Angiokeratoma corporis diffusum with features of a mucopolysaccharidosis

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SUMMARY Two cases of angiokeratoma corporis diffusum with mental retardation and some features of a mucopolysaccharidosis have been investigated biochemically, histopathologically, and by electron microscopy. It is submitted, on this evidence, that they are examples of a hitherto undescribed form of lysosomal enzyme deficiency disease.

The rash of angiokeratoma corporis diffusum (ACD) had been considered diagnostic of Anderson-Fabry disease until Patel¹ described it in association with fucosidosis. Later it was reported in the presence of a deficiency of β -galactosidase activity.² The affected girl and boy in the family recorded in this paper have angiokeratoma corporis diffusum, mental retardation, and some features of a mucopolysaccharidosis.

Case reports

CASE 1

This case, a girl born 8.5.64, is the second child in a sibship of four, the first and the third being normal; the fourth, a boy (case 2), is discussed below. The parents are of Scottish extraction and there is no known consanguinity. She is of short stature (133 cm), weighs 40.5 kg, and is kyphotic and pot-bellied. Her features are gargoyle-like, with coarse skin, sunken nasal bridge, protruding lips (fig 1), and stubby hands and feet. There is a flexion deformity of her elbows, knees, and fingers. Her hair is dark, coarse, and curly and the back of the trunk is hirsute. She has a constant coarse tremor of her hands. She is sluggish mentally and physically and is only able to respond to simple commands, indicate her needs, and dress with assistance. She does not communicate with patients other than her brother. Her head circumference is 54.0 cm and her mental age is 2 years 5 months (Stanford-Binet intelligence scale). She is in the medium grade category of mental deficiency. Since admission to hospital at the age of 4 she has had repeated unexplained pyrexial illnesses with respiratory and gastrointestinal involvement. There is marked

tortuosity of the retinal vessels, but the corneae are normal on slit lamp examination. There is no hepatomegaly, splenomegaly, or cardiomegaly. The eruption (figs 2, 3), first noted at the age of 8 on the anterior abdomen, now affects the upper chest, trunk, buttocks, thighs, and vulva. Hyperkeratosis is not a feature of these angiomas. X-rays of chest and thoracolumbar spine were reported as being within normal limits. Chromosome studies were completely normal, as was haemoglobin electrophoresis.

FIG 1 Gargoyle-like features, protruding lips, and sunken nasal bridge.

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FIG 2 ACD eruption on chest.

FIG 3 Prominent angiomas of vulva.

CASE 2

The brother of the previous case was born on 20.8.70. He, although a pleasant boy with a solemn expression, is mentally handicapped falling below the norms of the Stanford-Binet intelligence scale. Like his sister, he is in the medium grade category of mental deficiency. He requires prompting and assistance with routine daily tasks and, although having no meaningful speech, responds to simple commands.

He does not communicate with other patients and does not reciprocate his sister's affection for him. His height is 116 cm and weight 26.5 kg. He has gargoyle-like features and his head circumference is 53.5 cm. His hair was fine and fair initially, but is now dark and wiry. He has had frequent bouts of unexplained pyrexia. There are no corneal or fundal changes, but he has epicanthic folds. Sweating is normal. There is no hepatosplenomegaly or cardiomegaly and he does not have flexion deformity of his joints. His rash, which was first noticed when he was 5, is inconspicuous and affects the genitalia and medial aspect of thighs. Hyperkeratosis is lacking over the tiny angiomas. Biopsy has not been carried out. X-rays of thoracolumbar spine have been reported as being within normal limits. Chromosome studies and haemoglobin electrophoresis were normal.

Histology and electron microscopy

An angioma on the left thigh of case 1 was excised under local anaesthesia. Tissue was processed for routine light and transmission electron microscopy, including electron histochemistry for lysosome acid phosphatase. In section, the angioma consisted of a small number of compactly-grouped, very large calibre, subepidermal, capillary-type blood vessels (fig 4). The capillary walls consisted of endothelial cells limited by a basement membrane, external to which were fibroblasts and occasional smooth muscle cells embedded in loosely arranged collagen and elastin. A small minority of endothelial cells contained up to four secondary-type lysosomes per sectional profile; only one example of an endothelial lipid-containing lysosome was found.

