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ECTOPIC PRODUCTION OF ACTH AND CORTICOTROPIN-RELEASING HORMONE (CRH)

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Summary—The most common ectopic production of a pituitary hormone is the one of ACTH leading to Cushing's syndrome Ectopic ACTH-hypersecretion is the cause of Cushing's syndrome in 10–15% of all cases The ACTH-secreting tumours are often oat-cell carcinomas of the lung, less frequently pancreatic cancers, hypernephromas, or C-cell carcinomas of the thyroid Some of these tumours may be benign or semi-benign as the rare carcinoid tumours and cause great problems in the differential diagnosis of ACTH-dependent hypercortisolism Out of 173 of our patients with Cushing's syndrome observed in the last 12 years 21 were caused by ectopic ACTH-production Of these 21 patients 13 have a small cell carcinoma of the lung The ectopic ACTH-syndrome often has typical clinical features caused by the levels of ACTH and cortisol leading to hypocalaemic alcalosis with muscle weakness and wasting, carbohydrate intolerance, and hypertension with oedema The survival time in many of these patients is not long enough to allow them to develop typical signs of Cushing's syndrome though they are often highly pigmented These patients are easily diagnosed However, patients with small tumours which do not cause very elevated ACTH-levels and who have the more typical clinical signs of full-blown Cushing's syndrome are difficult to recognize For the differential diagnosis of ACTH-dependent Cushing's syndrome the corticotropin-releasing hormone (CRH) stimulation test and dexamethasone suppression test with high doses are helpful In special cases the venous sampling procedure for ACTH-measurements is necessary, also CT or NMR is helpful Ectopic CRH-production is a rare cause of ACTH-dependent Cushing's syndrome Patients with ectopic CRH-production and consecutive ACTH-hypersecretion from the pituitary have not been studied extensively There are especially no well documented results of the use of the CRH-stimulation test *in vivo* in this group of patients with Cushing's syndrome On the other hand, in the documented cases, not only CRH-, but also ACTH-production was found in the tumours So far, this rare cause of ACTH-dependent Cushing's syndrome has to be excluded or confirmed by the measurement of endogenous CRH-levels But until now we have not been able to detect one single case of ectopic CRH-production using a sensitive homologous CRH-radioimmunoassay over a period of more than 8 years in which we have seen nearly 120 newly diagnosed patients with ACTH-dependent Cushing's syndrome Only in the plasma and tumour tissue of two patients of other groups have we found high CRH-levels

INTRODUCTION

Ectopic production of a releasing hormone is a rare cause of endocrine diseases Growth hormone releasing hormone (GHRH) is the releasing hormone which is most frequently produced outside the hypothalamus [1] It has been shown to be the cause of acromegaly and gigantism in a number of cases, although it accounts for $<1\%$ of all acromegalics [1] In contrast ectopic corticotropin-releasing hormone (CRH)-production causing Cushing's syndrome is very rare [2, 3] The far more frequent cause of Cushing's syndrome is ectopic ACTH-production ACTH is the most commonly ectopically produced pituitary hormone which leads to Cushing's syndrome and is the cause of Cushing's syndrome in 10–15% of all cases [1, 4] Brown in 1928 [5] described a combination of a "non-endocrine" tumour and the clinical features of Cushing's syndrome Thorne [6] described the combination of bronchocarcinoma and Cushing's syndrome in 1952 Christy [7] demonstrated the presence of an adrenal growth-stimulating factor in such tumours in 1961, but it was not until 1962 that ectopic secretion of ACTH by these tumours was first demonstrated [8] Liddle *et al* [9] in 1965 were the first to use the name "ectopic ACTH-syndrome"

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In 1971 Upton and Amatruda [10] extracted peptides from malignant tumours One of the extracted peptides stimulated ACTH-release, both *in vivo* and *in vitro* It was therefore postulated that the tumours made a peptide with CRH-activity [10] Following the characterization and synthesis of an ovine CRH molecule in 1981 [11] ectopic production of CRH has been demonstrated in only a few cases [2] Until now there is no single case in which isolated ectopic CRH-production could be demonstrated In all published cases ectopic ACTH-production was also found [2]

In the following study some clinical data of ectopic CRH- and ACTH-production as well as the results of diagnostic and therapeutic management of these forms of Cushing's syndrome are presented

