THE IMPACT OF HETEROGENEITY ON THE DIAGNOSIS AND TREATMENT OF INTERSTITIAL CYSTITIS

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ABSTRACT

Interstitial cystitis (IC) is a disease for which the etiology remains unknown. IC is one of the most bothersome conditions in urological practice and it commonly affects females, presenting with symptoms of pain on bladder filling and urinary frequency. IC is a heterogeneous syndrome and frequently divided into two subtypes. Compared to the classic IC, the nonulcer type of IC appears different concerning symptomatic, endoscopic and histological findings, as well as the response to various forms of treatment.

This review gives an introduction to the IC syndrome, concerning clinical characteristics and diagnostic criteria. A variety of treatment modalities have been suggested throughout the years and are reviewed and assessed herein, such as hydrodistension of the bladder, intravesical instillation therapy, oral medication, transcutaneous electrical nerve stimulation, transurethral resection of diseased bladder tissue, supratrigonal cystectomy followed by enterocystoplasty and urinary diversion.

Key words: bladder; interstitial cystitis; pelvic pain; voiding dysfunction; treatment

INTRODUCTION

The descriptive term “interstitial cystitis” (IC) was introduced by A. J. C. Skene as early as 1887 (1), but it was not until three decades later that Guy L. Hunner described the ulcer, which is always found in the classic subtype of the disease (2,3). Subsequently, the term “submucous ulcer” was used as well, but when Bumpus demonstrated the general bladder involvement of the disease in 1930, the term “interstitial cystitis” was resumed (4). In 1949, John Hand published a comprehensive study performed on IC patients with varying endoscopic and histopathologic presentation. Several treatment alternatives were evaluated in his article, e.g. hydrodistension, bladder resection and a large number of other neurosurgical procedures (5).

Despite the long time elapsed since the disease was first described, the etiology and pathogenesis of IC are, however, still unknown. Therefore, the treatment regimens for these patients are empirical and symptomatic. The aim of this article is to introduce the disease with focus on diagnosis and therapy.

TWO DISEASES

Patients suffering from IC have symptoms of pain in the bladder region and urinary frequency (5,6). The symptoms are often so annoying that the patients are socially incapacitated (7,8). Though there are still difficulties in defining the disease, there are, however, many indications that interstitial cystitis is a heterogeneous syndrome with different histopathological, immunological and neurobiological features (9-18). IC is therefore often subdivided into two different subtypes: the classic “ulcerous” form of interstitial cystitis and the “early” (6), or “non ulcer” form (19,20). The differences between the two
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subtypes are reflected in clinical manifestation and age distribution. Since the underlying pathogenetic steps of interstitial cystitis remain obscure, varying treatment options have been tried including per oral treatment, intravesical instillation therapy and conservative or major reconstructive surgery. It has also been demonstrated that the two subtypes respond differently to many treatment procedures (21-26), but there has not been any report on progression from IC without ulcer to classic IC and this fact has also been emphasised by several authors (6,19,27). In the recent ten years, various reports from several authors have further highlighted the need for the subdivision of IC (28-31).

IMPACT OF IC ON THE PATIENT’S QUALITY OF LIFE

Undoubtedly, interstitial cystitis is a disease with unpredictable outcome, frequently refractory to treatment. It is never possible to know in advance whether the patients will improve, change for the worse or remain unchanged. As the disease progresses, the symptoms may become so severe that the patients are forced into social incapacitation (7). It is obvious that with a urinary frequency of 50 or even 100 times a day, a person’s way of living must be severely affected. Some patients have to work reduced schedules or go on a disability pension, while others are unable to fulfil essential family obligations. Many patients have to give up sport and leisure activities and travelling may prove difficult or even impossible. Some patients choose to give up sex altogether, rather than risk exacerbation of their symptoms (8).

DIAGNOSIS

Continuous difficulties in defining interstitial cystitis have resulted in different diagnostic criteria in the course of time. The National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIDDK) eventually attained consensus criteria in the late eighties, mainly in order to facilitate comparison of study groups affected by the disease (32).