FIG 4 Light microscopical appearance of angioma. The lesion consists of a small aggregate of large calibre capillary-type blood vessels in an immediately subepidermal location. (Haematoxylin and eosin. Original magnification $\times 400$.)

FIG 5 *Electron micrograph of non-angioma blood vessel showing numerous secondary-type lysosomes (arrows) in pericyte (P) and adjacent fibroblast (F). (Original magnification $\times 22\,500$.)*

OTHER DERMAL BLOOD VESSELS

A total of 23 dermal blood vessels of capillary, post-capillary venule, and arteriole types was examined. There was no endothelial abnormality but occasional pericytes contained secondary-type lysosomes in greater than normal numbers, up to nine per profile of sectioned cell (fig 5). A minority of these bodies contained lipid.

LYMPHATIC CHANNELS

Three lymphatic vessels showed no abnormality.

DERMAL FIBROBLASTS

A total of 44 fibroblasts was examined; only substantial profiles of spindle shaped cells with abundant rough endoplasmic reticulum were considered adequate. Thirty-two cells were normal and 12 contained secondary-type lysosomes in greater than normal numbers (fig 6). The number of secondary lysosomes per section of cell ranged from 4 to 25. All such lysosomes were composed of aggregated microgranular, amorphous, and lipoid constituents (fig 7). Definite neutral lipid was identified in only a

FIG 6 *Electron micrograph of upper dermis showing secondary lysosome-laden fibroblast (arrows). (Original magnification $\times 10\,500$.)*

FIG 7 *Electron micrograph of dermal fibroblast showing an aggregate of secondary-type lysosomes with pleomorphic [granular (G), amorphous (A), and lipid (L)] contents. (Original magnification $\times 60\,000$.)*

FIG 8 Acid phosphatase/electron microscopical preparation showing reaction product (RP) localised to the secondary-type lysosomes of a dermal fibroblast. (Original magnification $\times 28\,000$, unstained preparation.)

minority, with a maximum of four such lysosomes per section of cell. None of the lysosomes could be labelled categorically as examples of autophagic vacuoles. The average diameter of a lysosome was $0.5\,\mu\text{m}$, the largest being $1.5\,\mu\text{m}$. Thus, singly or in the usual aggregate, these structures were visible in light microscopical preparations treated with the Gomori procedure for acid phosphatase. The lysosomal nature of the structures identified by electron microscopy was confirmed by positive acid phosphatase reactivity (fig 8). The only identifiable component was lipid in nature, and these droplets were too small for light microscopic resolution.

Biochemistry

The levels of urinary glycosaminoglycans, including aspartylglycosamine, were normal. The enzymes tested, using fibroblasts, leucocytes, serum, or plasma (table 1), were all normal.

TABLE 1 Enzymes of patients tested

Enzyme	Case 1			Case 2	
	Leuco- cytes	Plasma or serum	Fibro- blast	Leuco- cytes	Plasma or serum
Acid esterase	—	*	*	—	*
Acid phosphatase	—	**	*	—	*
Aryl sulphatase (A)	*	*	*	—	*
Aryl sulphatase (B)	—	—	*	—	—
β -glucosidase	—	—	*	—	—
α -galactosidase (A)	**	**	*	*	—
β -galactosidase	*	*	*	*	*
Sialidase	—	—	*	—	—
α -mannosidase	**	**	*	*	*
β -N-acetylglucosaminidase (A and B)	—	*	*	—	*
β -glucuronidase	*	*	*	—	—
Galactocerebrosidase	—	—	*	—	—
α -N-acetylglucosaminidase	—	—	*	—	—
α -fucosidase	*	**	*	*	*
α -L-iduronidase	—	—	*	—	—
Heparin sulphamidase	—	—	*	—	—
Sphingomyelinase	—	—	*	—	—
α -arabinosidase	*	—	—	—	—

(1) All the above estimations were carried out quantitatively and were normal. **indicates that two laboratories undertook the assays.

