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The Painful Bladder Syndrome/Interstitial Cystitis (PBS/IC): A Literature Review

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Abstract

Painful bladder syndrome/interstitial cystitis (PBS/IC) is a complex chronic cystopathy characterized by bladder and/or pelvic pain associated with urinary symptoms such as urgency and frequency. It is part of women's pelvic pain syndromes, alongside urethral pain syndrome, vulvar pain (formerly vulvodynia), and vestibular pain (formerly vestibulodynia). PBS primarily affects middle-aged women but can occur at any age. It causes functional impairment that can lead to physical, psychological, and even socioeconomic alterations for patients. Due to its frequency and the interest aroused by its enigmatic nature, it holds a privileged place among chronic cystopathies. Its pathogenesis is, until now, obscure because several etiopathogeneses have been described without any being proven.

Keywords: Interstitial Cystitis; Painful bladder syndrome; Bladder mucosa

Introduction

Materials and Methods

By reporting an observational case and performing a review of the literature according to the CARE guidelines (using the PubMed database and guidelines from urology, general surgery, and pediatric learned societies), we present the definition of painful bladder syndrome, pathogenesis, diagnostic and therapeutic management methods. We used the following key word associations in French and English: "painful bladder syndrome," "pathogenesis", "interstitial cystitis". Only reviews published in English or French were analyzed.

The reviews were selected based on their level of evidence and their relevance.

Definition

The consensus definition: pelvic pain, pressure, or chronic discomfort lasting more than six months, perceived as being related to the bladder and accompanied by one of the urinary symptoms such as urinary frequency or permanent urge to urinate.

The Definition according to ESSIC

Disease of unknown origin consisting of a painful suprapubic complaint linked to bladder filling, accompanied by other symptoms such as daytime (>8/day) and nocturnal (>1/night) pollakiuria, in the absence of infection or other pathology, with the following characteristics:

- Cystoscopic: glomerulations and/or Hunner's ulcer.
- And/or histological: infiltration by mononuclear inflammatory cells including mast cells and granulation tissue.
- This is a diagnosis of exclusion which requires eliminating the different differential diagnoses. We can schematically describe two main forms:
- The non-ulcerative form of the neurogenic type, which concerns young women with normal bladder capacity.
- The inflammatory type of ulcerative form, less common in Europe, which affects older women and leads to a reduction in bladder capacity.

Epidemiology

Painful bladder syndrome is a rare condition, and accurately determining its incidence proves challenging due to frequent underdiagnosis. Nevertheless, an immediate estimate suggests approximately three cases per 1,000 women, with a ratio of ten women to one man. This estimation may shift as a standardized definition now considers a broader population categorized by endoscopic and histological criteria [1].

The average age at diagnosis is 45 years. However, it appears that PBS/CI incidence is underestimated among men and children [2]. It exhibits a higher prevalence in Anglo-Saxon and northern European countries.

According to Rovner [3], 94% of IC patients are of white ethnicity. Moreover, the majority of women with IC are of Caucasian descent. Some authors note that IC is rare among the Black American population, yet it is reportedly four times more prevalent among Jews according to Lechevallier [4].

Etiopathogeny

The pathogenesis of IC is not yet well established; it appears to be multifactorial involving the immune system, stress, the autonomic nervous system, and specific infectious or toxic agents. Several theories coexist:

- The epithelial theory remains predominant: an epithelial deficiency and of glycosaminoglycans (GAG) would explain an abnormal permeability of the wall to substances contained in urine and in particular potassium, which would be the cause of chronic inflammation of this wall.
- Mast cell theory: for reasons not yet clearly demonstrated, the mast cell cells of the bladder wall would be activated.
- Sensory dysregulation is associated with central spinal sensitization and/or sensory hyperinnervation.
- Functional somatic syndrome.
- Changes in cerebral gray matter (increased in patients) were observed on MRI. Recent publications have suggested a probable genetic support and a role played by urothelial transcription factors including retinoic acid receptors.

Diagnosis

Diagnosing bladder pain syndrome poses challenges due to the lack of standardized definitions and reliable diagnostic criteria. However, the criteria established by the International Continence Society and modified by the European Society for the Study of Interstitial Cystitis in 2005 have been instrumental in defining essential diagnostic criteria for IC/PBS [5].

To diagnose the condition, a thorough history-taking is essential. This involves identifying suprapubic pain associated with bladder filling, along with daytime frequency and nocturia. It is imperative to rule out other pathologies that may present with similar symptoms to SDV. Additionally, a hydro-distention test with bladder biopsies is conducted to detect typical Cystoscopic (Hunner's ulcers) or histological changes [6,7].

