Case reports

Hypobetalipoproteinaemia—a variant of the Bassen-Kornzweig syndrome

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SUMMARY A patient is reported with hypobetalipoproteinaemia and clinical features resembling the Bassen-Kornzweig syndrome (abetalipoproteinaemia) more completely than previously described. This supports a link between hypobetalipoproteinaemia and abetalipoproteinaemia and it is suggested that the Bassen-Kornzweig syndrome has a wide spectrum with serum betalipoprotein ranging from absent to normal. It is likely that there are different genetic entities with similar end results.

Absent serum β -lipoprotein (abetalipoproteinaemia) is usually associated with the Bassen-Kornzweig syndrome (Bassen and Kornzweig, 1950) which, in its complete form, is characterised by a Friedreich's type ataxia, acanthocytosis, steatorrhoea, fat-loading of the small-intestinal enterocytes, and atypical retinitis pigmentosa.

Reduced, but not absent, serum β -lipoprotein (hypobetalipoproteinaemia) is not usually associated with clinical illness, being detected on routine screening, but investigation of asymptomatic subjects has, on occasions, revealed acanthocytosis (Biemer and McCammon, 1975) and fat-loading of enterocytes (Cottrill *et al.*, 1974). However, of the 17 families reported (Kuo and Bassett, 1962; van Buchem *et al.*, 1966; Critchley *et al.*, 1968; Mars *et al.*, 1969; Richet *et al.*, 1969; Mawatari *et al.*, 1972; Aggerbeck *et al.*, 1974; Cottrill *et al.*, 1974; Biemer and McCammon, 1975; Glueck *et al.*, 1976; Sigurdsson *et al.*, 1977), five have one or two members with neurological disease and three of these families have a member with additional features of the Bassen-Kornzweig syndrome: one had ataxia, acanthocytosis, and fat-loading of jejunal enterocytes (Mars *et al.*, 1969); one had neuropathy, acanthocytosis, steatorrhoea, and retinitis (Kuo and Bassett, 1962); and one had ataxia and acanthocytosis (Critchley *et al.*, 1968). Since both hypo- and a-betalipoproteinaemia have been described within three families (Salt *et al.*, 1960; Cottrill, *et al.*, 1974; Biemer and McCammon, 1975), hypobetalipoproteinaemia may

well be a variant of the Bassen-Kornzweig syndrome, although the modes of inheritance may nevertheless be different (Cottrill *et al.*, 1974; Biemer and McCammon, 1975) and it is possible that the abetalipoproteinaemia which occurs in families with hypobetalipoproteinaemia may be a different condition from that which occurs alone.

Normal levels of serum α -lipoprotein have also been reported in association with acanthocytosis and neurological disease in five families (Estes *et al.*, 1967; Critchley *et al.*, 1968; Critchley *et al.*, 1970; Aminoff, 1972; Lowe *et al.*, 1977). Although the neurological disorder is dissimilar to that characteristically found in the Bassen-Kornzweig syndrome—involuntary movements being prominent in some, others being asymptomatic—it may also be a variant of the syndrome, as in two of the families hypobetalipoproteinaemia also occurred and in one of these families it was associated with typical ataxia (Estes *et al.*, 1967; Critchley *et al.*, 1968).

Thus the Bassen-Kornzweig syndrome may have a wider spectrum than is usually considered and serum betalipoprotein may range from absent to normal. In support of this we report a patient with hypobetalipoproteinaemia clinically resembling the Bassen-Kornzweig syndrome more completely than previously described.

Case report

The male patient was born in 1922. He did not walk until aged 4 years and as a child was always clumsy and unable to take part in sport. His speech had always been slurred. In childhood he had very loose bowel motions, a diagnosis of coeliac disease was

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made and he was treated with a low fat diet. His gait had gradually deteriorated and since 1974 he has required a stick for walking and a wheelchair for long journeys. Since 1975 he has complained of a burning sensation in the feet. He has received methixene (5 mg tds) regularly since 1965 with no noticeable effect. In 1972 he was referred for investigation of severe incapacitating diarrhoea that was worse after fatty food, his bowels being opened as often as seven times a day and the motion being pale, loose, fatty, and with a tendency to float. He was found to have steatorrhoea (faecal fat 70 mmol/24 h; normal <18), indicanuria (urinary indican 0.85 mmol/day; normal <0.47), a low serum folate, and a flat lactose tolerance test. Jejunal biopsies showed no villous atrophy. Stereomicroscopy showed white villi, and histology showed vacuolation of the enterocytes of the upper third of villi. Jejunal mucosal lactase activity was reduced. He was treated with both tetracycline and a lactose-free diet and after two weeks faecal fat had fallen to 31 mmol/24 h. There was a corresponding dramatic improvement in his bowel action, his bowels being opened no more than once daily and the motion being formed. After six months he resumed a normal lactose-containing diet with no recurrence of symptoms. In 1976 his plasma vitamin E level was found to be undetectable and Ephynal (tocopherol acetate) 100 mg tds was prescribed. Although there was subjective improvement, in that he volunteered that he felt much better and that he was taking more interest in things, there was no apparent neurological improvement. Two months later, in 1977, he was readmitted for further assessment.

