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ALZHEIMER'S DISEASE AT A GLANCE

Resumé

Alzheimer's disease is the most common cause of dementia in older people. It affects the parts of the brain that control thought, memory and language.

Alzheimer's disease depends on both genetic and environmental factors. Two types of Alzheimer's disease exist: familial AD (FAD), which follows a certain inheritance pattern, and sporadic AD, where no obvious inheritance pattern is seen.

At the molecular level, two abnormal structures in the brain are the hallmarks of AD: amyloid plaques and neurofibrillary tangles. Plaques are dense, largely insoluble deposits of protein and cellular material outside and around the brain's neurons. Tangles are insoluble twisted fibers that build up inside neurons.

The growing understanding of the variety of factors involved in AD's development, including oxidative damage and inflammation, have suggested new potentially fruitful avenues for prevention and drug treatment research.

Recent advances in the genetics of Alzheimer's have offered the possibility of widespread DNA testing for diagnosis and prediction of AD, which raises ethical, legal and social questions.

The EU resolution of 11/03/98 on Alzheimer disease, gives a view of the present situation in Community policies.

1 - INTRODUCTION

Recent decades have seen an increase in neurodegenerative diseases, probably as a result of the ageing of society. The EU can expect to have nearly half a million dementia patients every year.

Given the present tendency to live longer, we should be able to age with dignity.

There are different areas where we can work to fight against neurodegenerative diseases. On the one hand we should make a scientific effort to try and elucidate their causes so that we can prevent them and treat them. On the other hand, we have to underline the

great work that is being carried out by associations which provide great support to sufferers and their families. Without them it would be very difficult to face this situation. Last but not least, there must exist an appropriate European health policy concerned with this problem, coordinating and providing financial support to associations and researchers.

Neurodegenerative diseases share several pathogenic mechanisms, and sometimes it is difficult to tell them apart. Research into one disease may aid understanding the others. Here, I will focus on the most common of these diseases: Alzheimer disease.

2 - ALZHEIMER'S DISEASE

In 1906, the German physician Alois Alzheimer first identified, while examining the brain of a woman dead from a rare neurological disease, the abnormal clumps and the tangled bundles of fibers that are now considered as determinants of Alzheimer's disease.

Since then, the incidence of the disease has increased, making Alzheimer's the fourth leading cause of death in adults. The incidence of the disease rises steeply with age and is twice as common in women than in men. Although the risk of developing Alzheimer's Disease (AD) increases with age, AD and dementia symptoms are not a part of normal aging; the human brain often can function well into the tenth decade of life.

As we all know, Alzheimer's victims suffer from a progressive inability to remember facts and events, and even to recognize members of their own family.

Alzheimer's is a complex disease that is likely caused by a variety of influences. Scientists have identified several genetic and environmental factors that may increase the likelihood of developing the disease.

3 - CHARACTERISTICS OF THE DISEASE

3.1 Memory loss

Loss of memory in daily life leads to communication and behavioural problems. It is useful to consider the

different kinds of memory so as to understand how memory is affected by dementia:

- *Episodic memory*: This is the memory people have of events in their life ranging from the most mundane to the most personally significant. Within episodic memory, there are memories classed as short term (having happened in the last hour) and those classed as long term (having occurred more than one hour ago). People with Alzheimer's disease, at the beginning of the illness, do not seem to have any difficulty remembering distant events but may, for example, forget having done something five minutes ago. Memories of distant events, although not greatly affected tend to interfere with present activities. This can sometimes result in the person acting out routines from the past which are no longer relevant.
- *Semantic memory*: This category covers the memory of what words mean. It is the shared understanding of what a word means which enables people to having meaningful conversations. As episodic and semantic memory are not located in the same place in the brain, one may be affected and the other not.
- *Procedural memory*: This is the memory of how to carry out actions both physically and mentally. The loss of procedural memory can result in difficulties in carrying out routine activities such as dressing, washing and cooking.

