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PERSPECTIVES

Novel potential for the management of Alzheimer disease

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ABSTRACT
Pathologic characteristics of Alzheimer disease (AD) are β-amyloid (Aβ) plaques, neurofibrillary tangles (NFT) and neurodegeneration. Currently, there is no cure for AD. Cilostazol, a selective inhibitor of type 3 phosphodiesterase, is likely to be a promising agent for AD. In the brain of the experimental animals it significantly reduced the Aβ amyloid plaques. Initial clinical reports on the effect of Cilostazol in AD patients are promising. In mice, stem cells favourably influence the pathogenetic process critical in AD, by reducing deposits of Aβ plaques. Clinical trials of the drug, called Betablock, are already underway in Britain. Successful management and resolution of AD in man will still require further intensive research *(Fig. 4, Ref. 11)*. Text in PDF *www.elis.sk.*
KEY WORDS: Alzheimer disease, β-amyloid plaques, Cilostazol, stem cells.

Introduction

Alzheimer's disease (AD) is the most common human neurodegenerative disorder characterized by the progressive deterioration of cognition and memory in association with the presence of senile plaques, neurofibrillary tangles and massive loss of neurons.

Pathological characteristics of AD are β-amyloid (Aβ) plaques, neurofibrillary tangles (NFT) and neurodegeneration. Aβ fibrils from pores in neurons have been shown to lead to calcium influx and neuronal death. There appears to be an anatomic heterogeneity in AD (1). Three- dimensional MRI studies revealed that AD in earlier stages can be categorized into various subtypes, related to location of the cortical atrophy. An interesting hypothesis (2) suggests a pivotal role for the main brain source of norepinephrine in the locus coeruleus. Neurons originating at this epicenter modulate several processes that are defective in the brain of AD. Augmentation of brain noradrenergic neurotransmissions may reduce neuroinflammation and a cognitive decline.

There are multiple theories on mechanisms that facilitate AD. Speculations on the variability of intellectual profile in individuals at risk have been controversial. Another agent may be chronic traumatic encephalopathy (dementia pugilistica in boxers) that may induce neurodegenerative disorders, including AD (3). Extensive deposition of phosphorylated tau protein may induce sustained neuroinflammation.

In the absence of clear specific causal factors, a wide array of potential, mostly nutritional causes has been implicated (4). These include such widely divergent factors as exercise, fruit and statin intake. More targeted is the focus on antioxidants. Resveratrol is one of the most important phytoestrogens (5). An important, amyloid degrading enzyme neprilysin has an important role in degrading Aβ plaques. Its activity appears to depend on estrogen.

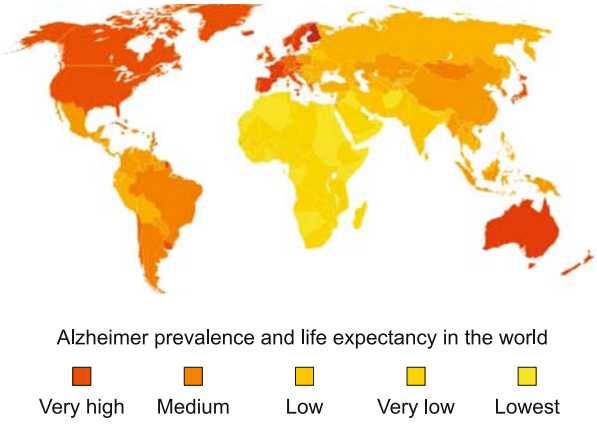

Fig. 1. Close correlation between life expectancy (LE) and Alzheimer disease (AD) in the world. Increasing colour intensity indicates higher LE but also AD. Partly according to Wikipedia.

Worldwide, nearly 36 million people have AD. This disorder is most common in Western Europe, USA, Canada and Australia and is the least prevalent in Sub-Saharan Africa (Fig. 1). There is a striking difference in AD mortality in Scandinavia. Mortality of AD in Finland is four times higher than in neighbouring Sweden and Norway (6) (Fig. 2). Even more, AD mortality in Finland (and in Iceland) is the highest in the world. Consequently, the Finnish genome, related to AD has been subjected to an intensive analysis. Recent studies on genetics of AD indicate strong genetic mechanisms involved in subjects at risk.

