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A REVIEW ON ALZEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is the most common cause of dementia. The word dementia describes a set of symptoms that can include memory loss and difficulties with thinking, problem-solving or language. These symptoms occur when Alzheimer's disease (AD) and other forms of dementia are a growing public health problem among the elderly in developing countries, whose aging population is increasing rapidly. This article reviews the pathophysiology, symptoms, treatment of this disease.

PATHOPHYSIOLOGY

Alzheimer's disease damages and kills brain cells. A brain affected by Alzheimer's disease has many fewer cells and many fewer connections among surviving cells than does a healthy brain As more and more brain cells die, Alzheimer's leads to significant brain shrinkage. Two types of abnormalities that are considered hallmarks of the disease are:

Plaques

These clumps of a protein called beta-amyloid may damage and destroy brain cells in several ways, including interfering with cell-to-cell communication. Although the ultimate cause of brain-cell death in Alzheimer's isn't known, the collection of beta-amyloid on the outside of brain cells is a prime suspect.

Tangles

Brain cells depend on an internal support and transport system to carry nutrients and other essential materials throughout their long extensions. This system requires the normal structure and functioning of a protein called tau. In Alzheimer's, threads of tau protein twist into abnormal tangles inside brain cells, leading to failure of the transport system. This failure is also strongly implicated in the decline and death of brain cells.

SYMPTOMS

Brain changes associated with Alzheimer's disease lead to growing trouble with:

Memory

Everyone has occasional memory lapses. It's normal to lose track of where you put your keys or forget the name of an acquaintance. But the memory loss associated with Alzheimer's disease persists and worsens, affecting your ability to function at work and at home.

People with Alzheimer's may:

- Repeat statements and questions over and over, not realizing that they've asked the question before
- Forget conversations, appointments or events, and not remember them later
- Routinely misplace possessions, often putting them in illogical locations
- Get lost in familiar places
- Eventually forget the names of family members and everyday objects
- Have trouble finding the right words to identify objects, express thoughts or take part in conversations.

Thinking and reasoning

Alzheimer's disease causes difficulty concentrating and thinking, especially about abstract concepts like numbers.These difficulties may progress to inability to recognize and deal with numbers.

Making judgments and decisions

Responding effectively to everyday problems, such as food burning on the stove or unexpected driving situations, becomes increasingly challenging.

Planning and performing familiar tasks

Once-routine activities that require sequential steps, such as planning and cooking a meal or playing a favourite game, become a struggle as the disease progresses. Eventually, people with advanced Alzheimer's may forget how to perform basic tasks such as dressing and bathing.

Changes in personality and behaviour

Brain changes that occur in Alzheimer's disease can affect the way you act and how you feel. People with Alzheimer's may experience:

- Depression
- Apathy
- Social withdrawal
- Mood swings
- Distrust in others
- Irritability and aggressiveness
- Changes in sleeping habits
- Wandering
- Loss of inhibitions
- Delusions, such as believing something has been stolen

Many important skills are not lost until very late in the disease. These include the ability to read, dance and sing, enjoy old music, engage in crafts and hobbies, tell stories, and reminisce.

This is because information, skills and habits learned early in life are among the last abilities to be lost as the disease progresses; the part of the brain that stores this information tends to be affected later in the course of the disease. Capitalizing on these abilities can foster successes and maintain quality of life even into the moderate phase of the disease.

Stages

The progression of Alzheimer's can be broken down into three basic stages;

- Preclinical (no signs or symptoms yet)
- Mild cognitive impairment
- Dementia.

The Alzheimer's Association has broken this down further, describing seven stages along a continuum of cognitive decline based on symptom severity - from a state of no impairment, through mild and moderate decline, and eventually reaching "very severe decline."

The association has published the seven stages online. It is not usually until stage four that a diagnosis is clear - here it is called mild or early-stage Alzheimer's disease, and "a careful medical interview should be able to detect clear-cut symptoms in several areas."

RISK FACTORS

Age

Increasing age is the greatest known risk factor for Alzheimer's. Alzheimer's is not a part of normal aging, but your risk increases greatly after you reach age 65. The rate of dementia doubles every decade after age 60. People with rare genetic changes linked to early-onset Alzheimer's begin experiencing symptoms as early as their 30s.

