Autonomic nervous dysfunction development in patients with primary Sjögren’s syndrome: a follow-up study

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Abstract

Objectives. To investigate autonomic dysfunction (AD) development in patients with primary SS (pSS) and the associations between AD and clinical, inflammatory and serological features of pSS.

Methods. Twenty-seven patients with pSS, who had previously been evaluated for AD, were included in the study. The patients were studied at baseline and at follow-up by objective autonomic reflex tests (ARTs) and by the autonomic symptom profile (ASP) questionnaire, evaluating AD symptoms. The median follow-up time was 5 years for the ART and 4 years for the ASP variables. The results were compared with previously investigated healthy ART controls and population-based ASP controls. Fatigue, anxiety and depression were assessed by the profile of fatigue and by the Hospital Anxiety and Depression scale.

Results. Three of five ART variables as well as the ASP total score were significantly abnormal both at baseline and at follow-up in pSS patients in comparison with controls. When comparing ART and ASP results in pSS patients between baseline and follow-up, only the lowest diastolic blood pressure (lDBP) ratio significantly deteriorated during the follow-up period. The ART and ASP variables were not significantly correlated. However, the ASP total score significantly correlated with measurements of fatigue, anxiety and depression.

Conclusions. Both objective signs and subjective symptoms of parasympathetic and sympathetic dysfunction were seen in pSS patients, both at baseline and at follow-up. During follow-up, only the lDBP ratio was found to significantly deteriorate. AD symptoms were significantly associated with fatigue, anxiety and depression.

Key words: Autonomic dysfunction, Primary Sjögren’s syndrome.

Introduction

Primary SS (pSS) is an autoimmune disease affecting exocrine glands and also frequently non-exocrine organs, including the nervous system. Numerous studies have reported signs of peripheral neuropathy [1–7] and autonomic dysfunction (AD) [7–12] in pSS. Since the degree of exocrine gland function and destruction correlate poorly [13, 14], and secretion is modulated by the autonomic nervous system (ANS), the impaired secretion could partly be caused by an interference with nervous signalling to the exocrine glands [13, 15]. In previous studies, using autonomic reflex tests (ARTs), parasympathetic and sympathetic dysfunction in pSS has been demonstrated [16–19], whereas studies on heart rate variability and baroreflex sensitivity have yielded contradictory results [19–23]. The AD in pSS has been ascribed to various immunological factors, including anti-muscarinic 3-receptor (M3R) antibodies, autoimmune ganglionitis and cytokines interfering with neurotransmission [7, 24–29]. Although both objective signs [16–20, 22–23] and
subjective symptoms [23, 30] of AD in pSS have previously been reported, the development of these over time has previously not been studied. The aims of this study were, therefore, to evaluate AD development in pSS and to study associations between AD and clinical, inflammatory and serological features of pSS.

Materials and methods

Patients

According to the American–European Consensus Criteria, 27 patients with pSS [31] [median age 62 (range 29–65) years, 25 females], previously studied for AD signs and symptoms [30], were included in the study. Baseline, none of the patients had any comorbidity or medication affecting ANS function. At follow-up, four patients were on such medication, which, however, was withheld 24 h before the ART. All patients at baseline had been studied by objective ART and had also completed the autonomic symptom profile (ASP) questionnaire [32, 33] on AD symptoms.

Controls

The controls consisted of 56 healthy subjects for the expiration/inspiration ratio (E/I ratio) and acceleration index (AI) [median age 40 (range 16–59) years, 22 females] all of whom had passed a health examination without signs of cardiovascular disease, respiratory disorders or diabetes [34], 80 healthy subjects for the vasocostrictory index (VAC index) [median age 43 (19–81) years, 37 females] all of whom were non-smokers, had no history of vascular disease and were not on any medication [35], 238 healthy non-diabetic individuals for the lowest systolic blood pressure ratio (SBP ratio) and lowest diastolic blood pressure ratio (DBP ratio) [median age 60 (16–96) years, 106 females] [36] and 200 population-based controls for the ASP [median age 45 (20–69) years, 100 females], who did not report having any disease or using any medication affecting ANS function [33].

ARTs

Deep breathing test. This test measured the heart rate variation, monitored by ECG, during deep breathing. An E/I ratio was calculated as the mean of the longest R–R (interbeat) intervals, during six maximal expirations divided by the mean of the shortest R–R intervals during six maximal inspirations [37]. The E/I ratio reflects parasympathetic function [37, 38].

