Autonomic nervous system dysfunction involving the gastrointestinal and the urinary tracts in primary Sjögren's syndrome

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Abstract

Objective

Antibodies reacting with the m3 subtype muscarinic acetylcholine receptor appear to be an important pathogenic factor in primary Sjögren's syndrome (pSS). As this receptor subtype is functionally important in the gastrointestinal and urinary tracts, and very little is known about the autonomic nervous system function in these organs in pSS patients, the occurrence and clinical significance of an autonomic nervous system dysfunction involving the gastrointestinal and urinary tracts were investigated.

Methods

Data on clinical symptoms attributable to an autonomic dysfunction were collected from 51 pSS patients. Gastric emptying scintigraphy and urodynamic studies were performed on 30 and 16 patients, respectively, and the results were correlated with patient characteristics and with the presence of autonomic nervous system symptoms.

Results

Gastric emptying was abnormally slow in 21 of the 30 examined patients (70%). Urodynamic findings compatible with a decreased detrusor muscle tone or contractility were found in 9 of the 16 patients tested (56%). Various symptoms of an autonomic nervous system dysfunction were reported by 2-16% of the patients.

Conclusion

Signs of an autonomic nervous system dysfunction involving the gastrointestinal and the urinary systems can be observed in the majority of pSS patients. This high occurrence is rarely associated with clinically significant symptoms. The authors presume a role of autoantibodies reacting with the m3 muscarinic acetylcholine receptor in the elicitation of the autonomic dysfunction.

Key words

Primary Sjögren's syndrome, anti-muscarinic acetylcholine receptor antibodies, gastric emptying scintigraphy, urodynamic studies, autonomic dysfunction.

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The work was supported by National Scientific Research Fund of Hungary grant OTKA038303 and Health Care Scientific Council of the Ministry of Health Care of Hungary grant ETT214/2001

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Received on February 10, 2003; accepted in revised form on July 1, 2003.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by a lymphocytic infiltration and a subsequent functional impairment of various exocrine glands. There is increasing evidence that, in addition to the structural damage to the involved glands caused by a lymphocytic infiltration, decreased stimulation by the autonomic nervous system of the glands plays an important role in the elicitation of the exocrine dysfunction (1). We have found that pSS patients demonstrate an impaired microvascular response to cholinergic stimuli as compared with healthy individuals (2). The presence of antibodies reacting with the rodent and human muscarinic acetylcholine receptor subtype 3 (m3AchR), the predominant receptor subtype in the lachrymal and salivary glands, has been demonstrated in pSS patients (3-5).

The m3AchR is also the functionally dominant acetylcholine-receptor in the gastrointestinal (GI) and the genito-urinary (GU) tracts (6,7), where it mediates contraction of the parietal smooth muscles and relaxation of the sphincter muscles (7). An impairment of these mechanisms, most commonly as a consequence of an autonomic neuropathy, leads to significant morbidity as evidenced in patients with diabetes mellitus (8). Although a cardiovascular autonomic neuropathy has been described in pSS (9-15), data are scarce or lacking as concerns autonomic neuropathy involving other organs, including the GI and the GU tracts.

With regard to the emerging importance of anti-m3AchR autoantibodies in pSS, and the fact that very little is known about the autonomic function in the GI and the urinary systems in this disease, we designed a clinical study among pSS patients to examine the autonomic nervous system function in these organ systems. We hypothesised that anti-m3AchR antibodies bind to receptors not only located in the salivary and the lachrymal glands, but also in other organs where the m3AchR subtype predominates, and thereby cause an autonomic dysfunction. Our aim was to attempt to clarify whether signs of an autonomic dysfunction can be detected in the GI and the urinary tracts.

Patients and methods

Study patients

From among the cohort of pSS patients followed up at the Department of Rheumatology at the University of Szeged, all those who did not have diabetes mellitus, chronic renal failure or any other disease that may cause an autonomic neuropathy, and who were younger than 75 years, were asked to complete a questionnaire relating to symptoms which may potentially be caused by an autonomic dysfunction. Fifty-one patients (48 women) satisfied the above-mentioned criteria (average age: 53 [range 31-71] years, and average time since the appearance of the first symptom of pSS: 14 [range 2-31] years). An answer was considered positive when no other medical condition potentially attributable to the elicitation of the symptom was present in the given patient. All of them fulfilled the American-European classification criteria for pSS (16). For the clinical tests, further exclusion criteria were defined, as discussed later; the numbers of patients participating in the individual clinical examinations was therefore smaller. The protocol was accepted by the Medical Ethics Committee of the University of Szeged.

