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Uhthoff's syndrome

G. D. PERKIN* AND F. CLIFFORD ROSE
From the Medical Ophthalmology Unit, St Thomas's Hospital, London

Uhthoff (1890), in a survey of the ophthalmological features of 100 patients with multiple sclerosis, described four who had blurring of vision during exercise. Subsequent reports have confirmed the association and added other precipitating factors. As part of a follow-up study of patients with optic neuritis (Rose, Friedmann, Bowden, and Perkin, 1972), the prevalence of this syndrome was ascertained and an attempt made to correlate its occurrence with various parameters of optic nerve function.

Methods

Altogether 125 patients admitted to the Medical Ophthalmology Unit of the Royal Eye Hospital with a diagnosis of optic neuritis were reviewed. The criteria for the diagnosis were those given by Rose (1972). Those with a history of visual symptoms exceeding 1 month were excluded.

During follow-up, patients were specifically asked about transient visual blurring and any precipitating factors. Visual acuities were recorded, colour vision tested, and macular thresholds and visual fields measured using the Friedmann visual field analyser.

In assessing final visual function, figures for visual acuities and macular thresholds have been used only if stable values had been recorded on at least two successive occasions, or, with single measurements of macular threshold, if at least 6 months had elapsed since the original attack.

Some of the patients were being treated with corticosteroids at the time of the initial attack. A separate analysis (Bowden, Bowden, Friedmann, Perkin, and Rose, 1974) showed that this had no effect on the final visual acuity, and these patients have, therefore, been included.

Results

Of the 125 patients, 41 (32·8 per cent) had noted episodes of transient visual blurring after recovery. Table I gives details of the precipitating factors, and shows that 25 patients were affected by one, ten patients by two, four patients by three, and two patients by four factors.

*At present Senior Registrar, The National Hospitals for Nervous Diseases (Maida Vale Hospital) and University College Hospital

Address for reprints: G. D. Perkin, Maida Vale Hospital, Maida Vale, London W9

The clinical features at presentation of patients with or without subsequent transient blurring are compared in Table II. The criteria for a diagnosis of multiple sclerosis were those of Rose and others (1972); the differences are not significant.

In Table III, a similar comparison is made at the time of the follow-up examination. Again, the differences are not significant.

Discussion

Although 60 years elapsed between Uhthoff's description and the confirmation by Brickner (1950) of the association between exercise and the deterioration of visual acuity in patients with previous optic neuritis, McAlpine and Compston (1952) subsequently suggested that up to one-third of patients with multiple sclerosis could have symptoms (including visual blurring) induced or worsened by exercise.

There has been no previous attempt to correlate the clinical features of optic neuritis with the subsequent development of transient visual blurring. Although no such correlations were found in this study, the difference between the two groups in the proportion of patients having more than one attack of optic neuritis in the originally affected eye only just fails to reach a level of significance. Among the seven patients with blurring of vision on exercise described by Thomson (1966), three had had two or more attacks of unilateral optic neuritis, as had two of the four patients with the

Table I *Factors producing transient blurring*

	Patients	
Factor	*No.*	*Percentage*
Affective disturbance	20	16
Exercise	14	11
Temperature change	10	8
Menstruation	10	8
Unknown	4	3·2
Increased illumination	4	3·2
Eating	2	1·6
Smoking	1	0·8

Table II *Clinical features of 125 patients at presentation*

Features at presentation	*With subsequent transient blurring*	*Without subsequent transient blurring*
No. of patients	41	84
Percentage of females	65·9	64·3
Age at presentation (mean) (years)	33·2	34·9
Eye affected (including multiple attacks)	Right 28 Left 28	Right 51 Left 50
Smokers (per cent)	65·9	54·3
20 cigarettes or more/day	24·4	24·4
Evidence of multiple sclerosis at onset (all criteria) (per cent)	53·7	39·5
Percentage* with visual acuity of 6/36 or better at onset	27·6	42·2
Duration of symptoms before admission (mean) (days)	15·2	16·0

*Excluding patients with previous attacks of optic neuritis in the same eye

Table III *Clinical features of 125 patients at follow-up*

Features at follow-up		*With transient blurring*	*Without transient blurring*
Attacks of optic neuritis (per cent)	Single episode	75·6	87·5*
	More than 1	24·4	12·5*
	in originally affected eye	17·1	5*
	More than 2	9·8	2·5*
	Multiple (L= left, R= right)	LL LL LL LR LR LR LLR RRL RRR LLRR	LL RR LR LR LR LR LR LR RRRL RRRRRLL
Evidence of multiple sclerosis at follow-up (all criteria) (per cent)		87·8	78·5
Mean follow-up for assessment of dissemination (months)		30·9	34·0
Percentage reaching visual acuity of 6/6†		77·4	75
Final macular threshold†		2·31	2·23
Time to measurement of stable macular threshold (weeks)		18	11
Colour vision: red/green abnormalities ± other defects† (per cent)		64·5 (unilateral 90)	44·4 (unilateral 81)
Percentage treated with steroids at onset		9·8	14·8

*These percentages were calculated on 80 patients. The possibility of multiple attacks had not been ascertained in the remaining four
†Excluding patients with multiple attacks of optic neuritis in the same eye

same symptom reported by Goldstein and Cogan (1964).

