Researchers identify new marker linked to malfunctioning glymphatic system

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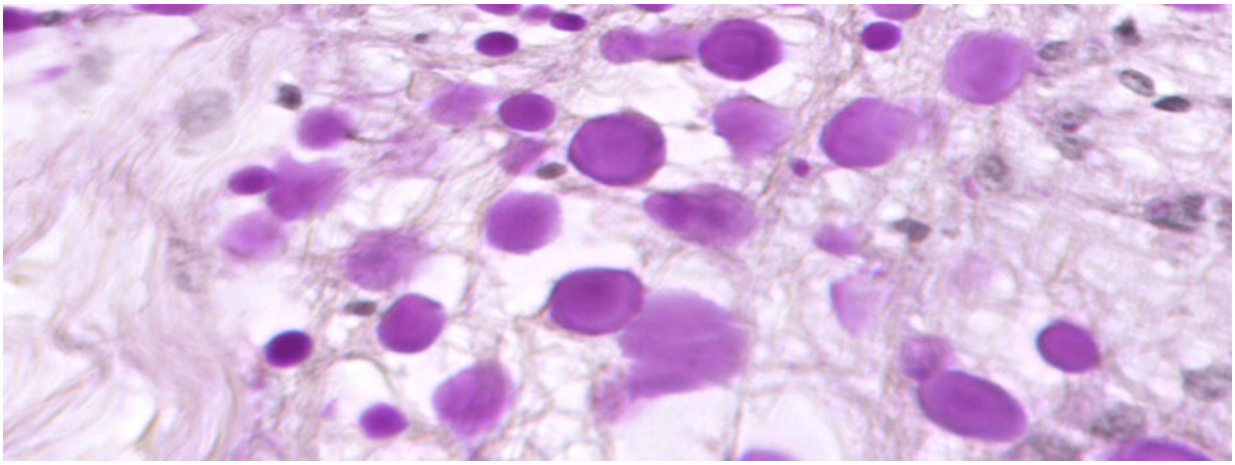

The wasteosomes or amylase bodies are structures that act as containers for brain waste products. Credit: University of Barcelona

A new study led by UB researchers shows that wasteosomes—structures that act as containers for brain waste products—indicate a malfunction of the glymphatic system, a recently discovered system that is an important brain-cleaning mechanism.

The study, published in the journal *Proceedings of the National Academy of Sciences* (*PNAS*), was carried out by a research team from the UB Faculty of Pharmacy and Food Sciences, the UB Institute of Neurosciences (UBNeuro) and the Network Center for Biomedical

Research in Neurodegenerative Diseases (CIBERNED). It has been directed by professors Carme Pelegrí and Jordi Vilaplana, with the participation of Marta Riba and Jaume del Valle, from the Faculty of Pharmacy and Food Sciences, UBNeuro and CIBERNED, and Laura Molina-Porcel, from the Neurological Tissue Bank of the Biobank of the Hospital Clínic de Barcelona and IDIBAPS.

Waste containers, a very recent vision

The wasteosomes or amylase bodies of the human brain were first described in 1837 by the renowned anatomist and physiologist Jan Evangelist Purkinje. For more than 150 years, the functions of these structures have generated much doubt and controversy among experts. "During the long history of the study of these structures, many and varied hypotheses have been generated about their nature and significance," the researchers note.

A previous *PNAS* study, published in 2019 and led by the same researchers, showed that amylase bodies act as containers for waste substances from the brain and can be expelled by astrocytes (the cells that generate them) into the cerebrospinal fluid (the fluid surrounding the brain). Later, the same group suggested the term wasteosomes, which means "body containing waste products," for the amyloid bodies.

The term was presented because it highlights the uptake of these substances and avoids the terminological confusion that the term amyloid and amylacea generated with amyloid proteins, which are characteristic of some neurodegenerative diseases such as Alzheimer's disease.

The new paper now shows that there is evidence that increased wasteosomes or starch bodies in the human brain are a manifestation of chronic failure of the glymphatic system.

Definition of lymphatic insufficiency

The glymphatic system is responsible for clearing the brain parenchyma. To date, the terms glymphatic system failure or glymphatic system dysfunction have been used to define its malfunction. In the new *PNAS* article, the concept of glymphatic insufficiency is defined as the inability of the glymphatic system to properly perform the brain's cleaning function. This makes it possible to describe that the failure can be acute or chronic, depending on the duration of the process, and to specify that the failure can be caused by a failure of the glymphatic system itself or by an overproduction of waste substances that exceeds the clearing capacity of this system.

This makes it possible to describe that the failure can be acute or chronic, depending on the duration of the process, and to specify that the failure can be caused by a failure of the lymphatic system itself or by an overproduction of waste substances that exceeds the clearing capacity of this system.

"Whether acute or chronic, and whether due to a failure of the glymphatic system or an overproduction of waste substances, the result of glymphatic insufficiency will be that waste substances will accumulate in the brain parenchyma, specifically in the areas affected by this insufficiency," the researchers explain.

Wasteosomes as markers of chronic lymphatic insufficiency

Once chronic glymphatic insufficiency has been defined, the researchers provide evidence that increased wasteosomes or starch bodies in the human brain are a manifestation of chronic glymphatic system insufficiency. The first indication of this relationship is that most factors

that are associated with large amounts of wasteosomes, such as aging, certain cardiovascular disorders and poor sleep quality, are also associated with disruptions of the glymphatic system.

"It should be noted that the glymphatic system shows a marked circadian rhythm and that its cleaning function occurs mainly during sleep," the researchers state. Moreover, it has been shown that the brain regions that tend to have the highest number of wasteosomes are often related to the drainage areas of this cleaning system.

These facts, which link wasteosomes to glymphatic insufficiency, together with the observation that wasteosomes are rarely detected in young people or in acute processes—they are therefore slow-forming structures—have led to a specific link between wasteosomes and chronic glymphatic insufficiency. Thus, according to the researchers, "the number of wasteosomes could be considered a marker of chronic glymphatic insufficiency, and can therefore show us whether this type of insufficiency exists and in which parts of the brain it occurs."

According to the researchers, this knowledge should facilitate the study of lymphatic insufficiency and make it possible to establish which variables have the greatest impact on the functioning or malfunctioning of this system. "Moreover," they add, "the fact that they are markers of chronic lymphatic insufficiency gives them a clinical meaning that they did not have until now and that had been questioned for years."

Implications for the study of neurodegenerative diseases

The study also mentions several elements and evidence that suggest that chronic lymphatic insufficiency is a risk factor for neurodegenerative diseases, especially neurodegenerative diseases that involve the

aggregation of certain fibrillar proteins, such as β-amyloid protein in Alzheimer's disease, phosphorylated tau in frontotemporal dementia and Alzheimer's disease itself, or α-synuclein in Parkinson's disease.

"In [the] case of lymphatic insufficiency, the elimination of these proteins is restricted, and all indications are that this contributes to the development of these diseases. Since wasteosomes can provide information about the variables that trigger glymphatic insufficiency and can help find strategies to fight it, they can help develop strategies to reduce the risk of developing these diseases," the researchers note.

Depending on the presence of wasteosomes, current knowledge seems to indicate that aging, chronic sleep disturbances and some cardiovascular diseases are the variables that have the greatest impact on the lymphatic system. "In any case, the field of the glymphatic system is growing exponentially and many research groups are focusing and concentrating on them, which suggests that new and outstanding results will be obtained soon," the researchers conclude.

More information: Marta Riba et al, Wasteosomes (corpora amylacea) as a hallmark of chronic glymphatic insufficiency, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2211326119

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