EXTENDED REPORTS

Parasympathetic failure does not contribute to ocular dryness in primary Sjögren's syndrome

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Abstract
Objective—To investigate the sympathetic and parasympathetic cardiovascular function in primary Sjögren's syndrome (SS) and to investigate the possible relation with ocular dryness.
Methods—41 (40 women) patients with primary SS, mean age 50 years (range 20–80) with a mean disease duration of eight years (range 1–30), were studied. In each patient direct arterial blood pressure (BP), heart rate (HR) and respiration were measured continuously for two hours. The function of the autonomic circulatory regulation was evaluated by measuring the heart rate response to deep breathing (6 cycles/min) and by means of the Valsalva manoeuvre and the responses of BP, HR and plasma noradrenaline (norepinephrine) concentrations to a 10 minute 60 degree head up tilt test. Pupillography was done to evaluate ocular autonomic function.
Results—The HR-Valsalva ratio was abnormal in 24% of the patients, and the HR variability during forced respiration was abnormal in 56% of the patients. The HR responses to both the Valsalva manoeuvre and deep breathing, as indicators of parasympathetic function, were abnormally low in 6 of 41 (15%) patients. In only two patients the decrease in systolic BP in response to the head up tilt test, as indicator of sympathetic function, was more than 20 mm Hg. However, increment of plasma noradrenaline concentration during head up tilt test and the overshoot of BP in phase IV of the Valsalva manoeuvre, as indicators of sympathetic function, were normal in both patients. Thus, no evidence for sympathetic dysfunction was found, whereas evidence for parasympathetic failure occurred sometimes. Autonomic pupillary function in patients with primary SS and healthy controls, as well as the Schirmer test in patients with or without evidence for parasympathetic dysfunction as based on the results of the Valsalva and deep breathing tests, were not significantly different.
Conclusion—Parasympathetic, but not sympathetic dysfunction seems to occur in a subgroup of primary SS. Results show that this does not necessarily contribute to the typical ocular dryness in this condition.
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Primary Sjögren's syndrome (SS) is a systemic autoimmune disease, characterised by lymphocytic infiltration of exocrine glandular tissue. Oral and ocular dryness are well known features of this disease, but extraglandular manifestations such as pulmonary fibrosis and vasculitis can also be present.[1]

In primary SS, abnormalities of the central and peripheral nervous system are found in up to 25% of the patients.[2–7]

Abnormalities of the autonomic nervous system, mostly concerning isolated symptoms such as disturbance of the pupillary light reflex, have been reported incidentally in primary SS.[8 9] In a recent study, performed in 19 primary SS patients and 56 controls, the heart rate (HR) variability during forced respiration, and systolic blood pressure (BP) at rest and during head up tilting were significantly lower in the patient group,[10] suggesting the presence of both sympathetic and parasympathetic dysfunction in SS.

This study was aimed at investigating the cardiovascular and ocular function of the autonomic nervous system in primary SS and to explore a possible relation between autonomic dysfunction and ocular dryness.

Methods

PATIENTS

Forty one patients with primary SS were recruited from the Department of Rheumatology, Zuiderziekenhuis, Rotterdam. All patients fulfilled the European Criteria for primary SS.[11] Moreover, the patients without an abnormal salivary gland biopsy (lip mucosa) all had an abnormal sialography. In all the patients at least one of the serological tests was positive (table 1).

None of the patients suffered from concomitant diseases, such as neurological disease, amyloidosis, renal failure or diabetes mellitus, all known to affect the autonomic nervous system. None of the patients used drugs interfering with the function of the autonomic nervous

system. Administration of non-steroidal anti-inflammatory drugs (used by 55% of the patients) was discontinued one week before the performance of the autonomic function tests.

Written informed consent was obtained from all patients. The study was approved by the Medical Ethical Committee of the University Hospital Rotterdam-Dijkzigt.

STUDY DESIGN

Cardiovascular function tests

The ECG showed a normal sinus rhythm in all patients. Before testing, the patients completed a questionnaire about symptoms of autonomic failure, including dizziness, headache, palpitations and reduced sweating. All studies were performed between 0800 and 1200. After arrival in the cardiovascular laboratory, the radial or brachial artery of the non-dominant arm was cannulated with a 22 gauge cannula (after local anaesthesia with a 1% lignocaine (lidocaine) solution) for direct, continuous BP measurement and blood sampling for catecholamines. HR was continuously measured by means of three precordial leads. The respiratory signal was derived from the ECG signal. After instrumentation, the patients rested on a motor driven tilt table for 30 minutes before the registration was started.

