Anisocoria in unilateral ophthalmic disease

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Abstract

Pupillary diameters in the affected and unaffected eyes of 327 patients with unocular red eye were assessed during fixation of a distant target. The mean pupillary diameters were similar in the unaffected eyes in each of eight diagnostic groups, but were significantly different ($F=3.84$, $p<0.001$) in the diseased eyes. With corneal abrasions ($p<0.001$), marginal keratitis ($p<0.05$), and acute anterior uveitis ($p<0.001$) the mean pupillary diameter for the affected eye was significantly smaller than that of the unaffected eye. The observed differences of pupillary diameter probably reflect the role of neuronal and autocoid mechanisms in the unilateral control of pupillary size.

The ocular response to injury comprises a reduction in the blood-ocular barrier, an intraocular pressure rise, and miosis.¹⁻⁴ It is probable that the changes in the blood-ocular barrier and intraocular pressure are due to concentration of prostaglandins within the eye,^{2,4} this being a result of both increased production within^{4,5} and decreased clearance from⁶⁻⁸ the eye. The miosis, however, is probably caused both by intracamerally prostaglandin accumulation and by substance P acting on the smooth muscle of the sphincter pupillae, this neuropeptide being released from trigeminal sensory radicals within the iris.⁹⁻¹¹ The stimulus for the release of substance P is probably depolarisation of afferent sensory trigeminal fibres in the cornea and other ocular structures, with the efferent path being mediated through an axonal reflex.¹² Central or peripheral trigeminal denervation reduces the accumulation of substance P and the miosis in response to injury.¹⁰ Calcitonin gene-related peptide (CGRP) occurs within trigeminal nerve fibres¹³⁻¹⁵ and dilates ocular blood vessels. CGRP and substance P might act synergistically in mediation of the ocular response to injury.^{16,17}

Miosis within an inflamed eye, as compared to the unaffected fellow eye, is generally recognised among ophthalmologists as frequently being a sign of significant ocular pathology. The actual incidence in various diseases would not, however, appear to have been recorded.

In the present report the changes of pupillary diameter are determined for various diseases causing unocular red eye, and the changes are considered in relation to the neuronal and autocoid mechanisms affecting pupillary diameter in a single eye.

Patients and methods

The pupillary diameter of patients with unilateral red eye, attending the Accident and Emergency Department of Moorfields Eye Hospital, was

assessed in a room with uniform illumination of moderate intensity (approximately 1000 lux). The patient was instructed to fixate a distant, non-accommodative target at 3 metres, and the pupillary diameters were assessed by matching with a comparative scale. The scale was held alongside the pupil, care being taken to avoid the visual axis of the patient. The scale had 'half-pupil' marks along one edge, with diameter increments of 1 mm, thereby permitting diameter estimates to 0.5 mm gradations.

After recording the assessment of pupil size, a problem orientated history and ophthalmic examination was performed. The iris colour was also recorded.

Results

Three hundred and twenty-seven patients (213 male, 114 female) were enrolled in the study. In 317 patients the condition was one of eight major diagnostic categories (Table 1), and others (6 male, 4 female) having various conditions, namely trauma (5 eyes), stromal keratitis (2 eyes), corneal abscess (1 eye), chemical injury (1 eye), and acute angle-closure glaucoma (1 eye).

There was a predominance of males over females in all diagnostic groups except episcleritis (with a similar sex incidence). Dendritic keratitis and corneal foreign bodies occurred almost exclusively in men (Table 1).

There was a significant difference between the mean ages at presentation (Table 1. One-way analysis of variance: $F_{7,309}=4.92$, $p<0.001$). Patients with subconjunctival haemorrhage were significantly older than those in each of the other seven diagnostic groups – that is, marginal or dendritic keratitis ($p<0.05$), corneal foreign body, episcleritis or iritis ($p<0.01$), and conjunctivitis or corneal abrasion ($p<0.001$). Similarly, those patients with marginal keratitis were significantly older than those with conjunctivitis ($p<0.01$) or corneal abrasion ($p<0.05$), and those with iritis were significantly older than those with conjunctivitis ($p<0.05$).

In the group overall, the side of involvement was similar (162 right, 155 left), though there was some variability between the subgroups. Likewise, with the exception of episcleritis, the ratio of involvement of blue/grey eyes with respect to brown/green was similar in all the groups (Table 1).

