

BRIEF COMMUNICATION

Bacteriuria increases the risk of edematous attacks in hereditary angioedema with C1-inhibitor deficiency

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Keywords

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Abstract

Urinary tract infections are considered among the most common infectious disorders in humans. Various infections may have a role in inducing HAE attacks. Our study intended to evaluate bacteriuria in the urinalysis of patients with C1-INH-HAE. Urine specimens contributed by 139 patients with C1-INH-HAE at the annual control visits were studied retrospectively for microorganisms. We analyzed the presence of bacteriuria in relation to the clinical symptoms. Taking into account three randomly selected urine specimens, we found that the cumulative number of edematous attacks was higher in patients with bacteriuria than in those without ($P = 0.019$, $P = 0.022$, $P = 0.014$). Considering the same patients, attack number was significantly higher (14.51 vs 8.63) in patients with bacteriuria than in those without ($P < 0.0001$). In patients with bacteriuria, we found a higher incidence of edema formation during the year before evaluation, which may suggest the triggering role of bacteriuria in the occurrence of edematous episodes.

Hereditary angioedema (HAE) with deficiency of the C1-inhibitor (C1-INH-HAE) is a rare, autosomal dominant disorder belonging to the group of bradykinin-mediated angioedemas. It is characterized by recurrent, subcutaneous, and/or submucosal edema formation (1). The clinical symptoms show inter- and intra-individual variation. The edematous episodes usually occur unpredictably, although certain trigger factors can be suspected in a proportion of cases. The identification of these is important, because primary prevention—that is avoiding specific trigger factors—is possible. The most common trigger factors are emotional stress, physical exercise, weather changes, trauma, and infections. Among the latter, upper airway infections appeared to be relevant trigger

factors in C1-INH-HAE, because of their capability to induce edema formation in the upper airways (2). The edema-inducing role of *Helicobacter pylori* infection has been demonstrated previously (3). The importance of urinary tract infections, which are among the most prevalent infections, as well as their possible role as trigger factors has not yet been explored. Urinary tract infections (UTI) are among the most prevalent infectious diseases with a substantial financial burden on the society. Nearly half of the female population experiences at least one episode of UTI during their lifetime (4). Colonization of the urinary tract by bacteria—asymptomatic bacteriuria (ABU)—is common in asymptomatic individuals. According to the current European Association of Urology's (EAU) guideline, ABU requires treatment only if this is of proven benefit for the patient (5).

Although ABU is a local, organ-specific entity, recent findings implicate a generalized immune response (6). Local antibacterial defenses may also play a role in edema formation. Cell wall components of certain Gram-positive and

Abbreviations

ABU, asymptomatic bacteriuria; C1-INH, C1-inhibitor; C1-INH-HAE, Hereditary angioedema with C1-inhibitor deficiency; HAE, Hereditary angioedema; LTP, long-term prophylaxis; RBC, red blood cell; UTI, urinary tract infection; WBC, white blood cell.

Gram-negative bacteria can activate, for example, the endogenous coagulation cascade (7, 8). Moreover certain bacterial proteases not only may activate the endogenous coagulation, but the kinin cascade as well (9, 10). High molecular weight kininogen and other contact system factors—bound to and accumulated on the bacterial surfaces—have their role in the release of proinflammatory kinins and can thus contribute to the onset of inflammatory symptoms (such as pain, fever, edema, and hypotension). Apparently, the significance of this process in the occurrence of ABU is negligible in healthy individuals, but in patients with C1-INH-HAE, for example, it may trigger edematous attacks.

Our aim was to evaluate bacteriuria and their possible role in triggering edematous episodes of C1-INH-HAE.

Patients and methods

In our study, we reviewed the medical records of 139 patients with C1-INH-HAE (58 males and 81 females) over 16 years old. We conducted a retrospective analysis of the results of 1288 annual microscopic urinary sediment analyses (microorganism counts). The samples were obtained between 1986 and 2014 over an observation period of 9 years on average (min.: 2 years, max.: 30 years). At the follow-up visits, urine samples were collected using a 'clean-catch' technique, from midstream urine. Patients were diagnosed and followed up regularly at the Hungarian Angioedema Center; their laboratory and clinical data were recorded in the Hungarian HAE Registry. Patients recorded their attacks in their patient's diary. At the annual follow-up visits, we collected data on general health status (e.g., the presence of actual symptoms if any, changes made in treatment regimen by other physicians). Checking the patients' records, we did not find a single case when a patient had urinary tract symptoms at the time of the visit. Urine samples were analyzed within an hour of collection.

Samples obtained from female patients during their menstruation cycles were excluded. In this study, bacteriuria was defined as 'the presence of bacteria' in the urinary sediment, except when the term 'few' was used to describe it. Samples containing a significant amount of squamous epithelial cells (≥ 15 /HPF) were excluded as well, because these findings may primarily indicate a contaminated specimen. Routine urine cultures were not performed as part of the annual control visits for these patients and therefore were unavailable for retrospective analysis.