On examination abnormalities were confined to the nervous system. He was mildly dysarthric and the gait was ataxic. The cranial nerves were normal; there was no nystagmus, ophthalmoscopy showed no evidence of retinitis pigmentosa, and dark adaptation was normal. In the arms, power and tone were slightly reduced and tendon reflexes were absent. There was finger-nose ataxia. Appreciation of deep pain and vibration was impaired; temperature, pin prick, and light touch appreciation were intact. In the legs, there was proximal muscle weakness and reduced tone. Knee jerks were absent but ankle jerks and plantar responses were normal. There was heel-shin ataxia. Appreciation of temperature and deep pain was normal but vibration and position sense were absent. Appreciation of light touch and pin prick was impaired below the ankles. Abdominal reflexes were present. These neurological abnormalities were thought suggestive of a posterior column lesion, cerebellar disease, peripheral neuropathy, and a proximal myopathy.

The results of investigation were as follows:

HAEMATOLOGY

Haemoglobin was 13.1 g/dl; white cells $3.3 \times 10^9/l$; platelets $130 \times 10^9/l$; film—5% of red cells were irregular with some typical acanthocytes; the ESR was 1 mm/h; serum folate 5.0 $\mu g/l$ ($N > 3.0$); red cell folate 125 $\mu g/l$ ($N > 160$); serum B_{12} 120 ng/l ($N > 110$); Schilling test—18% of oral ^{58}Co . B_{12} excreted in urine in 24 hours ($N > 12$); serum iron was 12 $\mu mol/l$ ($N > 11$); serum total iron binding capacity 69 $\mu mol/l$ ($N < 80$); prothrombin time was 12 seconds (control 12 seconds).

SERUM BIOCHEMISTRY

Albumin was 33 g/l ($N > 37$); urea and electrolytes were normal; vitamin E (while taking Ephynal) was 6 $\mu mol/l$ ($N > 12.2$); vitamin A 0.6 mmol/l ($N > 1.05$); carotene 0.076 mmol/l ($N > 0.74$).

CALCIUM STUDIES

Serum calcium was 2.19 mmol/l adjusted for albumin (Payne *et al.*, 1973) ($N > 2.25$); serum phosphate was 1.08 mmol/l ($N = 0.5 - 1.3$); serum alkaline phosphatase 9.9 KA units ($N < 13$); urinary calcium 2.84 mmol/24 h ($N = 1.25-10.0$); serum 25-hydroxy-cholecalciferol 4.6 ng/ml ($N = 3.5-30$); intravenous vitamin D test (Whittle *et al.*, 1969)—serum phosphate increased by 20%; radiographs of the lumbar spine showed a generalised loss of bone density and anterior wedging of D12 that was suggestive of metabolic bone disease; iliac crest bone biopsy showed osteomalacia.

BLOOD LIPID STUDIES

Plasma lipid and lipoprotein concentrations for the patient and the two first degree relatives are given in the Table. Electrophoresis of the patient's serum on agarose gel revealed a faint band due to β -lipoprotein

Table Blood lipid concentrations*

	Propositus	Son	Brother
Plasma triglyceride	0.51 (0.11-2.14)	1.65 (0.11-1.58)	2.14 (0.11-1.80)
Plasma cholesterol	1.20 (4.13-8.53)	4.30 (3.10-6.20)	5.25 (3.88-8.01)
VLDL—cholesterol	0.40 (0.26-1.03)	0.60 (0.13-0.65)	1.02 (0.13-0.90)
LDL—cholesterol	0.46 (2.07-5.43)	2.53 (1.55-4.39)	2.77 (2.07-4.91)
HDL—cholesterol	0.39 (0.78-1.68)	0.94 (0.90-1.81)	1.56 (0.78-1.68)
Apolipoprotein—B(g/l)	0.35 (0.6-1.3)	0.98 (0.6-1.3)	1.08 (0.6-1.3)

*All lipid concentrations are expressed in mmol/l, and for comparison, age-related normal ranges suggested by Fredrickson *et al.* (1978) are quoted in parentheses. The suggested normal range for apolipoprotein B concentration is that of Durrington, P. N. (personal communication). VLDL: very low density lipoprotein. LDL: low density lipoprotein. HDL: high density lipoprotein.

and the findings of appreciable, albeit markedly reduced, concentrations of low density lipoprotein cholesterol and apolipoprotein B confirm the diagnosis of hypobetalipoproteinaemia rather than abetalipoproteinaemia. High density lipoprotein cholesterol concentration was also reduced.