The average pupillary diameters in the unaffected 'white' eyes in the eight categories were not significantly different (Table 2, $F_{7,309}=1.57$). In contrast, for the 'red' eyes there were significant differences between the mean diameters for the various diagnoses $F_{7,309}=3.84$, $p<0.001$. The mean pupillary diameter for eyes with conjunctivitis (4.27 mm, 131 eyes) and iritis (3.65 mm, 44 eyes) were significantly ($p<0.001$) different, as were the diameters for eyes with

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Table 1 Characteristics and diagnosis for 317 patients with unilateral ophthalmic disease

Diagnosis	Number of patients	Sex ratio (male/female)	Age (yr) mean (SD) (range)	Inflamed eye (right/left)	Iris colour (blue/brown)
Subconjunctival haemorrhage	23	16/7 (2-29)	53.6 (17.9) (19-84)	10/13	15/8 (1.88)
Conjunctivitis	131	75/56 (1.34)	36.3 (14.7) (9-70)	70/61	83/48 (1.73)
Episcleritis	13	6/7 (0.86)	37.6 (13.7) (23-67)	6/7	5/8 (0.62)
Corneal foreign body	16	15/1 (15.0)	38.8 (10.3) (23-59)	5/11	10/6 (1.67)
Corneal abrasion	51	35/16 (2.19)	37.0 (11.5) (16-62)	25/26	34/17 (2.00)
Marginal keratitis	31	21/10 (2.10)	44.4 (14.5) (19-69)	20/11	19/12 (1.58)
Dendritic keratitis	8	8/0 (-)	36.8 (16.3) (20-60)	1/7	5/3 (1.67)
Acute Anterior uveitis	44	31/13 (2.38)	41.8 (16.8) (19-79)	25/19	29/15 (1.94)
Totals	317	207/110 (1.88)	(39.4 yr) (9-84)	162/155	200/117 (1.71)

Table 2 Estimates of pupillary diameters in each of eight diagnostic categories of patients with unilaterally inflamed ('red') eye

Diagnosis	Number of patients	Pupil diameter* of:		Difference* (mm) ('white'-'red')
		'white' eye	'red' eye	
Subconjunctival haemorrhage	23	3.89 (0.64)	3.96 (0.67)	-0.065 (0.23)
Conjunctivitis	131	4.31 (1.00)	4.27 (0.48)	t=1.36, p>0.1 +0.042 (0.26) t=1.84, p>0.05
Episcleritis	13	3.77 (1.11)	3.77 (1.11)	(-)
Corneal foreign body	16	3.75 (0.97)	3.63 (0.92)	+0.125 (0.34) t=1.47, p>0.1
Corneal abrasion	51	4.08 (1.14)	3.74 (1.05)	+0.343 (0.51) t=4.80, p<0.001
Marginal keratitis	31	4.10 (1.29)	3.89 (1.22)	+0.210 (0.51) t=2.29, p<0.05
Dendritic keratitis	8	3.75 (0.76)	3.25 (0.89)	+0.500 (0.66) t=2.14, p>0.05
Acute anterior uveitis	44	4.10 (0.87)	3.65 (0.84)	+0.455 (0.62) t=4.87, p<0.001

* Mean (standard deviation).

Table 3 The incidence of anisocoria in each diagnosis and the frequency of anisocoria in which the pupil is smaller on the affected ('red') side

Diagnosis	Number(%) of patients with anisocoria (blue/brown)	Number with red eye smaller anisocoria			Significance (p)*
		All eyes†	Blue eyes	Brown eyes	
Subconjunctival haemorrhage	2 (9%) (1/1)	0/2	0	0	0.48
Conjunctivitis	14 (11%) (7/7)	11/14	6	5	0.06
Episcleritis	0 (0%)	0	0	0	-
Corneal foreign body	5 (31%) (3/2)	4/5	3	1	0.37
Corneal abrasion	21 (41%) (14/7)	20/21	13	7	<0.0001
Marginal keratitis	10 (32%) (7/3)	9/10	6	3	<0.03
Dendritic keratitis	4 (50%) (3/1)	4/4	3	1	0.13
Acute anterior uveitis	24 (55%) (20/4)	22/24	19	3	<0.0002

* Two-tail probability of drawing observed overall incidence (†) of 'red eye smaller' anisocoria.

subconjunctival haemorrhage (3.96 mm, 23 eyes) and dendritic keratitis (3.25 mm, 8 eyes; $p<0.05$).

