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Hyperparathyroidism

Clinical Experiences from 208 Cases

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ABSTRACT

A clinical series of 208 patients with primary hyperparathyroidism diagnosed between 1958 and 1971 is reviewed. Part of this series has been reported earlier and this gives us a possibility to compare the early part of the series seen between 1958 and 1967 and the more recent part observed between 1968 and 1971. The frequency of diagnosed HPT in patients from the service area of the University Hospital of Uppsala gives a calculated minimum prevalence of 1/1 000 in the age groups above 40. The series of HPT is still dominated by patients with urinary tract symptoms. This is to some extent due to thorough screening of all patients with urinary calculi especially with recurrent stones. An increasing number of patients, however, present themselves with unspecific symptoms or symptoms simulating other diseases. In the diagnosis determination of the serum calcium is of main importance. Many cases are found accidentally through serum calcium determinations made routinely. The only biochemical test of additional decisive diagnostic value was the calcium infusion test *ad modum* Kyle. During recent years patients with recurrent kidney stones have been explored even if normocalcemic. Among these patients with positive findings the microscopic picture was in about 60 per cent that of hyperplasia. The experiences from this series indicate that in adenomatous HPT, removal of adenomatous tissue, leaving non-adenomatous glands intact, seems to be effective. A few cases of recurrence are supposed to be due to incomplete exploration.

INTRODUCTION

In 1969 we reported the observations on a series of 85 patients with primary hyperparathyroidism (HPT) seen at the University Hospital of Uppsala 1958–1967 (7). Since then, 1968–1971, we have observed another 123 patients with the same diagnosis. As the experience from the new series in some respects, concerning the tracing, the diagnosis and the surgical treatment, differs from the old series we wish to present this second report.

MATERIAL

The series consists of all cases of primary HPT—208 patients—seen at the University Hospital, Uppsala, between 1958 and 1971. In the following the cases from 1958–1967, 85 subjects, will be referred to as the early series, the cases from 1968–1971, 123 subjects, will be denoted the recent series. In 203 cases an unequivocal diagnosis was obtained by surgery and/or autopsy. Adenomas were found in 164 cases, hyperplasia in 38, one had carcinoma. The majority of the patients came from the hospital service area, i.e. somewhat more than Uppsala county having a population of about 230 000. These patients probably represent all cases diagnosed within the area. The minor part of the material consists of cases referred to us from hospitals outside this area. The yearly incidence from 1960–1971 is presented in Fig. 1.

CLINICAL OBSERVATIONS

The *age and sex distribution* is presented in Table I. As seen in the table, there is a predominance for females in the age-groups over 50. It is apparent that the distribution pattern of parathyroid hyperplasia as regards age and sex is quite different from that of adenoma, half the number of the hyperplasia cases being young and middle-aged men. There are two striking differences between the early and recent series. First, in the adenoma group the percentage of cases, males and females, falling in the age-group 40–59 had increased considerably. Second, the number of cases with hyperplasia in the early series was 6/85, in the recent series the ratio was 32/123.

Social and hereditary factors. The distribution on social groups of the Uppsala patients agreed with the general pattern of the area. There was no apparent over-representation of any specific type of profession, nor for urban or rural groups.

The dietary history of the patients revealed

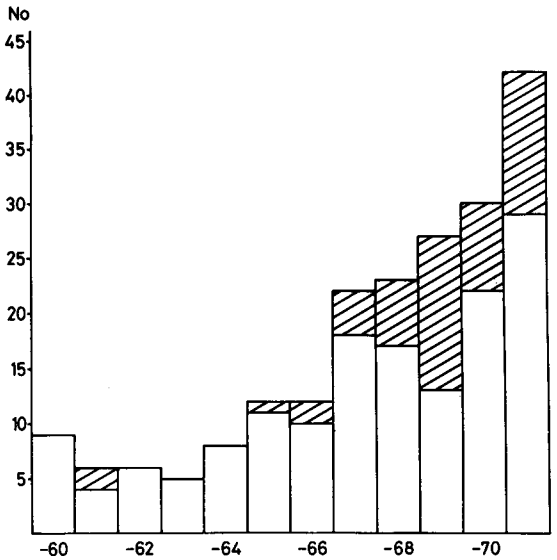

Fig. 1. Yearly incidence of diagnosed primary HPT in the University Hospital. Open bars represent patients from the hospital service area. Hatched bars represent patients referred from outside the area.

nothing of particular interest. The majority of the patients consumed milk and milkproducts to the same extent as the average Swede of the corresponding age and sex. There were very few total milk refusers. One patient had undergone a gastric resection for peptic ulcer.

