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REVIEW ARTICLE

Hunner lesion disease differs in diagnosis, treatment and outcome from bladder pain syndrome: an ESSIC working group report

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ABSTRACT

Objectives: There is confusion about the terms of bladder pain syndrome (BPS) and Interstitial Cystitis (IC). The European Society for the Study of IC (ESSIC) classified these according to objective findings [9]. One phenotype, Hunner lesion disease (HLD or ESSIC 3C) differs markedly from other presentations. Therefore, the question was raised as to whether this is a separate condition or BPS subtype.

Methods: An evaluation was made to explore if HLD differs from other BPS presentations regarding symptomatology, physical examination findings, laboratory tests, endoscopy, histopathology, natural history, epidemiology, prognosis and treatment outcomes.

Results: Cystoscopy is the method of choice to identify Hunner lesions, histopathology the method to confirm it. You cannot distinguish between main forms of BPS by means of symptoms, physical examination or laboratory tests. Epidemiologic data are incomplete. HLD seems relatively uncommon, although more frequent in older patients than non-HLD. No indication has been presented of BPS and HLD as a continuum of conditions, one developing into the other.

Conclusions: A paradigm shift in the understanding of BPS/IC is urgent. A highly topical issue is to separate HLD and BPS: treatment results and prognoses differ substantially. Since historically, IC was tantamount to Hunner lesions and interstitial inflammation in the bladder wall, still, a valid definition, the term IC should preferably be reserved for HLD patients. BPS is a symptom syndrome without specific objective findings and should be used for other patients fulfilling the ESSIC definitions.

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Introduction

By 1915, Skene, Fenwick and Hunner had described a disease of the urinary bladder manifested by unusual cystoscopic findings and characteristic symptomatology of frequency and bladder pain [1,2]. It was referred to as 'interstitial cystitis' (IC) or a 'rare type of bladder ulcer'. In the mid-twentieth century, the concept was widened to include patients not fitting into the framework of other diagnostic clusters of lower urinary tract symptoms and without the typical inflammatory lesions of the bladder wall. A paper by Messing and Stamey stating: 'We believe that the finding of multiple petechia-like hemorrhages (glomerulations) on the second distention of the bladder is the hallmark of IC, and that a reduced bladder capacity and a Hunner's ulcer represent a different (classic) stage of the disease' [3] set the scene and was followed by a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop in 1987 (revised 1990), creating standard criteria for patients to be included in clinical trials for IC [4]: pain and/or urgency together with cystoscopic findings of glomerulations and/or Hunner lesion. However, these criteria did not include all patients thought to have IC [5]. Consequently, the diagnosis could be made on the

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presence of any voiding symptoms or pelvic pain if the clinician felt that the patient had IC. It follows that the methods used to diagnose IC could be dramatically diverse and the characteristics of patients in clinical series very disparate.

Because of this increasing confusion concerning the understanding of the diagnosis IC, Jørgen Nordling established the European Society for the Study of IC (ESSIC), in Copenhagen 2004, to describe patient evaluation and define diagnostic criteria [6]. Around this time, the International Continence Society (ICS) introduced Overactive Bladder Syndrome (OAB) as a general symptom syndrome [7] based on the symptom of urinary urgency. This was one of the two symptoms – urgency and pain – in the NIDDK criteria for IC. Later it was found that 78.5% of patients with OAB demonstrate glomerulations after bladder distension [8] thereby fulfilling the NIDDK criteria for IC.

ESSIC [9], in concordance with the European Association of Urology (EAU) chronic pelvic pain guidelines committee [10], introduced bladder pain syndrome (BPS) as a pain syndrome, confusable diseases to be excluded. The ESSIC definition included phenotyping the patients according to cystoscopic appearance and histopathology.

One of the phenotypes in the ESSIC classification is the patient with Hunner lesions (not primarily an ulcer but an inflammatory lesion with typical histopathology findings, ESSIC type 3C) [9]. Patients with BPS with and without Hunner lesions differ in many ways, including several objective findings. The question has been raised as to whether Hunner lesion disease (HLD) should be classified as a separate, confusable disease (HLD or IC in its original meaning) or be kept as a BPS subtype. An ESSIC working group explored evidence to find out if and how patients with Hunner disease differ from BPS patients without Hunner lesion with regard to symptomatology, physical examination findings and laboratory tests including markers, endoscopy, histopathology, natural history, epidemiology and prognosis and treatment outcomes.