Orthostatic test. This test measured the heart rate, monitored by ECG, and blood pressure reaction to tilt, before as well as every minute after tilt. A mean of the R–R intervals before tilt (A) was calculated and the shortest R–R interval during the first minute after tilting (B) was determined. AI was calculated as \[ \frac{(A-B)\times 100}{A} \] [39, 40]. The AI seems to reflect mainly parasympathetic [41] and also partly sympathetic function [42, 43]. The systolic and diastolic blood pressures before tilt (SBPrest and DBPrest) as well as the ISBP and IDBPs during the first 8 min after tilt were determined. The ISBP and IDBP ratios were calculated as (ISBP ratio = ISBP/SBPrest and IDBP ratio = IDBP/DBPrest). These reflect sympathetic function [44].

Finger skin blood flow test. This test measured the reflex vasoconstriction to contralateral cold provocation. The subject’s finger skin blood flow was monitored by a laser Doppler imaging (LDI) instrument during a 40°C heating procedure and subsequently during immersion of the contralateral hand and forearm into a 15°C water bath. By dividing the lowest finger skin blood flow value during the first minute of cooling (LDIc) by the mean of the two last measurements at rest, before the cooling procedure (LDIh), a VAC index could be calculated as (VAC index = LDIc/LDIh). This index reflects the sympathetic function in the skin [35]. All ART variables were age-corrected and expressed as z-scores in comparison with controls.

ASP

The ASP is a validated questionnaire assessing AD symptoms [32, 45], which was recently translated into Swedish and validated in patients with type I diabetes [33]. Both the English and Swedish ASP have been used to study AD symptoms in patients with pSS [23, 30]. The ASP consists of questions evaluating nine domains of autonomic symptoms i.e. orthostatic intolerance, secretomotor dysfunction, male sexual dysfunction, urinary dysfunction, gastrointestinal dysfunction (divided into three subdomains namely gastroparesis, diarrhoea and constipation), pupillomotor dysfunction, vasomotor dysfunction, sleep disorder and reflex syncope. In addition, interspersed questions addressing psychosomatic and understatement tendencies are included. The psychosomatic and understatement domains are not included in the ASP total score [32, 33]. Two questions on psychosomatic symptoms from the original questionnaire addressed presence of dysphagia and experience that all food tastes the same. Since such symptoms cannot be regarded as psychosomatic in pSS patients, these questions were omitted and an adjusted psychosomatic index was calculated. The ASP scores were age-, gender-, height- and weight standardized in comparison with controls and expressed as z-scores. Due to a preponderance of zero values in the gastroparesis, reflex syncope, adjusted psychosomatic and understatement domains, these were expressed as raw scores.

Clinical variables

The patients’ notes were reviewed for signs of non-exocrine symptoms and smoking habits. Fatigue was evaluated by letting the patients fill in the Profile of fatigue (ProF), and a somatic fatigue score (ProF-S), a mental fatigue score (ProF-M) and a total fatigue score (ProF-total) [46, 47] were calculated. The presence of anxiety and depression was evaluated by letting patients fill in the Hospital Anxiety and Depression scale (HADS) and a HADS anxiety and a HADS depression score were calculated [48]. The degree of inflammation was evaluated by assessing ESR and serum levels of IgG, C3 and C4.
Moreover, sera were analysed for the presence of RF, ANA, anti-SS-A and anti-SS-B antibodies.

Statistics

The Mann–Whitney U-test was used for group comparisons, the Wilcoxon matched-pairs signed-rank test for in-group comparisons and the Spearman rank correlation test for correlations. Values were presented as median (interquartile range limits) or percentages with pathological results. $P < 0.05$ was considered statistically significant.

Ethics

The study was approved by the ethics committee at Lund University (LU563-2008). All participants gave written informed consent according to the Declaration of Helsinki.

Results

The follow-up times of the pSS patients were 5 years (5–6) for the ART and 4 years (4–4) for the ASP variables. In comparison with controls, the pSS patients were found to have a significantly decreased E/I ratio, ISBP ratio and IDBP ratio, and significantly increased scores in the orthostatic intolerance, gastroparesis, secretomotor dysfunction, pupillomotor dysfunction and ASP total domains, both at baseline and at follow-up. When comparing ART and ASP variables at follow-up in comparison with baseline, only the IDBP ratio was found to significantly deteriorate (Table 1). If patients on medication affecting autonomic nervous function were excluded, the findings above still remained significant. No significant correlations were found between the ASP total score and the ART variables at follow-up. When comparing ART variables at follow-up, in patients seropositive and seronegative for RF, the former were found to have a significantly decreased IDBP ratio $[−2.46 (−3.04, −0.75)]$ vs $−0.26 (−1.74, −0.15); P = 0.03$ and AI $[−0.78 (−0.96, 0.15)]$ vs $0.28 (−0.15, 1.33); P = 0.01$ in comparison with the latter. ANA-seropositive patients were found to have a significantly decreased IDBP ratio $[−1.87 (−2.90, −0.75)]$ vs $−0.01 (−0.15, 0.49); P = 0.00$ at follow-up in comparison with ANA seronegatives. In contrast, the ART variables at follow-up were poorly associated with anti-SS-A and anti-SS-B antibodies, lip biopsy findings, non-exocrine symptoms, disease duration, smoking habits, ESR, IgG, C3, C4 as well as the ProF and HADS variables. The ASP total score at follow-up significantly correlated with the ProF-S, ProF-M, ProF-total, HADS anxiety and the HADS depression score (Table 2), whereas the adjusted psychosomatic index did not (data not shown). However, the ASP total score at follow-up was not significantly associated with the other clinical, serological and inflammatory features of pSS, mentioned above.

