Europ. J. Cancer Vol. 16, pp. 855–857

0014-2964/80/0601-0855 $02.00/0

Cerebrospinal Fluid ACTH and Calcitonin in Patients with CNS Metastases from Small Cell Bronchogenic Carcinoma

MOGENS HANSEN,* HEINE H. HANSEN,* SVEN ALMQVIST† and LOTTE HUMMER‡

**Department of Chemotherapy R II–R V, Finsen Institute, Copenhagen, Denmark, †Immune Laboratory, Stockholm, Sweden, and ‡Department of Nuclear Medicine, Rigshospitalet, Copenhagen, Denmark*

Abstract—*ACTH and calcitonin concentrations in cerebrospinal fluid were measured in 22 patients with small cell carcinoma of the lung, including 14 patients with CNS metastases. ACTH concentrations were significantly higher in patients with CNS metastases as compared to those without. No difference was disclosed as regards calcitonin concentrations in cerebrospinal fluid between patients with and without CNS metastases. Measurement of ACTH in cerebrospinal fluid may be of diagnostic value in the detection of CNS metastases in patients with small cell carcinoma.*

INTRODUCTION

WITHIN the last few years, several clinical therapeutic investigations have focused on CNS metastases in patients with small cell carcinoma of the lung (s.c.c.), including the use of 'prophylactic brain irradiation'. These studies were based on the observation that the occurrence of CNS metastases was an increasing therapeutic problem during prolonged survivals resulting from the use of intensive combination chemotherapy. Although the use of prophylactic brain irradiation decreases the incidence of CNS metastases, it does not prolong the median survival or influence the number of long-term survivors in randomized clinical studies [1, 2]. Accordingly, it is still important to investigate methods for the detection of early metastatic disease to the CNS in patients with s.c.c..

The polypeptide hormones ACTH [3, 4] and calcitonin [4] are often produced in s.c.c. tumours, and increased concentrations are found in the peripheral blood in one quarter to two thirds of patients with s.c.c. [5]. Similarly, the presence in the CNS of metastatic s.c.c. might increase the concentrations of these polypeptides in the cerebrospinal fluid (CSF).

The purpose of this investigation was to elucidate the correlation between the concentrations in the CSF of ACTH and calcitonin to the occurrence of CNS metastases.

Accepted 31 October 1979.

MATERIALS AND METHODS

CSF samples were obtained by lumbar puncture in patients with s.c.c. clinically suspected of CNS metastases. Samples were taken for analysis of ACTH, calcitonin, protein and cell counts. Samples for ACTH and calcitonin analysis were kept below −20°C until the analyses were performed. The other samples were immediately subjected to routine analysis, including cytological examination by the use of the cytocentrifuge.

Determination of ACTH concentration

ACTH concentrations were measured by a radioimmunoassay technique [6]. All determinations were made in duplicate and in two dilutions of the CSF sample to ensure parallel dose–response curves for the CSF samples and the ACTH standard prepared in albumin-buffer solution.

Determination of calcitonin levels

Calcitonin levels were also measured by a radioimmunoassay [7]. Specific antibodies against human calcitonin were obtained in rabbits immunized with purified extract from fresh tumour tissue of medullary thyroid carcinoma. Synthetic human calcitonin was used

as the standard. A calcitonin-low serum was used for dilutions and standard.

Twenty-two patients were included in this study. All were suspected of having CNS metastases by the staff of our department. They were subsequently examined by a neurologist, and brain scan with 99^m technetium-pertechnetate was performed in 20 of the patients. Brain irradiation with 200 rad five times weekly for 4 weeks was given to six patients, who had verified brain metastases without concomitant peripheral relapse of s.c.c., and five of these patients improved significantly. Brain autopsy including microscopical examination of suspected areas was performed in 13 cases. Based on these procedures, the patients were classified as having CNS metastases or not at the time of the lumbar puncture without the knowledge of the results of the ACTH and calcitonin analyses.

In two patients with metastatic lesions in the spinal cord, samples of CSF were also obtained during treatment with large doses of prednisone (50 mg t.i.d.) and subsequent intraspinal instillations of methotrexate. Samples of CSF were also obtained during steroid treatment in a third patient in whom no metastatic lesions were detected at autopsy.

RESULTS

The median values and ranges of ACTH and calcitonin concentrations in the CSF of 14 patients with confirmed brain metastases and of eight patients without such metastases are shown in Table 1. The median value of ACTH concentrations is statistically significantly higher in the group of patients with CNS metastases ($P<0.01$, Mann–Whitney rank sum test), while no differences were observed when comparing the calcitonin concentrations.

The highest concentration of ACTH in the CSF from patients without verified CNS metastases was 25 ng/l, and 11 of 13 patients (85%) with CNS metastases had ACTH concentrations above this level. On the other hand, only one patient with CNS metastases had calcitonin concentrations in the CSF above the highest value in patients without verified CNS metastases.

Table 1. Median values of CSF ACTH and calcitonin concentrations in patients with and without CNS metastases

	ACTH (ng/l)	Calcitonin (pmole/l)
+CNS-metasases	33* (16–71)	120 (<100–1740)
−CNS-metastases	18* (11–25)	140 (<100–610)

*$P<0.01$.

