Comment

One of the patients (case 2) had unequivocal polycythaemia rubra vera. The other was diagnosed and managed at a time when estimations of arterial pressure of oxygen and red cell volume were not freely available, but nevertheless we believe that the diagnosis was firmly established. There are few previous reports of polycythaemia rubra vera occurring in siblings,²⁻⁵ none of whom were twins. We believe that this report, together with the previous description of primary thrombocythaemia in monozygotic twins, supports the possibility that a genetic factor may play some part in the pathogenesis of myeloproliferative diseases. We can find no reference to any association between polycythaemia rubra vera and deafness and assume the occurrence to be fortuitous.

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Shrapnel presenting with symptoms 62 years after wounding

Several reports exist of penetrating foreign bodies presenting up to 39 years after the initial injury.¹⁻³ We describe a patient who first presented 62 years after being wounded with shrapnel.

Case report

An 85-year-old man presented in May 1979 with a four-month history of an expanding painful swelling over the left lower chest. Examination showed a large fluctuant abscess with no axillary lymphadenopathy. Radiography disclosed no underlying effusion or pulmonary change, and the only other finding was mild congestive heart failure partially controlled by diuretic treatment. Investigations showed pronounced neutrophil leucocytosis ($26.0 \times 10^9/l$), erythrocyte sedimentation rate 17 mm in first hour, haemoglobin concentration 9.8 g/dl, and mean corpuscular volume 59%; a blood film showed hypochromia.

Surgical drainage of 30 ml of sterile pus was carried out and a piece of shell shrapnel 10×9 mm removed. With the benefit of hindsight the shrapnel was visible on the initial chest x-ray film. Further questioning elicited that he had received minor shrapnel wounds in 1917. He had recovered rapidly and returned to the front and had subsequently been captured and spent some months as a prisoner of war. He had had no symptoms after this until he had fallen against his left side in January 1979 and had subsequently complained of increasing pain.

Comment

The longest recorded interval of a foreign body presenting many years after the initial wounding is 39 years. This was in a woman presenting with a swelling of the lip attributed to a piece of glass that had become embedded after a land-mine explosion in 1940.³ A piece of shrapnel that had lodged in the chest wall during D-Day worked its way to the surface 35 years later in a 62-year-old man. With the removal of the shrapnel the patient lost the ability to forecast rain.

Other unusual late presentations include biliary colic caused by a grenade splinter migrating into the common bile duct 34 years after injury,⁴ choledochoduodenal fistula produced by migration of a bullet 32 years after injury,⁵ and haemorrhagic cyst formation in the region of the thyrohyoid membrane occurring 30 years after a penetrating injury.

We think that the presentation of symptoms 62 years after the original entry in the case described merits recording.

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Toxic optic neuropathy caused by benoxaprofen

Benoxaprofen is a recently introduced non-steroidal anti-inflammatory drug with useful analgesic and anti-inflammatory properties in the treatment of rheumatic diseases. It is a member of the propionic group of acidic anti-inflammatories but appears to vary from other compounds in this group since it has weak prostaglandin synthetase inhibitory activity but more effect on macrophage function.¹ Phototoxic and photoallergic rashes and onycholysis are well-described adverse reactions, but we report on a patient who developed a partially reversible toxic amblyopia while receiving this drug.

Case report

A 65-year-old woman underwent aortic and mitral valve replacement in 1975 for valve damage secondary to previous rheumatic fever and was subsequently treated with warfarin sodium. In May 1979 she developed an inflammatory polyarthritis with a strongly positive rheumatoid factor (rheumatoid antibody haemagglutination titre 1/320), a raised erythrocyte sedimentation rate, and radiological evidence of joint erosion. In May 1980 she developed an endoscopically proved gastric ulcer and was started on cimetidine in a maintenance dose of 400 mg nightly. In July 1980 benoxaprofen 600 mg nightly was started for her active rheumatoid arthritis, with definite improvement in the degree of pain and synovitis.

On 1 September 1980 she complained of progressive blurring of vision over 10 days unassociated with any ocular discomfort. Acuties were reduced to 6/12 in each eye with a small hypermetropic spectacle correction. She showed a severe red-green colour defect and had bilateral central scotomata to a 15 mm red target (Bjerrum's screen). Electroretinography showed normal rod and cone responses and normal dark adaptation pattern. Visual evoked responses to a 50 flash/min pattern reversal stimulus showed low-amplitude potentials that were grossly delayed (P100 = 185 ms right and left: normal $108 \pm SD 2$ ms). Benoxaprofen was stopped, and over the next month her vision improved.

By March 1981 visual acuities were 6/9 in each eye. The right visual field was full to both at 3 mm white and 15 mm red target, but in the left eye there was still a relative central scotoma to a 15 mm red target. An electroretinogram remained normal and the latency of the P100 component of the visual evoked response had improved to 138 ms right and 140 ms left. The optic discs remained ophthalmoscopically normal.

