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REVIEW PAPER

An update on treatment options for interstitial cystitis

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Abstract

Interstitial cystitis or bladder pain syndrome (IC/BPS) is a chronic pelvic pain syndrome related to the urinary bladder. The ideal treatment should match as much as possible with the pathophysiologic causes of the IC/BPS, but the scarcely available evidence limits this approach, with the majority of available treatments that are primarily targeted to the control of symptoms. The treatment strategies have traditionally focused on the bladder, which is considered the primary end-organ and source of pain. Nevertheless, the growing body of evidence suggests a multifaceted nature of the disease with systemic components. In general, guidelines recommend the personalized and progressive approach, that starts from the more conservative options and then advances toward more invasive and combined treatments. The behavioral changes represent the first and most conservative steps. They can be combined with oral medications or progressively with intravesical instillation of drugs, up to more invasive techniques in a combined way. Despite the multiple available options, the optimal treatment is not easy to be found. Only further investigation on the etiopathogenetic mechanisms, taking into account the differences among subgroups, and the interaction between central and peripherical factors may allow providing a real improvement in the treatment and management of these patients.

Key words: urinary bladder, interstitial cystitis, pelvic pain, intravesical administration.

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pelvic pain syndrome characterized by pain, pressure, or discomfort perceived to be related to the urinary bladder, that lasts more than 6 months with at least one other urinary symptom such as frequency or persistent urge [1]. Because other diseases can provide same symptoms, the exclusion of infection or other identifiable cause(s) is mandatory, as well as further investigation to document possible overlapping of multiple conditions [1, 2]. In the clinical setting, a shorter period of 6 weeks duration was proposed to allow early diagnosis and treatment [3].

The term BPS alone is considered the most appropriate, because the related clinical diagnostic criteria are more inclusive than those based only on cystoscopy and histological findings, which does not recognize up to the 60% of patients. On that basis, some guidelines does not further require cystoscopy for the diagnosis [1, 3-5]. The BPS is defined by clinical symptoms and is based on the hypothesis that women affected by this condition are a homogenous group having a disease with the same etiopathogenesis, with subgroups distinguished by positive signs [5]. Nevertheless, although in IC/BPS the terms BPS and IC are reported together due to formal/historical reasons, they are not actually the same concept. IC is a subgroup (type) of BPS with cystoscopic and histologic signs of interstitial inflammation fulfilling the diagnostic requirements of the original term "IC" [1]. IC diagnosis requires cystoscopy with bladder hydrodistension and/or some peculiar morphological findings in bladder biopsies. The findings of cystoscopy can be glomerulations or Hunner lesions; meanwhile, histologic evaluation of mucosal biopsy can show inflammatory infiltrates, granulation tissue, detrusor mastocytosis, and/or interfascicular fibrosis [1, 4, 5]. The diagnosis of BPS is actually based on clinical symptoms after the exclusion of other urological and gynecological conditions having similar presentation and/or on the cystoscopic/histologic findings [4]. Noteworthy, often patients refer to the gynecologist based on the chronic pelvic pain that characterizes the disease. In this scenario, an appropriate gynecological evaluation is of paramount importance to exclude other pathologies, such as endometriosis [2, 6-8]. Endometriosis is able to present with similar symptoms and can directly involve the bladder [9], and not rarely

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the two conditions are overlapping [10]. However, the correct identification of symptoms and the exclusion of other pathologies as well as the suspect of an overlapping condition are important to appropriately refer the patient to a urologist or urogynecologist [11].

The improved understanding of the BPS pathophysiology has raised the numbers of diagnosis, although the variations over time of BPS diagnostic criteria has meant that epidemiological studies reported different statistics on prevalence [5]. Based on the less and the most inclusive definitions, the BPS prevalence in women was reported ranging between 0.83% and 2.71% [12]. Similarly, the 6.53% vs. the 2.70% of women who met symptom criteria, respectively based on high sensitivity vs. high specificity definitions [13].

Although the growing body of evidence about the IC/BPS clinical presentation and pathophysiology, the real etiopathogenesis is not completely understood as well as the role of the different cystoscopic/histologic presentation. These factors limit the available evidence-based treatment options, that are of paramount importance to maximize treatment outcomes since the early stages of the disease [5, 14]. Noteworthy, the early diagnosis has a key role in the syndrome [15], that is a pain syndrome and can determine a pelvic cross-organ sensitization worsening symptoms and hardening management and resolution.

