SHORT REPORTS

Spontaneous pituitary necrosis

Spontaneous pituitary necrosis follows a variable clinical course. Three different clinical presentations are reported.

Case 1

A 44-year-old woman with acromegalic features and 27 years' amenorrhoea presented in coma which had been preceded by severe headache. She had pale nipples, fever (38°C), signs of meningeal irritation, and no pubic or axillary hair. The fundi and visual fields were normal. The cerebrospinal fluid (CSF) was under increased pressure and contained 0.5 g/l of protein and 0.02×10^9 lymphocytes/l (20/mm³). Her skull x-ray film showed an enlarged pituitary fossa, and spontaneous infarction of a pituitary tumour was diagnosed. Corticosteroid treatment rapidly improved her condition. Two years later endocrine assessment showed mild hypothyroidism (protein bound iodine (PBI) 240 nmol/l (3.1 µg/100 ml); normal 315-630 nmol/l (4.0-8.0 µg/100 ml)) and low plasma 11-hydrocorticosteroids (11-OHCS: 70 nmol/l (2.5 µg/100 ml) at 9 am; normal 190-720 nmol/l (6.9-26 µg/100 ml)). A standard insulin tolerance test produced hypoglycaemia with a minimum blood sugar level of 1.1 mmol/l (20 mg/100 ml) when the maximum values of plasma 11-OHCS and growth hormone (GH) were below normal (88 nmol/l (3.2 µg/100 ml) and 10.5 µg/l respectively). GH levels were not suppressed during a standard glucose tolerance test (minimum GH level 8.2 µg/l), confirming autonomous GH production by the pituitary tumour. Serum luteinising hormone was 3.6 U/l and serum follicle stimulating hormone was 5.4 U/l, compared with normal postmenopausal levels of 20 U/l and 12.5 U/l respectively. The fundi and visual fields remained normal. L-thyroxine was combined with cortisol therapy and regular follow-up was maintained. Seven years later bitemporal hemianopia had developed with further enlargement of the pituitary fossa and irregular destruction of the floor and anterior wall. A huge intrasellar tumour containing fresh blood stretching the optic nerves was removed. Histology showed a pituitary adenoma containing predominantly chromophobe cells with 15-20% acidophilic cells. Postoperative irradiation was given to avoid recurrence. She is currently well on replacement therapy and her visual fields have improved since surgery.

Case 2

A 26-year-old woman presented with amenorrhoea and galactorrhoea after oral contraceptive therapy. Skull x-ray films showed an enlarged pituitary fossa, and air encephalography (AEG) was performed to delineate the extent of the tumour. Thirty minutes after AEG she developed a severe headache, neck rigidity, and hypotension. The CSF protein content was 0.9 g/l with 0.13×10^9 lymphocytes/l (130/mm³). She recovered well on parenteral corticosteroids. Results of endocrine assessment performed two months after AEG showed that the adrenocortical response to hypoglycaemia had disappeared and the GH response remained impaired (table). Cortisol therapy was prescribed and she is currently well though her periods have not restarted.

Insulin tolerance test results in case 2 before and after air encephalogram (AEG). Clinical hypoglycaemia was achieved in both tests. Values in brackets obtained after AEG

Time (min):	0	30	60	90
Blood sugar (mmol/l)	4.0 (3.9)	1.8 (1.5)	3.4 (3.7)	3.8 (5.0)
Plasma 11-OHCS (nmol/l)	550 (60)	540 (30)	690 (30)	420 (50)
Serum GH (µg/l)	3.8 (1.5)	4.8 (4.3)	6.1 (1.9)	5.1 (1.4)

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml. 11-OHCS: 1 nmol/l $\approx$ 0.036 µg/100 ml.