The activity of the enzyme lecithin:cholesterol acyltransferase (LCAT) was assayed in the patient's plasma by a method similar to that of Glomset and Wright (1964). The principal modifications were pre-incubation of the labelled albumin suspension with the pooled substrate plasma for four hours and reduction of incubation volumes to 1 ml. The value was 23 nmol cholesterol esterified per ml plasma per hour. This activity may be compared with the range of activities of 58-70 found in the plasma from the patient's son and brother and two other normal subjects assayed at the same time.

TESTS OF SMALL-INTESTINAL STRUCTURE AND FUNCTION

Xylose absorption test—17% of a 5 g oral dose of xylose was excreted in the urine in five hours ($N > 22\%$); the lactose tolerance test was flat; faecal fat (on tetracycline) was 23 mmol/24 h ($N < 18$); urinary indican 1.02 mmol/24 h ($N < 0.47$); Lundh pancreatic function test showed normal tryptic activity; jejunal juice bacteriology was negative; jejunal juice aliphatic acids were not detected; small bowel enema showed dilated small bowel with thickened mucosal folds, peristalsis was normal but transit was moderately slowed; upper gastrointestinal endoscopy showed a normal oesophagus and stomach but the appearance of the duodenum was strikingly abnormal, being diffusely white as described in detail previously (Mitchell *et al.*, 1978); small-intestinal biopsies obtained after an overnight fast with a hydraulic multiple biopsy capsule showed on stereomicroscopy white villi, the whiteness being concentrated at the villous surface. There were also white fatty particles in the intervillous spaces. Histology showed normal villous and crypt architecture but the epithelial cells of the upper thirds of villi were vacuolated; fat stains of frozen sections showed that these vacuolated cells were loaded with fat, fat being virtually absent from the lamina propria (Figs. 1 and 2).

NEUROMUSCULAR STUDIES

Nerve conduction was impaired in sensory nerves of arms and legs; assessment of pattern-evoked visual response was normal; serum creatine kinase was normal; as was the electrocardiograph.

LIVER AND IMMUNOLOGICAL TESTS

Serum ALT varied from 50 to 300 IU/l ($N < 40$);

Fig. 1 Photomicrograph, showing fat-loading of enterocytes of upper part of villi and virtually no fat in the lamina propria. Oil red O and Sudan Black B. Approx. $\times 400$ (original magnification).

serum smooth muscle antibody test was positive; serum mitochondrial antibody test negative; serum antinuclear antibody test negative; serum IgG and IgA normal; serum IgM 3.46 g/l ($N < 2.5$); serum caeruloplasmin 0.34 g/l ($N = 0.20-0.34$); serum α_1 antitrypsin 3.22 g/l ($N = 2.0-4.0$); HBsAg negative; liver scintiscan was normal; liver biopsy histologically normal with no steatosis.

Treatment with tetracycline, Ephynal, and methixene was continued and, in addition, the osteomalacia was treated with 100 000 units of vitamin D intramuscularly at monthly intervals. The serum calcium became normal (2.27 mmol/l) after two months. He volunteered that he felt much better on this treatment, having more confidence on walking. However, no objective improvement was apparent and the time taken to rise from a chair 10 times did not improve significantly, which suggested that there was no improvement in the proximal myopathy.

Fig. 2 Photomicrograph, showing vacuolation of enterocytes of upper part of villi. H and E, approx. $\times 400$.

FAMILY STUDY

Both parents are dead. He has one sibling and he and his brother have one son each. Only the son of the patient (aged 28 years) and the brother (aged 48 years) were available for examination. Both were asymptomatic and on direct questioning there was no suggestion of steatorrhoea, lactose intolerance, poor dark adaptation, or neurological disease. Physical examination, including a detailed neurological examination and ophthalmoscopy, was negative. Blood films showed no acanthocytosis. Serum vitamin A, vitamin E, and carotene were normal. Blood lipids are shown in the Table. There was no evidence of betalipoprotein deficiency; indeed, the brother has mild type IV hyperlipoproteinaemia (Beaumont *et al.*, 1970) according to the criteria used (Fredrickson *et al.*, 1978).