While other complementary tests such as urodynamic assessment, the KCl test, and questionnaires are available, they are considered optional for IC/BPS diagnosis [7].

Systematic questioning is crucial, focusing on pelvic pain, pressure, or chronic discomfort persisting for over six months, perceived to be related to bladder filling and accompanied by urinary symptoms such as frequency or a constant urge to urinate.

The symptomatology of PBS/IC is diverse, but certain clinical characteristics facilitate diagnosis. It predominantly affects Women's (nine women for every man). Patients experience constant voiding without urgency, leading to significant pollakiuria, with an average of 16 urinations per day. This pollakiuria is painful and persistent, often of long-standing duration. Suprapubic pain may extend to the vaginal or urethral areas and is typically described as burning or tightness, exacerbated by bladder filling and relieved by urination. Pain tends to occur in intermittent bouts, alternating between intense periods and more bearable but persistent discomfort. Occasionally, this pain may manifest as pressure, discomfort, or embarrassment. Notably, these pains are non-mechanical in nature.

Many symptoms, especially pain, worsen during menstruation and sexual intercourse, leading patients to reduce their frequency or even cease them altogether. While urination may provide temporary relief from pain or discomfort, it often only offers short-term alleviation. This distinction is crucial between SDV and acute bacterial cystitis, which typically involves burning sensations during urination.

A triggering factor is often identifiable, including single or multiple episodes of bacterial cystitis, pelvic surgery, pelvic trauma, or psychological trauma. About one-third of patients report dietary factors that trigger or exacerbate symptoms, with acidic foods typically advised to be avoided.

In 30% of cases, there is an accompanying painful pathology, such as other pain syndromes, fibromyalgia, myofascial pain, chronic irritable bowel syndrome, Sjogren's syndrome, depression, etc.

Gynecological and neuro-perineal clinical examinations are generally limited and almost always normal. However, pain upon bladder pressure during vaginal examination (explaining frequent dyspareunia) or discomfort upon hypogastric or urethral palpation is present in 99% of cases. Consequently, there is no trophic or infectious locoregional perineo-vulvo-vaginal disorder observed during examination. Perineal sensitivity is normal, and sphincter tone and reflexes of the conus medullaris (including

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the anal cough reflex and clitorido-anal reflex) are present. Paraclinically, the cytobacteriological examination of urine is essential to rule out bacterial cystitis. Microscopic hematuria may be present 10% of cases. Urine cytology is particularly useful in ruling out urothelial carcinoma of the urinary tract. Cystoscopy typically reveals a normal bladder mucosa, except in cases of ulcerations called Hunner ulcers (described in 1915), and an exaggeration of bladder sensitivity to filling, which can reproduce unpleasant symptoms explaining pollakiuria. It also facilitates the elimination of other differential diagnoses (such as tumors, stones, etc.), allows for a bladder hydro-distension test, and helps to define bladder capacity under anesthesia, which is reduced in painful bladder syndrome, unlike in forms linked to pelvic hypersensitization. After emptying the bladder, characteristic glomerulations or petechiae are most often observed (described in 1949 by Hand) [8,9].

Urodynamic assessment is performed to rule out an overactive bladder [10]. The bladder filling volume triggering voiding needs is reduced, as is the maximum cystometric capacity. The average functional bladder capacity reported in the literature is 350 ml [11]. Bladder filling is generally painful, sometimes even resulting in hematuria at the end of the examination. However, cystometry can be normal in 3% of cases. Several studies have shown correlations between urodynamic parameters and the severity of symptoms, the presence of Hunner's ulcers, the intensity of glomerulations, and bladder capacity under anesthesia [13]. Ultrasound, CT scan, or MRI are not useful for positive diagnosis. Imaging is mainly used to eliminate differential diagnoses.

The Parson test [14], also known as the KCl test or Potassium Sensitivity Test (PST), is based on the theory of altered urothelial permeability. The test involves filling the bladder with 40 ml of a solution of KCl diluted in 100 ml of physiological saline and leaving it in the bladder for five minutes. The patient reports any occurrence of urinary urgency, pain, or frequency, and a score ranging from 0 to 5 is assigned based on the severity of the provocation 0 for absence of provocation and 5 for marked provocation (Pain Urgency Frequency score). A positive test is indicated by a score greater than two. Between 54% and 83% of patients with interstitial cystitis have a positive PST [15, 16]. A positive Parson test helps identify patients who may respond to treatment with heparin polysulfate and pentosan sodium polysulfate.