Case 3

A 69-year-old man reported persistent headache. Two days later he was admitted in coma with fever (39°C), neck rigidity, right oculomotor nerve palsy, and right hemiplegia. Skull x-ray films showed an enlarged pituitary fossa. The CSF was xanthochromic with many red and white cells; the protein content was increased to 2.5 g/l. An intracerebral haemorrhage was diagnosed and treated. He was discharged after a few days. Two years later he presented with progressive lethargy, drowsiness, confusion, and hypotension. PBI was 250 nmol/l (3.2 µg/100 ml), Thyopac-3 126 (normal 92-117), and 9 am plasma 11-OHCS 80 nmol/l (2.9 µg/100 ml). Investigations confirmed that he had developed pituitary failure. He is currently well on L-thyroxine and cortisol replacement therapy.

Discussion

The basic pathology of spontaneous haemorrhage into a pituitary tumour^{1,2} is unclear; it may be due to rapid enlargement of the adenoma with infarction or rupture of the fine-walled vessels in the tumour.^{3,4} There is rarely enough tissue left to maintain normal function. We are unaware of reports of further growth of a pituitary tumour after apparent infarction sufficient to cause compression of the visual pathways as seen in case 1. The visual fields and skull x-ray picture should obviously be checked periodically after spontaneous infarction of a pituitary tumour. Pituitary infarction precipitated by AEG is rare but has been reported in a patient with acromegaly.⁵ Spontaneous pituitary necrosis is more common although it is of interest that the clinical features of hypopituitarism in the third patient were not apparent for two years.

¹ Bleibtren, L, *Munchener medizinische Wochenschrift*, 1905, **52**, 2079.

² Brougham, M, Heusner, A P, and Adams, R D, *Journal of Neurosurgery*, 1950, **7**, 421.

³ List, C F, Williams, J R, and Balyeat, G W, *Journal of Neurosurgery*, 1952, **9**, 177.

⁴ Muller, W, and Pia, H W, *Deutsche Zeitschrift für Nervenheilkunde*, 1953 **170**, 326.

⁵ Belchetz, P E, and Mason, A S, *Proceedings of the Royal Society of Medicine*, 1972, **65**, 20.

Endocrine Unit, Department of Medicine, Royal Victoria Infirmary, University of Newcastle upon Tyne, Newcastle upon Tyne NE1 4LP

Y SACHDEV, MD, MAMS, clinical fellow

D C EVERED, MD, MRCP, consultant physician

R HALL, MD, FRCP, professor of medicine

Rapid clonidine withdrawal with blood pressure overshoot exaggerated by beta-blockade

A disconcerting problem in treating hypertension with clonidine is the possibility of a severe rebound rise in blood pressure if the drug is stopped abruptly.^{1,2} The reaction may resemble the crisis seen in patients with a pheochromocytoma. The combination of a beta-adrenoreceptor blocker with one of the vasodilator group of antihypertensive drugs (hydralazine, prazosin, clonidine) has become popular. Since beta-blocking drugs increase peripheral vascular resistance, theoretically a hypertensive crisis after a rapid withdrawal of clonidine could be aggravated in a patient who was also taking a beta-blocker. We report a case in which the patient started taking timolol and at the same time suddenly discontinued clonidine, and subsequently suffered a devastating blood pressure rebound.

Case report

A 60-year-old woman with a 10-month history of rapidly progressive glomerulonephritis and complicating hypertension was receiving prednisone 15 mg/day, warfarin 2 mg/day, and clonidine 0.15 mg eight-hourly. When seen for assessment she was well but her blood pressure was 180/140 mm Hg, her retinal arterioles were narrowed, and there were moderate arteriovenous crossing changes. The blood urea was 14.9 mmol/l (90 mg/100 ml) and the serum creatinine 186 µmol/l (2.1 mg/100 ml).