Family history and genetics

Your risk of developing Alzheimer's appears to be somewhat higher if a first-degree relative — your parent or sibling — has the disease. Scientists have identified rare changes (mutations) in three genes that virtually guarantee a person who inherits them will develop Alzheimer's. But these mutations account for less than 5 percent of Alzheimer's disease.

Most genetic mechanisms of Alzheimer's among families remain largely unexplained. The strongest risk gene researchers have found so far is apo lipoprotein e4 (APoE4), though not everyone with this gene goes on to develop Alzheimer's disease. Other risk genes have been identified but not conclusively confirmed.

Down syndrome

Many people with Down syndrome develop Alzheimer's disease. Signs and symptoms of Alzheimer's tend to appear 10 to 20 years earlier in people with Down syndrome than they do for the general population. A gene contained in the extra chromosome that causes Down syndrome significantly increases the risk of Alzheimer's disease.

Sex

Women seem to be more likely than are men to develop Alzheimer's disease, in part because they live longer.

Mild cognitive impairment

People with mild cognitive impairment (MCI) have memory problems or other symptoms of cognitive decline that are worse than might be expected for their age, but not severe enough to be diagnosed as dementia.

Those with MCI have an increased risk — but not a certainty — of later developing dementia. Taking action to develop a healthy lifestyle and strategies to compensate for memory loss at this stage may help delay or prevent the progression to dementia.

Past head trauma

People who've had a severe head trauma seem to have a greater risk of Alzheimer's disease.

Lifestyle and heart health

There's no lifestyle factor that's been definitively shown to reduce your risk of Alzheimer's disease.

However, some evidence suggests that the same factors that put you at risk of heart disease also may increase the chance that you'll develop Alzheimer's. Examples include:

- Lack of exercise
- Obesity
- Smoking or exposure to second hand smoke
- High blood pressure
- High blood cholesterol
- Poorly controlled type 2 diabetes
- A diet lacking in fruits and vegetables

These risk factors are also linked to vascular dementia, a type of dementia caused by damaged blood vessels in the brain. Working with your health care team on a plan to control these factors will help protect your heart — and may also help reduce your risk of Alzheimer's disease and vascular dementia.

Lifelong learning and social engagement

Studies have found an association between lifelong involvement in mentally and socially stimulating activities and a reduced risk of Alzheimer's disease. Low education levels — less than a high school education — appear to be a risk factor for Alzheimer's disease.

PREVENTION AND TREATMENT

Coconut oil: A recent University of Oxford study suggested that although the effects of coconut oil may be temporary, Alzheimer's and dementia patients have indeed seen short-term benefits resulting from its use. This research supports Dr. Newport's theory that ketones, which are byproducts of the breakdown of fats in the body, play an important role in brain

health. The idea is that by boosting ketones, found in coconut oil, we can improve cognitive function.

Vegetables: Especially leafy greens like spinach, kale, turnip greens and cruciferous vegetables like broccoli, which have been strongly linked to lower levels of cognitive decline in older age, according to a study in the Annals of Neurology.

Salmon and other cold-water fish, such as halibut, tuna, mackerel and sardines, which are rich in omega-3 fatty acids. Other omega-3 sources include beans, some nuts, flax seeds and healthy oils, like olive oil.

Berries and dark-skinned fruits which are rich in antioxidants. According to the Alzheimer's Association, some of the fruits that pack the most punch are blueberries, blackberries, strawberries, raspberries, plums, oranges, red grapes and cherries.

Coffee and chocolate are surprisingly good for you. Recent studies have shown that caffeine and coffee can be used as therapeutics against Alzheimer's disease. The caffeine and antioxidants in these two tasty treats may help ward off age-related memory impairment, along with cinnamon, olive oil and curry.

Extra virgin olive oil contains a substance called oleocanthal that helps boost the production of key proteins and enzymes that help break down the amyloid plaques associated with Alzheimer's disease.

Cold-pressed virgin coconut oil is a heart-healthy oil that is free of cholesterol and trans-fats, and boosts ketones. Coconut oil has been shown to improve the body's use of insulin, increase HDL (good cholesterol), boost thyroid function and acting as an antioxidant and natural antibiotic.