Discussion

We found both objective signs and subjective symptoms of parasympathetic and sympathetic dysfunction at baseline as well as after a 4- to 5-year follow-up period.

### Table 1 Results of the ARTs and the ASP domains in 27 patients with pSS and 56/80/238/200 controls

<table>
<thead>
<tr>
<th>ART and ASP variables</th>
<th>pSS patients baseline</th>
<th>pSS patients follow-up</th>
<th>Controls</th>
<th>$P$-value of pSS patients baseline vs follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/I ratio</td>
<td>$−0.50 (−1.21−0.07)*$</td>
<td>$−0.85 (−1.49−0.00)**$</td>
<td>$−0.25 (−0.62−0.60)$</td>
<td>0.12</td>
</tr>
<tr>
<td>AI</td>
<td>$−0.61 (−1.32−0.21)*$</td>
<td>$−0.17 (−0.94−0.37)$</td>
<td>$0.03 (−0.67−0.65)$</td>
<td>0.19</td>
</tr>
<tr>
<td>VAC index</td>
<td>$0.48 (0.37−1.35)$</td>
<td>$0.31 (−0.44−1.64)*$</td>
<td>$0.09 (−0.67−0.62)$</td>
<td>0.49</td>
</tr>
<tr>
<td>ISBP ratio</td>
<td>$−0.43 (−1.61 to −0.05)**$</td>
<td>$−0.52 (−1.25−0.28)**$</td>
<td>$0.00 (−0.61−0.70)$</td>
<td>0.50</td>
</tr>
<tr>
<td>IDBP ratio</td>
<td>$−0.62 (−1.00 to −0.20)**$</td>
<td>$−1.68 (−2.81 to −0.25)**$</td>
<td>$0.00 (−0.47−0.54)$</td>
<td>0.00</td>
</tr>
<tr>
<td>Orthostatic intolerance</td>
<td>$1.05 (−0.57−2.32)**$</td>
<td>$1.47 (−0.09−2.46)**$</td>
<td>$−0.39 (−0.78−0.79)$</td>
<td>0.26</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>$−0.01 (−0.92−2.00)$</td>
<td>$−0.03 (−0.63−1.85)$</td>
<td>$−0.51 (−0.71−0.32)$</td>
<td>0.56</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>$0.00 (0.00−1.50)**$</td>
<td>$0.00 (0.00−1.50)**$</td>
<td>$0.00 (0.00−0.00)$</td>
<td>0.88</td>
</tr>
<tr>
<td>Autonomic diaphoresia</td>
<td>$0.64 (−0.55−1.86)$</td>
<td>$0.65 (−0.54−2.11)*$</td>
<td>$−0.42 (−0.60−0.68)$</td>
<td>0.55</td>
</tr>
<tr>
<td>Constipation</td>
<td>$0.92 (−0.55−2.61)$</td>
<td>$0.99 (−0.57−2.56)$</td>
<td>$−0.30 (−0.52 to −0.18)$</td>
<td>0.44</td>
</tr>
<tr>
<td>Secretomotor dysfunction</td>
<td>$2.78 (2.24−3.65)$$**$</td>
<td>$3.37 (2.11−4.45)$$***$</td>
<td>$−0.45 (−0.72−0.52)$</td>
<td>0.61</td>
</tr>
<tr>
<td>Pupillomotor dysfunction</td>
<td>$1.67 (0.74−3.09)$$**$</td>
<td>$1.90 (0.84−3.07)$$***$</td>
<td>$−0.42 (−0.71−0.55)$</td>
<td>0.92</td>
</tr>
<tr>
<td>Vasomotor dysfunction</td>
<td>$−0.26 (−0.50−2.90)$</td>
<td>$−0.22 (−0.42−2.79)*$</td>
<td>$−0.33 (−0.49 to −0.20)$</td>
<td>0.30</td>
</tr>
<tr>
<td>Reflex syncope</td>
<td>$0.00 (0.00−0.00)$</td>
<td>$0.00 (0.00−0.00)$</td>
<td>$0.00 (0.00−0.00)$</td>
<td>1.00</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>$0.04 (−0.79−1.84)$</td>
<td>$0.44 (0.03−1.85)$$**$</td>
<td>$−0.05 (−0.79−0.35)$</td>
<td>0.28</td>
</tr>
<tr>
<td>ASP total score</td>
<td>$1.67 (0.63−3.26)$$**$</td>
<td>$2.44 (0.90−3.36)$$***$</td>
<td>$−0.21 (−0.82−0.72)$</td>
<td>0.20</td>
</tr>
</tbody>
</table>

