Juan Domingo Gisbert: "Combining CNIC and BBRC data will allow us to answer questions of great relevance for the prevention of Alzheimer's in healthy subjects"

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- ***Can Alzheimer's disease be prevented??***

Right now, the answer is "partially", and we hope that, in the future, the answer will be an emphatic "yes".

But this answer has two caveats. Although most people don't know it, up to a third of Alzheimer's cases can be prevented by adopting healthy lifestyles, which are basically the same as the ones recommended for cardiovascular health: taking care of your heart, doing exercise, etc. In the case of Alzheimer's, we know that it is also important to participate in activities that stimulate the brain and avoid depression: working, listening to music, playing an instrument, speaking to the neighbours, playing chess... Anything that stimulates the brain's sensorial or cognitive activity.

The people most genetically at risk are also the ones who benefit most from this type of preventive action. For instance, it has been shown that for carriers of the **APOE4 gene**, who have a very high risk for Alzheimer's and present very early signs of the disease such as higher concentrations of the protein beta-amyloid in the brain, taking up this type of activity reduces their risk to a level that is practically the same as that of subjects who do not have the risk factor.

- ***What is the relationship between depression and Alzheimer's disease?***

We know that there is a very close relationship between depression and Alzheimer's, to the extent that there is some speculation as to whether depression may even be an initial symptom of the disease. It is also possible that, if a person perceives that their intellectual capacity is diminishing, this could facilitate, or make them more vulnerable to, a state of depression.

In addition, there is the fact that people with depression tend to socially isolate themselves, and this reduces sensorial stimulation in the brain, which is counterproductive.

- ***Does genetic screening currently exist that can tell us which people have higher or lower risk of developing this disease?***

In the case of genetically determined, autosomal dominant Alzheimer's, there are well identified mutations that are the cause of the disease. In these cases, screening is indicated for people whose father or mother is known to have had the variant associated with the disease and wants to know if they will have it or not. This is done through genetic counselling programmes. But these cases are a very small fraction of Alzheimer's, less than 1%. And the families are clearly identified.

But most cases are what is known as sporadic Alzheimer's. In these cases, there are genetic risk factors, but that doesn't mean that someone with this risk factor will eventually develop the disease, or that someone who does not have it will not develop the disease.

- ***So, can we prevent the disease or not??***

This is what can be done now; but the world of Alzheimer's is rapidly changing. We now have biomarkers that allow us to detect the most frequent abnormalities that occur in the disease decades before symptoms appear. And those biomarkers are now easy to obtain with a simple blood test. So, we are starting to find biomarkers in blood that will allow us to identify which people have begun a

pathological process, even though they are completely healthy.

Once we have detected the people who are at a higher risk of having experienced onset of the disease, what we need is a way of changing its course. **In June, the United States approved a drug, aducanumab, that eliminates amyloid plaque from the brain, and it seems that this could have a beneficial effect on the cognition of patients who have incipient Alzheimer's disease**.

At the present time, clinical trials exist that are attempting to prevent the disease. This does not mean the type of drugs that eliminate amyloid protein in patients who have a diagnosis and established disease, people who have symptoms and therefore already present accumulated neurodegeneration. The idea is that they are investigating healthy people who show evidence of having amyloid in the brain, but whose cognition is intact. The objective is to preserve cognitive activity. These trials are already ongoing and that's why I believe that, in the not-too-distant future, we will be able to prevent this disease.

This drug's approval in the USA was extremely controversial. As a scientist, what is your view??

It is true that the evidence the pharmaceutical company provided to the FDA (Food and Drug Administration) on the clinical benefits of the drug is irregular and incomplete. It was based on a trial that the company halted after an intermediate analysis, which later, when the data was reviewed and to everyone's surprise, showed that in one of the two trials that had been conducted in parallel, the drug seemed to work and be effective in reducing the cognitive loss preestablished for the trial. So, the data from one trial were positive, whereas the data from the other were not.But for the later study, they performed an unplanned, retrospective analysis of only the subjects who had really completed the regimen, and they observed that among those people the positive effect on cognition was confirmed.

In my opinion, the FDA took a brave decision and, I believe, the correct one

This was what encouraged the company to present its data to the FDA. However, the US health authorities found themselves in a very difficult position because the evidence that this drug works did not meet the standards for approval.

During the approval process, the independent scientific panel unanimously voted against. But the FDA used its accelerated approval pathway, which establishes that a drug can receive temporary approval if there is a plausible effect on a surrogate marker that is predictive of the clinical effect. What this means is that the FDA has no doubt that the drug eliminates amyloid plaque from the brain. It also means that although the data of the clinical trials does not allow approval of the drug for its clinical effectiveness, it does allow us to think that elimination of amyloid plaque from the brain may have a beneficial effect on cognition.

Which is to say that the trial allowed us to confirm that amyloid plaque is eliminated from the brain. And this surrogate marker of the clinical effect is what the FDA used for their approval.

In my opinion, the FDA took a brave decision and, I believe, the correct one. I also think that it should be made quite clear that this drug does not cure Alzheimer's and that it has a limited clinical effect. **The trials are clearly not conclusive, and we need further information to see whether this drug, this type of drug, really has an impact on cognitive capacity**. But in this case, it is highly unlikely that another phase III clinical trial would have been undertaken.

So, now it is possible to begin administering this drug to patients and by doing so, obtain additional information about the clinical effects of the medication, and on management of adverse reactions.

And then there is another question that the clinical trials did not address. It has been shown that after 18 months, this drug reduces amyloid plaque in the brain to the levels of a young person. The question is whether administration of the drug should continue once these levels have been reached.

This type of question is what the phase IV trials agreed by the FDA and the company must answer.