3.2 Apraxia/Aphasia/Agnosia

- *Apraxia*: This term describes the inability to carry out voluntary and purposeful movements despite the fact that muscular power, sensitivity and coordination are intact.
- *Aphasia*: This term is used to describe the difficulty to speak or understand spoken, written or sign language as a result of a damage to the corresponding nervous centre. It might involve substituting a word for another which is linked by meaning, using one word for another which sounds similar or using a completely different word with no apparent link.
- *Agnosia*: It describes the loss of the ability to recognize what objects are and what they are used for. For example, a person with agnosia might attempt to use a fork instead of a spoon or a shoe instead of a cup. With regard to people this might involve failing to recognize who people are.

3.3 Communication

People with Alzheimer's have difficulties both in the production and comprehension of language.

3.4 Personality change

People with Alzheimer's disease might behave totally out of character, in an aggressive, ill-mannered or moody way.

3.5 Behaviour

A common symptom of Alzheimer's disease is wandering, both during the day and at night. Disorientation in time and space may also occur.

3.6 Physical changes

Weight loss can occur even when the normal intake of food is maintained. Another consequence of Alzheimer's disease is the wasting away of muscles and once bed-ridden there is the problem of bed sores. As people age their vulnerability to infection increases and many people with Alzheimer's disease die from pneumonia.

4 - MOLECULAR BASIS AND GENETICS

4.1 FAD and sporadic AD

Two forms of the disease can be distinguished: *familial early onset autosomal dominant Alzheimer disease (FAD)*, which affects only 1% of people sufferers and *sporadic Alzheimer's disease*, which accounts for the rest of the cases. Nevertheless, both forms of the disease present the same neuropathological features: the amyloid plaques and the neurofibrillary tangles in the brain.

FAD is due to mutations in three genes: amyloid protein precursor (APP), presenilin 1 (PS-1), and presenilin 2 (PS-2). The pattern of inheritance of this form of the disease is autosomal dominant, which means that the offspring have a 50/50 chance of developing AD if one of their parents suffers the disease.

Another difference between FAD and the sporadic form of the disease is that the former presents usually below the age of 60.

Sporadic AD seem to be associated with the carrying of the allele 4 of the ApoE gene which codes for a lipoprotein that helps transport cholesterol in the blood.

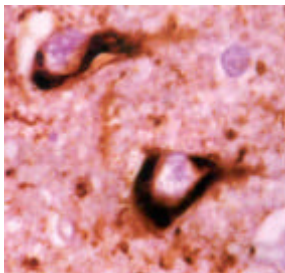
Genes associated with Alzheimer's	
Gene	Chromosome
APP	21
PS-1	14
PS-2	1
ApoE4	19
Tau	17

4.2 The ApoE gene

The ApoE gene can present in different variants (polymorphisms) in the population, called alleles. The carrying of the ApoE4 allele has been associated with the sporadic form of Alzheimer's disease, however it is not necessary nor enough to cause the disease. The ApoE gene creates a protein charged with transporting cholesterol in the blood. In a study published in March 2001 in *Neurology* the carrying of the ApoE4 allele has been reported to contribute to weight loss in women with AD. Genetic tests are available to identify the ApoE alleles a person has, because this apolipoprotein is also associated with heart disease. ApoE testing raises ethical, legal and social questions, and it should be protected by confidentiality laws.

4.3 The Tau protein

Tau, a microtubule-associated protein, facilitates the assembly and binding of microtubules in the cell. By supporting cytoskeletal structure and sustaining axonal transport, Tau plays a fundamental role in the maintenance of neuronal survival. Abnormally phosphorylated Tau is a key component of the neurofibrillar tangle, one of the characteristic lesions in Alzheimer's disease.



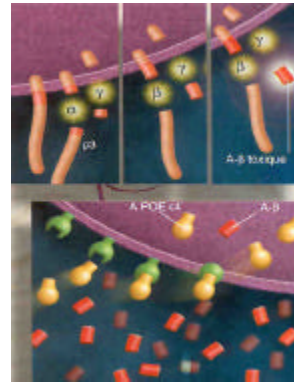
In recent years Alzheimer's research has focused in A β plaques, alleging that neurofibrillary tangles were a secondary lesion derived from this first. However, interest has shifted back towards Tau

with the finding that mutations in the Tau gene, located on chromosome 17, are associated with a variety of hereditary dementias other than Alzheimer's (Clark *et al*, 1998). These disorders are collectively called "frontotemporal dementia and parkinsonism linked to chromosome 17" (FTDP-17) and differ from Alzheimer's in the area of the brain that is affected and in the absence of A β plaques in these diseases. These studies support the idea that Tau in itself can be an important contributor to neurodegeneration. Determining exactly what relationship exists between plaques and tangles is a major goal of AD research.

