

Hyperparathyroidism associated with chronic pancreatitis in a family

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Hereditary hyperparathyroidism, occurring as an isolated endocrinopathy was first described by Goldman and Smyth in 1936. They described primary hyperparathyroidism in two siblings. Jackson and Boonstra (1967) collected 21 families with 107 hyperparathyroid members from the literature, including eight unrelated families of their own, all discovered in a single centre over a 10-year period. This condition tends to occur in younger patients who frequently have symptomless hypercalcaemia; the more likely parathyroid pathology is either chief-cell hyperplasia or multiple and re-

current adenomas than the sporadic form. Other endocrine involvement in three different families suggested to these authors that hereditary hyperparathyroidism is most likely a part of the Mendelian dominant syndrome of hereditary endocrine adenomatosis which is characterized by pleomorphic expression.

Since 1957 when Cope, Culver, Mixter, and Nardi defined an association between hyperparathyroidism and pancreatitis, many cases of pancreatitis complicating prolonged hypercalcaemia have been reported. Its incidence in primary hyperparathy-

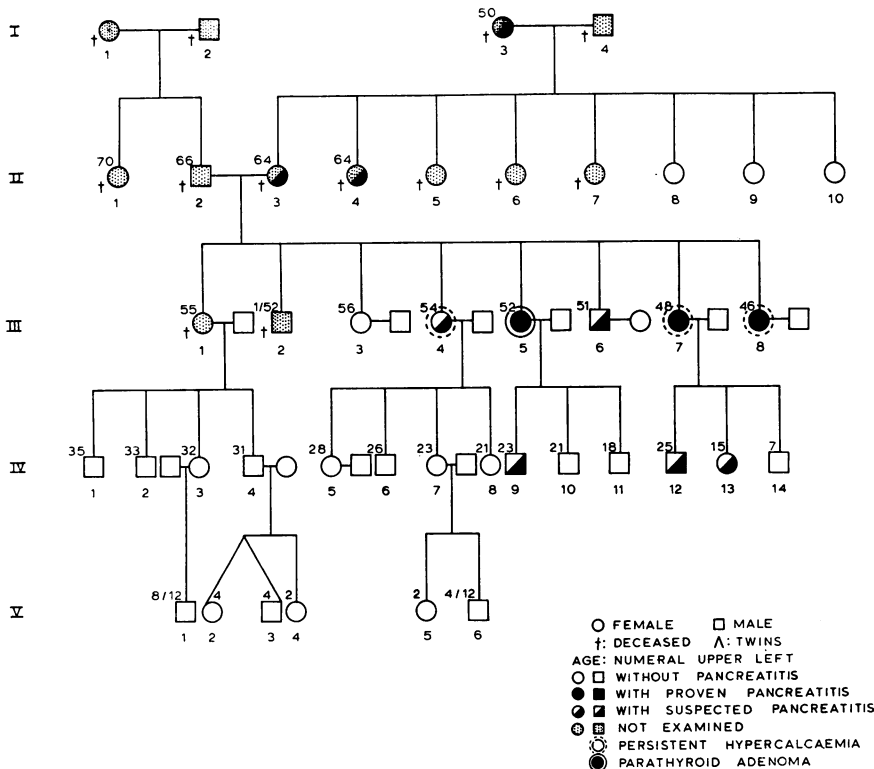


FIG. 1. Heredity of the family discussed in this paper in relation to both pancreatitis and parathyroid abnormalities.

roidism varies directly with investigatory diligence and published rates range from 7% to 19%. Chronic pancreatitis was present in a mother and her two sons in Jackson's (1957) original family of nine hyperparathyroid patients. In the same author's eighth family (Jackson and Boonstra, 1967) a 56-year-old housewife was found to have a raised serum calcium level and a parathyroid adenoma weighing 0.45 g was removed. A review of the patient's mother's record revealed that she had died of acute pancreatitis at the age of 73, had been normocalcaemic, but that an 'incidental' 0.5 cm oxyphil adenoma was found at necropsy.

The subject of the present report is a family we have studied since 1962 (Figure 1) in which there are three examples of chronic relapsing pancreatitis, all of whom are hypercalcaemic: neck explorations revealed a parathyroid adenoma in one (III-5) and normal parathyroids in the other (III-7). Two of these patients (III-7, III-8) had had surgery for pancreatitis several years before the calcium studies. Pancreatitis is suspected in eight other members, three of whom are dead, but only one (III-4) of those tested is hypercalcaemic.

