

## EXTENDED REPORT

## Increased prevalence of ocular glaucomatous abnormalities in systemic sclerosis

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**Background:** Cardiovascular diseases, vasospasm, and dysimmunity have been implicated in normal tension glaucoma (NTG).

**Objective:** To investigate the prevalence of ocular abnormalities suggestive of glaucoma damage in systemic sclerosis (SSc).

**Methods:** 61 patients with SSc (mean (SD) age 56.2 (12) years, mean (SD) disease duration 9.9 (9) years; 41 with limited cutaneous disease) and 37 control subjects with osteoarthritis (mean (SD) age 55.9 (12) years) were studied. They were systematically referred to an ophthalmologist. The evaluation was based on aplanation tonometry, ophthalmoscopy with retinal photography (evaluation of cup/disc ratio (c/d)), and automated static perimetry (determination of mean defects (MD)). Statistical analyses were performed with the  $\chi^2$ , Mann-Whitney, and Spearman tests.

**Results:** The mean visual acuity and intraocular pressure were similar in both groups. An excavation with a c/d >0.3 was found in 27 eyes from patients with SSc and 5 eyes from controls ( $p=0.009$ ); a c/d >0.7 was found in 4 eyes from patients with SSc and none in the controls (NS). Visual field defects (MD <-2 dB) were found in 55 eyes from patients with SSc and in 18 eyes from controls ( $p<0.0001$ ). A concomitant c/d >0.3 and MD <-2 dB was found in 21 eyes from 12 patients with SSc but in none of the control eyes ( $p<0.0001$ ).

**Conclusion:** Ocular abnormalities suggesting glaucomatous neuropathy without ocular hypertension were dramatically more prevalent in patients with SSc. These abnormalities seem to be mild but justify long term follow up. They are consistent with the vascular pathogenic hypothesis for NTG.

Systemic sclerosis (SSc) is a connective tissue disease characterised by prominent vascular involvement. Generalised vasospasm is one of the main features of SSc.<sup>1</sup> Ocular vasospasm is thought to induce optic nerve head damage, and this phenomenon was recently shown to contribute to the pathogenesis of glaucoma.<sup>2</sup> High intraocular pressure (>21 mm Hg) is known to be the main risk factor associated with glaucoma;<sup>3</sup> however, a substantial number of patients with open angle glaucoma have a normal intraocular pressure. This suggests that another risk factor, possibly vascular, is involved in this subset of patients. We prospectively compared the prevalence of ocular abnormalities associated with glaucoma in a group of patients with SSc compared with control subjects with osteoarthritis (OA).

## MATERIALS AND METHODS

Consecutive patients satisfying the SSc classification criteria of LeRoy *et al*<sup>4</sup> during an 18 month period (September 2000 to February 2002) and patients admitted to hospital for OA (osteophytes on x ray examination) during a 6 month period (September 2000 to February 2001) were systematically referred to one experienced ophthalmologist. Informed consent was obtained for all patients and controls. Patients admitted to hospital for an organ failure, patients with a history of ocular hypertension or presenting a cataract were excluded. The ophthalmological examination included visual acuity, slit lamp examination, aplanation tonometry, and indirect ophthalmoscopy. Intraocular pressure (IOP) was evaluated in the morning when it is usually at its peak. Colour fundus photographs were taken with a Canon angiography camera. Optic nerve cupping was measured by the cup to disc (c/d) ratio. Two ophthalmologists, masked to the patient's disease, independently reviewed each field; differences in grading were resolved at a joint meeting.

Automated static perimetry was carried out with the Humphrey field analyser (Carl Zeiss SA), and a 24-2 SITA standard test was performed. This test includes statistical software using an extensive data bank of normal visual fields, the mean deviation (MD) is the overall mean deviation of the tested eye from age corrected normal values: for the purpose of the study, a visual field MD of <-2 dB was considered significant, a number of loss of fixation >2 was considered as an exclusion criterion.