(2) Electrophoretic analysis only was also carried out in white cells in case 1 on β -N-acetylglucosaminidase (A and B), α -fucosidase, acid α -glucosidase, β -glucuronidase, and α -galactosidase A, in plasma of α -fucosidase of both cases, and β -N-acetylglucosaminidase A in case 1 (Dr Swallow).

(3) Fibroblast enzymes were assayed by Drs Butterworth and Besley, leucocyte enzymes by Drs Logan and Swallow, and serum or plasma was studied by Drs Butterworth and Besley and Dr Swallow.

Tissue culture

Of the cultured fibroblasts, 30% contained cytoplasmic inclusions.

Discussion

Angiokeratoma corporis diffusum has been described in association with Anderson-Fabry disease, fucosidosis, and β -galactosidase deficiency.

The best known of these entities was described independently in 1898, first by Anderson³ and then by Fabry⁴; the cause of the condition was shown by Kint⁵ to be a deficiency of the lysosomal enzyme α -galactosidase.

Fucosidosis was first described by Durand *et al*⁶ and the deficient enzyme identified as α -fucosidase.⁷ Three variants have been described to date,⁸ ACD being associated with the form having a relatively good prognosis with regard to survival. The association was first noted by Patel *et al*,¹ subsequently by Boronne *et al*,⁹ and in the United Kingdom by Primrose^{10,11} and elaborated by MacPhee and Logan.¹²

β -galactosidase deficiency was first reported in one case by Loonen *et al*² and further details were added by Koster *et al*.¹³ Cerebellar defects, progressive loss of vision, and intellectual deterioration with myoclonic fits developed.

Syndromes which present with a clinical picture of gargoylism include mannosidosis, aspartylglycosaminuria, mucosulphatidosis, and mucopolipidoses, but in these there is no excess of urinary mucopolysaccharides. Angiokeratoma has not been reported in these conditions.

The similarities and the differences between Anderson-Fabry disease, fucosidosis, β -galactosidase deficiency, and the present cases are listed in table 2. Cases 1 and 2 have, in common with Anderson-Fabry disease, histologically proved angiomas and a tendency to recurrent bouts of unexplained pyrexia, while the girl has tortuosity of the retinal vessels. The main difference from typical Anderson-Fabry disease is that the rash is more obvious in the girl than in her brother; in addition its onset was at an early age for Anderson-Fabry disease, and its distribution in the sister includes not only the genitalia but also the upper chest, as in the case of fucosidosis described by Primrose.¹¹ Slit lamp

examination of the cornea in both children was negative, and pain in the extremities is not a feature. There is evidence in both children of progressive physical and mental deterioration, neither of which is found in Anderson-Fabry disease.

Features in common with fucosidosis include the eruption, coarse features, and mental and neurological deterioration. The girl, with the more profuse eruption, appears to resemble the patient described by Primrose.¹⁰ They differ from the majority of cases of fucosidosis in that there is, as yet, no evidence of cardiomegaly or of splenomegaly.

In contrast with β -galactosidase deficiency, neither shows evidence of marked cerebellar disturbance, although the girl has a tremor. There is no loss of sight nor are there cherry red spots in the retina.

Comparison of the lysosome morphology in case 1 with that found in the mucopolysaccharidoses and mucopolipidoses¹⁴ and sphingolipidoses¹⁵ also points to a separate disorder (table 3). The increase in numbers and size of the lysosomes, and their constant 'secondary' nature, does not correspond to any specific condition within these three groups. In particular, complex lipids, typified by the lamellated bodies in fucosidosis and Hurler's disease, are totally absent in this case. Similarly, the clear vacuolation of lysosomes characteristic of mucopolysaccharide overload, and the usual plethora of autophagic bodies seen in the mucopolipidoses, are absent.