For the first 15 minutes of the registration the subjects were in the supine position. During the last five minutes of this period the respiration rate was controlled to 16 breathings/minute by means of a metronome. Then the subjects were tilted to 60° head up tilt and registrations were continued for another period of 15 minutes; during the last five minutes of this period with a fixed respiration rate.

A decrease in systolic BP of > 20 mm Hg during the last five minutes of head up tilt was considered to indicate orthostatic hypotension—that is, sympathetic dysfunction.

At the end of the supine rest and at the end of the head up tilt periods blood samples were taken for the determination of plasma catecholamines. After the tilt test, the patients were placed again in the supine position and a Valsalva manoeuvre was performed after an equilibration period of 10 minutes.

For the Valsalva manoeuvre the patient had to blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mm Hg for 15 seconds. The longest interbeat interval shortly after the ending of this Valsalva manoeuvre (within 20 beats) to the shortest interbeat interval during the manoeuvre was measured.[12] The result was expressed as the Valsalva ratio. A value of <1.20 points at parasympathetic failure.[12] After the Valsalva manoeuvre the patient had to breathe deeply and evenly at six breaths per minute (five seconds in and five seconds out). The maximum and minimum HR during each 10 second breathing cycle was measured. The mean of the differences during three successive breathing cycles gives the "maximum-minimum heart rate". A value of < 15 beats represent parasympathetic abnormality.[12]

Ambulatory BP measurements

At the end of the laboratory measurements, the patients were equipped with a monitor for ambulatory BP measurements (Spacelabs 90207, ambulatory BP monitor, Spacelabs, Redmond, USA) of a full 24 hour period at home. During the day (0700 to 2300) measurements were performed at 20 minute and during the night (2300–0700) at 30 minute intervals. The activities of the patients during the BP measurements were recorded in a daily log.

Mean BP values were computed for the day and night period separately.

A decrease in night time BP of ≥ 10% as compared with the day time BP is considered to be normal.[13]

Pupillography

Pupillography was performed one day after the cardiovascular tests. To study the ocular autonomic nervous system, an infrared light reflection method (IRIS) was used.[14]

In short, after one minute adaptation to darkness, infrared light was emitted from diodes located on a frame in front of one eye. On the same frame foto-transmitters detected the infrared light reflected from the iris. The pupillary system was stimulated with a pulse light stimulus with a fixed intensity (retinal illuminance 46000 Troland) with a pulse duration of 1.2 seconds, which is long enough to obtain maximal constriction and short enough to prevent pupillary adaption resulting in re-dilatation. The period between two consecutive stimuli was five seconds, permitting complete re-dilatation before the presentation of a new stimulus. Each eye was measured during six light responses with a sample frequency of 100 Hz.

The constriction and dilatation latency times of these six responses were averaged. Average constriction latency time (CL, the time between the start of the light pulse and the start of the constriction of the pupil) and the average latency time of the maximal constriction velocity (MCV, the time between the start of the light pulse and the maximal constriction velocity) were determined as parameters of ocular parasympathetic function.

The average dilatation latency time (DL, the time between the disappearance of the light pulse and the start of the dilatation of the pupil) was determined as a parameter of ocular sympathetic function.[14]

Thirty three age matched apparently healthy women, who were relatives of patients or hospital employees, served as controls for the pupillography tests.

MEASUREMENTS

Measurement of unstimulated tear production (Schirmer test)

Standardised paperstrips (IOLAB Pharmaceuticals, CA, USA) were placed in the lower eyelid of unanaesthetised eye. The degree of wetting of the strips (in mm) five minutes after placement was used as a measurement of tear production.[15]

Table 1 Demographic and clinical data of 41 patients with primary SS

Age (y)	50 (20–80)
Sex (% women)	98
Disease duration (y)	8 (1–30)
ESR (mm 1st h)	39 (11–110)
ANA (% positive)	67
RF (% positive)	53
SS-A (% positive)	64
Schirmer test (mm/5min)	8.7 (0–35)
Saxon (mg/2min)	1.5 (0–20.7)
Sialography (% positive)	80
Salivary gland biopsy (% positive)★	89

All values are presented as mean and range unless indicated otherwise. ESR = erythrocyte sedimentation rate. ANA = antinuclear antibodies. RF = rheumatoid factor. SS-A = Sjögren's syndrome A antibodies. ★Lymphocytic infiltration in salivary gland biopsy ($\geqslant 2$ foci of >50 lymphocytes/4 mm^2 gland tissue).