“CLASSIC” IC

Endoscopically, classic IC presents with reddened mucosal areas. These are often associated with small vessels radiating towards a central scar that ruptures with increasing bladder distension.

Histological specimens obtained from lesions in classic IC contain a great number of inflammatory cells and a characteristic mast cell response (10,15,19).

Classic IC is a destructive inflammation and some patients eventually develop a small capacity fibrotic bladder. Outflow obstruction of the upper urinary tract may also occur in the final stage of classic IC.

“NONULCER” IC

In nonulcer IC, the bladder mucosa is normal at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign. However, a recent report showed that there is no difference in cystoscopic appearance between patients with nonulcer IC and women without bladder symptoms planning to undergo tubal ligation (33), hence making this hallmark of nonulcer IC questionable.

Histologically, there are no or scant inflammatory signs in nonulcer disease.

THERAPY

Oral Medication

As a symptomatic treatment of IC, oral medication is usually first given.

Amitriptyline, which is a tricyclic antidepressant, has been reported to alleviate symptoms in IC (24,34). The drug is thought to act via various mechanisms such as blockade of acetylcholine receptors and inhibition of reuptake of released serotonin and norepinephrine. As amitriptyline is known to block the histamine H1 receptor, it is also believed to act via sedation, possibly via its H1-antagonism (35). Generally, 25 mg is administered before bedtime, when needed with gradual increase to 75 mg over a three week period.
Sodium pentosan polysulfate (Elmiron®) has been tried in a double blind, placebo-controlled study. Subjective improvement in pain, urgency, frequency and nocturia was reported in the patients taking the drug as compared to placebo (36). In an open multicenter study, Fritjofsson et al. demonstrated that pentosan polysulfate had a more favourable effect in classic than in nonulcer IC (23). Sodium pentosan polysulfate is thought to substitute for a defect in the glycosaminoglycan (GAG) layer, a pathogenetic explanation to IC that has been proposed by Parsons and co-workers (37). We normally give 150-200 mg twice daily between meals. Absorption is incomplete.

Hydrodistension

As both subtypes of interstitial cystitis are related to abnormal sensory function, various surgical and nonsurgical approaches have been tried in order to interrupt neural transmission. The long-term results are, however, disappointing.

Hydrodistension has also been advocated to alleviate symptoms in interstitial cystitis (38). Its mechanisms of action are suggested to be the destruction of the submucosal nerve plexus and tension receptors in the bladder wall (39). Pain and frequency have been reported to improve with this therapy, although symptomatic relief is sometimes not achieved or only in the short-term perspective (38). In fact, some authors have found that bladder distension does not work as well in IC as in other irritative bladder disorders (40).

Intravesical Instillation

DMSO (dimethyl sulfoxide) is the treatment of choice in intravesical therapy for IC. DMSO is a scavenger of the intracellular OH radical believed to be an important trigger of inflammatory process (41). Although its mechanism of action in IC is not fully elucidated, this substance has multiple effects and DMSO treatment is associated with a low frequency of serious adverse effects. Another advantage is that it appears possible to teach IC patients to administer intravesical DMSO themselves (42).

Urologists may also consider offering multiagent intravesical therapy in interstitial cystitis patients who do not respond to single-agent therapy. Ghoneim et al. reported on a favourable response in IC patients to a combination of DMSO, methylprednisolone, and heparin sulphate (43). DMSO is, according to our routine, administered twice weekly as 50 ml sterile filtered 50% solution. It is sometimes combined with heparin and bicarbonate for local application (RIMSO-50).

Lidocaine, a local anesthetic, has been reported to give long-lasting symptom relief in a pilot study (44) and is another option for intravesical treatment. Although the initial response to instillation may be excellent, a drawback with this method is that very frequent instillations are needed, sometimes three or four times a day. Moreover, catheterizations may be painful in this group of patients and hence difficult to perform repeatedly.