The clinical and biological characteristics of the patients with SSc were collected at the time of the ophthalmological evaluation in routine clinical care for all patients. The total Rodnan's skin score (sum of a 0–4 scale of skin thickness made by palpation of 26 separate cutaneous surface areas) was used to assess cutaneous involvement.<sup>5</sup> Pulmonary involvement was assessed by computed tomography scan, forced vital capacity (FVC), and carbon monoxide transfer factor divided by the alveolar volume (TlCO/VA). The systolic pulmonary artery pressure (PAP) was determined by Doppler echocardiography. Immunological status was determined: antinuclear antibodies, antitopoisomerase I, and anticentromere were investigated. Statistical analyses were performed using the  $\chi^2$  test and Mann-Whitney's test for comparisons and Spearman's test for correlations.

## RESULTS

Five patients with SSc and an organ failure were excluded. Three patients receiving continuing treatments for ocular hypertension (two controls and one patient with SSc) and six

**Abbreviations:** c/d, cup to disc ratio; FVC, forced vital capacity; IOP, intraocular pressure; MD, mean defect; NTG, normal tension glaucoma; OA, osteoarthritis; PAP, pulmonary artery pressure; SSc, systemic sclerosis; TlCO, carbon monoxide transfer factor; VA, alveolar pressure

**Table 1** Ophthalmological results

	SSc (n = 122 eyes) (61 patients)	Controls (n = 74 eyes) (37 patients)	SSc v controls (p value)	lSSc (n = 80 eyes) (40 patients)	dSSc (n = 42 eyes) (21 patients)
Visual acuity, mean (SD)	0.86 (0.2)	0.93 (0.1)	NS	0.87 (0.2)	0.83 (0.2)
Ocular tension, mean (SD)	14.7 (3)	15.4 (3)	NS	14.5 (3)	15 (3)
Excavation c/d >0.3*	27 (15)	5 (4)	<0.005	18 (10)	9 (5)
Excavation c/d >0.7*	4 (3)	0 (0)	NS	2 (1)	2 (2)
MD <-2 dB*	55 (30)	18 (12)	p<0.0001	40 (21)	15 (9)
Concomitant c/d >0.3 and MD <-2 dB*	21 (12)	0 (0)	<0.0001	14 (8)	7 (4)

MD, mean deviation; lSSc, limited cutaneous SSc; dSSc, diffuse cutaneous SSc.

\*No of eyes (No of patients).

patients known to have cataracts (three controls and three patients with SSc) were excluded from the study. Three patients with SSc and one control were excluded owing to an unreliable visual field test.

Sixty one patients with SSc (mean (SD) age 56.2 (12)) were included: mean (SD) disease duration was 9.9 (9) years, 21 patients had diffuse cutaneous disease (34%) and 40 limited disease (66%).<sup>3</sup> The mean (SD) Rodnan's skin score was 22.9 (4.7) for patients with the diffuse form and 6.9 (5.8) for those with the limited form. All patients with SSc had Raynaud's phenomenon (100%), 20% were smokers, 16% had secondary Sjögren's syndrome, 16% had an upper PAP of 40 mm Hg, 46% had lung fibrosis, 13% had FVC below 75%, 39% TLco/VA below 80%, 13% had systemic arterial hypertension, and 2% diabetes. Antinuclear antibodies were positive in 90% of the patients with SSc, antitopoisomerase I in 28%, and anticentromere antibodies in 20%. All patients with SSc were treated with calcium channel blockers, 20% received angiotensin converting enzyme inhibitor, 28% low dose prednisone (<10 mg/day), 33% non-steroidal anti-inflammatory drugs. The mean (SD) age of controls with OA (n = 37) was 55.9 (12) years, 32 were female, 27% were smokers, 68% had OA localised at the spine and 27% at the knee, 41% had systemic arterial hypertension, 11% diabetes, 14% were treated with calcium channel blockers, 11% with angiotensin converting enzyme inhibitor, and 57% with non-steroidal anti-inflammatory drugs.

Table 1 shows the results of the ophthalmological tests. IOP was normal for all patients with SSc and controls. An excavated disc with a c/d >0.3 and Humphrey field's defects

were dramatically more prevalent in patients with SSc (p<0.005 and p<0.0001). Fourteen patients with abnormal visual field had a repeat examination 2 days later, the concordance rate between the two examinations for MD abnormalities was 79%; the results of the second visual field were taken into account for statistical analysis. Twenty one eyes from 12 patients with SSc (17% eyes; 20% patients) had concomitant c/d >0.3 and MD <-2 dB, whereas none of the eyes in the control group did (p<0.0001). SSc characteristics did not correlate and were not associated with ocular abnormalities. Figure 1 illustrates normal (1A) and excavated papillar (1B).