The beta-adrenoreceptor blocking drug timolol 5 mg daily was added to the patient's antihypertensive regimen. In error, she immediately discontinued the clonidine. Forty-eight hours later she developed a throbbing frontal headache, mild confusion, and profound lethargy. Over the next 24 hours the headache became excruciating, the confusion more marked, she developed

ataxia, and began to vomit. She then became semiconscious and on admission to hospital had a grand mal convulsion. Her blood pressure was 300+/185 mm Hg, the pulse rate 110/min, and the fundi showed widespread flame-shaped haemorrhages and cotton-wool spots together with mild papilloedema. The plasma creatinine had increased to 230 μ mol/l (2.6 mg/100 ml). The blood pressure was controlled with intravenous diazoxide and her clinical condition improved dramatically when clonidine by mouth was reintroduced. A 2.5-hour urine collection begun on admission to hospital had a normal vanillylmandelic acid ratio and contained only 1 μ g of urinary catecholamines (normal up to 100 μ g/24 hours).

Discussion

Because a rebound rise in blood pressure may occur if clonidine is stopped suddenly or taken inconsistently the importance of taking the drug regularly must be emphasised to the patient. An alternative drug might be a better choice for patients thought to be unreliable with their medication and for elderly patients. We think that the blood pressure "overshoot" resulting from abrupt clonidine withdrawal in our patient was potentiated by coexisting beta-adrenoreceptor blockade. Clonidine should always be withdrawn slowly, and when the patient is also taking a beta-blocking drug clonidine should be withdrawn even more carefully.

¹ Hunyor, S N, *et al*, *British Medical Journal*, 1973, 2, 209.

² Bailey, R R, *New Zealand Medical Journal*, 1975, 81, 268.

Department of Renal Medicine, Christchurch Hospital, Christchurch, New Zealand

ROSS R BAILEY, MD, FRACP, nephrologist
T J NEALE, BMEDSC, MB, senior renal registrar

Adverse neonatal reaction to maternal administration of intravenous chlormethiazole and diazoxide

Chlormethiazole ethandisulphonate (Heminevrin) was first used to treat alcoholism and delirium tremens. It has sedative and hypnotic actions together with inhibitory effects on the respiratory, thermoregulatory, and vomiting centres. It has no neuromuscular blocking effect. The manufacturers claim that the doses used have no appreciable depressive effect on the fetal respiratory centre. The drug was first used as a 0.8% solution by continuous intravenous infusion to treat severe maternal pre-eclamptic toxemia.^{1 2} The dose used was variable as the drip rate varied during labour to keep mothers heavily sedated but capable of responding to speech. Only nine out of 50 infants had Apgar scores of less than five at one minute and none less than five at five minutes. There were no untoward side effects. The hypotensive agent used by MacGillivray³ and Varma⁴ was Protervatrine A and B, and, again, there were no untoward effects.

Patients and results

From 5 May 1974 to 5 September 1975 21 live-born infants of 21 mothers with toxemia of pregnancy were admitted to the neonatal intensive care unit. Nineteen of the mothers had moderate to severe pre-eclamptic toxemia and two had eclampsia. All had received, during labour, a 0.8% intravenous infusion of chlormethiazole in doses ranging from 500 to 3000 ml (4-24 g). The state of their infants bore no relation to the dose used. Fourteen mothers received, in addition, intravenous boluses of 75 to 150 mg of diazoxide, which were repeated as necessary to control hypertension. All infants whose mothers had been treated with chlormethiazole in this hospital over the 16-month period are included in this report. Other drugs used both before and during labour bore no relation to the state of the infant in the immediate neonatal period. These included methyldopa, barbiturates, reserpine, clonidine, general anaesthesia, and pethidine in varying combinations.

In the immediate neonatal period 13 of the 21 infants suffered hypotonia, hypoventilation, or apnoea. The duration of the hypotonia was fairly constant

(24 to 36 hours) except in cases 3 and 6 (see table). Apnoea requiring intermittent positive pressure ventilation (IPPV) occurred from birth in cases 9, 10, and 11 but not until 2 to 3 hours of age in cases 1 and 4. In retrospect, case 13 should also have been managed on IPPV. Seven infants were atonic from birth. Five of these required IPPV. The remaining two had considerable hypoventilation but their short periods of apnoea were managed by using an Ambu bag. There were three deaths. One was a 900-g infant of 28 weeks gestation who had marked hypotonia. He was well oxygenated but died of the respiratory distress syndrome.