The ART results were age-corrected and expressed as $z$-scores (S.D.). Most ASP domains were corrected according to age, gender, height and weight and were expressed as $z$-scores (S.D.); however, the gastroparesis and reflex syncope domains were expressed as raw scores. Since only two pSS patients were male, the sexual dysfunction domain was omitted. Results are presented as median (interquartile range limits). *$P < 0.05$ vs controls; **$P < 0.01$ vs controls; ***$P < 0.001$ vs controls.
Only the IDBP ratio significantly deteriorated during follow-up, whereas other objective and all subjective autonomic nervous function variables did not. The ART and ASP variables did not significantly correlate. However, the AI and the IDBP ratio at follow-up were significantly decreased in RF-seropositive patients, the latter also in ANA-seropositive patients in comparison with corresponding seronegatives. Finally, the ASP total score at follow-up was significantly associated with fatigue, anxiety and depression.

The increase in objective signs and subjective symptoms of parasympathetic and sympathetic dysfunction confirms our previous findings [16, 30] and is in line with most of the previous studies [17–20, 22–23]. However, this is the first study to evaluate AD development over time. During follow-up, only one of the five ART variables and none of the ASP domain scores significantly deteriorated. One possible explanation for the relative lack of more pronounced deterioration could be the long disease duration and relatively short follow-up time. It cannot be excluded that AD deterioration occurs early in pSS and thereafter stabilizes. If the putative anti-M3R antibodies are involved in exocrine dysfunction, gastrointestinal dysmotility and bladder dysfunction [11, 49], the appearance of these antibodies might be an early event resulting in persisting symptoms of parasympathetic dysfunction in organs containing the M3R. Inflammation of ganglia, on the other hand, might evolve more gradually, thereby causing a deterioration of orthostatic blood pressure reaction over time. The lack of deterioration of the ASP variables could also be due to the fact that some ASP domains also measure the effects of end-organ damage.

The ART and ASP variables at follow-up did not significantly correlate. This could be due to the differences in mechanisms behind objective signs and subjective symptoms of AD in pSS. For example, objective cardiovascular ART may not measure the physiological effects of anti-M3R antibodies that might still result in various symptoms, whereas the effects of a sympathetic ganglionitis might be easier to detect by ART. Furthermore, cardiovascular ART do not necessarily reflect autonomic nervous function in other parts of the ANS. Finally, end-organ damage may also obscure possible associations between objective and subjective AD. Albeit the small size of the study and multiple comparisons raises concerns when interpreting the results, the association between RF, ANA and decrement of certain ART variables could imply that immunological mechanisms may be involved in orthostatic dysfunction in pSS.

Although inflammatory and serological parameters did not correlate with subjective AD symptoms, various fatigue, anxiety and depression variables did. It could be suspected that this association might be due to an overall tendency to report symptoms among pSS patients. However, the lack of significant correlations between the ProF and HADS variables and the adjusted psychosomatic index makes such an explanation unlikely. The association between anxiety, depression and fatigue in pSS is well established [50] and a relationship between fatigue and AD has previously been proposed [11, 51, 52]. In contrast to our findings, one of these studies reported that fatigue was related to decreased blood pressure in pSS patients [51]. On the other hand, another study did not find any significant association between fatigue and blood pressure but did find one between fatigue and plasma levels of noradrenaline [52]. Finally, the anti-M3R antibodies have also been proposed to play a role in pSS-related fatigue [11]. If the anti-M3R antibodies or cytokines, in the future, were to be associated with fatigue and AD in pSS, this could explain the association between fatigue and AD symptoms.

In conclusion, we found both objective and subjective signs of parasympathetic and sympathetic dysfunction in pSS patients at baseline and after a 4- to 5-year follow-up period. During follow-up, only the IDBP ratio was found to significantly deteriorate. In addition, AD symptoms were significantly associated with fatigue, anxiety and depression.

### Rheumatology key messages
- Both objective and subjective signs of AD were seen in pSS patients.
- Only one objective AD variable significantly deteriorated over the follow-up period.
- AD symptoms were significantly associated with fatigue, anxiety and depression.

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