FIBRINOGEN, CHOLESTEROL AND SMOKING AS RISK FACTORS FOR NON-ARTERITIC ANTERIOR ISCHAEMIC OPTIC NEUROPATHY

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SUMMARY

Non-arteritic anterior ischaemic optic neuropathy (AION) is thought to be due to occlusion of the posterior ciliary circulation. Raised lipid and fibrinogen concentrations are recognised risk factors for vessel occlusion in cardiovascular disease and stroke but, although suspected as risk factors in non-arteritic AION, they have not been studied in this condition. We therefore performed a case-control study on 41 patients with non-arteritic AION, looking at these and other atherosclerotic risk factors. The odds ratio of cholesterol being >6.5 mmol/l in non-arteritic AION was 2.7 (95% confidence interval 1.09 to 6.65; $p<0.05$) and of fibrinogen being >3.6 g/l was 5 (2.66 to 9.39; $p<0.05$). Smoking was also found to be significantly associated with non-arteritic AION, the odds ratio being 16 (3.23 to 79.23; $p<0.001$). These were the only risk factors found to be significantly associated with non-arteritic AION. This raises the possibility that appropriate medical management of these factors could be given to prevent recurrence in the fellow eye.

Anterior ischaemic optic neuropathy (AION) is a significant cause of visual impairment.¹ It is characterised by a sudden painless loss of visual acuity or visual field, associated with a swollen disc. The ischaemia is due to occlusion of the posterior ciliary artery circulation.^{2,3} In only 10-20% of cases is this associated with temporal arteritis.⁴⁻⁶ The majority of cases are termed non-arteritic AION. In a few of these cases specific conditions have been associated, including: systemic vasculitis,⁷ migraine,⁸ blood loss,⁹ abnormalities of coagulation,¹⁰ glaucoma¹¹ and cataract surgery.¹² However, in most cases the aetiology is unknown. The atherosclerotic process is thought to be a major cause,¹ but the incidence of

risk factors for this process, in patients with non-arteritic AION, has not been fully studied. We have therefore performed a case-control study to assess such associations, looking in particular at cholesterol, fibrinogen and smoking. These are recognised risk factors for vessel occlusion in cardiovascular disease and stroke.^{13,14}

There is a high incidence of this condition becoming bilateral.⁶ If positive associations with these risk factors were found then currently available treatments might help decrease the incidence of this devastating outcome.

PATIENTS AND METHODS

We studied 41 consecutive patients with an age range of 52-83 years (mean 66.7 years), 27 men and 14 women, who were diagnosed as having non-arteritic AION between 1986 and 1992 (Table I). All were Caucasian. Two patients presented with second eye involvement.

Table I. A comparison of the patients with non-arteritic AION and controls

	Cases	Controls
Age (years)		
Average	66.7	66.9
Range	52-83	49-85
Race	Caucasian	Caucasian
Sex	27M, 14F	27M, 14F
Hypertension		
On medication	4	10
New diagnosis	9	0
Diabetes mellitus		
Diet	3	0
Oral hypoglycaemics	2	3
Insulin	1	1
Arteriopathy		
Carotid bruit	2	0
Cerebrovascular accident	1	0
Myocardial infarction	1	0
Claudication	1	1
Over ideal weight	8	5
Hypothyroidism		
New diagnosis	1	0
On treatment	1	1

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Table II. Comparison of mean fibrinogen, cholesterol and triglyceride concentrations between cases and controls

	Total no. of subjects	Case (mean)	Control (mean)	Difference in means (95% confidence interval)	Paired <i>t</i> -test <i>p</i> value
Fibrinogen	24	4.18 g/l	3.61 g/l	0.57 (0.21 to 0.93)	<0.005
Cholesterol	40	6.63 mmol/l	6.04 mmol/l	0.59 (0.02 to 1.15)	<0.05
Triglyceride	40	1.77 mmol/l	2.12 mmol/l	(Not significant)	