Symptoms

A study using a PubMed survey compared questionnaire scores but did not identify any specific questionnaires able to demonstrate symptom differences between HLD and other ESSIC types [11]. Killinger et al. examined whether the characteristics of pain might differ in HLD and non-Hunner presentations [12]. A statistically significant finding was that pain at vaginal penetration was different in HLD patients. The same group reported that chronic diagnoses such as fibromyalgia, migraine and temporo-mandibular joint (TMJ) disorders were more prevalent in non-HLD subjects [13]. Van Moh et al. found significant symptom differences between HLD and non-HLD: patients with HLD had less urologic pain and anxiety attacks and were less likely to have a history of Irritable Bowel Syndrome (IBS), but they had significantly more night-time frequency [14]. In contrast, comparing UPOINT domain scores, Doiron et al. found more severe pain in the HLD group and also more urinary frequency and nocturia compared to the non-HLD group. UPOINT domains did not differ between groups and there was a similar prevalence in IBS diagnosis or IBS-like symptoms in both groups [15].

In conclusion, specific questionnaires and symptoms are not able to pick up significant symptom differences to distinguish between HLD and non-HLD BPS.

Physical examination

Confusable diseases

A detailed history is crucial to identify details of symptoms important for further investigation. It directs attention to areas where pain is felt, and which should be examined closely, for example in the urethral, inguinal, vulvar or lower abdominal areas. The pelvic floor should always be evaluated. Pain areas outside the pelvis are also common and should be taken into account. However, there is still no notion about differences related to HLD *vs.* non-HLD.

Are there special features of physical examination findings in HLD patients?

No prospective data are available about specific differences in physical examination findings in HLD. Retrospectively, there are difficulties in obtaining valid results as available series are heterogeneous, the quality of cystoscopy findings differs, examination procedures are not standardized, and patients are not naive to treatment which may interfere with the findings.

Laboratory tests and markers

Laboratory tests

Hematuria is common in BPS patients with prevalence up to 40%. Hematuria was as common in HLD as in non-HLD patients [16], while pyuria was seen in 44% in HLD *vs.* 17% in non-HLD ($p < .001$). In a study of cyclosporine treatment, the potassium sensitivity test (PST) was 100% positive in patients with HLD compared to 85% in those without [17].

Markers to differentiate BPS phenotypes

An abundance of candidates tested had to be regarded as unreliable for robust categorization [18]. HLD can be diagnosed by excessive nitric oxide evaporation from the bladder [19], also used to evaluate the response to treatment with cyclosporine A [20]. A recent option is analysis of urine Macrophage Migration Inhibitory Factor (MIF) found to be elevated in patients with HLD and also in patients with other inflammatory/painful bladder conditions [21].

In conclusion, it is not possible to categorize by standard laboratory tests alone and markers still play a very limited role in the detection and diagnosis of BPS including HLD.

Endoscopy

Cystoscopy is the method of choice to diagnose Hunner lesions, done under local as well as general/spinal anesthesia. Signs are a reddened area of varying extension which includes fine vessels radiating toward a central pale scar [9,22], often with a small blood clot or fibrin deposit attached to the scar area.

At bladder distension under anesthesia there is a rupture of the lesion into the lamina propia, with petechial oozing of blood from small vessels in a waterfall-like manner [2,9,22]. Mucosal cracks sometimes seen during bladder distension in non-HLD bladders have a very different appearance, being quite superficial, multiple, in non-inflamed areas and should not be misinterpreted as HLD [23]. Profuse bleeding without circumscript lesions is another finding not to be misinterpreted as HLD.

There is an extreme variation of presented prevalence figures ranging from 3.5% to 56%, see Epidemiology section. Among possible explanations a most important one seems to be differences in clinical routines (according to reports at international meetings, still not published). When cystoscopy and bladder distension is a prescribed routine like for example in Scandinavia, Japan, Korea and Russia the prevalence has been reported to be high while in other parts where cystoscopy is optional and depending on the preference of the examiner like in parts of the U.S.A. and Canada detection seems to be remarkably low.