MATERIALS AND METHODS

Kramer and Tisdall's (1921) method was used for the estimation of serum and urinary calciums; when high values were found the levels were checked using MacIntyre's (1961) flame photometric technique. Serum and urinary phosphates were measured after the method of King and Armstrong (1934). All hypercalcaemic patients were subjected to the cortisone suppression test of Dent (1956) which was continued for 10 days. The formula of Nordin and Frazer (1956) was used to calculate the urinary phosphate excretion index (PEI). In studying exocrine pancreatic function we used the evocative secretin-pancreozymin serum test of FitzGerald, FitzGerald, Fennelly, McMullin, and Boland (1963) and measured serum amylase and lipase according to the techniques of Myers, Free, and Rosinski (1944) and the modified Sigma-Tietz technique (Sigma Technical Bulletin, no. 800, 1963) respectively, the results being

reported in terms of milligrams of reducing sugar and millilitres of NaOH respectively.

Urines were screened for abnormal aminoaciduria by two-dimensional paper chromatography and for porphobilinogen with the Watson-Schwartz test (1941). The glomerular filtration rate (GFR) was estimated by endogenous creatinine clearance. Routine clinical procedures were used for the other investigations.

RESULTS

The case summaries of the four siblings found to have a serum calcium level of 11.0 mg% or more are shown in Tables Ia and Ib. Cases III-7 and III-8 had chronic pancreatitis proven at laparotomy and in the case of III-5 the diagnosis rests on firm historical, clinical, and biochemical grounds. A three-day fat balance and stool nitrogen excretion and glucose tolerance tests were normal in all four. The cortisone suppression tests failed to reduce the serum calcium levels significantly. Routine urinary screening tests for porphobilinogen excretion were negative but a significant lysine-cystine aminoaciduria was found in each case. Skeletal radiographs revealed nothing significant and pancreatic calcification was not detected.

During neck exploration a lower left parathyroid adenoma, 1.3 cm × .75 cm, was found in III-5 and removed. Clinical response was dramatic and serum and urinary calciums are now normal. During neck surgery on the proposita (III-7) only three parathyroids were identified and all except one fifth of one was removed. A recent serum calcium level was 8.6 mg%. Histology of the excised glands was normal. Their other two sisters have refused parathyroid surgery.

The suspicion of pancreatitis in the five members who are dead (I-3, II-3, II-4) is tenable on the statements of their surviving siblings and offspring. Hospital studies for prolonged dyspepsia and pain in all three had not proven fruitful. Case III-6 is an alcoholic; his recurrent bouts of abdominal pain are typical of pancreatitis. Physical examination

TABLE Ia

CLINICAL AND LABORATORY FEATURES LEADING TO THE DIAGNOSIS OF PANCREATIC DISTURBANCE IN FOUR MEMBERS OF THE FAMILY

No. in Pedigree	Sex and Age	Initial Serum Calcium (mg%)	Maximum Urinary Calcium (mg/24 hr)	PEI (normal ± 0.12)	GFR (normal 125 ml/min)	Aminoaciduria	Neck Exploration
III-4	F 54	11.0	463	0.250	115	Lysine-cystine	Not done
III-5	F 52	12.4	362	0.218	44.7 65.4	Lysine-cystine	Single left lower parathyroid adenoma
III-7	F 48	12.0	581	0.215	116.9	Lysine-cystine	3 normal parathyroids 2 and four-fifths removed Histology: normal
III-8	F 46	11.4	291	0.108	77.5 71.0	Lysine-cystine	Not done