The National Institute of Health (NIH) proposed criteria in 1987 with the primary objective of defining homogeneous patient groups for scientific studies. However, these criteria do not allow for a precise diagnosis of CDS/IC. Stricte application of these criteria would exclude 60% of patients recognized as having the disease [17, 18]. In 2008, the European Society for the Study of Interstitial Cystitis (ESSIC) proposed alternative diagnostic criteria

Treatment

The primary objective of treatment is symptom relief to enhance the patient's ability to lead a more functional family and social life. Despite extensive research, technological advancements, and studies conducted, a true cure is currently not feasible. Treatment for SDV is highly individualized and often yields disappointing results, with no current treatment holding marketing authorization (MA) for this indication.

The choice of treatment should be based on a thorough assessment of symptoms and the patient's complaints, carefully weighing the benefits and risks of available therapies. It should also involve careful and regular monitoring. Treatment for PBS/IC varies, ranging from conservative to surgical approaches, and varies based on the severity of the disease.

Patients themselves must actively participate in the therapeutic regimen by attempting to gradually increase the time between urinations, aiming to rehabilitate the bladder and increase its capacity. In three studies [19], a reduction of 50 to 75% in symptoms was observed in at least 50% of subjects. It is advisable to avoid drinks and foods that acidify urine and contribute to increased bladder irritation, such as coffee, tea, carbonated beverages, alcohol, fermented products, or foods rich in tyrosine (organ meats, cheese, certain cereals), as well as spices, seasonings (mayonnaise, vinegar), and acidic foods (citrus fruits, tomatoes). Finally, patients must learn to manage triggering factors such as stress, allergies, physical exercise, and travel.

Diagnostic uncertainty and ineffective treatments often lead to feelings of abandonment and despair among patients. Many individuals find the selves unable to work or engage in sexual intercourse, experiencing relationship failures, suicidal thoughts, or even attempted suicide. Therefore, psychological care becomes essential for therapeutic success. The attention that doctors can give to the psychological aspects of the illness and their support can significantly improve the therapeutic response.

In terms of treatment, several oral medications have been used to alleviate symptoms, including:

- Sodium pentosan polysulfate (Elmiron®): PPS: Its mechanism of action involves a direct effect by restoring the mucin layer of the bladder urothelium and an indirect mechanism by binding toxic substances in the urine. The recommended daily dose is 100 mg three times a day. The optimal effect is typically achieved after 6 to 12 months of treatment. Rare side effects occur in approximately 1 to 4% of cases, especially dyspepsia. The response to treatment varies between 28 and 32% and is often partial [20].

- Antidepressants: These medications can improve the quality of sleep, thereby reducing nocturia. They are prescribed at low doses due to the potential for debilitating side effects (e.g., amitriptyline, fluoxetine, sertraline).

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- Gabapentin (Neurontin®): This antiepileptic drug is increasingly used in the management of chronic pain. It is effective in patients where pain is the dominant symptom [34] and is used as second-line treatment. Gabapentin is believed to have a neuromodulateur effect on pain. The initial dose is 100 mg administered three times daily, with fatigue being a common side effect [21].

- Antihistamines: Hydroxyzine (Atarax®): The effectiveness in symptom control remains controversial. Its activity involves the inhibition of mast cell degranulation. Hydroxyzine is initiated at a dose of 10 to 75 mg at bedtime. The effect is only achieved after 3 months of treatment.

- Cimetidine (Tagamet®): The usual dose is 200 mg × 2/day. It allows for clinical improvement in 74% of patients treated with cimetidine.

- Cyclosporine A (Neoral®): Low-dose administration of cyclosporine A (1.5 mg/kg × 2/day) has shown efficacy in patients with CI, with a superior response compared to PPS (Elmiron®).

- Anticholinergics: Anticholinergic agents such as oxybutynin and tolterodine, used to relax the bladder muscle, have been employed to treat pollakiuria in patients with SDV/CI. Although all these medications may have a sedative effect on the bladder in some patients, it has been demonstrated [36] that their prolonged use could cause urinary retention problems. Therefore, their use in SDV/CI should be cautious.

