Ischaemic optic neuropathy—a combined mechanism

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SUMMARY A clinical pathological study is reported of a patient who developed bilateral ischaemic optic neuropathy following a massive gastrointestinal haemorrhage with associated vascular complications in watershed areas of the myocardium and brain. Additional factors of giant cell arteritis and diabetic ketoacidosis contributed to the unique pathology. The distribution of infarction to the optic nerve has been related to known studies on the blood supply of the optic nerve.

Blindness following severe blood loss is well recognised, but few histopathological specimens have been obtained within a short time after such an episode.¹ Bilateral anterior ischaemic optic neuropathy has been observed following uncontrolled diabetes without acidosis and as a complication of diabetic hyperosmolar nonketotic coma.²⁻⁵ The following is a clinicopathological case report of a patient who developed sudden bilateral blindness and myocardial and cerebral infarction subsequent to massive gastrointestinal haemorrhage and diabetic ketoacidosis. The histopathology and distribution of ischaemic optic nerve changes will be described and related to both the antecedent vascular pathology and the blood supply of the optic nerve.

Case report

On 21 August 1977 an 82-year-old white female presented in the Emergency Department, complaining of blurred vision present for 3 days. Examination showed a best corrected vision of 20/60-, nuclear sclerotic and peripheral cortical lens opacities, mild corneal staining, and intraocular pressures of 10 mmHg in both eyes. She was alert, and the remainder of the examination, including pupillary responses and optic disc appearance, was unremarkable. Her blood pressure was 140/55 mmHg, with a regular pulse of 78/min. She was a known diabetic maintained on 23 units of NPH and 27 units of Toronto insulin daily. Her blood sugar was 302 mg/100 ml (16.8 mmol/l), urine showed +1 sugar and +1 ketones. The complaints were thought

to be related to her fluctuating blood sugar, so she was referred to her general practitioner for diabetic assessment and to her own ophthalmologist for continuing care.

The following day she was brought to the Emergency Department having been found at home unconscious and covered with bloody faeces. She was observed to be hypovolaemic secondary to gastrointestinal bleeding and severe ketoacidosis. Significant findings included absent bowel sounds, blood pressure of 90/50 mmHg, sinus tachycardia (96 per minute), left ventricular hypertrophy with strain pattern, and acute inferior myocardial ischaemia. Laboratory values included a blood sugar of 842 mg/100 ml (46.7 mmol/l), urinary 4+ ketones, pH 7.28, haemoglobin 7 g/dl, haematocrit HCT 24.5, leucocyte count of $19.9 \times 10^9/l$ (83% polymorphs) and platelet count of $529 \times 10^9/l$. She was treated with intravenous replacements including 4 pints (2.3 l) of packed red blood cells, insulin, potassium, a nasogastric tube, and antacids. Within 6 hours her clinical state improved, she regained consciousness, and was immediately aware of bilateral blindness. Her haemoglobin had risen to 12 g/dl and the leucocytosis persisted. Ophthalmic examination showed amaurotic pupils, no light perception, slightly cloudy corneae, intraocular pressures of 12 mmHg OU, normal motility with poor visualisation of the optic discs. The presumed diagnosis was bilateral ischaemic optic neuropathy secondary to hyperosmolar ketoacidosis and gastrointestinal haemorrhage. Temporal arteritis was considered, so a test of the sedimentation rate was ordered and 125 mg of methylprednisolone (Solumedrol) was given. Methylprednisolone was continued in regular doses of 25 mg intravenously 4 times a day.

Previous admissions to hospital had been for treatment of severe diabetic ketoacidosis, appendi-

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ectomy, hepatomegaly (biopsy confirmed minimal fatty vacuolation), and thoracic nerve herpes zoster. She had a history of diverticulosis and a rectal polyp was removed in 1963, as well as mild peripheral neuropathy, arteriosclerotic heart disease, and hypertension. Previous laboratory values included a slightly raised serum creatinine and a normal sedimentation rate, last recorded at 3 mm/h in March 1976. Six months prior to this admission her fluorescein angiograms showed minimal right macular oedema and a recorded vision of 20/80 right eye and 20/60 left eye.

On day 3 she was still in brittle diabetic control with frequent paroxysmal ventricular ectopic beats, and there was no evidence of fresh gastrointestinal haemorrhage. Her blood pressure was 100/60 mmHg, pulse 90, and respiratory rate 36 per minute. Ocular examination showed persistence of amaurotic pupils, no light perception, slight pallor of the optic discs, with minimal congestions of the retinal veins and a left 6th nerve palsy.

On day 4 her tachypnoea persisted, and a clinical diagnosis of acute pulmonary oedema secondary to fluid overload was made. Her visual status remained unchanged except for development of bilateral 6th nerve palsies. Her sedimentation rate was reported at 11 mm/h and steroids were totally discontinued.

On day 5 she developed an extensive right cerebral infarct with left hemiparesis and difficulty in swallowing. Her respiratory rate was 30 per minute, left pleural effusion was seen on x-ray, and she maintained a blood pressure of 140/80 mmHg. During the ensuing days her clinical course deteriorated, she developed a temperature of 38.5°C, and her haemoglobin and leucocyte counts remained raised. She never regained vision and she died 15 days after admission to hospital. Necropsy was performed within 24 hours of her death.

