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Report

Cardiovascular autonomic dysfunction in primary Sjögren's syndrome

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***Objective*. To assess the occurrence and clinical significance of a cardiovascular autonomic nervous system dysfunction in primary Sjögren's syndrome (pSS).**

***Methods*. Fifty-one pSS patients participated in this case-control study. Heart rate and blood pressure variability measurements, spontaneous baroreflex sensitivity examinations and cardiovascular reflex tests were performed.**

***Results*. The results of the heart rate and blood pressure variability measurements and also the baroreflex sensitivity parameters of the pSS patients peaked in the lowest percentile ranges of a database on 559 healthy control subjects ($P < 0.05$). In three of the five cardiovascular reflex tests, the frequencies of abnormal results were significantly higher among the patients than among the controls ($P < 0.05$), and the median autonomic neuropathy score was also elevated (3 *vs* 0 in the controls; $P < 0.0001$).**

***Conclusion*. Signs of an autonomic nervous system dysfunction involving the cardiovascular system can be discerned in the majority of pSS patients.**

KEY WORDS: Antireceptor antibody, Autonomic dysfunction, Baroreflex sensitivity, Blood pressure variability, Cardiovascular reflex test, Heart rate variability, Primary Sjögren's syndrome.

There is increasing evidence that decreased stimulation by the autonomic nervous system of the salivary and lacrimal glands plays an important role in the elicitation of the exocrine dysfunction in primary Sjögren's syndrome (pSS) [1]. Antibodies to the muscarinic acetylcholine receptor subtype 3 (m3AchR) have been demonstrated in pSS [2–4]. Cardiovascular autonomic neuropathy has been investigated in pSS by various study groups [5–11]; however, possibly as a consequence of the differences in the methods applied, the results are not consistent. Therefore, with regard to the emerging importance of anti-mAchR autoantibodies in pSS, and the clinical significance of an autonomic nervous system dysfunction, we attempted to clarify the occurrence and severity of cardiovascular autonomic neuropathy by using both the standard cardiovascular reflex tests and the more sensitive and up-to-date heart rate variability (HRV) examinations.

Patients and methods

Study patients

A questionnaire relating to symptoms that may potentially be caused by an autonomic dysfunction was completed by 51 pSS patients [48 women, average age 53 yr (range 31–71 yr)]. All of them fulfilled the American–European classification criteria for pSS [12]. Patients older than 75 yr or those with diabetes mellitus or any other disease that may cause an autonomic neuropathy were not included in this study, the examined patient population was otherwise unselected.

Examination of heart rate and blood pressure variability

Heart rate (HR) and blood pressure (BP) were recorded continuously for a period of 10 min with a Marquette bedside ECG monitor and with a Finapres 2300 non-invasive beat-to-beat BP monitor (Ohmeda, St Louis, MO), respectively.

The following standard HRV and blood pressure variability (BPV) indices were calculated. (i) The time domain analysis yields descriptive statistical data on the variability of the cycle length (RR-interval) and BP values registered during the 10-min examination period: minimum, maximum and mean RR-interval; SDRR (standard deviation of the mean RR-interval); RMSSD (the square root of the average of the squared differences between each consecutive RR-interval); pNN50 (the percentage of intervals that differed from the adjacent interval by >50 ms); and the minimum, maximum and mean systolic BP (SBP) [13]. (ii) Frequency domain analysis involves power spectral analysis of the effects modulating the oscillations in the RR-intervals and SBP. Parameters indicating the impacts on SBP in the low-frequency (LF) or high-frequency (HF) band (LF-SBP, HF-SBP) and of the RR-interval values in the LF band (LF-RRI) were calculated. (iii) As the vagus nerve is the efferent pathway of the baroreflex

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circuit, the measurement of baroreflex sensitivity (BRS) provides precise data on the parasympathetic innervation of the heart [14]. Spontaneous BRS can be assessed at rest during the simultaneous registration of RR-interval and SBP values, as with an intact baroreflex function, every spontaneous rise or fall in BP is immediately followed by the appropriate change in the HR. The slope of the function of coupled RR-interval and SBP changes was considered as a measure of BRS.

We compared our results on pSS patients with our previous results obtained by the systematic examination of a large healthy population of 559 subjects [15]. Since the control group comprised persons with a maximum age of 60 yr, of the original 51 pSS patients only those aged 60 yr or below could be evaluated. As three further patients who had either organic heart disease or extrasystolia were also excluded from the HRV/BPV studies, 39 patients (37 women) remained eligible for these examinations. For methodological reasons, the evaluation of BRS was feasible in 30 patients.

