Gut Lesions in Fabry's Disease Without a Rash

D. M. FLYNN*, B. D. LAKE, C. B. BOOTHBY†, and ELISABETH P. YOUNG

From The Hospital for Sick Children and the Institute of Child Health, Great Ormond Street, London

Flynn, D. M., Lake, B. D., Boothby, C. B., and Young, E. P. (1972). *Archives of Disease in Childhood*, 47, 26. **Gut lesions in Fabry's disease without a rash.** Twin boys with Fabry's disease and 6 affected relatives were described. Limb pains and retinal vessel tortuosity were present but no patient had angiokeratomata. One boy had a severe enteropathy with small and large bowel involvement which was investigated. Thin-layer chromatography showed that excesses of ceramide di- and trihexosides were excreted in the urine. Leucocyte α -galactosidase activity was measured: hemizygous males showed very low activity, while obligate and probable heterozygous females had values intermediate between those of the patients and the normal controls.

Fabry's disease first described by Anderson (1898) and Fabry (1898), is an X-linked disorder of lipid metabolism shown to be caused by a deficiency of ceramide trihexosidase (Brady *et al.*, 1967). This deficiency results in the accumulation of ceramide trihexoside in many sites and produces a varying clinical picture with severe symptoms in some patients and no symptoms in others. The commoner clinical features are the rash of angiokeratoma corporis diffusum, extremity limb pains, renal failure, hypertension, and premature cerebrovascular disorders, but none is invariably present. Gut lesions are rare. It is rarely diagnosed in childhood in the absence of a family history or rash to suggest it. We present twin boys and 6 affected relatives with Fabry's disease, without a rash but with evidence of gut pathology. We also confirm that the diagnosis may be made by thin-layer chromatographic examination of urine sediment and by studying leucocyte α -galactosidase activity.

Case Histories

Twin boys of similar appearance were seen at age 10 years because of cramps in the legs for 5 years. The cramps were more frequent in hot weather and were inconstantly precipitated by exercise and pyrexia, exacerbated by the presence of the other twin, and relieved by hospitalization, and by cooling the legs e.g. by placing them outside the bedclothes. Initially the cramps occurred every few weeks and lasted a few hours but became more frequent and more severe. Both boys had mild deafness due to secretory otitis. Stuttering

and educational handicaps were present. The birth-weights were 2.3 kg (D., first twin) and 1.69 kg (A., second twin). At age 9 the IQ of D. was 76 and of A. was 58.

The twins were observed for five years and the cramps continued. No clinical or biochemical evidence was found to support diagnoses of peripheral neuropathy, hypoparathyroidism, hypokalaemia, or McArdle's syndrome, and therapy with salt, diphenhydramine, and calcium gluconate was ineffective. Though at age 8 years the weights and heights of both twins were on the 50th centile, their ranking gradually fell, and at age 14½ years D., the firstborn but now the smaller, was 142 cm, and A. was 148 cm (3rd centile).

Patient A. (Twin II). At 14½ years of age, A. developed lethargy, pallor, and pyrexia, and lost weight from 39 kg (10th centile) to 31 kg, and was admitted to hospital. For the first time the cramps were described as burning pains and were also present in the hands. Shortly after admission he began to pass two or three loose stools a day.

On examination (Fig. 1a) he was pale and pyrexial (38.5 °C) and complained of frequent limb pains. His lips were somewhat thickened and parted. There was slight palmar erythema but no rash. Careful examination before and after the diagnosis was established failed to reveal any evidence of angiokeratomata. There was no sexual hair and no penial or testicular enlargement. The retinal arteries showed marked tortuosity but the conjunctival vessels were normal. Slit-lamp examination showed a slight corneal haze. The blood pressure varied between 110–135/70–90 mmHg in the right arm and 105–115/79–90 mmHg in the left arm. Tone, power, co-ordination, and sensation and deep reflexes were normal. There was no calf tenderness.

Hb was 10 g/100 ml and a film showed a slight anisocytosis. Total WBC 10,600/mm³ with 70%

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*Present address: The Royal Free Hospital, Grays Inn Road, London.

†Present address: The Radcliffe Infirmary, Oxford.