Five subjects belonged to one family and were consanguineous. Hyperplasia was found in 3, 2 had an adenoma. (This family will be described elsewhere.)

History and symptoms. The frequency of the main symptoms are shown in Table II. It is evident that kidney stones and urinary tract symptoms still dominate the clinical spectrum of HPT. This is especially true for males among which 3/4 have urolithiasis, it is true to a lesser degree for females. Among the elderly women with HPT kidney stones were found in less than 1/3. Fifteen patients were admitted in a severe state of pernicious HPT (parathyroid crisis) (5).

None in the hyperplasia group had signs of skeletal involvement. In other respects there was no significant difference in the symptomatology between cases with hyperplasia and adenoma.

The most apparent difference between the early and recent series was the decreased incidence of gastrointestinal and local skeletal symptoms. Skeletal involvement demonstrable on X-ray examination was found in 11/85 in the early series, the incidence in the recent was 3/123.

The main cause bringing the patient to examination and diagnosis is presented in Table III. As seen in the table every second patient comes to the diagnosis primarily because of urinary tract disease. In 25% of the patients more or less un-

Table I. *Sex and age distribution, total series*

Figures in brackets = hyperplasia

Age	Men	Women	Total
–19	1 (0)	0 (0)	1 (0)
20–39	18 (8)	10 (3)	28 (11)
40–59	30 (9)	69 (7)	99 (16)
60–	15 (6)	65 (5)	80 (11)
	64 (23)	144 (15)	208 (38)

Table II. *Incidence of main symptoms*

	Per cent of total material	Per cent of age-group above 60
Urolithiasis	54 (♂ 73 ♀ 45)	36 (♂ 73 ♀ 28)
Urinary tract symptoms but no stones	14[a]	28[a]
Gastrointestinal symptoms	19	39
Tiredness	21	48
Muscular weakness	16	35
Mental symptoms	14	14
Skeletal and joint pains	6	—
Osteoporosis	1.5	—
Local skeletal disease and osteitis fibrosa	6	—
Parathyroid "crisis"	7	18

[a] Nearly all females.

Table III. *The main cause bringing the patient to diagnosis*

	Per cent of total material	Per cent of age-group above 60
Urinary tract symptoms	48	30
Gastrointestinal symptoms	9	6
Skeletal and joint symptoms	2	5
Neuromuscular symptoms	10	21
Mental symptoms	10[a]	10[a]
High serum-calcium accidentally found	21	25

[a] Nearly all females.

Table IV. *Probable duration of HPT*

Duration (y.)	Per cent of total material	Per cent of age-group above 60
<1	10	14
1–5	31	31
5–15	25	13
>15	12	15
Impossible to estimate	22	27

specific symptoms such as peptic ulcers, muscular weakness or unexplained mental disturbance led to the suspicion of the diagnosis. In the remaining 20–25% the unexpected discovery of an elevated serum calcium value initiated the proper investigation.

Duration of the disease. The probable duration of the disease, to judge from the individual history, is shown in Table IV. There was no significant difference between the adenoma and hyperplasia groups nor between the early and recent series.

Co-existing diseases. Adenomatous changes of the thyroid gland were found in about 1/3 of the cases. Five subjects had or had had hyperthyroidism, one had spontaneous myxoedema.

Hypertension was registered in 10% of the total material, which is approximately the figure to be expected in a material with a sex and age distribution like the present.

Diabetes mellitus was present in 8%. This is a somewhat high figure but not remarkably so.

Bronchial asthma was present in 9 cases. Sarcoidosis was found in 3. (These cases will be described elsewhere.) Apparent cardiac disease was found in 6 cases, 3 had suffered a previous cardiac infarction, 3 had rheumatic valvular disease.

One subject was previously operated for an adrenocortical adenoma, another had undergone hypophysectomy for acromegaly.

Malignant disease was found in 7 instances. There were 2 cases of myeloma, 2 had polycythemia, one hypernephroma, one thyroid cancer and one malignant lymphoma.

