Excessive permeability in diabetic maculopathy

MARGARET KEARNS, A. M. HAMILTON, AND EVA M. KOHNER

From the Hammersmith Hospital, Royal Postgraduate Medical School, and Moorfields Eye Hospital, London

SUMMARY Four cases of diabetic maculopathy with excessive permeability are described. Fluorescence angiography is distinctive, showing profuse early leakage from the entire capillary bed of the posterior pole. Careful studies have failed to reveal any cause for this excessive permeability response at the macula or any constantly associated medical abnormality. The prognosis for visual acuity is poor, and photocoagulation has only rarely been successful in maintaining or improving vision in these patients.

Diabetic maculopathy continues to be a major problem in diabetic patients of all ages. Visual acuity is often severely affected, and treatment by photocoagulation has not had the same highly favourable results as in the treatment of proliferative retinopathy with disc new vessels (DRS, 1976; British Multicentre Group, 1977). The natural history of diabetic maculopathy has never been clearly elucidated, probably because it embraces several subgroups which behave differently. In this communication we describe one particular rare subgroup. This unusual form of maculopathy is characterised by excessive permeability of all capillaries of the posterior pole. On examination, little or no abnormalities are seen apart from the oedema. On fluorescein angiogram there is early extensive leakage from the capillaries in the macular area.

Case reports

CASE 1

A 29-year-old nursing sister was referred to the Hammersmith Hospital in 1974 because of diabetic retinopathy. In the past she had episodes of iritis in both eyes (1970-72). She had noticed gradual deterioration in vision in her left eye in 1972 and more sudden, severe loss of vision especially in the right eye in 1973. She had been diabetic since the age of 13. Her treatment was a single daily dose of lente insulin, initially 100 units, reduced to 44 units in recent years, and she always had heavy glycosuria. Over the 6 months before coming to the Ham-

smith Hospital she had noticed swelling of her ankles. It was only partially controlled by taking frusemide 80 mg daily.

On examination, her visual acuities (VA) were 6/18 on the right (R) and 6/24 on the left (L). She had no rubeosis, her intraocular pressure was normal, as were her anterior chambers. She had early cortical cataracts. The vitreous was normal; in particular no cells were seen. Fundus examination showed cystic macular oedema and early disc new vessels in both eyes (Fig. 1a). General examination showed that she was of ideal body weight; her blood pressure (BP) was 140/80 mmHg lying and standing. She had foot and ankle oedema, absent ankle reflexes, and reduced vibration sense.

Investigations showed normal blood urea, creatinine, cholesterol, triglycerides, haemoglobin (Hb), and white cell count (WBC). Serum proteins were normal, but albumin was at the lower limit of normal. Her blood sugar control was poor, and most blood sugars were over 15 mmol/l whatever time of day they were taken.

Florescein angiograms showed good initial capillary perfusion, with early profuse leakage from all the capillaries in the macular region, and disc leakage (Fig. 1b and c).

Medical course. General diabetic control was improved by changing her insulin dosage to soluble and isophane (NPH) 8 units each twice daily. Over the last 4 years her urine has been mostly free of sugar and blood sugar levels were mostly less than 9 mmol/l. Her ankle oedema persists but is improved on frusemide 120 mg/day and spironolactone 50 mg 3 times daily. In 1978 further blood tests investigating capillary endothelial damage by measuring factor VIII levels, platelet aggregation,

Correspondence to Dr Eva M. Kohner, Hammersmith Hospital, Du Cane Road, London W12 0HS

Fig. 1 (a) From a colour photograph of R macular region from Case 1 when patient first seen. The perifoveal area looks featureless and there are only a few hard exudates and haemorrhages peripherally. (b) Fluorescein angiogram in capillary phase from Case 1 when first seen. Diffuse leakage. (c) Same as Fig. 1b but in late phase showing extensive leakage throughout posterior pole

serum fibrinogen, and fibrin degradation products were normal. Blood urea, serum electrolytes, creatinine, and proteins remained normal, and no specific cause for the excessive capillary leakage was thus found.