FIG. 1a and b.—Facial appearances in A. (a) at age 14 years and 6 months, and in D. (b) at age 14 years and 10 months.

polymorphs; ESR 59 mm/1 hr. The stools were strongly positive to occult blood testing with 0.2% o-tolidine, and pus cells were visible microscopically. The serum vitamin A was 22 IU/100 ml (normal 70–200), and the serum folic acid 3.6 μ g/100 ml (normal 5.9–21). Jejunal and rectal biopsy results are described later. Ascorbic acid 100 mg was given intravenously on two occasions. On the first occasion, 5 mg was excreted in the urine in the next 3 hours; on the second occasion, 4 mg was excreted (normal 50 mg). The blood urea and urinalyses were normal. A number of other investigations failed to reveal any abnormality including repeated stool cultures, motor nerve conduction time, and electromyogram, immunoglobulins, and sweat electrolytes. Urinary concentrations of thiamine and niacin were also normal.

Radiological investigations. Barium meal and follow-through showed clear evidence of dilatation and transverse barring in the jejunum with widening in the ileum (Fig. 2). Such appearances can be seen in coeliac disease, among other conditions. Barium enema showed initially that the distal half of the transverse colon and the descending colon were empty, narrow, tubular, and devoid of haustration, appearances that indicated a segmental colitis involving the transverse and descending colon (Fig. 3). The skeletal age measured later at a chronological age of 15.1 years was 12.5 years (Greulich and Pyle, 1959). This was more than 2 SD below the mean. There was absorption of the bone at the distal end of the distal phalanx of the index finger (Fig. 4) and loss of tufting in other distal phalanges.

Progress. Initially a diagnosis of ulcerative colitis was considered and he was treated for 10 days with sulphasalazine but became more febrile and developed a

FIG. 2.—Barium meal and follow-through appearances in patient A. Note dilatation, flocculation, and coin-stacking appearances.

FIG. 3.—Barium enema appearances in patient A. Note narrow tubular colon, particularly in descending part, devoid of haustration.

sensitivity rash. Crohn's disease or an enteropathy with secondary burning foot syndrome were also thought possible. Intramuscular injections of thiamine alone caused some alleviation of both diarrhoea and limb pains. Other B group vitamins, including pantothenic acid, and vitamins A, D, and C, and folic acid were given orally and parenterally.

After 4 weeks the diarrhoea stopped and limb pains remitted. After 11 weeks, he began to gain weight and was discharged on oral vitamin supplements but later relapsed and again developed similar, though less severe leg pains which are still present.

Patient D. (Twin I). This twin had no episode of weight loss but was admitted for assessment at 14½ years (Fig. 1b). His cramping limb pains were less severe than those of his brother. There was no sexual hair, no rash, and the facial appearance was similar to that in his twin. There was some palmar erythema. The conjunctival vessels were normal. The retinal vessels were tortuous, especially the veins, and slit-lamp examination showed a faint corneal haze. The blood pressure was 110/70 mmHg. He tended to walk with mild ankle inversion but there were no abnormal neurological findings.

There was no biochemical evidence of malabsorption. On a barium meal and follow-through the jejunum did not show such a clear-cut feathery pattern as usual and the longer folds were prominent on some films, but these features were of doubtful significance. His bone age was 2·5 years behind his chronological age and there were phalangeal changes similar to those of his brother. His pains decreased temporarily after injections of pantothenic acid.

As a result of a suggestion from Staff Nurse Ann Neville, the twins were then investigated for Fabry's disease. This diagnosis was confirmed by laboratory studies on jejunal mucosa, urine, and leucocytes.

Family Studies

Relatives from two generations were subsequently examined as shown in Fig. 5 and the Table. Of these two had abnormal eye signs. Only two relatives had both abnormal symptoms and signs, while in the definitely affected cousin, aged 4 years (Pr 11), there were neither abnormal signs nor symptoms. This boy subsequently developed typical limb pains. No relative showed or remembered having a rash. Relatives AI 6, and Pr 7-11 were re-examined one year later and the previous findings were confirmed. In the second ascending generation there were five male children and

FIG. 4.—Terminal phalanx of index finger showing absorption of bone and loss of tufting, in patient A.

TABLE
Family and Index Patient Studies

Location in Pedigree Chart (Fig. 5)	Sex	Age When Examined (yr)	Symptoms	Abnormal Signs	Urinary* Chromatography CDH CTH	α -galactosidase† Activity	Conclusion
Pr 3	F	17	Episodic leg pain	Tortuous retinal vessels§	Not examined	ND	Probable carrier
Pr 4	M	15	Index patients } Nil Nil Limb pains after exercise for 6 mth	See text	++ ++	4.0	Affected
Pr 5	M	15		Nil	++ +++	2.9	Affected
Pr 6	M	16		Nil	— —	ND	Noræal
Pr 7	F	14		Nil	+ ±	59	Normal
Pr 8	F	12		Tortuous conjunctival vessels; retinal vessels NAD	++ ++	22	Carrier
Pr 9	F	11	Nil	Nil	+ ±	78	Normal
Pr 10	F	10	Nil	Retinal vessel tortuosity	++ ++	38	Carrier
Pr 11	M	4	Nil	Nil	++ ++++	3.6	Affected
AI 2	F	44	Nil	Not examined	Not examined	ND	Not examined
AI 4	F	41	Nil	Tortuous conjunctival vessels	++ +	51	Carrier
AI 5	M	43	Nil	Nil	— —	ND	Normal
AI 6	F	39	Leg pains from 12-23 yr	Nil	+ +	34	Carrier