Examination of gastric emptying

The gastrointestinal autonomic nervous function was examined by assessment of the gastric motility with gastric emptying scintigraphy. The examination was performed in the morning after an overnight fast. The patients ingested a radiolabelled meal (2 hard-boiled eggs labelled with 20 MBq ^{99m}Tc-human serum albumin macroaggregate + one bread roll and 200 ml water). A dynamic scintigraphic study was performed about the gastric region. Digital images were taken at a frequency of 1 minute/frame for 2 hours. As a parameter of gastric emptying, the emptying half-time ($t_{1/2}$), i.e. the time until the radioactivity in the stomach had decreased to half the initial value, was determined. Two of the 51 patients had a condition that may influence gastric emptying

(previous surgical polypectomy and pernicious anaemia, respectively), and they were therefore considered ineligible for this examination. Of the remaining patients, 30 consecutive subjects (27 women) participated in this examination. The patients did not have any sign of an organic upper gastrointestinal disease; moreover, gastroscopic examinations on 23 of the patients did not reveal such abnormalities either. The use of prokinetics or other drugs which influence the autonomic nervous system or smooth muscle contractility was suspended at least 3 days before the examination. During the validation process for this procedure, the cut-off value for an abnormal $t_{1/2}$ was determined as the average + 1 SD of the $t_{1/2}$ values for 7 healthy individuals (6 women) with an average age similar to that of the pSS patients. Thus, a $t_{1/2}$ value >74 minutes was considered abnormal.

Urodynamic examinations

For assessment of the autonomic neural effects on the urinary tract, standard urodynamic examinations were performed. Uroflow measurements and cystometric examinations were carried out in a manner completely identical to the routine diagnostic examinations. An overall evaluation of all the clinical data and the urodynamic charts was made following the international guidelines for diagnostic urodynamic examinations (17). As an autonomic nervous system dysfunction leads to an altered detrusor muscle tone or contractility, the following parameters were considered for the purposes of statistical analysis: maximum cystometric bladder capacity (normal: 320-590 ml), peak detrusor pressure (i.e. the difference of the peak intravesical pressure and the intra-abdominal pressure; normal: 35-60 cmH_2O), and the maximum urinary flow rate (normal: 15-36 ml/sec). The normal values we applied are standard values established for adult females (17). Urological or gynaecological examinations, routine laboratory urinary tests, and abdominal and pelvic ultrasonographic examinations revealed that 8 patients have an organic disease (3 men had bilateral prostate hypertrophy and 5 women had cystocele), and were excluded from the urodynamic examinations. The administration of drugs influencing the autonomic nervous system or the function of the bladder was suspended an appropriate period before the measurements. Six patients refused to participate; of the remaining patients, 16 women took part in the urodynamic examinations. The groups of patients who participated in either the gastric or the urological examinations and of those who did not take part were similar as regards the demographic, clinical and immunoserological characteristics and the frequencies of complaints possibly attributable to an autonomic neuropathy.

Sensory nerve function assessment

The somatic sensory nerve function was assessed by examination of the vibration perception threshold. A calibrated vibrameter was placed on the medial malleolus, and the patients' perception of the vibration was examined and graded on a scale 0-8 (7-8: normal; 6: borderline; < 6: abnormal).

Statistical methods

The $t_{1/2}$ values exhibited a normal, while the urodynamic variables a non-normal distribution. The mean or the median values were compared via an independent samples t-test or a Mann-Whitney U-test between the patient and control groups. The frequencies of the various abnormalities in the two groups were compared by means of a χ^2 test. The correlation of the $t_{1/2}$ values with the patient parameters was examined with linear regression analysis or with Pearson's correlation test. The relationships between the urodynamic variables and the various patient data were analysed with Spearman's rank correlation test.

Table I. The occurrences of the most important organ manifestations and serological parameters in the 51 pSS patients enrolled in the study. A labial biopsy was performed in 35 of the 51 patients.