ECTOPIC CRH-PRODUCTION

Ectopic CRH-production causing Cushing's syndrome is very rare [2] So far, this rare cause of ACTH-dependent Cushing's syndrome has to be excluded or confirmed by the measurement of endogenous CRH-levels But until now we have not been able to detect one single case of ectopic CRH-production using a sensitive homologous CRH-radioimmunoassay over a period of more than 8 years, in which we have seen nearly 120 newly diagnosed patients with ACTH-dependent Cushing's syndrome Only in the plasma and tumour extract of a patient of Dr Rohde's group in Berlin [12] and in the plasma of a patient of Dr Furlani's group in Verona [13] have we found high CRH-levels Figure 1 shows the results of the dynamic tests of the ACTH-secretion of a 31-year-old woman, whom we observed more than 14 years ago This female patient had a history of Cushing's syndrome going back $1\frac{1}{2}$ years, beginning right after pregnancy Because of the high, but not excessive ACTH-levels and the partial suppression of these levels after 2 days of 2 mg dexamethasone every 6 h (Fig 1) and because of the moderate ACTH-increase after stimulation with lysine-vasopressin (Fig 1) we diagnosed pituitary ACTH-dependent Cushing's disease However, neurosurgical exploration did not reveal a microadenoma The patient therefore underwent bilateral adrenalectomy The surgeon found during the operation a metastatic pancreatic tumour Perhaps this tumour had produced CRH which would be compatible with the observation of partial ACTH-regulation by

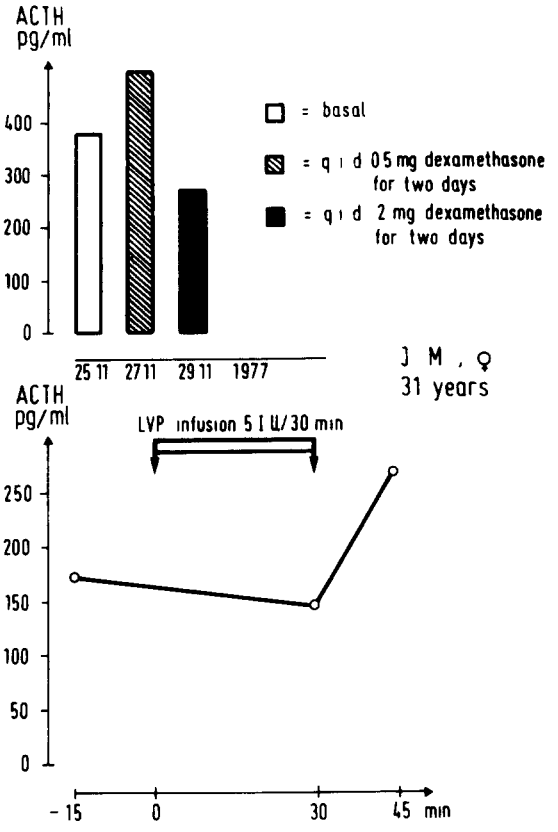

Fig 1 Dynamic tests of ACTH-secretion in a female patient with ACTH-dependent Cushing's syndrome [4]

dexamethasone and CRH However, at the time we did not have the opportunity of proving this hypothetical diagnosis by measuring this releasing hormone in plasma or tumour tissue

So far, in all published cases of ectopic CRH-production, a co-existence and co-secretion of CRH and ACTH could be demonstrated [2, 10] Until now no single case of ectopic CRH-production without ACTH-co-secretion is documented

ECTOPIC ACTH-PRODUCTION

Ectopic ACTH-production is the cause of Cushing's syndrome in about 10–15% of all patients with endogenous Cushing's syndrome [1, 4] Figure 2 summarizes the results of ACTH-measurement in 173 patients with Cushing's syndrome, which we observed over 12 years [1] Out of these 173 cases 21 were caused by ectopic ACTH-production (Fig 2) Out of the 21, 13 had a small-cell carcinoma of the lung The typical clinical features of ectopic ACTH-syndrome are caused by the usually very high ACTH- and cortisol-levels leading to hypocalaemic alcalosis and hyperpigmentation These patients are

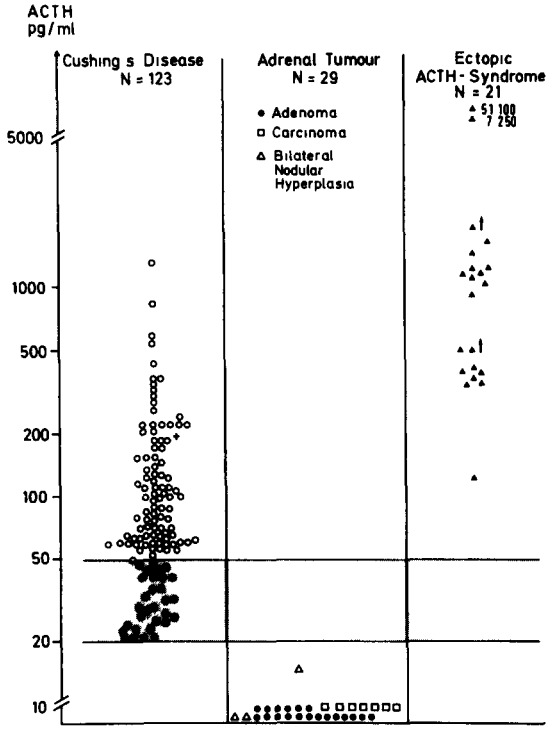

Fig 2 ACTH-levels in 173 patients with Cushing's syndrome [1]