Measurement of unstimulated saliva production (Saxon test)

To perform the Saxon test,[16] a piece of parafilm (5×5 cm) and a plastic tube were weighed and the person was asked to chew vigorously on parafilm for two minutes. The chewed parafilm and all the saliva produced were placed together in the tube. The amount of saliva produced was obtained by subtracting the original weight from the weight of the tube after chewing. Weights were measured on a Mettler laboratory balance, which is accurate to 0.1 mg.

Plasma catecholamines

For the determination of plasma catecholamine concentrations (noradrenaline (norepinephrine), adrenaline (epinephrine), dopamine), arterial blood was collected in chilled heparinised polystyrene tubes containing glutathione (1.2 mg/ml). The tubes were centrifuged within 30 minutes (4°, 10 min, $3000 \times g$) and the plasma was stored at $-80°$. Plasma concentrations of catecholamines were measured by fluorometric detection after high performance liquid chromatography separation as described previously.[17]

Normal catecholamine values (mean (SD)) of a resting supine healthy, age and sex matched control population in our laboratory are: 25 (2) pg/ml for adrenaline, 261 (109) pg/ml for noradrenaline and 13 (8) pg/ml for dopamine.

STATISTICS

Values are presented as mean (SD), unless indicated otherwise. Values of most parameters of the patient group were evaluated against the normal values as described in the method section. The Wilcoxon test was used to establish differences between patients and controls,

Table 3 Pupillary constriction and pupillary dilatation latency times in 41 patients with primary SS and 33 controls

	Sjögren patients	Controls	
CL (ms)	250 (190–320)	250 (180–300)	NS
MCV (ms)	310 (260–410)	325 (270–370)	NS
DL (ms)	400 (140–520)	350 (200–500)	NS

All values are presented as median and range. CL = constriction latency time. MCV = latency time of the maximal constriction velocity. DL = dilatation latency time. NS = not statistically significant.

where appropriate. Relations between parameters were analysed by means of Pearson's correlation coefficients. A p value of < 0.05 was considered to indicate statistically significant differences or a significant relation.

Results

CARDIOVASCULAR AUTONOMIC FUNCTION TESTS

Table 1 gives the demographic and clinical data of the patients. None of the patients had obvious clinical manifestations of autonomic dysfunction, as based on the questionnaire. Head up tilt testing showed an abnormal result (decrease in systolic BP > 20 mm Hg) in only two of the patients (table 2). The response of plasma noradrenaline concentration to the head up tilt test and the overshoot of BP in phase IV of the Valsalva manoeuvre in these two patients, as in all other patients, was normal. Baseline values of other plasma catecholamines, as well as their responses to head up tilting, were normal in all patients, including those with an abnormal head up tilt test. No relation was found between age and plasma catecholamine response to head up tilting.

The HR-Valsalva ratio (mean value 1.47, range 1.00–2.38) was below the normal cut off value of 1.20 in 10 (24%) of the patients. The difference between the maximal and minimal heart rate response to forced respiration (mean value 13.3, range 2.0–29.0) was below the normal cut off value of 15 in 23 (56%) of the patients. An abnormal result for the two tests combined was observed in 6 (15%) of the patients.

A significant negative correlation was found between age and the HR-Valsalva ratio ($r = -0.33$, p <0.05) and between age and HR during forced respiration ($r = -0.34$, p< 0.05). No relations were found between disease duration and HR-Valsalva, nor between disease duration and HR during forced respiration.

All but one of the patients had a normal nocturnal decline in BP. The average daytime ambulatory BP for the whole group was 120 (11)/77(9) mm Hg and the average night time BP for the whole group 108 (13)/62 (8) mm Hg.

PUPILLOGRAPHY

Values of CL, MCV and DL between patients and healthy controls did not differ significantly (table 3). In patients and in healthy controls, age versus CL and age versus MCV were correlated (for all correlations: r >0.40, p<0.05). Schirmer and Saxon test results were not correlated with any of the variables of the pupillography.

