

Link between Herpes Simplex Virus and Alzheimer's Disease

Potential Role of Mushroom Nutrition Supplementation in Prevention

Professor Tito Fernandes, profcattitofernandes@gmail.com

Scientific Director, Lúrio University, Nampula, Mozambique, Tel: +25826214040; +258829565760

Herpes exists in two common forms. The majority of the population acquires Herpes Simplex Virus (HSV-1), which causes cold sores, during childhood from non-sexual contact. Herpes Simplex Virus 2 (HSV-2), also known as genital herpes, is transmitted by sexual contact.

In 2000, researchers led by Dr. Frank M. LaFerla at the department of Neurobiology and Behaviour at the University of California Irvine, Irvine, USA, demonstrated that a synthetic protein that resembles the Herpes Simplex Virus (HSV-1) mimics the structure and function of a protein called β -amyloid, a toxic agent that accumulates in the brains of Alzheimer patients.⁽¹⁾

Genetic sequencing revealed that two-thirds of the viral protein is identical to the β -amyloid protein. The researchers showed that, like β -amyloid, it could destroy brain neurons, a key feature in the development of Alzheimer's. Moreover, in laboratory experiments, the viral protein formed abnormal twisted fibres (neurofibrillary tangles, called 'tau') like those found in the brains of Alzheimer's patients-the definitive hallmark of the disease.⁽²⁾

According to Dr. LaFerla "Most people are exposed to HSV-1, but do not develop Alzheimer's. However, recent studies show that people genetically predisposed to Alzheimer's are more likely to develop the disease if they are exposed to herpes".⁽³⁾

In support of Dr. LaFerla's hypothesis, in December 2008, Professor Ruth Itzhaki and her team in the United Kingdom, at the Manchester University's Faculty of Life Sciences published in the Journal of Pathology that the HSV-1 DNA is located very specifically in amyloid plaques: 90% of plaques in Alzheimer's disease sufferers' brains contain HSV-1 DNA, and most of the viral DNA is located within amyloid plaques⁽⁴⁾.

The team had previously shown that HSV-1 infection of nerve-type cells induces deposition of the main component, β -amyloid, of amyloid plaques. Together these findings strongly implicate HSV-1 as a major factor in the formation of amyloid deposits and plaques, abnormalities thought by many in the field to be major contributors of Alzheimer's disease.

The University of Manchester's data strongly suggest that HSV-1 has a major role in Alzheimer's disease and point to the usage of antiviral agents for treating the disease, in fact in preliminary experiments they have shown that acyclovir reduces the amyloid disposition and also reduces certain other features of the disease which they have found are caused by HSV-1 infection. Further research has been conducted on the potential use of acyclovir, penciclovir and foscarnet as therapeutic agents for the treatment of Alzheimer's disease ⁽⁴⁾⁽⁵⁾⁽⁶⁾.

In addition to the use of anti-HSV1 antiviral agents to disrupt the HSV1 virus, researchers at the Medical University of South Carolina have suggested the use of immunoglobulin (IG) GM genes based on their putative role as the modulators of host immune response. In some studies, the intravenous use of immunoglobulin acts synergistically with the antiviral, acyclovir.⁽⁷⁾⁽⁸⁾

More recently, in May of 2013, Dr. LaFerla and his associates at the Institute of Memory Impairments and Neurological Disorders at the University of California, Irvine, Irvine California published in the American Journal of Pathology, that there could be another method to reduce Alzheimer's disease (AD).

The researchers demonstrated that aspirin-triggered Lipoxin A4 (LXA4) (15 μ g/kg) s.c, twice a day, reduced NF- κ B activation and levels of pro-inflammatory cytokines and chemokines, as well as increased levels of anti-inflammatory IL-10 and transforming growth factor B (beta). Such changes in the cerebral milieu resulted in recruitments of microglia in an alternative phenotype as characterized by the up-regulation of YM1 and arginase-1 and the down-regulation of inducible nitric oxide synthase expression.⁽⁹⁾ In effect the researchers contend that activating LXA4 signaling may represent a novel therapeutic approach for AD⁽¹⁰⁾.

Given the potential gastrointestinal discomfort associated with aspirin intake, is there another manner to achieve to trigger LXA4 as well as provide both anti-viral protection and anti-oxidant protection in the form of SOD (Super-oxide dismutase) supplementation?

Why Mushroom Nutrition?

In the past ten years, the clinical development of mushroom nutrition has determined that *Coriolus versicolor* (biomass) has viral protective properties, while *Hericium erinaceus* (biomass) is extremely high in SOD content.

Given this information, there are four reasons to consider the use of mushroom nutrition in the preventative use for patients with Alzheimer's disease if HSV-1 induced:

Coriolus versicolor has a clinically verified use in the reduction of viruses (EBV, CMV and HHV-6) related to the Chronic Fatigue Syndrome condition^(11,12).

