Review Articles

Review of what's new in Alzheimer's disease?

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The latest worldwide estimate of Alzheimer's disease prevalence shows that 26.6 million people were living with the disease in 2006. The researchers predict that the global prevalence of Alzheimer's will quadruple by 2050 to more than 100 million, at which time 1 in 85 persons worldwide will be living with the disease. More than 40 percent of those cases will be in late stages, requiring a high level of care. The pace, to find a cure for this disease is rapid and exhausting. The following gives a summary of what may be available to the patient and physicians in the near future.

In Diagnosis

The need for early diagnosis is vital for prevention. It is estimated that build-up of A-beta and tau, begins 15 years before symptoms begin. When symptoms begin, more than 50% of cell loss has occurred.

Geert De Meyer, Ph.D., of Innogenetics (Belgium) and colleagues are testing an assay, to detect and measure the concentrations of various forms of Aý (b-amyloid) in blood. In recent trials a single blood sample from each individual was taken and measured, using the new assay for concentrations of beta amyloid forms including Aý1-42, Aý1-40, and other Aý forms.

The researchers found that persons at risk for developing Alzheimer's according to their clinical/CSF biomarker profiles had significantly different Aý levels in their blood compared with those whose clinical/CSF biomarker profiles did not show risk of Alzheimer's. According to the scientists, approximately 60 percent of the patients tested could be classified by the test as having either a clearly enhanced or a decreased risk for progression to Alzheimer's.

Cerebrospinal fluid (CSF) measurement of total tau is not a specific indicator for AD because tau can be elevated after stroke and in Creutzfeld-Jacob disease. However, the level of phosphorylated tau or p-tau is a specific indicator for AD because p-tau specifically reflects the phosphorylation state of tau in the formation of tangles in AD. Even total tau can be useful in the differential diagnosis of AD from these conditions. Because A-beta42 (but not A-beta40) in the CSF is lowered in AD and p-tau is elevated, the p-tau181/Abeta42 ratio can be used as a diagnostic marker.

In Radiology

The Brazilian researchers compared the FDG PET brain glucose metabolism with Tc-99m ethylcysteinate dimer (ECD) single-photon emission computed tomography (SPECT) brain regional cortical blood flow in patients with Alzheimer dementia. This study showed that similar functional cerebral regions are involved on PET and SPECT in Alzheimer's disease, although PET seemed to be more powerful in depicting the extent and severity of the functional impairments.

There has also been a growing interest in imaging beta-amyloid deposits directly with PET in Alzheimer dementia. An Australian study evaluated the relationship between amyloid burden as assessed by Pittsburgh Compound-B (PIB) PET and cognitive decline in predominantly normal elderly population (age 73 ± 6 years). These investigators observed that subjects with declining cognition were more likely to show cortical PIB retention than in stable subjects, suggesting that amyloid deposition is not a part of normal aging and likely represents preclinical Alzheimer's disease. The researchers from the University of Pennsylvania compared the amyloid imaging agents [F-18]3'-F-PIB and [C-11]PIB in patients with Alzheimer's disease and in healthy subjects. The F-18-labeled compound showed uptake and retention characteristics similar to those of C-11-labeled compound in the more important cortical brain regions with SUV in the range of 3.1 to 4.5.

In Treatment of the future

An anti-amyloid compound

Tramiprosate binds to amyloid beta protein and interferes with its ability to build plaque. Tramiprosate is an orally administered amyloid beta antagonist that is currently in Phase III clinical trials to assess its safety, efficacy and disease modifying effects in patients with mild to moderate Alzheimer's. Tramiprosate has been shown to protect against Aý-induced cytotoxicity in neuronal and organohippocampal cultures, decrease amyloid burden in transgenic mice, reduce CSF Aý levels in AD patients and be generally well tolerated in humans.

Brain Cell Death Inhibitor

Dimebon is a novel oral small molecule shown to be well tolerated and improve cognition, function, behaviour, and global impression of change. Preclinically, dimebon has demonstrated cognition and memory-enhancing properties and protected neurons in the cerebellum cell culture against the neurotoxic action of ý-amyloid fragment. In vitro, Dimebon displayed Ca2+-blocking properties and pronounced anticholinesterase activity for butyrylcholine esterase and acetylcholine esterase. It also exhibited strong anti-NMDA activity in the prevention of NMDA-induced seizures in mice. . The improvement at the end of 12 months was more than at the end of 6 months which

suggests that Dimebon didn't just stabilize the patients' condition, it improved it over time. The one-year data confirmed the durability of the treatment and safety profile.

Immunotheraphy

Immunization of AD patients with synthetic Aý42 (AN1792) was studied in an immunotherapeutic clinical trial that was discontinued following reports of encephalitis. A one-year follow-up showed that AN1792 antibody responders showed improvements on some cognitive measures and a decrease in brain volume compared to placebo.

The study assessed efficacy and safety profiles 4.5 years after immunization with AN1792. Compared to the placebo group, the antibody responders showed significant favourable results in the ability to look after themselves and pursue leisure activities. After the first year, brain volume changes in antibody responders and placebo patients were similar. No additional cases of encephalitis were observed.

Anti - Diabetic

A treatment for type 2 diabetes, rosiglitazone, has been studied for the treatment of Alzheimer's disease. Researchers studied the effect of an extended release form of rosiglitazone (XR) on Alzheimer's patients for 72 weeks. This was a follow up open label extension (48 weeks) to a randomised 24-week controlled trial. The results of the 24 week randomised controlled study suggested that rosiglitazone may help some Alzheimer's patients depending on their APOE genotype. Patients that were "APOE e4-negative" did benefit from the treatment, and showed some improvement. But patients who were "APOE e4-positive" either did not improve or continued to decline.