The difference between fellow eyes ('white' eye pupillary diameter minus 'red' eye pupillary diameter) is presented in Table 2. Average differences were significantly different from zero in the groups with marginal keratitis ($p<0.05$), corneal abrasion ($p<0.001$), or iritis ($p<0.001$).

The incidence of anisocoria varied with the different diagnoses – between 0% with episcleritis and 55% with uveitis (Table 3). The relative

frequency of anisocoria in blue/grey eyes as compared with brown/green eyes with the same diagnosis ranged from 1.0 for subconjunctival haemorrhage or conjunctivitis to 5.0 for iritis (Table 3). This contrasts with an iris colour frequency-ratio of 1.71 for blue/grey eyes with respect to brown/green eyes.

In the 80 eyes with anisocoria, 'red eye smaller' anisocoria occurred in 70 eyes, and the proportion was similar in the two groups of iris colouration (for each of the diagnoses – Table 3). The incidence of 'red eye smaller' anisocoria, without respect to iris colour, ranged from 0% (with subconjunctival haemorrhage) to greater than 90% (marginal keratitis, iritis, corneal abrasion, or dendritic ulceration). The probability of drawing the incidences as observed, or ones more extreme, is presented in Table 3. In each of the three conditions with significant anisocoria the symptoms were of similar duration in those eyes with and those without unequal pupils. With marginal keratitis the mean duration of symptoms in the anisocoric group was 4.6 days (SD 8.3 days, 10 eyes), whereas those with equal pupils had 3.9 days' mean duration (SD 3.1 days, 21 eyes), and, similarly, with corneal abrasion (anisocoric: 2.6, SD 4.4 days, 21 eyes; isocoric: 2.3, SD 3.2, days, 30 eyes) and with iritis (anisocoric: 5.0, SD 7.2, days, 24 eyes; isocoric: 9.8, SD 15.6, 20 eyes).

Discussion

In the present investigation a relative miosis, significant in both degree and incidence, was present in eyes with corneal abrasion, marginal keratitis, and acute anterior uveitis. This possibly reflects the mechanisms involved in the ocular response to injury.

Corneal abrasion is associated with marked stimulation of afferent fibres of the trigeminal nerve, manifest clinically as extreme pain. In these eyes it is probable that the miosis is mediated through a trigeminal axon reflex, with release of substance P (and possibly CGRP) at nerve fibres on the sphincter pupillae.

With acute anterior uveitis the miosis is probably due to an accumulation of prostaglandins and other autoids within the inflamed eye.¹⁷⁻¹⁹ The presence of pain with acute anterior uveitis might, however, imply a partial mediation through trigeminal axon reflexes. Similarly, the miosis of marginal keratitis is probably induced by both neuronal and autoid mechanisms, marginal keratitis being an immune process occurring at a site rich in trigeminal sensory innervation.

Subconjunctival haemorrhage, conjunctivitis, and episcleritis did not cause a significant miosis in the present investigation, perhaps because these diseases occur in tissues remote from the anterior chamber of the eye and in tissues with relatively poor trigeminal innervation.

The absence of significant miosis with corneal foreign bodies or dendritic keratitis (Tables 2 and 3) would appear to be enigmatic, these lesions arising in tissues with considerable trigeminal innervation. However, although a corneal foreign body disrupts corneal (trigeminal) nerves, this occurs over a very much

smaller area than that with most corneal abrasions. Moreover, whereas an abrasion exposes nerve endings, those under a foreign body are not exposed to the external environment. The relatively painless nature of corneal foreign bodies, as compared with abrasions, is compatible with a reduced trigeminal afferent stimulation. The lack of a significant miosis with herpetic dendritic keratitis is probably due to insufficient numbers in this group (eight cases). It is possible, however, that both the absence of intraocular inflammation and a malfunctioning of virus affected trigeminal neurons might reduce the incidence of miosis in such eyes.

To elucidate further the mechanisms causing miosis in ocular disease it would be of particular interest to ascertain whether blockage of the trigeminal afferent response with topical anaesthesia reduces or prevents the miosis in, for example, patients with corneal abrasion. Similarly, the use of antagonists to prostaglandin synthesis might prevent the miosis associated with marginal keratitis or acute anterior uveitis, this reflecting a role for autoids in these diseases.

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