.

5. Summary and treatment of AD

To review the pathophysiology of AD is: 1) aging creates oxidative injury to CNS; 2) an injury to CNS precipitates local inflammation; 3) soluble Aβ is among the local CNS cytokines; 4) free radicals and further cytokine response activates microglia; 5) CNS microinflammatory sites become self-perpetuating; 6) apoptosis occurs in an increasing number of neurons at the inflammatory sites; 7) neurodegeneration becomes more widespread with clinical manifestation; 8) systemic cytokine response to CNS inflammation occurs ending in immune compromised death.

Current pharmacologic interventions of AD consist of AChE inhibitors which make dysfunctional acetylcholine neurons work more efficiently. There are four such agents: tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®). Two these agents (tacrine and rivastigmine) are active in blocking BuChE, which downregulates NMDA receptor density resulting in decreased likelihood of neuronal apoptosis. A second pharmacologic approach to treatment of AD is with moderate-affinity antagonists to NMDA receptors, which are found in high density in the cortex and hippocampus [7]. There is one agent in this class marketed – memantine (Axura®, Namenda®). Combinations of memantine with an AChE should prove quite beneficial in slowing progression of AD.

Off label treatments include use of non-steroidal anti-inflammatory drugs. To date prospective clinical trials have been mostly negative and NSAIDs are not benign when used chronically. Estrogen for female and testosterone for male AD patient has been proposed for over twenty years. Again prospective studies have not unequivocally supported these treatments.

Alternative treatments include chelation therapy to remove zinc, copper and iron form Aβ depositions. The trials of clioquinol, a zinc/copper chelator, do appear to be promising. Antioxidants from theory alone should be helpful. In several studies Ginkgo biloba and Vitamin E, have shown promise.

The number of antioxidant agents however is vast. They include: 1) *antioxidant vitamins* (beta carotene, vitamin A, Coenzyme Q10, vitamin B2, folic acid, vitamin B3, vitamin B5, vitamin B6, vitamin B12, vitamin C, vitamin E); 2) *antioxidant amino acids* (L-Glutathione, L-Lysine, L-Methionine, and L-Taurine); 3) *antioxidant minerals* (boron, manganese, magnesium, selenium, and in small amount zinc); 4) *antioxidant herbals* (curcumin, Ginkgo biloba, ginseng, Gota kola, grape pip proantho- cyanidins, and many others); 5) *lipid metabolism antioxidants* (lipoic acid, phosphatidylcholine, phosphatidylserine, phosphatidyl-β-ethanolamine, and others) [33]. It seems logical that a combination of several agents from each class of antioxidants may be of value [33]. A principle advantage is that such agents are available, relatively non-toxic, inexpensive, and of known value for other problems of aging such as cardiovascular disease, stroke, and cancer [9]. A recent study by Zandi et al demonstrated reduced risk of development of Alzheimer's disease in users of combined antioxidants in 4,740 subjects [38]. In a brief trial, Lehmann et al. combined three B-complex vitamins to show biochemical improvement in MCI patients [18].

The author predicts that widespread trials of antioxidant combinations will prove beneficial to AD, MCI, Parkinson's and other neurodegenerative diseases. Further, known injuries such as head trauma, onset of hypertension, and the like will be treated with combination antioxidant therapies in the future. Where etiologies are specific and treatable, such as Chlamydia pneumoniae or such a lipid envelope virus like *Herpes Simplex type I*, treatment will be administered as well. Where the etiology is an associated disease, such as diabetes or atrial fibrillation, control of the initial disease will be more aggressive and with purpose.

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References

[1] D.M. Appelt, C.J. Hammond and A. MacIntyre, *A model for sporadic Alzheimer's disease: detection of AD-like pathology in the brains of BALB/c mice following infection with Chlamydia pneumoniae*, 32nd Neuroscience Meetings(Orlando, FL), Program No 18.10: November 3, 2002.

[2] M.K. Aronson, W.L. Ooi and H. Morgenstern, Women, myocardial infarction and dementia in the very old, *Neurology* **40** (1990), 1102–1106.

