CLINICAL RESEARCH

Experience with selective venous sampling in diagnosis of ACTH-dependent Cushing's syndrome

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Abstract

Twenty-three patients with adrenocorticotrophic-hormone-(ACTH)-dependent Cushing's syndrome were subjected to selective venous catheterisation and sampling for ACTH on a total of 26 occasions. Out of 10 patients with pituitary-dependent disease, nine had raised ACTH concentrations in one or both high internal jugular vein samples. Eight patients had 11 proved sites of ectopic hormone production: of these, six were correctly identified by the sampling technique, and in four of them this was the only accurate method of localisation. The results of one catheterisation were misleading, and on 10 occasions they were inconclusive; five patients remained undiagnosed by any method. Overall, 15 of the 26 catheterisations provided diagnostically valuable information.

Selective venous catheterisation and sampling for ACTH is effective in confirming a pituitary source of the hormone and may be valuable in locating the source of ectopic ACTH production in some cases.

Introduction

Differentiating pituitary-dependent Cushing's syndrome from that due to ectopic production of adrenocorticotrophic hormone (ACTH) may be difficult or impossible with conventional techniques.[1-3] Discovering occult ectopic sources may similarly not be possible with present radiological methods.[1 2 4]

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The value of venous catheterisation with blood sampling for hormone measurements to locate hormonally active tumours has been shown with parathyroid and adrenal adenomas[3 5 6] and with phaeochromocytomas.[7] Similar techniques are in common use for investigating renovascular hypertension.[8] Single examples of its use in Cushing's syndrome have been described,[9-15] and recently Findling *et al* reported its use in 10 patients with this condition.[16] They found it to be of value in confirming the pituitary origin of ACTH in five out of six patients, but failed to locate ectopic sources in four others.

We have performed 26 selective venous catheterisations in patients with ACTH-dependent Cushing's syndrome and report here our results.

Patients and methods

Twenty-three patients underwent selective catheterisation and venous sampling on a total of 26 occasions. All had clinical and biochemical evidence of ACTH-dependent Cushing's syndrome[17] with the following four diagnostic characteristics: absence of circadian rhythm of plasma cortisol and ACTH; absence of plasma cortisol response to insulin-induced hypoglycaemia; absence of plasma cortisol suppression (to less than 180 nmol/l; 6·5 μg/100 ml) after dexamethasone 0·5 mg six-hourly for 48 hours; and persistently detectable plasma immunoreactive ACTH. All had biochemical evidence suggestive of ectopic ACTH production (clinical diabetes mellitus or unprovoked hypokalaemia, or both) or one or more findings atypical of pituitary-dependent disease, such as resistance to high-dose dexamethasone (8 mg/day for 48 hours) or poor ACTH response to the metyrapone test. All patients gave informed consent to the procedure.

Catheterisation technique—Selective catheterisation was performed under local anaesthesia by a femoral approach using the Seldinger technique. A selection of preformed catheters was used, each with a side hole within 3 mm of the tip. Phlebography of the adrenal veins was sometimes performed, but not at other sites.

Sampling—Figure 1 shows the full range of sites sampled. For any individual patient 10-20 sites were chosen depending on the clinical indications but always including both high jugular veins. A small amount of contrast was injected at each site to confirm the exact position of the catheter tip before sampling. The inferior petrosal sinuses were not sampled.[11 16] Control "peripheral" samples were taken from a separate line simultaneously with the high jugular

samples and at several other sites. Inferior vena caval and subclavian samples were collected via the catheter. In addition, 13 patients had between five and 13 further samples taken from a peripheral line at 20-minute intervals on a separate occasion within seven days of the catheter study ("rapid sampling") to establish the variation in concentrations of circulating ACTH.