- The products utilized for intravesical treatment can be administered individually or in a combination, known as a cocktail, which may include various active ingredients, including an analgesic. The recommended frequency of instillations can vary depending on the specific medication utilized. Instillations can be performed either on an outpatient or inpatient basis, particularly in cases requiring multiple instillations per week, which some individuals may prefer. Most fluids utilized for instillation should remain in the bladder for 15 to 60 minutes to ensure effectiveness, with the duration varying depending on the specific product used.

- Dimethyl sulfoxide (DMSO): Only two randomized controlled trials have been conducted thus far to assess the efficacy of DMSO. Perez Marrero [22] noted improvement in 93% of patients treated with DMSO, albeit with a relapse rate of 59%. The primary parameters evaluated included pain, urgency, and bladder capacity. In terms of objective improvements, 93% of patients receiving dimethyl sulfoxide (DMSO) reported symptom improvement compared to 35% of patients receiving placebo. Subjectively, 53% of DMSO-treated patients reported significant improvement versus 13% of placebo-treated patients. Recurrences, occurring a few months after treatment cessation, are quite common. In such cases, potential therapeutic options include basic treatment or combination therapy with heparin or intravesical corticosteroids.

- Heparin: When administered intravesically, heparin acts similarly to an endogenous GAG, restoring part of the natural function of the bladder urothelium and enhancing the protective role of the mucin layer. The ideal instillation schedule has not been firmly established. Weekly bladder instillation of 20,000 to 40,000 IU of heparin diluted in 10 cc of physiological saline for 4 to 6 weeks is a feasible approach. Chronic use of heparin is beneficial; the product should be retained for 30 to 45 minutes. Approximately 4 to 12 months are necessary before observing symptom improvement.

- BCG Therapy (Bacillus Calmette-Guérin): BCG is an attenuated strain of Mycobacterium bovis whose exact mechanism of action is not yet fully understood. This agent is utilized in bladder tumors that do not infiltrate the muscle and is believed to increase nitric oxide levels. Instillations are administered weekly for a duration of 6 weeks. Studies have shown a response rate of 21% for BCG compared to a rate of 12% for placebo when discontinuing BCG therapy in clinical practice [23].

- Sodium Hyaluronate (Cystistat®): Only a small proportion of patients respond to treatment, and for most of them, this response is transient [24,25]. Recently, hyaluronic acid was found to be more effective than heparin in terms of prolonging the effect of bladder hydrodistension, as evidenced in a non-randomized comparative study conducted on patients who underwent a bladder hydrodistension test [23].

- Chondroitin Sulfate 0.2% (Uracyst-S®): This substance is naturally present in the bladder lining's GAG. Clinical improvement following instillation of this substance has been reported.

- Vanilloid Neurotoxins: The protocol involves weekly instillation of 50 ml of a 0.01% resignification solution for 4 weeks. While it leads to an improvement in scores, it does not result in a reduction in pain or urinary frequency. However, the use of intravesical capsaicin instillation in IC/PBS has declined due to the severe burning sensation it causes.

- Silver Nitrate: Intravesical treatment of interstitial cystitis with silver nitrate dates to 1928. However, the "leak" of the product into the peritoneum or retroperitoneum can be dangerous and even fatal. As a result, it is no longer recommended.

- On the surgical front, several therapeutic options are available:

- Hydro-distension Serving both diagnostic and therapeutic purposes, hydro-distension leads to improvement in symptoms for 30 to 50% of patients. This procedure typically provides relief for 4 to 12 months. Its effectiveness is sustained through a voiding schedule and endovesical instillations. Maintenance therapy post-therapeutic hydro-distension typically involves endovesical instillations, usually initiated 20 to 30 days after hydro-distension. However, the rate of improvement diminishes with repeated hydro-distensions.

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- Botulinum Toxin (Botox®): Derived from Clostridium botulinum, botulinum toxin blocks the release of acetylcholine, resulting in prolonged paralysis of the affected sites. Toxin A is commonly used in urology, with doses ranging between 100 and 200 U injected submucosally in 20 to 30 sites. When followed by bladder hydrodistension two weeks later, botulinum toxin injection can improve pain.

- Sacral Neuromodulation: This technique requires a significant improvement of over 50% in symptoms and a counter-test confirming the reappearance of symptoms upon cessation of stimulation to justify definitive implantation. It leads to a reduction in urinary frequency and pain, as well as an improvement in symptom scores in 60% of patients. Sacral neuromodulation is reserved for patients unresponsive to oral or intravesical treatment, with cystectomy being the only viable therapeutic option.

- Total Cystectomy or Superrational Cystectomy with Enlargement Enter cystoplasty: These procedures are reserved for patients with symptoms resistant to all conservative therapeutic approaches.

