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Urinary tract microbiota in patients with multiple sclerosis and neurogenic pelvic dysfunction

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ABSTRACT

Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system common among young people. Neurogenic bladder often is a common symptom of the disease. Young people with MS often have to make treatment and family planning decisions at the same time.

The possibility of realizing reproductive plans is closely related to urological complications of the disease, high risk of urinary tract infections, and sexual dysfunction. In addition, disease modifying therapies for MS play a significant role in increasing the likelihood of infectious complications. Therefore, the issue of infection prevention in MS is critical. Effective personalized prevention of urogenital infections is possible with a clear understanding of the microbiota composition.

DNA sequencing methods have changed the conventional idea that normal urine is sterile and gave rise to the concepts of asymptomatic bacteriuria in healthy people. Moreover, data on the genitourobiome of patients with neurological diseases have recently emerged. Extended knowledge about the microbiology in the genitourinary system of neurological patients is necessary to unleash the capacity of health-preserving technologies.

The aim of the review was to integrate currently available data concerning the microbiocenosis of the lower urinary tract and vagina with underlying neurogenic pelvic dysfunction, including MS, as well as to present data on the association between closely located biotopes and the effect of MS therapy on the risks of developing genitourinary infections.

Keywords: multiple sclerosis, neurogenic bladder, vaginosis, microbiota

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Микробиота мочевых путей у пациентов с нейрогенной дисфункцией тазовых органов при рассеянном склерозе

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РЕЗЮМЕ

Рассеянный склероз (РС) является хроническим прогрессирующим заболеванием центральной нервной системы, распространенным среди лиц молодого возраста. Частый симптом болезни – это нейрогенная дисфункция тазовых органов. Молодым людям с диагнозом РС зачастую приходится одновременно принимать решения, связанные с лечением и планированием семьи.

Возможность реализации репродуктивных планов тесно связана с урологическими осложнениями заболевания, высоким риском инфекционных процессов мочеполовой системы, сексуальной дисфункцией. Кроме того, многие препараты, изменяющие течение РС, играют значительную роль в увеличении вероятности инфекционных осложнений. В связи с чем актуальной проблемой являются вопросы профилактики инфекций при РС. Эффективная персонализированная профилактика урогенитальных инфекций возможна при четком представлении о составе микробиоты.

Методы секвенирования ДНК позволили изменить классические представления о том, что здоровая моча стерильна. Были сформированы представления о бессимптомной бактериурии у здоровых людей, и в последние годы появляются сведения о генитоуробиоме пациентов с неврологическими заболеваниями. Расширение знаний о составе микроорганизмов мочеполовой системы неврологических пациентов необходимы для формирования потенциала здоровьесберегающих технологий.

Цель обзора: обобщение известных к настоящему времени сведений о микробиоценозе нижних мочевых путей и влагалища при нейрогенной дисфункции тазовых органов, в том числе при РС, представление данных о связи близко расположенных биотопов и влиянии терапии РС на риски инфекций мочеполовой сферы.

Ключевые слова: рассеянный склероз, нейрогенная дисфункция мочеиспускания, вагиноз, микробиота

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INTRODUCTION

Currently, the environment and the way it impacts the genetic factors are considered the basis for the development of autoimmunity in the human body. The composition of the gut microbiota and the gut – brain axis are being increasingly considered as a prerequisite for the development of immune-mediated conditions of the nervous system, including multiple sclerosis (MS). In the modern world, this concept is of great importance since microbial dysbiosis arises from the so-called Western diet, widespread use of antibiotics, and excessive sanitation.

Until recently, scientists have focused specifically on studying the gut microbiota in MS patients. Recently, research has been conducted on other loci in the host organism. It has been shown that oral cavity microorganisms might affect the level of inflammation in MS, thereby contributing to the mechanisms of the disease [1]. It should be noted that data on the composition and functioning of other biotopes are scarce or even lacking. At the same time, it is suggested that neighboring loci may be closely connected. It is likely that changes in the composition and functional activity of the microbiota in one location can lead to dysfunction in nearby areas.