[3] M.E. Bamberger and G.E. Landreth, Microglial interaction with beta-amyloid: implications for the pathogenesis of Alzheimer's disease, *Microsc Res Tech* **54** (2001), 59–70.

[4] I.L. Campbell, A.K. Stalder and Y. Akwa, Transgenic models to study in the actions of cytokines in the central nervous system, *Neuroimmunomodulation* **5** (1998), 126–135.

[5] J.L. Cummings, Alzheimer's Disease, *NEJM* **351** (2004), 56–67.

[6] R. Dantzer, Sickness behavior: a neuroimmune-based response to infectious disease, in: *Psychoneuroimmunology, An Interdisciplinary Introduction*, M. Schedlowski and U. Tewes, eds, Kluwer Academic/Plenum Publishers, Dordrecht, 1999, pp. 235–240.

[7] P.M. Doraiswamy, Non-cholinergic strategies for treating and preventing Alzheimer's disease, *CNS Drugs* **16** (2002), 811–824.

[8] W.B. Ershler, Biological interactions of aging and anemia: a focus on cytokines, *JAGS* **51**(Suppl) (2003), S18–S21.

[9] K.M. Fairfield and R.H. Fletcher, Vitamins for chronic disease prevention in adults, *JAMA* **287** (2002), 3116–3126.

[10] C.E. Finch and R.E. Tanzi, Genetics of aging, *Science* **278** (1997), 407–411.

[11] S.A. Frautschy, D.L. Horn and J.J. Sigel, Protease inhibitor coinfusion with amyloid ∃-protein results in enhanced deposition and toxicity in rat brain, *J Neurosci* **18** (1998), 8311–8321.