Conclusion

Painful bladder syndrome continues to be an enigmatic condition, with its etiopathogenesis (involving permeability disorders, inflammation, allergies, and autoimmunity) remaining hypothetical and highly debated. The syndrome manifests as a combination of pain, urinary urgency, and frequency, and its diagnosis is one of exclusion. A sterile result in cytobacteriological urine examination is essential, while urodynamic assessment is crucial for ruling out an overactive bladder. Cystoscopy is employed to confirm the diagnosis, identifying two distinct forms: ulcerative and non-ulcerative. Treatment strategies encompass dietary modifications, oral pharmacological interventions, endovesical instillations, and, in some cases, surgical interventions.

References

1. Mouracade P, Saussine C (2010) Bladder Pain Syndrome/Interstitial Cystitis: Pathophysiology, Diagnosis, and Treatment. EMC (Elsevier Masson SAS, Paris), Urology
2. Parsons Cl (1992) Management of interstitial cystitis and painfull voiding problems in women. IC n°71-AUA Office of Education-AUA 87th Annual Meeting-Washington May.
3. Rovner E (2005) Interstitial cystitis. Medicine.
4. Lechevallier E (2004) Interstitial cystitis: Management. Current issues.
5. Mouracade H Lang, D Jacqmin, CSaussine (2008) Use of new diagnostic criteria for interstitial cystitis in daily practice: about 156 cases. Prog Urol 18(10): 674- 677.
6. Keller L, McCarthy DO, Neider RS (1994) Measurement of symptoms of interstitial cystitis: A pilot study. Urol Clin North Am 21: 67.
7. Parsons CL, Koprowski PF (1991) Interstitial cystitis: successful management by increasing urinary voiding intervals. Urology 37: 207-212.
8. Mouracade P, Saussine C (2010) Syndrome de la douleur vésicale/ cystite interstitielle: physiopathology, diagnostic et treatment. EMC (Elsevier Masson SAS, Paris), Urologie.
9. Mouracade P, Saussine C (2008) La cystite interstitially. Prog Urol 18 (7): 418-425.
10. Sant GR (1997) Interstitial cystitis. Curr Opin Obstet Gynecol 9: 332-336
11. Steinkohl WB, Leach GE (1989) Urodynamic findings in interstitial cystitis. Urology 34: 399-401.
12. Kirkemo A, Peabody M, Diokno AC et al (1997) Associations among urodynamic findings and symptoms in women enrolled in the Interstitial Cystitis Data Base (ICDB)Study. Urology 49: 76-80
13. Parsons CL, Zupkas P, Parsons JK (2001) Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. Urology 57: 428-432.
14. Chambers GK, Fenster HN, Cripps S, Jens M, Taylor D et al. (1999) An assessment of the use of intravesical potassium in the diagnosis of interstitial cystitis. J Urol 162: 699-701.
15. Gregoire M, Liandier F, Naud A, Lacombe L, Fradet Y, et al. (2002) Does the potassium stimulation test predict Cytometric, Cystoscopic outcome in interstitial cystitis? J Urol 168: 556-557.
16. Gillenwater JY, Wein AJ (1988) Summary of the NI of arthritis, diabetes, digestive and kidney diseases. Workshop of I.C. - N.I.H. - Bethesda M.D, August 28-29, 1987, J Urol 140: 203-206.
17. Sant GR (1991) Interstitial cystitis. Monographs in Urology 12(3): 37-62.
18. Fleischmann J (1994) Calcium channel antagonists in the treatment of interstitial cystitis. Urol Clin North Am 21(1): 107-111.
19. Parsons CL, Benson G, Childs SJ, Hanno P, Sant GR (1993) A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosan polysulfate. J Urol 150: 845-888.
20. Sasaki K, Smith CP, Chuang YC, Lee JY, Kim JC, et al. (2001) Oral gabapentin(neurontin)treatment of refractory genitourinary tract pain Tech Urol 7(1): 47-49.
21. Perez-Marrero R, Emerson LE, Fezltis JT (1988) A controlled study of DMSO in interstitial cystitis. J Urol 140: 36-39.
22. Morales A, Emerson L, Nickel JC (1996) Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol 156(1): 45-48.
23. Shao Y, Shen ZJ, Rui WB, Zhou WL (2010) Intravesical instillation of hyaluronic acid prolonged the effect of bladder hydrodistention in patients with severe interstitial cystitis. Urology 75(3): 547-550.

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