Ocular course. In 1974, because of the severe retinopathy, she entered the paired eye photocoagulation study (British Multicentre Group, 1977). The right eye was drawn for treatment with the xenon arc (448 burns given as a pattern bombing). The left eye was untreated as a control. Over the 4 years' follow-up the vision in the right eye has remained static. Vision in the left eye has deteriorated

to 6/60 (partly owing to increase in lens opacities). The macular oedema persisted, and fluorescein angiograms of the right eye remained the same (Fig. 2a-c). New vessels in both eyes have improved.

CASE 2

A 50-year-old parole officer was referred to the Hammersmith Hospital in February 1974 because of blurred vision. The ocular symptoms had been present since he began treatment for his diabetes 2 years previously. His vision had previously been excellent. At the age of 48 years he had presented to his local doctor with blurred vision, impotence for

Fig. 2 (a) Same as Fig. 1a, but 4 years later. Photocoagulation scar seen lateral to macula. Note apparent normality of macular area. (b) Fluorescein angiogram of right macula of Case 1, 4 years after photocoagulation. Extensive leakage in capillary phase still present. (c) Extensive leakage from all capillaries in late phase of fluorescein angiogram

2 years, and increasing thirst, polyuria, and weight loss. The diagnosis of diabetes was made, and treatment with a 120-g carbohydrate diet, glibenclamide 12.5 mg, and long-acting phenformin 50 mg daily started. From that time blood sugars taken at the clinic were all well under 10 mmol/l.

On examination his visual acuities were R 6/6 and L 6/9. He had no rubeosis, normal intraocular pressures, and normal anterior chambers. Fundus examination showed bilateral cystic macular oedema (Fig. 3a). His BP was raised at 180/115 mmHg, and he had reduced vibration sense. Otherwise medical examination was normal, and in particular he had no ankle oedema, no signs of peripheral neuro-

pathy, and was only 5% above ideal body weight.

Investigations showed normal blood urea, proteins, triglycerides, cholesterol, Hb, and WBC. Blood sugars were under 10 mmol/l. He had no proteinuria.

Fluorescein angiography showed symmetrical maculopathy with early good perifoveal perfusion, and early profuse leakage from all the capillaries at the posterior pole (Fig. 3b-c). There was also some peripheral capillary non-perfusion.

Medical course. Blood pressure was controlled with clonidine and beta blockers, but diabetic management has been maintained unchanged. He has kept in good health and maintained good control of his BP and diabetes. In 1978 further blood tests

Fig. 3 (a) Case 2 from colour photograph of left macular area showing haemorrhages and exudates in the macular region. (b) Fluorescein angiogram in capillary phase shows good perfusion and early leakage. (c) Fluorescein angiogram in late phase shows diffuse leakage throughout the macular area

searching for evidence of generalised capillary endothelial damage showed factor VIII levels, platelet studies, fibrinogen, and fibrin degradation products to be in the normal range.

Ocular course. In 1974 he was entered in the paired eye photocoagulation trial (British Multi-centre Group, 1975), and the left eye was drawn for xenon arc photocoagulation (335 burns as a pattern bombing). The right eye was untreated as a control. Over the 4 years' follow-up vision has decreased gradually to 6/60 in both eyes by 1978. Visual loss has been due to persistent gross leakage at the maculae leading to cystic macular oedema and finally bilateral macular holes (Fig. 4a-c).

CASE 3

A 42-year-old builder presented to Moorfields Eye Hospital in 1977 complaining of decreasing vision in both eyes. Diabetes had been diagnosed at 32 years of age when he presented to his local doctor with weight loss and polyuria. He was treated with 44 units lente insulin as a single daily dose. His control had always been poor, showing 2% glycosuria most of the time. Control was made difficult by his high daily alcohol intake (approximately 16 pints of beer and 3 double whiskies). On examination his visual acuity was 6/9 in both eyes. He had no rubeosis, normal intraocular pressures, and normal anterior chambers. Fundus examination showed

Fig. 4 (a) Case 2, 4 years after photocoagulation. Scars lateral to macula, cystic oedema, and macular hole. (b) Fluorescein angiogram in capillary phase shows that all remaining capillaries leak fluorescein. Note macular hole. (c) Fluorescein angiogram in late phase shows extensive leakage; unchanged from pretreatment angiogram

cystic macular oedema. General examination revealed a fit-looking man of ideal body weight, without diabetic complications apart from reduced vibration sense and absent ankle reflexes.