correctly diagnosed without problems However, patients with small tumours, e g bronchocarcinoids, and not very elevated ACTH-levels are often difficult to recognize [2, 3] Table 1 summarizes the typical ACTH-patterns in patients with ACTH-dependent hypercortisolism In patients with Cushing's disease ACTH-levels may be moderately or significantly elevated and do not respond to insulin-hypoglycaemia. They respond clearly to CRH and are usually suppressed by high doses of dexamethasone Patients with an ectopic ACTH-excess usually have very highly elevated ACTH-levels, which do not respond to hypoglycaemia and CRH and are usually not suppressible with high doses of dexamethasone, but exceptions occur If both functional tests are used, one has the opportunity to make the correct differential diagnosis of ACTH-dependent Cushing's disease [14]. Patients with ectopic CRH-production seem to behave like patients with ectopic ACTH-syndrome, though we do not have much data on these few patients Endogenous depression which may be accompanied by hypercortisolism can be differentiated by the fact that the ACTH-levels at basal state are normal, do respond to insulin-hypoglycaemia, show a blunted response to CRH and a normal suppression after high doses of dexamethasone [2] Figure 3 summarizes our experience with the CRH-stimulation test in 9 patients with ectopic ACTH-syndrome In contrast to patients with pituitary ACTH-dependent Cushing's disease [2], there is no increase of ACTH after CRH-stimulation except in 2 cases, who showed significant ACTH-increases The cortisol levels which are often already maximally stimulated, do not reflect changes of ACTH-levels after CRH in these two patients (Fig 3) Two patients had only moderately elevated ACTH-levels (Fig 3, broken lines) The first one was a female patient with a bronchial carcinoid tumour, the other a patient with an unknown small "non-endocrine" tumour

In single cases catheterization studies of the cerebral sinus which drained the pituitary gland are necessary A lack of a gradient between the ACTH-levels and the sinus petrosus inferior and in the periphery suggest that the source of the ACTH-hypersecretion is not localized in the pituitary but elsewhere The combination of the catheterization studies and CRH-stimulation leads to a better differentiation between pituitary ACTH-dependent Cushing's disease and Cushing's syndrome due to ectopic ACTH-production [15]

The difficulty in correctly diagnosing ACTH-dependent Cushing's syndrome is exemplified by the following 2 cases [1] In case 1, all test results pointed to pituitary ACTH-dependent Cushing's disease, though no microadenoma was detected during surgical sella-exploration Six years after bilateral adrenalectomy, ACTH increases further and a pituitary tumour was

Table 1 Pattern of ACTH-secretion in patients with ACTH-dependent hypercortisolism [1]

Test	Cushing's disease	Ectopic ACTH-syndrome	Ectopic CRH-syndrome	Endogenous depression
Level of basal ACTH	↑ or n	↑↑ or ↑	↑	n
ACTH during IHT	No increase	No increase		↑
ACTH after CRH	↑↑ or ↑	No increase, seldom ↑		Blunted ↑
ACTH after high dex	↓	No suppression, seldom ↓	No suppression	Abnormal