Organ involvement/laboratory abnormality	No.	(%)
Articular involvement*	42	(82)
Raynaud's phenomenon	20	(39)
Purpura	11	(22)
Renal involvement**	11	(22)
Pulmonary fibrosis	3	(6)
Non-Hodgkin's lymphoma	3	(6)
Antinuclear antibody positivity	35	(69)
Anti-SSA	42	(82)
Anti-SSB	26	(51)
Minor salivary gland focus score ≥ 1	30	(86)

*Articular involvement: arthralgia not due to degenerative joint disease, or arthritis.
**Renal involvement: renal tubular acidosis or biopsy-proven tubulointerstitial nephritis.

Results

Patient characteristics and symptoms

Clinical characteristics of the 51 patients are presented in Table I. The number of patients who experienced the particular symptoms potentially attributable to an autonomic dysfunction are demonstrated in Table II.

Gastric emptying scintigraphy

The gastric emptying was significantly slower in the pSS patients than in the healthy controls. The average (±SD) $t_{1/2}$ of gastric emptying was 94 ± 35.9

Table II. The numbers of pSS patients complaining of symptoms possibly attributable to an autonomic dysfunction. The total number of patients tested was 51.

Complaint	No. of pts.
Postprandial fullness	6
Vomiting/nausea after eating	1
Bloating	4
Diarrhea	3
Urge incontinence	4
Stress incontinence	8
Difficulty in starting voiding	1

minutes in the patients and 59.6 ± 16.7 minutes in the controls ($p<0.05$). 21/30 pSS patients (70%) yielded an abnormal gastric emptying $t_{1/2}$; moreover, in 9 of them, a markedly elevated $t_{1/2}$ (more than 120 minutes) was observed. Representative images of normal gastric emptying of a healthy control subject and prolonged gastric emptying of a pSS patient are shown in Figure 1.

Urodynamic examinations

In the 16 examined pSS patients, we detected an abnormally high bladder capacity in 9 patients (56%) and an abnormally low capacity in 1 patient (mean: 553 ml, SD: 152 ml). The peak detrusor pressure was lower than normal in 6 patients (38%), while a decreased maximum uroflow value was found in 5 (31%). At least 1 of the latter 2 tests was abnormal in 9 patients; thus 56% of the patients exhibited some sign of a decreased detrusor muscle contractility. On the other hand, for each of the above parameters, one patient demonstrated an abnormally high value (different patients in the two tests). Examples of cystometric charts demonstrating normal conditions, an abnormally high bladder capacity, and a decreased peak detrusor muscle pressure are presented in Figure 2.

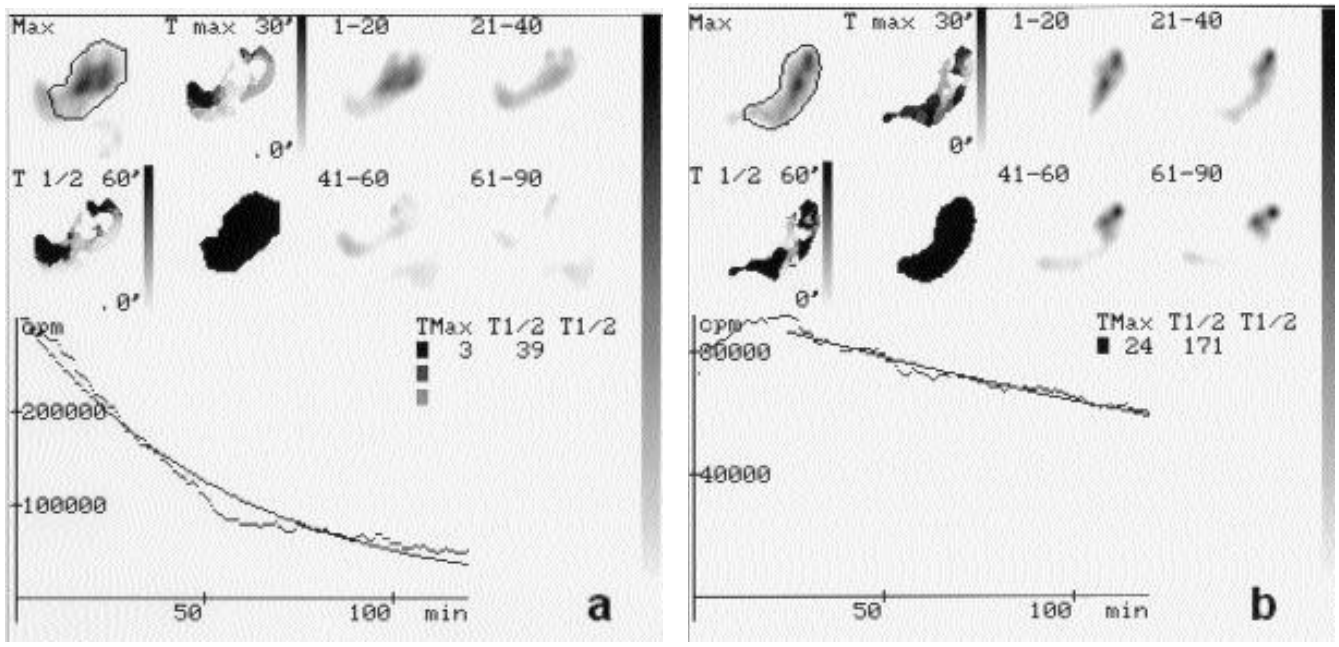
Correlations between test results and patient characteristics