Cardiovascular reflex tests

Five simple and fast tests were carried out following the standard methods of Ewing *et al*. [16]: (i) HR changes in response to deep breathing; (ii) HR changes in response to the Valsalva manoeuvre; (iii) HR changes in response to standing up (30/15 ratio); (iv) SBP changes in response to standing up; (v) diastolic BP changes in response to a sustained handgrip. In every test, normal values were scored 0, borderline values 1 and abnormal values 2. The sum of the scores gave the total autonomic neuropathy score [16]. A score of 0–1 was taken as normal, 2–3 as borderline and >3 as abnormal [16]. Patients with organic cardiac disease or any arrhythmia, or those who were treated with beta- or alpha-adrenergic receptor blockers or vasodilating drugs were not eligible. After the exclusion of these patients, the tests were performed on 39 patients (37 women) and the results were compared with those on 39 age- and sex-matched healthy controls.

Sensory nerve function assessment

The somatic sensory nerve function was assessed by examination of the vibration perception threshold with a calibrated vibrameter.

Statistical methods

In the HRV, BPV and BRS examinations, to test whether the numbers of patients in the various percentile ranges differ from the expected distribution, the χ^2 test was used. Cardiovascular reflex test results on the patients and the controls were compared via a Mann–Whitney U-test or a χ^2 test. The relationships between the results of the examinations and the various patient data were analysed with Spearman's rank correlation test or with a Mann–Whitney U-test.

Results

Nine patients experienced palpitations, three reported complaints consistent with orthostatic hypotension and one patient mentioned episodes of presyncope.

For the purpose of comparison with the healthy controls, the 37 participating pSS patients were allocated into four subgroups according to age and sex. For each of the test parameters, we defined the percentile values in the appropriate age and gender subgroup of healthy controls for the results on every patient. The mean RR-interval and SBP values were distributed relatively evenly in the patients, similarly to their distribution in the healthy population ($P > 0.05$). In contrast, the SDRR, pNN50, RMSSD, LF-RRI, HF-RRI and LF-SBP percentile values were clustered in the lowest percentile range, i.e. the majority of the pSS patients exhibited parameters that were below the 20th percentile for the corresponding age- and sex-matched healthy population ($P < 0.001$ for all parameters). Similarly, we noted a significant difference from the normal distribution ($P < 0.05$) with regard to the BRS values. In summary, pSS patients have HR and BP values similar to those in the healthy population, but the variability in both the HR and the BP is restricted and BRS is decreased. In Fig. 1, we present the distribution of selected, representative parameters in the pSS patients and the healthy controls.

The results of the cardiovascular reflex tests are summarized in Fig. 2. In every test, higher percentages of the pSS patients than of the controls demonstrated an abnormal result, and this difference was statistically significant in two parasympathetic and one sympathetic test ($P < 0.05$). When the average values were compared between the two groups, the pSS patients exhibited significantly lower median values in the tests of the HR response to standing up (1.0 *vs* 1.12, $P < 0.001$) and to deep breathing (14 *vs* 21 beats/min, $P < 0.05$) and of the diastolic BP change in response to a sustained handgrip (16 *vs* 25 mm Hg; $P < 0.001$), while in the two remaining tests, the average values of the two groups were not significantly different. Sixteen patients gave abnormal and 17 borderline autonomic neuropathy scores [total: 33 (85%) *vs* 7 (18%) in the controls; $P < 0.0001$]. The median autonomic neuropathy score in the patient group was 3 (range 1–8), while that in the control group was 0 (range 0–5; $P < 0.0001$).

Similarly, as in the general population [15], the BRS values displayed a significant negative correlation with age ($r = -0.44$, $P = 0.012$). None of the above test results correlated with the pSS duration, the presence of any extraglandular manifestation or immunoserological positivity, the sensory nerve function or the stimulated saliva production. The nine patients who reported palpitations had lower values (i.e. more abnormal) of all of the HRV and BPV parameters than the patients without this complaint; this difference was statistically significant in the case of RMSSD ($P = 0.026$) and was close to the border of statistical significance in the cases of pNN50 ($P = 0.073$) and down-BRS ($P = 0.076$).

