New Perspectives in Acquired Angioedema

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First described by Caldwell et al. in 1972 [1], acquired angioedema is an extremely rare disease characterized by a complement C1-inhibitor deficiency, hyperactivation of the classical pathway of the complement, with potentially recurrent attacks of abdominal pain and life-threatening laryngeal involvement due to bradykinin-mediated angioedema. There are slightly fewer than 200 AAE patients reported in the literature. Clinically, the angioedema symptoms that characterize AAE cannot be differentiated from those present in patients with the hereditary type who have a deficiency of C1-INH due to mutations in one of the two alleles coding for this protein [2]. Angioedema recurs at unpredictable intervals that last from 2 to 5 days and presents with disfiguring, non-pitting, non-pruritic edema of the skin (face, limbs, genitals), and severe abdominal pain from edema of the gastrointestinal mucosa leading to temporary bowel occlusion.

AAE has traditionally been considered to consist of two types. Type I AAE is associated with lymphoproliferation and excessive C1-INH consumption. Type II AAE is secondary to anti-C1-INH autoantibody production and is usually associated with a monoclonal gammopathy of unknown significance or, occasionally, with a lymphoid hemopathy. It subsequently became clear, however, that this distinction is artificial, since many patients have lymphoproliferative diseases together with autoantibodies to C1-INH. Treatments for AAE are the same as those for HAE, with the exception of anti-CD20 monoclonal antibodies, such as rituximab, which was recently introduced and is aimed at depleting B lymphocytes.

A recent Danish article [3] summarized national data on nine patients with AAE, making it the largest group ever described in a single publication. All the patients were older than 40 years at the time of their first angioedema attack, in accordance with the reported age at onset being past the fourth decade of life in 94% of affected individuals. The Danish patients had low values of complement C1-INH antigen, C1-INH function, C4 and C1q at least once. Five patients had been tested for anti-C1-INH autoantibodies, and the results were positive in 2 of them, coincurring with 71 positive patients among 136 patients. Six patients were diagnosed as having a hematologic condition during the follow-up period. None of the nine patients had a lymphoproliferative disorder when the angioedema first appeared. Two patients had abnormal blood counts and/or enlargement of lymph nodes at the initial hospital presentation for AAE, and further examinations led to their being diagnosed as having splenic marginal zone lymphoma and small lymphocytic lymphoma. Flow cytometric analyses of peripheral blood were performed in three patients, and the results led to a presumptive diagnosis of a hematological condition that was confirmed by bone marrow biopsy.

Branlec and his group [4] described seven patients with AAE (six with type II and 1 with type I) who were treated with rituximab. Clinical efficacy was complete for three and partial for two, while the remaining two were therapeutic failures (one failure was the patient with type I AAE). Only two patients had improved biological parameters, with normalization of their C1-INH levels and diminished anti-C1-INH autoantibodies, and those outcomes were observed 1–9 months after the last infusion of the second rituximab cycle. An associated lymphoproliferation did not affect the response to treatment.

In a study published in this month’s issue of *IMAJ* [5], Dreyfus and colleagues present evidence that rituximab therapy results in reduced levels of immunoglobulin G autoantibodies binding C1-INH protein, suggesting that the reduction of autoantibody levels may be the mechanism of successful rituximab therapy. Their 41 year old female patient suffered from autoimmune disease and was diagnosed as having HAE based on low C1q, C2, C3 and C4, and the presence of anti-C1esterase inhibitor. She failed to respond to ecallantide, a novel kallikrein inhibitory peptide, as well as to methylprednisolone and androgens. She was then treated with four infusions of rituximab at a dose of 375 μg/m², after which her angioedema resolved completely, with normal C1-INH level and undetectable anti-C1-INH antibody. The authors proposed that the monitoring of both total serum IgG and autoreactive antibodies against C1-INH protein be standard treatment, both prior to and following rituximab treatment, in order to establish diagnosis and guide therapy.

The good news is that modern pharmacology can benefit patients with AAE. Rituximab can be offered if antibody to C1esterase inhibitor is detected in their blood. The level of autoreactive antibodies...
should be periodically checked to assist in monitoring the therapeutic results and adjusting the treatment accordingly.

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References

Capsule

Variability in the CIITA gene interacts with HLA in multiple sclerosis

The human leukocyte antigen (HLA) is the main genetic determinant of multiple sclerosis (MS) risk. Within the HLA, the class II HLA-DRB1*15:01 allele exerts a disease-promoting effect, whereas the class I HLA-A*02 allele is protective. The CIITA gene is crucial for expression of class II HLA molecules and has previously been found to associate with several autoimmune diseases, including MS and type 1 diabetes. Gyllenberg et al. performed association analyses with CIITA in 2000 MS cases and up to 6900 controls as well as interaction analysis with HLA. The authors found that the previously investigated single-nucleotide polymorphism rs4774 is associated with MS risk in cases carrying the HLA-DRB1*15 allele (P = 0.01, odds ratio OR 1.21, 95% confidence interval 1.04–1.40) or the HLA-A*02 allele (P = 0.01, OR 1.33, 95%CI 1.07–1.64) and that these associations are independent of the adjacent confirmed MS susceptibility gene CLEC16A. They also confirm interaction between rs4774 and HLA-DRB1*15:01 such that individuals carrying the risk allele for rs4774 and HLA-DRB1*15:01 have a higher than expected risk for MS. In conclusion, these findings support previous data that variability in the CIITA gene affects MS risk, but also that the effect is modulated by MS-associated HLA haplotypes. These findings further underscore the biological importance of HLA for MS risk.

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Capsule

Dynamics and associations of microbial community types across the human body

A primary goal of the Human Microbiome Project (HMP) was to provide a reference collection of 16S ribosomal RNA gene sequences collected from sites across the human body that would allow microbiologists to better associate changes in the microbiome with changes in health. The HMP Consortium has reported the structure and function of the human microbiome in 300 healthy adults at 18 body sites from a single time point. Using additional data collected over the course of 12–18 months, Ding and fellow-researchers used Dirichlet multinomial mixture models to partition the data into community types for each body site and made three important observations. First, there were strong associations between whether individuals had been breastfed as an infant, their gender, and their level of education on the one hand, and their community types at several body sites on the other. Second, although the specific taxonomic compositions of the oral and gut microbiomes were different, the community types observed at these sites were predictive of each other. Finally, over the course of the sampling period, the community types from sites within the oral cavity were the least stable, whereas those in the vagina and gut were the most stable. These results demonstrate that even with the considerable intra- and interpersonal variation in the human microbiome, this variation can be partitioned into community types that are predictive of each other and are probably the result of life-history characteristics. Understanding the diversity of community types and the mechanisms that result in an individual having a particular type or changing types will allow us to use their community types to assess disease risk and to personalize therapies.

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“When you re-read a classic, you do not see more in the book than you did before; you see more in yourself than there was before”
Clifton Fadiman (1904-1999), American intellectual, author, editor, radio and television personality