Neither the gastric emptying $t_{1/2}$, nor the 3 urodynamic parameters showed a correlation with the results of the sensory nerve function test, the disease duration, the presence of any extraglandular manifestation or immunoserological positivity or the stimulated saliva production measured with the Saxon test (18). In all of the patients who had symptoms of autonomic dysfunction and underwent the urodynamic examinations, abnormal test results were obtained: the patient who experienced occasional difficulties in starting the voiding was found to have both an abnormally high bladder capacity and decreased peak detrusor muscle contractions. A further 4 patients with stress incontinence and one patient with urge incontinence demonstrated results compatible with a decreased detrusor contractility. However, the statistical analysis failed to reveal a correlation between the presence of symptoms and the test results on either organ system.

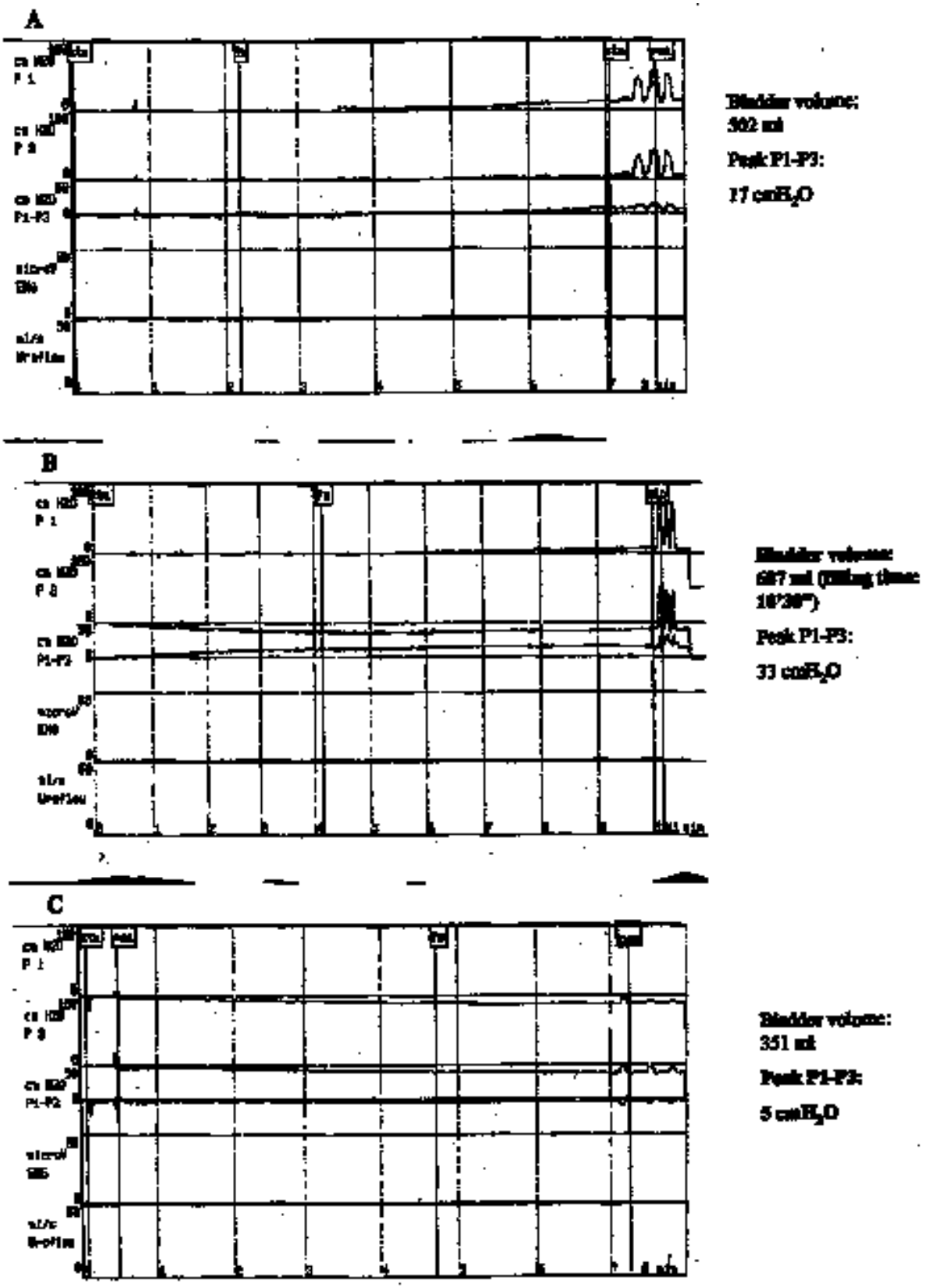
Discussion

In this cross-sectional clinical trial, we investigated the prevalence, severity and clinical correlates of GI and urinary tract autonomic dysfunction in pSS patients. The methods applied are accepted methods for the assessment of autonomic neuropathy; however, as anti-acetylcholine-receptor autoantibodies are a special feature in pSS, and these antibodies may also influence the innervation mechanism, we preferred use of the term "autonomic dysfunction" to "autonomic neuropathy". Several case reports have described occasional pSS patients with signs of an autonomic neuropathy such as orthostatic hypotension, urinary retention, segmental anhydrosis or Adie's tonic pupil (19-21). In recent years, a number of controlled clinical trials have been published in connection with cardiovascular autonomic neuropathy in pSS (9-15). However, to our knowledge, only one article mentions gastric motility in pSS (22), and no clinical trial has been published on the urogenital involvement.

In patients with diabetes mellitus, examination of the gastric emptying is an accepted method of indication of gastrointestinal autonomic neuropathy (23). The parasympathetic influence predominates in the regulation of the upper gastrointestinal tract motility, including the stomach (24). A loss of vagal tone, resulting in the inhibition of