4.4 The senile plaques

Senile plaques are mainly constituted of a peptide called β -amyloid, which is the result of the cleavage of a precursor protein, APP.

The latter can be processed in two different ways, one of which leading to the production of amyloid protein.



The enzyme responsible for this process is called gamma-secretase. However, amyloid protein is not toxic until it acquires the β -sheet conformation. Another component of senile plaques is the apolipoprotein already mentioned.

Apolipoprotein can work as a chaperone protein, commanding the form of other proteins. It could then participate in A β peptide metabolism.

Presenilins are also involved in this metabolism, although their precise role is not yet clarified. Investigators at Harvard Medical School and the Brigham and Women's Hospital in Boston altered the normal presenilin 1 aminoacid sequence in two critical locations and found that beta-amyloid formation was reduced. This evidence suggest that presenilin 1 is either gamma-secretase itself or a unique cofactor required for gamma-secretase activity. (Wolfe *et al*, 1999)

5 - ENVIRONMENTAL FACTORS

As we have already said, Genetics alone can not easily explain the events emerging in Alzheimer's disease.

Several environmental factors have been explored: aluminium, solvents, electromagnetic fields... but none of them seems to present a serious risk.

On the other hand, there is evidence to suggest that a person who has received a severe blow to the head may be at risk of developing Alzheimer's disease.

Race, profession, geographical and socio-economic situation are not determinants of the disease. However, there is mounting evidence to suggest that people with a higher level of education are at less risk than those with a lower level of education.

Infectious agents like prions have also been evoked, as there are some forms of Alzheimer disease that present A β deposits similar to those of prion's proteine.

6 - PREVENTION AND TREATMENT

Once we have understood the molecular basis of the disease we will have more chances to prevent and cure it, although this is not a straightforward matter. Many questions remain to be answered and there is still a lot of work to do to clarify the course of events. Not only treatment of Alzheimer's disease, but also prevention should be considered as a better solution, especially

where sufferers are elderly and treatment is more difficult.

6.1 Estrogen

Research from several medical centers suggest that women who use *estrogen replacement therapy (ERT)* to ease the symptoms of menopause, may also have some protection against the development of the disease.

Estrogen has both antioxidant and anti-inflammatory effects and enhances the growth of select neurons that release acetylcholine.

A report of a long-term study from the National Institute on Ageing (NIA), associated ERT in postmenopausal women with a 50% reduction in the risk of developing Alzheimer's disease. On the other hand, other results published in the *Journal of American Medical Affairs (JAMA)* in February 2000, indicate that ERT has no significant effect on the course of the disease. In the words of Glenn Smith, "while estrogen may reduce the risk of developing Alzheimer's, it is not an effective therapy for the disease." ETR is limited to women because of its potential feminizing effects in men.

6.2 DHEA, Pregnenolone and Melatonin

DHEA is a steroid hormone produced by the suprarenal glands. It is a precursor for the production of the sexual hormones testosterone and estrogens and its generation decreases with stress and age. It was commercialized and announced in the media as the new "fountain of youth" as a result of its effects in improving energy levels, endurance to stress and activating the immune system.

Pregnenolone is naturally synthesized from cholesterol. A part of it gives birth to DHEA and another part is used to produce progesterone, cortisol and aldosterone. So it is in a sense DHEA's mother and testosterone and estrogens' grandmother. Pregnenolone's levels are very high in the brain, and this hormone is said to have the strongest effects in improving memory.

Finally, melatonin is another hormone synthesized by the pineal gland. It is produced during the night in response to darkness and its main function is to regulate our biological clock; it improves sleep, stimulates the immune system and protects the central nervous system. Melatonin has been proved to be a very strong antioxidant.

