α_1 Antitrypsin Deficiency in Chronic Liver Disease, and a Report of Cirrhosis and Emphysema in Adult Members of a Family

P. KUMAR, M. LANCASTER-SMITH, P. COOK,
A. STANSFELD, M. L. CLARK, A. M. DAWSON

British Medical Journal, 1974, 1, 366-367

The association of α_1 -antitrypsin deficiency with chronic obstructive lung disease (Laurell and Eriksson, 1963; Eriksson, 1965) and infantile liver disease (Sharp *et al.*, 1969; Porter *et al.*, 1972) is well recognized. More recently deficiency of this glycoprotein has been shown in a small number of patients with onset of cirrhosis apparently during adult life. (Berg and Eriksson, 1972; Cohen *et al.*, 1973; Campa *et al.*, 1973; Palmer *et al.*, 1973). Cytoplasmic periodic-acid Schiff (P.A.S.)-staining granules seen in liver sections pretreated with diastase, which react with antibodies against α_1 -antitrypsin, are characteristic of α_1 -antitrypsin deficiency even in the absence of other liver disease (Sharp, 1971). Children with cirrhosis associated with α_1 -antitrypsin deficiency rarely survive into adult life. We therefore report the discovery of the above histological features in an adult cirrhotic patient with a childhood history of liver disease, who has subsequently been found to have α_1 -antitrypsin deficiency. In view of the known autosomal recessive mode of inheritance of α_1 -antitrypsin deficiency (Sharp *et al.*, 1969) the patient's family was also studied. In order to study the overall incidence of α_1 -antitrypsin deficiency serum concentrations were estimated using M Partigen plates (Behringwerke Ltd.) in a group of patients with chronic liver disease.

Case Report

A young man aged 25 (subject III 1), the only child of English parents, had had prolonged jaundice six weeks after birth and at the age of 5 was noted to have hepatosplenomegaly on routine preschool examination. He remained in good health until he had a haematemesis when he was 16 and was found to have a splenomegaly of 17 cm, hepatomegaly of 4 cm, and Cruveilhier-Baumgarten syndrome and corneal arcs were noted. Investigation showed oesophageal varices on barium swallow, a serum bilirubin of 3.6 mg/100 ml, alkaline phosphatase 20 King-Armstrong units/100 ml, and serum albumin 2.9 g/100 ml. An end-to-side portocaval anastomosis was performed, and gross cirrhosis of the liver found at operation was confirmed histologically. Investigations for Wilson's and glycogen storage diseases were negative. He subsequently had intermittent haematuria and a persistently raised blood urea and reduced creatinine clearance, though intravenous pyelography was normal. Lung function tests, including the transfer factor, were within the normal range. Recent review of liver biopsy sections pretreated with diastase and stained with P.A.S. showed the typical cytoplasmic inclusion bodies of α_1 -antitrypsin deficiency. Serum α_1 -antitrypsin concentration was in the severely deficient range (fig. 1) and starch-gel electrophoresis (Fagerhol, 1969) showed the Pi Z phenotype. At present the patient remains fairly well on diuretic therapy and works full time.

St. Bartholomew's Hospital, London EC1A 7BE

P. KUMAR, M.B., M.R.C.P., Lecturer in Gastroenterology
A. G. STANSFELD, F.R.C.PATH., Reader in Histopathology
M. L. CLARK, M.D., M.R.C.P., Senior Lecturer in Medicine
A. M. DAWSON, M.D., F.R.C.P., Consultant Physician

London Hospital, London E.1

M. LANCASTER-SMITH, M.B., M.R.C.P., Senior Registrar

M.R.C., Human Biochemical Genetics Unit, University College,
London W.C.1

P. COOK, M.B., Scientific Officer

FIG. 1—Serum concentrations of α_1 -antitrypsin. Miscellaneous column includes: extrahepatic portal hypertension (two patients), hydatid cyst (one patient), Gaucher's disease (one patient), and obstructive jaundice (one patient).