The diagnostic criteria were sudden typical painless loss of visual acuity, or visual field, associated with a swollen disc. Temporal arteritis was excluded on the basis of clinical presentation, a normal erythrocyte sedimentation rate and a temporal artery biopsy (if clinically appropriate; 10 were performed and all were negative). The patients were all assessed for known causes of non-arteritic AION, in particular for evidence of systemic vasculitis, haematological disorders, recent history of severe blood loss, severe migraine, cataract surgery and glaucoma. Such patients were excluded from the study. All the patients had a full physical examination (by P.M.D.) and data on hypertension, diabetes, smoking and evidence of atherosclerotic disease were recorded. The patients' medication and other conditions that might affect lipid and fibrinogen levels were also recorded. Hypertension was defined according to the World Health Organization criteria as a systolic pressure greater than 160 mmHg and a diastolic pressure greater than 95 mmHg on three occasions, or when established on antihypertensive drug therapy. A record of 'smoker' was made for any patient who had smoked regularly in the 10 years before presentation. Total cholesterol concentrations and triglyceride concentrations were measured in 40 patients and fibrinogen concentrations in 24 patients by standard techniques.

Forty-one age-, sex- and race-matched controls were randomly selected from a pre-operative cataract assessment clinic. The same information was obtained from these subjects, with their consent. The patients were age-matched within 5-year bands. The mean age of the controls was 66.9 years.

Cataract patients were used as controls as they are routinely examined and investigated prior to surgery and this enabled age and sex matching to be carried out from a group of patients from the same geographical area. The group was also a hospital-based population, as was the AION group. Cataract patients may not be as healthy as a completely random selection of patients (for example they are more likely to be diabetic¹⁵), but this makes any

statistical difference found likely to be even more significant.

Data on the matched case-control pairs were examined using the paired *t*-test to compare the difference in means for lipid and fibrinogen concentrations. In order to allow for the effect of any abnormally large individual concentrations in a relatively small group, the results were also compared using a specific cut-off concentration as significant: >6.5 mmol/l for total cholesterol and >3.6 g/l for fibrinogen. These are recognised as risk factors for cardiovascular disease and stroke.¹⁶ A cholesterol concentration >6.5 mmol/l is also the concentration above which treatment is recommended by the British Hyperlipidaemia Association.¹⁷ Using these levels an odds ratio was calculated and its significance tested with McNemar's test. The association with smoking, hypertension, atherosclerotic disease and diabetes was also tested by this method. This study had approval from the local ethics committee (Birmingham Heartland's Hospital).

RESULTS

Raised fibrinogen, cholesterol and smoking were found to be statistically significantly associated with non-arteritic AION (Tables II, III). Smoking was found to be very significantly associated, but the number of smokers in the control group was found to be lower than the national average. The presence of hypertension, diabetes mellitus, arteriopathy, obesity and hypothyroidism were not found to be of statistical significance although there was a trend for such factors to be present in the patients with non-arteritic AION (Table I). Triglyceride concentrations were not significantly different between the two groups. Some patients in both groups were on medications known to affect lipid concentrations. Four of the cases and 10 controls were taking antihypertensive medication. Two of the cases and 5 controls were on thiazides. Since such drugs tend to increase serum cholesterol this might have reduced the observed difference in cholesterol concentration between the two groups.

Table III. Comparison of fibrinogen concentrations >3.5 g/l, cholesterol >6.5 mmol/l and incidence of smoking between non-arteritic AION patients and controls

	No. of cases		No. of controls		Odds ratio (95% confidence interval)	<i>p</i> value (McNemar's)
	Yes	No	Yes	No		
Fibrinogen >3.6 g/l	17	7	7	15	5 (2.66 to 9.39)	<0.05
Cholesterol >6.5 mmol/l	21	19	9	31	2.7 (1.09 to 6.65)	<0.05
Smoking	21	20	6	35	16 (3.23 to 79.23)	<0.001

Table IV. Previous case-control studies showing associations found

Study	No. of cases	Associations with				
		Hypertension	Diabetes mellitus	Pre-existing atherosclerotic disease	Increased chance of developing atherosclerotic disease	Increased mortality
Repka (1983) ⁴	169	45–64 years	17–64 years	No	No	No at 5 years
Guyer (1985) ⁵	205	<65 years	17–64 years	Yes	Yes	No at 3 years
Beri (1987) ⁶	388	45–64 years	All ages			
Sawle (1990) ²⁷	63					Yes at 5.3 years