Discussion

In this trial, we investigated the prevalence, severity and clinical correlates of cardiovascular autonomic dysfunction in pSS patients. The methods applied are accepted methods for the assessment of autonomic neuropathy; however, as anti-AchR autoantibodies are a special feature in pSS, and these antibodies may also influence the innervation mechanism, we prefer use of the term autonomic dysfunction to autonomic neuropathy.

The examination of HRV and BPV revealed that, while having a normal HR and BP in general, a great majority of the pSS patients have a restricted variability of both HR and BP. HRV and BPV reflect the continuous adaptation of the circulation to the changing conditions, and are mediated predominantly by the autonomic nervous system. In view of the physiological correlates of the particular parameters [13], our results conclusively indicate that signs of both a sympathetic and a parasympathetic cardiovascular autonomic dysfunction can be observed in a great proportion of pSS patients.

The cardiovascular reflex tests also revealed marked differences as compared with the healthy controls, but these data are far less consistent. The ratio of patients with an abnormal result was statistically significantly higher than in the controls in only two of the three parasympathetic tests and in one of the two sympathetic tests. The median global score was 3, which is a borderline value, being much lower than that for diabetic patients, for whom average scores of 6 or even higher are the typical published values [17, 18].

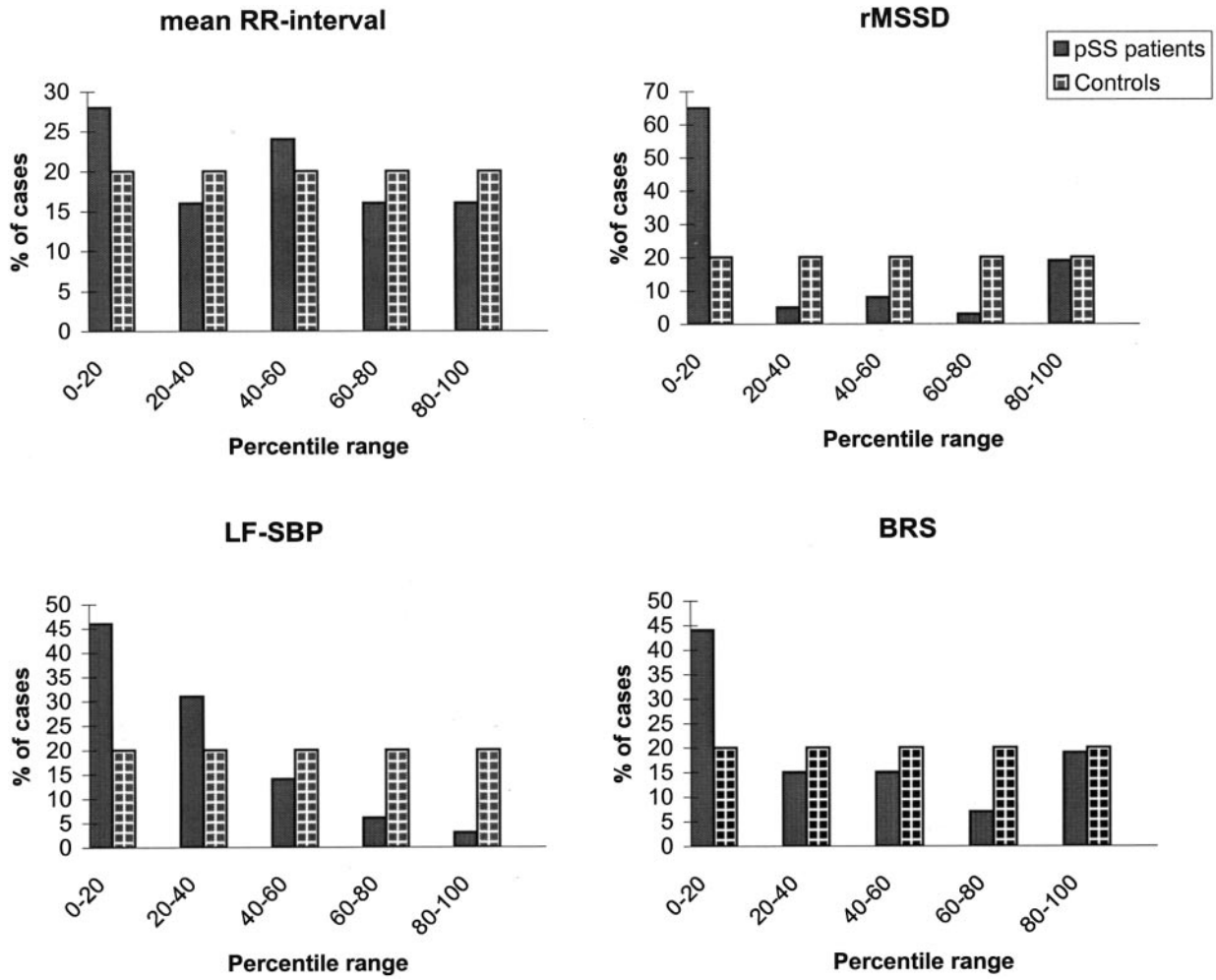

FIG. 1. Representative diagrams of four parameters recorded during the HRV and BPV measurements. The results are represented as percentile values of those for a group of age- and sex-matched healthy individuals. As an illustration, the percentile distribution of the healthy subjects is also presented. MeanRRI, mean RR-interval. There was no significant difference between the patients and the controls ($P > 0.05$), i.e. the average resting heart rate was similar in the two groups. RMSSD, a time domain analysis parameter relating mainly to a parasympathetic nervous system dysfunction. LF-SBP, a frequency domain analysis parameter relating mainly to a sympathetic nervous system dysfunction. BRS, baroreflex sensitivity. For the latter three parameters, the distribution of the patients in the various percentile ranges is significantly different from that of the controls ($P < 0.001$). For a more detailed explanation of the parameters, see Patients and methods.