During decades the significance of HLD has been depreciated and the result has been loss of knowledge and disagreement on how to make this diagnosis. An international consensus on how to cystoscopically identify a Hunner lesion is urgently needed. Figure 1 (A–D) illustrates some typical HLD features. Glomerulations appear to be a nonspecific phenomenon without any association with HLD [24,25].

The anesthetic bladder capacity is a parameter of importance: a reduced capacity together with other characteristics is a further indication of HLD as being a destructive inflammation that can result in bladder contracture at end-stage [26].

In conclusion, the ability to identify the various cystoscopic features of the lesion is decisive to be able to make a correct diagnosis.

Histopathology

Biopsy retrieval and histopathology evaluation are important in the diagnosis of BPS to exclude confusable diseases. In non-HLD phenotypes, the majority of histopathology

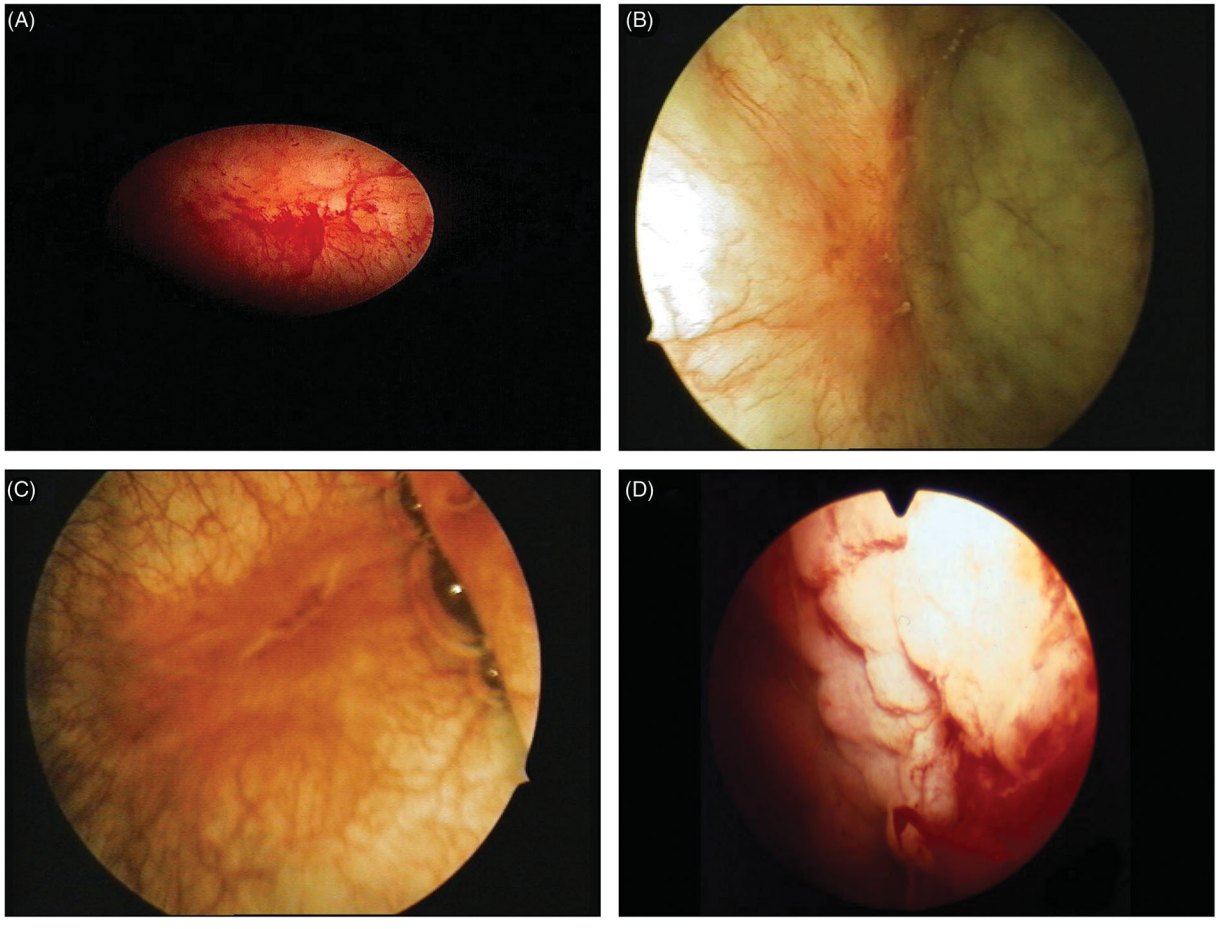

Figure 1. (A) Initial phase of bladder distension: waterfall-like bleeding from discrete Hunner lesion. (B) Star-like lesion with small, central fibrin attachments (no distension). (C) Extensive Hunner lesion with peripheral vessels radiating toward the inflamed area (no distension). (D) Marked edema surrounding Hunner lesion post-distension.