Chondroitin sulphate (Cystistat®), proposed to substitute for the previously mentioned defect in the GAG layer, has recently been introduced as instillation therapy for IC (45). In the latter study, 71% of the patients were alleviated from symptoms up to twelve weeks post-treatment but owing to the fact that the patients were not randomized, the outcome is to be considered as preliminary. In their study the subtype of IC was not specified. 40 mg weekly for four weeks is advocated, at remission followed by monthly administration.

Bacillus Calmette-Guerin (BCG) instillation therapy has recently been shown to yield good results in symptomatic treatment of IC. Zeidman et al. reported in a small prospective study on favorable outcome after BCG treatment for IC, which had previously proved resistant to other conservative measures (46). These preliminary results were later corroborated in two prospective randomized studies by Peters et al., who likewise demonstrated favorable outcome for IC patients after treatment with BCG (47-48). The BCG therapy is thought to modulate urothelial immune responses and Peters and co-workers speculated that the mechanism of action of BCG in IC could be a downregulation of an interleukin-6 driven type 2 T helper cell response (48). In none of the above-mentioned three studies, however, the subtype of IC was specified.
Quite recently, we presented a prospective double-blind study in which the patients were randomised to treatment with either BCG or DMSO. In our study, we could not demonstrate any benefit from treatment with BCG (OncoTICE) intravesically 12.5 mg weekly for six weeks, compared to DMSO. We also observed that DMSO had no positive effect on maximal functional capacity. On the other hand, we found that in patients with classic IC, the treatment with DMSO resulted in significant reduction of pain as well as reduction of urinary frequency (26).

**Electrical Stimulation**

Suprapubic transcutaneous electrical nerve stimulation (TENS) is proposed to relieve pain in IC by stimulating the myelinated afferents in order to activate segmental inhibitory circuits (49) according to the theory of Melzack and Wall (50) of blockade of afferent impulses by a gate control mechanism. By stimulating more easily excitable afferents from the painful area, the artificial stimulus competes with and blocks the pain impulses. The stimulus may simultaneously elicit autonomic nerve effects like inhibition of detrusor activity (51). Another mechanism is the release of opiates, especially endorphins. The outcome of therapy differs markedly between the two categories of IC, the classic subtype responding better to TENS. In a follow-up study, 33 patients with classic IC and 27 with non-ulcer disease were treated by means of suprapubic, high or low frequency TENS for one to two hours twice daily at maximum, non-painful intensity. The response to treatment was clearly better in the classic subtype of IC. Remarkably, in some cases of classic IC, chronic lesions of the mucosa disappeared during treatment and there was also a total remission of symptoms (22). TENS is administered by means of carbon rubber electrodes positioned 10 cm apart immediately above the pubic bone (Figure 1). The electrodes are applied with a broad tape to enable the patient to be ambulant during treatment for one to two hours twice daily. Treatment is initiated using intensity as high as possible starting with high frequency stimulation (50-100 Hz). If the effect is inadequate or lacking, low frequency stimulation is tested as well (2-10 Hz). The trial should go on for at least two months before evaluation.

**Conservative Surgical Treatment**

Transurethral resection (TUR), as well as laser-fulguration of ulcers, have been found to have a good symptomatic effect on patients with classic interstitial cystitis (21, 52-54).