Treatment option overview

The ideal treatment should match as much as possible with the pathophysiologic causes of the IC/BPS, but the scarce evidence limits this approach with the majority of available treatments primarily targeted at symptom control [5]. Treatments strategies have traditionally focused on the bladder, that is considered the primary end organ and source of pain, where most of the IC/BPS symptoms seemed to manifest. Nevertheless, the growing body of evidence on the IC/BPS pathophysiology suggested a multifaceted nature of the disease with systemic components [16]. On that basis, the available treatment options increased from the local (bladder/pelvic) approach to the systemic approach, supporting a multifactorial and comprehensive management [14]. In general, guidelines recommend the personalized and progressive approach, that starts from the more conservative options and then advances toward more invasive and combined treatments [3, 17].

Conservative treatment

The conservative management of IC/BPS represents the first-line treatment option. Behavioral and diet changes, psychological stress management, urogynecological exercises, and heat or cold therapy represent the first therapeutic strategies [3, 17]. All these interventions are available only after adequate patient education, that represents the first actual step. Patient needs to be made aware about the bladder function, what is known about IC/BPS, that multiple trials may be required before acceptable symptom control, that often multiple simultaneous approach are necessary, and that specific behavior might improve or worsen IC/BPS symptoms [18]. Because most of these interventions are inexpensive and risk free, they should be encouraged. Diet restriction with the reduced consumption of coffee, tea, alcohol, chocolate and spicy food are reported improving IC/BPS symptoms. This intervention may allow to identify which specific food or fluid may affect each patient. Additionally, the regulation of diet and fluids intake reduces constipation and normalizes the frequency of urination [18, 19]. Pelvic floor relaxation exercises (placing knees against the chest, reclining with spread legs, or squatting) and bladder training have also been shown to improve symptoms increasing intervals between urinations and void volume [20, 21]. Although all of these approaches are able to improve IC/BPS, the psychological support with appropriate coping strategies and stress management has a key role in these women. IC/BPS symptoms are reported related to stress [22-24] and depression similarly to other chronic pain syndromes [25-28]. Psychological, emotional, and social support resulted in an improved health, quality of life, and symptoms [18].

Non-pharmacological treatment

The utility of pelvic floor physical therapy for the management of BPS is related to the hypertonic pelvic floor muscle dysfunction reported in affected women, although it is not known if these alterations are primary or secondary to IC/BPS [29]. Physical therapy is aimed to release the myofascial trigger points and the connective tissue. Randomized controlled trial reported an improvement in pain, urgency, frequency and quality of life (QoL) for women who underwent myofascial physical therapy as compared to women who underwent general therapeutic massage [30]. These results were confirmed by further studies investigating the effectiveness of physical massage in BPS, that can be usually recommended for most patients [11, 20, 31, 32].

Similarly to physical therapy, because of safety and relatively affordability, acupuncture can be considered an option in women affected by IC/BPS based on studies suggesting the effectiveness of the technique, although the evidence is limited and more data are required [11, 29, 33-35].

Conversely, conflicting results are reported about the effectiveness of transcutaneous nerve stimulation. The transcutaneous stimulation of peripheral sensory nerves aims to modulate the pain impulses and has the advan-

tage of being available in outpatient setting. Nevertheless, it requires continuous and daily use for months to achieve modest symptoms improvement [11, 29].

Oral medications

Oral pharmacotherapy for IC/BPS represents a second line therapy that should be combined with conservative treatments [3, 33, 36].