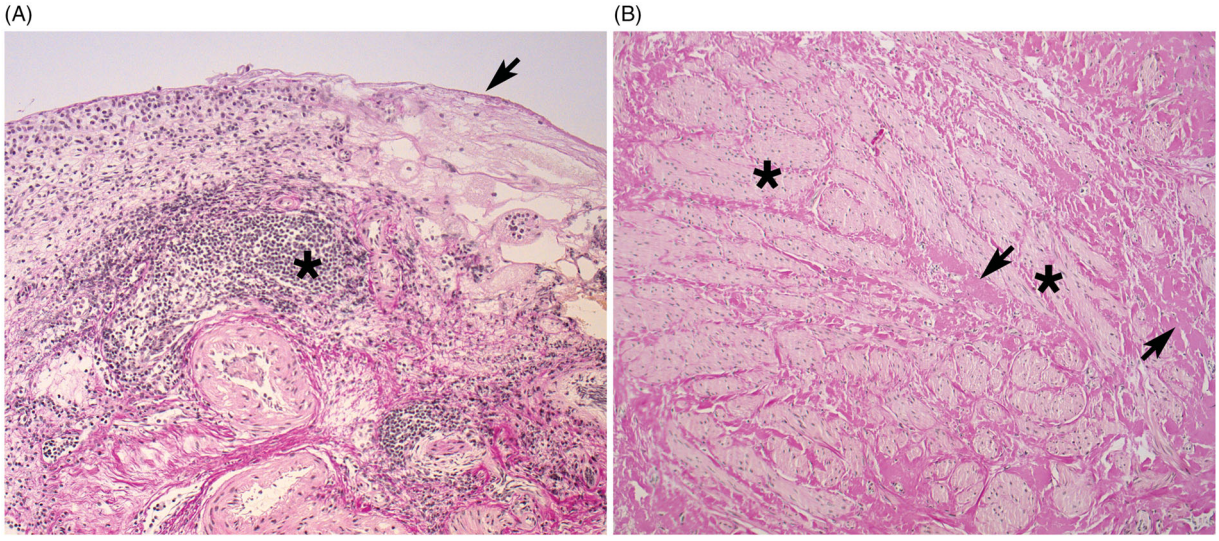

Figure 2. (A) Superficial part of bladder mucosa showing denudation of urothelium. Signs of ulceration with fibrin (arrow). Chronic inflammation with germinal center (star). HTX/Eosin, magnification 200. (B) Deeper part of bladder mucosa showing detrusor bundles (stars) separated by fibrosis (arrows). Van Gieson, magnification 200.

features are slight and non-specific, while certain signs are characteristic for HLD. Deep biopsies including bladder muscle have been recommended, since the disease process involves superficial as well as deeper layers of the bladder wall. Specimens from patients with HLD display striking histologic alterations with prominent ulcerations that may be covered by fibrin mixed with inflammatory cells, in particular neutrophils. The lesions are often wedge-shaped and involve the superficial part of the lamina propria, often extending into the muscularis mucosae. Underlying granulation tissue is present in the vast majority of the subjects. There is often denudation of the urothelium, but if present reactive changes are common (Figure 2(A)).

Fibrosis in the underlying mucosa is an important feature, both inter- and intrafascicular fibrosis in detrusor bundles (Figure 2(B)) [23].