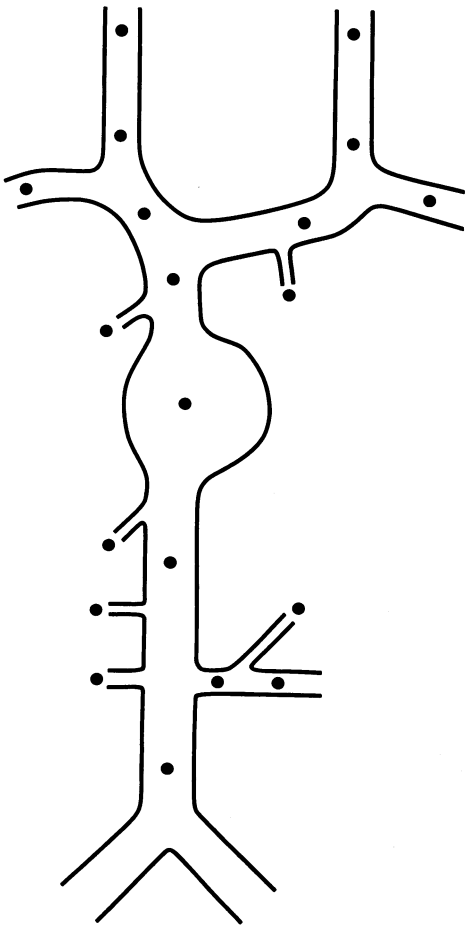

FIG 1—Schematic view of vascular tree indicating sampling sites (●).

Assay—Plasma ACTH (ng/l) was measured by the method of Rees *et al.*[18] The normal (0900) range for this assay is less than 10-80 ng N-ACTH/l. All samples from one catheterisation were assayed in a single batch.

Interpretation of ACTH concentrations—In view of the intermittent and pulsatile nature of ACTH secretion we employed a control range made up from the peripheral and rapid-sampling values: concentrations were regarded as significantly raised only if they exceeded the maximum value of this range.

Results

The procedure was well tolerated, except for mild and transient discomfort associated with injection of dye to locate the catheter tip. Apart from groin haematomas, the only complication was infarction of the right adrenal in one patient; this occurred after adrenal phlebography rather than sampling, and was painful.

Ten patients were thought to have pituitary-dependent disease, as evidenced by suppression of plasma cortisol (to less than 50% of baseline) during dexamethasone 2 mg six-hourly for 48 hours (10 patients), an exaggerated ACTH response to metyrapone (nine patients), and operative finding of a pituitary adenoma (one patient). No evidence of any other source of ACTH was apparent during follow-up for one to six years (see table I). Of the other 13 patients, eight had 10 proved sites of ectopic ACTH production (table II) and five remained undiagnosed (table III).

PITUITARY-DEPENDENT DISEASE

Of the 10 patients with pituitary-dependent disease, nine had raised high jugular venous ACTH concentrations compared with the maximum of the control peripheral or rapid-sampling ranges (table I; fig 2). Peak concentrations were seen in high internal jugular samples in six cases and lower values in the jugular vein in three others, though in each of the latter at least one of the high jugular samples was raised (see fig 3; case 4). The tenth patient had raised values in both low jugular but not high jugular samples.

Ratios of the high jugular ACTH concentration to the maximum of both control ranges ranged from 1·04 to 4·05 (fig 2).

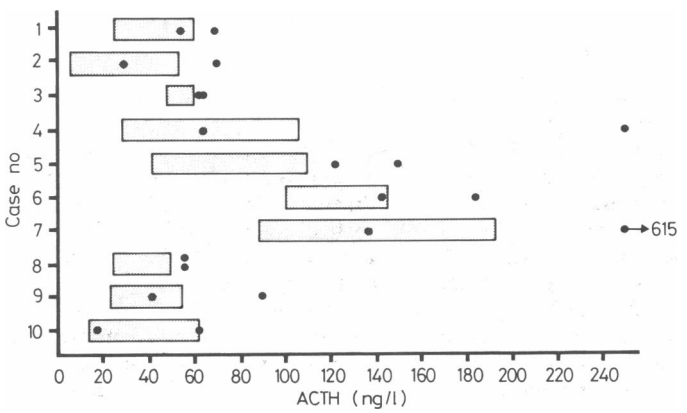

FIG 2—High jugular vein ACTH concentrations (●) in patients with pituitary-dependent disease. Control ranges shown by stippled areas. Case numbers as in table I.

