Evaluation of Parathyroid Function in Patients with Hypergastrinaemia and Pernicious Anaemia

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ABSTRACT

In order to evaluate the possible causal relationship between raised serum gastrin levels and the development of primary hyperparathyroidism (HPT) which is suggested from experimental studies we evaluated parathyroid function in a group of 32 patients with hypergastrinaemia and pernicious anaemia. The values for serum calcium and parathyroid hormone were determined as well as the fasting urinary excretions of cyclic AMP and calcium. There was no relationship between the serum gastrin levels and any of the other studied parameters and there was no consistent pattern suggesting parathyroid hyperfunction.

A retrospective analysis of hospital records from 441 patients operated for primary HPT showed a prevalence of pernicious anaemia of 1.8 %. This figure is higher than that found in the unselected age-matched population (0.31 %). However, taken together this study does not support the hypothesis that hypergastrinaemia is of particular importance for the pathogenesis of primary HPT.

INTRODUCTION

Several pieces of evidence suggest that gastrin might be involved in the pathogenesis of primary hyperparathyroidism (HPT). In patients with primary HPT raised gastrin levels have been found in an increased frequency often persisting even after parathyroidectomy (5, 10, 16, 21). When hypergastrinaemia was experimentally induced in rats hyperplasia of the parenchymal cells of the parathyroids was seen (7) and in-vitro studies suggest that gastrin might be a stimulus for secretion of parathyroid hormone (PTH) (22).

In order to further evaluate the possible relationship between hypergastrinaemia and primary HPT we studied parathyroid function in a group of patients with pernicious anaemia where achlorhydria and hypergastrinaemia is an obligatory finding. In addition, the prevalence of pernicious anaemia was determined among patients with primary HPT.

PATIENTS AND METHODS

Altogether 32 patients (13 males, 19 females) with a mean age of 67 $\pm$ 10 (SD) (range 44-82) years were studied. They all had a verified history of pernicious anaemia based on typical haematological findings including marrow biopsy and a full response to treatment with vitamin B_{12}. Their duration of disease was from 1 to 21 years (mean 9.8 $\pm$ 6.9 years). Gastric acid secretion was investigated in 27 patients and they were found to have achlorhydria. All patients except one had normal values for serum creatinine, 4 had diabetes and 3 received regular treatment with thiazides.

The patients were studied as out-patients (Central Hospital, Eskilstuna), where they reported after an overnight (12 hours) fasting. Blood samples were taken in evacuated tubes, whenever possible without tourniquet. Urine was collected during a 2-hour period as previously described (11). Blood samples were centrifuged and serum was decanted. Serum was frozen at -80°C and urine was frozen at -20°C until analyzed.

Calcium, creatinine and albumin concentrations were determined as part of the clinical routine at the Department of Clinical Chemistry. The serum calcium concentrations were adjusted for variations of the serum albumin content, the correction factor being 0.019 mmol/l for each g/l that the individual albumin concentration deviated from the normal mean of 46 g/l. With this correction the normal range in our laboratory is 2.20-2.60 mmol/l.

Serum gastrin concentrations were determined by a radioimmunosorbent method (13) with the gastrin antibodies coupled to bromcyanide-activated cellulose. The antiserum used was a generous gift from Professor J Rehfeld, Copenhagen, Denmark, and has been characterized previously (15). Synthetic Human Gastrin I (SHG ICI Chemicals, U.K.) was used for preparation of standards and for ^{125}I-labelling with the Chloramine-T method. The results are presented as pmol equivalents of SHG/l. The normal value for serum gastrin in our laboratory is less than 55 pmol/l.

Immunoreactive PTH concentrations were measured by a radioimmunoassay method employing ^{125}I-labelled bovine PTH (Inolex) and sheep antiserum (S478) against porcine and bovine PTH. This assay measures intact human PTH and the C-terminal 2/3 of the molecule. The antiserum reacts predominantly with a mid-portion (44-68) of the hormone but not with a N-terminal (1-34) fragment or a small C-terminal (53-84) fragment (9). The reference range, as estimated from 50 healthy individuals is 0.4-1.2 arbitrary units (arb. U/l) per litre, whereas among 40 consecutive patients with verified primary HPT the mean value was 2.3 $\pm$ 1.6 arb. U/l (12).

Urinary cyclic AMP was determined by a radioimmunoassay method as previously described (23). The normal range for the fasting urinary cAMP is 0.2-0.7

µmol/mmol creatinine and for the fasting urinary calcium 0.05-0.50 mmol/mmol creatinine (11).

A retrospective study of hospital records was also carried out of all patients operated at our hospital during the years 1959-1979 for primary HPT (1). The prevalence of pernicious anaemia in this material of 441 patients was compared to figures from a recent survey of the apparently healthy population of approximately 20,700 individuals in a nearby rural Swedish district (18).