Hence, HLD displays marked inflammatory changes in the lamina propria, including the presence of lymphocytes, plasma cells, mast cells, macrophages and neutrophils. Eosinophils are generally absent. Lymphoid germinal center formation is frequently seen. The role of the mast cell in HLD has been repeatedly indicated [27–29]. Proteinase immune staining with mast cell tryptase (Figure 3) yields higher numbers of mast cells in classic IC/HLD mucosal stroma and detrusor musculature compared to counts in non-HLD and normal bladders. The combination of observations mentioned above is pathognomonic for HLD.

Superficial mucosal biopsies are more easily obtainable but at the cost of diagnostic reliability; to distinguish between HLD and confusable diseases such as ulcerative hemorrhagic cystitis or other inflammatory conditions will be difficult.

Conditions decisive for a report to be relied on are, in addition to the necessity to deliver high-quality specimens, to cooperate with a dedicated pathologist.

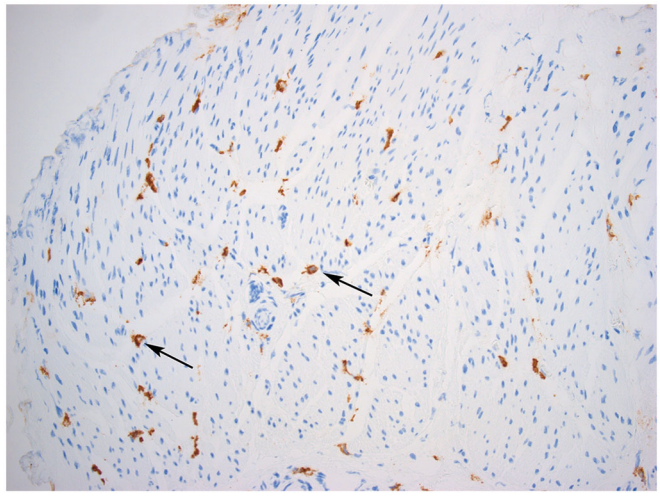

Figure 3. The detrusor muscle with mastocytosis showing mast cells positive with Mast Cell Tryptase (arrows). Magnification 200.

In conclusion, important microscopic features to consider when making the diagnosis are ulceration, granulation tissue, chronic inflammation including inflammatory cell patterns, fibrosis and mast cell counts. Unequivocal HLD diagnosis requires support by typical histopathology findings.

Treatments and outcomes

Local ablation of lesions represents a cornerstone in the treatment of HLD [30–34] an alternative being *intra-lesion injections* of steroids [35,36]. Initial technical shortcomings may have had an impact on slow acceptance of local ablation. Greenberg et al. [30] did not get overwhelming long-term success with TUR of Hunner lesions. However, Fall [31] reported that in 30 HLD patients complete TUR resulted in disappearance of pain in all and a decrease in urinary frequency in 21, with long-term remission of symptoms in the

majority. A second resection often resulted in prolonged duration of symptom remission. Peeker et al. [32] analyzed long-term results of complete TUR in 103 HLD subjects treated from 1974 to 1997: 92/103 patients had symptom relief, sustained for more than 3 years in 40% of subjects, in some up to 7 years. Payne reported on endoscopic ablation of HLs with fulguration in 23 patients: 18 patients had a significant decrease in pain, and 4 patients remained symptom-free for 7 years [33]. Chennamsetty et al. reported results of electrocoagulation on 76 patients treated from 1997 to 2013 with an overall improvement in 90% of patients; 56% had a marked improvement [34]. Although Malloy and Shanberg [37] did not find a too impressive long-term outcome of neodymium-YAG laser treatment of Hunner lesions, Rofeim et al. [38] later reported excellent results.

Thus, there is concordance of results in centers with a special interest in HLD. Completeness of surgery is key. Local ablation of lesions is one of the small numbers of options with very good efficacy – not applicable in other BPS presentations.

Cyclosporine A. In a study comparing pentosan polysulfate sodium and cyclosporine, cyclosporine A resulted in a high success rate for patients with HLD while success was limited in patients without HL [39].

TENS is a simple, cheap, non-destructive means of treating BPS. In an open study, the response rate was found to be much better in patients with HLD compared to non-HLD. In a few patients, long-term TENS even resulted in apparent cure of HLD [40].

