INTERSTITIAL CYSTITIS AS A PLAUSIBLE CAUSE OF OVERACTIVE BLADDER IN SYSTEMIC SCLEROSIS: A HYPOTHESIS

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Abstract
Patients with chronic inflammatory disease of the bladder, known as interstitial cystitis (IC), tend to have autoimmune diseases, such as Sjogren's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis and, rarely, systemic sclerosis (SSc). SLE patients with IC are prone to present with overactive bladder (OAB) symptoms. Lower urinary tract involvement is less usual in SSc but OAB symptoms are quite common among SSc patients with lower urinary tract involvement. The underlying mechanisms of lower urinary tract involvement, including OAB, in SSc could be as follows: i) vasculopathy, ii) fibrosis and/or sclerosis of bladder wall, iii) systemic sclerosis-associated myopathy, and iv) autonomic dysfunction. However, the role of IC leading to OAB is unclear. This hypothesis suggests that in patients with SSc, OAB may be associated with IC.

Keywords: Hypothesis, Interstitial cystitis, Lower urinary tract symptoms, Overactive urinary bladder, Systemic scleroderma


INTRODUCTION
Interstitial cystitis (IC), also called as interstitial cystitis/bladder pain syndrome (IC/BPS), is a chronic inflammatory disease of the bladder characterized by pain, urgency, and frequent urination, all of which emerge as a result of reduced bladder capacity or overactive bladder [1,2]. The underlying pathophysiological mechanism of this debilitating condition is still unclear. Recently, IC has been divided into two categories according to the presence or absence of reddish mucosal lesions with abnormal capillary structures in the bladder, which are known as Hunner lesions [3]. IC with Hunner lesions (Hunner-type IC) is regarded as a distinct immunological inflammatory disease entity characterized by urothelial erosion and lymphoplasmacytic infiltration [4]. Mounting evidence suggests that Hunner-type IC is quite common in patients with systemic autoimmune diseases, such as Sjogren’s syndrome, systemic lupus erythematosus (SLE), and rheumatoid arthritis [2].

SLE is a chronic autoimmune disease that can involve the lower urinary tract, resulting in lupus cystitis (LC), which occurs in 0.6% to 2.3% of all SLE patients. The mechanism of LC is not well defined. Possible pathophysiology is explained by vasculitis, associated with immune complexes (IgA, IgG, IgM, C1q and C3) and chemokines and cytokines (MCAF and IL-8) [5]. Even though symptoms are similar in LC and IC, LC is considered to be a different entity, the symptoms of
which are mostly affected by lupus activity [6]. LC symptoms are frequent, urgent, nocturnal, and painful micturition, known as overactive bladder (OAB) symptoms [7,8]. In a study investigating OAB symptoms in patients with SLE and primary Sjögren’s syndrome, it was shown that OAB symptoms might emerge in SLE patients with IC, and the authors concluded that there may be a close link between OAB and IC [9].

Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by vascular injury and progressive tissue fibrosis, mostly involving the skin, many internal organs and, rarely, the lower urinary tract. Lower urinary tract involvement causes symptoms such as urgency and frequent urination, affecting the quality of life in patients with SSc. Urinary incontinence and OAB are the most common entities in SSc [10]. It is not unexpected that SSc might be associated with IC [1]. However in contrast to the situation with SLE, there are no data showing the relationship between IC and SSc. The hypothesis presented herein suggests that IC may be one of the factors leading to OAB in SSc.

Systemic sclerosis and lower urinary tract symptoms
Urinary tract involvement is quite rare in SSc. Interestingly, this involvement is observed more often in limited cutaneous SSc than in diffuse cutaneous SSc [10,11]. The pathogenesis of urinary tract involvement in SSc remains uncertain. However, several mechanisms have been suggested. These mechanisms are: i) vasculopathy caused by dysfunction of endothelial cells that is the key event in the pathogenesis of SSc; ii) fibrosis and/or sclerosis of the bladder wall; iii) systemic sclerosis-associated myopathy, also known as scleromyositis; and lastly, iv) autonomic dysfunction [10,12,13].