GENERAL NECROPSY

Post-mortem examination revealed a gastric ulcer overgrown with candida, which was the source of her massive gastrointestinal bleeding. In addition diverticulosis and a leiomyoma of the duodenum were noted, neither of which was responsible for the bleeding. Examination of the lungs revealed a terminal bronchitis. The heart showed extensive old scarring, and there were areas of necrosis in the posteroseptal region, with absorption of muscle cells, suggesting lesions 2 to 3 weeks old. The coronary arteries were patent throughout, though areas of atherosclerotic stenosis were observed, and microscopic sections showed intimal thickening. The larger vessels, including aorta, had severe atherosclerosis and calcification, while the arterioles of the kidneys, adrenals, and pancreas showed

hyalinisation. No evidence of giant cell arteritis was seen in any of the vessels. The hemiplegia was attributed to a massive right cerebral infarction, which undoubtedly was the most direct cause of her death. The infarct extended from frontal to occipital lobes, with additional widespread focal ischaemic changes throughout the brain, shown by minimal necrosis in the middle layers of the cerebrum. The 6th nerve palsies were ascribed to herniation secondary to brain swelling, as no infarctions were noted in the brain stem in the region of the nuclei.

In summary, this woman had poorly controlled diabetes with severe vascular complications of myocardial and cerebral infarction secondary to massive gastrointestinal haemorrhage.

OCULAR AND OPTIC NERVE EXAMINATION

Right and left globes, optic nerves, and surrounding vessels up to the orbital apex were examined. The globes were sectioned horizontally and processed with 1 cm of attached optic nerve on the right and 0.5 cm on the left. The remaining optic nerves and vessels were serially cross-sectioned. Macroscopically the globes were of normal size, and both showed posterior polar dot and blot haemorrhages with no significant disc abnormalities. A cotton-wool spot was noted below the superior temporal artery in the left eye. Sections were stained with haematoxylin and eosin, phosphotungstic acid, Holmes, periodic acid Schiff (PAS), Perls, elastic, luxol fast blue-haematoxylin-eosin, and Bodian stains.

Microscopically both globes were characterised by minimal lacy vacuolation of the iris pigment epithelium, sclerosis of the sphincter muscle, atrophic hyalinisation with focal calcification of the ciliary body, and thickening of the basement membrane of the pigment epithelium. The lens had cortical degenerative changes, and the retina showed peripheral cystoid degeneration as well as equatorial and posterior polar haemorrhages in the inner nuclear and outer plexiform layers. Retinal arteriolar hyalinisation and thickening of the basement membrane of capillaries were noted.

The right optic disc was slightly oedematous, and there was a striking ischaemic infarct in the immediate retrolaminar area which gradually extended laterally to one side of the nerve with intact neuronal tissue immediately proximal to it (Fig. 1, RA and B). The proximal cross-sections of the nerve showed axial infarction which gradually extended peripherally to the pial sheath and involved the entire nerve (Fig. 1, RC, D, E). The axial changes consisted of varying distribution of focal nerve fibre bundle infarctions, some involving the total bundle and

others the centre of individual bundles (Fig. 2). In addition areas of infarcted neuronal tissue immediately adjacent to radial septa were observed (Fig. 2 inset). There was loss of astrocytes, nerve fibres, and myelin, with infiltration by macrophages laden

with engulfed luxol fast-blue and PAS positive material (Fig. 3). The right ophthalmic artery was characterised by marked fibroblastic proliferation of the intima, numerous multinucleated giant cells surrounding fragmented sections of internal elastic

Fig. 1 *R—Right optic nerve. RA—Focal retrolaminar ischaemic infarction. RB—Intact neuronal tissue. RC—Axial infarction. RD—Extended infarction. RE—Total infarction. Arrows—narrow lumen of ophthalmic artery. L—left optic nerve. LA—Retrolaminar infarction. LB, C, D, E—Total nerve infarction. Arrows—narrow vascular lumen of ophthalmic artery. (Luxol fast blue and H and E stain, $\times 7.5$).*

Fig. 2 *Right optic nerve. Axial changes consisting of focal nerve fibre bundle infarction. (LFB and H and E, $\times 15$). (Inset: infarcted neuronal tissue adjacent to radial septa. LFB and H and E, $\times 25$).*

lamina, haemosiderin laden macrophages, and lymphocytic and plasma cell infiltration of the media and adventitia (Fig. 4). The lumen, although narrowed, was not completely occluded at any point (Fig. 1, RD, E). The posterior ciliary arteries had subintimal fibrosis and thickening of the vessel walls.

The left optic nerve had focal evidence of retrolaminar infarction with preservation of cylinders

immediately proximal to it (Fig. 1, LA). The entire optic nerve was infarcted in cross-sections from 0.5 cm posterior to the globe to the apex of the orbit (Fig. 1, LB, C, D, E). The left ophthalmic artery illustrated similar histopathological inflammatory features as the right side, but anteriorly it was almost completely occluded (Fig. 5 and Fig. 1, LC, D arrows). That is, there was widespread destruction of internal elastic lamina, infiltration of the adventitia and media, multinucleate giant cells, and subintimal fibrosis. Neither the right nor left ophthalmic vessels showed an acute thrombus.