Bowel and bladder dysfunction is part of the varied MS clinical pattern and is reported in 50–90% of patients [2]. On average, 6 years after the disease onset, urinary tract infections (UTIs) are diagnosed in lower urinary tract (from 13 to 74%) and 8% in upper urinary tract (from 0 to 25%), while chronic renal failure and urosepsis are some of the leading causes of death in patients with MS. At the same time, obstructive and mixed forms of urination disorders bring the highest level of threat due to progression of infectious inflammation and are significantly more common in MS.

The aim of this review was to summarize the present knowledge about the composition of the urinary

tract microbiota in patients with neurogenic bladder, especially in MS, and to interpret the risks of infectious diseases of the genitourinary system. The information search was conducted both in Russian and English using keywords, such as multiple sclerosis, urinary microbiota, vaginitis, neurogenic bladder, and lower urinary tract infections. For the information search, PubMed and elibrary.ru databases were used. A total of 251 publications (clinical studies, meta-analyses, randomized controlled trials, systematic reviews) over the past 15 years were identified and 46 relevant articles on the problem under study were selected.

MICROBIOTA OF THE LOWER URINARY TRACT

Until late, urine culture tests proved urine to be sterile, and the availability of bacteria therein was referred to an inflammatory response and UTIs. Yet, modern highly sensitive diagnostic tests established that the urinary tract of a healthy person is not sterile throughout its entire length. The year 2010 marked the emergence of a new understanding of asymptomatic bacteriuria (AS) owing to the studies by D.E. Nelson et al. [3] and a group of Russian scientists under the supervision of M.I. Kogan [4]. Their findings on the presence of bacteria in the urine of healthy men and women was confirmed by H. Siddiqui et al. in 2011 by metagenomic sequencing [5].

A.J. Wolfe et al. studied urine sampled from healthy women by various methods. The presence of bacteria in these samples was assessed by urine culture test, light microscopy, and *16S* rRNA gene sequencing. Urine samples obtained from the urethra by spontaneous voiding contained bacteria both from urinary and genital tracts. Microorganisms identified in urine samples simultaneously collected using a transurethral catheter and suprapubic aspiration had similar properties and additionally contained nonculturable bacteria, which allowed the authors to conclude that the bladder was not sterile [6].

In later years, new information has come to light regarding urinary microbiota in healthy individuals and in a number of diseases and conditions: overactive bladder [7], urinary incontinence [8], chronic prostatitis [9], interstitial cystitis [10, 11], bladder and prostate cancer [12–14], urolithiasis [15]. Genomics techniques revealed the existence of a microbial community in the bladder, which standard culture test failed to determine.

Thus, all people normally have bacteriuria, and given the fact that not only bacteria, but also other microorganisms (viruses, fungi) are found in the urinary tract, it is now more justified to use the concept of "urinary tract microbiome" instead of the term "bacteriuria". The urinary normobiome differs genderwise. Men have a significantly higher relative content of *Corynebacterium* bacteria, while women have a higher content of *Lactobacillus*. Moreover, given high importance of the microbiome, some scientists even suggest using the term "urinary tract dysbiosis" instead of "urinary tract infection" (UTI) [16].

Despite the fact that a large number of studies are dedicated to the composition of the bladder microbiome [17–19], no data are available on colonization of the upper urinary tract, due to obvious technical difficulties. It has been suggested that microorganisms are present in the urinary tract throughout its entire length [6]. This discovery is crucial. Excessive and unjustified attempts to sanitize the genitourinary tract for AS cause resistance to antimicrobial medications, which in turn leads to inadequate treatment of UTIs, increased morbidity, and mortality.

