New developments in type of hereditary angioedema with normal CI-inhibitor level

Abstract
In this mini-review, new developments in hereditary angioedema with normal C1-inhibitor level (HAE-nC1-INH) in 2018 will be briefly told. The first description of its hereditary form has been defined by Osler in 1888. The biochemical reflection of disease was explained by Donaldson and Evans in 1963. In the recent past, there have been three types of hereditary angioedema defined as type I-type III. However, the disease is presently categorized into 2 types in accordance with the C1-inhibitor function: hereditary angioedema with C1-INH deficiency (HAE-C1-INH) and HAE-nC1-INH.

Keywords: Hereditary angioedema, C1-Inhibitor level, Plasminogen, Angiopoietin-1, angioedema, plasminogen gene, glycoprotein, De novo mutations, kringle, biochemical reflection

Introduction
In this mini-review, new developments in hereditary angioedema with normal C1-inhibitor level (HAE-nC1-INH) in 2018 will be briefly told.

History of Hereditary Angioedema and Current Hereditary Angioedema Types
The angioedema initially was reported by Milton. The first description of its hereditary form defined 12 years later by Osler. In the past, there have been three types of HAE defined as type I-type III. However, HAE is presently categorized into 2 types in accordance with the C1-INH function: HAE with C1-INH deficiency (HAE-C1-INH) and HAE-nC1-INH. Hereditary angioedema has later been understood that it is mostly caused by C1-INH antigen (protein) or functional deficiency, which is due to structural abnormalities of the C1-INH (SERPING1) gene situated on chromosome 11(q12-q13.1). C1-INH antigen is a 110-kDa glycoprotein containing 478 amino acids and a 22-residue signal peptide. Aberrations of the C1-INH gene in cases with HAE-C1-INH are very diverse, by way of more than 490 mutations recorded and only a few mutations detected more than once. The mutations are dissimilar in the two types of HAE-C1-INH. In type I of HAE-C1-INH, they are very assorted, are dispersed through the C1-INH gene, and involve large rearrangements, comprising of partial deletions and, less frequently, partial duplications. On the contrary, the mutations found in HAE-C1-INH type II are positioned in the identical location in exon 8 of the C1-INH gene, which encodes the active center or hinge region, producing inactive C1-INH. De novo mutations have been progressively more reported in roughly 25% of cases with HAE-C1-INH.

i. Hereditary angioedema with normal C1-INH
Hereditary angioedema with normal C1-INH was firstly defined in 2000. Subjects with HAE-nC1-INH have normal protein levels and activity of C1-INH. In the majority of these HAE-nC1-INH patients, the genetic basis of HAE is unknown (HAEunknown). In approximately 30% of patients, it is found to be related with the F12 gene (HAE-FXII) mutations in 2006. A point mutation (Thr328Lys or Thr328Arg) or a large deletion (deletion of 72 base pairs: c.971_1018+24del72*) or an 18-bp duplication in the coagulation factor XII (FXII) gene is detected in HAE-FXII.

ii. New developments in hereditary angioedema with normal C1-INH
In 2018, new two HAE types were described in HAE-nC1-INH related with firstly plasminogen (HAE-PLG) and then angiopoietin-1 (HAE-ANGPT1) gene mutations. A mutation in the plasminogen gene associated with disease activity has recently been discovered identifying another type of HAE with normal C1-INH levels (HAE-PLG). This missense mutation c.9886A>G was located in exon 9 of the plasminogen (PLG) gene, p.Lys330Glu (K330E) in the kringle 3 domain of the PLG protein, in patients with HAE-nC1-INH. A missense mutation in angiopoietin-1 gene (ANGPT1, c.807G>A) is also thought to be linked with HAE-nC1-INH.

The vasculature in cases with p.Ala119Ser mutation turn out to be prone to increased vascular permeability caused by various mediators, other than just bradykinin.

iii. What do new developments change in clinical practice?
Especially for allergists taking care of adolescence and adults keep in mind that they should rule out HAE-PLG and HAE-ANGPT1 by gene testing before making a diagnosis of HAE unknown in old type III form of HAE cases (HAE-nC1-INH), if there is no HAE-FXII gene defect.

iv. Future expectations
It is expected that there will definitely be other gene defects discovered in HAE unknown forms of HAE-nC1-INH patients.

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Conflicts of interest

The author declares no conflicts of interest.

References


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