New approaches to treat Alzheimer Disease

A few months ago, a promising study about Alzheimer Disease (AD), a type of dementia, was published in JACC (Journal of the American College of Cardiology). Dementia affects around 50 million people worldwide and around 60-70% of them suffer AD. It is estimated that in 2050 there will be more than 115 million people diagnosed *(WHO, 2019).*

Dementia is a disease that damages cognitive capacity interfering in daily activities. AD is a progressive dementia that worsens through time and lasts around 10-12 years, when the patient dies due to infections or other organic failure. This decline on cognitive function can start at early ages, around 50-60 years, or later, although it is not yet established the cause that triggers the disease because it is a multifactorial neurodegenerative disease. Around 10% of cases it is a hereditary transmission due to mutations in specific chromosomes which would ease the deposition of amyloid burden and, thus, cause neurotoxicity. Furthermore, there are other risk factors to consider, such as high blood pressure for a long period of time, brain injury, high homocysteine levels (molecule that might be involved in chronic diseases such as cardiopathy, depression and possibly AD), medical history of dementia or Down syndrome and low vitamin B12. It is also important to have an active brain training during life to avoid this kind of diseases.

AD is characterised by B-amyloid accumulation which is established in senile plaques and begins some events that contribute to cellular death, lipid oxidation, cellular membrane disruption which leads to an inflammatory response, causing neuroinflammation and cerebral atrophy due to neuron loss. Neurofibrillary tangles, which are aggregates of tau protein, also contribute to these processes and, eventually, to cognitive impairment.

This kind of dementia is also characterised by diminish synaptic density, neuron loss and neuronal degeneration in hippocampus. Neuron loss can lead to a lack of neurotransmitters that will cause the main symptomatology of AD. It is also included a blood-brain barrier disruption, allowing plasmatic protein loss and provoking cerebral blood flow changes and an increase in thrombin and platelet activation, enhancing fibrine clot formation. Hence, there is a vascular involvement in AD, as once described Alois Alzheimer, who identified for the first time the disease symptoms in 1906.

On the first stage, there is a minor symptomatology, the patient has full autonomy and only complex tasks can be a handicap. As the disease progresses, the patient requires more attention until he is completely dependent on an assistant. It affects memory, language comprehension and execution, performance of intentional movements and spatial perception.

No cure has been found to treat this disease. However, the aim in therapeutics is to lessen the progress, control behaviour issues and support family members and assistants. Some vitamins have been related with cognitive function maintenance, including vitamin B12, B6, E and folic acid, in early phases. Moreover, antioxidants or phytomedicines such as *Ginkgo biloba*, might contribute on improving the symptoms, although they are not enough as an individual therapy. It is also available a kind of drugs, acetylcholinesterase inhibitors, that help keeping a neurotransmitter (acetylcholine) that

lacks in this disease, improving behaviour, apathy, functional capacity, deliria and memory. These are donepezil, rivastigmine and galantamine, which have some common adverse effects: gastrointestinal discomfort, loss of hunger and cardiac rhythm disorders. There is also other drug used in moderate-severe cases called memantine, which is an uncompetitive NMDA-receptor antagonist and avoids neuronal overstimulation caused by glutamate and, this way, avoids neurotoxicity as well. However, these drugs might lessen the symptoms during a relative short period of time but not stop AD's progression

As there is no effective treatment to cure or at least delay AD's progression scientists decided to take a turn and try to avoid senile plaques and clots by improving blood circulation. Therefore, coagulation was the target of the experiment carried out by CNIC (*Centro Nacional de Investigaciones Cardiovasculares Carlos III),* as they considered that, by improving blood circulation through the brain and avoiding clot formation by anticoagulant use, the disease would be less aggressive. Nevertheless, there are some limitations in anticoagulant use, which are constant monitorization and bleeding risk and this is the reason why the tested drug was dabigatran, due to the lower haemorrhagic frequency.

Dabigatran, the drug used in this experiment, is a direct prothrombin inhibitor used in stroke prevention in patients with a particular arrythmia with one or more risk factors (previous stroke or ischemic transitory accident, diabetes mellitus, older than 75 years, cardiac insufficiency, arterial hypertension) and venous thromboembolism prevention in post-surgical patients. Seldom are there interactions between dabigatran and other drugs, which is an advantage regarding other anticoagulants, and, in the same way, there is lower intracranial bleeding risk. There is an antidote called idarucizumab in case of life-threatening haemorrhages. Several precautions must be considered, since there is a haemorrhagic risk. It is not recommended in patients who have hypersensitivity, kidney failure, hepatic illness, active haemorrhages (ulcers, recent intracranial bleeding, oesophageal varices or vascular aneurysm), concomitant anticoagulant treatment or other drugs that can interact. In any case, this is one of the anticoagulants with less risk of bleeding.