TRANSLOCATION MECHANISM OF MICROORGANISM MIGRATION

As of today, a growing number of researchers are attempting to study the microbial biocenosis of the genitourinary tract both in healthy individuals and in patients with UTI in terms of its relationship with the large intestine microbiota. This approach is aimed at elaborating the etiopathogenesis of infectious diseases in the genitourinary tract. In addition, it is assumed that anorectal disorders (in particular, constipation) may trigger the development of UTIs [20]. Given the fact that a number of neurological diseases, including MS, are characterized by pelvic dysfunction in the clinical presentation, urination disorders often coexist with bowel dysfunction.

Attempts to investigate the translocation mechanism of bacterial migration from the large intestine to the organs of the genitourinary system led to the conclusion that uropathogenic gut bacteria effectively colonize the urinary tract. For instance, healthy women with no UTI episodes in history had fecal *Escherichia coli* isolates in urine, which in general were closely related in the genomic pattern to fecal *E. coli* fecal isolates recovered from UTI patients [21]. When studying cases of UTI caused by *Klebsiella pneumoniae*, this microorganism was also reported to originate from the colon [22].

Yu. L. Naboka et al. presented data on significant correlation coefficients between microorganisms

recovered from urine and those from the colon, which indirectly confirms the translocation mechanism [23]. Alternatively, it is known that normal urine microbiome is characterized by the predominance of *Lactobacillus* in women and *Corynebacterium* in men. *Corynebacterium* microorganisms are common representatives of skin microbial flora in men, while vagina is colonized by various species of the *Lactobacillus* genus, which probably indicates the existence of translocation migration mechanisms between these loci. Therefore, the existence of a fecal – perineal – urethral transmission route of microbial flora to the genitourinary tract is still currently being discussed [24].

MICROBIOTA IN NEUROGENIC BLADDER

Data on the urinary tract microbiome in neurological patients with neurogenic bladder as part of their clinical pattern are scarce and refer to a small group of patients with traumatic spinal cord injury. A cross-over study aimed at examining urinary microbiome compared 27 patients with spinal injury and symptoms of neurogenic bladder with healthy volunteers, using 16S rDNA sequencing and the metaproteomics technique. It is worth noting that more than one technique of urinary diversion was used for 19 patients (intermittent catheterization, Foley catheter).

The top ten bacterial taxa predominant in abundance and variability in urine samples included Lactobacillales, Enterobacteriales, Actinomycetales, Bacillales, Clostridiales, Bacteroidales, Burkholderiales, Pseudomonadales, Bifidobacteriales, and Coriobacteriales. Moreover, Lactobacillales and Enterobacteriales comprised the two most abundant and variable taxonomic groups [25]. Clear *Lactobacillus* predominance was detected in the urine of healthy women in the control group. At the same time, a progressive decrease was noted in the abundance of representatives of normal vaginal microbial flora in women with neurogenic bladder with any type of voiding (whether spontaneous or using a catheter). It is likely that increasing time of catheter use of more than 3 months and an increase in the severity of neurogenic bladder affect the ability of *Lactobacillus* to colonize the urinary tract [25].

An alternative explanation for this phenomenon may be due to the proximity of the external urethra to the vaginal microbiocenosis, therefore bacteria of the *Lactobacillus* genus are considered as contaminants of the urinary tract. However, taking into account the work by A.J. Wolfe et al., who proved the presence of *Lactobacillus* representatives in urine sampled both by transurethral catheters and by suprapubic aspiration directly from the bladder, this assumption seems unlikely [6] *Lactobacillus* bacteria produce lactic acid and thereby control the growth of virulent bacteria incapable of surviving in a more acidic environment. It is suggested that the presence of *Lactobacillus* in the urethra and / or bladder may have a protective effect in both women and men. So, Q. Dong et al. confirmed the presence of *Lactobacillus* microorganisms in clean urine samples of healthy men [26].

This hypothesis has critical implications for individuals with neurogenic bladder. The need to use assistive technology increases the risk of UTI, while dysbiosis of the urinary tract provides a favorable environment for the growth of pathogenic microorganisms. Thus, representatives of *Lactobacillus* are considered as commensal microorganisms reflecting the state of eubiosis more often in women than in men. The microbiome in the risk group for developing UTIs may be characterized by a lower level or even obvious absence of *Lactobacillus*. Taken together, these data suggest that the clinical goal of sterile germ-free urine may not be optimal for the patient.