In a recent study conducted by Pacini et al. the frequency of urinary tract involvement was reported to be significantly more common in SSc patients than in healthy controls. In this study, urinary incontinence and OAB were more common in SSc patients with sarcopenia and reduced bone mineral density [10]. In a study by Sanchez et al., sexual dysfunction and lower urinary tract symptoms were investigated in SSc and OAB was found to be the most frequently reported lower urinary tract symptom in these patients [11]. Motegi et al. showed that SSc patients might tend to develop OAB. Moreover, old age, a long history of morbidity, high rates of anti-centromere antibody positivity, high incidence of gastroesophageal reflux disease, low rates of anti-SS-A antibody positivity, and a low incidence of internal lung disease were found in SSc patients with OAB than in SSc patients without OAB [14]. Overall, OAB is rather common in SSc and its prevalence varies from 27.9% to 84.9% [11,14]. Even though the mechanisms underlying OAB are not well known, the possible causes are likely to be multifactorial. The mechanisms listed earlier can be counted among these causes. Intriguingly, there is no data to suggest that the involvement of the uroepithelium and lamina propria may cause OAB.

Systemic sclerosis and interstitial cystitis
A study by Ochs et al. investigated autoantibodies in patients with IC and showed that 36% of these patients had antinuclear antibody positivity (1/40 and above ANA levels were accepted as positive). In this study, the ANA pattern was mostly nucleolar, suggesting that IC might be more related to SSc than SLE [1]. However, in a nationwide population-based study evaluating the risk of autoimmune diseases in patients with IC, it was demonstrated that the odds of rheumatoid arthritis were 1.516 times higher and Sjogren’s syndrome were 1.962 times higher. Interestingly, the authors found no increased risk of SLE and did not report any SSc-related outcomes due to the limited number of patients [15].

HYPOTHESIS
IC might be an overlooked factor causing lower urinary tract symptoms in SSc. The clinical manifestations of IC mainly resemble those of OAB, which is prevalent in patients with SSc. Therefore, OAB symptoms can be explained by the presence of IC. This is unproven but causality between these phenomena may be revealed through comprehensive and well-designed studies.

STUDY DESIGN
Case reports, case series, observational and interventional studies, as well as narrative and systematic reviews help to generate hypotheses. These hypotheses need to be tested by observational and interventional studies, and systematic reviews [16,17].

A recent review article summarizing pathophysiology, assessment, and treatment of OAB symptoms in patients with IC suggested that further studies may be helpful to understand IC symptoms overlapping with OAB [18]. Thus, observational studies may be designed initially to reveal the association between IC and OAB in SSc. Determining the eligible study population, based on appropriate inclusion and exclusion criteria should be the first step. Patients’ data, such as socio-demographic variables, medical data (especially, accompanying diseases and medications), disease-related parameters (disease duration, disease subtype, disease severity and activity, and organ involvement) should be recorded [19].
After selecting patients with SSc, IC and OAB symptoms should be evaluated. In general, OAB symptoms are assessed through medical and surgical history, physical examination, laboratory evaluations, urodynamic tests (uroflowmetry and cystometry), electromyography (to assess urethral sphincter activity), and validated assessment tools [20]. In particular patient-reported outcome measures and self-assessment questionnaires, such as the OAB symptom score (OABSS), the 8-item overactive bladder questionnaire (OAB-v8), and Overactive Bladder-Bladder Assessment Tool (OAB-BAT) are frequently preferred in clinical trials [14, 21,22]. In contrast, the diagnosis of IC is made according to American Urological Association and East Asian clinical guidelines [3,23,24]. Accordingly, cystoscopy (and histological) and/or urodynamic studies are recommended in case the diagnosis is still in doubt after a careful medical history, physical examination, and laboratory examination [24]. Last but not least, well-designed methodology that strengthens the study and statistical analyses that accurately identify associations are critical components of creating a research paper that will contribute to the literature [19,25].

CONCLUSION

Here, the present a hypothesis that suggests that IC might play a role in emerging OAB in patients with SSc. Growing evidence shows that patients with IC are prone to having autoimmune systemic diseases, such as SLE, Sjogren’s syndrome, rheumatoid arthritis, and Hashimoto thyroiditis. However, the connection between IC and SSc is still controversial. The relationship between IC and/or LC and OAB has been proven in SLE but a similar relationship to that in SLE has not yet been demonstrated in SSc. Therefore, this hypothesis assumes that OAB is likely to be associated with IC but this remains unproven as yet. In order to reach this conclusion firmly, comprehensive and longitudinal studies are needed to shed light on the etiopathogenesis of OAB in SSc patients.