TABLE Ib

LABORATORY DATA RELATING TO THE DIAGNOSIS OF PARATHYROID OVERACTIVITY IN THE HEREDITY OF THE FAMILY

No. in Pedigree	Sex and Age	Relevant Symptoms and History	Pancreatitis ¹	Comments and Associated Conditions
III-4	F 54	Recurrent pancreatic pain + flatulent dyspepsia since age of 6; worse during pregnancies; headaches frequent	<i>Suspected</i> 1 History + tenderness over pancreas 2 Spot serum amylases: 2.83 3.10	Previously jaundiced on 2 occasions Recent cholecystogram and barium meal (1965) normal
III-5	F 52	Typical pancreatic pain + abdominal tenderness for 36 yr, very severe during menstruation and in pregnancies Biparietal headaches + polyuria for 12 yr, dysuria and constipation for 3 yr 1944—euthyroid goitre noted 1956—renal colic due to a solitary calculus 1957-67—chronic pyelonephritis	<i>Definite</i> 1 History + physical examination 2 S—P test: amylase lipase 3.17 1.1 2.67 0.5 2.84 0.3 3.00 0.2 3 Relief of pain after parathyroidectomy	Small colloid goitre; renal insufficiency (blood urea 49 mg %, uric acid 6.8 mg %, viz. GFR) Clinical and biochemical response to parathyroidectomy Serum calcium 9.6 mg % Urinary calcium 55 mg/24 hours
III-7	F 48	Proposita: milk intolerance + pancreatic pain since childhood, worse during menses and in pregnancies; 10 lb weight loss Steatorrhoea + depression on first admission 1961—Laparotomy—nil found ?pancreas 1962—S-P test abnormal—chronic pancreatitis. Sphincterotomy + cholecystectomy 1966—Constant back pain—hypercalcaemia	<i>Definite</i> 1 History + physical examination 2 S-P test: amylase lipase 3.0 0.8 4.28 0.8 3.73 1.4 3.0 1.04 3 Positive laparotomy	Small cyst at thyroid isthmus removed Normochromic anaemia (Hb 10.4 g) postoperative serum calcium 12.5 mg % but level now 8.6 mg %.
III-8	F 46	Periodic pancreatic pain accompanied by syncope since childhood; milk intolerance, constipation and lassitude 1932—acute abdomen; treated expectantly 1964—laparotomy: partial gastrectomy for a 'tumour proved to be an encapsulated area of fat necrosis saddling lesser curvature 1966—S-P test abnormal Sphincterotomy and cholecystectomy Subacute pancreatitis postoperatively Hypercalcaemia	<i>Definite</i> 1 History and physical examination 2 S-P test: amylase lipase 3.0 0.5 3.78 0.6 4.44 0.9 4.67 0.7 3 Positive laparotomy	Thyroid normal anaemia mild (Hb 11.0 g) Serum amylase: 2.2 mg R.S./ml after laparotomy.

Amylase mg R.S./ml: 2.9 lipase STU/ml: 1.3 normal max.

showed widespread upper abdominal tenderness. A spot serum calcium, phosphate and amylase were normal.

In generation IV only those with complaints have been studied: calcium and amylase studies on IV-9, IV-12, and IV-13 were normal but in these the early onset of indigestion and abdominal pain and tenderness may be indicative of pancreatitis as gastroduodenal radiology was otherwise normal.

It is of interest that III-3 was found to have a toxic goitre in 1959 and was treated with ¹³¹I. During a cholecystectomy for cholelithiasis in 1963, the pancreas was palpably normal. A recent serum calcium level was 10.3 mg%. The Table indicates that III-5 and III-7 also had small goitres.

DISCUSSION

In this family there is a ready explanation for chronic pancreatitis in those members with hypercal-

caemia. However, in those who survive with suspected pancreatitis the explanation is not easily apparent. If III-6 proves to have definite pancreatitis, his long history of alcoholism is the most likely precipitating cause as the serum calcium level is normal. One interesting finding in all those examined with pancreatitis was lysine-cystine aminoaciduria, a feature reported in 50% of the individuals in families with hereditary pancreatitis originally described by Comfort and Steinberg (1952) and recently summarized by Gross, Ulrich, and Maher (1962) which feature has hitherto been confined to six families under observation at the Mayo Clinic. We have not found any evidence in the present series of the severe pancreatic endocrine and exocrine insufficiency which is mentioned as typical of the latter condition, nor have we found the heavy pancreatic calcification which, in the adult in the absence of alcoholism, is nearly a *sine qua non* for

the diagnosis of hereditary pancreatitis. Two possible explanations for the aminoaciduria in the present kindred is the independent coexistence of the incompletely recessive form of lysine-cystinuria (Harris, Mittwoch, Robson, and Warren, 1955) or it may be due to hypercalcaemic renal glomerulotubular damage as evidenced by an impaired GFR in two patients (Table Ib). The absence of radiological bone change in the presence of hyperparathyroidism may be attributable to increased calcium intake and/or absorption which is able to balance the urinary calcium loss. We found that the Ca^{++} content of the water from the district this family lived in, a limestone area, was 1.48 m-equiv/litre which is 20 times the calcium content of London drinking water.

In agreement with what Jackson and Boonstra (1967) have drawn attention to we have found that three individuals in this family had goitres; one patient developed hyperthyroidism. Perhaps in this family we are also dealing with hereditary endocrine adenomatosis, although evidence of other glandular involvement is wanting.

SUMMARY

A family with hereditary hyperparathyroidism and relapsing chronic pancreatitis is described. Parathyroid pathology was found in only one member. In another, subtotal resection of the parathyroids was carried out, causing a fall in serum calcium to a hypoparathyroid level. Two other hypercalcaemic members with pancreatitis have declined further study or surgery.

Drs Ailish Forristal (Kilkenny), Thomas P. Walsh (New Ross), and Michael G. O'Brien (Inistioge) assisted us considerably in studying this family. Professor Patrick

FitzGerald carried out both neck explorations and Dr Robert Towers reviewed all the histological specimens. This study was carried out during the tenure of a full-time research fellowship of the Medical Research Council of Ireland awarded to one of us (M.C.C.).

Reprint requests to be sent to O.F.

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