The microbiological pattern of neurogenic bladder varies depending on the method of urine diversion. Thus, when a catheter is used, *studies describe the predominance of other microorganisms from* the Lactobacillales family, like *Aerococcus* and *Enterococcus* bacteria in addition to a significant decrease in the *Lactobacillus* representation. Two species of aerococci, *A. urinae* and *A. sanguinicola*, may cause UTIs. In addition, the number of Enterobacteriaceae in the urinary microbiota of patients with neurogenic bladder increases with increasing duration of symptoms.

Similar data on the urinary microbiota composition in neurogenic bladder caused by spinal cord injury or *spina bifida* were obtained by E.S. Filippova et al. [27]. The authors noted a correlation between the results of urine culture test and 16S rRNA sequencing data. Consistent with earlier studies, the urobiome of these patients consisted of a variety of *Enterobacterales*. Representatives of *Escherichia*, *Klebsiella*, *Lactobacillus,* and *Enterococcus* were the most common microorganisms.

Metagenomic sequencing provides an opportunity to identify microorganisms undetectable in urine culture tests. In a number of patients, up to 21 genera

were revealed in the urine, namely Cellulomonad (*Cellulomonas* spp.), Prevotellaceae (*Prevotella melaninogenica, Prevotella* spp.), Flavobacteriaceae, and Bacillales Family X. Incertae Sedis, Gemella (*Gemella asaccharolytica*), Carnobacteriaceae (*Carnobacterium* spp.), Veillonellaceae (*Veillonella spp*.), Peptoniphilaceae (*Parvimonas* spp.), Sphingomonadaceae (*Sphingomonas* spp.), Pseudoalteromonadaceae (*Pseudoalteromonas* spp.), Moraxellaceae (*Acinetobacter* spp.), and Vibrionaceae (*Vibrio* spp.).

URODYNAMIC FUNCTIONAL STATUS OF THE BLADDER AND UROBIOME

The mechanisms underlying the interaction of the bladder and microbial flora are diverse and are the subject of scientific debate. One of them is disturbance in bladder wall blood supply due to high intravesical pressure. Tissue ischemia provides favorable conditions for gut microbial flora to colonize the mucosa. Moreover, impaired wall tropism leads to histologic changes in the detrusor, namely, the volume of muscle fibers decreases and connective tissue develops in their place. Such transformations involve a decrease in bladder plasticity and increased ischemia [27, 28].

Another issue related to neurogenic bladder is a high risk of vesicoureteral reflux in the context of high intravesical pressure. Such a disturbance in urodynamics, in turn, is a proven risk factor for UTI in patients with neurogenic bladder [27, 29]. Therefore, the prevention of UTIs in a patient with a neurological disease is based on correction of urodynamics, control of neurogenic detrusor overactivity, prevention of vesicoureteral reflux, and the choice of the optimal urine diversion technique. The place of probiotics in preventing UTIs is still yet to be discussed, since there is insufficient knowledge about the composition and functions of the urinary tract microbiota and a lack of clinical studies that would confirm the proven effectiveness of such a preventive approach.

One of the modern methods incorporating all preventive objectives is therapy for detrusor overactivity with botulinum toxin type A. In a pilot project, E.S. Filippova et al. observed that the qualitative composition of the urinary tract microbiome changed during botulinum therapy for neurogenic bladder. The authors noted a trend toward restoration of eubiosis, specifically, three women out of four demonstrated an increase in Lactobacillaceae and a decrease in Enterobacteriaceae bacteria family [27].

LOWER URINARY TRACT MICROBIOTA AND MULTIPLE SCLEROSIS

Many neurological diseases have pelvic dysfunction in their clinical pattern. However, in publications, special attention is paid to microbiological changes in urine in spinal injury and congenital pathology of the spine.