Table 2 Blood pressure, heart rate and plasma catecholamine concentrations in patients with primary SS during supine rest and orthostatic challenge

	All patients		Patient no 16		Patient no 24	
	supine	*tilt*	*supine*	*tilt*	*supine*	*tilt*
Systolic BP	135 (20)	131 (12)	147	117	146	122
Diastolic BP	66 (8)	71 (12)	65	49	69	58
Mean BP	89 (12)	91 (14)	92	76	95	79
Heart rate	71 (10)	81 (12)	55	64	82	102
Noradrenaline	161 (91)	319 (132)	141	238	265	330
Dopamine	10 (5)	11 (6)	9	20	17	9
Adrenaline	37 (24)	71 (74)	45	67	86	204

All values are represented as mean (SD). Blood pressure in mm Hg. Heart rate in beats/minute. Values of plasma noradrenaline, dopamine and adrenaline concentrations in pg/ml.

The results of pupillography and the Schirmer/Saxon test results in the subgroup of patients with an abnormal HR-Valsalva ratio and abnormal maximum-minimum HR response and in the subgroup of patients without these abnormalities were similar.

Discussion

In this study, in a relatively large group of well defined patients with primary SS, the cardiovascular autonomic nervous system and the autonomic innervation of the pupil were investigated. No clinical evidence of autonomic failure was noted. In this patient group, no evidence was found for dysfunction of the cardiovascular sympathetic nervous system. The concentration of plasma noradrenaline was normal in all patients, and they all had a normal overshoot of BP in phase IV of the Valsalva manoeuvre. Although in two patients systolic BP in response to head up tilting decreased by more than 20 mm Hg, there was no evidence for sympathetic dysfunction as shown by the other tests. Also sympathetic ocular function was normal in all patients.

Abnormalities of HR variability in response to both the Valsalva manoevre and forced respiration were found in 15% of the patients. This indicates the presence of parasympathetic dysfunction in this subgroup. We did not find evidence for dysfunction of the parasympathetic innervation of the eye in the primary SS patients with or without cardiovascular parasympathetic abnormalities. This may suggest that the parasympathetic disturbances in primary SS are discrete and not of generalised nature. The observation that a subgroup of our patients did have evidence for cardiac parasympathetic dysfunction but normal results with pupillography could also imply that pupillography is a less sensitive method to detect parasympathetic dysfunction.

This, however, is not supported by findings in patients with diabetes mellitus, in whom pupillography correlates well with cardiovascular function tests and has been proved to be a very sensitive method to discover subclinical autonomic dysfunction.[14]

Although several case reports concerning autonomic dysfunction, varying from pupillary disturbances to orthostatic hypotension in patients with primary SS have been published,[7-9 18-20] only one controlled study on the cardiovascular autonomic nervous system in primary SS has been published.[10] In this study, autonomic nervous function was evaluated by deep breathing and tilt table tests in 19 patients with primary SS and in 56 age matched controls. The HR variability during forced respiration and systolic BP at rest and during tilt were significantly reduced in the patient group. As in our study, no correlations were found between the cardiovascular and other autonomic function tests and the results of the Schirmer test. This may suggest that the production of tear fluid is influenced by the autonomic nervous system in a different way. On the other hand, it may be asked whether the Schirmer test is sufficiently sensitive in this context. Previously, we found abnormal parasympathetic ocular test results in patients with rheumatoid arthritis and ocular dryness compared with those without dryness.[21] Possibly, more severe lymphocytic lacrimal gland infiltration in patients with primary SS as compared with those with RA may have masked any potential effect of parasympathetic dysfunction on tear production in this study.

In other systemic diseases, such as amyloidosis, diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis, more severe autonomic (mostly parasympathetic) disturbances have been found in 30–60% of the patients. Concurrent with the present results significant clinical signs of autonomic dysfunction were only rarely present.[22-27]

The pathogenesis of autonomic neuropathy in connective tissue diseases has not yet been elucidated. It has been suggested that an immunological mechanism, inducing small vessel vasculitis of the vasa nervorum of the autonomic nerves may be involved. The beneficial effect of immunosuppressive treatment early in the course of autonomic dysfunction in patients with primary SS and systemic lupus erythematosus is compatible with such a mechanism.[20 28]

In conclusion, minor and discrete impairment of the cardiovascular parasympathetic nervous system may occur in subgroups of patients with primary SS. However, it is unlikely that impaired parasympathetic function contributes to the ocular dryness in this condition.

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