

# Associated diseases in interstitial cystitis/bladder pain syndrome

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## Associated diseases in IC/BPS patients

Associated diseases are diseases that occur more often together in the same person than by chance. Associated diseases for IC/BPS (interstitial cystitis/bladder pain syndrome) include allergy, fibromyalgia, irritable bowel syndrome, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome (table 1).

### Allergy

An allergy occurs when a person's immune system causes an adverse reaction to substances in the environment that are harmless to most other people. These substances (so-called allergens) are found in dust mites, pets, pollen, insects, ticks, moulds, foods and many medications.<sup>15</sup> Adverse reactions without involvement of the immune system are called intolerance. Intolerance mainly occurs to food ingredients and drugs.

People experience different symptoms, depending on the allergen, the individual's immune system, previous contact with the same allergen and where it enters the body. Allergic reactions can involve many parts of the body, even at the same time. Examples are:

- nose, eyes, sinuses and throat
- lungs and chest
- stomach and bowel
- skin

When allergens are inhaled, the release of histamine causes the lining of the nose to produce more mucus and become inflamed. It causes the nose to run and itch, and violent sneezing may occur. Eyes may start to water and people may get a sore throat.

Asthma can be triggered during an allergic reaction. When an allergen is inhaled, the lining of the passages in the lungs swells and makes breathing difficult.

Foods that commonly cause allergy include peanuts, seafood, dairy products and eggs. Cow's milk allergy in infants may occur and can cause eczema, asthma, colic and stomach upset. Some people cannot digest lactose (milk sugar). While lactose intolerance causes stomach upsets, it should not be confused with allergy.

Skin problems that can be triggered by allergy include atopic dermatitis (eczema) and urticaria (hives).<sup>15</sup>

The severity of allergic reactions varies considerably, from innocent hay fever to lethal anaphylactic reactions. Management of allergies consists of avoiding the allergen. If this is not possible, antihistamines may prevent or suppress symptoms. Patients with potential severe and lethal anaphylactic reactions, e.g. to peanuts, should carry an epinephrine (adrenaline) auto-injector (EpiPen™).

Allergies occur in up to 40% of IC/BPS patients. Intolerance may also be frequent, but no data on the prevalence in IC/BPS are available.

**Table 1.** Examples of associated disorders diagnosed in IC/BPS patients in comparison with the general population <sup>2,5,6</sup>

diagnosis	prevalence (%)	
	IC/BPS	general population
allergy	40.6	22.5
irritable bowel syndrome	25.4	2.9
sensitive skin	22.6	10.6
vulvodynia	10.9	15.0
fibromyalgia	12.8	3.2
chronic fatigue syndrome	7.7	8.5
migraine	18.8	18.0
asthma	9.2	6.1
Crohn's disease/ulcerative colitis	7.3	0.07
rheumatoid arthritis	4-13	1.0
systemic lupus erythematosus	1.7	0.05
Sjögren's syndrome	8.0	0.5

In a survey study in the United States, 40.6 % of the patients with IC/BPS stated that they suffered from allergy and in a Swedish study 41-47%.<sup>1,2</sup> In a Japanese study, young IC/BPS patients (20-39 years) were studied in more detail and compared with an older IC/BPS group (50-69 years). The study looked at the number of allergies, the type of IC/BPS symptoms ("painful type" or "frequency and urgency type"), skin tests, blood tests and the course of the IC/BPS following hydrodistension.<sup>3</sup> In two patients from the young group, IC/BPS was considered to be part of generalised allergic diseases. In 25 patients an association was assumed between IC/BPS and the allergy and in 15 of these the symptoms of allergy and IC/BPS alternated or ran parallel. Eleven patients had multiple allergies. In the young patients, 86% had one or more allergies, in the older patients this was 19%.

### Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a functional disorder of the intestines and not an inflammatory condition. Key symptoms are abdominal pain or discomfort associated with defecation or a change in bowel habit, with features of disordered defecation. IBS was previously called spastic bowel or spastic colitis but these terms should be avoided.

IBS is not life-threatening. Treatment of IBS focuses on improving symptoms and may consist of avoiding foods that trigger symptoms, drinking plenty of fluids, eating high-fiber foods and regular exercise.<sup>16</sup>

In questionnaires, 25-43% of IC/BPS patients reported having IBS, 2-4x more than the normal prevalence.<sup>1,4</sup>

IBS is clinically relevant in patients with IC/BPS as abdominal bloating may be responsible for pressure on the stomach (dyspepsia) and bladder.