Huperzine

A new type of ChEI (cholinesterase inhibitor), known as ZT-1, transforms nonenzymatically into its active compound, huperzine A (Hup A). Hup A is a reversible, potent and selective acetyl cholinesterase inhibitor extracted and isolated from the Chinese medicinal herb Huperzia serrata. Hup A has been used in China to treat disorders such as memory loss, schizophrenia and hypertension, and following a series of clinical trials carried out in China, it has been approved for use in the treatment of AD.] Hup A is licensed as a dietary supplement to enhance cognition.

Hup A has demonstrated memory-enhancing effects in a broad range of behavioural animal models. Clinical trials have revealed that Hup A produced significant improvements in memory deficiencies in aged patients and in patients with AD. The results from a 12 week, double-blind, randomised and placebo-controlled clinical trial with 202 patients diagnosed with possible or probable AD confirmed the efficacy of Hup A on cognition and function. After treatment with Hup A at a dose of 400 µg/day, patient outcomes as measured by the MMSE, ADAS-Cog, Clinical Dementia Rating and ADL improved significantly at week 6 and further improved at week 12. Only mild adverse events were recorded.

Secretory phospholipase A_2-IIA (sPLA_2-IIA)

Is an inflammatory protein known to play a role in the pathogenesis of many inflammatory diseases. Although this enzyme has also been implicated in the pathogenesis of neurodegenerative diseases, there has not been a direct demonstration of its expression in diseased human brain. THE sPLA2-IIA-immunoreactive astrocytes present in AD hippocampus and inferior temporal gyrus (ITG). In ITG, the majority of sPLA2-IIA-positive astrocytes were associated with amyloid ß (Aß)-containing plaques. Studies with human astrocytes in culture demonstrated the ability of oligomeric Aß and interleukin-1ß (IL-1ß) to induce sPLA2-IIA mRNA expression, indicating that this gene is among those induced by inflammatory cytokines. Since exogenous sPLA2-IIA has been shown to cause neuronal injury, understanding the mechanism(s) and physiological consequences of sPLA2-IIA up regulation in AD brain may facilitate the development of novel therapeutic strategies to inhibit the inflammatory responses and to retard the progression of the disease.

Gamma Secretase inhibitor

A phase-II trial of a gamma-secretase inhibitor (LY450139) is currently being studied as a potential disease-modifying treatment for Alzheimer's the molecule inhibits the gamma-secretase enzyme which contributes to the formation of Aý (b amyloid). Patients with Alzheimer's were given 100 mg or 140 mg each day for six to 12 weeks.

Eric Siemers, M.D. and colleagues conducted this study to assess the safety and tolerability of LY450139 as well as its effect on Aý levels in blood and CSF.

Fifty-one participants with mild to moderate Alzheimer's were randomised; 43 completed the study. Aý1-40 concentrations in blood were reduced by 58.2 percent for the 100 mg group and by 64.6 percent for the 140 mg group. According to the researchers, a number of side effects were reported, but they were generally mild in severity and the drug was generally well tolerated. Safety assessments showed 38.9 percent complained of mild fatigue or sleepiness, compared to 13.3 percent in the placebo group. There were three adverse event gastrointestinal related discontinuations. There was a mean prolongation of "QTcF interval" of 16.8 msec (corrected for baseline values) on electrocardiograms in the 140 mg group.

Statins

Amyloid B is 39-43 amino acid residues long and is derived in part from the transmembrane region of the amyloid-precursor protein (APP). The initial pathophysiological role of Aß is widely agreed on.] A mounting body of experimental in vitro and in vivo data indicate that brain cholesterol homeostasis is coupled with brain amyloid metabolism, although the mechanism is not known. However, the causative role of cholesterol in the pathogenic cascade of excessive Aß deposition in the brain of AD patients is not proven. Cell culture studies demonstrate that membrane cholesterol controls the direction of the processing of the APP. Under similar experimental conditions, reduced Aß levels were found to increase ?-secretase activity. Suggesting that membrane cholesterol variations are coupled with activity shifting of APP-cleaving secretases.

Mediterranean Diet

Some physicians are beginning to recommend this (MeDi) diet for the prevention of Alzheimer's disease in view of the two recent trials. There have been no major clinical trials and other groups have not replicated same results. On the other hand, considering the positive results of two studies, and taking into account that the [Mediterranean] diet has been shown to be

beneficial for many other diseases, it would make sense for patients to adopt it as early as possible.

Anti-inflammatory (NSAID)

The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), had been running for 3 years when it was stopped, having randomised 2400 participants over the age of 70,after discovering, that both celebrex and naproxen appeared to increase the risk of cardiovascular (CV) events and stroke by 50% compared with patients on placebo. Researchers and physicians now feel that it was done in haste and results have been encouraging.

Vascular Risks

There is growing evidence that factors that increase the risk of vascular events like heart attack or stroke also increase the risk of cognitive decline. Results of recent trials, showed that patients whose vascular risk factors were treated appeared to decline at a slower rate and that it took them three years to decline as much as untreated patients.

Conclusion

Many treatment models have shown a promising reduction of disease but no disease-modifying drug has yet been approved for use. Although that day may not be far away. Dietary factors, such as the MeDi, regular exercise, and reduction in vascular events, seem to modify the disease course and may help to prevent or delay AD.

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