Investigations showed normal blood urea, triglycerides, cholesterol, Hb, and WBC. Factor VIII level, fibrinogen, fibrin degradation products, and platelet function tests were normal. His blood sugar levels were always above normal.

Fluorescein angiography showed good initial capillary perfusion and profuse early leakage from all the capillaries in the macular region.

Medical course. Over the 12 months to 1978 his diabetic control remained very poor but otherwise

he was well. Because of his poor diabetic control he was admitted to the Hammersmith Hospital and treated for 2 weeks with continuous subcutaneous insulin infusion (Pickup *et al.*, 1978). On this regimen blood sugars were mostly below 10 mmol/l throughout the 24 hours. He was discharged on twice-daily soluble and isophane insulin and maintained improved control. However, at this time on his local doctor's advice he recommenced single daily insulin injection, with deterioration of his diabetic control.

Ocular course. His visual acuity had fallen to VAR 6/36 and VAL 6/60 despite argon laser treatment to both posterior poles—given as a focal and

Fig. 5 (a) Case 3 from a colour photograph of left macula after 400 argon laser burns and 2 weeks on continuous insulin infusion. Cystic macular oedema, haemorrhage, and laser scars visible. (b) Fluorescein angiogram in capillary phase showing dilated leaky vessels. (c) Fluorescein angiogram in late phase shows cystic macular oedema and leakage

grid pattern, 87 burns on the right and 400 burns on the left prior to admission to hospital. While on continuous insulin infusion his vision improved to R 6/24 and L 6/18, though the fundus appearance and fluorescein angiogram remained the same (Fig. 5a-c). At his last visit, 2 months after discontinuing twice daily insulin, his visual acuity had decreased to R 6/60 and L counting fingers. The fluorescein angiogram was unchanged.

CASE 4

A 52-year-old clerical worker presented to the Hammersmith Hospital in 1974 after loss of vision

in both eyes over the preceding 9 months. One year previously she had been diagnosed diabetic, after presenting to her local doctor with symptoms of thirst, weight loss, and frequency. At that time her vision was normal. The diabetes had been treated with 100-g carbohydrate diet, long-acting phenformin 50 mg twice daily, and chlorpropamide 500 mg daily.

On examination her visual acuities were VAR and VAL 4/60 each. She had no rubeosis, normal intraocular pressures, normal anterior chambers, and early cortical lens opacities. Fundus examination revealed cystic macular oedema. On general examin-

Fig. 6 (a) Case 4. Colour photograph of right macular region shows confluent hard exudates. There are also multiple haemorrhages. (b) Fluorescein angiogram in capillary phase showing marked dilatation of capillaries and leakage. (c) Extensive fluorescence of posterior pole in late phase of angiogram indicates widespread hyperpermeability. New vessels on disc seen at edge of picture

ation she was of ideal weight with very few abnormal findings apart from slightly raised BP at 160/100, a raised resting pulse of 110, and absent ankle reflexes.

Investigations showed normal blood urea, proteins, cholesterol, triglycerides, Hb, and WBC. Her urine was always free of sugar and protein.

Fluorescein angiography showed extensive early leakage from all the capillaries at the posterior pole with areas of peripheral non-perfusion.

Medical course. Her general health remained good, but her blood urea had risen to 11.4 mmol/l, while her serum creatinine remained normal. During the last year her diabetic control had deteriorated

and blood sugars are now 10 to 15 mmol/l. Further investigations in 1978 for signs of generalised capillary damage, factor VIII, prothrombin time, fibrinogen, fibrin degradation products, and platelet studies were all normal.

