Virchows Archiv A Pathol Anat (1990) 417:449–455

Virchows Archiv A
Pathological Anatomy and Histopathology

Case report

Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease

Report on a case simulating hypertrophic non-obstructive cardiomyopathy

M. Elleder [1], V. Bradová [1], F. Šmíd [1], M. Buděšínský [5], K. Harzer [4], B. Kustermann-Kuhn [4], J. Ledvinová [2], Bělohlávek [3], V. Král [6], and V. Dorazilová [1]

1st Institute of Pathology [1], Laboratory for Proteosynthesis [2], 2nd Internal Clinic [3], School of Medicine, Laboratory for Neurochemistry, Institute for Brain Research, University of Tubingen [4], Institute of Organic Chemistry and Biochemistry [5] and Laboratory of Physiological Regulations [6], Czechoslovak Academy of Sciences, Prague

Received March 19, 1990 / Accepted June 21, 1990

Summary. Fabry's disease was diagnosed in an adult patient as a lipid storage-induced non-obstructive hypertrophic cardiomyopathy. Stable angina pectoris started 15 years before death, was followed by slowly progressive heart failure and repeated pulmonary thromboembolism with death at 63 years. Autopsy disclosed enormous cardiomegaly (1100 g), cardiac storage of ceramide trihexoside (CTH) of the same intensity as in classical cases of generalized Fabry's disease (11 mg lipid/g wet weight) restricted to cardiocytes. Other tissues (liver, kidney, brain, pancreas, pulmonary artery, coronary arteries) were free of storage. Using proton magnetic resonance analysis on formaldehyde-fixed tissue the stored CTH was identified as globotriaosylceramide. It was enzymatically degradable by control cell cultures but left uncleaved by mutant reference Fabry cells. Alpha – galactosidase activities in peripheral leucocytes of all four of the patient's daughters were in the heterozygous range. The diagnostic difficulties in this monosymptomatic novel variant of Fabry's disease are stressed.

Key words: Fabry's disease – Cardiomyopathy

Introduction

Fabry's disease (McKusick 30150) is an X-linked storage disease defined as alpha-galactosidase (E.C. 3.2.1.22) deficiency. From the clinical point of view it is a multisystem disorder leading to a polysymptomatic phenotype due to lipid storage in the cardiovascular, peripheral, or central nervous systems. The kidney, skin and cornea may be involved specifically (Desnick and Bishop 1989). Cases of an oligosymptomatic phenotype, though rare, have been described (see Discussion).

We present a rare monosymptomatic case of lipid storage restricted solely to cardiocytes, representing a new variant of Fabry's disease.

Offprint requests to: M. Elleder, 1st Institute of Pathology, School of Medicine, Studnickova 2, Prague 2, Czechoslovakia

Case report

M.D., male, born in 1925, was hospitalized for the first time at the age of 50 for phlebothrombosis of the leg. He complained of slight breathlessness during physical effort, sometimes accompanied by praecordial oppression. Cardiological examination disclosed fluctuating hypertension, and ECG changes interpreted as subacute infarction. Five years later the blood pressure became fixed at a higher level (160–200/100 mg) but was successfully controlled with trimepranol, amilorid and hydrochlorothiazide (Moduretic) and prenylamine. Seven years later his dyspnoea on effort worsened considerably and appeared even at rest, accompanied by irregular heart action. There was no improvement despite intensive cardiotonic therapy. The last weeks of his clinical history were dominated by a new episode of phlebothrombosis in the leg and successive pulmonary thromboembolism. He died with signs of bilateral cardiac failure, aged 63 years.

The ECG changes can be summarized as prominent abnormal depolarization with slowed down activation, left bundle branch block, left ventricular hypertrophy with ischaemic-metabolic changes, and atrial enlargement. M-mode echocardiography showed marked left ventricular hypertrophy with borderline increase in the ventricular cavity size (57 mm in diastole, 34 mm in systole) and global ejection fraction decreased below 0.7. The systolic septum width was 24 mm, diastolic 22 mm, indicating hypokinesis. The posterior wall was slightly hypokinetic (systolic width 17 mm, diastolic 13 mm). The left atrium was dilated (54 mm); the free right ventricle wall was moderately hypertrophic. The valves were normal and there was no sign of left outflow