Discussion

COMMENT ON PRESENT CASE

The neurological findings in our patient are fairly typical of those found in the Bassen-Kornzweig syndrome except that, in addition, he may have had a

proximal myopathy due to osteomalacia consequent upon malabsorption. Steatorrhoea is also characteristic of the syndrome but in our patient it may have been due partly to bacterial contamination of the small intestine, as steatorrhoea improved on treatment with tetracycline. This contamination may have resulted from slowed intestinal transit associated with the neurological disorder, although this has not been described previously. Alactasia may also have contributed to the steatorrhoea and, interestingly, this abnormality has previously been found in abetalipoproteinaemia (Yuill *et al.*, 1976). An underlying defect of fat transport across the small-intestinal mucosa was probably responsible for the steatorrhoea remaining after treatment with tetracycline and a lactose-free diet, as fat loading of enterocytes was apparent with virtual absence of fat from the lamina propria. This histological appearance is very typical of the Bassen-Kornzweig syndrome with abetalipoproteinaemia and has also been described in hypobetalipoproteinaemia (Mars *et al.*, 1969; Cottrill *et al.*, 1974). The endoscopic and stereomicroscopic appearances of the mucosa have not been described previously, although they are striking and presumably reflect the fat-loading of the villous enterocytes. The acanthocytes were typical of those seen in the Bassen-Kornzweig syndrome but they were much less numerous than usually found with abetalipoproteinaemia.

The reduced LCAT activity which we have observed, and which others have observed in abetalipoproteinaemia (Herbert *et al.*, 1978), is probably due in part to reduced amounts of circulating enzyme, as it is apparent when substrate lipoproteins derived from the plasma of normal subjects are present in the assay system. The cause of the reduced LCAT activity is uncertain. Liver disease is a common cause of secondary LCAT deficiency, but our patient has little evidence of this. Patients with intestinal malabsorption (Miller and Thompson, 1973) or reduced turnover of triglyceride-rich lipoproteins (Miller, 1979), both probably present in our patient, also frequently have reduced LCAT activity.

GENETICS

The inheritance of the Bassen-Kornzweig syndrome is not fully understood. The marked clinical resemblance of our patient to those with abetalipoproteinaemia strengthens the likelihood of a link between some patients with abeta- and hypobeta-lipoproteinaemia. It has been suggested that abetalipoproteinaemia is inherited as an autosomal recessive and that hypobetalipoproteinaemia is a separate condition inherited as an autosomal dominant. However, as both conditions occur in the

same family (Salt *et al.*, 1960; Cottrill *et al.*, 1974; Biemer and McCammon, 1975), it may be that abetalipoproteinaemia in this setting represents a homozygous state for the dominant gene. Thus the homozygote may have abetalipoproteinaemia and the heterozygote may have either hypo- or normobetalipoproteinaemia. The neurological and red cell features of the Bassen-Kornzweig syndrome may not be directly related to the lipid abnormality as they may occur in family members with normal serum lipids, and acanthocytes from patients with abetalipoproteinaemia maintain their abnormal morphology when incubated with normal serum (Cooper and Gulbrandsen, 1971). The possibilities should be considered, therefore, that these abnormalities are either produced by a closely associated genetic abnormality, or that both are reflections of a more basic underlying defect and require some additional factors for their expression.

PATHOGENESIS

Impaired secretion by the liver and intestine of lipoproteins containing apolipoprotein B probably underlies the intestinal malabsorption and the plasma lipoprotein abnormalities seen in abeta- and hypobeta-lipoproteinaemia. The mechanism for the other clinical features is unknown. They are unlikely to be a consequence of LCAT deficiency as they are not observed in familial LCAT deficiency (Gjone, 1974).

TREATMENT

The three main problems requiring treatment are the neurological disorder, the retinitis, and the steatorrhoea. As the neurological changes and retinitis may be irreversible, any treatment should be given as early as possible and continued indefinitely. Vitamin E deficiency is usually marked and prolonged treatment with this vitamin may halt progression of the neurological disorder and retinitis (Muller *et al.*, 1977). Vitamin E therapy may also restore *in vitro* resistance to haemolysis (Dodge *et al.*, 1967) but does not prevent acanthocytosis. Vitamin A is also usually deficient and its effect on retinal function is well known. Correction of deficiency may improve retinal function (Mills *et al.*, 1977) but the retinitis does not appear to improve. Supplements of linoleic acid—for example, 7 g corn oil daily—may halt neurological deterioration (Muller *et al.*, 1977). Infusions of LDL have been tried but no response has been seen in the short term. The effect of repeated infusions over a long period has not been assessed. The steatorrhoea may be troublesome and other causes should be sought as illustrated in our report. Similarly, other deficiencies consequent upon the malabsorption should be assiduously sought and

corrected. A low fat diet improves the steatorrhoea but may accentuate any nutritional deficiency (Losowsky *et al.*, 1974). Medium chain triglyceride supplements, although sometimes recommended, possibly should not be given since they may exacerbate malabsorption of long chain fat (Muller *et al.*, 1977) and perhaps also lead to cirrhosis (Partin *et al.*, 1974).

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