Fig, 1. (**a**) Radionuclide gastric emptying study in a healthy control subject (gastric emptying $t_{1/2}$ = 39 minutes); and (**b**) study of prolonged gastric emptying in a pSS patient ($t_{1/2}$ = 171 minutes). The graphs show the radioactivity (cpm) recorded in the region of the stomach as a function of time (min).



Fig, 2. Cystometric charts of 3 pSS patients. (**A**) normal conditions; (**B**) increased cystometric bladder capacity; (**C**) decreased detrusor muscle contractile pressure. The charts show pressure values (cmH_2O) during the examination registered using an intravesical (P1) and an intra-abdominal (P3) manometer, and the detrusor muscle contractile pressure, which was calculated as P1-P3. The urinary bladder was filled with sterile isotonic distilled water at an average rate of 70 ml/min. **Sta**: start of the filling; **Fs**: time of the first sensation of the need for voiding; **Pea**: peak pressure values during voiding; **Sto**: pressure values at the timepoint when voiding was intentionally interrupted by the patient.

gastric emptying, is characteristic of an autonomic neuropathy in diabetes mellitus (8). With gastric emptying scintigraphy, severely delayed gastric emptying was observed in many diabetic patients (23, 25). In this study, we determined the $t_{1/2}$ cut-off value of normal gastric emptying in healthy subjects to be 74 minutes. This figure is in the same range as obtained in other published studies with conditions similar to those in this trial (26,27). Our results indicate that the gastric emptying is prolonged in 70% of pSS patients, and a considerable proportion of these patients exhibit a markedly decreased gastric motility. As organic changes that may influence the gastric emptying were not detected in the patients, this abnormality is most probably a consequence of an impaired parasympathetic activity. Data on gastric emptying in pSS patients have been reported in only one study, aimed at an evaluation of the oesophageal involvement in scleroderma and pSS (22). Similarly to us, the authors found that the gastric emptying was slower in the pSS patients than in the controls. It is of note that pSS patients rarely had complaints of an impaired gastric emptying, and even the 8 patients in our study who had complaints of postprandial fullness had merely mild symptoms which they reported only upon direct questioning. Nevertheless, the exact clinical significance of gastric symptoms can be assessed only by means of longitudinal studies.