BIOCHEMICAL OBSERVATIONS

The main biochemical findings are presented in Table V. In about 5% of the total series all biochemical parameters were normal. The serum magnesium level was usually normal except in most of the "crisis" cases who had hypomagnesemia. An abnormal serum creatinine level (above 1.2 mg/100 ml) was found in 25% of the cases. All except one were adenoma-cases. The creatinine clearance was abnormal in about 35%. Abnormal urinary concentration tests were found in about 20%.

Table V. *Biochemical findings*

	Adenoma (%)	Hyperplasia (%)
Serum calcium		
Normal or border line values	10	70
Most values 5.3–5.9 mE/l	60	20
Most values above 6.0 mE/l	30	10
Serum phosphate		
Normal or border line	79	79
Most values below 0.7 mE/l	21	21
Urinary calcium excretion		
Normal values	40	55
Values above 12 mE/24 hrs	60	45
Phosphate clearance		
Below 15 ml/hr	45	74
Above 15 ml/hr	55	26
Tubular reabsorption of phosphate		
Above 85%	36	78
Below 85%	64	22
Calcium infusion, "Kyle" test (new series only)		
Normal	15	25
Positive	85	75

SURGICAL OBSERVATIONS

Procedure. The neck explorations were performed according to the principles for goitre surgery. In the adenoma cases all 4 glands were inspected, if possible, and the adenoma removed. In the hyperplasia cases 3 of 4 glands were removed, the smallest being left. When the 4th gland was also obviously enlarged a partial resection of that gland was made, too.

Anatomy. One or more adenomas were found in 164 cases, hyperplasia in 38. One subject had a parathyroid carcinoma. A solitary adenoma was

Table VI. *Clinical results*

Total series	208
Operated	201
Positive findings	196
Cured by surgery but no positive findings	5
Positive findings but not cured	4
Refused surgery	2
Died before surgery	5
Died in connection with surgery	4

found in 147 cases, multiple adenomas, usually 2, were found in 17 subjects. In the recent series the localization of the adenoma was: right upper 25 %, right lower 25 %, left upper 15 %, left lower 35 %. An atypical localization of the adenoma was encountered in 17 cases. In 7 the adenoma was found in the thyroid gland, in 5 behind the trachea or larynx, in one in the thymus gland, in 4 in the mediastinum.

Histology. Microscopic examination revealed chief cell adenoma in 150 cases. Five were of the oxyphil type, 9 were mixed or atypical. (The histology of the hyperplastic glands will be described in detail elsewhere.)

Clinical results. The clinical results are summarized in Table VI. Four patients had to be reoperated. In two cases the adenoma was not found at the first exploration, in two a second adenoma had to be removed.

In the early series 15/85 required vitamin-D-substitution initially after operation. In 8 of these the substitution therapy could be discontinued after a few months. In the recent series only 1/123 required vitamin-D-substitution.

Remaining recurrent nerve paralysis occurred in 5 subjects. A psychotic post-operative reaction was observed in one case in the early series (7). This patient had severe hypomagnesemia.

Four cases died in connection with surgery. All 4 had the clinical picture of parathyroid crisis (5) and 3 belonged to the early series. No other complications were observed.

In another 19 patients suspected for primary HPT surgical neck exploration revealed normal parathyroid glands. Twelve of these patients were normocalcemic. Among the 7 hypercalcemic patients one had sarcoidosis, one multiple myeloma and one hypernephroma. In one case the hypercalcemia was probably due to thiazide therapy, in three the cause of the hypercalcemia is still unknown.

DISCUSSION

There are two essential differences between the early and the more recent part of the series. One is the striking increase in number of cases with parathyroid hyperplasia. It is of interest to note that an increase in the percentage of cases with parathyroid hyperplasia in recent years is also apparent in the Cleveland Clinic material (1). The other is the tendency towards a lower average age of the patients at the time of diagnosis, most markedly seen in the age groups above 40. The main reason for these differences in our material is probably found in the slight change in indications for surgery which have been practiced by us within the last years. Before 1968 neck exploration for suspected HPT was not undertaken in normocalcemic patients unless there was at least some single serum calcium value above 5.2 mE/l. Since then we have explored an increasing number of cases with the serum calcium entirely normal though in the upper range (4).

When systematic screening is started for a disease like HPT it is natural that the most obvious cases come to attention first. This reasonably means that there initially is an overrepresentation for cases of long duration and with severe symptoms. This in turn will favour a selection of elderly patients. There are good reasons to believe that we still have a falsely high average age due to delayed diagnosis.