Pentosan polysulfate

The only oral medication approved by the U.S. Food and Drug Administration (FDA) for treatment of IC/BPS is the pentosan polysulfate (PPS) [36]. PPS is a synthetic sulfated polysaccharide, which therapeutic function is supposed to be the reduction of urothelial permeability by reconstituting the glycosaminoglycan (GAG) layer of the bladder urothelium, that is thought to be compromised in patients affected by IC/BPS [5]. The symptoms of IC/BPS are supposed to be related to urothelium abnormalities caused by the disruption of the GAG layer overlining apical cells, which normally regulate the passage of cations and protects the urothelium from bacteria and toxic substances [37, 38]. PPS is one of the most studied therapies for IC/BPS, and different studies, randomized controlled trials, and meta-analysis supported the improvement of symptoms with PPS treatment as compared to placebo, with the reduction of pain, urgency, and frequency [39, 40]. Nevertheless, more recent randomized controlled trials provided conflicting results, reporting no statistically significant differences of symptoms between PPS treatment and placebo [41, 42]. On that basis, the Royal College of Obstetricians and Gynecologists (RCOG) no longer recommend PPS for treatment of IC/BPS considering the undemonstrated efficacy and the adverse effects of diarrhea, vomiting, rectal bleeding and alopecia [43]. Nevertheless, it is still recommended in other guidelines, although recognizing the limited evidence [3].

Tricyclic antidepressants

Tricyclic antidepressants have a wide range of interactions with different pattern of neurotransmitters receptors. Among them, Amitriptyline is the most studied for the treatment of IC/BPS and act blocking the reuptake of released serotonin and noradrenaline, histamine 1 receptors, and acetylcholine receptors. It is supposed that the urgency and frequency symptoms are alleviated by the anticholinergic effects, meanwhile interaction with neurotransmitters reuptake may have an analgesic effect [14]. Different studies reported an improvement of symptoms ranging between the 50% and 70% in the treated group as compared to placebo, although efficacy is directly related to the dosage as well as side effects, such as nausea, constipation, dry mouth, weight gain, blurred vision, lightheadedness, and sedation [44]. The therapeutic efficacy resulted strictly related to the highest tolerated dose, that, ranging between 25 mg to 100 mg, reported a clinical improvement up to the 63% of patients [45-47]. Nevertheless, the majority of patients are not able to tolerate and achieve the therapeutic dose with a rate of side effects up to the 79% [47].

Histamine and leukotriene receptor inhibitors

Mast cells infiltrates and detrusor mastocytosis are reported in patients affected by BPS with histological signs of IC, and it was supposed that the mediators released in hypersensitivity reaction by these cells may lead to urinary symptoms [48, 49]. On that basis, histamine receptor inhibitors were investigated as possible therapeutic option in these patients as molecules able to reduce the mastocytes activation and subsequently BPS symptoms [14]. Among them, cimetidine and hydroxyzine were the most investigated so far. Cimetidine (H2 antagonist) was related to a significant improvement of suprapubic pain and nocturia as compared to placebo in a randomized controlled trial, although the histology of the bladder biopses was reported unchanged [21, 50, 51]. Hydroxyzine is a H1 antagonist with anticholinergic activity, that reported in different observational studies an improvement of symptoms up to the 90% of treated patients, with sedation representing the primary side effect. Conversely, in a randomized controlled trial these results were not confirmed [42]. Both drugs have limited and conflicting evidence supporting their therapeutic role in IC/BPS, and some guidelines do not recommend their use [43]. On the contrary, others includes histamine receptor inhibitors in second line therapies due to their safety therapeutic profile with few side effects beyond sedation [5].

Other than histamine, leukotriene plays a key role in the activation of mast cells and eosinophils [52]. In patients with IC/BPS higher levels of leukotriene were identified in the urine of women with detrusor mastocytosis, supporting a potential key role of these mediators in the pathophysiology of IC/BPS [53]. In line with this evidence, montelukast, a leukotriene receptor-1 antagonist, was reported able to improve symptoms of patients affected by IC/BPS in a pilot study and in a case report [54, 55].

Immunosuppressants

In addition to mast cells infiltrates, in women affected by IC/BPS infiltration of the bladder mucosa by CD4 T lymphocytes and eosinophilic leukocytes was

reported. This inflammatory components suggest an autoimmune pathogenesis of the disease, and humoral or cell-mediated mechanisms targeting the bladder mucosa may cause the episodic exacerbation of the IC/BPS [56, 57]. On that basis, cyclosporine A was investigated as immunosuppressant for the treatment of refractory cases of IC/BPS. Different observational studies reported an improvement of symptoms with reduced pain, increased max bladder capacity, and voided volume [58]. A subsequent randomized trial showed cyclosporine A superior to PPS with higher improved pain, frequency, void volume and nocturia at 6 months [59]. Overall, all the available pieces of evidence summarized in a systematic review support the effectiveness of cyclosporine A in the treatment of IC/BPS, even in patients who had failed one or more oral therapies [60]. Although the promising long-term therapeutic effects, the use of cyclosporin A is not without side effects. Nephrotoxicity, reduced glomerular filtration rate, increased creatinine levels, and hypertension are side effects regularly reported and should be always monitored and weighted with therapeutic benefits [58-61]. On that basis, the better understanding of the mechanism of action of cyclosporine A may allow to identify women who will benefit from the treatment and the minimum dose required to achieve a satisfactory result. Due to these side effects, cyclosporine A is recommended in patients affected by IC/BPS refractory to all other therapies [3, 33].