Major surgery: Patients with small anesthetic bladder capacity (who almost invariably have HLD) are better candidates for major surgery. The results are favorable in end-stage HLD, prevalent operations being urinary diversion with/without cystectomy or supratrigonal cystectomy and entero-cystoplasty [41,42]. In non-HLD patients, the situation is the opposite. Reconstruction procedures have been encumbered by lack of efficacy and major complications and should be used very restrictively [42], although experiences differ from center to center.

In conclusion, lesion ablation and steroid injection are efficacious and apply only to HLD because local areas to be treated do not exist in other BPS patients. Other treatments differ substantially when utilized in HLD *vs*. non-HLD patients and taken together the differences in treatment opportunities call for separation of HLD from other presentations of BPS either as a separate phenotype with its own ICD11 code or as a separate disease.

The epidemiology of Hunner lesions

Few studies devote specific attention to HLD epidemiology. HLD has been regarded as relatively rare and current medical coding strategies do not make any distinction between patients with or without HLD, making retrospective analyses difficult to perform. Most BPS investigations are based on patient populations derived from tertiary care centers, unlikely to truly reflect general population demographics.

Table 1. Percentage of HLD patients within varied studies.

Year	Author	HL Prevalence/ Total No. IC/BPS patients
1949	Hand [43]	13%/223
1993	Koziol et al. [45]	20%/374
2004	Forrest and Schmidt[a] [44]	10%/92
2008	Braunstein et al. [16]	39%/223
2012	Logadottir et al. [26]	55%/393
2013	Killinger et al. [12]	17%/214

[a]Forrest evaluated only males.

Furthermore, criteria for the diagnosis vary widely between centers and studies, some not requiring cystoscopy.

While a focal region of gross inflammation on the bladder wall without evidence of neoplasia or other well-described pathology might indeed be a Hunner lesion, many clinicians will characterize a Hunner lesion as an area of inflammation that develops only during hydrodistention of the bladder. This variation in diagnostic criteria becomes particularly problematic when evaluating early studies such as Hand where patients were grouped by inflammatory changes and response to bladder filling rather than the presence or absence of HL [43]. Despite these limitations, common epidemiologic threads between studies do exist.

Prevalence data

Data regarding the prevalence of HLD are quite disparate, ranging from 3.5% to 56% (Table 1), see also comments in Endoscopy section.

Of note, the authors of this paper treating hundreds of patients with BPS with and without Hunner lesions have never seen it and although internationally this has been a point of vital importance nothing in the literature suggests that non-Hunner disease becomes Hunner positive disease or vice versa.

Age

Most studies suggest that patients with HLD tend to be older than those without (Table 2).

Gender

As seen in non-HLD BPS populations, most studies suggest a female predominance in those suffering from HLD. Forrest and Schmidt postulated that this female bias might be related to the historical shunting of men to chronic prostatitis/chronic pelvic pain syndrome diagnosis [44]. Studies evaluating both men and women consistently demonstrate a higher prevalence of HLD in females [12,16,26,45,46]. Dejuana and Everett evaluated 110 patients with HLD and identified a 9:1 female to male ratio (99 women and 11 men) [47]. Braunstein et al. compared clinical presentation and symptom severity in 86 HLD patients to 137 non-HLD patients. About 77% of the HLD cohort was female (66/86) and 23% was male (20/86), compared to the non-HLD cohort in which 86% were female (118/137) and 14% were male (19/137) [16]. Logadottir et al. found that 52.7% (217/379) of

Table 2. Age of HL patients *vs.* non-HL patients.

Year	Author	HL mean age of symptom onset	HL mean age of diagnosis or at time of study[a]	Non-HL mean age of symptom onset	Non-HL mean age of diagnosis or at time of study[a]	Comments
1949	Hand [43]	41	53.5	35.5	43	No males were noted to have HL
1977	DeJuana and Everett [47]		58[a]			Female predominate; HL was inclusion criteria for study
1993	Koziol [45]	43.6	57.1[a]	42	52[a]	
2008	Braunstein et al. [16]		60[a]		47[a]	Female predominate in HL and non-HL patients
2012	Logadottir [26]		62		42	Female predominate in HL and non-HL patients
2013	Killinger et al. [12]		62[a]		55[a]	

their BPS patients had HLD. Of these, 80.6% (175/217) were women and 19.4% (42/217) were men [26]. Most strikingly, amongst 223 IC/BPS patients evaluated by Hand, 29 patients had findings consistent with HLD (termed grade 3 by the author) and all were female [43].

