Step forward in research into new treatments for brain edema

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Cerebral edemas are accumulations of fluid into the intra- or extracellular spaces of the brain and it can result from several factors such as stroke or head trauma, among others.

Cerebral edema is a serious problem in neurology. While in other organs swelling does not lead to an urgent situation, in the brain it leads to coma and death. Although there are therapeutic solutions such as surgery, more effective treatments are needed.

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare type of leukodystrophy (affects the white matter) of genetic origin. MLC can be considered as a model of chronic edema, as patients suffering from birth a high accumulation of water.

A study of the pathophysiology of this rare disease has uncovered one mechanism that destabilizes the homeostatic balance of brain cells causing edema. This study is published in the latest issue of the journal *Neuron*. The journal accompanies the paper with a commentary of the editor and an explanatory video on its website.

Researchers from IDIBELL, the University of Barcelona (UB) and CIBERER (Spanish Network Research Centre on Rare Diseases) have found that one function of the protein GlialCAM, which is genetically altered in patients with MLC, is to regulate the activity of the channel that allows the passage of chloride ions between brain cells to regulate ion and fluid balance.

When this protein is lacked, the channel is not working properly and the fluid builds up in the brain glial cells forming edema.

Raul Estevez, director of this work, and Virginia Nunes, a partner of the study, believe that the importance of this finding is twofold. "On one hand", explains Virginia Nunes, "it allows us to better understand the pathophysiology of this disease minority" and "on the other hand", Raul Estevez continues, "we have identified a mechanism that can open doors to treatments based on the activation of this channel to restore homeostatic balance and perhaps treat brain edema in general."

Both researchers agree to say that this case demonstrates that the investigation of a rare disease that affects a small proportion of the population can serve as a model to identify mechanisms to think of new treatments for common diseases.

MLC Leukodistophy

Megalencephalic Leukoencephalopathy with subcortical cysts (MLC) is a rare type of leukodystrophy that appears during the first year of life, characterized by macrocephaly (oversized head). A few years later, it appears a slow neurological deterioration with ataxia (lack of motor coordination) and spasms. Magnetic resonance techniques revealed inflammation of the cerebral white matter and subcortical cysts, particularly in the anterior temporal regions.

In the 75% of MLC patients it has been identified mutations in the gene MLC1, which cause the disease. Virginia Nunes and Raul Estevez have recently identified a second gene causing MLC, named GlialCAM.

In the present study they have been identified precisely a GlialCAM protein as an ion channel subunit chloride that allows its entering and exiting the brain so that the cells can regulate the homeostatic balance.

More information: Jeworutzki E., López-Hernández T, Capdevila-Nortes X., Sirisi S., Bengtsson L., Montolio M., Zifarelli G., Arnedo T., Müller C., Schulte U., Nunes V., Martínez A., Jentsch T., Gasull X., Pusch M. And Estévez R. GlialCAM, a Protein Defective in a Leukodystrophy, Serves as a ClC-2 Cl–Channel Auxiliary Subunit. *Neuron* 73, 951-961, March 8, 2012. Doi 10.1016/j.neuron.2011.12.039

Maduke M. And Reimer R. Biochemistry to the rescue: a ClC-2 auxiliary subunit provides a tangible link to leukodistrophy. *Neuron* 73, 855-877, March 8, 2012. Doi 10.1016j.neuron.2012.02.012