Comment

A reversible toxic amblyopia has been described in patients taking ibuprofen, the first of the propionic subseries to be introduced.^{2,3} Larger, prospective studies⁴ have failed to confirm this association, suggesting an idiosyncratic response to the drug.

In our patient the clinical and electrophysiological evidence suggest that the visual deterioration was the result of a toxic optic neuropathy due to benoxaprofen, her other treatment having remained unchanged. Confirmation could have been sought by reintroducing the drug, but this was not ethically justifiable. Although this is the first example of

visual impairment we have seen with this drug, we think that others using it should be aware of this serious, adverse reaction.

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Amenorrhoea, galactorrhoea, and hyperprolactinaemia induced by methyldopa

Among the side effects of methyldopa are decreased potency and failure of ejaculation in men and non-puerperal lactation in both premenopausal and postmenopausal women.^{1,2} Steiner *et al*³ found increased serum concentrations of prolactin after single doses of methyldopa during long-term treatment and suggested that this might be the mechanism of galactorrhoea, though they pointed out that no studies had been made of patients with this side effect. Hyperprolactinaemia of renal failure is enhanced by treatment with methyldopa.⁴ Troublesome galactorrhoea and other side effects of hyperprolactinaemia might therefore be expected to be detected first in patients with renal disease treated with methyldopa.

We report on two patients with amenorrhoea, one of whom had galactorrhoea, due to methyldopa in whom hyperprolactinaemia was confirmed.

Case reports

CASE 1

A 41-year-old hypertensive woman started taking methyldopa in 1972, increasing the dose gradually to 4 g/24 h at the beginning of 1978. In 1974 her periods stopped and this was interpreted as postmenopausal amenorrhoea. At the end of 1978 she developed prolonged irregular bleeding, which was erroneously regarded as postmenopausal. Concentrations of follicle-stimulating and luteinising hormones, however, were normal at 0.4 and 2.4 U/l respectively, and she had prolactinaemia of 1865 mU/l (figure). Two repeat samples over the next three months were also raised at 1069 and 1743 mU/l respectively. X-ray films of the skull and tomograms of the pituitary fossa were normal.

Methyldopa was gradually withdrawn; one month after it was stopped the serum prolactin concentration had fallen to 214 mU/l, and over the following three years she had normal, regular periods and serum prolactin concentrations within the normal range (figure).

CASE 2

A 17-year-old girl with proliferative glomerulonephritis developed severe hypertension requiring variable doses of methyldopa up to 750 mg daily to achieve normotension. Her periods became irregular with frequent episodes of amenorrhoea lasting for several months. At the age of 19, after 12 weeks of amenorrhoea, she was found to be pregnant. The pregnancy was terminated at 12 weeks and she developed persistent galactorrhoea, breast tenderness, and nodularity. The discharge of milk fluctuated with the dose of methyldopa. Serum prolactin concentration was 6364 mU/l when the dosage of methyldopa was 250 mg thrice daily, dropping to 3790 mU/l when the dosage was 125 mg daily. X-ray films of the skull and tomograms and a computed tomogram of the pituitary fossa were normal.

Methyldopa was stopped and bromocriptine started. One month later her galactorrhoea had stopped and her periods returned to normal; the prolactin concentration fell to 210 mU/l. Bromocriptine was stopped after six months; normal periods continued for a further three months and slight galactorrhoea recurred and persisted. Serum prolactin concentration rose again to 5319

Serial concentrations of follicle-stimulating hormone, luteinising hormone, and prolactin in case 1. Hatched area represents postmenopausal values of the hormones; upper limit of normal for serum prolactin concentration is 450 mU/l.

mU/l and remained high. Continuous ambulatory peritoneal dialysis was started, and by the age of 23 years she had been receiving this for 12 months.

Comment

In case 1 a clear-cut relation existed between hyperprolactinaemia, amenorrhoea, and administration of methyldopa, all abnormalities clearing up simultaneously when the drug was withdrawn.

In case 2 the pregnancy, terminated at 12 weeks, may have played some part in precipitating galactorrhoea. At that time the renal function (plasma creatinine concentration 125 μ mol/l (1.4 mg/100 ml)) was not decreased to a degree that usually causes hyperprolactinaemia, and the extremely high prolactin concentrations found after the withdrawal of bromocriptine were well above those usually found in chronic renal failure. Probably she eventually developed a prolactinoma, though we have no confirmatory evidence for this. Whether the prolactinoma was the result of prolonged treatment with methyldopa in a patient with impaired renal function or whether the treatment merely drew to light a prolactinoma that would have declared itself later in any case remains speculative.

Galactorrhoea or menstrual abnormalities in patients receiving methyldopa are an indication for estimation of the serum prolactin concentration.

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