Interstitial cystitis and associated disorders

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Interstitial cystitis & painful bladder syndrome

Interstitial cystitis (IC) is a chronic bladder disease characterized by symptoms of cystitis. These are pain in or around the bladder, an urgent need to urinate and frequent urination both in the daytime and at night. The pain usually increases as the bladder fills. However, no urinary tract infection or other cause can be identified.

During the past few years, there has been much international discussion concerning the name and definition of the disease. IC is currently considered to be a form of painful bladder syndrome (PBS). PBS is defined a as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of identifiable infection or other pathology.[1] In the case of IC there are additionally cystoscopic and/or histological signs of inflammation (see note). Recent publications often refer to PBS/IC or IC/PBS.

The symptoms of PBS/IC have serious consequences for the social and personal life of the patients. In the case of many patients, it may take many years before the diagnosis of IC is finally established. An additional problem for many patients is that IC often occurs in association with other diseases. This concerns allergies, fibromyalgia, irritable bowel syndrome, and various autoimmune diseases such as inflammatory bowel disease (Crohn's disease and ulcerative colitis), systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome.

Allergy

In a survey study in the United States, 40.6 % of the patients with IC stated that they suffered from allergy and in a Swedish study 41-47%.[2,3] This is 2x more frequent than in the general population (see Table 1). In a Japanese study, young IC patients (20-39 years) were studied in more detail and compared with an older IC group (50-69 years). The study looked at the number of allergies, the type of IC symptoms ("painful type" or "frequency and urgency type"), skin tests, blood tests and the course of the IC following hydro-distension.[4] In two patients from the young group, IC was considered to be part of generalised allergic diseases. In 25 patients an association was assumed between IC and the allergy and in 15 of these the symptoms of allergy and IC 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%.

Table 1. *Examples of associated disorders diagnosed in IC patients in comparison with the general population* [2,3,8]

	prevalence (%)		
diagnosis	IC	general population	RR in IC*
allergy	41-47	22.5	2
irritable bowel syndrome	25.4	3-15	2-9
sensitive skin	22.6	10.6	2
vulvodynia	10.9	15.0	0.7
fibromyalgia	12.8	3.2	4
chronic fatigue syndrome	7.7	8.5	1
migraine	18.8	18.0	1
asthma	9.2	6.1	1.5
Crohn's disease/ulcerative colitis	1-7.3	0.07	14-100
systemic lupus erythematosus	1.7	0.05	34
rheumatoid arthritis	4-13	1.0	10
Sjögren's syndrome	8.0	0.5	15

* RR: relative risk; RR>1 indicates that the disorder is more prevalent in IC than in the general population; RR=1: equally prevalent and RR<1 disorder is less prevalent than in IC

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is not an inflammatory condition of the intestines but mainly an abnormal motor function ("movement") of the intestines. It was previously called *spastic bowel* or *spastic colitis*. The symptoms comprise an abnormal pattern of bowel movements and abdominal pain. Four types of IBS are recognised on the basis of the main symptom: 1. abdominal pain 2. constipation 3. intermittent constipation and diarrhoea, and 4. diarrhoea. The most common types are 1-3. IBS occurs in 3-15% of the population. It generally starts in adulthood and is diagnosed 4x more frequently in women than in men. In the USA survey already referred to, 25% of IC patients stated that they suffered from IBS.

The diarrhoea only occurs during the daytime and is usually a question of small amounts. The diarrhoea may be exacerbated by eating and emotional stress. There is often mucus with the stools but not blood (unless constipation has also caused haemorrhoids).

Note

The ICS (International Continence Society) definition requires cystoscopic and histologic abnormalities.[1] In the ESSIC (European Society for the Study of IC/PBS) definition, one of both is sufficient (ESSIC Meeting 16-18 June 2005, Baden, Austria).