ECTOPIC SOURCES OF ACTH

In the eight patients with proved ectopic sources of ACTH (10 sites in all) the catheter studies were less conclusive (table II). Correct location was found in six cases—namely, two thymic tumours (see fig 3; case 11b), two recurrences in the right neck, an adrenal non-catecholamine-secreting phaeochromocytoma, and a mediastinal

TABLE I—*Details of patients with pituitary-dependent disease*

Case No	Age (years)	Sex	Peak ACTH concentrations and venous sites*	Peripheral ACTH range*	Rapid-sampling ACTH range*	Conclusion from studies
1	27	F	90, superior vena cava; 75, azygos; 70, left high internal jugular	46–50	25–60	Pituitary-dependent (proved at hypophysectomy)
2	42	F	70, left high internal jugular	23–53	26–36	Pituitary-dependent
3	56	F	76 and 67, left and right innominate; 68, superior vena cava; 63 and 62, high internal jugulars	49–61		Pituitary-dependent
4	56	M	249, right high internal jugular	29–75	48–107	Pituitary-dependent
5	29	M	150 and 123, high internal jugulars; 145, right innominate; 130, superior vena cava	94–110	42–103	Pituitary-dependent
6	25	M	184, right high internal jugular	101–145		Pituitary-dependent
7	45	M	615, right high internal jugular	101–193	89–148	Pituitary-dependent
8	31	F	56, both high internal jugulars	30–41	24–50	Pituitary-dependent
9	47	M	90, right high internal jugular	24–55		Pituitary-dependent
10	15	F	92 and 72, low internal jugulars	21–58	14–63	Inconclusive

*Concentrations of ACTH expressed in ng N-ACTH/l.

TABLE II—*Details of patients with proved ectopic sources of ACTH*

Case No	Age (years)	Sex	Peak ACTH concentrations and venous sites*	Peripheral ACTH range*	Rapid-sampling ACTH range*	Conclusion from catheter study	Final diagnosis
11a	41	F	All within control range	32–89		Inconclusive	
11b	41	F	708, thymic; 468, superior vena cava	41–362	103–450	Thymic tumour	Surgical cure (4 cm thymic tumour), ACTH immunostaining positive
12	69	F	All within "peripheral" range	3536–4407		Inconclusive	Hepatic tumour (necropsy)
13a	36	M	597 + 376, thymic	130–450	163–264	Thymic tumour	Apparent surgical cure (4 cm thymic tumour), malignant carcinoid
13b	36	M	162, right subclavian; 108, superior vena cava; 101, right low internal jugular	61–66	63–94	Right neck recurrence	Surgical removal of metastasis with clinical remission for two years
13c	36	M	194, right subclavian; 166, right low internal jugular	135–146		Right neck recurrence	Node mass later seen on CT scan
14	55	M	1641 + 1288, right adrenal	123–209		Right adrenal tumour	Surgical cure (non-catecholamine secreting phaeochromocytoma)
15	51	F	3089, thymic	112–351	90–479	Thymic/mediastinal tumour	5 mm mediastinal node (necropsy). No primary tumour found
16	34	M	422 + 255, low internal jugular; 213, left high internal jugular	41–120		Pituitary-dependent	Surgical cure (5 cm pancreatic tumour)
17	37	F	All within "peripheral" and "rapid sampling" range	43–120	80–182	Inconclusive	Surgical cure (1·5 cm bronchial carcinoid)
18	26	F	All within peripheral range	70–122		Inconclusive	Surgical cure (4 mm bronchial carcinoid)

*Concentrations of ACTH expressed in ng N-ACTH/l.

TABLE III—*Details of patients who remained undiagnosed*

Case No	Age (years)	Sex	Peak ACTH concentrations and venous sites*	Peripheral ACTH range*	Rapid-sampling ACTH range*	Comment
19	63	M	102, thymic	77–97		No source found. Bilateral adrenalectomy
20	37	F	104, right adrenal; 81, left adrenal; 50, superior vena cava	22–44		Suicide. No necropsy
21	56	F	136, right subclavian	41–107	59–125	No source found
22	28	F	All within peripheral range	321–427		No source found
23	73	F	Multiple samples > 500	323–370		Clinically, deposits in liver from carcinoid primary of unknown site (adrenocortical deposits of carcinoid cells on histological examination after adrenalectomy)

*Concentrations of ACTH expressed in ng N-ACTH/l.