DISCUSSION

Non-arteritic AION is a potentially blinding condition and can become bilateral in up to 73% of cases over a period of time.¹⁸ No specific treatment has been found to prevent second eye involvement. The condition is due to inadequate posterior ciliary artery circulation,^{2,3} and so atherosclerotic risk factors might be expected to be associated and indeed have been suspected for some time,¹⁹ but the picture is not clear cut. Hypertension has been found to be associated in patients under 65 years.^{4,6} Diabetes has been found to be associated, in one study, in patients of all ages,⁶ but in other studies a relationship was seen only in patients under 64 years.^{4,5,20} Pre-existing cardiovascular disease was found to be associated in one study, but again not in another.⁵ (These findings are summarised in Table IV.) We did not find an association with hypertension, diabetes or coexistent atherosclerotic disease, but the number of patients studied was relatively small and only 18 of them were under 65 years.

We did find a significant association between non-arteritic AION and serum cholesterol and fibrinogen levels, as well as smoking. Smoking can affect the level of fibrinogen and especially lower the level of fibrinolytic activity.²¹ However, fibrinogen has been found to be an independent risk factor for ischaemic heart disease and stroke, after adjusting for other risk factors, in particular cholesterol and smoking.^{13,16,22,23} In this study, of the 18 patients with raised fibrinogen and AION, 9 were smokers and 9 were not, suggesting that raised fibrinogen is also an independent risk factor for non-arteritic AION. Fibrinogen is a significant component in the complex balance of thrombotic and fibrinolytic factors, and elevated levels may encourage the formation of thrombus on atheromatous plaques.²² Variations in concentrations of other factors may also be important in predisposing to the development of non-arteritic AION.¹⁰ High total cholesterol concentrations are associated with ischaemic heart disease.¹⁴ This is due to high plasma levels of low density lipoprotein (LDL). It is thought that LDL undergoes an oxidative modification enabling its uptake by macrophages, leading to the development of fatty streaks, the first stage in the formation of atherosclerotic plaques. LDL also affects platelet aggregation.²⁴ Smoking has been found to be an important risk factor in the development of non-arteritic AION

in one previous study.²⁵ Smoking is a well-recognised risk factor for atherosclerotic disease.²⁶ It is thought to cause atherosclerosis by causing endothelial damage and affecting platelet aggregation. Possibly these factors could have an effect on the small posterior ciliary arteries causing non-arteritic AION before other vascular disease is clinically apparent. This might explain why atherosclerotic conditions have not always been found to be associated with non-arteritic AION, as the study periods involved have often been relatively short (for example, Repka *et al.*⁴ 5 years and Guyer *et al.*⁵ 3 years). Increased mortality found in one study does, however, suggest that such conditions may be developing.²⁷ In the Northwick Park Study the mean interval between finding a raised fibrinogen concentration and an ischaemic heart disease event was 9 years.²⁸

Lowering blood cholesterol concentrations has been found to decrease the incidence of ischaemic heart disease.²⁹ At present there is no specific method of lowering fibrinogen, but low-dose aspirin may have a beneficial effect. In view of the other coagulation abnormalities that may be found, warfarin has even been suggested as a possible preventive therapy against recurrence of AION, in selected cases.¹⁰ The finding of a raised level of fibrinogen does, however, identify patients at risk of cardiovascular disease and so encourages the need to modify other risk factors, such as hypertension, smoking and lifestyle. A previous study has suggested that cessation of smoking reduces the risk of developing non-arteritic AION to that of the non-smoking population.²⁵

These data raise the possibility that an aggressive therapeutic regimen to lower multiple risk factors could be successful in reducing the rates of recurrence of AION, as has been demonstrated with a similar approach in patients with retinal vein occlusion.³⁰ Indeed preliminary results from follow-up of our patients who have been treated with this approach show that only 13% (5/39) of the patients have developed bilateral AION over an average follow-up of 27 months. This is encouraging, as an overview of previous studies found the incidence of bilateral involvement to vary from 10.5% to 73%.⁶ However, follow-up did continue for up to 10 years in some studies.⁶

Key words: Anterior ischaemic optic neuropathy, Cholesterol, Fibrinogen, Smoking.

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