All three hormones share the characteristics that their production dramatically decreases with age, and they have beneficial effects in protecting neurons. Therefore, their synthetic forms have been used, with good results, to treat Alzheimer's disease.

6.3 Cholinesterase inhibitors

Another approach to the treatment of Alzheimer's disease has been the use of cholinesterase inhibitors. Cholinesterase is an enzyme that cleaves choline neurotransmitters in order to stop the synaptic signal. Drugs like tacrine, donepezil, metrifonate, rivastigmine and galantamine (*Grutzendler, J.; Morris, J.C., 2001*) block this enzyme, increasing the availability of acetylcholine in central synapses, and having significant effects on the cognitive status of patients and a positive effect on mood and behaviour.

6.4 Mental fitness

Studies show that maintaining mental fitness may delay the onset of dementia.

One of these studies focused on a large order of nuns who seemed to exhibit low rates of Alzheimer's in spite of their average age of 85. Many of the nuns had advanced academic degrees and led an intellectually challenging life into old age. Some researchers believe that lifelong mental exercise and learning may promote additional synapses and delay the onset of dementia.

The same conclusion has been reached in a study with Swedish twins reported at *the World Alzheimer Congress 2000*.

6.5 Vitamin E

Free radicals are oxygen molecules with missing electrons created during the course of normal metabolism. In the search for their missing electron, free radicals oxidate other cell components such as fat, protein or DNA, which damages the healthy cells, including brain neurons.

To combat the effect of free radicals, the body uses antioxidants, one of which is vitamin E. We can find this vitamin in vegetable oils, eggs, fish, green leafy vegetables and dried beans.

Vitamin E is needed for the production of normal red blood cells and the stimulation of the immune system. It has also been shown to protect against cardiovascular disease by directly attaching to LDL (low-density lipoprotein) in charge of transporting cholesterol in the blood.

A surplus of free radicals may contribute to some illnesses, including Alzheimer's. According to a study published in the *New England Journal of Medicine (April, 1997)*, people with moderate Alzheimer's disease who were given high doses of vitamin E experienced a temporary slowing of the progression of the disease, perhaps by detoxifying free radicals. However, even if these patients showed an improvement in their ability to engage in the activities of daily living, there was no effect in their cognitive

functioning, which includes memory, attention, language and comprehension. Waiting for more research to be done in this field, it is still too early to recommend vitamin E supplements in the general population for preventing Alzheimer's disease.

6.6 Low levels of B vitamin linked to Alzheimer's

Folic acid plays an important role in the development of the central nervous system and in maintaining its integrity throughout life. One of the folate functions, along with the vitamins B6 and B12, is to convert homocysteine to the more useful aminoacid methionine. Low blood levels of B-12 and folate can lead to elevations of in the aminoacid homocysteine, which may in turn damage nerve cells.

Most people get enough vitamin B-12 in their diets, but some, including the elderly, stand a greater chance of being deficient.. The vitamin is found in meat, fish, eggs and milk. Folate occurs in leafy green vegetables, dried beans and peas and citrus fruits.

In a study carried out by Swedish researchers at the Karolinska Institute in Stockholm, investigators found that men and women aged 70 or older who had low levels of either vitamin were twice as likely as those with normal levels to develop Alzheimer's disease over a 3-year period.

6.7 Dietary restriction

Alzheimer's disease is characterized by increased levels of oxidative stress, perturbed energy metabolism and accumulation of insoluble (oxidatively modified) proteins, among which are A β and Tau.

An overwhelming body of data from studies of rodents and monkeys has documented the profound beneficial effects of dietary restriction in reducing the incidence of age-related diseases. Recent findings suggest that dietary restriction may enhance resistance of neurons in the brain to metabolic, excitotoxic and oxidative insults relevant to the pathogenesis of Alzheimer's disease and other neurodegenerative disorders. While waiting for the results of further studies, it would seem prudent to recommend dietary restriction as a preventive approach for neurodegenerative disorders.