It has been established that *Escherichia coli*, *Pseudomonas aeruginosa,* and *Klebsiella pneumoniae* are most common in urine in MS. These data were obtained in studies using culture tests. We have not found data on the use of methods that allow for identifying nonculturable bacteria in the urine of patients with MS and neurogenic pelvic dysfunction. It is known that MS is characterized by high prevalence of UTIs and a high relapse rate [30].

Accordingly, in a prospective analysis of 798 MS clinical cases, every third person with primary progressive MS had a history of UTI; every fifth patient with relapsing – remitting MS (RRMS) experienced vaginitis or UTI; 40% of patients with secondary progressive MS had a history of UTI or vaginal infection [31]. However, there are no clear concepts concerning the composition of the lower urinary tract microbiocenosis in MS patients.

It should be noted that sometimes UTIs provoke increased clinical disease activity, aggravating MS [32]. In addition, pharmacological treatment for AS is still often used unnecessarily in clinical practice, even though experts currently emphasize that this approach has no evidence of clinical effectiveness. Since AS treatment causes a significant increase in more resistant strains of bacteria, it should be prescribed in exceptional cases for recurrent acute UTIs, prior to UTI treatment procedures, during pregnancy, or in patients requiring immunosuppression [32].

Lower urinary tract infection with multidrug resistant microbial flora, recurrent UTIs, and irrational use of antibiotics create another problem – antibiotic resistance. Moreover, UTIs in this group of patients are associated with high hospitalization rate and increased mortality. Unlike other neurological patients, those with MS represent a special population exposed to multiple risk factors for the development of infections, such as constant immunomodulatory treatment, episodes of high-dose glucocorticoid therapy for disease exacerbations, focal damage to the spinal cord and concomitant pelvic dysfunction, which often leads to the need for bladder catheterization.

MS patients receive lifelong treatments aimed at modifying the functioning of the immune system, the so-called MS disease-modifying therapy (DMT). In Russia, there are about 11 medicinal compounds registered; they vary by mechanisms of action and degree of influence on the immune system. DMTs in Russia include glatiramer acetate (GA), interferon β-1b and β-1a, teriflunomide (TFN), dimethyl fumarate (DMF), fingolimod, natalizumab (NAT), ocrelizumab, acrelizumab, cladribine, etc. The likelihood of the effect of DMTs on the lower urinary tract microbiota remains a matter of debate.

In 2020, J. Hellgren et al. suggested that the use of rituximab, a medication not registered in Russia for the treatment of MS, may increase the risk of developing UTIs [33]. C.G. Chisari et al. confirmed that the use of rituximab can increase the incidence of UTIs in MS [34]. However, these studies did not investigate the correlation between the duration of rituximab therapy and the incidence of UTIs. Later, M.A. Mesgarof et al. showed that the incidence of UTI increased proportionately to the increasing time of rituximab use [31].

Currently, there is a controversy regarding the use of DMTs and the risk of UTI. It was observed that UTIs were significantly more common in patients receiving alemtuzumab. In two clinical studies, the incidence of UTIs was higher with alemtuzumab compared to interferon β-1a and slightly lower (but not statistically significant) in another study [31, 35].

Some studies confirmed that treatment with interferon β-1b may increase the incidence of UTIs [32, 36]. On the other hand, the 2021 expert consensus on infectious complications during DMT stated that the interferon group did not increase the risk of UTI in MS patients, like the majority of other DMTs, such as GA, TFN, DMF, NAT, fingolimod, cladribine, and ocrelizumab [30]. However, in a more recent study, M.A. Mesgarof et al. obtained data on the significant effect of interferon β-1b therapy and its duration on the likelihood of developing UTI; in turn, interferon β-1a did not increase the risk of UTI [31].

In 2021, B.A. Cree et al. conducted a randomized clinical trial on the effectiveness and safety of fingolimod for the treatment of MS; GA was chosen as a reference-listed drug [37]. In their publication, the authors considered UTI as an adverse event of therapy in the GA group. In addition, M.A. Mesgarof et al. also found that exposure to GA increased the incidence of UTIs, while the duration of its use did not significantly affect this risk [31].