Previous studies on this topic found signs of a parasympathetic and a sympathetic dysfunction in rather variable proportions of pSS patients (between 24 and 100% in the various tests). Although the methods of these investigations ranged from simple autonomic reflex tests and reflex test panels to spectral HRV and BPV analyses, the control selection procedures were very similar. Age- and sex-matched healthy volunteers were recruited, and the control/patient ratio seldom exceeded 1:1. It seems that autonomic reflex tests perform best in diabetic populations [16]. It is well documented that gross abnormalities indicating severe neuropathy are associated with an adverse outcome [19]. Therefore, these tests are well suited for the mass screening and risk stratification of diabetics in routine clinical practice. More subtle abnormalities of the cardiovascular autonomic regulation might be difficult to assess by reflex test methods.

In contrast with the reflex test studies, conclusive results were obtained from the HRV/BPV and BRS analyses. Some of the variables assessed in our present study, such as the spontaneous BRS, have been shown to vary tremendously in the healthy population [15, 20]. Comparisons with single age- and sex-matched control subjects may therefore be subject to chance influences. Accordingly, we related the variables of the pSS subjects to a large database on age- and sex-matched healthy volunteers.

In summary, we conclude that a cardiovascular autonomic dysfunction is common, but usually relatively mild in pSS, and only the sensitive HRV examination and the application of a large control population are suitable for a consistent demonstration of its presence. In view of its high occurrence, one can speculate that it has some pathogenic role in this disease. It was earlier reported that a 25 amino acid epitope of the human m2AchR, which is the functioning receptor subtype in the heart [21], did not react with the serum of any of the examined pSS patients [4]. However, these findings do not preclude that anti-m2AchR antibodies with different epitope specificities may operate. An autonomic neuropathy may be a further potential mechanism. Due to its potential pathophysiological significance, we consider it worthwhile to further characterize the potential immunological mechanisms which lead to autonomic nervous system abnormalities in pSS.

On the other hand, the clinical consequences of the cardiovascular autonomic dysfunction are generally mild. Our pSS patients rarely experienced symptoms potentially attributable to it, and