DRUG THERAPY

There are no disease-modifying drugs available for Alzheimer's disease but some options may reduce its symptoms and help improve quality of life. There are four drugs in a class called cholinesterase inhibitor approved for symptomatic relief in the US;

Cholinesterase inhibitors

- Donepezil (brand name Aricept)

- Rivastigmine (Exelon)
- Tacrine (Cognex).

A different kind of drug, memantine (Namenda), an NMDA receptor antagonist, may also be used, alone or in combination with a cholinesterase inhibitor.

Cholinesterase inhibitors are a class of medicines that block cholinesterase-an enzyme that breaks down the neurotransmitter acetylcholine. AD is linked with low levels of acetylcholine, hence inhibiting or blocking the breakdown of acetylcholine through cholinesterase inhibitors may help to improve brain function.

Treatment effects have been demonstrated with several different cholinesterase inhibitors, indicating that the class of agents is consistently better than placebo. However, the disease eventually continues to progress despite treatment and the average effect is often modest. However, global changes in cognition, behaviour and functioning have been detected by both physicians and caregivers, indicating that even small measurable differences may be clinically significant. These drugs are similar yet have distinct pharmacology profiles such as onset of action, side effect profile, potential drug interactions, ease of administration (e.g. twice a day versus three times a day), and route of metabolism. Donepezil is indicated for treatment of AD in the USA. However, no published results are available for severe dementia, though open-label follow up from trials suggests that these drugs continue working as the cholinergic deficit increases. Benefits reported for these medications tend to occur at higher doses. However, the higher the dose, the more likely the side effects.

Given the increase in AD prevalence, more studies are needed to determine the role of cholinergic medicines in patients with severe AD and to provide comparative data on therapeutic options for this subset of patients. Efficacy is always likely to be limited by the nature of the stage of the disease. The more severe the dementia, the more neuronal damage and the less the number of surviving cholinergic neurons hence the limitation of the effectiveness of an AChEI – once all receptors are saturated there is no more effect that can be produced – there is a ceiling.

While none of these (cholinesterase inhibitors and NMDA) are FDA approved for vascular dementia (VaD); the growing body of evidence indicates that these may be equally effective

in VaD. The implication is that for clinical trials of these therapies may be less susceptible to misclassification (AD v VaD) than putative therapies that intervene is AD specific pathology.

The cholinesterase inhibitors (donepezil and rivastigime) may not be cost effective for the management of AD but the study that reached this conclusion has been challenged by the industry which has asserted that it was under powered. Results of this study were asserted to " … incompatible with many drug company-sponsored observational studies and advertisements claiming remarkable effects of cholinesterase inhibitors". In addition, previous claims that donepezil can stabilize cognitive deterioration and delay

Glutamatergic Agents

One of the pathological hypotheses suggested to cause AD is neurotoxic mechanisms resulting is excessive amounts of amino acids being released. AD patients have a loss of glutamatergic pyramidal neurons, while the glutamatergic receptors NMDA (Nmethyl-Daspartate) are preserved. An over stimulation of these receptors could lead to neuronal loss which could affect the pathophysiology of Alzheimer disease. A glutamatergic NMDA receptor blocker, called memantine is effective in treating severe

AD. The drug has been approved in Germany since 1970's, but clinical trial data to support its use have been limited. Data from recent clinical trials investigating the safety and clinical efficacy of memantine show that it is effective for moderate to severe AD.

The medication is still being studied and is approved in the United States and several European countries**.**

PSYCHIATRIC MANAGEMENT OF NON COGNITIVE SYMPTOMS

While an important aspect of AD, there a numerous therapies many with issues and challenges in the AD patient.

Non-cognitive symptoms of dementia tend to evolve over time, so regular monitoring allows adaptation of treatment strategies to current individual needs. For example, among the behavioural disturbances common in Alzheimer disease, depression is more common early in the illness, while delusions and hallucinations are more common in the middle and later stages. Behavioural issues to be addressed include major depression and other depressive syndromes, suicidal ideation or behaviour, hallucinations, delusions, agitation, aggressive behaviour, disinhibition, anxiety, apathy, and sleep disturbances.

