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Microbiota dysbiosis in hereditary angioedema patients

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ABSTRACT

I have read the article titled "Throat microbiota alterations in patients with hereditary angioedema" by Wang et al (2022) with great interest. This study examined the change in throat microbiota and its association with laryngeal edema (LE) attacks and attack severity in hereditary angioedema (HAE) patients. This study demonstrated the comparative richness of Bacteroidetes and Prevotellaceae in recent LE attacks and detected positive association between the attack severity scores and Bacteroidetes richness. Nevertheless, I have some questions and concerns about the methodological design of their study. For instance, in the article, the description of HAE and HAE patients is not exactly correct. I do not also agree with the authors on the effect of long-term prophylactic danazol use in HAE patients of this study. It is very important when or how the swab was obtained after the LE attack. The last, not the least, point now is what the authors suggest to improve this dysbiosis in these HAE patients. The discussion to elaborate these points in the study could be helpful and enlightening for readers and future research in this area.

DEAR EDITOR

I have read the article titled "**Throat microbiota alterations in patients with hereditary angioedema**" by Wang et al[1] with great interest. This study examined the change in throat microbiota and its association with laryngeal edema (LE) attacks and attack severity in hereditary angioedema (HAE) patients. They demonstrated the comparative richness of Bacteroidetes and Prevotellaceae in recent LE attacks and detected positive association between the attack severity scores and Bacteroidetes richness. Nonetheless, I have some questions and concerns about the methodological design of their study.[1]

In the article,[1] the description of HAE and HAE patients is not exactly correct. In mentioned 2020 United States Hereditary Angioedema Association Medical Advisory Board guidelines, HAE is classified by deficient levels of C1–INH (C1 esterase inhibitor) protein and function.[1] The authors say that they enrolled C1–INH-related HAE patients. What exactly do they mean by C1–INH-related HAE? The word "related" is not understood? Does "related" mean deficiency? There are 2 known main different groups of HAE types, including at least 8 subtypes.[2] Did not this group include the normal C1–INH HAE group or any of its subtypes? Did this study group just include type 1 and type 2 HAE patients? In the article,[1] these points are not understandable.

I do not agree with the authors on the effect of long-term prophylactic danazol use in HAE

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patients of this study. There were 16/36 patients using danazol for long-term prophylaxis. They did not demonstrate that danazol significantly affected the configuration of throat microbiota. And they made just 4/16 patients had undergone follow-up sampling to evaluate microbiome changes before and after the danazol therapy. However 4 patients and a 2-month observation period were very short in number and period for the evaluation of microbiota. These patients received long-term prophylactic danazol treatment even for years. Just 2 months is not enough to measure the effects of years and see any change in throat microbiota in these patients. Secondly, it is known that the spectrum of gut microbiota differs consistent with sexual development (puberty, pregnancy, and menopause) as well as sex hormones. As the gastrointestinal microbiome is involved in the excretion/circulation procedure of sex hormones, the notion of "microgenderome" representing the role of sex hormones on the gut microbiota has been proposed.[3] For instance, high androgen level characterized by polycystic ovary syndrome (PCOS) is related with gut microbiota disruption. 5α-Dihydrotestosterone was also shown to be able to decrease gut microbiota mixture.[4] In a study with 33 cases, the co-existent bacterial groups that augmented in PCOS were *Bacteroides*, *Escherichia/Shigella*, and *Streptococcus*.[5] Therefore, the observed abundance of Bacteroidetes in the HAE patients of this study[1] might be simply related to long-term prophylactic Danazol use. As mentioned in the article,[1] danazol use may result in Bacteroidetes abundance, which causes to bradykinin increase in the body.[6] Therefore, danazol use in the prophylactic treatment of these patients, might not be logical and helpful at all. And the authors should have discussed the effects of androgens on microbiota under current literature.

It is very important when or how the swab was obtained after the LE attack. It is understood from the classification of these groups (LE.1 m; NLE.1 m; GE.1 m, NGE.1 m) that a swab was obtained after LE. If it was after, how many days after the LE attack? Were all the swabs taken on the same day after LE? Moreover, the authors did not mention how many LE attacks were in a month (LE.1 m) or in a previous month (NLE.1 m).[1] It could be just one or several LE attacks in a month. One of these possibilities may have changed the effect of LE attack on throat microbiota.

There is also a discrepancy in waiting periods to evaluate microbiota in the study (1 month for an LE attack and 2 months to see the danazol effect on microbiota). The authors chose a one-month interval to describe the recent edema because their earlier study[7] showed a decrease in the richness and diversity of gut microbial communities among HAE cases with abdominal attacks. However, their previous study[7] was all about the gut but this study was about throat, and also no significant changes in the microbial community were detected in cases with recent attacks of gastrointestinal edema in this study.[1] Thus, it might have required different time intervals for the evaluation of LE attacks.

In conclusion; the last, not the least, point now is what the authors suggest to improve this dysbiosis in these HAE patients? For instance, do they suggest use of any probiotics? This discussion could be helpful and enlightening for future research in this area.

Abbreviations

HAE, hereditary angioedema; LE, laryngeal edema; C1-INH, C1 esterase inhibitor: PCOS, polycystic ovary syndrome: NLE, never laryngeal edema: GE, gastrointestinal edema: NGE, never gastrointestinal edema.

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Availability of data and materials

Data are available on request from authors.

Author contributions

ÖÖ did everything.

Ethics approval

Not available.

Authors' consent for publication

All authors approved the submission.

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Nothing to declare.

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