ACTH was not detectable in the CSF during steroid treatment in the patient without CNS metastases. ACTH concentrations before and after steroid treatment and after intraspinal methotrexate treatment in the two patients with spinal lesions are seen in Table 2. It is worthy of note that ACTH remained elevated during steroid suppression in both patients. Calcitonin was <100 pmole/l in both patients at all instances.

Table 2. CSF ACTH concentrations in two patients treated with high dose steroids and intraspinal methotrexate

	CSF-ACTH (ng/l)	
Before treatment	After steroids for >2 days	After intraspinal methotrexate
71	46	63
31	28	<1

DISCUSSION

Elevated CSF concentrations of adenohypophyseal hormones have been found in patients with pituitary tumours with suprasellar extension [8]. With regard to metastatic disease, human chorionic gonadotropin has been found elevated in the CSF in patients with germ cell tumours [9], and CEA concentrations were found elevated in breast cancer patients with meningeal carcinomatosis [10]. The present findings indicate that the ACTH concentrations in the CSF are significantly increased by CNS lesions in patients with s.c.c..

It is reasonable to suggest that the source of the elevated CSF ACTH in patients with CNS metastases was the tumour cells within the CNS. Increased plasma concentrations of tumour produced ACTH together with breaks in the blood–brain barrier might, however, also explain the findings. None of these suggestions are supported by the results for calcitonin in the CSF. Thus, calcitonin is also produced in s.c.c. tumours [4], and serum calcitonin concentrations are increased in about two thirds of the patients with s.c.c. [5]. Accordingly, CSF calcitonin might be increased in patients with CNS metastases by

either of the two mechanisms proposed to explain the increased CSF ACTH concentrations. The different findings for ACTH and calcitonin in the CSF may be accounted for by other mechanisms, such as the secretion rate from tumour cells, diffusion from plasma into the CSF, and the elimination rate from the CSF.

Elucidation of the difference between calcitonin and ACTH concentrations in the CSF requires separate investigations. It might also be worth while to investigate whether CSF ACTH measurements could disclose CNS metastases in asymptomatic patients. If this be the case, the measurement of ACTH in the CSF might be of value therapeutically in selecting the group of patients who might benefit from 'prophylactic' brain irradiation.

REFERENCES

1. H. H. Hansen, P. Dombernowsky, F. R. Hirsch, M. Hansen and J. Rygård, Intensive combination chemotherapy plus localized or extensive radiotherapy in small cell anaplastic bronchogenic carcinoma. A randomized trial. *Proc. Amer. Soc. clin. Oncol.* **18,** 350 (1977).
2. M. Hansen, H. H. Hansen and P. Dombernowsky, Restaging of long term survivors with small cell anaplastic carcinoma of the lung. *Proc. Amer. Soc. clin. Oncol.* **20,** 415 (1979).
3. G. A. Bloomfield, I. M. Holdaway, B. Corrin, J. G. Ratcliffe, G. M. Rees, M. Ellison and L. H. Rees, Lung tumours and ACTH production. *Clin. Endocr.* **6,** 95 (1977).
4. K. Abe, J. Adachi, S. Miyakawa, M. Tanaka, K. Yamaguchi, N. Tanaka, T. Kameya and Y. Shimosato, Production of calcitonin, adrenocorticotropic hormone, and beta-melanocyte-stimulating hormone in tumors derived from amine precursor uptake and decarboxylation cells. *Cancer Res.* **37,** 4190 (1977).
5. M. Hansen, H. H. Hansen, F. R. Hirsch, J. Arends, J. D. Christensen, J. M. Christensen, L. Hummer and C. Kühl, Hormonal polypeptides and amine metabolites in small cell carcinoma of the lung—with special reference to stage and subtypes. *Cancer (Philad.)* (in press).
6. L. Hummer, A radioimmunoassay of plasma corticotrophin. In *Radioimmunoassay and Related Procedures in Medicine* 1977, vol. II, p. 391. International Atomic Energy Agency, Vienna (1978).
7. S. Almqvist, M. Telenius-Berg and B. Wästhed, Serum calcitonin in medullary thyroid carcinoma. Radioimmunoassay technique and diagnostic value. *Acta med. scand.* **196,** 177 (1974).
8. R. M. Jordan, J. W. Kendall, J. L. Seaich, J. P. Allen, C. A. Paulsen, C. W. Kerber and W. P. Vanderlaan, Cerebrospinal fluid hormone concentration in the evaluation of pituitary tumors. *Ann intern. Med.* **85,** 49 (1976).
9. K. D. Bagshawe and S. Harland, Immunodiagnosis and monitoring of gonadotrophin-producing metastases in the central nervous system. *Cancer (Philad.)* **38,** 112 (1976).
10. B. Yap, H. Yap, R. S. Benjamin, G. P. Bodey and E. J. Freireich, Cerebrospinal fluid carcinoembryonic antigen in breast cancer patients with meningeal carcinomatosis. *Proc. Amer. Ass. Cancer Res.* **18,** 98 (1978).