Behaviour	Agent
Agitation/aggression	Antipsychotics,anticonvulsants, antidepressants, anxiolytics
Anxiety	Antidepressants, anxiolytics, anticonvulsants
Apathy	Antidepressants, stimulants
Disturbed effect/mood	Antidepressants, anticonvulsants
Altered ideation/perception	Antispsychotics
Vegetative features	Antidepressants, anxiolytics, stimulants

Current Pharmaceutical Product "Pipeline" for AD Treatment

Early intervention is important since psychiatric symptoms can respond to treatment more readily than cognitive and functional deficits. Table above shows the behavioural clusters manifested in AD and relevant classes of medications for intervention.

New Medicines in Development for Alzheimer disease

Drug name	Indication	Company	Development Status
ABT-126 acetylcholinesterase inhibitors	Alzheimer disease	Abbott	Phase 2
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LY2886721	Alzheimer disease	Eli Lilly and Company	Phase 1
AZD3480	Alzheimer disease	Targacept Inc.	Phase 2
AVP-923 (dextromethorphan/quinidine)	Alzheimer disease, mild cognitive impairment	Avanir Pharmaceuticals	Phase 2
MABT5102A	Alzheimer disease	Genentech	Phase 2
AZD5213	Alzheimer disease	AstraZeneca	Phase 2
gantenerumab	Alzheimer disease	Hoffmann-La Roche	Phase 3
AAB-003 (PF-05236812)	Alzheimer disease	Pfizer	Phase 1
BMS-241027	Alzheimer disease	Bristol-Myers Squibb	Phase 1
MABT5102A	Alzheimer disease	Genentech	Phase 2
BIIB037	Alzheimer disease prodromal or mild AD	Biogen Idec	Phase 1
GSK2647544	Alzheimer disease,	GlaxoSmithKline	Phase 1

Research into New Therapeutic for AD

There are a lot of clinical trials going on at present, research into possible interventions is moving fast. This section provides some information on some of the areas of ongoing research for AD. The past five years has seen a growth in the number of drugs being developed for AD. Future compounds under research are aimed at delaying progression of the illness.

 Immunotherapy

The exact mechanisms leading to Alzheimer disease (AD) are largely unknown which limits possible sources of target for effective immunization. During the last decade, much efforts have been done from pharma industries on targeting clearance of Aβ from the brain of AD patients via the administration of Aβ antigens (active vaccination) or anti-Aβ antibodies (passive vaccination).

Active immunotherapy

Based on promising results from animal models, the first phase I human clinical trial using active vaccine with multiple doses of Aβ42 in adjuvant (AN1792 and QS-21) was performed on 80 patients with mild to moderate dementia. A significant percentage of patients developed antibodies to Aβ, although at different titers, and no adverse events were reported.

Following the success of this trial, a phase II trial was designed and performed in 2001 with a cohort of 372 patients to evaluate vaccine efficacy. This trial was stopped after the report of serious adverse events from 18/298 patients (6%), who developed meningoencephalitis. Although the trial was stopped prematurely, results from post mortem biopsies of AD patients enrolled in the trial showed promising results. Indeed, there was a marked reduction in Aβ deposition in some patients, as well as significant reduction of plaques deposition in different cortical regions. Residual plaques showed a particular appearance suggesting phagocytosis from microglia. Long term follow-up of immunized patients showed no signs of cognitive improvement or survival although.

Aβ42 immunization titers lasted for years in several immunized patients. They also showed greater reductions in brain volume which has never been explained.

Passive immunotherapy

Passive immunization has also been investigated ultimately, in two major clinical trials. The first two trials were performed in individuals with mild to moderate Alzheimer dementia. In this large phase III trial, patients were administered intravenously a humanized recombinant Aβ monoclonal antibody directed against the N terminus of Aβ (AAB-001 or Bapineuzumab).

The AAB-001 antibody is a humanized version of mouse monoclonal antibody m3D6 directed against the first 8 amino acids at the N-terminus of Aβ that has been shown to be able to decrease amyloid plaques in mouse models of AD.

