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References

1. [NRMP] National Resident Matching Program. Results and data February 2010. <http://www.nrmp.org/wp-content/uploads/2013/08/resultsanddatasms2010.pdf>. Accessed July 4, 2018.
2. [NRMP] National Resident Matching Program. Results and Data February 2018. <http://www.nrmp.org/wp-content/uploads/2018/02/Results-and-Data-SMS-2018.pdf>. Accessed July 4, 2018.
3. Macy ML, Leslie LK, Boyer D, Van KD, Freed GL. Timing and stability of fellowship choices during pediatric residency: a longitudinal survey. *J Pediatr*. 2018;198:294–300.

Is hereditary angioedema related to an increased risk of atherosclerosis?



We paid close attention in reading the interesting paper by Nebenführer et al,¹ whose findings excluded the presence of endothelial dysfunction in hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) patients. Their results are opposite of those recently published by our research group.² Because the issue is important, impaired endothelial function being correlated with future occurrences of adverse cardiovascular events and cardiac death,³ we think that a few points should be worthy of debate.

The relationship between hereditary angioedema (HAE) and atherosclerosis is undoubtedly controversial, although some evidence tends to confirm it.^{2,4–6} Furthermore, regarding a possible pathophysiological explanation, HAE may share an endothelial dysfunction that was probably not caused by the disease per se, but instead by bradykinin receptor–asymmetric dimethylarginine (ADMA) pathway activation or danazol, resulting in unfavorable changes in serum lipid levels.^{1,2}

Based on these premises, many factors may have contributed to the varying results:

- The participants' age, as honestly acknowledged by the authors, which was considerably lower than that of the subjects in our study (mean age, approximately 30 vs 48 years). Endothelial function is known to begin to deteriorate at approximately the end of the fourth decade of life, and we found a strong relationship between reactive hyperemia and chronological age as well.^{1,2}
- Gender distribution. In our sample size, 75% of the recruited patients were female, and 48% were female in the study by Nebenführer. Hereditary angioedema is likely to be more frequent and severe in women than in men.⁷
- Again, as pointed out by the authors, the distinct techniques of measurements (fingertip plethysmography vs flow-mediated dilation at the brachial artery) also may have increased discrepancy in the results, because they rely on different physiological processes/responses¹
- We enrolled C1-INH-HAE individuals as well as a subgroup of HAE patients with mutations in the *F12* gene (FXII-HAE), whereas in the study by Nebenführer et al, only C1-INH-HAE patients were recruited. Although we did not find statistically significant differences when comparing reactive hyperemia in C1-INH-HAE and FXII-HAE subgroups, this issue also may explain the reported different findings.^{1,2}

- We also measured blood levels of ADMA, a strong inhibitor of nitric oxide synthesis, whose increase occurs simultaneously with an increase in global cardiovascular risk.⁸ A statistically significant inverse correlation was also found between reactive hyperemia and patients' ADMA levels, even when excluding the possible influence of lipids.¹ The increased ADMA hematic concentration is another strong factor supporting the hypothesis of an accelerated atherosclerotic process in HAE patients.
- Finally, none of our patients was taking danazol or attenuated androgens, so our findings were not influenced by these drugs, which are known to impair lipid levels, thus leading to accelerated atherosclerosis, and also to increased coagulation activation when used in long-term prophylaxis.^{4,9} This striking difference with the other patients gives increasing reliability to our findings.

To sum up, the marked heterogeneity in the 2 studies' designs also may explain their different results. Because HAE is a rare disease, with consequent difficulties in recruiting enough patients to apply multivariate statistical analysis, now is the time to plan a multicentric study, with clear criteria of inclusion/exclusion, to definitively resolve this tricky issue.

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References

1. Nebenführer Z, Szabó E, Kajdácsi E, et al. Flow mediated vasodilation assay indicates no endothelial dysfunction in hereditary angioedema patients with C1- inhibitor deficiency. *Ann Allergy Asthma Immunol*. <https://doi.org/10.1016/j.anai.2018.10.004>.
2. Firinu D, Bassareo PP, Zedda AM, et al. Impaired endothelial function in hereditary angioedema during the symptom-free period. *Front Physiol*. 2018;9:523. <https://doi.org/10.3389/fphys.2018.00523>.
3. Maurer M, Bader M, Bas M, et al. New topics in bradykinin research. *Allergy*. 2011;66:1397–1406.
4. Széplaki G, Varga L, Valentin S, et al. Adverse effects of danazol prophylaxis on the lipid profiles of patients with hereditary angioedema. *J Allergy Clin Immunol*. 2005;115:864–869.

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5. Szegedi R, Széplaki G, Varga L, et al. Long-term danazol prophylaxis does not lead to increased carotid intima-media thickness in hereditary angioedema patients. *Atherosclerosis*. 2008;198:184–191.
6. Demirtürk M, Polat N, Güz G, et al. There is an increased risk of atherosclerosis in hereditary angioedema. *Int Immunopharmacol*. 2012;12:212–216.
7. Bouillet L, Gompel A. Hereditary angioedema in women: specific challenges. *Immunol Allergy Clin North Am*. 2013;333:505–511.
8. Bassareo PP, Puddu M, Flore G, et al. Could ADMA levels in young adults born preterm predict an early endothelial dysfunction? *Int J Cardiol*. 2012;159:217–219.
9. Birjmohun RS, Kees Hovingh G, Stroes ES, et al. Effects of short-term and long-term danazol treatment on lipoproteins, coagulation, and progression of atherosclerosis: two clinical trials in healthy volunteers and patients with hereditary angioedema. *Clin Ther*. 2008;30:2314–2323.