Likewise, there should be some kind of criticism of scientists, because sometimes it is easier to limit ourselves to criteria of scientific rigour, to state that something has not been absolutely proven, and to forget that there are people in the world who are suffering and need this type of drug. Ultimately, patients want something that is useful, and they are willing to accept the risk. Patients already know the bleak outlook of this disease and so, as I mentioned before, I think that the FDA made the right decision and has been brave.

- ***There are other drugs undergoing clinical trials that follow similar lines of investigation, and also medicines aimed at other targets. In the future, will therapies to prevent or treat Alzheimer's be a combination of medications, as also happens for othe?***

Nowadays, as well as **aducanumab**, there are another two drugs which control the production of amyloid and are the subjects of trials that end in 2023 and 2024. There is also another study on prevention among healthy people, which is scheduled to end in 2027. These are the next milestones for elimination of amyloid protein.

But apart from those studies, we already have several clinical trials that have completed phase II, with results in combatting Tau, another protein characteristic of Alzheimer's. And the first results suggest positive effects on cognition. There are also studies aimed at modulating the inflammatory effect on the brain, among other mechanisms. There is more than one route to attack this disease.

- ***We are living in times of biomarkers and imaging for all diseases, including Alzheimer's. In this case, what is the contribution of innovative imaging techniques?***

Drugs target Alzheimer's disease, tau and amyloid, so we have to identify which patients or healthy individuals have abnormalities in these two proteins. Until two years ago, this was done using extremely expensive and highly invasive techniques such as PET or lumbar puncture (spinal tap), which is painful.

These are also techniques that, apart from their expense, are not suitable when it comes to screening the general population to identify specific individuals who already have tau or amyloid abnormalities. So, the development of biomarkers in blood will facilitate prevention efforts in the world of Alzheimer's in the same way as they do in the cardiovascular field for evaluating cholesterol and so on.

What this means is that we had techniques that were only valid for research and in the experimental field, but now they are going to reach clinical practice in the short-term, if there are finally drugs that modify the progression of this disease. It's a combination: the two things must go together.We need not only the tools that change progression of the disease, but also the means to detect which people might benefit from the drugs.There is also a synergistic effect since this is not simply progress in parallel. To date, there have not been studies on prevention because they were logistically almost impossible, it would have been necessary to recruit thousands of healthy people who showed evidence of anomalous markers.

And until now this type of population was only found in research cohorts, like those we have in the Pasqual Maragall Foundation. Recruiting 1,300 healthy people with amyloid abnormalities worldwide was practically impossible.

Another aspect is that studies on prevention last a long time because we are talking about a disease

that has a very slow progression.

We know that when amyloid protein is present, decades may elapse until the onset of symptoms, which means that it is not enough to find people who have amyloid protein abnormalities, we need to clearly know what moment of the preclinical phase the subjects are in and select people who are closer to cognitive decline. If not, you have a study in which there are two groups: one who receive a placebo and the other who receive the drug. If neither of these two groups of patients experience cognitive decline because almost all of them are far from the onset of disease symptoms, you cannot show the drug's effectiveness.Now, the fact of having markers in blood is of great help in making this type of study much easier and realistically feasible. Which means that markers, apart from their use in future clinical practice, will help in the development of new drugs, particularly in preclinical phases.

- ***What information will be obtained from the combination of Barcelonaβeta Brain Research Center's Alfa database and PESA-CNIC-Santander?***

I think that the two cohorts, the BBRC's Alfa and the PESA, share the same perspective on prevention in general and in characterising risk factors that can have great future impact. **The CNIC has done this in the cardiovascular area. But they are established cohorts with complementary characteristics**: in ours, the volunteers have a higher risk of Alzheimer's, evidently, and a very low cardiovascular risk because they are individuals who are concerned about looking after themselves, whereas PESA places more emphasis on cardiovascular effect, in characterising vascular risk and identifying subclinical atherosclerosis.

I believe that combining the data from the two cohorts will allow us to answer an important question, which is, we know that controlling cardiovascular risk factors has an impact on Alzheimer's, what we don't know is why. Why does doing physical activity protect against Alzheimer's? It really is not clear.

It has been shown that vascular damage contributes to the severity of symptoms after onset of the disease. But there is probably a closer connection between cardiovascular health factors and Alzheimer's disease.

So, the CNIC cohort is ideal to answer these questions, and combining the data of CNIC and the BBRC will allow us to answer relevant questions about prevention of this disease in healthy subjects.

- ***How did your interest in the field of Alzheimer's arise?***

I am an engineer by training, and studied biomedical engineering, which is where my knowledge in the field of biology comes from. I have always worked in research and in neuroimaging. First in Madrid's Gregorio Marañón hospital, which allowed me to take my first steps in the world of clinical medicine, understand what questions arise in it, and how neuroimaging can respond to these questions.

In 2004, I worked in a molecular imaging centre where we did imaging of patients from the Hospital del Mar, but also clinical trials for pharmaceutical companies and on laboratory animals. It was rewarding because I had access both to clinical and experimental phases.

In 2010, I began to work at the Pasqual Maragall Foundation on the Alfa project as an expert in neuroimaging.

In addition to my scientific interest in Alzheimer's, which I believe is the greatest challenge facing medicine from a scientific point of view, and in neuroimaging, which has become my specialism and has had a central role in contributing to better understanding of the disease, I have a personal interest. Some years ago, my father died of Alzheimer's, at a time when there were almost no treatment options, and this was one of the reasons that inspired me to follow this route.

- *Juan Domingo Gisbert gave the Seminar Can Alzheimer's be prevented? organized by Marta Cortés, Valentín Fuster, Borja Ibáñez and María Moro*