ACTIVATION OF THE FICOLIN-LECTIN PATHWAY DURING ATTACKS OF HEREDITARY ANGIOEDEMA

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Introduction: The activation of the plasma enzyme systems is insufficiently controlled in hereditary angioedema caused by the deficiency of functional C1-INH (HAE-C1-INH), a disorder characterized by recurrent subcutaneous and/or submucosal edematous attacks. Recently, a few studies suggested that it is not the MBL-lectin pathway, but the ficolin-lectin pathway (ficolin-LP), which might play a role in the pathomechanism of HAE-C1-INH. As the role of ficolin-LP in the development of edematous attacks is still enigmatic, we analyzed its activity during such episodes.

Methods: Thirty-five HAE patients, who have experienced severe edematous attacks on 112 occasions, were enrolled. We analyzed blood samples drawn during attacks, and 39 samples obtained from the same patients during symptom-free periods. The serum concentrations of ficolin-3, ficolin-3/MASP-2 complex, antigenic C1-INH, C4, as well as the extent of ficolin-3 mediated activation of the lectin pathway (F3-TCC) were measured using in-house methods. Commercially available kits were used to quantify C1-INH activity, as well as C4d, and C3a levels.

Results: Levels of functional C1-INH and ficolin-3/MASP-2 complex were elevated ($p=0.0009$ and $p=0.0224$), whereas F3-TCC was lower ($p=0.0002$) during attacks, compared with the symptom-free period of the same patients. During symptom-free periods, the extent of F3-TCC significantly correlated to the concentrations of antigenic C1-INH ($R=0.3152$, $p=0.0006$) and C4 ($R=0.5307$, $p<0.0001$), whereas the ficolin-3/MASP-2 complex level correlated significantly with the C4d ($R=0.8571$, $p=0.0107$) concentration. During attacks, the level of the ficolin-3/MASP-2 complex correlated with ficolin-3 ($R=0.5319$, $p=0.0025$), functional C1-INH ($R=0.5391$, $p=0.0066$), and C3a ($R=-0.4981$, $p=0.0096$) levels. Interestingly, an inverse relationship was found between the ficolin-3, MASP-2, as well as MAP-1 levels, and the time from the onset of the attack to blood sampling. The levels of ficolin-2, ficolin-3 and MAP-1 were slightly elevated during submucosal attacks, compared to the subcutaneous location.

Conclusions: The strong association between the level of the ficolin-3/MASP-2 complex and C1-INH activity suggests that the ficolin-LP undergoes activation during edematous attacks in HAE-C1-INH patients. We presume that the ficolin-3 mediated activation of LP may contribute to the consumption of the small reserve of functional C1-INH and thus, it can lead to uncontrolled activation of the plasma cascade systems, and thereby to edema formation.