*CDH, CTH, ceramide di- and trihexoside; the quantity of each present in the urine is arbitrarily graded from (—) (nil) through $\pm$ to great + + + +.

† α -galactosidase activity: units expressed as $m\mu$ 4—moles methyl umbelliferyl- α -D-galactoside hydrolysed/mg protein per hour. Normal values (17 subjects, all ages) 56-120 units. Lowest normal adult = 73 units.

‡ND = Not done.

§This finding was reported by the patient's optician and has not yet been confirmed.

none is remembered as having leg pains or any other symptoms. It is probable that AII 11 developed a new mutation in view of the unaffected brothers AII 2-6.

Laboratory Studies

Jejunal biopsy (Pr 5). Prominent capillary loops were seen under the dissecting microscope. In paraffin sections the villous pattern was normal and there was no infiltrate in the lamina propria. Neurons in Meissner's plexus were enlarged and vacuolated, and stained positively with Sudan Black and Luxol Fast Blue. All blood vessels contained birefringent deposits of a sudanophilic, Luxol Fast Blue positive material, and the muscle cells in the muscularis mucosae also contained

a similar substance. A biopsy of rectal mucosa showed similar, though less marked, changes.

Urine. Microscopical examination of urinary deposits was performed in members of both families (Table). The smear preparations were fixed in formaldehyde vapour and stained with PAS, Sudan Black, Toluidine Blue, and Luxol Fast Blue.

The spun deposits from the index patients contained numbers of cells which were coarsely granular, stained intensely with PAS, and were weakly sudanophilic. There was no metachromasia with Toluidine Blue and no staining with Luxol Fast Blue. Examination with polarized light showed the cells to be birefringent.

Deposits from AI 6 and her family contained numerous epithelial cells, and evaluation was impossible.

Aliquots (100 ml) of 24-hour urine specimens were centrifuged, the supernatant decanted, and the deposit drained. The deposit was then twice extracted with chloroform-methanol (2 : 1 v/v) and the extract evaporated to dryness under nitrogen. Final drying was accomplished under vacuum over phosphorus pentoxide. The extract was redissolved in a known volume of chloroform-methanol (2 : 1 v/v). Chromatography using silica gel on glass plates was carried out using 20 ml equivalents of urine. The solvent system was chloroform-methanol-water (14 : 5 : 1 v/v). The chromatogram was sprayed with diphenylamine to detect hexosides and the colour developed at 130 °C (Fig. 6).

The results are summarized in the Table. The intensity of the bands is arbitrarily graded, nil to + + + +. Weak bands of various gangliosides were

FIG. 5.—Pedigree of twins with Fabry's disease. Index patients indicated by arrows are Pr 4 (D) and Pr 5 (A). Carrier status of AI 2 and AII 11 not determined. Arabic figures denote individuals in propositus (Pr) and first and second ascending (AI, AII) generations. Other symbols are standard (Nelson et al., 1969).

FIG. 6.—Thin-layer chromatogram of extract of deposit from 10 ml urine. Lane 1—Normal control; Lane 2—A (Pr 5); Lane 3—D (Pr 4). CDH = ceramide dihexoside; CTH = ceramide trihexoside; and O = origin.

also present in most samples from both families, with the exception of the normal father, AI 5.

Leucocyte enzyme studies. Leucocyte α -galactosidase activity was assayed by the method described by Kint (1970), using 4-methyl umbelliferyl- α -D-galactoside as substrate (Table). In 17 normal child and adult subjects, values between 56 and 120 units were recorded. The lower adult normal level recorded was 73 units. The three affected males had values of 4 units or less. Values for the two obligate heterozygote females and for two of the four possible heterozygote females studied were intermediate between the affected males and the lower limit of the normals.

X_g^a blood grouping and colour vision. X_g^a status was determined in Pr 4 and 5, and 7–11 inclusive and in AI 4 and 6. All were X_g^a positive. Colour vision was tested in the same relatives and in the index patients and was normal in all (Opitz *et al.*, 1965).