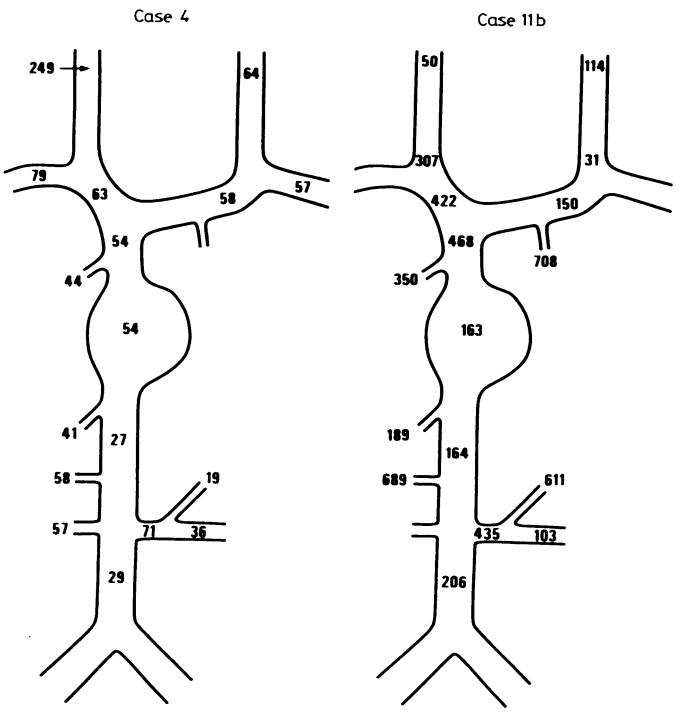

FIG 3—ACTH concentrations (ng/l) at sites sampled during catheterisations in cases 4 (pituitary-dependent disease) and 11b (proved thymic tumour).

lymph node. One patient, subsequently cured by resection of a pancreatic tumour, had raised high jugular venous ACTH concentrations. Four catheterisations were inconclusive. Eventual diagnoses were made in three of these five patients by computed tomography (two bronchial carcinoids and one pancreatic islet-cell tumour), one at necropsy (hepatic tumour), and one after repeat catheterisation (thymic tumour; case 11).

Table III gives the findings in the five patients who remained undiagnosed.

Moderately raised ACTH concentrations were seen in one or both adrenal veins or the left renal vein in 10 of the 26 catheters. Six of these occurred in patients with pituitary-dependent disease and four in those with ectopic sources.

Discussion

Past experience of this technique in Cushing's syndrome has been limited, usually to single cases.[9–15] The only series reported to date (in 10 patients) confirmed the value of the method in patients with pituitary-dependent disease, using inferior petrosal sinus sampling, but did not locate any of four ectopic sources.[16]

Our studies were more comprehensive than any earlier report. We used multiple and simultaneous sampling to establish the range of peripheral plasma concentrations as a control, since ACTH secretion from both pituitary and ectopic sources is intermittent and pulsatile. Unless the background variation is clearly established the relevance of single, apparently raised values during a catheterisation study cannot be assessed. Apart from the major sites of ACTH production, we found that in 38% of cases (10 out of 26) one or both adrenal vein ACTH concentrations were raised: the mechanism for this is not clear.

Our results indicate that in pituitary-dependent disease selective sampling of the high jugular veins provides further evidence of the pituitary origin of ACTH in 90% of cases. The procedure is well tolerated and is perhaps of particular value when other data such as plasma potassium or metyrapone testing are atypical for pituitary-dependent disease. These results were obtained without the use of sampling from the inferior petrosal sinus, in contrast to the study of Findling *et al*,[16] who did not obtain diagnostically raised ACTH values from the jugular bulb and vein: they, however, used only single simultaneous peripheral control values and did not always succeed in bilateral sampling.