### **Fibromyalgia**

Fibromyalgia (FM) is a poorly understood chronic pain syndrome characterized by widespread musculoskeletal pain, nonrestorative sleep, fatigue, psychological distress, and specific regions of localized tenderness, all in the absence of any apparent organic disease. FM occurs in 3% of the population and more commonly in women than in men. Management of FM is complex. Medication is rarely helpful, physical therapy, occupational therapy and counselling may be useful.<sup>17,18</sup>

In the USA survey, 12.8% of IC/BPS patients stated that they suffered from fibromyalgia, 4x more frequent than in the general population.<sup>1</sup>

### **Crohn's disease and ulcerative colitis**

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases of unknown cause. Common symptoms are abdominal pain, diarrhoea and weight loss. Some consider them to be autoimmune diseases. CD is usually limited to the terminal ileum, colon or both but may affect the entire gastrointestinal tract. Severe inflammation may result in bowel obstruction. Fistulae between the bowel and other organs such as the bladder are common.

UC is limited to the colon as far as the gastrointestinal tract is concerned. Both CD and UC may be complicated by extra-intestinal abnormalities such as joint inflammation and skin lesions.

CD and UC are often combined under the term inflammatory bowel disease (IBD). Treatment of CD depends on the severity and location of the disease. It consists mainly of anti-inflammatory medication, such as corticosteroids and biologicals targeting TNF- $\alpha$ .<sup>19</sup> Resection of inflamed bowel may also be an option if other therapies failed.<sup>19</sup>

Treatment of UC also involves drug therapy and/or surgery. 5-aminosalicylic acid (5-ASA) is often the first step in the treatment of ulcerative colitis. Corticosteroids, immunomodulating drugs and TNF- $\alpha$ -blockers are used in severe ulcerative colitis. Surgery can often eliminate UC but that usually means removing the entire colon and rectum.<sup>20</sup> In the USA survey, 7.3% of IC/BPS patients stated that they suffered from IBD. This is 100x more frequent than in the general population.<sup>1</sup>

### **Rheumatoid arthritis**

Rheumatoid arthritis (RA) is a systemic disease characterised by the specific way in which joints are affected by chronic inflammation. The disease is associated with systemic lupus erythematosus and particularly with Sjögren's syndrome. RA occurs in 1-2% of the population.

Destruction of many joints was the usual outcome until recently. Treatment now consists of NSAIDs (nonsteroidal anti-inflammatory drugs), steroids, DMARDs (disease-modifying antirheumatic drugs) such as methotrexate, leflunomide, hydroxychloroquine and sulfasalazine. Biological agents targeting TNF- $\alpha$  or B lymphocytes are very successful, especially when combined with DMARDs, but increase the risk of infections.<sup>21</sup>

Peeker *et al* mentioned that RA occurred in 13% of their classic IC patients (with "ulcers") and in 4% of IC patients

**Table 2. Summary of the criteria for the diagnosis of systemic lupus erythematosus (American College of Rheumatology 1997)**

1. malar rash
2. discoid rash
3. photosensitivity
4. oral/nasopharyngeal ulcer
5. arthritis
6. pleuritis or pericarditis
7. proteinuria > 0.5 g/day
8. neurologic/psychiatric disorder
9. haematologic disorder
10. anti-DNA, anti-Sm, or antiphospholipid antibodies
11. antinuclear antibodies (ANA)

without ulcers.<sup>2</sup> This is about 10x more frequent than in the general population.

### **Systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is the autoimmune disease which has been known for many years to have a relationship with IC/BPS. IC/BPS in SLE patients was often called *lupus cystitis*.

SLE is a generalised autoimmune disease that occurs more frequently in women (10x) and nonwhites (2x). Symptoms and signs that occur most frequently are arthritis, red skin lesions after sun exposure such as a red butterfly lesion of the face, pericarditis and pleuritis (inflamed membranes around the heart and lungs), glomerulonephritis and increased lysis of red blood cells (haemolytic anaemia), white cells (leukopenia) and platelets (thrombocytopenia).