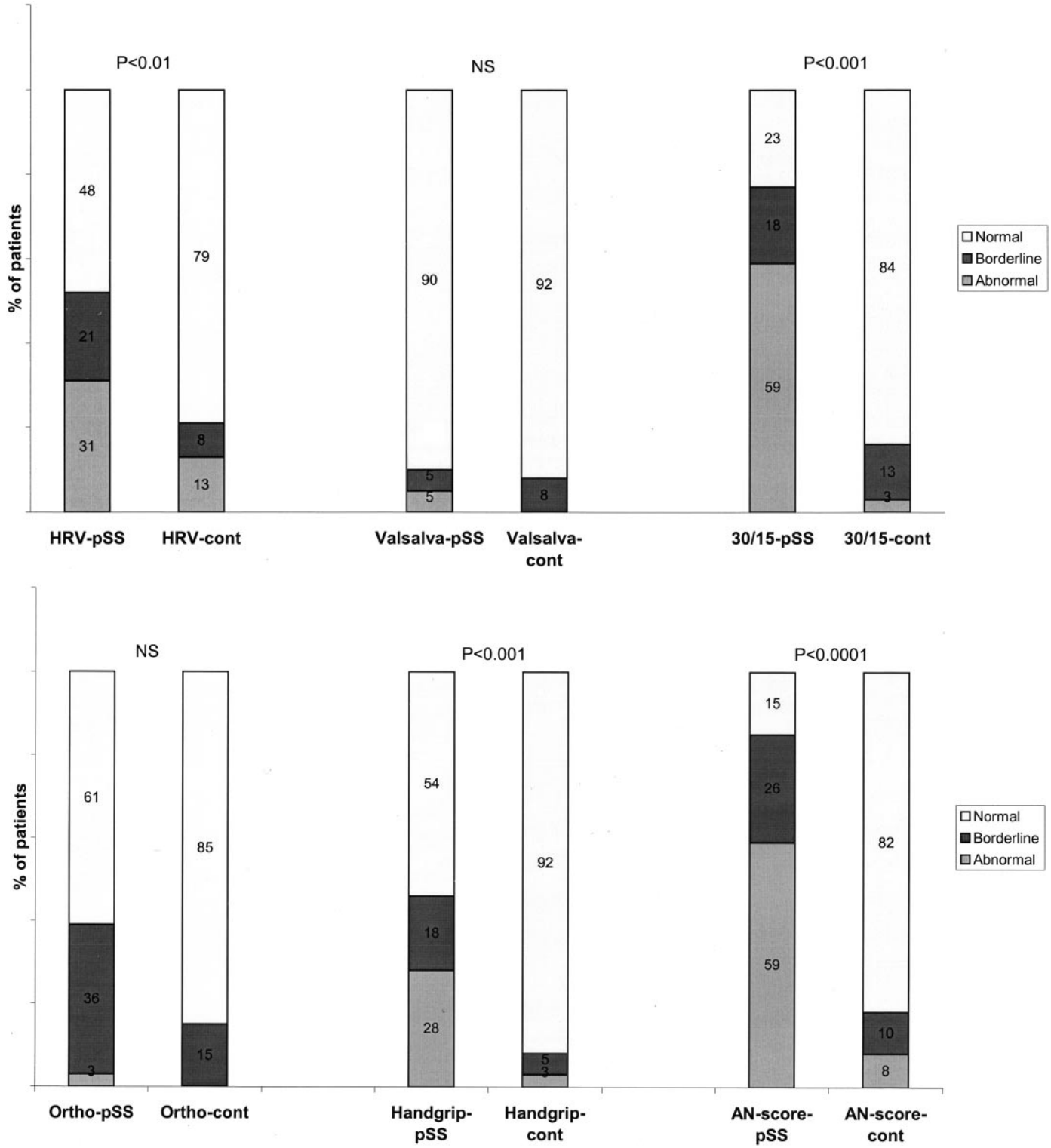

FIG. 2. The distributions of the results of the cardiovascular reflex tests in the pSS patients and the controls. (**a**) Tests relating mainly to the parasympathetic function: heart rate changes in response to deep breathing (HRV), to the Valsalva manoeuvre, and to standing up (30/15). (**b**) Tests relating mainly to the sympathetic function: SBP changes in response to standing up (orthostatic challenge: ortho) and diastolic BP changes in response to a sustained handgrip (handgrip). The total autonomic neuropathy score (AN score) results are also presented here. Cont, control; NS, non-significant difference.

significant cardiac symptomatology has not been reported in studies on large cohorts of pSS patients [22]. Nevertheless, upon direct questioning, nine of the pSS patients (18%) reported episodes of palpitations. Notably, in these patients the autonomic dysfunction was more pronounced than in the pSS patients without this symptom when examined with the HRV/BPV examinations, while the reflex tests failed to identify these patients. We conclude that it is not warranted to routinely test every pSS patient, but in occasional patients with complaints suggestive of an autonomic dysfunction, short-term HRV/BPV examinations are

useful in the verification of an underlying autonomic nervous system abnormality, while the cardiovascular reflex tests are less valuable in this respect because of their lower sensitivity.

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Conflict of interest

The authors have declared no conflicts of interest.

Rheumatology	Key points/messages
	1. Cardiovascular autonomic dysfunction was revealed in the majority of pSS patients. 2. It is usually clinically mild. 3. HRV measurements are superior to reflex tests in its detection.

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