Discussion

Histopathological specimens of recent bilateral optic nerve infarction secondary to gastrointestinal haemorrhage have not been well described in the literature.¹ This clinicopathological report describes a patient with acute ischaemic necrosis of the heart, brain, and optic nerve following a haemodynamic crisis. We believe that watershed areas of the circulation, notably the middle layers of the cerebrum, the posteroseptal myocardium, and the retrolaminar optic nerve, were infarcted as a result of hypoperfusion-induced ischaemia. Additional pathology of giant cell arteritis, diabetic acidosis, widespread sclerotic vascular changes, and a possible hypercoagulation state are significant coincident factors in discussing the pathogenesis in this patient.⁶⁻¹⁰ The unique features of focal retrolaminar infarction immediately related to a zone of preserved neuronal tissue with proximal infarction may reflect on the vascular supply of the orbital optic nerve.

Clinical cases of simultaneous bilateral amaurosis

Fig. 3 *Right optic nerve. Macrophages laden with engulfed PAS positive material (arrows). (PAS, $\times 18$).*

Fig. 4A, B *Right ophthalmic artery. Multinucleated giant cell surrounding fragmented sections of internal elastic lamina (arrow) (LFB and H and E, $\times 25$). (Inset $\times 24$).*

secondary to acute blood loss are well documented.^{11,12} The gastrointestinal tract is a frequent site of bleeding, and blindness occurs within 48 hours in about 50% of the patients.¹³ Clinical descriptions of the fundus after acute blood loss commonly note the presence of pale, oedematous discs with peripapillary flame-shaped haemorrhages and cotton-wool spots. Retinal arterial narrowing and tortuous congested veins may also occur.¹ Late changes included total optic atrophy or glaucoma-like cupping of the optic disc.^{6,10-15} Numerous authors note the particular vulnerability of the retrolaminar tissue to infarction when pathological processes involve the short posterior ciliary arteries.¹⁶⁻¹⁹ Hayreh²⁰ suggests that it is due to an imbalance between the perfusion pressures and the intraocular

pressure compounded by systemic hypotension. The presence of minimal clinical disc changes note in our case has been described previously by Spencer and Hoyt in cases of retrolaminar infarctions.¹⁸

Prior to the haemodynamic crisis the right ophthalmic artery was partially narrowed, whereas the left was almost totally occluded by the giant cell arteritic process. This was evidenced by multiple focal areas of degeneration of the elastic lamina, infiltration of lymphocytes, plasma cells, and giant cells involving the media and adventitia. The presence of intimal fibrosis, haemosiderin laden macrophages, and low grade inflammatory changes point to a long-standing arteritic process. In spite of this the patient's vision was recorded at the same level of 20/60 on the day before admission and for

Fig. 5 *Left ophthalmic artery. A. Infiltration of media and adventitia by lymphocytes (H and E, $\times 15$). B. Fractured elastic lamina (arrows) (Weigert's elastic stain, $\times 15$).*

at least 6 months before her haemodynamic crisis.

The presence of viable tissue proximal to the infarct, most notable on the right side, may be related to the anastomotic circulation in the anterior optic nerve and orbit.^{17 18 21} Collaterals vessels between the internal and external carotid systems supplying the anterior orbit have been previously described. Further, it is suggested these collaterals are sufficiently large to take over when the circulation of the internal carotid is obstructed.²² The proximal right axial infarction reflects on the vulnerability of the central nerve, since it is supplied by an endarteriolar system (Fig. 1, RC).

Microscopically, the focal infarction of neuronal bundles reflects on 2 pathophysiological situations. The central infarctions suggest a collapse of the terminal capillary bed. The ischaemic necrosis along radial septa illustrates sectoral arteriolar collapse of the pial vessels (Fig. 2, inset).

A unique feature of this case is pathological evidence of giant cell arteritis involving the ophthalmic arteries alone without evidence in other anatomical sites.^{9 23} In addition our patient had a normal sedimentation rate even in the presence of hypovolaemia. A normal ESR has been previously observed in a minority of patients with ophthalmic giant cell arteritis.^{9 23}

The obvious question is whether the giant cell arteritis alone could account for the bilateral acute ischaemic nerve changes. We believe not, since bilateral simultaneous ischaemic optic neuropathy due to giant cell arteritis is very rare.^{9 23} In addition the nature of the ischaemia on the right side reflects both capillary and arteriolar collapse rather than sectoral obstruction, which is more characteristic of reported cases of giant cell arteritis. This hypothesis is supported by the clinical and pathological infarctions of the heart, brain, and optic nerves.

In summary, this patient had a massive gastrointestinal haemorrhage with vascular complications of myocardial, cerebral, and optic nerve infarction. Additional factors of giant cell arteritis and diabetic ketoacidosis contributed to the unique pathology.²³⁻²⁶ The distribution of optic nerve infarction has been related to known studies on the blood supply of the optic nerve.

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