There are no other published series of the prevalence of transient visual blurring after optic neuritis with which to compare the figure of 32·8 per cent obtained in this study. McAlpine and Compston (1952), however, described in patients with established multiple sclerosis a short-lived deterioration of any symptom with exercise in 34·7 per cent, with emotional stimuli in 33 per cent, and with heat in 13·5 per cent.

The exacerbation of visual and other symptoms by increased temperature was probably first recorded by Young and Bennett (1927) in patients treated with typhoid vaccine therapy. Lindemulder (1930) and Collins (1938) observed similar effects in patients treated with hot baths. Subjective worsening of symptoms by heat occurred in up to 62 per cent of the patients with multiple sclerosis interviewed by Simons (1937). The phenomenon has since been recorded by many authors (Franklin and Brickner, 1947; Brickner,

1950; Guthrie, 1951; McAlpine and Compston, 1952; Edmund and Fog, 1955; McDowell, Jeffreys, and Nelson, 1958; Nelson and McDowell, 1959; Earl, 1964; Goldstein and Cogan, 1964; Thomson, 1966; Namerow, 1968). Although cooling generally has the opposite effect, deterioration has been reported (Simons, 1937; McAlpine and Compston, 1952). The frequency with which hot baths produce symptomatic exacerbations becomes more striking when it is recalled that hot baths also produce over-breathing with hypocapnia (Hill and Flack, 1909) which is now known to cause improvement in certain manifestations of the disease—for example, scotoma size (Davis, Becker, Michael, and Sorensen, 1970).

Pratt (1951) showed that a significantly higher proportion of patients with multiple sclerosis had symptoms exacerbated by certain emotional stimuli, than controls with other diseases of the nervous system. During menstruation patients usually improve symptomatically (McAlpine and Compston, 1952), although McFarland (1969) described one case with pronounced exacerbations.

Smoking was first implicated as a factor by Franklin and Brickner (1947). Its transient adverse effect on vision was noted by Brickner (1950) and on other symptoms by Courville, Maschmeyer, and Delay (1964). In view of the adverse effect of smoking on visual acuity in other situations, a separate assessment of residual optic nerve function was made, according to the smoking habits at the time of the original attack. Apart from a just significantly ($P < 0.05$) higher incidence of colour vision defects in those smoking 20 or more cigarettes a day compared with non-smokers, no influence was detected (Perkin, Bowden, and Rose, 1975).

Although the symptom of transient visual blurring with certain stimuli seems to be particularly associated with multiple sclerosis, it is probably not confined to this disease. McDowell and others (1958) described four patients with other disorders of the central nervous system who developed visual blurring on immersion in a hot bath.

The pathogenesis of these phenomena is uncertain. Most patients in this series were affected by a single factor, and it seems unlikely that such diverse precipitants as heat, smoking, and eating could all operate by the same mechanism. It has been suggested that a critical reduction in blood flow in the region of the plaques induced by cutaneous, muscular, or splanchnic vasodilatation explains the effect of heat, exercise, or eating. With the experimental evidence that increasing temperature can cause conduction block in demyelinated nerve fibres (Davis and Jacobson, 1971), an alternative mechanism for the effect of heating, and possibly exercise, has appeared. Thus, in one patient investigated by Namerow (1968), exercise produced a deterioration in visual acuity only when accompanied by a rise in body temperature, although a similar case described by Goldstein and Cogan (1964) maintained a stable temperature during exercise, despite a deterioration in vision.

Rasminsky (1973) showed that a rise in temperature by as little as 0·5°C can cause reversible conduction block in single demyelinated peripheral nerve fibres. The blocking effect, however, involves only the most severely demyelinated internodes, those less affected actually showing a reduced conduction time. Rasminsky suggested, on the basis of these findings, that patients with multiple sclerosis who develop symptoms with a slight increase in body temperature must have many fibres with severely demyelinated internodes. He concludes that the overall conduction velocity of such fibres would be significantly reduced.

Although the extent of the delay in latencies of the visually-evoked responses found in some patients with multiple sclerosis probably cannot be explained solely on the basis of slowing of conduction in demyelinated fibres (McDonald, 1974; Heron, Regan, and Milner, 1974; Asselman, Chadwick, and Marsden, 1975), if this slowing remains an important factor in their development, certain predictions are possible.

First, the incidence of transient visual blurring in relation to heating should be maximal in those patients with the longest latencies. Secondly, observation of the responses in patients who undergo heating would be expected to show a reduction in amplitude of the response (due to conduction block in many of the fibres contributing to it) with possibly a shortening in latency (because of enhanced conduction in the unblocked fibres).

In considering the pathogenesis of the Uhthoff phenomenon in conditions other than multiple sclerosis, it may well be significant that two of the three patients described (McDowell and others, 1958) in whom a diagnosis had been made had conditions (pituitary tumour with suprasellar extension, and Friedreich's ataxia) that were capable of causing prolonged latencies in visually-evoked responses.

Summary

A total of 125 patients with a previous episode of optic neuritis was followed to assess the subsequent prevalence of transient visual blurring. 32·8 per cent developed this symptom and the precipitating factors were identified. No correlations were found between the development of the symptom and the parameters of optic nerve function studied.

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