New understanding of mysterious 'hereditary swelling'

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For the first time ever, biomedical researchers from Aarhus University, Denmark, report cellular defects that lead to a rare disease, hereditary angioedema (HAE), in which patients experience recurrent episodes of

swelling requiring immediate treatment. This new understanding is an important step toward gene therapy for patients.

Symptoms include an upper arm swelling to twice its normal size, swollen stomach with colic pain, vomiting or diarrhoea, or a life-threatening variant with severe swelling of the face, lips, tongue and larynx leading to obstructed airways and death by suffocation.

The swelling in hereditary angioedema happens because the lack of a specific blood protein called C1-inhibitor causes the blood vessels to leak fluid. During an attack, patients must be quickly given the correct medicine. Patients therefore have a difficult and medically dangerous lifestyle. Now, more than a half-century after the first molecular details of the disease were described, there is pivotal new knowledge about the disease's biology.

"We have succeeded in identifying what takes place in the liver cells that produce the protein C1-inhibitor. This is the crucial first step toward treating these patients with gene therapy, which is the interesting long-term perspective of our study," says Professor Jacob Giehm Mikkelsen from the Department of Biomedicine at Aarhus University, Denmark.

The research project documents that the hereditary genetic mutations, which the patients inherit from one of their parents, have a negative effect on the healthy gene from the other parent. In the *Journal of Clinical Investigation*, the authors write that the dominant negative SERPING1 variants cause intracellular retention of C1-inhibitor in hereditary angioedema.

"One of the mysteries about this disease has been the question of why the patients produce so little of the protein," says MSc Didde Haslund, who is a Ph.D. student and the article's first author.

"Because with two hereditary genes—a defect from one of the parents and a normal one from the other—you would think that the production might be around half the normal amount. Yet these patients produce only 10 to 20 percent of the normal level. But now we have an explanation at the cellular level, and this is crucial for the continuing work on gene therapy as a future treatment option," she says.

One of the difficulties related to the disease is that it only affects one in 10,000 to 50,000 people. This corresponds to fewer than 330 people in the whole of Scandinavia, which has the unfortunate consequence that medical doctors regularly mistake it for allergy, even though allergy medicine has no effect in the event of an attack.

"The diagnosis is made with a blood test that measures the concentration and function of C1-inhibitor in the blood. However, this requires that the medical doctor is aware of the disease," says Jacob Giehm Mikkelsen. "You might sometimes think that with so few patients, perhaps we ought to concentrate on something that can help more people. But on the other hand, we actually have a national strategy for rare diseases, because as a whole, this is a large patient group. The individual rare diseases don't affect many people, but taken together, there are between 30,000 and 50,000 Danes with rare diagnoses."

Hereditary angioedema is characterised by attacks occurring suddenly and unexpectedly. They may be provoked by a range of factors ranging from physical exertion and other forms of physical stress to infections, hormonal factors and individual drugs. Generally, the diagnosed patients are assigned to Odense University Hospital, as this is the national competence centre for treatment. Anette Bygum, professor and research director at the hospital, initially contacted Jacob Giehm Mikkelsen to learn more about the possibilities of gene therapy, thereby arousing his curiosity.

"For the whole team, Annette Bygum's inquiry turned out to be the beginning of a journey into a world that we who normally work on basic research are not part of on a daily basis. We have discussed our research with practitioners, presented the results for patients and international patient associations and shared our experiences with the medicinal industry. We were invited to join the club, and this has led to both an interdisciplinary project and a crucial research result," says Jacob Giehm Mikkelsen.

More information: Didde Haslund et al. Dominant-negative SERPING1 variants cause intracellular retention of C1 inhibitor in hereditary angioedema, *Journal of Clinical Investigation* (2018). DOI: 10.1172/JCI98869

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