The clinical results with bapineuzumab were equivocal in terms of cognitive benefit. The occurrence of ARIA-E (amyloid-related imaging abnormalities)-effusion or edema after bapineuzumab, and more rarely ARIA-H (hemosiderin deposits), which may not actually be hemorrhages (especially in ApoE ε4 carriers), has raised concerns on the safety of these antibodies directed against the N-terminus of the Aβ peptide. The North American studies 301 and 302 completed as planned; the two complementary studies in Europe were early terminated in August 2012.

One possible explanation for the ARIA-E or ARIA-H induced by bapineuzumab is that it targets the non-soluble forms of the Aβ protein. Other trials, targeting the midregion of the Aβ -Aβ monoclonal antibody directed against the midregion of the Aβ peptide, was shown to neutralize soluble Aβ species, prone to be toxic. Solanezumab Phase II study showed a good safety profile as well as indications of a possible clearance of the Aβ peptides in brain of AD patients. Antibody administration was well tolerated with doses up to 400 mg weekly.

These promising results gave rise to two Phase III trials on AD patients with solanezumab. This study, led by Eli Lilly & Co.'s recently provided its results. Although it missed its primary outcome, the trials showed some signs of slowing cognitive decline perhaps more evident in milder subjects. Statistics found a 34% less mental decline in mild Alzheimer patients compared to those on a placebo treatment for 18 months according the Eli Lilly & Co.'s analyses. According experts in the field, the results are not as clear as stated by Eli Lilly & Co.'s in particular results on the cognitive endpoints.
Further studies need to be performed. Researchers and medical doctors have suggested that treatment must be given earlier on, at the prodromal stage, or even earlier.

A clinical trial, targeting healthy asymptomatic individuals with a genetic mutation leading to early onset (generally aged less than 50 years) AD dementia is now being launched by Genentech & Co.'s.72 Subjects will be injected with crenezumab, a humanized Aβ monoclonal antibody. The study will involve about 300 participants from Colombia and the United States. The participants come from the same family in Medellin and can be traced. They all share a rare genetic dominant mutation that typically triggers Alzheimer symptoms

around the age of 45. This trial is unique and has great expectations from the scientific and medical communities as it will help determine if the amyloid hypothesis is correct. Results are expected by 2015.118 The generalizability of the results of this particular study for sporadic or late onset cases of Alzheimer disease will have to be investigated further.

CONCLUSION

In 2012, dementia was declared a public health priority by the World Health Organization (WHO). Due to the ageing of the world population the number of patients with Alzheimer disease will rise significantly. If no treatment is available, this will be a major health issue with enormous financial burdens to health care systems.

Thus, there is an urgent need for both early diagnosis with specific markers as well as effective therapies that could be taken at the different stage of the disease. Currently only short term symptomatic treatment is available. While there is research and development already in this area, much work still is required. Additionally, challenges for clinical services include early diagnosis, and intervening early with the most appropriate and effective medicine.

There are several barriers to closing the obvious pharmaceutical "gaps" with regard to AD. Specific recommendations include the following:

The EU and EU-based philanthropic organizations need to recognize and help overcome the various scientific and systemic barriers to improving pharmaceutical R&D for Alzheimer disease and provide funding for making animal models more accessible and affordable. Also new grant agreements should be implemented that compensate investigators and institutions while making the models more widely available. There is a need for improved AD assessment tools, with increased sensitivity and efficiency for patient evaluation for AD primary prevention. More specifically, curtailing time requirements for clinical staff, data monitoring and data entry could decrease costs for trials.

An important research goal should also be the development and evaluation of new instruments in relevant domains that are sensitive, reliable, and valid for detecting changes in normal aging and early AD and before disease onset. Furthermore, it would be helpful if these can be self-administered and not require significant professional involvement. New uses

of technology, such as computerized assessments and telephonic methods are some options and may be desirable in this field.

There needs to be more collaboration and a multidisciplinary approach in the areas of research and development for AD. Grant review should be by government and industry to facilitate bench to bedside Neurobiologists, clinicians, chemists need to work together. Funding resources and guidelines that can assist scientists in preclinical drug development is required.

New funding models should be explored which can support core research facilities and no tenured staff in academic institutions, such as the creation of endowments for facilities and pharmaceutical and biotech consortia. Innovation is needed to encourage diversity of approaches to fight AD.

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