Coriolus versicolor has been used to increase the regression rate of LSIL lesions in HPV patients and to reduce the viral load in HPV patients. ⁽¹³⁾

Hericium erinaceus has an extremely high SOD content, which in the presence of proteolytic enzymes per 500 mg tablet has a SOD content of 19.430×10^3 U⁽¹⁴⁾. This high SOD content is important given that with herpes simplex virus infection, apoE4 intensifies virus latency and is associated with the increased oxidative damage of the central nervous system, and there is some evidence that herpes simplex virus infection in combination with the apoE4 genotype may be associated with increased risk of Alzheimer's disease (AD)⁽¹⁵⁾.

For those patients not able to both tolerate the side effects of anti-HSV1 virals and/or afford intravenous immunoglobulin IG therapy, having an alternative.

The following is a proposed two part study to determine if biomass form of both *Coriolus versicolor* and *Hericium erinaceus* are able to trigger LXA4 stimulation of microglia and indirectly reduces Alzheimer disease symptoms in early stage patients. Working with the University of Catania, the protocol structure is the following:

Protocol to determine if *Coriolus versicolor* and *Hericium erinaceus* stimulates Lipoxin A4 (LXA4) activation in peripheral blood and in the CNS of rats treated with an equivalent human dose of 3 g per day MRLs given, orally, separately or in combination, morning and evening, for 1 and, respectively, 3 months. At the end of experimental period animals will be sacrificed and the activity of LXA4 will be determined in serum, lymphocytes and in different brain regions (cortex, striatum, substantia nigra, hippocampus and cerebellum) and compared with LXA4 of untreated animals, as control.



Professor Vittorio Calabrese, calabres@unict.it
 University of Catania, Catania, Italy, Tel:+39 3288310716

20 control subjects and 20 patients with early stage AD diagnosis will be treated with MRLs (*Coriolus versicolor* and *Hericium erinaceus*) for a period of 180 days (See section III). For each mushroom (*Coriolus versicolor* and *Hericium erinaceus*) the supplementation schedule should be six tablets (500 mg) per day or 3 g per day (3 tablets in mornings before breakfast and 3 tablets in evening before dinner). Supplementation period: 180 days. After the treatment period blood samples will be taken and LXA4 activity will be determined in serum and lymphocytes together with heme oxygenase-1 expression as marker of anti-inflammatory and antioxidant potential.

Upon determination of the potential for mushroom nutrition to trigger LXA4 activity, the next step will be to clinically test the hypothesis in early stage Alzheimer's patients.

Protocol Outline for use of Mushroom Nutrition in Early Stage Alzheimer Patients.

Table I: Proposed Human Trial Protocol and Corresponding Cost per Day for Use of Mushroom Nutrition in AD.

A. Patient Selection:

1. Test for Lyme disease and or associated conditions with Lyme disease.*
2. Patients with genetic precondition (based on family history) to Alzheimer's.
3. Patients with high HSV-1 viral load. (Need to define).
4. Cognitive testing to determine a baseline (see point 5).
5. Determine number of "senior moments" per week.
6. Supplement for six months and retest against HSV-1 viral load, cognitive baseline test and number of "senior moments" per week.

B. Supplementation Schedule:

For each mushroom (*Coriolus versicolor* and *Hericium erinaceus*) the supplementation schedule should be six tablets (500 mg) per day or 3 g per day (3 tablets in mornings before breakfast and 3 tablets in evening before dinner). Supplementation period: 180 days.

C. Success Criteria after 180 days:

Testing for:

	<i>Coriolus versicolor</i> 500mg tablets 6 tablets/day = 3g	<i>Hericium erinaeacus</i> 500mg tablet 6 tablets/day = 3g	
MONTH 1	180 TABLETS	180 TABLETS	
MONTH 2	180 TABLETS	180 TABLETS	
MONTH 3	180 TABLETS	180 TABLETS	
MONTH 4	180 TABLETS	180 TABLETS	
MONTH 5	180 TABLETS	180 TABLETS	
MONTH 6	180 TABLETS	180 TABLETS	
TOTAL	1080 TABLETS	1080 TABLETS	
Bottle of 90 Tablets	12	12	
Assumed cost per bottle 26.00	318	318.00	
cost per day (€)	1.77	1.77	3.53

*If due to untreated Lyme disease, then one has to understand that the *Borrelia burgdorferi* bacterium is not the only potential cause of the neurological disorder as the disorder is multi-factorial due to potential of co-infections caused by the initially weakened immune state of the individual. In Lyme disease, one has to diagnose the bacterium and then address the immune state of the patients with specific supplementation and diet change ⁽¹⁶⁾.

1. Significant changes in cognitive state from day 0 to day 180.
2. Significant changes in HSV-1 viral load.
3. Significant changes in "well-being" i.e. rate of change in "senior moments experienced in a week".

