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Manifestation of angiokeratoma diffusum in a girl patient with heterozygous genotype for Fabry disease

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The case of a 16 years old girl patient having angiokeratoma corporis diffusum with Fabry heterozygosity is published together with the clinical and genetical screening investigations of the family members.
The problem of the detection of the heterozygotes is discussed.

Brady et al [1] detected the deficiency of the lysosomal enzyme ceramide trihexosidase in the cases with ceramide trihexoside lipidosis (Anderson—Fabry disease). Corneal opacity, angiokeratoma corporis diffusum, crises of fever, burning pain in the extremities, peripheral edema, renal dysfunction belong to the clinical characteristics in the hemizygous males. The birefringent glycosphingolipid is deposited in the endothelial and smooth-muscle cells in blood vessels, in ganglion cells, in reticuloendothelial, myocardial and the connective tissue cell and in the epithelial cells of the parenchymal organs. X-linkage had been elucidated with pedigree studies and linkage analysis with blood group Xg [6, 13, 16].

Two isozymes (A and B) of alfa-galactosidase (AG = ceramide trihexosidase) were demonstrated with electrophoretic and enzymatic studies [3, 10]; the B form is identical with N-acetyl-alfa-galactosidase [5].

The manifestation of the clinical symptoms in the heterozygous genotypes (females) is a rarity; according to the data of Patrick [14] the pathological involvement of the kidneys, cardiovascular and the central nervous system is about 1 per cent, the paresthesia is about 10 per cent, manifestation of the angiokeratoma is about 20 per cent, cornea opacity is about 80 per cent. So the publication of the dermatological and ophthalmological symptoms of a Fabry-heterozygous girl might be interesting together with the specific enzyme analysis of the genetically affected family.

Case Report

Andrea J. (born on 7th Apr. 1970) 16-year-old girl patient has been sent to our Paediatric Department for specific enzyme investigations from the Dermatological Department of County Hospital Kecskemét with characteris-

tic cutaneous vascular, crusta covered teleangiectases in the superficial skin layer in the gluteal regions and on the thighs with bilateral symmetric tendency (diameter: 1—5 mm). The conjunctiva was involved, too (Figs. 1, 2).

From the skin biopsy material the histological — histochemical investigations showed the typical picture of angiokeratoma corporis diffusum Fabry (Fig. 3).

Clinical and enzyme investigations, method and results

The members of the family J. have been screened ophthalmologically, nephrologically, neurologically and for alfa-galactosidase activity from the peripheral leukocytes with the method of Griffith [9] using 4-methyl umbeliferyl-alfa-D-galactopyranoside as substrate.

Fig. 1. The typical subcutaneous teleangiectases in our Fabry-heterozygous patient

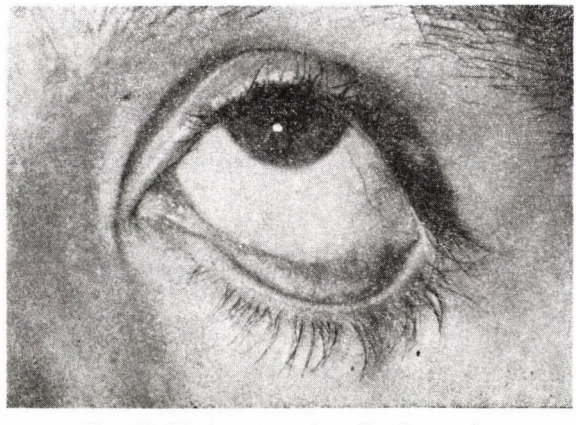

Fig. 2. Tortuous conjunctival vessels

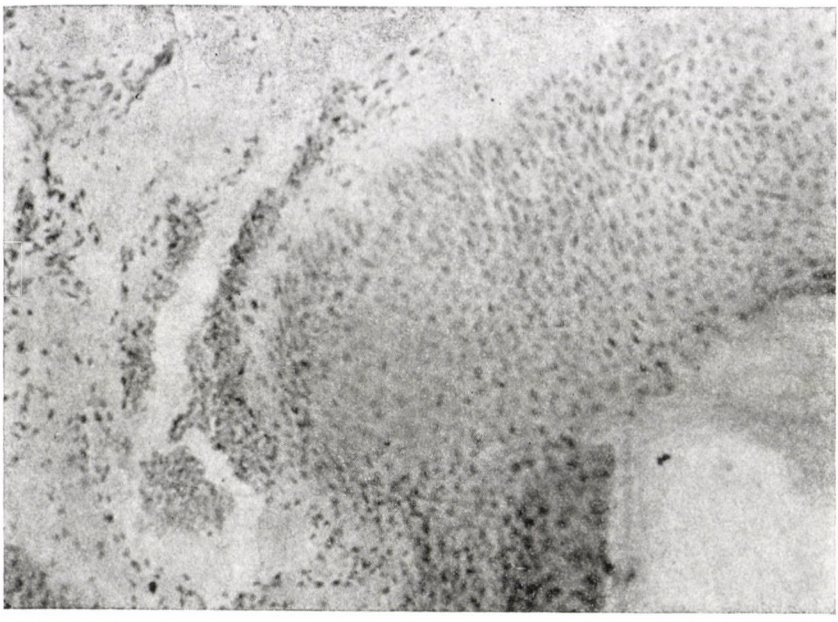

FIG. 3. Photomicrographs of the skin lesions, with dilated vessels and hyperkeratosis