6.8 Inhibitors of Apoptosis

When human beings commit suicide, it's almost always a tragedy. But within the organism, cellular suicide or apoptosis is vital to life. It occurs during development and removes damaged cells in the adult in a neat, orderly way. However, an excess in apoptosis can contribute to some degenerative diseases such as Alzheimer's.

Age-related increases of cellular oxidative stress, and impairment of energy metabolism, results in disruption of neuronal calcium homeostasis and an increased vulnerability of neurons to excitotoxicity and apoptosis. Inherited forms of Alzheimer's disease which result from mutations in APP and presenilins, accelerate the neurodegenerative cascade by increasing the production and deposition of neurotoxic forms of amyloid beta-peptide and by perturbing calcium homeostasis.

Researchers have found that the brains of Alzheimer patients contain dying neurons that display characteristic signs of apoptosis, such as DNA breaks. It was in 1993 when, for the first time, two teams of researchers in University of California and the Institute of Pharmacological Research in Milan showed that A β , which builds up in the brains of people with Alzheimer's, causes cultured neurons to die from apoptosis.

Because of the lack of good animal models of the disease, no one has been able to test whether inhibitors of apoptosis can protect against cell death in Alzheimer's as they can in animal models of stroke. But until uncertainties about interference in neuronal apoptosis are clarified, researchers continue to be interested in potential therapeutic application of these findings.

6.9 Vaccination

In a study published in 1999, a team of researchers announced that they had tested a vaccine, known as AN-1792, on groups of mice genetically programmed to develop amyloid plaques in their brains. The vaccine prevented the formation of plaques in these mice when injected at an early stage, and it seemed to reduce the number of plaques in the brains of older mice.

Most probably, AN-1792, triggers an immune response that creates anti-amyloid- β antibodies, which bind to the plaques, and stimulates microglial cells that start to remove them. But a lot of questions remain to be answered: *"even if we can prevent plaques from forming or get rid of old plaques in human brains"*, says Dr. Knopman, *"will the person affected with Alzheimer still become or remain forgetful?"*

Research in mice has shown that memory deficits improve after repeated vaccinations; nevertheless, the brains and immune systems of mice are very different from those in humans. AN-1792 is still in the first phase of clinical trials in the latest. Studies have only examined the safety of the vaccine, but it is not known whether it will prove effective in treating plaques and memory loss.

6.10 Stem cell therapy

In the very early stages of embryonic development, cells have the capability of dividing indefinitely and then differentiating into any type of cell in the body. Recent studies have revealed that much of this remarkable development potential of embryonic stem cells is retained by small populations of cells within most tissues in the adult. Intracellular signals that control the proliferation, differentiation and survival of stem cells include a variety of growth factors, cytokines and cell adhesion molecules that are being identified. The possibility that a decline in the numbers or plasticity of stem cell populations contributes to ageing and age-related disease is suggested by recent findings (*Rao, MS; Mattson, MP; 2001*). The remarkable plasticity of stem cells would allow the "tweaking" of endogenous or transplanted stem cells in such a way that they can replace damage or lost brain cells in an array of neurological disorders.

6.11 Telomerase activation

Telomers are specialized structures that limit the end of chromosomes and tend to shorten with age. Telomerase is an enzyme that specifically completes the ends of telomeres by the means of the reverse transcriptase activity of its catalytic subunit, TERT. Telomerase is expressed in neurons throughout the brain in development, but it is absent from neurons in the adult brain. TERT exhibits neuroprotective properties in experimental models of neurodegenerative disorders (*Mattson, MP., 2000*) suggesting that manipulations that induce telomerase in neurons may protect against age-related neurodegeneration.

7 - GENETIC TESTS FOR ALZHEIMER'S DISEASE

The use of genetic information raises important public, social and moral issues.

Scientists, ethicists and other health professionals joined together in October 1995 to write a public policy statement about the appropriateness of ApoE testing and the role of genetic counseling for AD. Discussions leading to the statement took place at a conference in Chicago, sponsored by the National Institute on Ageing (NIA) and the Alzheimer's association.