The location and severity of the abdominal pain can vary, with occasional periods of painful cramp. The abdominal pain may increase by eating and stress, but improve by breaking wind and by going to the toilet. The diarrhoea and abdominal pain of IBS are often at their worst in the morning. The patient goes to the toilet a number of times in succession and then no more for the rest of the day. There appears to be an increase in gas formation in the intestines in the form of wind and a bloated, rumbling abdomen. It is possible that there may in fact be no real increase, but simply that the upper sections of the intestines contain more gas and the lower ones less. 25-50% of the people with IBS also have stomach disorders in the form of a heavy, uncomfortable, burning sensation (dyspepsia), nausea and sometimes even vomiting.

IBS is an abnormality in the peristalsis of the intestines and investigation of the intestines reveals no other visible abnormalities. The diagnosis can only be made on the basis of the typical symptoms and if no abnormalities are found in intestinal investigations.

Treatment consists of adapting diet and lifestyle. Although symptoms may vary at different periods, the course of IBS itself is uncomplicated. However, constipation increases the risk of *diverticula* (bulging sacs pushing out of the wall) in the terminal section of the colon, the *sigmoid*. Diverticula may become inflamed (*diverticulitis*), thereby causing severe disease.

Fibromyalgia

Fibromyalgia occurs in 3% of the population and more commonly in women than in men. In the USA survey 12.8% of IC patients stated that they suffered from fibromyalgia, 4x more frequent than in the general population. The main symptom is pain all over the body, followed by fatigue, morning stiffness and sleep disturbances.

For a diagnosis of fibromyalgia, a physical examination must show that at least 11 of 18 designated tender points are painful when a specific pressure is applied.

A striking feature is that there are no signs of inflammation in general or of the muscles and joints. The fact that the pain in fibromyalgia differs from pain with other causes is demonstrated by the fact that even very strong painkillers, have little or no effect on the pain. The cause of fibromyalgia is unknown but a role of the neuroendocrine system is suggested.

Inflammatory bowel disease

Crohn's disease and ulcerative colitis are inflammatory bowel diseases of unknown cause. Some consider them to be autoimmune diseases. They are often combined under the term *inflammatory bowel disease* (IBD). This was also the case in the USA survey where 7.3% of IC patients stated that they suffered from IBD. This is 100x more frequent than in the general population. It is possible, however, that patients with "spastic colitis" (irritable bowel syndrome) may have mistakenly classified themselves as suffering from IBD and that the real prevalence of IBD in IC patients is much lower.

Crohn's disease

Crohn's disease is a chronic inflammatory bowel disease. This disease is known by a variety of names depending on which sections of the intestinal tract are affected. If the disease only occurs in the last section of the small intestine, the ileum, it is also known as *ileitis terminalis*, terminal ileitis or regional ileitis. If the disease is present in the large intestine, it is called Crohn's colitis.

Diseased segments of intestine often alternate with normal segments of intestine. The diseased segments are then known as skip lesions. The disease can also occur in both the large and small intestines. In principle it can occur in any part of the intestinal tract, but the most common sites are the small intestine and large intestine. In addition, many patients have other disorders, for instance around the anus. These may be fistulas, fissures or abscesses. Fistulas are small tunnels in the tissue that connect the cavities between two organs (for example: two separate parts of the intestines, between the intestines and the bladder or between the intestines and the vagina) or the cavity of one organ with the surface of the body. Fissures are cracks or splits in the mucous membrane, while abscesses are hollow spaces filled with pus that did not previously exist. The rectum is frequently disease-free. Fibrous tissue may form (*fibrosis*) in inflamed sections, leading to narrowing (*stenosis*) of the intestine.

Sections of intestine that are affected are often swollen by inflammation. Examination of intestinal tissue under the microscope often shows that the inflamed tissue contains many lymphocytes and granulomas. Granulomas are accumulations of specific cells that do not normally occur in the tissue, surrounded by lymphocytes. The inflammation is often present in all layers of the intestine. The mucous membrane, the innermost layer of the intestine, is often swollen

(*oedema*), greatly engorged with an excess of blood (*hyperaemia*) and may be ulcerated.