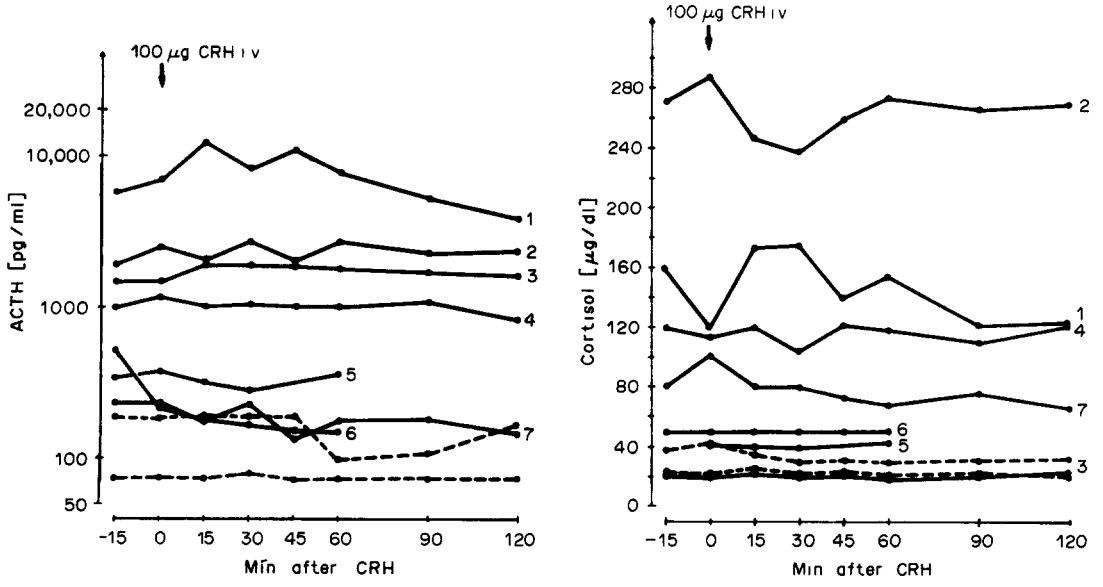

Fig 3 CRH-stimulation test in 9 patients with ectopic ACTH-production, 7 patients had an oat-cell carcinoma of the lung [1–7] For details of the 2 other patients (broken lines) see text [2]

detected and removed In the second case the tests did not suggest pituitary ACTH-hypersecretion, though no other ACTH-source could be found Six years after therapeutical bilateral adrenalectomy a small lung tumour was diagnosed and removed, which led to a decrease of ACTH-levels [1]

Altered POMC-maturation is common in non-pituitary tumours and decidedly unusual in pituitary corticotroph adenomas This subtle mechanism may be profitably used to detect abnormal POMC-fragments in blood that would pinpoint, but not identify, a non-pituitary origin of the ACTH-secretion Bertagna *et al* [16] demonstrated that partial degradation of ACTH into CLIP is fairly common in non-pituitary tumours CLIP escapes detection by most ACTH-radioimmunoassays (RIAs) and immunoradiometric assays (IRMAs) Since the LPH are unaffected by the POMC-processing, the plasma LPH ACTH-ratio is increased [16] Ectopic ACTH-production of carcinomas of the lung without clinical signs of Cushing's syndrome was first described by Gewirtz and Yalow [17] We looked with a N-terminal specific ACTH-RIA at the ACTH-secretion of such patients and found clearly elevated levels in only 5 patients with an oat-cell carcinoma and in 4 patients with other tumours They all had, at least retrospectively, clinical signs of Cushing's syndrome [4]

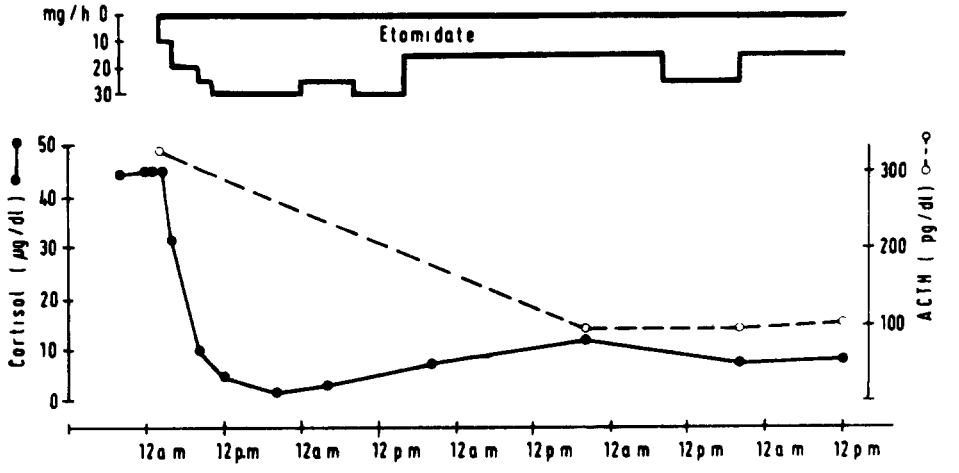

Fig 4 Serum cortisol- and plasma ACTH-levels of a patient with ectopic ACTH-syndrome before and during continuous etomidate infusion [21]