The public policy statement supports the use of ApoE testing for diagnostic purposes only in conjunction with other tests during medical evaluations of patients who show AD symptoms. Because AD develops in the absence of ApoE4 and because many with ApoE4 seem to escape the disease, it doesn't recommend using ApoE testing as a predictive method.

In situations in which predictive testing using ApoE might be valid, it will be critical to assess the impact of this knowledge on healthy individuals and their relatives, given that there is no effective way to prevent or cure the disease.

Safeguards should be established to ensure informed consent and to ensure that individuals at higher risk will not be subjected to discrimination by employers or insurance companies.

Coordinated basic and clinical research studies are essential prior to introduction of ApoE testing into clinical practice. Perhaps a greater utility for ApoE testing will emerge in evaluating therapeutic options for an individual patient.

8 - EU AND ALZHEIMER'S

Alzheimer's disease has been a subject of debate in the EP in the past and continues to count among the priorities in Biomedical Research.

8.1 Resolution of 11/03/98 on Alzheimer's disease

"The European Parliament,

- having regard to its resolution of 17 April 1996 on Alzheimer's disease and the prevention of disorders of the cognitive functions in the elderly⁽¹⁾,
- having regard to the amendment of Article 129 of the EC Treaty on public health, introduced by the Treaty of Amsterdam, which, while failing to strengthen the Union's powers in this field as had been hoped for, nevertheless stipulates that a high level of human health protection must be ensured in the definition and implementation of all Community policies and activities,
- having regard to the Commission proposal concerning the Fifth Framework Programme for research and technological development activities (1998-2002) which has included, under the priority issue of the quality of life and management of living resources, a key action relating to population ageing, with the overall goal of promoting healthy ageing and independence in old age, referring specifically to Alzheimer's disease,
- A. whereas the gradual ageing of the population of the European Union and the increase in lifespan are leading to a rise in the incidence of diseases linked to age, including Alzheimer's disease and related syndromes,
- B. whereas some five million families in all the Member States are afflicted with indescribable and ongoing emotional, psychological and financial difficulties,

C. whereas the large number of projects submitted to the Commission each year by associations representing the patients and their families in Europe, in the context of the promotion of actions to combat Alzheimer's disease, demonstrates that this scourge has become a genuine socio-economic problem in all the Member States,

1. Deplores the fact that neither the Commission nor the Member States have yet responded adequately to its requests to step up efforts to combat this fast-growing disease;

2. Regrets in particular that the Commission has still not launched an action programme to combat Alzheimer's disease and other neurodegenerative disorders which would both provide an impetus for European research and coordinate measures taken in the Member States;

3. Urges the Commission again to submit, as part of the future communication on public health, a specific programme of action against Alzheimer's disease and related syndromes, as called for in its aforementioned resolution of 17 April 1996;

4. Emphasizes, considering the ageing of the population and the ensuing increase in the number of Alzheimer patients, the importance of research in this area, and highlights in this connection the key action in the Fifth Framework Programme for Research & Technological Development;

5. Reminds the Commission that provision has been made for Community financial support to implement action programmes in respect of other diseases, such as those related to pollution, rare diseases and diseases caused by injuries, and therefore calls for similar criteria to be adopted in respect of Alzheimer's disease;

6. Calls for the Commission to conduct a survey on the social and financial consequences of Alzheimer's disease in the European Union and to notify the European Parliament of its findings at the same time as it submits the aforementioned action programme;

7. Instructs its President to forward this resolution to the Commission, the Council and the governments of the Member States."

9 - CONCLUSION

It is reasonable to think that Alzheimer disease results from the contribution of multiple factors which modulate the apparition of senile plaques and neurofibrillary tangles and lead, after decades of evolution, to neuronal death and brain desorganisation. Instead of trying to reduce to an unique disease a so huge affection, we should best consider Alzheimer disease as a syndrome with several origines, which depends sometimes more on genetic factors and others on environmental aspects.

We are slowly succeeding in resolving the puzzle but we still have to wait for a really efficient treatment.

Although animal models are being very useful in understanding the disease they are limited; no mouse lives for decades in a such complex genetic context as human's, nor in a comparable environment.

Now that we have decoded human's genome, research will focus on patient's brains, which express the pathological proteins.

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