Adverse neonatal reaction to maternal administration of intravenous chlormethiazole and diazoxide

Case No	Sex	Gestation (weeks)	Birth weight (g)	Grade and duration of hypotonia (h)	Apnoea (A) Hypoventilation (H)	Duration of IPPV (h)	Outcome
1	F	38	2380	++ + 30	A	24	Alive
2	F	37	3210	++ + 48	A and H		Alive
3	F	32-34	1170	+ 12	No side effects		Alive
4	M	40	2700	++ + 24	A and H	2½	Alive
5	M	38	3320	+ + 36	A (episodic)		Alive
6	F	33-34	1410	+ 12	No side effects		Alive
7	M	39	3650	+ + 38	A (episodic)		Alive
8	M	38	4270	+ 24	No side effects		Alive
9	M	36	1850	++ + 36	A	36	Alive
10	F	31	1350	++ + 36	A	36	Died
11	M	34-35	1850	++ + 36	A	44	Died
12	M	28-29	900	+ + 11	A		Died
13	M	36	2720	++ + 39	A and H		Alive

+ = Slight to moderate hypotonia. ++ = Severe hypotonia. +++ = Atonic.
IPPV = Intermittent positive pressure ventilation.

Two of the five infants treated with IPPV from birth died of severe respiratory distress syndrome. Their hypotonia recovered at 36 hours of age as expected, together with the appearance of spontaneous respirations. Nevertheless, oxygenation could not be maintained by using continuous positive airways pressure and the infants subsequently died while on IPPV. A third infant (case 9) with severe respiratory distress syndrome was successfully managed on IPPV from birth and weaned on to continuous positive airways pressure. The three surviving infants treated with prolonged IPPV appear normal so far (at 16, 9, and 2 months of age). All affected infants apart from one (case 2) came from the group of mothers treated with both chlormethiazole and diazoxide (12 out of 14 mothers so treated). The mother of one (case 2) was treated with 1500 ml (12.0 g) of chlormethiazole, together with massive doses of anticonvulsants because of grand mal secondary to a cerebrovascular anomaly, and was thus possibly not suffering from eclampsia. Adverse reactions were not related to the doses used. For example—one mother (case 6) received 3000 ml (24 g) of chlormethiazole while two others (cases 5 and 7) received only 450-500 ml (3.5-4 g) during labour.

Discussion

Depression in infants of mothers with pre-eclamptic toxemia who have been treated with intravenous chlormethiazole has not been reported. The hypotensive drugs used in combination, however, are different from those in other series. Milner and Chouksey⁵ have reported that diazoxide alone had no untoward effect on four infants studied. Possibly, therefore, chlormethiazole and diazoxide may act synergistically to produce such severely depressed infants, as both the dose of the drugs and the severity of the maternal pre-eclamptic toxemia seem unrelated to the severity of this depression. Our experience suggests that when such depression occurs it may be managed successfully with intermittent positive pressure ventilation provided that the respiratory distress syndrome is not also present.

I thank the registrars and sisters of the neonatal intensive care unit who ensured the survival of these babies and Miss K Read for her secretarial help.

¹ Duffus, G M, Tunstall, M, and MacGillivray, I, *Lancet*, 1968, 1, 335.

² Duffus, G M, and MacGillivray, I, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1969, 76, 645.

³ MacGillivray, I, *Lancet*, 1972, 1, 198.

⁴ Varma, T, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1972, 79, 513.

⁵ Milner, R D G, and Chouksey, S K, *Archives of Disease in Childhood*, 1972, 47, 537.

Department of Paediatrics, Christchurch Hospital, Christchurch, New Zealand

ROSEMARY A JOHNSON, MB, FRACP, neonatal paediatrician