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DEFICIENCY OF MANNOSE BINDING LECTIN AND DIAMINE OXIDASE AND A PREDISPOSITION TO RECURRENT URINARY TRACT INFECTIONS IN WOMEN

Hypothesis / aims of study

Urinary tract infection (UTI) is one of the most common bacterial infections in women with 50-60% of women experiencing an episode of UTI during their lifetime. Recurrent urinary tract infections are defined by the International Continence Society (ICS) as “at least three symptomatic and medically diagnosed UTI in the previous 12 months”. This is thought to affect 25% of women with a history of UTI. Recurrent urinary tract infections currently pose a challenge to achieving successful treatment in many patients with just antibiotics alone. Establishing other aetiological factors in development of recurrent UTI’s would allow better targeting of treatment to improve rates of treatment success.

Mannose-binding lectin (MBL) is an acute-phase serum complement protein produced predominantly by the liver. MBL has both a collagenous and a lectin region and by binding to carbohydrates on various microbes (including gram positive and negative bacteria, viruses and yeasts) causes lysis via the lectin complement pathway, or opsonophagocytosis through a separate process. MBL plays an important role in the antibacterial defense especially in view of the recent development of vaccines for these infections. MBL deficiency is known to predispose to recurrent respiratory infections, meningococcal and conditions of suppressed immunity due to drugs or disease state (1,2).

Inflammation of the bladder can occur due to infectious and none infectious causes. Acute inflammation is characterized by increased vascular permeability and activation of a biochemical cascade of inflammation causing release of pro-inflammatory mediators including histamine. Excessive levels of histamine (histamine intolerance) result from either excessive production of histamine by mast cells at a cellular tissue level, or through excessive levels of circulating histamine resulting from a reduction in histamine degradation and through bacterial infection of tissues where bacteria degrade histidine to histamine (3). Diamine oxidase (DAO) is the main enzyme involved in histamine metabolism. Low levels of DAO are diagnostic for histamine intolerance and the resultant excessive histamine levels lead to increased histerminergic effects which include reduced bladder capacity and pain.

We hypothesis that a deficiency of MBL and its association with concomitant immunodeficiency along with histamine intolerance and DAO deficiency is associated with the development of recurrent UTI’s in women.

Study design, materials and methods

In this retrospective observational study we have analyzed the distribution of MBL deficiency and concomitant antibody or cellular immunodeficiency in a large cohort of adult women presenting with symptomatic recurrent UTI’s. MBL levels were measured using ELISA. A serum MBL level of <1g/ml is diagnostic of deficiency and a diagnosis of antibody deficiency was based on the quantification of immunoglobulin (Ig)-A, IgM, IgG plasma, and IgG subclass serum levels. We also performed a blood test for DAO activity and a level below 10 IU/ml was considered diagnostic of probable histamine intolerance. A comparison of MBL, immunoglobulin and DAO levels was made between our patients with recurrent urinary tract infections and healthy controls with no bladder symptoms.

Results

We included 158 women with recurrent UTI’s with a mean age in years of 49 (SD 15). Not all patients had all tests because they were ordered on a clinical basis. Of the patients with recurrent UTI’s 90 of these women had an MBL level performed. MBL deficiency was diagnosed in 37/90 (41%) which is significantly higher than the 4% rate in the healthy cohort (1).
Immunoglobulin levels were determined in 135 women. The overall rate of immunoglobulin class and subclass deficiency was 67/135 (49.6%). We observed diminished serum levels of at least one immunoglobulin class (IgG, IgA, IgM) in a total of 8/90 (8.9%) patients. Only one patient had more than one immunoglobulin deficiency. When further examining IgG subclasses (IgG_1, IgG_2, IgG_3, IgG_4) there were 45/135 (33.3%) women who had one IgG subclass deficiency and there were 13/135 (9.6%) who had more than one IgG subclass deficiency giving a total of 58/135 (43.0%) women with a diagnosed IgG subclass deficiency. The highest rate of deficiency was observed with the IgG_1 subclass with a rate of 16/134 (11.9%). 56/158 (35%) were found to have a low diamine oxidase level indicating probable histamine intolerance.

Interpretation of results

This is the first report indicating the possibility of both MBL deficiency and histamine intolerance measured by DAO having a significant association with the development of recurrent UTI’s in women. MBL deficiency was diagnosed in 41% of women with recurrent urinary tract infections which is significantly higher than the 4% rate in the healthy cohort (1). Compared to the reported rates of histamine intolerance in the general population of 1-1.5%, the rates within our cohort with recurrent UTI’s are significantly higher (35%). We frequently observed reduced levels of IgG immunoglobulin levels in patients with recurrent UTI’s. The most common phenotypes affected were IgG_1, IgG_3 and IgG_4 deficiencies whereas deficiencies of total IgG, IgA and IgM were less frequent amongst this group.

Concluding message

The results of this study suggest an association between immunological deficiency and histamine intolerance in women with recurrent UTI’s. We therefore recommend within a cohort of patients presenting with recurrent urinary tract infections performing MBL, IgG subclasses and a DAO level. This will result in better definition of the potential role of immunodeficiency and histamine intolerance in a substantial subgroup of patients with recurrent urinary tract infections. It explains the reason why immune

modulation with vaccines and histamine blockade with treatment such as Cimetidine have been shown to be useful in placebo controlled trials.

References
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Disclosures
Funding: no disclosures **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** 12/LO/0394 **Helsinki:** Yes **Informed Consent:** Yes