The experiment was designed with transgenic mice who suffered AD and non-transgenic, who did not suffer the disease. Each type of mice was divided in two groups so that one of each would be fed with dabigatran etexilate, which metabolises to dabigatran inside the body, and the other with placebo. When mice were 8 weeks old, before β-amyloid deposition, blood samples were analysed in all groups. The diluted thrombin time showed a delayed clot formation in treated mice plasm, and it was slightly higher in the ones that did not have de disease. During the treatment, cerebral blood flow was checked, and spatial memory was tested, the first one by magnetic resonance imaging and the other one by using Barnes maze. There was a significative reduction on the time mice spent to find the exit in the group with AD who was fed with dabigatran. Mice who was fed with placebo didn't remember where the exit was. Therefore, this drug is beneficial in memory retention. Additionally, a lower blood perfusion in the brain was detected in non-treated mice, 15% less than the healthy ones. This was prevented in mice treated with dabigatran, so it also maintains a better cerebral blood flow.

Mice were sacrificed at week 30 and 60, when brain tissue was examined with different tests. Insoluble fibrine was quantified in cortex and hippocampus in both cases and differences were sought between the treated and non-treated group. Fibrine deposition

increased as the mouse grew old and AD progressed. After a long-term treatment with dabigatran there was not as many fibrine in the brain as in the placebo group's brain. The amyloid plaques grew between week 30 and 60, but in the treated group it grew about 24% less compared to placebo group. Moreover, the most toxic oligomeric β-amylase, diminished about 50% if they were treated with dabigatran. Likewise, anticoagulation reduced neuroinflammatory activity around 30% in 60-week mice, since decreased lymphocyte T recruitment inside the brain. AD also has an abnormal hypertrophic effect in cells around capillary which is neutralised by dabigatran so that blood-brain barrier can keep its integrity and avoiding fibrin extravasation. Additionally, dabigatran prevents aquaporin distribution, which participates in B-amylase uptake, elimination and active transport.

Summarizing, β-amylase strongly interacts with fibrin and fibrinogen (responsible for coagulation) and induces clot formation resistant to degradation. Long-term anticoagulant decreases amyloid plaques and B-amylase oligomer levels avoiding clots. Dabigatran effect was stronger in a long-term intake since AD is chronic and fibrin accumulation increases with time. Not only did dabigatran allow better B-amylase elimination through blood-brain barrier, than it also diminished deposition in cortical vessels that cause cerebral angiopathy and improved blood flow. Thus, memory and cognitive function improved and neuroinflammation decreased. Concluding, dabigatran can delay AD symptoms if it is early treated.

Despite all those beneficial effects, some limitations should be considered. For instance, there is a greater incidence of intracellular haemorrhage in AD patients and amyloid cerebral angiopathy. This vasculopathies are related with worse cognitive activity and the use of this antithrombotic agent has been discussed among this group of people. Nevertheless, dabigatran has a low bleeding risk and it did not cause any haemorrhage during the study and it also has an antidote in case of serious bleeding. However, more trials are required to extrapolate long-term therapy in humans, but this drug is already on sale, so transition might be faster. It also would be interesting to study whether it would be useful in an already established disease. Furthermore, as AD is a multifactorial disease, there should be a combined therapy according to each individual.

Elisenda Tejedor Estrada,

Badalona, 16th November 2019

References

CIMA*: Centro de Información online de Medicamentos de la AEMPS*. Madrid: CIMA; 9/2019 [Mencioned in 11/2019]. *Ficha técnica pradaxa 110mg cápsulas duras.* Available in: https://cima.aemps.es/cima/dochtml/ft/08442005/FT_08442005.html

Cortes-canteli, M., Kruyer, A., Fernandez-Nueda, I., Marcos-Diaz, A., Ceron, C., Richards, A.T., Jno-Charles, O. C., Rodriguez, I., Callejas, S., Norris, E.H., Sanchez-Gonzalez, J., Ruiz-Cabello, J., Ibañez, B., Strickland, S., Fuster, V. *"Long-Term Dabigatran Treatment Delays Alzheimer's Disease Pathogenesis in the TgCRND8 Mouse Model".* JACC: Journal of the American College of Cardiology (2019), vol. 74 (15), pàgs. 1910-1923

Cummings, J.L., Cole, G. *"Alzheimer Disease".* American Medical Association (2002), vol. 287 (18), pàgs 2335-2338

Fidel-Romano, M., Nissen, M.D., Del Huerto-Paredes, N. M., Parquet, C.A., *"Enfermedad de Alzheimer". Revista de Posgrado de la Cátedra de Medicina* (2007), vol. 75, pàgs. 9-12

Reisberg, B., Doody, R., Stöffler, A., Schmitt, F., Ferris, S., Möbius, H.J. *"Memantine in Moderate to Severe Alzheimer's Disease".* The New English Journal of Medicine (2003), vol. 348, pàgs. 1333-1341

WHO: World Health Organization. Geneva: WHO; 9/2019 [Mentioned in 11/2019]. *Dementia*. Available in: https://www.who.int/es/news-room/fact-sheets/detail/dementia