THERAPY OF ECTOPIC ACTH-PRODUCTION

The only causal therapy is the removal of the ACTH-producing "non-endocrine" tumour, but this is possible only in a minority of the cases In single cases, therapy with cytotoxic drugs can also alleviate the ACTH-excess In the majority of the cases the therapy is directed against adrenal hypercortisolism by an adrenolytical therapy whereas a bilateral adrenalectomy is necessary only in single cases [3, 18, 19] There are different adrenolytical drugs [18], but greater experiences exist only with o,p'-DDD [3, 4, 18] In the last years imidazole-derivatives have also been used for adrenolytical therapy [18, 20], especially ketoconazole and etomidate Figure 4 shows the effects of an infusion of etomidate We treated a 53-year-old man with hypercortisolism due to ectopic ACTH-production with this sedative therapy because of severe psychotic symptoms and severe hypocalaemia, alcalosis and hypertension, which made a transfer to our intensive care unit necessary During continuous infusion of etomidate at 15–30 mg/h, cortisol levels fell to 5 μg/dl within 8 h After reduction of the etomidate infusion cortisol levels increased, but fell again when the dose of the drug was increased In contrast to the response in healthy people to short-term etomidate infusion, ACTH also decreased after 3 days [21], a phenomenon also observed with other imidazole-derivatives, e g ketoconazole [22, 23] In other cases a non-hypnotic low-dose etomidate therapy led to a rapid correction of hypercortisolaemia in Cushing's syndrome [20]

Another possibility of treating selected cases with ectopic ACTH-syndrome may be treatment with somatostatin-analogue [24] We have shown years ago that a somatostatin infusion can acutely lower high ACTH-levels in a male patient with ectopic ACTH-production from a metastatic medullary carcinoma of the thyroid [25] Now the long-acting somatostatin-analogue SMS 201-995 (Sandostatin) allows long-term therapy in such cases Figure 5 shows the ACTH- and cortisol-levels before and under Sandostatin-therapy of a young female patient with ectopic ACTH-production This patient, who had a small carcinoid lung tumour as the cause of ectopic ACTH-syndrome, was at first operated upon successfully She had a relapse during and after pregnancy but now we can not find any trace of the tumour Therefore, we started the Sandostatin therapy (Fig 5), which has so far been successful

CONCLUSIONS

Ectopic ACTH-hypersecretion is the cause of Cushing's syndrome in 10–15% of all cases, whereas ectopic CRH-production is a rare cause of ACTH-dependent Cushing's syndrome The differential diagnosis between pituitary and ectopic ACTH-dependent Cushing's syndrome may cause great problems in single cases In most cases symptomatic therapy is only achieved by reducing the steroid excess

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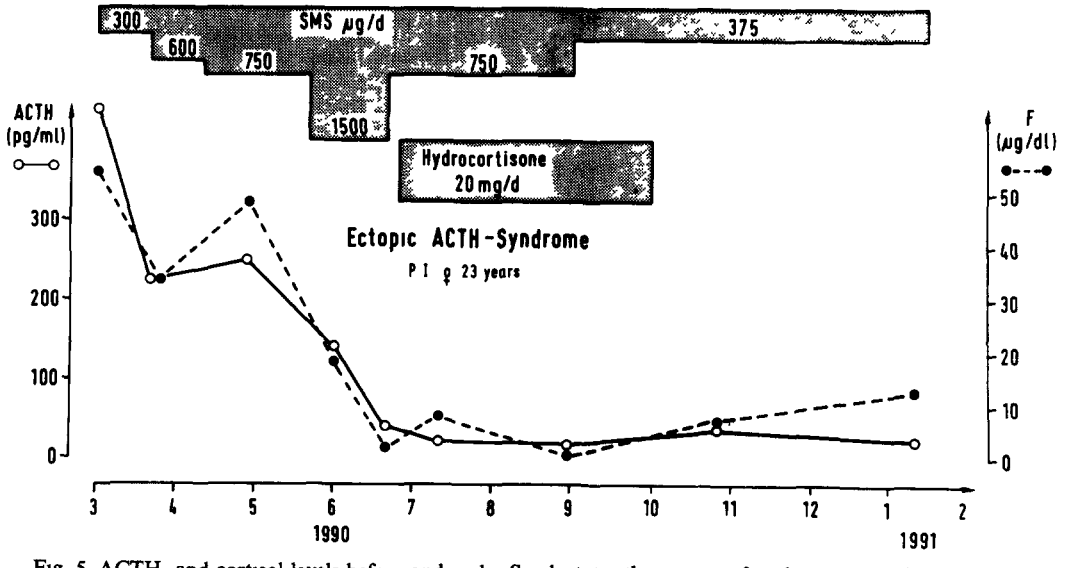

Fig 5 ACTH- and cortisol-levels before and under Sandostatin therapy in a female patient with ectopic ACTH-syndrome

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