"Various diseases and all very mechanistically different, are included under the name of vascular dementia, or better called, cognitive vascular deterioration"

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María Ángeles Moro leads the CNIC's Neurovascular Pathophysiology Laboratory.

María Ángeles Moro is Professor of Pharmacology at the UCM School of Medicine, and co-director of the Neurovascular Research Unit of the same university. Her main lines of research are stroke and vascular dementia, fields in which she has identified new therapeutic and diagnostic targets, among which are nuclear receptors, excitotoxic mechanisms, the contribution of myeloid cells to the inflammatory and resolute response, and mechanisms of physiological and pathological remodeling through neurogenesis and angiogenesis.

She belongs to the Stroke*,* British Journal of Pharmacology *y* Journal of Cerebral Blood Flow and Metabolism. She has been a Collaborator of the General Subdirectorate of Research Projects of the State R&D Plan, MINECO (2013-2016), and deputy of the ANEP Biomedicine team (2004-2007). In addition, she has participated / participates as an expert in panels of the Spanish National Plan and, since 2001, as Chair, Vice-Chair or evaluator in more than 40 panels (MSCA, ERC, etc.) of the European Commission (through the Research Executive Agency, European Research Council Executive Agency, and EUCYS) and, more recently, of the Ibero-American Program of Science and

Technology for Development (CYTED). She is an ad hoc reviewer for numerous international publications and evaluation agencies (Wellcome Foundation and Alzheimer's Research Trust, UK; ANR, France; CINECA, Italy; NCN, Poland) and External Examiner of Trinity College Dublin (2010-2013). Since 2016 she is "Fellow of the British Pharmacological Society" (FBPhS).

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- ***What is the relationship between neurovascular damage and diseases related to dementia?***

The relationship is very direct, and, in fact, although it has been considered that cerebral vascular damage is the second most frequent cause of cognitive deterioration, after Alzheimer's disease, new evidence indicates that mixed type dementias (vascular and Alzheimer) are actually the most numerous. Furthermore, there is increasing evidence that shows that Alzheimer's disease can pass silently and manifest itself clearly after cerebrovascular damage. Therefore, it is surprising the little amount of research that is dedicated to other types of dementia, other than Alzheimer's disease.

- ***We keep living longer and longer.***

And with the increase in life expectancy it is logical to increase the prevalence of age-related diseases. We work on vascular dementia, in which cognitive disorders have a vascular cause. It is important to highlight that various diseases, and all very mechanistically different, are included under the name of vascular dementia or, better called, cognitive vascular deterioration. As I said, the fact of living longer also has a downside, which is the increase in the chances of the development of these diseases. And not only is the risk higher, but, in addition, age increases the severity of cardiovascular disease, including cerebrovascular disease. Do not forget that the various types of dementia affect about 40 million people in the world and that by 2050 this figure could reach 150 million or more, which will make this type of disease a major social and health problem.

- ***Which is more decisive: age or lifestyle?***

Both. Age goes deeper into lifestyle factors. The English physiologist Thomas Sydenham said that "A man is as old as his arteries". At a cardiovascular level it has been observed that many of the problems derived from atherosclerosis or hypertension, such as vascular remodeling or endothelial dysfunction, also occur as a result of aging without any other risk factors. In addition, as we said, age makes these additional risk factors aggravate and thus have more time to develop.

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Although in young people the body has resistance mechanisms, the increase in unhealthy habits will cause a greater incidence of cardiovascular disease in the future.

- ***Is it possible to fight against aging?***

If we know which mechanisms, possibly yes. Hence the importance of research, such as the one recently published by Dr. Marta Cortés Cantelli and Dr. Valentín Fuster in the Journal of the American Medical Association (JACC) which demonstrates the value of an anticoagulant in a mouse model with Alzheimer's disease. And there are other factors such as senescence, pathological aging, which is of great interest in this context. If we know the mechanisms and act upon them, we have seen that, in animal models, cognitive deficits can be reversed.

We have demonstrated the role of neurogenesis alterations in the hippocampus in various models of vascular dementia. Likewise, in autopsies of people with Alzheimer's disease, brains show a much smaller neurogenesis than in healthy people. This indicates that this is another mechanism that

causes dementia, associated with aging, and that it is possible that at some point we can reverse it.

In the case of post-stroke dementia, aberrant neurogenesis occurs but more importantly, we have shown that if we inhibit the development of this neurogenesis, cognitive function is restored

- ***Can we think of neurogenesis as a possible target for future therapies in these diseases?***

Yes. Adult hippocampal neurogenesis is a crucial process in memory formation. In Alzheimer's dementia there is a reduction in neurogenesis, although we still don't know if cognitive function would be restored if we reversed this reduction. Our contribution in different models of vascular dementia is proof that neurogenesis is altered, although with differential mechanisms. In the case of post-stroke dementia, aberrant neurogenesis occurs but more importantly, we have shown that if we inhibit the development of this neurogenesis, cognitive function is restored. Interestingly, in other typical models of vascular dementia, such as the one caused by carotid stenosis, the opposite happens: neurogenesis decreases.

In summary, in the models of vascular dementia that we have studied, there is a causal relationship between cognitive deficits and alterations in hippocampal neurogenesis. And in the case of Alzheimer's disease, the data points in the same direction, although there are possibly more causes.

- ***You have just joined the CNIC. Can you tell us what your line of research at the center will be?***

Vascular dementia, despite its high prevalence and consequences, it has received very little attention and its mechanisms still remain very unknown. All of this is even more complicated because, as we have said, dementia is not one, but many different pathophysiological entities. Taking advantage of the great critical mass and the avant-garde technology that exists at the CNIC, our objective is to develop innovative approaches and new paradigms to increase our understanding of the molecular and cellular mechanisms involved in vascular dementia, in order to identify therapeutic and diagnostic targets. The establishment and characterization of experimental models that recapitulate these diseases, will also allow us to develop non-invasive, sensitive and specific neuroimaging markers for each of the different subtypes of vascular dementia. Ultimately, our goal is to transfer our results in order to improve prevention and treatment of affected patients.

In the scenario of cerebrovascular disease, we will also continue our studies on ischemic and hemorrhagic stroke, focusing on its prevention and the development of more effective treatments for both the acute phase and for the more chronic stages of these pathologies.

- *María Ángeles Moro has participated in the CNIC Conference entitled 'New concepts in cardiovascular diseases related to age'.*

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