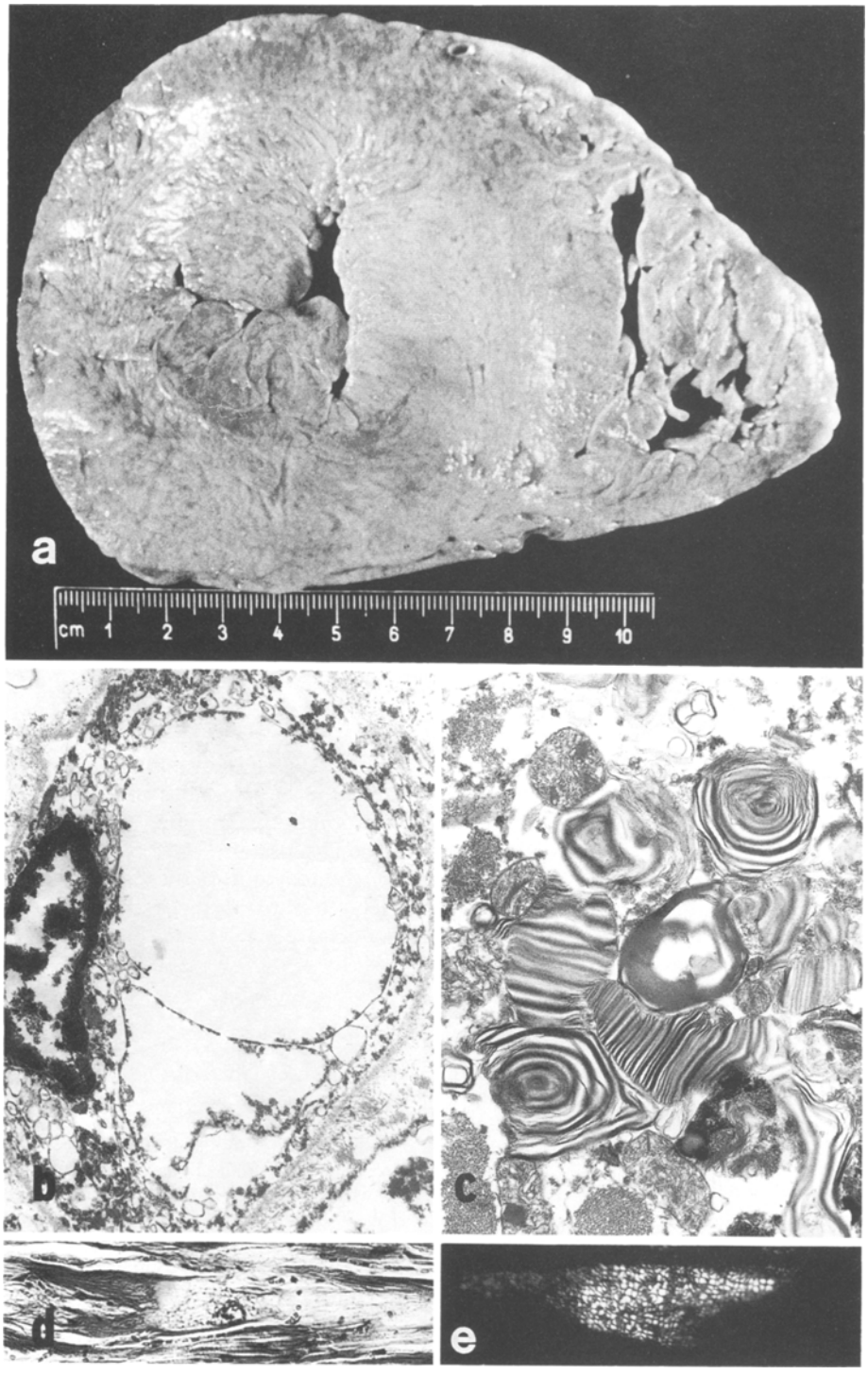

Fig. 1. a Cross-section of the heart. Absence of storage in a capillary (**b**) contrasting with massive storage in cardiocytes (**c**). In optical microscopy these displayed prominent vacuolization (**d**) and birefringent lipid deposition (**e**). **b** ×4500; **c** ×15000; **e** ×400

tract obstruction despite the loud systolic murmur with maximum over the mitral region propagating toward the axilla and partly to the large vessels.

Abnormal laboratory findings included a plasma cholesterol which was constantly slightly elevated (6–8.9 nmol/l) and which, in conjunction with an increase in triglycerides (3.4–4.1 nmol/l), was indicative of hyperlipoproteinaemia type IV. Uric acid was at the upper limit of normal (430–610 μmol/l). There was a terminal increase in serum creatinine (122–134 μmol/l) interpreted as a consequence of heart failure. The urine was normal on repeated examination. Fundoscopy was normal except for slight angiopathy.