Antinuclear antibodies (ANA) can be found in virtually all untreated patients. In addition, in many SLE patients it is possible to detect one or more other auto-antibodies such as anti-DNA and anti-Sm.

Antiphospholipid antibodies may cause venous and/or arterial thrombosis and a wide variety of complications in pregnancy. Criteria for the diagnosis of SLE are summarised in table 2. A patient may be said to have SLE if 4 out of 11 items are present at any time.

The clinical presentation is heterogeneous and organ damage shows strong variations between patients, from mild disease to lethal complications.

Treatment predominantly involve immunomodulation and immunosuppression and is targeted to the specific organ manifestation. SLE continues to cause substantial morbidity and premature mortality.

In the USA survey, 1.7% of IC/BPS patients stated that they suffered from SLE, this is 34x more frequent than in the general population.<sup>22</sup>

### **Sjögren's syndrome**

Sjögren's syndrome is a systemic autoimmune disease characterized by dry eyes and dry mouth. Other organ systems are affected in many patients. Sjögren's syndrome is one of the most common systemic autoimmune diseases. Sjögren's syndrome can also be diagnosed in many patients

with another systemic autoimmune disease such as SLE, RA or MCTD (mixed connective tissue disease). In this situation, it is called secondary Sjögren's syndrome in contrast to primary Sjögren's syndrome when there is not another systemic autoimmune disease.

Fatigue is a common debilitating symptom. Around 8% of the patients develop a MALT (mucosa-associated lymphoid tissue) lymphoma.

The diagnosis of Sjögren's syndrome is usually made according to the American-European criteria for Sjögren's syndrome or newer variants.<sup>9</sup> The former consists of 6 defined items and can be summarized as follows:

1. ocular symptoms
2. oral symptoms
3. ocular signs
4. salivary gland histopathology
5. salivary gland involvement demonstrated by radiology, scan or salivary flow
6. auto-antibodies to SSA/Ro and/or SSB/La

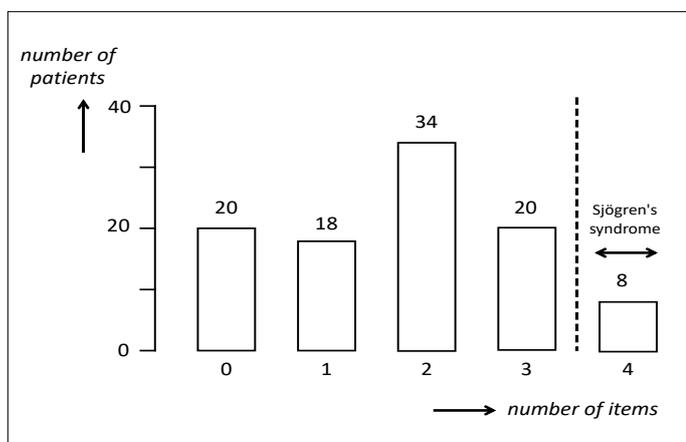
The criteria allow a diagnosis of Sjögren's syndrome if 4 out of items 1-6 (one of which must be 4 or 6) or 3 out of items 3-6 are present.

Treatments can be grouped into regimens for dryness and for systemic manifestations. Dry eyes may be treated with topical tear replacement and dry mouth with saliva substitutes. Muscarinic agonists such as pilocarpine and cevimeline may improve dryness in about 60% of the patients.

Hydroxychloroquine may be useful for treating arthralgia, vasculitis and fatigue. Rituximab, an anti-CD20 monoclonal antibody that depletes B lymphocytes, is useful for treatment of B cell lymphomas and antibody-mediated disease manifestations such as severe thrombocytopenia.

In 1992, van de Merwe *et al* investigated 100 IC/BPS patients for the presence of a second autoimmune disease, in particular Sjögren's syndrome.<sup>6-8,14</sup> Item 3 was only tested if item 1 was present and item 4 only if item 2 was present. Item 5 was never tested because of lack of reproducibility or sensitivity.

Table 3 shows the prevalence of each of the investigated items in the IC/BPS patients. Figure 1 shows the frequency distribution of the number of items present in individual patients.