Rosiptor (AQX-1125)

The novel SH2-containing inositol-5′-phosphatase 1 (SHIP1) activator AQX-1125 was recently investigated as potential new oral medication for the treatment of IC/BPS. It was supposed able to modulate the immune/inflammatory response thought the trigger of SHIP1 protein, which modulates phosphoinositide signaling. A phase two randomized double-blind controlled trial investigated the efficacy of a 6 weeks treatment vs. placebo, reporting promising results. Women with moderate to severe IC/BPS reported a significant improvement of pain and urinary symptoms after 6 weeks of treatment with oral AQX-1125 as compared to placebo [62]. Nevertheless, these results were not confirmed by the phase three randomized double-blind controlled trial, that compared 12 weeks of daily 100 mg or 200 mg of oral SHIP1 activator treatment with placebo. The trial concluded that SHIP1 activation is a safe but ineffective therapeutic approach to IC/BPS [63].

Intravesical medications

Treatments based on intravesical medications consist in the direct instillation of the therapeutic substance into the bladder via a catheter, that usually is combined with low-pressure, short-term hydrodistension [64]. These treatments require to rule out other pathologies and are usually recommended when less invasive treatments have failed [3, 33, 65]. In general, a regular maintenance treatment is required and recommended in those patients who report symptoms improvements [3, 33, 43].

The majority of available treatments in this category are aimed to reconstitute the glycosaminoglycan (GAG) layer of the bladder urothelium, that is thought to be compromised in patients affected by IC/BPS [5]. As reported above, the etiopathogenesis of IC/BPS is supposed to be related to urothelium abnormalities caused by the disruption of the GAG layer overlining apical cells [37, 38]. This layer is composed by different GAG, such as dermatan sulfate, chondroitin sulfate, heparan sulfate, keratin sulfate, and hyaluronic acid; and the intravesical instillation of exogenous GAG components, as monotherapy or mixed with other medications, is supposed to be able to restore this impaired layer [14].

Dimethyl sulfoxide

Dimethyl sulfoxide (DMSO) is one of the most common used intravesical medications and the only one approved by the FDA; it is usually instilled weekly for 6 weeks, alone or mixed with other medications [66]. DMSO exerts a combination of anti-inflammatory effects, collagen dissolution, smooth muscle relaxation, and nerve blockade. Three randomized-controlled trials and different cohort studies reported a symptoms improvement in up to the 95% of patients, with particular benefit for patients with ulcerative IC/BPS and without advantage provided by mixing with other medications [67]. Nevertheless, the optimal dose, timing, and type of IC/BPS most likely benefit from DMSO are not established. Of note, in more than the 35% of patients symptoms relapse within 8 weeks, and some patients cannot tolerate the pain after instillation and garlic odor [67, 68]. Although the available evidence, DMSO effectiveness is unclear, and not all guidelines recommend its use [3, 69].

Heparin and pentosan polysulfate

Heparin is a mucopolysaccharide part of the GAG family, that mimics the GAGs lining the urothelium. Moreover, it is supposed able to exert anti-inflammatory effects, promote the urothelium growth, induce fibroblast and smooth muscle proliferation, and favoring angiogenesis, with little systemic absorption [14]. Different observational studies reported a symptoms improvement in the 56-73% of patients after intravesical heparin instillation for three months, with a side effect

profile comparable to placebo [69-71]. Although these pieces of evidence, the available randomized controlled trials investigated the intravesical instillation of heparin combined with lidocaine, reporting a significant improvement of IC/BPS symptoms in patients underwent heparin/lidocaine instillation as compared to placebo [72]. Similar results were provided by a later observational study after 12 weeks of therapy [73]. On that basis, the strongest evidence is provided by the use of heparin in combination with other medications, instead of monotherapy [14]. However, a randomized controlled trial comparing heparin/lidocaine with lidocaine alone reported significant better results in the combined therapy, supporting a specific role of heparin [74].

