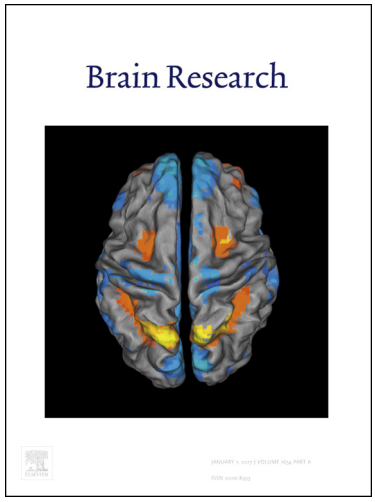

Why Does Finland Have the Highest Dementia Mortality Rate? Environmental Factors May Be Generalizable

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Why Does Finland Have the Highest Dementia Mortality Rate?

Environmental Factors May Be Generalizable

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Why Does Finland Have the Highest Dementia Mortality Rate?

ABSTRACT

Finland has the highest death rate from dementia in the world and its environmental features can be instructive in understanding hidden causes of dementia. Environmental factors there include: 1) a climate that is both very cold and humid resulting in housing frequently harboring molds that are capable of producing a neurotoxic mycotoxin 2) the Gulf of Finland as well as Finnish lakes harbor cyanobacteria that produce the neurotoxin , beta-N-methyl amino-L-alanine, known to cause dementia and related disorders 3) the aforementioned toxins can be potentiated by the presence of mercury and methyl mercury which can be found in Finnish waters 4) soil in Finland is naturally low in selenium and selenium deficiency may reduce the quantity and effectiveness of glutathione's ability to protect against neurotoxins. A high rate of fatal dementia could be the consequence of these environmental factors. Studies that can support or disprove this hypothesis are suggested. Such environmental toxins are likely to promote Alzheimer's disease elsewhere in the world where such a combination of neurotoxins may also occur.

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Introduction

Increasingly dementia researchers are finding increasing evidence that microbes are involved in the development of dementia disorders[1]. Evidence that beta-amyloid has anti-microbial activity[2] has lent credence to this concept. Studies have demonstrated a role for micro-organisms in the development of Alzheimer' disease (AD) include oral spirochetes, viruses, and fungi[3] as well as chlamydia4. Entry to brain tissue may gained via ingestion, inhalation, direct oral- brain route, and blood borne with an impaired blood-brain barrier. The development of a chronic inflammatory response appears to underlie neuronal destruction and beta-amyloid deposition5and the development of AD.

Finland has the highest death rate for dementia in the world[6] exceeding those of the USA and Canada and the other Nordic countries who also have high rates. This small advanced nation provides a unique opportunity to develop testable hypotheses concerning the causes of AD so that research and preventive efforts can be developed efficaciously. Dementia mortality in Finland has risen nearly eightfold in the past half century[7] so there is a compelling need to address the causes. The aforementioned other countries also have major public health concerns regarding a high incidence and prevalence of dementia as well, and what is the case with Finland may likely apply in varying degrees to them as well. Death rates and prevalence rates are related to one another although somewhat imprecisely because not all recorders of causes of death follow the international guidelines and severity of dementia may also vary depending on the type of dementia[8] and the causative factors.

This review examines the somewhat unique environmental, climatological, and geological features of Finland that may be promoting the high rate of dementia mortality there. Described herein are neurotoxins in the environment that exposure to which may promote AD as well as soil and water qualities that contribute to the high dementia rate.

Empirical Data: Fungal Toxins

Of note, Finland has a somewhat unusual climate, being both very cold and very humid with humidity averaging over 80% over the winter months[9]. The extreme cold promotes effective insulation of homes and businesses while the humidity is permissive to fungi to growth. The net effect is that many homes and other buildings have problem with mold growth. One study found 80% of residences had current or previous moisture faults[10] and another recent survey found visible mold in 38% of homes[11]. Studies detailing the type of mold found in the homes include several species of Aspergillus, Stachybotrys, and Pencillium[12]. These molds are known to produce ochratoxin A as well as other toxins which has been shown to produce apoptosis in neuronal cells in cell culture in a dose dependent fashion[13].

Bredesen, an experienced AD researcher, reported that mycotoxins can induce a chronic inflammatory response that can be manifested as AD and the exposure is frequently inhalational in nature[14]. Pencillium, Stachybotrys, and Aspergillus molds were identified in homes of several of the patients described in this series (and these molds correspond to those found in Finnish homes). The inflammatory response described by Bredersen in these patients suffering from dementia was characterized by elevation of complement component, C4a, transforming growth factor beta1 (TGF-beta) as well as several cytokines. Bredesen also reports

that this syndrome occurred mostly in patients with certain HLA DR/DQ haplotypes (11-3-52B and 4-3-53) and such a genetic predisposition may be a prerequisite to developing the syndrome following exposure and may explain its sporadic incidence.

Exposure to mycotoxins may also occur through food consumption including plant food supplements that may harbor ochratoxin[15].

Also regarding fungi and dementia, Spanish researchers recently detected Candida species in the brains of AD patients but not in the brains of control subjects[16]. As noted, amyloid-beta itself has anti-fungal activity[17] . In a similar regard the antimicrobial peptide, beta-1-defensin, is upregulated in the hippocampus of AD sufferers[18].

Curcumin which appears in several studies to have preventive properties with regard to AD[19] also has anti-fungal potency[20]. Of historical note Oskar Fischer, a colleague of Alzheimer, first proposed a role for fungus in the development of AD in 1909 when he observed the histologic appearance of brain plaques the resembling actinomycosis[21].