RESULTS

All patients with pernicious anaemia had clearly elevated levels of gastrin, which ranged from 80 to 5500 pmol/l with a mean ($\pm$ SD) of 2000 $\pm$ 1200 pmol/l. In 24 of the 32 cases values above 1000 pmol/l were detected. The mean values for serum calcium and PTH as well as for urinary cAMP and fasting calcium excretion all fell within the normal range (Table 1).

Table 1. Mean values ($\pm$) SD of parathyroid hormone (PTH) and calcium in serum and of fasting excretions of cyclic AMP and calcium in urine in patients with pernicious anaemia and hypergastrinaemia.

	Serum values		Urine values	
	PTH (arb. U/l)	Calcium (mmol/l)	cAMP (µmol/mmol creat)	Calcium (mmol/mmol creat)
Patients	0.84 + 0.61	2.45 + 0.09	0.61 + 0.41	0.25 + 0.17
Normal range	0.40 - 1.20	2.20 - 2.60	0.17 - 0.67	0.05 - 0.50

There was no relationship between gastrin and PTH concentrations (Fig. 1) nor between gastrin and calcium values (Fig. 2). Neither was there any relationship between gastrin and fasting urinary calcium or cAMP.

Two patients had serum calcium concentrations just above the upper normal limit(2.62 mmol/l in both cases) and one of them had also a slightly elevated value for urinary cAMP. In 2 normocalcaemic individuals raised levels for PTH were found (1.31 and 3.55 arb. U/l) and in 2 others an elevated urinary cAMP (1.3 and 2.6 µmol/mmol creatinine) but they had normal values for the fasting urinary calcium.

Among the 441 patients operated for primary HPT altogether 8 individuals (1.8 %), mostly elderly females, had a verified diagnosis of pernicious anaemia. Diagnosis of the blood disorder had preceded the detection of HPT with periods from 2 to 29 years. In the population study 0.31 % of all individuals had a diagnosis of pernicious anaemia (18) (Table 2). This difference is statistically significant (p <0.001. Fisher's exact test).
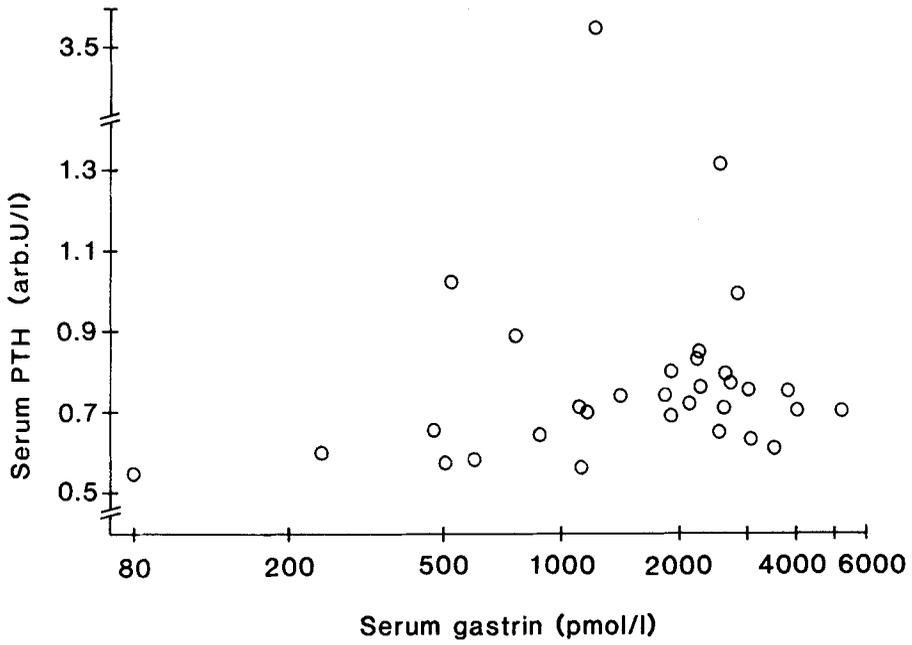
<u>Fig. 1</u>

Relationship between the serum concentrations of gastrin and parathyroid hormone (PTH) in patients with pernicious anaemia (r= -0.0616, p> 0.7).
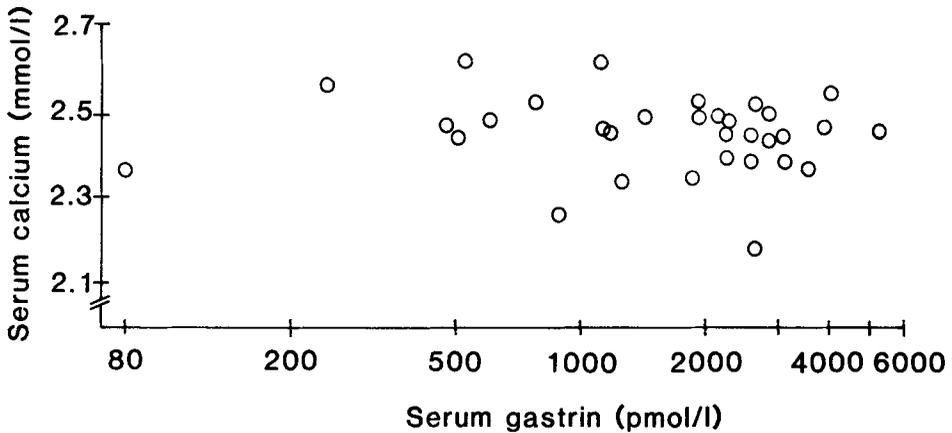

<u>Fig. 2</u>

Relationship between the serum concentrations of gastrin and calcium in patients with pernicious anaemia (r= -0.10, p= 0.58).