In the family history, the patient's father was found to have died after gastric surgery for peptic ulcer aged 57. The mother succumbed to myocardial infarction aged 73. His three brothers are reportedly healthy; one died in an accident. Two sisters and four daughters are healthy and free of any clinically detectable Fabry lesions (normal ECG, echocardiography, skin biopsy).

Autopsy findings were dominated by enormous cardiomegaly (1100 g). The left ventricle was concentrically hypertrophied with wall thickness ranging from 22 to 30 mm, being maximally expressed in the septum but without any sign of left outflow tract obstruction. The right ventricle was dilated with wall thickness 5–6 mm (measured in the outflow tract) (Fig. 1a). The trabecular network was prominent in both ventricles. The heart muscle was

firm, and yellowish. There was dense fibrosis in the left ventricle, accentuated anteroapically. The atria were dilated with slight hypertrophy. The parietal endocardium, the valves and the pericardium were normal. The coronary arteries were minimally affected with occasional atheromatous plaques in the anterior descending branch (50% reduction of the lumen). Aortic atherosclerosis was mild in extent.

The rest of the findings were unremarkable except for chronic congestion, thrombosis of the left femoral vein and successive pulmonary thromboembolism with recent lingular infarction. The kidneys were of normal size, had smooth surfaces and unremarkable inner structure and calyces.

Materials and methods

Tissues fixed in 10% formaldehyde were the starting material for all the analytical procedures. Routine histology was followed by lipid histochemical techniques encompassing birefringence, periodic acid-Schiff (PAS), ferric haematoxylin, Sudan black B, and cresyl violet carried out in both unextracted frozen sections and after extraction with chloroform-methanol 2:1 (v/v) for 30 min at room temperature (Elleder 1977). Lipopigment was detected using autofluorescence, Sudan black B, PAS, and permanganate-aldehyde fuchsin in paraffin sections after additional lipid extraction.

Ultrastructure was studied in samples fixed with 10% phosphate-buffered paraformaldehyde, dehydrated in ethanol and embedded in Araldite-Epon mixture. The myocardium was also examined after delipidization with chloroform-methanol (2:1) after Elleder and Šmíd (1977). The sections were contrasted with uranyl acetate and lead citrate.

For thin-layer chromatography (TLC) and ceramide trihexoside (CTH) quantitation, the tissue extract was subjected to alkaline methanolysis (Esselman et al. 1972) and chromatographed on high-pressure TLC plates (Merck, Darmstadt, FRG) in solvent system chloroform-methanol-water 65:25:4. Detection was by the Orcinol reagent. The spots were quantitated densitometrically after Nilsson and Svennerholm (1982). Differentiation between ceramide lactoside and ceramide digalactoside was done using isopropanol-28% NH_4OH water 75:10:15 as a solvent system.

For lipid isolation tortally porous silica-gel Separon SGX (Tessek, Prague, ČSFR) was used for the separation of glycolipids. A linear C:W>M gradient 83:16:05 (by volume) up to 55:42:3 (700 g+700 g) was used for the elution. The fractions were monitored photometrically using the orcinol reaction. The mass spectra of the stored lipid and its peracetylated and permethylated derivatives were measured using the FAB (fast atom bombardement) technique in positive and negative ion desorption. Proton NMR spectra were run on FT (Fourier transform) NMR spectrometer Varian XL-200 (at 200 MHz frequency) at 30° C. The solutions of ca 3 mg of the isolated lipid in the mixture of $CDCl_3+CD_3OD$ (1:1) and/or $CD_3SOCD_3+D_2O$ (95:5) were used for NMR experiments.

Alpha-galactosidase was assayed fluorometrically according to Dean and Sweeley (1977).

In the CTH degradation assay the ceramide double bonds of the isolated CTH were radio-labelled with tritium (Amersham Code TR 3) yelding 10^8 dps/mg lipid. An enzymatic assay of CTH alpha-galactosidase using the labelled lipid was carried out as follows. One microgram of lipid and 1 mg crude sodium taurocholate were dried and redissolved into a mixture of enzyme preparation and buffer. The enzyme preparation was 0.15 ml leucocyte or cultured skin fibroblast homogenates (0.2 and 0.06 mg protein, respectively). It was mixed with 30 µl sodium acetate buffer (0.5 M, pH 5.0) by brief sonication. After 15 h incubation at 37° C, 20 µl of the assay suspension was analysed by radio-TLC. The radioactivities were counted by liquid scintillation of the peak areas scraped off the thin layer. Authentic lactosyl- and glucosylceramide were used as controls.