Results

The relationship between urinalysis results and the numbers of HAE attacks

First, we analyzed the relationship between the findings of 1288 urinalyses and the numbers of associated HAE attacks. The urinalysis confirmed bacteriuria in 298 samples (from 16 males and 69 females). The different numbers of urine samples available from the individual patients might cause some bias in the estimates. Notwithstanding this, the statistical

Table 1 The presence/absence of bacteriuria, and the mean number of edematous attacks during the preceding year (based on the analysis of 1288 urine samples)

Number of attacks in the preceding year	No bacteria in the urine Mean (SD)	Bacteria in the urine Mean (SD)	Significance
Total	8.65 (29.340)	11.98 (25.892)	<0.0001
Subcutaneous	5.37 (19.887)	7.33 (16.974)	<0.0001
Abdominal	2.51 (14.209)	3.66 (10.752)	<0.0001
Upper airway	0.31 (1.650)	0.5 (1.429)	0.001
Genital	0.35 (3.622)	0.29 (1.455)	0.607

Significance was estimated by Mann–Whitney *U*-test. Statistically significant values are marked by bold typeset.

analysis confirmed a significant, positive correlation between bacteriuria and the annual number of edematous attacks. Statistical significance persisted even when this relationship was tested for different attack locations (i.e., for the occurrence of subcutaneous, abdominal, or upper airway edema), except for genital edema (Table 1).

Relationship between randomly selected urine samples and attack numbers

To eliminate the pitfalls of the method shown in Table 1, we extracted three random urine samples from each patient. Then, we reevaluated the cumulative numbers of edematous attacks as well as of the episodes with different locations in patients with/without bacteriuria in all three random subsets, using the same methodology shown in Table 1. Edematous attacks occurred in significantly greater numbers in patients with bacteriuria than in those without. As regards the locations of the attacks, the correlation was significant only for subcutaneous edema (Table 2).

Attack numbers in individual patients with or without bacteriuria

Next, annual attack numbers were compared between patients with/without bacteriuria. Seventy-six patients had a

Table 2 Statistical significance in the three randomly selected urine samples was tested for the difference in cumulative attack number in subjects with or without bacteriuria (Mann–Whitney *U*-test)

Attacks	Significance in group I	Significance in group II	Significance in group III
Total	0.022	0.019	0.014
Subcutaneous	0.194	0.028	0.016
Abdominal	0.180	0.145	0.331
Upper airway	0.398	0.545	0.080
Genital	0.520	0.940	0.532

Significantly higher attack numbers were seen in cases of bacteriuria (significant values are set in bold).

mixed set of samples, positive and negative for bacteria. These samples were collected at one-year intervals, in nearly all instances. Patients with major changes in their long-term prophylactic therapy were excluded. Comparing these subsets showed that patients with bacteriuria experienced significantly more edematous attacks per year (14.51 vs 8.63 attacks/year, $P < 0.0001$). Significance persisted even when the data were tested for both female and male patients ($P = 0.002$, $P = 0.034$).

Conclusions

We analyzed the possible relationship between bacteriuria and the clinical manifestation of C1-INH-HAE. In patients with bacteriuria, we found a higher incidence of edema formation during the year before evaluation. The diagnosis of asymptomatic bacteriuria is strictly defined and based on urine cultures; hence, the shortcoming of our study is the absence of urine cultures. However, this finding may suggest a triggering role for bacteriuria in the edematous episodes.

According to the guidelines, asymptomatic bacteriuria requires treatment only in certain cases—in particular, in catheter-acquired bacteriuria that persists 48 h after catheter removal, during pregnancy, and before urological procedures (11). Based on the foregoing, the treatment for asymptomatic bacteriuria may be justified in patients with C1-INH-HAE experiencing severe and frequent edematous attacks. We intend to confirm the triggering role of bacteriuria in C1-INH-HAE by conducting prospective studies with the use of urine cultures.

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Author contributions

ZZ and HF conceived and designed the study; acquired, analyzed, and interpreted the data; drafted the article; wrote and critically revised the manuscript; and involved in the final approval of the version to be published. NV and KVK acquired and analyzed the data, drafted the article, wrote and critically revised the manuscript, and involved in the final approval of the version to be published. LV conceived and designed the study, acquired and analyzed the data, drafted the article, and involved in the final approval of the version to be published. EI analyzed and interpreted the data, drafted the article, and involved in the final approval of the version to be published. GK conceived and designed the study, interpreted the data, drafted the article, and involved in the final approval of the version to be published. MN acquired and interpreted the data, drafted the article, and involved in the final approval of the version to be published.

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Conflicts of interest

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