The World Health Organization considers dementia of AD to belong to 10 most important deadly disorders. Due to ever increasing age of the world population, the prevalence of AD is on continuous rise (Fig. 3) (7). Most often, AD is diagnosed in people

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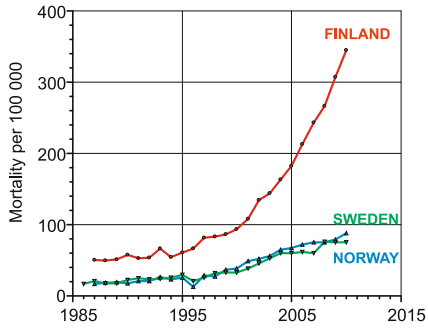

Fig. 2. Mortality from AD is in Finland four times higher than in Norway or Sweden. According to WHO (6).

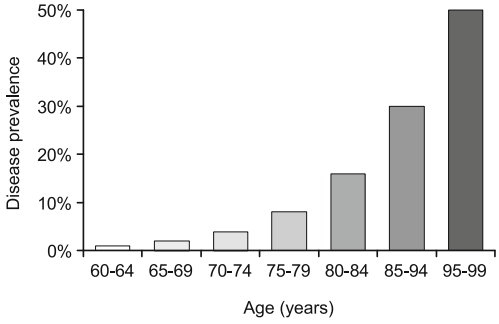

Fig. 3. AD doubles in frequency every 5 years after the age of 60. Partly according to (7).

over 65 years of age. AD is predicted to affect globally one in 85 individuals by 2050 (8).

Currently, there is no cure for AD. No treatment stops or reverses AD progression, though some can lessen symptoms. Optimization of supportive care, prolongation of basic functions and maintenance of status quo will depend on further discovery of effective medications. As of 2014, more than 1,500 clinical trials have been or are being conducted to test various treatments in AD (US National Institutes of Health, 30 October 2014).

In 2014, there was a report from researchers in Japan and China suggesting that stem cells may hold a potential to modify pathogenesis AD (9). Stem cell therapy may reduce chronic inflammation and oxidative stress, but it also may generate new neurons and replace the damaged ones, modulating their immune system through microglia activation. The most important mechanism of stem cell effect appears to be inhibition of deposits of β-amyloid plaques (Fig. 4). These findings were described in mice and have to be verified in man.

Among varieties of vasoactive drugs, cilostazol, a selective inhibitor of type 3 phosphodiesterase, is likely to be a promising agent for AD (10). This compound significantly inhibits in experimental animals the amount of β-amyloid plaques in brain. Clinical studies reported that cilostazol might have a preventive effect on cognitive decline in patients with AD (11). Clinical trials of the drug, called Betablock and made by Dublin's Elan Pharmaceuticals, are already underway in Britain (no publication).

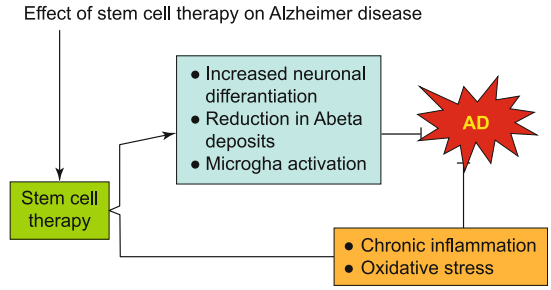

Fig. 4. Stem cell therapy inhibits in mice via various pathways the pathogenesis of AD. Partly according to (11).

Conclusion

Presently, strategies are being tested that prevent, inhibit or eradicate the development of specific plaques in AD. This neurodegenerative disorder is associated with high mortality and it is becoming more common as the population ages. Animal models have shown a promise for cilostazol, stem cell modulation of their immune system, also for an active and passive immunization, targeting Aβ plaques. However, in humans there is insufficient information that would suggest an overwhelming benefit of novel therapeutic modalities.

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