Family Study.—The proband's father (subject II 1), aged 56, had an eight-year history of emphysema, and lung function studies showed severe obstructive airways disease. Liver function tests and plasma albumin were normal. He had severe α_1 -antitrypsin deficiency (fig. 1) with Pi Z phenotype (fig. 2). The proband's mother (subject II 2) and paternal grandmother (subject I 2) had no evidence of liver or pulmonary disease and had the Pi MZ phenotype (figs. 1 and 2).

FIG. 2—Pedigree of family showing α_1 -antitrypsin deficient subjects with emphysema and cirrhosis.

Chronic Liver Disease Patients.—Thirty adult patients were studied (16 men, 14 women). The aetiologies of the liver conditions, numbers in each group, and the serum concentrations of α_1 -antitrypsin are shown in fig. 1. Other than subject III 1, who had α_1 -antitrypsin deficiency, all the patients with liver disease had normal or comparatively high levels of α_1 -antitrypsin, which agrees with previous studies (Sharp *et al.*, 1969; Lieberman and Mittman, 1970). Their serum albumin levels varied from 2.7 to 4.3 g/100 ml but there was no correlation with α_1 -antitrypsin concentrations, which confirms the findings of Sharp *et al.* (1969).

Comment

Berg and Eriksson's (1972) retrospective survey of necropsy material from adults with α_1 -antitrypsin deficiency suggests that hepatic fibrosis and cirrhosis is commonly found in this condition. In contrast, the small number of adult cirrhotic

patients with α_1 -antitrypsin deficiency reported to date (Ishak *et al.*, 1972; Berg and Eriksson, 1972; Cohen *et al.*, 1973; Campra *et al.*, 1973; Palmer *et al.*, 1973) and the fact that in most of them liver disease was unsuspected or discovered fortuitously, unlike our patient, imply that it is a rare cause of symptomatic cirrhosis in adults. Nevertheless, α_1 -antitrypsin deficiency should be considered in adult cirrhotic patients with unusual pathological features and when there is no other obvious aetiology. Suspicion should also be raised when there is a history of hepatic disease in infancy or childhood, as seen in our patient and the case reported by Ishak (1972), even though it is apparently very rare for such children to survive into adult life. Homozygous or heterozygous deficiency of α_1 -antitrypsin will be common among close relatives of such patients, as shown by our family study. Recognition of these subjects in affected families is probably important, since avoidance of contributory causes of obstructive airways disease, such as smoking, may prevent or halt the progress of the condition. This may also apply to alcohol with respect to the liver, but at present the prognosis of hepatic disease in adults is unknown and it is only

by identification and follow up of these patients that further knowledge will be obtained.

References

- Berg, N. O., and Eriksson, S. (1972). *New England Journal of Medicine*, 287, 1964.
 Campra, J. L., Craig, J. R., Peters, R. L., and Reynolds, T. B. (1973). *Annals of Internal Medicine*, 78, 233.
 Cohen, K. L., Rubin, P. E., Echevarria, R. A., Sharp, H. L., and Teague, P. O. (1973). *Annals of Internal Medicine*, 78, 233.
 Eriksson, S. (1965). *Acta Medica Scandinavica*, 177, Suppl. 1.
 Fagerhol, M. K. (1969). *Scandinavian Journal of Clinical Laboratory Investigation*, 23, 97.
 Ishak, K. G., Jenis, E. H., Marshall, M. L., Bolton, B., and Battistone, G. C. (1972). *Archives of Pathology*, 94, 445.
 Laurell, C. B., and Eriksson, S. (1963). *Clinical Laboratory Investigation*, (1963) 15, 132.
 Leiberman, J., and Mittman, C. (1970). *Annals of Internal Medicine*, 73, 9.
 Palmer, P. E., Wolfe, H. J., and Gherardi, G. J. (1973). *Gastroenterology*, 65, 284.
 Porter, C. A., *et al.* (1972). *British Medical Journal*, 3, 435.
 Sharp, H. L. (1971). *Hospital Practice*, 6, 83.
 Sharp, H. L., Bridges, R. A., Krivit, W., and Freier, E. F. (1969). *Journal of Laboratory and Clinical Medicine*, 73, 934.