VAGINAL MICROBIOTA AND MULTIPLE SCLEROSIS

MS itself has no adverse effects on fertility, gestation, or childbirth, yet such patients should be especially careful when planning pregnancy. The decision on the possibility of carrying to term is affected by immunotropic therapy and the course of the disease and concomitant conditions, in particular neurourological disorders that increase the risk of UTI.

The composition of the vaginal biotope in MS patients is yet to be studied in detail. We have not found studies devoted to the quantitative and qualitative microbiological composition of the vagina in MS. However, similar to the concept of susceptibility of MS patients to infectious diseases, there is a problem of increasing incidence of bacterial vaginitis in women with MS. This is indicated by some studies and descriptions of clinical cases of infectious vaginitis in women receiving DMT [31].

A long-term follow-up program of patients receiving NAT in context of DMT proved infections to be the most common adverse events of therapy, of which UTIs developed in 0.3% of cases [38]. G.M. Makris et al. note that recurrent vaginitis should be considered as a possible side effect that occurs with long-term NAT treatment [39]. They described a clinical case of a patient with RRMS who suffered from persistent gynecological infections, and culture tests detected pathogenic microorganisms in vaginal secretions. The mentioned female patient received NAT treatment for three years. The chronic infectious and inflammatory condition led to the repeated use of both local and systemic antibacterial and antifungal drugs.

Previously, a number of authors also mentioned natalizumab as a risk factor for the development of vaginitis in MS women [40, 41]. However, the study by M.A. Mesgarof et al. revealed no association between MS treatment with this monoclonal antibody and the development of vaginitis [31].

The use of rituximab within anti-B-cell therapy for MS may also be accompanied by a suboptimal status of the vaginal microbial flora which underlies the disappearance of lactobacilli and increases the risk of infectious complications [42].

J.M. Lee et al., in their interpretation of adverse events of fingolimod therapy, in 2015 reported vaginitis to be a side effect of the drug [43]. M.A. Mesgarof et al. also concluded that fingolimod treatment increased the risk of vaginitis regardless of the duration of therapy [31]. However, more recent

studies have shown contradicting data; a number of studies have not noted an increase in the incidence of vaginal infections [44, 45].

Contemporary literature contains almost no evidence that GA is a risk factor for the development of vaginitis, with the exception of the study by M.A. Mesgarof et al., which demonstrated that long-term GA therapy may contribute to the infectious process in the vagina [31].

The study on the relationship between the type of MS and the incidence of vaginal infections and inflammatory diseases established that vaginitis most often occurred in RRMS, but no significant differences were observed [31].

It should be noted that most studies had a number of limitations related to the number of patients, the methods used, and the influence of concomitant factors.

CONCLUSION

Modern ideas about the urinary tract microbiota in patients with neurogenic bladder suggest the presence of asymptomatic bacteriuria with a pronounced decrease in the bacteria of the normal flora. Voiding dysfunction and its duration, as well as the urinary diversion method are recognized risk factors for UTI, but unanimity was not reached regarding the effect of other factors. Many issues remain unresolved regarding the genitourobiome of MS patients.

This category of neurological patients is a risk group for the development of infectious and inflammatory diseases of the genitourinary system. The probable translocation of microorganisms between loci and the relationship between the functional status of the bladder and the composition of the microbiome may become the basis for new preventive and treatment strategies to solve the problem of UTI, maintain reproductive health, and support family planning. Currently, further research of genitourinary microbiocenosis in MS patients is required to expand fundamental knowledge and improve the quality of medical care.

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Authors' contribution

Luzanova E.I. – conception and design, analysis and interpretation of the data. Karpova M.I., Abramovskikh O.S. – justification of the manuscript or critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Chetvernina E.A., Kupriyanov S.V. – conception and design.

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