The disease frequently begins gradually and the time that elapses between the first symptoms and the time when it is diagnosed is often four years. The symptoms of the disease partly depend on the site(s) of the inflammation.

If the disease is only present in the small intestine, the symptoms often consist of abdominal cramp (particularly after meals), weight loss and diarrhoea. If the disease is in the large intestine, the stools may often contain blood which can of course also cause diarrhoea. In addition, patients with Crohn's disease are often anaemic for a number of reasons such as iron deficiency (chronic blood loss), the inflammation itself, folic acid deficiency (jejunitis) or vitamin B_{12} deficiency (ileitis).

Crohn's disease is not always restricted to the intestines. Extra-intestinal symptoms (outside the intestines) may also occur in this disease. *Pyoderma gangraenosum* is a nonbacterial, ulcerative inflammatory condition of the skin). *Erythema nodosum* is an inflammation of subcutaneous tissue, usually on the front of the lower legs. It also occurs in numerous other diseases such as tuberculosis, sarcoidosis, streptococcal infections and as a hypersensitivity reaction to certain drugs, especially those containing sulpha. Inflammation of the eyes may occur, such as that of the cornea (*conjunctivitis*), iris (*iridocyclitis, uveitis*) and sclera (*scleritis*). *Arthritis* (inflammation of joints) is mainly seen in Crohn's disease affecting the large intestine and also in ulcerative colitis. It frequently concerns the large joints such as ankle or knee, often asymmetrically. *Ankylosing spondylitis* is an inflammatory condition of the joints of the pelvis and spinal column. The hip and shoulder joints may also be affected, but other joints are less common. People with Crohn's disease or colitis ulcerosa are more susceptible to this disease than others.

The cause of Crohn's disease is unknown. It occurs in approximately 1 in 10,000 people and is just as common in men as in women. Although there may be more than 1 person in a family affected by the disease, there is no evidence that the disease is contagious.

Ulcerative colitis

Ulcerative colitis is an intestinal disease that resembles Crohn's disease but has a number of significant differences. Ulcerative colitis only occurs in the large intestine (*colon*), sometimes only in the *rectum*, but never in other parts of the intestine. The disease often begins quite suddenly. The main symptoms of ulcerative colitis are loss of blood from the rectum, diarrhoea, fever, abdominal pain and weight loss. Periods with symptoms alternate with symptom-free periods.

The disease is limited to the mucous membrane and does not penetrate the entire wall of the intestine. Formation of fibrous tissue with stenosis, fistulas and granulomas in affected tissues rarely occur. As in the case of Crohn's disease, extra-intestinal symptoms may occur. The cause of ulcerative colitis is unknown.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the autoimmune disease which has been known for many years to have a relationship with IC. IC in SLE patients was often called *lupus cystitis*. In the USA survey 1.7% of IC patients stated that they suffered from SLE, this is 34x more frequent than in the general population.[2]

SLE is a generalised autoimmune disease that occurs more frequently in women (10x) and non-whites. 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 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.

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)

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic (generalised) 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 about 1% of the population. Peeker *et al* mentioned that RA occurred in 13% of their classic IC patients (with "ulcers") and in 4% of IC patients without ulcers.[3]

Sjögren's syndrome

Sjögren's syndrome is an autoimmune disease characterised by a functional disorder of the lacrimal and salivary glands.[5] This disease can also affect virtually every organ in the body, which is why it is described as a generalised or systemic autoimmune disease.

Disorders that may occur in various organs are also known as separate diseases (*e.g.* Raynaud phenomenon, atrophic gastritis, pernicious anaemia, interstitial nephritis, hypersensitivity vasculitis, bronchitis sicca, lymphocytic interstitial pneumonitis, autoimmune thrombocytopaenia, haemolytic anaemia, lymphocytopaenia antiphospholipid syndrome, pancreatitis, non-bacterial prostatitis). This even applies to the characteristic abnormalities in the lacrimal glands (keratoconjunctivitis sicca) and salivary glands (focal lymphocytic sialadenitis). Frequent complications are severe dental decay, oral candidiasis and non-Hodgkin lymphoma.