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AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The author declares no conflicts of interest with respect to the authorship and/or publication of this article.

DISCLAIMER

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ИНТЕРСТИЦИАЛЬДЫ ЦИСТИТ ЖУЙЕЛІК СКЛЕРОЗДАҒЫ ҚҮҰҚТЫҢ ШАМАДАН ТЫС БЕЛСЕНДІЛІГІНІҢ ҰҚТЫМАЛ СЕБЕБІ РЕТІНДЕ: ГИПОТЕЗА

Түйіндеме

Интерстициальды цистит (ИЦ) деп аталатын құқықтың созылмалы қабыну ауруы бар науқастанда, эдетте, Шегрен синдромы, жүйелі қызыл жегі (ЖЖЖЖ), ревматоидты артрит және сиірек жүйелі склероз (ЈС) сияқты аутоиммунды аурулар бар. ЖЖЖЖ және ІЦ бар емделушілер құқықтың шамадан тыс белсенділік бәлгіліріне бейім (ҚШТБ). ЖС кезінде тәменгі зәр шығару жолдарының зақымдауы сиірек кездеседі, бірақ тәменгі зәр шығару жолдары зақымдаған ЖС-на шалдық қаң науқастандар ҚШТБ белгілері айтарлықтай қеңійтен тараған. ЖС кезінде ҚШТБ-мен қоса тәменгі зәр шығару жолдарының зақымдауын ұнтызғы механизмдері келесідей болуы мүмкін: 1) васкулопатия, 2) құққ қабырғасының фиброзы және/немесе склерозы, 3) жүйелі склерозден байланысты миопатия және 4) вегетативті дисфункция. Дегенмен, ҚШТБ-ға алып келетін ІЦ ролі түсініксіз. Бұл гипотеза ЖС-қа шалдық қаң науқастандар ҚШТБ-сы ІЦ-мен байланысты болуы мүмкін екенін қорсетеді.

Түйінді сөздер: гипотеза, интерстициальды цистит, тәменгі зәр шығару жолдарының сіңімтәрді, несепарадың шамадан тыс белсенділігі, жүйелік склеродермия

Дайықсyz ұшын: Гекчен Н. Интерстициальды цистит жүйелік склероздағы құқықтың шамадан тыс белсенділігінің ұқтымақ себебі ретінде: гипотеза. Орталақ Азия медициналық гипотеза және этика журналы 2022:3(2):98-102. https://doi.org/10.47316/cajmhe.2022.3.2.02

ИНТЕРСТИЦИАЛЬНЫЙ ЦИСТИТ КАК ВЕРОЯТНАЯ ПРИЧINA СВЕРХАКТИВНОСТИ МОЧЕВОГО ПУЗЫРЯ ПРИ СИСТЕМНОЙ СКЛЕРОЗЕ: ГИПОТЕЗА

Резюме

Пациенты с хроническим воспалительным заболеванием мочевого пузыря, известным как интерстициальный цистит (ИЦ), как правило, имеют аутоиммунные заболевания, такие как синдром Шегрен, системная красная волчанка (СКВ), ревматоидный артрит и, редко, системный склероз (СС). Пациенты с СКВ и ИЦ склонны к появлению симптомов гиперактивного мочевого пузыря (ГАМП). Поражение нижних мочевыводящих путей при СС встречается реже, но симптомы ГАМП довольно распространены среди пациентов с СС с поражением нижних мочевыводящих путей. Основные механизмы поражения нижних мочевыводящих путей, включая ГАМП, при СС могут быть следующими: 1) васкулопатия, 2) фиброз и/или склероз стенки мочевого пузыря, 3) системная склероз-ассоциированная миопатия и 4) вегетативная дисфункция. Однако роль ИЦ, приводящего к ГАМП, неясна. Эта гипотеза предполагает, что у пациентов с СС ГАМП может быть связан с ИЦ.

Ключевые слова: гипотеза, интерстициальный цистит, симптомы нижних мочевыводящих путей, гиперактивный мочевой пузырь, системная склеродермия

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