## DISCUSSION

As far as we know, this is the first prospective study to investigate the prevalence of normotensive glaucomatous damage in SSc. The results show that their prevalence is dramatically increased in patients with SSc.

Glaucoma is an optic neuropathy leading to visual field defects and a characteristic cupping of the optic disc.<sup>2-6</sup> High IOP is its main risk factor. However, in some cases damage increases despite normal values of IOP. This suggests that patients with glaucoma can be divided into subgroups with high and normal tension.<sup>7</sup> There is no consensual definition for normal tension glaucoma (NTG) and for the purpose of this study, we compared the prevalence of the following findings between patients and controls: c/d >0.3,<sup>3</sup> visual field changes (MD <-2 dB), and IOP >21 mm Hg.

A French epidemiological survey<sup>8</sup> found an NTG incidence of 6.8% among 954 patients who consulted the



**Figure 1** (A) Normal papillar from one control patient with OA. (B) Optic disc photograph of the left eye of one patient with SSc with excavated papillar: an enlarged optic cup is seen, with concentric loss of the neural rim.

ophthalmologist on their own, which differs from a systematic screening. Our control subjects and patients with SSc were systematically referred, which may explain the lower rate of abnormalities found in our control group. NTG has previously been investigated in immune related diseases, but not specifically in SSc. Cartwright *et al* performed a case-control study, retrospectively analysing the charts of 67 patients with NTG: 20% of NTG cases were associated with an immune related disease compared with 8% in the control group with ocular hypertension.<sup>9</sup> Yamamoto *et al* investigated glaucoma (normotensive or hypertensive) in 153 patients with collagen diseases: 16% had an abnormal examination at the first step and 4% were diagnosed as having NTG after a further examination.<sup>10</sup> Then, they compared the results with those of a Japanese population based survey: the prevalence of collagen disease was only significantly higher for women with glaucoma, but not for the whole population. Numerous patients had undifferentiated collagen diseases, but a group of 41 patients with SSc was included, one of these patients had NTG.

Our data demonstrate a striking prevalence of normotensive ocular glaucomatous abnormalities. However, these remained mild, without severe lesions and established glaucoma: none of the patients investigated here had abnormal visual acuity and the abnormalities highlighted might have been missed in a regular eye examination. With glaucoma lesions, until central vision is unaffected, the visual acuity does not decrease. The lack of specific investigation may explain why glaucomatous abnormalities have not been reported until now in SSc. However, they suggest a glaucomatous propensity and justify long term follow up to assess the ophthalmological risk. Wax *et al* suggested an association between NTG and anti-SSA (Ro) autoantibodies.<sup>11</sup> In our study, 10 patients with SSc had secondary Sjögren's syndrome, but this was not associated with an increased risk of NTG.

SSc is associated with major generalised vasospastic abnormalities.<sup>1</sup> There is increasing evidence for the role of vascular pathogenesis in NTG and vasospasm is of substantial interest.<sup>2</sup> The mean finger blood flow is decreased in patients with low tension glaucoma and the choroidal blood flow seems to be dysregulated in patients with digital vasospasm.<sup>12</sup> Thus, vascular dysregulation or the lack of autoregulation, rather than clear cut ischaemia, may contribute to glaucomatous damage.

The pathogenesis of vasospasm has still not been elucidated. However, it is noteworthy that the concentration of endothelin-1, implicated in SSc,<sup>13</sup> has also been found to be increased in patients with NTG.<sup>14</sup> Furthermore, the effects of endothelin-1 on ocular haemodynamics can be reversed by a low dose of nifedipine, which also improves the visual field in patients with presumed vasospasm.<sup>15</sup> These notions are

consistent with the possible implication of generalised vasospasm in some glaucomatous lesions.

## CONCLUSION

Ocular abnormalities, suggesting glaucoma damage, were dramatically increased in patients with SSc in comparison with control patients with OA. These abnormalities seem to be mild but justify long term follow up to assess the possible ophthalmological risk of developing severe glaucomatous damage. They are also consistent with a vascular pathogenic hypothesis for NTG.

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