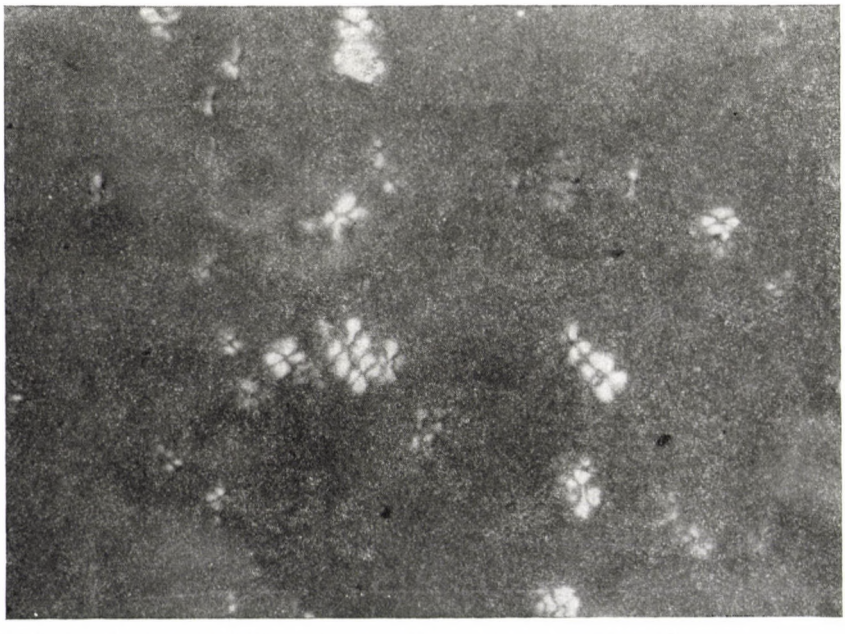

FIG. 4. Photomicrograph of the urinary sediment from our Fabry-heterozygote patient: lipid accumulation by interference-contrast microscopy (×1200)

TABLE I

Clinical and genetical data of family J.

Name (year)	Cornea opacity	Urine sediment bire-fringent lipid material	Urine osmol. mosm /l	Reno-gramm	ECG Echo-card.	Alfa-galacto-sidase* nM/1 mg prot./h.	%	Genostate
Andrea J. [16] Dg: Angiokeratoma Fabry	+	+	1231	neg.	neg.	64	49.2	heterozygote
László J. [12] (brother)	—	+	1059	neg.	neg.	60	46.2	homozygote?
Mrs. J. [42] (mother)	—	—	1026	—	neg.	98	75.4	heterozygote
Mr. J. [47] (father)	—	—	1090	—	neg.	141	108.5	healthy homozygote
Control [12]	—	—	—	—	—	130	100	healthy homozygote

* from leukocyte homogenisate

The clinical and laboratory data are seen in the Table I. The values of the enzyme activies and the determined genotypes are summarized there, too.

According to the specific leukocyte enzyme activity, the girl patient (AJ) and the mother have proved to be heterozygote for Fabry disease and the father has proved to be a healthy homozygote. The brother (László J) has high residual leukocyte alfa-galactosidase activity, too. Lipid droplets accumulating in distal tubular epithelial cells were detected by interference contrast microscopy from the urinary sediment of the girl patient and of her brother without clinical symptoms (Fig. 4). The isotope renography was normal in both of them.

Cornea opacity was found only at our Fabry-heterozygous girl patient.

The cardiological investigation (ECG and echocardiography) has given normal results in the whole family.

DISCUSSION

We have got intermediary specific enzyme level from the lekocytes in the case of our girl patient with angiokeratoma corporis diffusum and of the mother and of the brother. The first two persons proved to be Fabry heterozygotes according to the enzyme results. The clinical skin and nephrological manifestations are unusual in the gene carriers. The detection of the genetical identity of the brother has made much problems for us, because of his intermediary alfa-galactosidase enzyme activity from leukocytes. He might be a homozygous Fabry case manifested only in lipid droplet urinary excretion without any other symptoms at that time with a relative higher residual enzyme capacity in the leukocytes; he must be strongly observed in the future.

The most frequent clinical symptom

among the heterozygous females is the cornea opacity [19]. The heterozygotes are generally less severely affected than hemizygous males. Cardiovascular changes, such as hypertension, abnormal electrocardiogram, hypostenuria, erythrocyturia, leukocyturia, proteinuria, might rare be manifest at the gene carrier females. Colley et al [4] were the first to declare the lipid deposition in the kidneys. Detection of heterozygosity depends on the demonstration of the alfa-galactosidase deficiency from different tissues as intestine, kidney, liver, plasma, tears, and urine [1, 11, 17, 2, 7, 8]. The most reliable method is the alfa-galactosidase determination in the homogenisate of the leukocytes [12] or in cultured skin fibroblasts or in hair follicles [18]. In the case of the brother of our Fabry heterozygous girl patient having high residual specific enzyme capacity in the leukocytes, might be a lower alfa-galactosidase activity in the skin fibroblasts or in other organs. According to the enzyme investigation from the leukocytes it was impossible to decide his genotype. He must be homozygous genotype, according to his sex.

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