Previously, we have investigated the oesophageal motor function in pSS patients (28). In that study, the predominant abnormality appeared to be a decreased oesophageal body peristaltic velocity. We concluded that both a diminished salivary function and oesophageal motor abnormalities are factors in the development of swallowing difficulties in pSS patients. As the oesophageal body muscles are partly innervated via the parasympathetic nervous system, we suggested a cholinergic autonomic dysfunction as one potential explanation of an impaired oesophageal motor function. These findings are in keeping with the present results and suggest that abnormalities in the upper GI tract attributable to a parasympathetic autonomic dysfunction can be detected in a great proportion of pSS patients. However, we note that we failed to reveal a correlation between the abnormalities of the gastric and the oesophageal motility measured in 6 patients who participated in both trials (data not shown).

To the best of our knowledge, this is the first report on a systematic search for signs of an autonomic dysfunction involving the urinary bladder in pSS patients, despite some reports of urinary retention in patients with this disease. However, animal experiments have revealed that serum from pSS patients has an inhibitory effect on isolated rabbit urinary bladder smooth muscle contractions, this effect being mediated by anti-m3AchR antibodies (29). The normal function of the urinary bladder is mainly under the control of the parasympathetic nervous system, which facilitates the contraction of the detrusor muscle and the relaxation of the internal sphinchter. The loss of parasympathetic stimuli due to sacral plexus injury or diabetic autonomic neuropathy leads to urinary retention, bladder atonia or flaccidity (30). In this study, the most frequent complaint concerning the urinary bladder was consistent with a mild stress-incontinence, which is usually a consequence of factors other than an autonomic dysfunction in women of similar age to that in this study group. However, the difficulty in starting voiding, mentioned by one patient, may be explained by a parasympathetic dysfunction, as an obstructive disorder had been excluded. Similarly to the results on the GI system, asymptomatic changes, i.e. an increased bladder capacity, a decreased detrusor pressure and a decreased maximal uroflow were detected in approximately half of the patients. As obstructive changes or other organic pelvic diseases were excluded, these results are consistent with a decreased detrusor muscle tone and contractility, and, similarly as with flaccid neurogenic bladder, a decreased parasympathetic influence can be suspected (30).

The precise mechanisms leading to autonomic dysfunction in pSS patients remains an open question. A reasonable explanation can be the role of an autonomic neuropathy, similarly as in several other chronic diseases. In diabetes mellitus, the autonomic neuropathy usually, but not necessarily correlates with the degree of somatic neuropathy (31), and also with the disease duration (32). Moreover, a correlation can usually be observed between the severity of the autonomic neuropathy in different organ systems in the same patient (33). In this study, we examined the vibration perception, which correlates well with the overall status of the peripheral nervous system (34). In our pSS patients, correlations similar to those in diabetic patients could not be detected, and the present test results did not exhibit a correlation with those of examinations on the cardiovascular autonomic function (unpublished observations). It is of note that an autonomic dysfunction, albeit highly prevalent, appears to be less severe in pSS patients than in diabetics. Therefore, more precise and detailed neurological examinations may be necessary to reveal subtle abnormalities in the peripheral somatic and autonomic nerves.

A further potential explanation of an autonomic dysfunction can be the interference of antirecepor antibodies with the autonomic innervation process. Since similarly as for the salivary and the lachrymal glands, the functionally predominant muscarinic receptor subtype in the GI and the GU tracts is also the m3 subtype, our findings are in favour of the hypothesis that anti-m3AchR antibodies also bind to receptors located in organs other than the exocrine glands. This concept is strongly supported by the recent finding that the immunoglobulin G fraction purified from the sera of pSS patients specifically inhibited the m3-muscarinic receptor-mediated contractions of the mouse colon (35). This interaction may contribute to the elicitation of the extraglandular manifestations of pSS. Nevertheless, to obtain direct evidence, further examinations of the fine antigenic and organ specificities and of the physiological actions of anti-mAchR antibodies are necessary.

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