PPS is a heparin analogue, that other than the previously reported oral administration is used as intravesical medication with the aim to directly restore the GAG layer. Different placebo controlled trials reported an improvement of symptoms after the weekly intravesical administration [40, 75], and a combination of both oral and intravesical administration provided further improvement in a randomized control trial [76].

Chondroitin sulfate and hyaluronic acid

Both chondroitin sulfate and hyaluronic acid are components of the GAG layer lining the urothelium, and the intravesical instillation is aimed to restore the protective barrier [14]. Different pieces of evidence support the intravesical administration of chondroitin sulfate and hyaluronic acid alone or in combination as effective treatment for the IC/BPS [77-79]. Two randomized controlled trials comparing the combined intravesical administration of these two GAGs or only chondroitin sulfate vs. DMSO reported a symptoms improvement in both groups with higher pain relief in the chondroitin sulfate alone and plus hyaluronic acid arm [68, 80]. Nevertheless, although promising results, chondroitin sulfate reported a limited magnitude of effect when used in monotherapy [81], as well as the effect of hyaluronic acid were questioned by three unpublished randomized controlled trials [33]. On that basis, the use of these GAGs is not recommended as monotherapy but as part of a multimodal approach [33].

Lidocaine

Lidocaine is a local anesthetic with anti-inflammatory effects administered intravesical in the alkalinized form, that allow a better penetration of the bladder epithelium [14].

Different studies reported a significant improvement of symptoms after lidocaine instillation with a rapid effect, even in monotherapy or combined with other medications [82-84]. Moreover, its use was recently proposed as a method to characterize the peripheral vs. central components of the syndrome in affected patients [85]. The main limit of lidocaine as monotherapy is the short-term effects, that induced the research of new strategies to provide a continuous administration of the drug. On that basis, a water-permeable tube pellet continuously releasing lidocaine was developed and tested as drug delivery device to be introduced in the balder by cystoscopy. In a prospective pilot study, the device resulted well tolerated and effective with the reduction of pain, urgency, and voiding frequency [86]. In general, lidocaine remains as one of the main intravesical instillation option in different guidelines [3, 33, 43].

Liposomes

Liposomes are biocompatible drug carriers composed by phospholipids and sphingomyelins. They are able to adhere onto the membrane surface of the urothelium and to favor the endocytosis with subsequent penetration of drugs, toxins, and oligonucleotides into the epithelium after the intravesical administration [87]. Because sphingomyelin is a phospholipid of cell membranes, it is supposed able to repair and promote healing of the external cell layer and decrease the permeability of urothelium lining. On that basis, empty liposomes composed by sphingomyelin were investigated in a prospective open-label cohort study, that reported an improvement of pain, urinary urgency, and overall symptoms with no side effects [88]. In addition, liposomes were investigated as carrier of botulinum toxin A in patients with refractory IC/BPS as alternative to the needle injection, although no benefit was reported as compared to placebo [89].

Others

Although in general they are not recommended by guidelines, some drugs are intravesically administered for their supposed effects in conjunction with other treatments, such as steroids, capsaicin, resiniferatoxin, and sodium cromoglycate [17, 90]. Among the corticosteroids, triamcinolone was proposed both via intravesical instillation and via submucosal injection through cystoscopy reporting an improvement of symptoms in the 70% of the patients [91].

Intravesical physical treatment

The intravesical physical treatments represent the third line option in the treatment of IC/BPS and consist in the bladder hydrodistension under general anesthesia and in the electrocoagulation of the Hunner's lesions [3, 17]. Hunner's lesions and glomerulations are present in the 4-10% of patients with BPS and repre-

sent a specific cystoscopic finding of IC [92]. The electrocoagulation of these lesions was associated to an improvement of symptoms in up to the 90% of women [93-95], although a significant proportion of them needs to repeat the procedure after 2-5 years [96]. Usually, Hunner's lesion ablation is performed associated to the bladder hydrodistension with improvement of results when combined [94]. The bladder hydrodistension under general anesthesia was investigated both alone and combined with other procedures, such as the above reported lesion ablation and the instillation of intravesical medications. The available evidence showed an improvement of symptoms up the 30-55% of patients, although the beneficial effects are variable and decline over time requiring repeated procedures [93-95, 97, 98]. Randomized controlled trials are not available and cases of bladder rupture or necrosis were reported [99, 100]. However, hydrodistension is one of the most commonly performed procedure and is recommended as optional treatment after conservative and medical options have failed [33, 43].