During the last 5 years the frequency of diagnosed HPT has been about 20 cases a year from the Uppsala area. The higher number in 1970 and 1971 is probably incidental and due to the extended indication for surgical exploration (see above). This means a yearly incidence of around 1/5 000 in the age groups above 40. Considering the average duration of the disease before diagnosis, over 5 years, the minimum prevalence of HPT is probably at least 1/1 000 in the age groups over 40.

The material is still dominated by patients with urinary tract symptoms. This is especially true for men. The predominance should be viewed against the fact that cases with urinary tract calculi are especially keenly screened. Several patients with recurrent urolithiasis have also been explored in spite of being normocalcemic. If this latter group is excluded it will be observed that the diagnosis

of HPT was made in patients with unspecific symptoms or symptoms simulating other disease in more than 50% of the series. In the age groups above 60 this figure is close to 75%.

In our previous report (7) we had a frequency of apparent skeletal involvement of well above 10%. In the recent part of the series this frequency has decreased to less than 5%. The distribution over the years of "the skeletal" cases has been fairly constant, about one a year. We believe that the frequency of gross skeletal involvement in HPT is constant but low, the frequency figures found depending on the number of "non-skeletal" cases diagnosed.

The diagnostic mainstay still is hypercalcemia. However, in our series there is an increasing number of normocalcemic cases. This is especially seen in the group of hyperplasia. The only biochemical parameter of decisive diagnostic value in these cases seems to be the lack of effect of a calcium infusion, the "Kyle test" (parathormone assay not being available) (8). The normocalcemic group has been described in detail previously (4).

In recent years several reports have appeared discussing the effect of the parathormone on the acid-base-equilibrium (cf. e.g. 6, 9). A more or less clear tendency towards metabolic acidosis has been found in over 50% in some clinical series. Among our patients only very few had acidosis, all these were severely ill. The distribution of serum bicarbonate, and serum chloride values were perfectly normal in the rest of the material. At present we cannot offer any explanation of this difference between our experience and the reports mentioned above, except that the patints with acidosis may represent an advanced HPT.

It has been suggested that parathyroid hyperplasia in many cases, if not all, is an early stage in the development of what eventually will become an adenoma (cf. e.g. 2, 4). With this in mind the surgical principles followed by us in the adenoma cases might be subject to objection. We have explored all parathyroid glands and removed only the adenoma or adenomas. Should the primary cause of the HPT persist it would be more logical to routinely perform a subtotal resection of the remaining parathyroid tissue. We have refrained from such a policy for two reasons. First, the frequency of postoperative hypoparathyroidism is low in our series and would probably increase considerably. Second, in our experience there has not been a single case of recurrent HPT indicating the formation of a new adenoma nor have we seen a case with hyperplasia after a previous operation for an adenoma. The recurrences observed by us have been due to incomplete exploration. However, in some cases we have taken biopsies from "normal" glands. In some of these cases the microscopic picture has been that of hyperplasia.

The low incidence of hypoparathyroidism in the recent part of our series, 1/123, deserves a comment. In many cases a slight hypocalcemia will appear on the 3rd–4th postoperative day, in most cases only to disappear a week later. As long as the patient is kept under hospital supervision until a normal serum calcium level is regained there is no need for substitution therapy in the vast majority of patients. As a matter of fact such substitution might be harmful by suppressing the stimulation of the remaining parathyroid tissue.

The necessity of surgical treatment of HPT, especially in early cases, in elderly patients and so-called asymptomatic cases has been discussed (3). In our experience there are practically no asymptomatic cases. The general state of the elderly patient is usually considerably improved following surgery even in cases with an unspecific clinical picture. Early cases of HPT usually present with recurrent urinary tract stones. In our material 28 cases with recurrent kidney stones have been followed for more than 5 years after parathyroid surgery. There was no case of kidney stone recurrence. Our opinion, based on this experience, is: HPT should be surgically treated unless there are obvious contraindications.

Nine patients expired—all of these had the clinical picture of pernicious HPT—parathyroid crisis. Five of these patients died before coming to surgery. Only one of the deaths falls into the recent part of the series (with 5 "crisis" cases). As previously reported (5) we believe that this improvement of the prognosis is due to our present policy of treatment for these cases including i.a. immediate restoration of fluid balance with especial observation of K^+ and Mg^{++}, eventually hemodialysis and subsequent emergency surgery. This might also be the reason why we have not observed a single instance of digitalis intoxication in the recent series (cf. 7).

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