Cure of Insulin-dependent Diabetes Mellitus by Removal of a Glucagonoma

S. L. LIGHTMAN, S. R. BLOOM

British Medical Journal, 1974, 1, 367-368

Exogenous glucagon can cause diabetes mellitus in some animals (Salter *et al.*, 1969; Frey *et al.*, 1972) but this has never been satisfactorily shown in man. Pancreatic glucagonomas have previously been reported in association with diabetes mellitus (McGavren *et al.*, 1966; Yoshinaga *et al.*, 1966) but these cases had extensive pancreatic involvement and resection of the tumour proved impossible. Thus it is still unknown whether diabetes in man can be caused by raised plasma glucagon levels.

We report on a patient who presented with insulin-dependent diabetes mellitus and a dermatosis which appeared to be specifically associated with islet-cell tumours. The resection of a glucagonoma together with three-quarters of her pancreas resulted in the disappearance of the rash and the return to near-normal of her glucose tolerance.

Case Report

A 50-year-old housewife presented in 1969 with perineal irritation. There was no family history of diabetes mellitus and glycosuria was not found. A candida infection was successfully treated but returned in 1970 together with perineal intertrigo. Glycosuria was detected and a 50-g oral glucose tolerance test was performed. The results were found to be normal and it was noticed that she had a low renal threshold for glucose.

Her rash became rapidly worse and spread to her fingers and shins, where the red, scaly eruption proved refractory to treatment. The dermatosis followed a relapsing course and in January 1973 the patient began to lose weight. She then presented with extensive intertrigo of the groin, perineum, and buttocks, together with exfoliating lesions of the palms and fingers and papules over the elbows and shins. She also complained that her tongue felt sore, and on examination it was seen to be smooth and shiny and vermilion.

The patient again had glycosuria, and a random blood sugar was 230 mg/100 ml. The haemoglobin was 11.4 g/100 ml with normal indices, E.S.R. 18 mm in the first hour, and the alkaline phosphatase, bilirubin, SGOT, vitamin B₁₂, and folic acid were all normal. Chlorpropamide did not control her diabetes mellitus and she was put on soluble insulin 40 units/day in divided doses. This dose had to be rapidly increased during the next two months (table I), during which time she had frequent fasting blood sugars above 200 mg/100 ml. At no time was any ketonuria detected.

TABLE I—Antidiabetic Therapy

Date	Drug	Route	Diet
12/1/73	Chlorpropamide 250 mg every morning	Oral	140 g carbohydrate orally
16/1/73	Chlorpropamide 500 mg every morning	Oral	"
20/1/73	Sol. insulin 40 U/day	Subcutaneous	"
18/2/73	Sol. insulin 48 U/day	Subcutaneous	"
3/3/73	Sol. insulin 68 U/day	Subcutaneous	"
6/3/73	Operation		
6/3/73	Sol. insulin 36 U/day	Intravenous infusion	125 g carbohydrate as i.v. dextrose
7/3/73	Sol. insulin 24 U/day	Intravenous infusion	"
11/3/73	Sol. insulin 16 U/day	Intravenous infusion	"
12/3/73	Sol. insulin 18 U/day	Subcutaneous	130 g carbohydrate orally
16/3/73	Glibenclamide 15 mg/day	Oral	"
22/3/73	Glibenclamide 10 mg/day	Oral	"
28/3/73	Glibenclamide 5 mg/day	Oral	"
30/3/73	None		

A tentative diagnosis of a pancreatic tumour was made, based on the similarity of this case to three previously-described cases of pancreatic tumour, which were associated with a red raw tongue, an intractable rash, and diabetes mellitus of recent onset (Becker *et al.*, 1972; Church and Crane, 1967; Wilkinson, 1971). Investigation of her exocrine pancreatic function was performed by an intravenous

Plymouth General Hospital, Plymouth PL4 8QQ

S. L. LIGHTMAN, M.F., B.CHIR., House Surgeon (Present address: Hammersmith Hospital, London W12 0HS)

Institute of Clinical Research, Middlesex Hospital Medical School, London W1P 7DE

S. R. BLOOM, M.A., M.R.C.P., Research Registrar