Though locating ectopic sources appeared to be the most promising role for selective catheterisation,[10 11] this has not hitherto been shown to be so.[16] We, however, identified six

ectopic sourcse. In four of these no other method, including computed tomography, had shown any possible source of ACTH, and in four of the six a curative operation was possible. Four patients remained undiagnosed and a further one died. All had undergone extensive investigation including computed tomography without definite evidence of the site of ACTH production. Reasons for the high failure rate (10 out of a possible 16) may include periodic hormone secretion,[19] failure to cannulate appropriate veins, and dilution or metabolism of ACTH from the bronchial and portal circulations: interestingly, neither bronchial carcinoid tumour was detected.

Though Findling *et al* failed to locate any of the four ectopic sources, their petrosal sinus ACTH values in these studies were not raised and, in one case, they showed an arteriovenous ACTH gradient suggestive of a pulmonary source of ACTH, later confirmed as a bronchial carcinoid. Arterial sampling may therefore provide further evidence of a pulmonary source of ACTH. Only one catheterisation provided misleading information: this suggested a definite pituitary source. Though purely speculative, it may be that this tumour was producing corticotrophin-releasing factor, as has been reported for a pancreatic tumour.[20]

Advances in the technology of computed tomography, with increased resolution, may lessen the need for such invasive investigations. We have recently shown the efficacy of computed tomography in detecting small lung tumours producing ACTH,[21] and it is clear that this technique is superior to venous sampling in this region. Several of our studies did, however, successfully locate ACTH secretion when computed tomograms had been negative and, in other instances, provided evidence of the hormonal activity of small structural abnormalities discovered by the scan.

Overall, 15 of the 26 catheter studies gave valuable positive evidence of the source of ACTH. We conclude that selective venous catheterisation and sampling is a safe and effective method of locating the site of ACTH production in patients with Cushing's disease and in some patients with ectopic sources of ACTH. It offers an important adjunct to the investigation of patients in whom doubt remains about the source of their Cushing's syndrome.

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ONE HUNDRED YEARS AGO As our readers are aware, Professor Lister made some experiments during the past year with various preparations of eucalyptol, and he is at present testing the suitability of iodoform. Iodoform is chemically nearly related to chloroform, their formulae differing only in the substitution of the one halogen for the other (Iodoform = CHI_3). Both bodies have powerful antiseptic properties, the addition of less than 1 per cent of chloroform, for instance, to an animal or vegetable infusion will prevent decomposition for, at least, many months. Iodoform occurs in the form of a dense yellow crystalline powder. Hence it is more convenient than other ordinary antiseptics for the treatment of local sores, for introducing into chronic sinuses or into scrofulous joints after incision; but it is not easy of application to an amputation or to most other operation wounds; and is quite unsuitable for use with the spray. For this reason Professor Lister still operates under the carbolic acid spray, though he now seems to attach rather less importance to its continuous use, and will stop it, for instance, for a short time during an operation if the cloud it produces be found to interfere with a clear view of the wound. The dressings used consist of cotton wool impregnated with iodoform, and the drug itself is, in certain cases, powdered over the wound from a sprinkling-box. "Iodoform wool" has also been extensively used at University College Hospital, and we learn from Mr Gerard, pharmacist to that hospital, that the great difficulty encountered in preparing the wool is to obtain an even distribution of the iodoform. The desired end is best obtained by treating the powdered drug with ether, in the proportion of about eighty-eight parts of ether to eight of iodoform. In about four pints of this mixture, half a pound of fine clean cotton-wool is soaked for a short time; the wool is afterwards placed in a drug-press. About three pints of ether can be squeezed out, and, when dry, the wool contains about 10 per cent of iodoform. The same objection is made against this wool as against salicylic wool—namely, that its use spreads about the room an irritating dust, with this further disadvantage, that the odour is to most people very offensive. A little glycerine added to the ether used in its preparation, checks the former tendency, and the latter drawback is minimised by the addition of eucalyptus oil. The wool ought to be stored in air-tight boxes, and not handled more than necessary before use. It is too early, as yet, to speak decisively of the value of this antiseptic from experience gained in England, but we believe that it has given a good deal of satisfaction to those who have used it, and has proved itself especially valuable in cases where carbolic acid is, either from idosyncrasy or from the delicate nature of the parts involved, too irritating to be borne. (*British Medical Journal*, 1882.)