A possible mode of action of TUR is believed to be the removal of intramural nerve endings engaged by the inflammatory process. Mast cells are considered to play a pivotal role in classic IC and are, intriguingly, redistributed into the epithelium (53,55). This is a very rare finding in human biology, seen only in a few conditions, e.g. seasonal rhinitis (56). Accumulated evidence shows that mast cells are innervated (18,57,58) and the interaction of mast cells with the peripheral nervous system might be the explanation of a good symptomatic response to TUR. Focal aggregates of lymphocytes and plasma cells are also a characteristic feature of classic IC (59) and resection of areas with an intense inflammatory reaction would in fact decrease the local production of a large number of inflammatory mediators of importance for the distressing symptoms. Thus, there are several plausible explanations of the beneficial effect of TUR on bladder lesions. When we perform
TUR on patients with classic IC we first measure bladder capacity under general anaesthesia after distension to full capacity at a pressure of 70-80 centimetres of water. TUR is then performed with a low-pressure continuous irrigating cystoscope, hence avoiding prolonged bladder distension and allowing continuous resection of lesions, which are sometimes extensive. All lesions should be carefully outlined for complete resection and all involved areas, including the peripheral oedema zone, should be removed (Figure-2) with the diathermy equipment preset for pure cutting at as low intensity as possible. The resection should include half or more of the muscular coat underlying the lesions. Direct pin-point coagulation of bleeding vessels is recommended to ensure adequate hemostasis, avoiding broad fulguration. Postoperatively, an indwelling catheter should be left in place until the urine becomes clear.

**Major Open Reconstructive Surgery**

Supratrigonal cystectomy followed by ileocystoplasty (60,61) or colocystoplasty (62,63) has been performed in some patients, or some stages of the disease, preferably end-stage disease, where IC does not at all respond to conservative treatment. This method, however, appears only to be feasible for the classic subtype of IC (25). On patients with end-stage classic IC we perform the procedure as follows: Access to the abdominal cavity is obtained via a lower midline laparotomy incision. After cystotomy, the ureters are intubated with two baby-feeding catheters anchored to the ureteral ridge with 4-0 catgut sutures.

*Figure 2 - First resection chip removed (arrows) during complete resection of a Hunner’s ulcer, including the peripheral edema zone (marked by a dotted line), the resection including half or more of the muscular coat underlying the lesion.*
Figure 3 - The trigone remnant after subtotal resection of the bladder: A)- Note baby-feeding catheters inserted in each of the ureteral orifices; B)- Antimesenterical detubularisation of the ileal segment; C)- Ileal segment folded and sutured to a U-shape; D)- Completion of the substitute by folding the U-shaped segment in order to form a sphere; E)- The substitute anastomosed to the trigone remnant.
Subtotal resection of the bladder is performed, leaving only the internal urethral meatus and both ureteral orifices (Figure-3A). A 40 cm segment of the ileum is isolated, taking care to preserve the vascular supply, and with the distal transection margin located 30 to 40 cm proximal to the ileocecal valve. The segment is detubularised antimesenterically (Figure-3B), double-folded to a spherical shape (Figure-3C and D) and anastomosed to the trigone remnant using an uninterrupted reabsorbable 3-0 suture (Figure-3E). Postoperatively, an external drain tube should be left in place for one to three days, depending on the amount of discharge. The baby feeding ureterostomies are extracted after one week. An indwelling evacuation catheter should be left open, inside the cystoplasty, for 10 days, after which clamping of the catheter may begin with the emptying intervals initially being one hour, gradually increasing. The catheter is usually removed after two to three weeks.

**Urinary Diversion and Supplementary Simplex Cystectomy**

In cases of IC where all conservative treatments have failed, simple urinary diversion with an ileal conduit has been used to overcome severe symptoms (6). The construction of a continent reservoir has also been used for IC in recent years (64). In spite of the fact that diversion procedures carry a significant long-term morbidity (65), there is no doubt room for urinary diversion in patients with severe symptoms from IC refractory to all other kinds of treatment.

As a rule, patients with nonulcer IC are younger than those with classic disease. Therefore, a continent reservoir is generally constructed for patients with nonulcer IC refractory to conservative treatment. In some cases, a simple ileal conduit is preferred. Diversion may primarily be performed without simultaneous cystectomy. Should the patient’s symptoms not be alleviated after the diversion, which unfortunately sometimes occurs, cystectomy will be made extraperitoneally later on. In the vast majority, we have been able to overcome persisting distress by supplementing the diversion procedure with cystourethrectomy. However, in keeping with previous reports (66), we have had occasional cases in which even this ultimate surgical treatment effort has been without result.

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