Ocular course. In 1974 she was entered in the paired eye photocoagulation study, and the left eye was drawn for xenon arc photocoagulation in a peripheral pattern bombing 250 burns. Both eyes deteriorated rapidly. The right, untreated eye developed disc new vessels and confluent hard exudates within 1 year (Fig. 6a-c), and thrombotic glaucoma proceeded to no light perception. The

left eye lost further vision from retinal detachment to counting fingers at 1 metre.

Discussion

The patients presented here all had maculopathy of a severe nature. All the capillaries at the posterior pole leaked fluorescein immediately the dye reached them.

It is not clear from our observations why these patients should have had such extensive leakage. There was no evidence of any inflammatory process in the eyes. Only 1 of the 4 patients (Case 1) had mild proteinuria and severe ankle oedema, indicating hyperpermeable capillaries in other parts of the body. Moreover, blood tests done to identify generalised endothelial cell damage—factor VIII related antigens, fibrinogen, fibrin degradation products—were normal. It is known that capillaries in skeletal muscle of long-term diabetics have increased permeability (Trap-Jensen and Lassen, 1968), but the cause of this is not known, and it is not necessarily associated with extensive retinal capillary leakage leading to maculopathy in most diabetics. Schatz and Patz (1976) reported a group of diabetics with this type of maculopathy and noted that these patients were all young. While 2 of our patients were less than 45, 2 were 50 or more, indicating that youth is not necessarily a feature of the condition. A similar type of maculopathy has been observed in some young, pregnant diabetics and women on oral contraceptive pills. In contrast to the 4 patients reported here, in these women the cystic macular oedema has improved on treatment with diuretics, stopping the pill, or completing the pregnancy.

Renal function was remarkably normal in our present patients when they presented with visual loss. The effect of blood pressure on maculopathy has not been clearly established, but it appears that raised BP accelerates the progression of retinopathy in general (Harrold, 1971; Kohner, unpublished observation). Of the patients reported here only 1 had high BP and 1 mildly raised BP. Treatment of the BP did not alter the course of the retinopathy, and vision continued to deteriorate rapidly, irrespective of blood pressure levels. The role of diabetic control has not been clearly established in the development and treatment of this condition. The 2 insulin-dependent diabetics may have been favourably influenced by improvement of their control. The only eye which retained 6/18 vision belongs to one of the patients whose diabetes became well controlled with most blood sugars under 10 mmol/l. It is tempting to implicate poor diabetic control in the other young person as a cause of the severe

loss of vision, especially as hospitalisation with near normal blood sugar levels during continuous insulin infusion improved his vision significantly. However, macular oedema may be variable, particularly when, as in this case, the patient's alcohol intake is drastically reduced. It remains no more than a clinical impression that it is worth while to optimise control in insulin dependent (type I) diabetics.

In the type II diabetics (Cases 2 and 4) blood sugar control was satisfactory when the severe maculopathy developed. The patient (Case 4) who was on maximum doses of oral hypoglycaemic agents probably should have been on insulin. Her poor vision deterred us from changing her on to this treatment. Conclusions are difficult to make, but it is possible good control has very little beneficial effect on the retinopathy of type II diabetics. This impression is in agreement with the findings of the study by the UGDP (1977). Furthermore, it is possible that once a certain severe degree of retinopathy is present the lesions, especially non-perfused areas, are irreversible. In this as in other maculopathies there was a progressive occlusion of small vessels in the retinal periphery. In the first 2 patients it was observed at presentation. In Patient 4 it occurred during the period of follow-up, and in Patient 3 after completion of the report. Capillary non-perfusion occurs in all forms of diabetic retinopathy and is not thought to be relevant to the excessive permeability seen in these patients. Photocoagulation is of some benefit in most forms of maculopathy (Patz *et al.*, 1973; British Multicentre Group, 1975). In our group it seemed to have very little effect. This is in agreement with the findings of Schatz and Patz (1976), whose patients with severe macular oedema also did not respond to extensive treatment. In conclusion, in type I diabetics with this rare condition good physiological diabetic control should be aimed at in the first instance, photocoagulation should be tried early, but it is important to maintain a guarded visual prognosis.

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