In a tissue culture loading experiment 7 µg CTH with 20 µCi was dissolved in 100 µl ethanol and added to 5 ml culture medium above a confluent fibroblast layer with approx. 0.2 mg protein. After 4 days' incubation at 37° C, the radioactive medium was replaced with CTH-free medium and incubation continued for 1 day. The twice saline-washed cell layer was extracted in situ with methanol (0.7 ml, 30 min). The ethanol extract was removed, mixed with 0.3 ml chloroform and the mixture used for a 30-s re-extraction of the cell layer. This final extract was analysed by radio-TLC as in the above cell homogenate experiment.

Results

The storage process was manifested selectively in the heart muscle, with vacuolization or foamy transformation of the fibres (Fig. 1 d). Some of these displayed signs of disintegration being surrounded by small collections of foamy histiocytes. Many fibres were embedded in loose fibrous tissue. The conduction system (sinoatrial node, His bundle) was histologically either normal or slightly vacuolated. Lipid histochemistry showed a large number of liquid lipid crystals giving strong Maltese-cross-type birefringence, suggestive of a neutral glycolipid (stained with PAS, unstained with Cresyl violet) and absence of phospholipids (ferric haematoxylin method). There was a paucity of discrete cardiocyte lipofuscin granules in the cardiocytes in the delipidized sections together with some irregularly distributed PAS-positive diastase-resistant material.

Electronmicroscopy showed classical membranous cytoplasmic bodies consisting of concentric membranes with a 4.5 nm periodicity, sometimes bound by a single membrane (Fig. 1 c). Rarely, they contained admixture of lipofuscin residues from which they could be separated using lipid extraction. Focally there was a marked reduction of myofibrils leaving either free space or caused by deposition of randomly oriented filaments often arranged to form 5.7- to 6.7-nm-thick tubules with a high tendency to form abortive periodic structures. The latter displayed either a straight or curvilinear course. The material resisted lipid extraction and was even more recognizable in delipidized specimens. There were no signs of storage either in the endothelium or in other interstitial cells of the myocardium (Fig. 1 b).

Despite an extensive examination no lipid storage was recognized in any cell type in the coronary arteries, in the aorta, pulmonary artery, pancreas, liver, brain cortex and stem or kidney, using both histochemistry and electron microscopy. Kidney was available only as paraffin-embedded material.

TLC of the total lipid extract of the left ventricle muscle showed abnormal glycolipid spectrum with high accumulation of CTH (Fig. 2 a; and Table 1). Ceramide dihexoside (CDH) was increased very slightly against controls (Fig. 2 a). Both CTH and CDH were isolated on Sepharose SGX columns (Fig. 2 b) and subjected to further analysis. Using the isopropanol TLC solvent system (see Methods) CDH appeared to be composed of both ceramide lactoside and digalactoside (Fig. 2 c).

Mass spectroscopic analysis of CTH, of isolated CTH, its peracetylated and permethylated derivatives was performed. FAB mass spectra in positive and negative ion desorption were in agreement with the structure