Sjögren's syndrome occurs in 0.6% of the adult population and - like IC - 10x more frequently in women than in men. This implies that 1% of the female population and 0.1% of the male population suffer from Sjögren's syndrome.

Table 3 lists the most important symptoms and blood abnormalities in Sjögren's syndrome along with the percentage of prevalence. Table 4 summarizes a number of features of Sjögren's syndrome that show a remarkable similarity to those of IC.

Table 3. *Examples of frequencies of clinical features and blood abnormalities in Sjögren's syndrome*

clinical features	%	blood abnormalities	%
eye irritation	>95	anaemia	25
dry mouth	>95	low white blood cell count	23
fatigue	80		
joint pain	80	low platelet count	11
Raynaud phenomenon	33	monoclonal antibodies	67
sensory neuropathy	23	rheumatoid factor	45
leukocytoclastic vasculitis	25	antinuclear antibodies	50
thyroid disease	15	antibodies to	
celiac disease	12	· SS-A/Ro	60
non-Hodgkin lymphoma	5	· SS-B/La	45
		· RNP	15
		· thyroid	40
		· mitochondria	10
		· parietal cells	30

Table 4. *Some features that Sjögren's syndrome has in common with interstitial cystitis*

- occurs 10x more frequently in women than in men
- occurs more frequently in patients with rheumatoid arthritis and systemic lupus erythematosus
- high prevalence of arthralgia and drug intolerance
- abnormal blood tests such as increased IgG, decreased C4 and antinuclear antibodies
- inflammatory infiltrate mainly consists of CD4-positive T lymphocytes

Relationship between IC and Sjögren's syndrome

In 1992, as a consequence of the similarity observed between IC and Sjögren's syndrome, we began a clinical study of IC patients to investigate whether the presence of a second autoimmune disease could be demonstrated.[6,7] We recently presented data on 100 consecutive patients with IC who were investigated for the presence of Sjögren's syndrome.[8] The IC patients had characteristic irritative urinary voiding symptoms, no evidence of infection or other bladder disease, typical cystoscopic appearance demonstrable with maximal bladder distension, bladder biopsies ruling out other diseases and showing inflammation in the mucosa and submucosa with lymphocytic infiltrate and increased numbers of mast cells.

The diagnosis of Sjögren's syndrome was made according to the recent version of the European criteria for Sjögren's syndrome.[9] These consist of six defined items and can be summarized as follows:

A. characteristic ocular symptoms
B. characteristic oral symptoms or parotis enlargment
C. ocular signs (Schirmer test 5 mm/5 min or less; rose bengal dye test 4+ or more)
D. salivary gland histopathology
E. salivary gland involvement demonstrated by radiology, scan or salivary flow
F. auto-antibodies to SS-A/Ro and/or SS-B/La.

The criteria allow a diagnosis of Sjögren's syndrome if 4 out of items A-F or 3 out of items C-F are present. This latter situation did not occur in our patient group as we did not further investigate patients for Sjögren's syndrome if both ocular and oral symptoms were absent. Item C was only tested if item A was present, item D was only tested if item B was present. Item E was never tested because of lack of reproducability or sensitivity.

Table 5. *Prevalence of separate items of the European criteria for Sjögren's syndrome in 100 patients with interstitial cystitis* [8]

Item	Prevalence (%)
ocular symptoms	68
oral symptoms	60
abnormal ocular test	16
abnormal salivary histology	16
antibodies to SS-A/Ro and/or SS-B/La	12

Table 5 shows the prevalence of each of the investigated items in the IC patients. Figure 1 shows the frequency distribution of the number of items present.