Other agents also share this combination of properties. Rutin, a multifunctional natural flavonoid glycoside, quercetin 3,0 rutinoside, has properties that make it a candidate to protect against neurodegenerative disorders[22] and it too has substantial anti-fungal activity[23]

BMAA Neurotoxin and Heavy Metals:

Another neurotoxin that the Finnish people may come into contact with is beta-N-Methyamino-L-alanine (BMAA), a product of cyanobacteria, also known as blue green algae. Although the

neurotoxicity of BMAA was worked out on the other side the world (Guam) by Cox and colleagues[24], it has also been found in the mollusks and fish in the Baltic Sea[25] and the risk is increased in the western parts of the Gulf of Finland, possibly related to differences in salinity[26]. Moreover methylmercury potentiates the toxicity of BMAA rendering non-toxic levels toxic by synergistically depleting the antioxidant glutathione[27]. The Nordic countries have high atmospheric mercury for various reasons and this has also raised the mercury level in fish in lakes in the region[28]. The Finnish diet averages over 72 pounds of fish in a year[29] (quite high comparatively but not the highest). Methyl mercury levels tended to be higher there than elsewhere[30]. Other Nordic countries with similar ecosystems make up 4 of the top eight countries with the highest rate of dementia death[31]. Iceland which has the highest rate of fish consumption[32] has the second highest rate of AD[33] suggesting that fish consumption from certain bodies of water may contribute to the development of AD. Other dietary products such as cereals potatoes, and milk has also been found in Finland to contain cadmium and arsenic as well as mercury[34], and all heavy metals that could contribute to neurotoxicity.

Several other factors including genetic susceptibility may have bearing as well.

Geological Considerations

The geological conditions in Finland indicate a low concentration of selenium in soil and ground water[35].Low selenium levels in the soil in Finland could conceivably also contribute to the pathogenesis of AD. Selenium is a vital part of glutathione peroxidase, the anti-oxidant enzyme that is essential to protect human neuronal cells from toxic injury. However selenium enriched

fertilizer was used in Finland from 1985 but has been reduced since 1991[36]. Arsenic levels in ground water may be high there as well. This too could contribute to the development of AD[37] and warrants addition measurements.

Hence the high incidence of fatal dementia in Finland appears to be the consequence of a series of environmental factors that promote neuronal cell death by neurotoxins, both biologic and metallic, and the reduction of the protective capacity against such neurotoxins.

Suggested Evaluation of the Hypothesis

There are several ways to assess this hypothesis:

1) Patients with AD should be evaluated for the presence of mycotoxins, and BMAA as well as biomarkers for a chronic inflammatory response. Urinary biomarkers may be used to assess exposure to mycotoxins as well as from brain tissue samples using immunoaffinity columns and fluorometry techniques[37]. BMAA can be measured in CSF using triple quadrupole mass spectrometer connected to an ultra-high performance liquid chromatography (UHPLC) instrument[38]. Brain tissue samples in tissue banks of those who have died with AD should be evaluated for the presence of these biotoxins. Age and gender matched controls without dementia or other neurological disorders should be compared.
2) Assessment of heavy metals including mercury, cadmium arsenic, lead, copper, and iron should be measured in both groups as well as brain tissue samples because metals can magnify the effects of biologic toxins even at levels that are non-toxic in themselves. At higher levels of metal accumulation, they can be toxic independent of biotoxins.

3) Measurement of glutathione should also be made as possible measure of oxidative resistance as well as assessing selenium status.

4) Detoxification protocols have been described regarding BMAA and mycotoxins and further research is needed to verify whether such protocols are effective or not. Prospective clinical trials of these regimens should be evaluated with regard to AD patients who test positive for evidence of biotoxins. This is probably a subset of all AD cases, as other types of AD occur and provide a background incidence. Research in this area should proceed carefully with the appropriate controls and safety monitoring.

4) Steps to reduce toxic exposure through measures to reduce molds and cyanobacteria should be increased and the impact of these measures on the incidence of AD should be measured in longitudinal population studies. Monitoring of food and water for biotoxins in Finland and elsewhere should be increased and public reporting should be made available.

Discussion and Recommendations

Studies of environmental factors in the development and prevention of dementia in Finland can advance scientific understanding of this world wide health problem. None of these risks of AD are unique to Finland and are found in other Scandinavian countries that also have high death rates from dementia. Homes in the USA also have mold-related health issues[39] as do other countries. Cyanobacteria blooms plague waters in Canada and USA[40] two other countries in the top highest rate of dementia deaths, and elsewhere throughout the world.

The Baltic states such as Estonia have considerably lower rates of fish consumption[41] and mercury contamination[42] and have much lower rates of dementia[6].

The populations of other countries could benefit from the proposed research and public health measures to reducing the incidence and prevalence of dementia.

Preliminary reports of treatment at the first onset of symptoms of AD has been described[43,44]. Further studies are needed to assess any treatment regimen's efficacy and safety. There is a compelling need to further the understanding of the multiple causes of AD, and Finland has the opportunity to lead in these efforts. The complex processes of AD development include and extend beyond amyloid beta and tau protein phosphorylation to include chronic inflammatory processes that appear to be reduced by peroxisome proliferator-activated receptor (PPAR) activation[45]. A combination of biotoxins, heavy metals and other toxins such as pesticides[46] have complex interactions that effect glial cell and neurons in neurodegenerative diseases.

Better treatments regimens can then be based on a new understanding of the environmental causes of AD.

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Highlights for , BRES-D-17-00562R1, Why Does Finland Have the Highest Dementia Mortality Rate? Environmental Factors May Be Generalizable

- Finland has a high dementia rate related to environmental and geological factors
- Climate contributes to mold in domiciles capable of producing neurotoxic mycotoxins
- Cyanobacteria in Finnish waters contribute BMAA neurotoxins
- Presence of environmental methylmercury is a factor
- Low soil levels of selenium reduce glutathione and protection against neurotoxins