Extensive biochemical investigations have been carried out in different laboratories at different times, and from these it can now be stated that these children do not have the enzyme defects found in Anderson-Fabry disease, fucosidosis, or β -galactosidosis. Mannosidosis, mucopolysaccharidoses, and mucopolipidoses have been excluded. No other enzyme

TABLE 2 *Four distinct aetiological types of ACD*

Features	Anderson-Fabry	Fucosidosis	β -galactosidase deficiency	Present cases
Angiectasis	Usually	Adult type	One case	Brother and sister
Distribution	Lower abdomen and genitalia	Chest and genitalia	Umbilicus and genitalia	Chest and genitalia
Inheritance	X-linked recessive	? Autosomal	?	? Autosomal
Age of onset	After 10 years	Recessive About 10 years	8 years or over	Recessive 3-5 years
Corneal involvement	Yes	Yes	Yes	No
Tortuosity of retinal vessels	Yes	Yes	Not known	Female yes, male no
Cherry red spot and optic atrophy	No	No	Yes	No
Pain in extremities	Yes	No	No	No
PUO	Yes	Yes	Yes	Yes
Gargoyle features	No	Yes	Yes	Yes
Mental retardation	No	Yes	Yes	Yes
Radiological changes	No	Yes	Yes	Possible
Renal involvement	Yes	No	No	No
Hepatosplenomegaly	No	Yes	No	No
Cerebellar abnormality	No	No	Yes	Female tremor, male no
Enzyme deficiency	α -galactosidase	Fucosidase	β -galactosidase	Unknown
Growth retardation	Variable	Yes	Yes	Yes
Sweating	Decreased	Normal or decreased	?	Normal
Spasticity	No	Yes	?	Yes

TABLE 3 *Lysosome morphology in case 1*

Disease	Lysosome morphology (electron microscopy)
Hurler's disease	Vacuolation and lamellation
Hunter's disease	" " "
Chondroitin 4-sulphaturia	" " "
Mucosulphatidosis	" " "
Sanfilippo's syndrome	Vacuolation
Morquio's syndrome	"
Scheie's syndrome	"
Maroteaux-Lamy disease	"
Mannosidosis	"
Gangliosidosis	Vacuolation and filaments
Mucopolipidosis I	Vacuolation plus droplets
Mucopolipidosis II	Polymorphic/autophagic
Mucopolipidosis III	Minor abnormalities
Fucosidosis	Fine granularity and lamellation
Anderson-Fabry disease	Pleomorphic and lamellation
β -galactosidase deficiency	Extra-lysosomal lamellar inclusion
Present case	Vacuole formation in RE cells Pleomorphic/secondary type

defect has so far been established in any tissue examined. There is a possibility that the defective enzyme may be a variant that cannot be detected by the substrate used, which is usually synthetic. Alternatively, there may be a deficiency of a co-factor which is necessary to allow the enzyme to be effective in vivo. It is our submission that the deficient enzyme has not yet been identified, and that its absence results in the accumulation of a lysosome storage product; such an enzyme may well be closely related to one of those responsible for a well recognised deficiency state. Two further cases of ACD have been described in twin brothers aged 42, first by Beurey *et al.*¹⁶ and later in greater detail by Peltier *et al.*¹⁷ No enzymatic deficiency was detected in them. The brother who was studied was mentally retarded but does not appear to have shown the clinical features of a mucopolysaccharidosis. However, microscopy suggested a storage disease of this type. It is possible that these brothers may have a similar disease. In view of the clinical similarities to fucosidosis and Anderson-Fabry disease, it may be significant that α -fucosidase is involved in the degradation of the blood group glycosphingolipids three steps before the production of a ceramide dihexoside. This is also produced by α -galactosidase deficiency in Anderson-Fabry disease while β -galactosidase is involved in the same degradation process.

The occurrence of two affected sibs suggests an autosomal recessive mode of inheritance. The family history tends to rule out consanguinity in the parents, although they do come from the same sparsely populated and remote area of the north-west coast of Scotland.

It is submitted that the two cases presented in this paper are examples of a hitherto undescribed form of lysosomal enzyme deficiency disease.

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carried out ophthalmological examinations, and photography was done by Mr C Hunt. Mr A Rennison was responsible for the electron microscopy.

We were introduced to the children by Dr Paula Gosling, now of Mount Pleasant Hospital, Hastings, who has maintained a keen interest in them and in the results of the investigations.

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Note added in proof

Lowden and O'Brien have recently reclassified the patient of Loonen *et al.*² as having a deficiency of sialidase rather than β -galactosidase (*Am J Hum Genet* 1979; 31:1).