**Figure 1.** Frequency distribution of the number of items of the American-European criteria for Sjögren's syndrome present in 100 patients with IC/BPS

**Table 3.** Prevalence of separate items of the American-European criteria for Sjögren syndrome in 100 patients with IC/BPS

item	prevalence (%)
ocular symptoms	68
oral symptoms	60
abnormal ocular test	16
abnormal salivary histology	16
antibodies to SSA/Ro or SSB/La	12

It is concluded that in 8% of the patients with IC/BPS a diagnosis of Sjögren's syndrome according to the American-European classification criteria could be made. In addition, 20% of the patients had three items of these criteria and no other disease was found that could account for the present items. In a clinical situation, a diagnosis of Sjögren's syndrome (Sjögren's-like syndrome or incomplete Sjögren's syndrome) is justified in these 20% too.<sup>7,10</sup>

This finding of a relationship between IC/BPS and Sjögren's syndrome has led to a hypothesis in which autoantibodies against the muscarinic M3-receptor, which is present on exocrine cells and the detrusor muscle, play a role in causing early symptoms as well as causing local inflammation later on.<sup>11,14</sup> Unfortunately, it is not yet possible to reliably demonstrate M3-receptor stimulating and blocking auto-antibodies.

Several authors have also studied the relationship between IC/BPS and Sjögren's syndrome. Peeker *et al* surveyed the clinical records of 222 patients with IC/BPS for diagnoses of autoimmune disorders. 43% of the IC/BPS patients had some type or degree of hypersensitivity/allergy. Rheumatoid arthritis occurred in 10% and inflammatory bowel disease in 1% but no diagnoses of Sjögren's syndrome were found.<sup>2</sup> Using a questionnaire, Leppilahti *et al*, on the other hand, recently found IC/BPS-like urinary symptoms in 5% of 870 patients with Sjögren's syndrome.<sup>12</sup>

In a recent nationwide Taiwanese study of 11526 newly diagnosed patients with primary Sjögren's syndrome and 115260 controls, the hazard ratio (HR) of OAB (overactive bladder) and IC/BPS were significantly increased (HR for OAB 1.68 and for IC/BPS 2.34).<sup>23</sup>

#### Distal renal tubular acidosis

Interstitial nephritis as part of Sjögren's syndrome may cause distal renal tubular acidosis (DRTA) and occurs in up to 50% of Sjögren's syndrome patients, usually in a mild form. DRTA causes metabolic acidosis and compensatory hyperventilation to correct the acidosis. More pronounced DRTA causes hypokalemia (low serum potassium) due to increased loss of potassium by the kidneys into the urine. Moderate hypokalemia may cause muscular weakness, myalgia, and muscle cramps, and constipation (disturbed function of skeletal and smooth muscles, respectively). With more severe hypokalemia, flaccid paralysis, hyporeflexia, and tetany may result. Severe fatigue may be caused by the compensatory chronic hyperventilation.

Treatment with potassium citrate, *e.g.* 3x per day 0.5 to 2 grams, may correct both the acidosis and the hypokalemia. There are no literature data on the prevalence of DRTA in IC/BPS but DRTA in IC/BPS is likely to be due to an accompanying incomplete or complete Sjögren's syndrome. It is not known whether the increased urinary potassium concentration in DRTA contributes directly to the bladder symptoms of IC/BPS. Alternatively, the activity of DRTA and IC/BPS could also run parallel if both result from the same underlying pathological process.

### Treating patients with more than a single disease

In general, each of the associated diseases of IC/BPS should be diagnosed and treated by the corresponding medical specialist. This implies, however, that several specialists will have to work together to avoid adverse effects of specific drugs or combination of drugs. Anti-muscarinic medication for urinary frequency may worsen complaints and abnormalities of dry eyes and dry mouth; drinking plenty of fluids in IBS may worsen urinary frequency of IC/BPS.

On the other hand, symptoms of both Sjögren's syndrome and IC/BPS may improve when treated with hydroxychloroquine.

### Conclusion

The clinical relevance of associated diseases is that a high index of suspicion for several of these associated diseases is indicated in IC/BPS patients and *vice versa*.

The most common second disease in IC/BPS patients is allergy, followed by irritable bowel syndrome.

The most common generalised autoimmune disease in patients with IC/BPS is Sjögren's syndrome. The association with Sjögren's syndrome is interesting as it supports the possibility of a common pathogenic mechanism.<sup>11,14</sup>

Good cooperation between various medical specialists in a multidisciplinary approach is essential for optimal management of patients with IC/BPS and associated diseases.

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