D. Potential Daily Cost per day of Mushroom Supplementation to Patient

Supplementation at the price of a full treatment for six months would be equal to two "Big Macs" and soft drinks per day.

Concluding Remarks:

In sum, given the fact that there may be a viral trigger for the onset of Alzheimer's disease and given the recently confirmed profile of mushroom nutrition supplying both immune modulation and SOD supplementation, it seems with worth the effort to

- a) determine if mushroom nutrition does trigger lipoxin A4 activity in the microglia; and if so:
- b) conduct a clinical trial in early stage patients with an established (and recognized) parameters for success. Such parameters could be a) decrease in onset of AD and b) decrease in rate of increase "tau" production.

Conclusion

Given the expanding number of patients with Alzheimer's disease and the increasing cost of care for Alzheimer patients, government healthcare services require safe, clinically reliable and cost effective protocols that treat the symptoms of Alzheimer's disease; the aforementioned two part protocol may offer a cost effective tool for the management of this condition in developing and developed countries.

References

- 1 American Chemical Society (2000, May 12). *New Evidence Found Linking Herpes and Alzheimer's*. Science Daily. Retrieved July 26, 2013, from <http://www.sciencedaily.com/releases/2000/05/000512083302.htm>.
- 2 University of Manchester (2008, December 7). *Cold Sore Virus Linked To Alzheimer's Disease: New Treatment, Or Even Vaccine Possible*. Science Daily. Retrieved July 26, 2013, from <http://www.sciencedaily.com/releases/2008/12/081207134109.htm>
- 3 MA Wozniak, AP Mee and RF Itzhaki. *Herpes simplex virus type I DNA is located within Alzheimer's disease amyloid plaques*. *The Journal of Pathology*, Volume 217, Issue 1 , Pages131 - 138 2009 DOI: 10.1002/path.2449
- 4 Carter CJ. *Alzheimer's disease plaques and tangles: cemeteries of phyrhic victory of the immune defence network against herpes simplex infection at the expense of complement and inflammation-mediated neuronal destruction*. *Neurochem Int*. 2011 Feb 58(3):301-20 doi 10 1016/j.neuint.2010.12.20.003 Epub 2010 Dec 15.
- 5 Wozniak MA, Frost AL, Preston CM, Itzhaki RF. *Antivirals reduce the formation of key Alzheimer's disease molecules in cell cultures acutely infected with herpes simplex virus type 1*. *PLoS One*. 2011;6(10):e25152 doi 10 1371/ journal.pone.0025152. EPUB 2011 Oct 7.
- 6 Pandley JP. *Immunoglobulin GM genes as functional risk and protective factors for the development of Alzheimer's disease*. *J. Alzheimers Dis* 2009;17(4) 753-6 doi 10.3222/JAD-2009-1094.
- 7 Wozniak MA, Itzhaki RF. *Intravenous immunoglobulin reduces amyloid and abnormal tau formation caused by herpes simplex virus type 1*. *J Neuroimmunol* 2013 Apr 15:257 (1-2):7-12 doi 10. 1016/ jneuroim.2013.01.005 Epub 2013 Feb 4.
- 8 Medeiros R, Kitazawa M, Passos GF, Baglietto-Vargas D, Cheng D, Cribbs OH, LaFerla FM. *Aspirin-triggered lipoxin A4 stimulates alternative activation of microglia and reduces Alzheimer disease-like pathology in mice*. *Am J Pathol*. 2013 May, 182(5);1740-9 ..
- 9 Jean A. Monro, *Chronic Fatigue Immune Dysfunction Syndrome*. *J Integrative Medicine* 2004; 8:101-108
- 10 Jean A. Monro. *Treatment of Cancer with Mushroom Products*. *Arch Env Health* 2003;58:533-537.
- 11 Silva Couto J, Pereira da Silva D. *Evaluation of the Efficacy of Coriolus versicolor Supplementation in HPV Lesions (LSIL)*. Poster presented at the 20th European Congress of Obstetrics and Gynecology, Lisbon, Portugal March 4-8th, 2008.
- 12 Cornelius C. , Cavallaro M., Cambria M.T., Toscano M.A., Calabrese V. *Comparative Enzyme Analysis of Polyporus umbellatus, Agaricus blazei, Pleurotus osteratus and Hericium erinaceus*. *Clinical Journal of Mycology* 2009 Vol II Page 4 to 7.
- 13 Kulmann I, Minihane Am, Huebbe P, Nebel A , Rimbach G. *Apolipoprotein E genotype and hepatitis c, HIV and herpes simplex disease risk: a literature review*. *Lipids Health Dis*. 2010 Jan 28.9.8 doi 10.1186/1476-511-9.6
- 14 Miklossy J. *Emerging roles of pathogens in Alzheimer disease*. *Expert Rev Mol Med*. 2011 Sept 20; 13 e 30 doi 10 1017/S14623994 1 1002006.