Table 2. Prevalence of pernicious anaemia in patients operated for primary hyperparathyroidism (HPT) in Uppsala 1959-1979 compared to data from a population survey (18).

	HPT patients (n = 441)				Population study (n = 20 700)			
	Males		Females		Males		Females	
	n	%	n	%	n	%	n	%
15-44					2	0.1		
45-64					5	0.2	7	0.3
65-74	1	4.2	4	4	8	0.7	7	0.6
75-			3	4.2	14	1.7	22	2.2
All ages	1	0.9	7	2.2	29	0.3	36	0.4

DISCUSSION

Gastrin has been shown to have trophic actions besides its stimulatory effect on the acid-secreting parietal cells. It stimulates RNA, DNA and protein synthesis in the mucosa along the intestinal tract with the exception of oesophagus and antrum. Also the pancreas is a target organ for the trophic action of gastrin (6, 8).

Previous experimental work in our group (7) suggested that, in the rat, hypergastrinaemia could stimulate to parathyroid hyperplasia. In these experiments, the induction of hypergastrinaemia through antral exclusion was associated with an increased volume of the parathyroids owing to hyperplasia of the parenchymal cells. However, the serum calcium levels were not affected.

In the present study of patients with hypergastrinaemia and pernicious anaemia there was no pattern of general parathyroid hyperfunction. Naturally we have no information as to the histological appearance of the parathyroid glands in these cases. Thus we do not know if there might have been hyperplasia of the glands without hypercalcaemia as in the work by Grimelius et al. (7). In that study, however, the rats were exposed to hypergastrinaemia for 14 weeks only, while in the present work the patients had a duration of disease from 1 to 21 years. In a work by Vantini et al. (19) an intravenous infusion of pentagastrin induced a significant increase of both calcitonin and PTH levels, and a decrease in serum calcium levels was concomitantly seen.

Demonstration of hypercalcaemia is a requisite for the diagnosis of primary HPT. In addition, several methods can be used for evaluation of parathyroid function including determinations of the serum concentrations of PTH or of the urinary excretions of cAMP. Furthermore various indirect evidence of parathyroid hormone activity based on the renal handling of calcium and phosphate has been reported to be of clinical value (3, 17). The large number of tests that have been developed to assess parathyroid function indicates that none of them is entirely satisfactory for clinical purposes.

We have previously found that determinations of both total urinary cAMP (23)- and serum concentrations of PTH (20) will separate most patients with hypercalcaemia and primary HPT from patients with normal parathyroid function. A common picture in primary HPT is also a high fasting urinary calcium (11, 14), due to actions of PTH on bone.

For all these parameters, which more or less closely reflect parathyroid function, the patients with pernicious anaemia and hypergastrinaemia as a group presented values that were closely compatible with those found in apparently healthy subjects. Furthermore, there was no suggestion of any correlation between the individual serum levels of gastrin on one hand and serum PTH or calcium concentrations on the other. Thus it seems unlikely that there is any consistent relationship between the raised gastrin values in pernicious anaemia, and parathyroid function.

One patient displayed a pattern which was compatible with mild primary HPT (slight hypercalcaemia and elevated urinary cAMP). This was presumably a chance finding since the prevalence of HPT in the apparently healthy elderly population seems to be at least one per cent (4). In 3 other normocalcaemic cases either PTH or urinary cAMP was elevated. These patients presented no other signs of HPT nor were they known to suffer from any other disease of possible importance. It seems most likely that the laboratory data in these cases reflect the ineffectiveness of any single test to fully discriminate normal individuals from those with parathyroid hyperfunction.

We also carried out a retrospective analysis of our material of patients operated for HPT with regard to the prevalence of pernicious anaemia, which was significantly higher in those patients with primary HPT than in the unselected population. It is, however, doubtful if this really means an increased risk for a patient with pernicious anaemia to develop HPT. Pernicious anaemia, or any other disease one looks for, is likely to be diagnosed in an increased frequency in any thoroughly investigated patient material such as ours (2). It is also reasonable to assume that pernicious anaemia was under-diagnosed in the unselected population material in the study by Tyrberg & Smedby (18). Some complex relationship between the two diseases cannot be excluded however. On the other hand, if pernicious anaemia really means an increased risk for developing HPT this must be a weak factor as only 8 out of 441 patients developed both diseases during an observation time of up to 29 years.

Taken together the information in this study indicates that hypergastrinaemia, in pernicious anaemia, is not of particular importance for the development of primary hyperparathyroidism.

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