[12] A.J. Gibb, Neurotransmitter receptors, in: *Neurotransmitters, Drugs and Brain Function*, R.A. Webster, ed., John Wiley & Sons, Ltd, New York, 2001, pp. 66–69.
[13] A.L. Guillozer, J.F. Smiley and D.C. Mash, Butyrylcholinesterase in the life cycle of amyloid plaques, *Am Neurol Assoc* **42** (1997), 909–918.
[14] Z. Guo, L.A. Cupples and A. Kurz, Head injury and the risk of AD in the MIRAGE study, *Neurology* **54** (2000), 1316–1323.
[15] B. Halliwell and J.M.C. Gutteridge, *Free Radicals in Biology and Medicine*, (3rd Ed.), Oxford University Press, Oxford, 2001, pp. 721–751.
[16] T. Hanninen and H. Soininen, Mild cognitive impairment as a warning sign of dementia, in: *Research and Practice in Alzheimer's Disease*, B. Vellas and L.J. Fitten, eds, Springer Publishing Co, New York, 2000, pp. 93–97.
[17] J.S. Jacob, D.P. Cistola and F.F. Hsu, Human phagocytes employ the myeloperoxidase-hydrogen peroxide system to synthesize dityrosine, trityrosine pulcherosine, and isodityrosine by a tyrosyl radical-dependent pathway, *J Biol Chem* **271** (1996), 1950–1956.
[18] M. Lehmann, B. Regland, K. Blennow and C.G. Gottfries, Vitamin B12-B6-Folate Treatment improves Blood-Brain Barrier function in patients with hyperhomocysteinaemia and mild cognitive impairment, *Dement Geriatr Cogn Disord* **16** (2003), 145–150.
[19] M.A. Lovell, J.D. Robertson and W.J. Teesdale, Copper, iron and zinc in Alzheimer's disease senile plaques, *J Neurol Sci* **158** (1998), 47–52.
[20] F.J. Martinez-Torres, S. Wagner and B. Kluge, *Expression and activity of matrix metalloproteinases* (*MMPS*) *2 and 9 in a murine model of Herpes Simplex virus encephalitis*, 32nd Neuroscience Meetings (Orlando, FL), Program No 395.12: November 4, 2002.
[21] M. Mizuno, K. Yamada and J. He, *Interaction of BDNF and NMDA receptor in spatial memory formation*, 32nd Neuroscience Meetings (Orlando, FL), Program No 81.04: November 3, 2002.
[22] M.D. Nguyen, J.P. Julein and S. Rivest, Innate immunity: the missing link in neuroprotection and neurodegeneration?, *Nat Rev Neurosci* **3** (2002), 216–227.
[23] M.E. Obrenovich, J.A. Joseph, C.S. Atwood, G. Perry and M.A. Smith, Amyloid ∃: a (life) preserver for the brain, *Neurobiology of Aging* **23** (2002), 1097–1099.
[24] R.W. Oppenheim, D.M. Prevette, T. Gould, H. Enomoto and J. Milbrandt, *Neururonal development and survival in mice deficient in the GDNF Co-receptor RET*, 32nd Neuroscience Meetings (Orlando, FL) Program No 428:16: November 5, 2002.
[25] A. Ott, R.P. Solk and F. van Harskamp, Diabetes mellitus and the risk of dementia: the Rotterdam study, *Neurology* **53** (1999), 1937–1942.
[26] D. Quaglino, L. Ginaldi and N. Furia, The effect of age on hemopoiesis, *Aging Clin Exp Res* **8** (1996), 1–12.
[27] R.C. Petersen, G.E. Smith and S.C. Waring, Mild cognitive impairment: clinical characterization and outcome, *Arch Neurol* **56** (1999), 303–308.
[28] C.A. Rottkamp, C.S. Atwood, G. Perry and M.A. Smith, The State v. amyloid ∃: the trial of the most wanted criminal in Alzheimer's disease, *Peptides* **23** (2000), 1333–1341.
[29] C.A. Rottkamp, A.K. Raina, X. Zhu, E. Gaieve, A. Bush, C. S. Atwood, M. Chevion, G. Perry and M.A. Smith, Redox active iron mediated amyloid ∃ toxicity, *Free Radical Biology and Medicine* **30** (2001), 447–450.
[30] L. Scorrano, S.A. Oakes and J.T. Opferman, BAX and BAK regulation of endoplasmic reticulum Ca^{2+}: a control point for apoptosis, *Science* **300** (2003), 135–139.
[31] M.A. Smith, C.S. Atwood, J.A. Joseph and G.A. Perry, Ill fated amyloid ∃ vaccine, *J Neurosci Research* **69** (2002), 285.
[32] M.R. Sanchez-Carbente, L. Covarrubias and V. Narvaez-P, *Is oxidative stress involved in cell death in the developing spinal cord*? 32nd Neuroscience Meetings(Orlando, FL), Program No 31.1: November 3, 2002.
[33] W.K. Summers, *Neuroceutical for improving memory and cognitive abilities*, US Patent No. 6,733,797, May 11, 2004.
[34] K. Takata, Y. Kitamura and M. Umeki, Possible involvement of small oligomers of amyloid-beta peptidesin 15-deoxy-delta (12,14) prostaglandin J(2) sensitive microglial activation, *J Pharmacol Sci* **91** (2003), 330–333.
[35] M. Vila, D.C. Wu and S. Przedborski, Engineered modeling and the secrets of Parkinson's disease, *Trends Neurosci* **24**(11 Suppl) (2001), S49–S55.
[36] J. Vilcek, The cytokines, in: *The Cytokine Handbook*, (3rd ed.)., A.W. Thomson, ed., Academic Press, New York, 1998, pp. 1–20.
[37] C.J. Wilson, C.E. Finch and H.J. Cohen, Cytokines and cognition – the case for a head-to-toe inflammatory paradigm, *J Am Geriatrics Soc* **50** (2002), 2041–2056.
[38] P.P. Zandi, J.C. Anthony, A.S. Khachaturian, S.V. Stone, D. Gustafson, J.T. Tschanz, M.C. Norton, K.A. Welsh-Bohmer and J.C.S. Breitner, *Reduced risk of Alzheimer disease in user of antioxidant vitamin supplements Arch Neurol* **61** (2004), 82–88.