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Editorial

Possible Infectious Process in the Investigation of Patients with Interstitial Cystitis

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Introduction

Interstitial Cystitis (IC) or Painful Bladder Syndrome (PBS) is a clinical problem typified by urinary frequency, urgency and pelvic pain. Not all patients have all symptoms to the same degree. As to date, there has been no clear pathophysiology or etiology elucidated and diagnostic criteria are not totally defined. In spite of years of research, neither specific markers, pathological diagnoses (histological), nor laboratory findings are characteristic for this problem. Differential diagnoses of chronic urinary frequency, urgency and pelvic pain include: 1. Gynecological causes; 2. Urological causes; 3. Infectious processes; 4. Neurological problems; and 5. other problems including intestinal problem s, joint disease and sequelae from surgery [1].

The frequency as demonstrated in the literature demonstrates differing prevalence based on country of origin and the criteria used for diagnosis. It is thought that 90% of patients with this problem are women. Although once unheard of, it is now understood that adolescents can have IC with all its manifestations.

Possible pathogenesis has suggested all, none, or some of the following:

- Pathogenic role of mast cells in the detrusor and/or mucosal layers of the bladder
- Deficiency in the glycosaminoglycan layer on the luminal surface of the bladder, resulting in increased permeability of the underlying sub-mucosal tissues to toxic substances in the urinz[4]
- Infection with a poorly characterized agent (e.g., a slow-growing virus or extremely fastidious bacterium)
- Production of a toxic substance in the urine
- Neurogenic hypersensitivity or inflammation mediated locally at the bladder or spinal cord level
- Manifestation of pelvic floor muscle dysfunction or dysfunctional voiding
- Autoimmune disorder

The pathophysiology is poorly understood. None of these possible etiologies fully explains the presentations of the disease seen in patients, their response to treatment nor the course of the disease.

Research Hypothesis and Research Theme

In the past, attempts to culture infectious organisms in the bladder were unsuccessful. The ability to grow organisms (pathogenic or not) has also been shown to be unsuccessful. Culture-independent molecular approaches, based on the targeted amplification and sequencing of 16S rRNA genes have furthered our understanding of the microbial world, and have led to the identification of many uncultivable organisms. Sequencing of bacterial 16S rRNA genes from various parts of the human anatomy, including skin, mouth, gastrointestinal tract and vagina has demonstrated that each of these areas has diverse microbial populations, and has revealed some correlations between these microbial communities and disease.

Few studies have attempted to use 16S sequencing approaches to explore a possible bacterial etiology for interstitial cystitis. In Keay et al. (J. of Urology 159(1):280-283 1998), bacteria were found in biopsy samples from 6 healthy and 6 IC patients, and sequencing of two samples revealed several differences between the corresponding microbiota. A number of earlier studies focused primarily on diseased patients and characterized the presence of primarily gram-negative microbes in IC patients [2].

All these previous studies were simple proofs of the principle that bacteria can be identified within IC patients and that some differences may exist. Due to the limited technologies available at that time, these studies were unable to generate a deep sampling of the urinary tract microbiome, nor to quantitatively characterize any significant differences between IC patients and healthy controls. To my knowledge, there have been no extensive studies performed in recent years that take advantage of modern technologies (in particular high-throughput sequencing). For this reason,testing the normal bladder urine for communities of microbial populations and compare these results with those of patients with interstitial cystitis, using modern analysis techniques might prove fruitful. These techniques include both new sequencing technologies, and DNA extraction/preparation methods, as well as new computational tools developed for the analysis of 16S data.

One of the hypotheses that should be tested is whether the etiology of interstitial cystitis has a microbial component. Even if we do not find any particular pathogen (bacterial or viral) to be associated with IC, a better characterization of the urinary tract flora in women with IC could have important implications for early diagnosis (e.g., microbiome signatures could signal the onset of disease) or palliative treatment (e.g., treating the microbiome either with antibiotics or probiotics could relieve some of the symptoms).

Methodology Employed

All appropriate investigational procedures for the patients

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should be adhered to including the project should be presented to an Institutional Review Committee and suitable consents need to be obtained. Patients with interstitial cystitis and control patients (reproductive age with no pelvic pain) need to undergo testing which should include obtaining urine samples, performing examinations and history taking, and treatment. They will have had no treatment for interstitial cystitis or a urinary tract infection for six months.

Urine samples will be acquired by catheterized specimens at the time of the patient undergoing a procedure and these samples will be subjected to a urine analysis, a culture and sensitivity (C+S) of the urine, cytology and sequencing. Cultures of the vagina including routine, GC and Chlamydia should be performed in the office on the initial visit. Pap smears to look at cytology and HPV should, also, be performed. Time interval studies may be performed.

Prior to investigating the patient, questionnaires will be completed and evaluated. These will include the PUF (Pain, Urgency and Frequency) questionnaire, the O'Leary- Sant questionnaire and possibly the SF-16 psychological questionnaire. A complete history including review of systems, past and present medical history, family history and history related to the pain experienced will be explored and recorded. Pain levels will be measured and pain diagrams will be filled out. A physical examination will be performed. Obviously, special attention should be shown to the area between the umbilicus and the area of the thighs with emphasis on pelvic structures, urological structures, neurological examination and nerve supply L1-S5. Pain, if it exists on examination, will by note. Ancillary testing will be performed including cystoscopy, hysteroscopy, curettement and laparoscopy. Imaging studies (MRI, CT scans, and pelvic sonography) can be carried out as necessary. Urine samples will be collected through trans-urethral catheterization at the time of surgery, a technique that in the past was shown to adequately capture the diversity of the urinary tract micro biome.

16S Sequencing and Analysis

DNA will be extracted from the samples and concentrations in the samples will be measured, and the 16S rRNA gene will be amplified using bar-coded PCR primers according to the protocols developed for the Human Microbiome Project (see hmpdacc.org for details). The resulting pools of DNA will be equalized for concentration and multiplexed into a single run of sequencing on a 454 GS-XLR instrument (Roche).

The sequencing data should be processed using the standard base-calling pipeline recommended by the instrument manufacturer, then sequences will be quality trimmed, separated according to the barcode sequences into sample-specific pools, and the barcodes and adapters removed. The sequences will be clustered into conservatively-defined Operational Taxonomic Units (OTUs) using DNA clust (dnaclust. sourceforge.net, Ghodsi et al. [3]. Bioinformatics. 2011; December). OTU abundances will be compared between the healthy and disease groups using the statistical package Metastases [4] in order to identify OTUs that are differentially abundant between the two groups. The OTUs will also be taxonomically classified through database searches against the RDP database (rdp.cme.insu.edu).

Summary

This potential project might shed a light into the understanding of the true etiology of the disease and prove it to be a microbial problem. Results from the analysis of children's diarrhea in Africa have shown that many organisms do not grow in culture. It will be exciting to see if the research done in the future bears fruit.

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