In 8% of our IC patients a diagnosis of Sjögren's syndrome according to the European criteria was made. In addition, 20% of the patients had 3 items of the 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") is justified in these 20% too.[6,8]

This finding of a relationship between IC and Sjögren's syndrome has led to a hypothesis in which autoantibodies to the muscarinic M_3-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.[10] Unfortunately, it is not yet possible to reliably demonstrate M_3-receptor stimulating and blocking antibodies. Since then, several authors have also studied the relationship between IC and Sjögren's syndrome. Peeker *et al* surveyed the clinical records of 222 patients with IC for diagnoses of autoimmune disorders. 43% of the IC patients had some type of hypersensitivity/allergy. Rheumatoid arthritis occurred in 10% and inflammatory bowel disease in 1% but no diagnoses of Sjögren's syndrome were found.[3] Using a questionnaire, Leppilahti *et al,* on the other hand, recently found IC-like bladder symptoms in 5% of 870 patients with Sjögren's syndrome.[11]

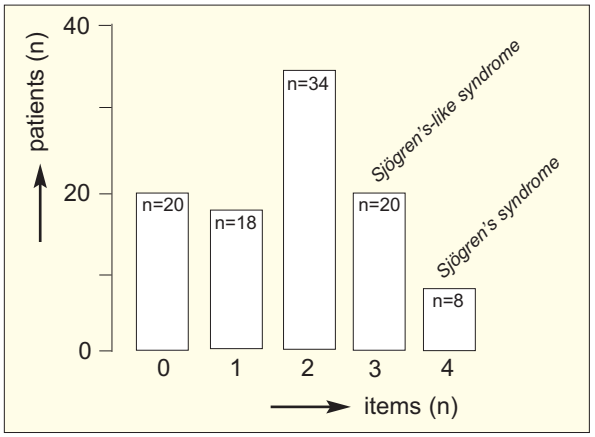

Figure 1. *Frequency distribution of the number of items of the European criteria for Sjögren's syndrome present in 100 patients with interstitial cystitis* [8]

Conclusions

The clinical relevance of the findings is that a high index of suspicion for associated diseases is indicated in IC patients. Whereas allergies and irritable bowel syndrome cause local problems and are not very difficult to detect, Sjögren's syndrome is a systemic disease with a complicated course in many patients and is a disease that is greatly underdiagnosed.

References

1. Abrams P, Cardozo L, Fall M *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn 2002;21:167-78.
2. Alagiri M, Chottiner S, Ratner V, *et al.* Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology 1997;49:52-7.
3. Peeker R, Atanasiu L, Logadottir Y. Intercurrent autoimmune conditions in classic and non-ulcer interstitial cystitis. Scand J Urol Nephrol 2003;37:60-3.
4. Yamada T. Significance of complications of allergic diseases in young patients with interstitial cystitis. Int J Urol 2003;10 (suppl):S56-58.
5. van de Merwe JP. Syndroom van Sjögren. Ned Tijdschr Allergie 2001;1:120-5.
6. van de Merwe JP, Kamerling R, Arendsen HJ, *et al.* Sjögren's syndrome in patients with interstitial cystitis. J Rheumatol 1993;20:962-6.
7. van de Merwe JP, Kamerling R, Arendsen HJ, *et al.* Sjögren's syndrome, keratoconjunctivitis sicca and focal lymphocytic sialoadenitis in patients with interstitial cystitis. *In:* Sjögren's Syndrome - State of the Art, *ed* Homma M, Sugai S, Tojo *et al.*, Proceedings of the Fourth International Symposium, Tokyo, Japan, August 11-13, 1993. Kugler Publ. Amsterdam /New York 1994, pp 347-9.
8. van de Merwe JP. Sjögren's syndrome in patients with interstitial cystitis. Preliminary results in 100 patients. Int J Urol 2003; 10 (suppl):S69.
9. Vitali C, Bombardieri S, Jonsson R, *et al.* Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus Group. Ann Rheum Dis 2002;61:554-8.
10. van de Merwe JP, Arendsen HJ. Interstitial cystitis: a review of immunological aspects of the aetiology and pathogenesis, with a hypothesis. BJU Int 2000;85:995-9.
11. Leppilahti M, Tammela TL, Huhtala H, *et al.* Interstitial cystitis-like urinary symptoms among patients with Sjögren's syndrome: a population-based study in Finland. Am J Med 2003;115:62-5.

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