Zygosity of twinning. The twins' mother had been told at birth that they were monozygous. Confirmation of the monozygosity was obtained by Dr. R. Sanger who found that each twin had the same status in each of 12 different blood groups. From these data and the fact that the twins were of like sex, it was calculated that the chances of dizygosity were only $P = 0.026$.

Discussion

Our patients had the same slim build and stooping posture, with thickened, often parted lips previously described. It is thought that they also had the palmar erythematous noted by Johnston, Weller, and Warland (1968). The retinal and conjunctival vessel abnormalities, corneal haze, and limb pains are all characteristic of the condition. In our patients, interest centres principally on the presence of gut abnormalities, the absence of a rash, the urine chromatography results, and leucocyte α -galactosidase activity.

Gut abnormalities. Wise, Wallace, and Jellinek (1962) refer to diarrhoea in four patients with Fabry's disease including one of the first to be described (Günther, 1913). Their Case 1 had attacks of diarrhoea lasting a few months at ages 20 and 25, and the rash had been noted at the age of 13 years. Sigmoidoscopy showed a friable mucous membrane, and barium enema revealed narrowing of the 'ileo-pelvic segment' of the colon and absent haustration.

Pompen and van Wayjen (1958) described two patients with diarrhoea. The first had periodic attacks of diarrhoea since age 15 years, passing up to seven watery stools a day. Sigmoidoscopy showed a granular mucosa, and barium enema revealed decreased haustration of the descending colon and parts of the transverse colon. The gut features resembled ulcerative colitis but the typical rash was present. There was no family history. Their second patient (unrelated) developed similar attacks of diarrhoea at age 40 years and died two years later. At necropsy, the colon had a firm wall, over 6 cm thick, and there were large necrotic hardenings. The upper small gut showed similar, but less severe changes. Typical skin lesions were present. No barium meal results were described.

Urbain, Philippart, and Peremans (1969) reported on a 23-year-old man with colitis, pyrexia, and hypo- γ -globulinaemia, in whom biopsy and urinary chromatography were characteristic of Fabry's disease. Barium studies of the stomach and small bowel showed no abnormalities. The transverse colon showed a complete absence of haustration, indicated by barium enema. Five years later there was no evidence of a rash. Campbell and Halford (1964) described a woman of 62 years with no rash, but with diarrhoea and a peripheral neuropathy.

Our patient, Pr 5, resembles the first two mentioned above, with diarrhoea and similar barium enema appearances simulating ulcerative colitis; he differs in not having a rash, in presenting in the

paediatric age group, and in the radiographic and biochemical evidence of malabsorption. The features on barium meal examination do not appear to have been reported previously. These consisted of dilatation and flocculation and coin-stacking appearance of the barium in the ileum and jejunum. The low folic acid and vitamin A levels confirmed malabsorption. A diagnosis of Fabry's disease should be considered when gut lesions are associated with tortuosity of retinal and conjunctival vessels, even if no rash is present. Fabry's disease is not mentioned in the differential diagnosis of malabsorption in standard texts (Cooke, 1968; Nelson, Vaughan, and McKay, 1969). Weight loss in several reported patients appeared before episodes of diarrhoea.

Absence of rash. The presence of excess ceramide trihexoside, and the deficiency of ceramide trihexosidase activity have become the hallmarks of Fabry's disease, rather than any clinical features, such as the rash. As ceramide trihexoside can be detected by thin-layer chromatography of the urine, identification of patients with Fabry's disease has been rendered much more straightforward. Cases other than the present family in which there was no rash have been described, but reports of the diagnosis of Fabry's disease in children without a rash and without a family history are rare.

In adults, Jensen (1966) described the necropsy findings of Fabry's disease in four brothers who died of uraemia in their 30's. Two had no rash, another developed a rash only in the year before his death, and in the fourth the presence or absence of a rash was not stated. Hamburger *et al.* (1964) described a mother and son with familial nephropathy, renal biopsy changes compatible with Fabry's disease, and tortuous retinal vessels, but no rash. Kemp (1967) described two brothers without a rash: one died at 37 with myocardial infarction and histological evidence of Fabry's disease, and another showed characteristic lesions on renal biopsy. Urbain *et al.* (1969) described a patient of 33 years without a rash or family history. Johnston *et al.* (1968) described adults and an adolescent without a rash, but with a family history, as did Fone and King (1964). Clarke *et al.* (1971) presented two unrelated adults with changes of Fabry's disease on renal biopsy, excess ceramide tri- and dihexoside in the urine, and deficient leucocyte α -galactosidase activity.