Race

The few studies that gathered data all demonstrated a notably high HLD prevalence amongst Caucasians [12,43,44,46]. Indeed, DeJuana and Everett described that 100% of their HLD population were Caucasian [47]. Killinger et al. presented similar findings: 94.4% (34/36) of HLD patients and 97.2% (171/176) of non-HLD patients were Caucasian (p=.34) [12]. Clearly, the relationship between race and HLD may be affected by multiple factors including the location of the study population and socioeconomic dynamics. Of all demographics reviewed with reference to HLD, race data are undoubtedly the least reliable.

Comorbid conditions

The association between BPS and other chronic medical conditions such as chronic fatigue syndrome, irritable bowel syndrome, TMJ dysfunction, fibromyalgia, migraine and vulvodynia has been well reported in the literature [48]. Peters et al. evaluated 639 women (425 controls, 36 with HLD and 178 with non-HLD) and on the mean number of comorbid diagnoses the non-HLD group reported the most, followed by the HLD group, and controls (3.5 (+/− 2.3), 2.3 (+/− 2.0), 1.2 (+/− 1.5), respectively, $p < .01$). Additionally, a disproportionately higher number of patients with fibromyalgia, migraine and TMJ (p=.03, p=.03, $p < .01$, respectively) were identified in the non-HLD *vs.* the HLD group [13].

Associations with autoimmune conditions such as Sjögren's syndrome have also been noted.

In conclusion, despite the high prevalence of BPS, basic epidemiologic data are lacking with regard to the HLD type of disease. Common links between investigations suggest that this condition is relatively uncommon and is more frequently diagnosed in relatively older patients. Few data exist with respect to gender or ethnicity or to support a transition from non-HLD to HLD. Our current poor knowledge of HLD epidemiology is primarily attributable to the combination of HLD and non-HLD in almost all clinical studies. Again, future studies need to longitudinally evaluate HLD and non-HLD BPS as two separate entities.

Discussion

In a survey like the present one it is not possible to include all existing arguments for improving scientific and clinical precision applying to BPS/IC but there are further recent reports agreeing with the idea of HLD as a disease separate from BPS [49,50]. It should be remembered that IC was originally described as a disease characterized by the presence of Hunner lesions and the sign of interstitial bladder wall inflammation, a still valid definition. It is, therefore, our opinion that the diagnosis of IC should be reserved for Hunner lesion patients (alternatively denominated HLD) with a separate ICD coding. BPS does not fulfill these criteria: that designation should be used for other patients fulfilling the ESSIC definition, with HLD as a confusable disease.

Retention of IC as a general term for bladder pain conditions and persistent reluctance to move to a more precise basis of clinical division depends to a large degree on well-founded concerns about reimbursement issues, by patients as well as by physicians. However, when there is medical progress, changes in regulatory instructions should follow. Furthermore, all regulations have to be formulated with great circumspection to ensure that there is no detrimental influence on the quality of science and clinical care as a result of less judicious administrative decisions.

Summary and conclusions

It is evident today that BPS includes two distinct main phenotypes: Hunner lesion patients and non-Hunner lesion patients. It can be assumed that additionally defined phenotypes will be identified, especially in the non-lesion group. From the present evidence, it is clear that you cannot distinguish between the two by means of symptoms, physical examination and laboratory tests including markers, except for NO – evaporation from the bladder [19]. Cystoscopy is still the method of choice to diagnose a Hunner lesion and histopathology the method of choice to confirm it. It is of paramount importance to distinguish between the two main categories since treatment and prognosis differ substantially! HLD patients can be offered treatments yielding almost complete symptomatic relief for years, while such treatments are not available for non-HLD lesion patients, where treatment results are unpredictable and in many cases inadequate. It is time to accept that classic IC with Hunner lesions and BPS always should be evaluated separately in science [22] as well as in clinical routine.

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No potential conflict of interest has been reported by the author(s).

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