Neuromodulation

The neuromodulation both proximal, by sacral neuromodulation, and distal, with the use of botulinum toxin A, represents a fourth line of treatment limited to patients refractory to other options previously described [17, 33, 43].

Botulinum toxin A

Intravesical botulin toxin A injection for the treatment of IC/BPS was investigated in seven randomized controlled trials and multiple prospective studies [101-103]. The toxin acts inhibiting the acetylcholine release at the motor neurons endplate with muscle relaxation and is supposed providing antinociceptive and anti-inflammatory activity [104]. It is usually utilized for the treatment of overreactive bladder syndrome via cystoscopic injections in the detrusor muscle [14]. The same treatment in patients affected by IC/BPS was reported by different randomized controlled trials associated to a significant improvement of symptoms, pain, frequency of urination, and maximum bladder capacity. Conversely, nocturia, dysuria, and maximal urinary flow rate resulted not improved [101-103]. In general, the intravesical botulin toxin A injection is a safe and effective procedure, even after repeated treatment due the limited duration (9-10 months) of the effect [105-107]. Nevertheless, the cost and the possible side effects, particularly the urinary retention requiring catheterization, suggest performing this treatment with caution and only after other less invasive approaches have failed [3, 33, 43].

Based on these side effects, the noninvasive intravesical instillation of the toxin was investigated as alternative administration route, showing limited efficacy with only a significant improvement of bladder voiding volume [108].

Sacral neuromodulation

Sacral neuromodulation is an invasive treatment approved for other bladder syndromes but not for the management of IC/BPS [109]. Nevertheless, different guidelines consider this treatment an option for patients refractory to other less invasive treatment approaches [3, 33, 43]. Although evidence is based only on non-randomized and non-controlled trials, a growing body of literature shows a significant improvement of symptoms, such as pain, frequency of urination, urgency, and maximum bladder capacity, even after long-term follow-up [110]. The use of this approach as one of the last options is related to different issues. Only the 50-60% of patients are eligible for permanent implantation, and up to the 50% of them require to remove the implant [110-112]. The technique and device is expensive and related to failure in symptoms improvements and to the development of side effects, such as uncomfortable sensations, painful stimulation, seroma, and infections [33].

Surgery

The surgical approach is the last option in case of severe symptoms significantly affecting the quality of life and refractory to all other available treatments [3, 33, 43]. The available surgical procedures are the partial supratrigonal cystectomy with augmentation cystoplasty and the urinary diversion with or without cystectomy. Partial supratrigonal cystectomy was associated to an improvement of pain, urinary symptoms, and quality of life [113, 114]; in addition, urinary diversion was reported effective to improve symptoms in the 75-85% of woman, with required cystectomy in the others for persistent pain [115, 116]. Although a limited and selected number of patients require such treatment, a few of them will still continue to report pain. The patients more likely to have improvement of symptoms were reported those with evident bladder disease, such as Hunner's lesions and fixed reduced bladder capacity [5]. Considering the radicality of the treatment and the possible failure in symptoms improvements, referring to a specialized center is mandatory.

Conclusions

A wide range of treatment options is available for the management of patients with IC/BPS. After the correct diagnosis, the personalization of treatment with

a progressive and multimodal approach represent the key element for the correct management of these patients. However, although the multiple treatment available options, which allow a wide range of possible combinations and a high level of personalization, the optimal treatment is not easy to be found. Because of the limited knowledge about the etiopathogenesis and the nature of the disease, most of the available treatments have a limited effect and are actually aimed to manage symptoms.

On that basis, further investigation is required to clarify the multifactorial etiopathogenetic mechanisms, the differences between possible subgroups, and the interaction between central and peripherical factors. Only this further evidence may allow to provide a real improvement in the treatment and management of these patients.

Disclosure

The authors report no conflict of interest.

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