The above patients and the present family, all nearly or completely free from a rash, show that the diagnosis may have to be made without cutaneous evidence, though this may well appear

later. Fabry's disease without a rash must be considered in the differential diagnosis of limb pains, arthritides, obscure pyrexia, and weight loss, hypertension and renal failure.

Age of onset of rash. The age of onset is of some importance to paediatricians. Wise *et al.* (1962) considered that, in the majority and perhaps all cases, the rash appeared before the age of 10 years, quoting two cases in which the rash appeared in infancy, and that systemic symptoms without a rash were rare. To ascertain the correlation between the age of onset of symptoms and the presence or absence of a rash at a stated age, 26 patients in whom these two ages were mentioned were collected from the literature (Curry and Fleisher, 1961; Wise *et al.*, 1962; Fone and King, 1964; Dempsey *et al.*, 1965; Rae, Lee, and Hopper, 1967; Johnston *et al.*, 1968; Loeb *et al.*, 1968). This method is subject to obvious limitations. Of 22 patients who developed limb pains at age less than 15 years, 11 had a period of one or more years without a rash. Limb pain *without* a rash is, therefore, a relatively frequent mode of presentation of Fabry's disease in the paediatric age group.

Delayed puberty. Neither of the index patients showed any evidence of puberty when examined at age 15 years, and both had the expected similar delay in bone age (2½ years). Puberty was therefore abnormally late (Marshall and Tanner, 1970). Adults with Fabry's disease are not reported as having short stature. Female carriers have no pubertal delay. Similar pubertal delay in males has been reported previously (Johnston *et al.*, 1968).

Clinical features in females. Of the two adult females in our study, one had limb pains from age 12 to 23 and another showed tortuous conjunctival vessels. Variable penetrance in heterozygous females has been tentatively established, and occasionally this may be complete. Burda and Winder (1967) described a 47-year-old woman who died of renal and cardiac failure.

Urine studies. The microscopical examination of urinary sediment can, on occasions, be helpful and cells can be found which contain a substance with a staining characteristic expected for deposits of a ceramide trihexoside-cholesterol complex. However, if there are numerous epithelial cells, interpretation can be impossible.

Chromatographic examination of the extracted deposits gives a clear indication of the disease state. Here the amount of ceramide trihexoside is

grossly raised and there is also an increased excretion of ceramide dihexoside. It is probable that the carrier state is indicated by slightly raised ceramide dihexoside and ceramide trihexoside levels (Philippart, Sarlieve, and Manacorda, 1969). The normal varies somewhat, but small amounts of cerebroside, ceramide dihexoside, and trihexoside may be excreted on occasions.

Other features. The significance of the abnormal vitamin C studies remains obscure. Diminished sweating has been frequently described but our patients produced over 200 mg sweat in response to the usual pilocarpine iontophoresis test, and presumably hypohydrosis does not become manifest until a later stage.

Pathogenesis. Involvement of peripheral nerves has been shown by Kocen and Thomas (1970). They found moderate depletion of myelinated nerves and deposits of glycolipid in perineural cells. There was no other evidence of peripheral neuropathy, and nerve conduction studies were normal. The loss of the smaller nerve fibres with sparing of the larger fibres may explain the sensory neuropathy in the presence of normal nerve action potentials.

The renal failure usually found in the later stages of the disease is probably caused by the lesions in the glomerulus (ballooning of glomerular epithelium) and in the tubules which interfere with renal function.

Ubiquitous deposition of ceramide trihexoside in smooth muscle cells accounts for the lesions in blood vessels giving rise to the skin lesions and for the later cardiac failure. The gastrointestinal symptoms may well be related to the deposits in the ganglion cells and muscle of the intestinal wall.

In common with certain other sphingolipidoses, Fabry's disease is characterized biochemically by the accumulation of a substance which is probably derived from the degradation of erythrocyte globoside (*see below*).

Kint (1970) has shown that leucocytes from patients with Fabry's disease are deficient in α -galactosidase activity and this is confirmed in the patients presented here and by Clarke *et al.* (1971). This suggests that the terminal galactosyl residue of the ceramide trihexoside is linked through an α -galactosyl bond rather than through the β -linkage proposed by Sweeley, Snyder, and Griffin (1970). In our families, intermediate levels of α -galactosidase activity were found for the obligate heterozygote females and two of the four possible heterozygote females tested.

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Correspondence to Dr. D. M. Flynn, The Royal Free Hospital, Grays Inn Road, London W.C.1.