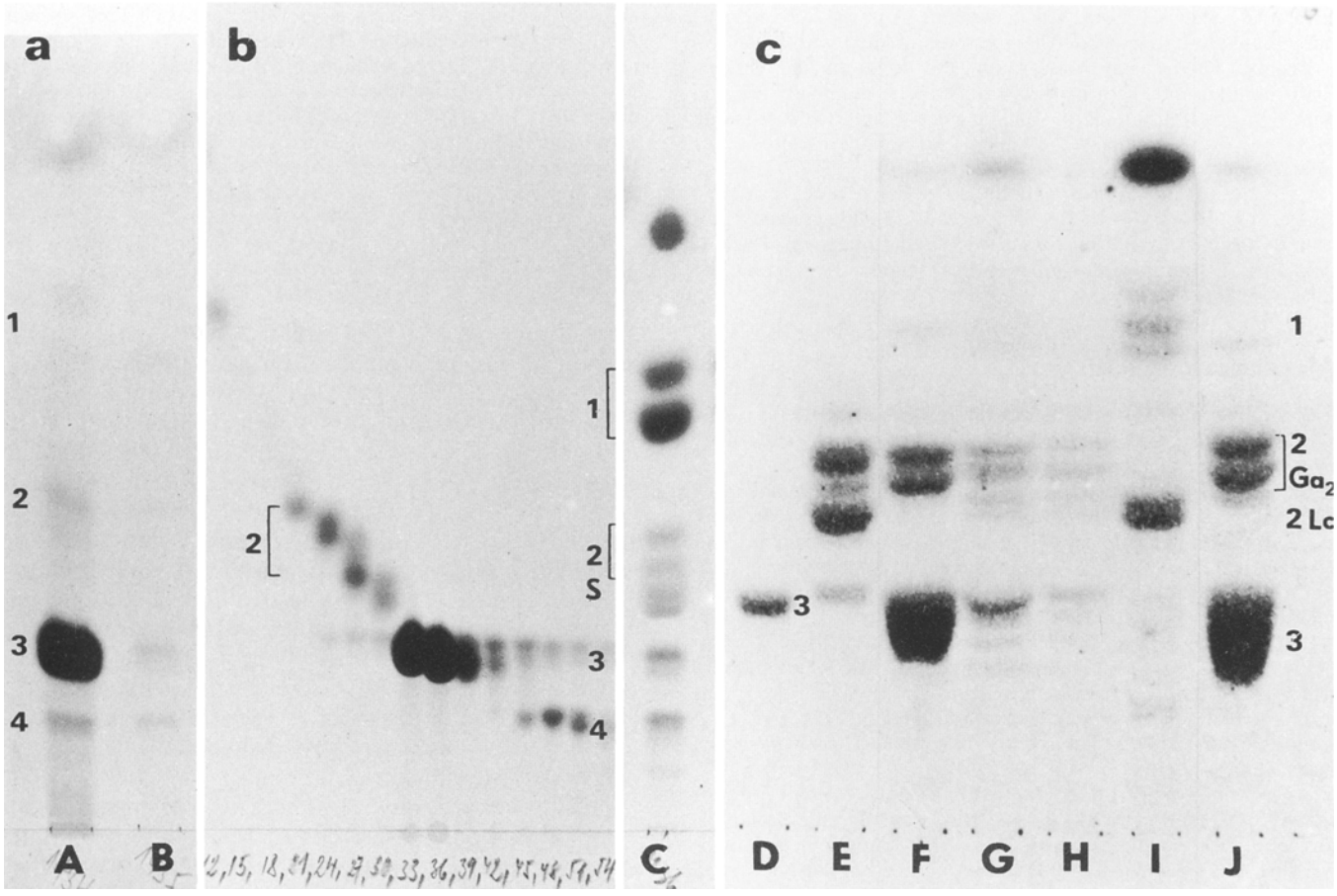

Fig. 2. a Thin-layer chromatography (TLC) heart muscle glycolipid pattern (solvent system chloroform:methanol:water 65:25:4) showing massive accumulation of ceramide trihexoside (CTH) (*A*) against controls (*B*). **b** TLC map of heart muscle glycolipids obtained on Silica-gel Sepharon SGX column. High-purity CTH (fractions 33–39) were used in subsequent analysis. Solvent system as in **a. c** Discrimination between ceramide lactoside and digalactoside by TLC using solvent system isopropanol:28% NH_4:water 75:10:15 v/v/v. Marked accumulation of ceramid digalactoside was found in the CDH fraction of our patient (*E*) similarly as in the urinary sediment of reference Fabry hemizygotes (*F, J*) and heterozygotes (*G, H*). Detection (**a–c**): orcinol-H_2SO_4 reagent. *1*, Ceramide monohexoside; *2*, ceramide dihexoside; *S*, sulphatides; *Ga_2*, ceramide digalactoside; *Lc*, ceramide lactoside; *3*, ceramide trihexosides; *4*, ceramide tetrahexosides; *D*, isolated CTH; *C, I*, reference glycolipid standards

Table 1. Heart weight and myocardial lipid storage in Fabry's disease

Case	Sex	Age (years)	Diagnosis	Heart weight	Stored CTH (mg/g wet wt)
907/89	M	75	Control	340 g	0.46
892/89	M	75	IHD	380 g	0.29
292/89	F	69	RHD+IHD	620 g	0.35
77/89	F	81	HHD	650 g	0.47
862/89	M	80	IHD	770 g	0.35
503/89	M	61	dCMP	900 g	0.35
M.D.[a]	M	63	FD var.	1100 g	11.5
V.Z.[b]	M	47	FD	520 g	13.6
Lou 1966	M	49	FD	760[c]	14.0
Desnick et al. 1976	M	55	FD+VHD	800	13.0
Ogawa et al. 1985	M	58	FD var.	375	16.5

CTH, Ceramide trihexoside; IHD, ischaemic heart disease; HHD, hypertensive heart disease; dCMP, dilatative CMP; RHD, rheumatic heart disease; VHD, valvular heart disease (storage induced); FD, Fabry's disease classical phenotype; FD var., Fabry's disease – purely cardiac variant

[a] Present case

[b] Classical FD (unpublished)

[c] See Jensen (1966) for clinical details

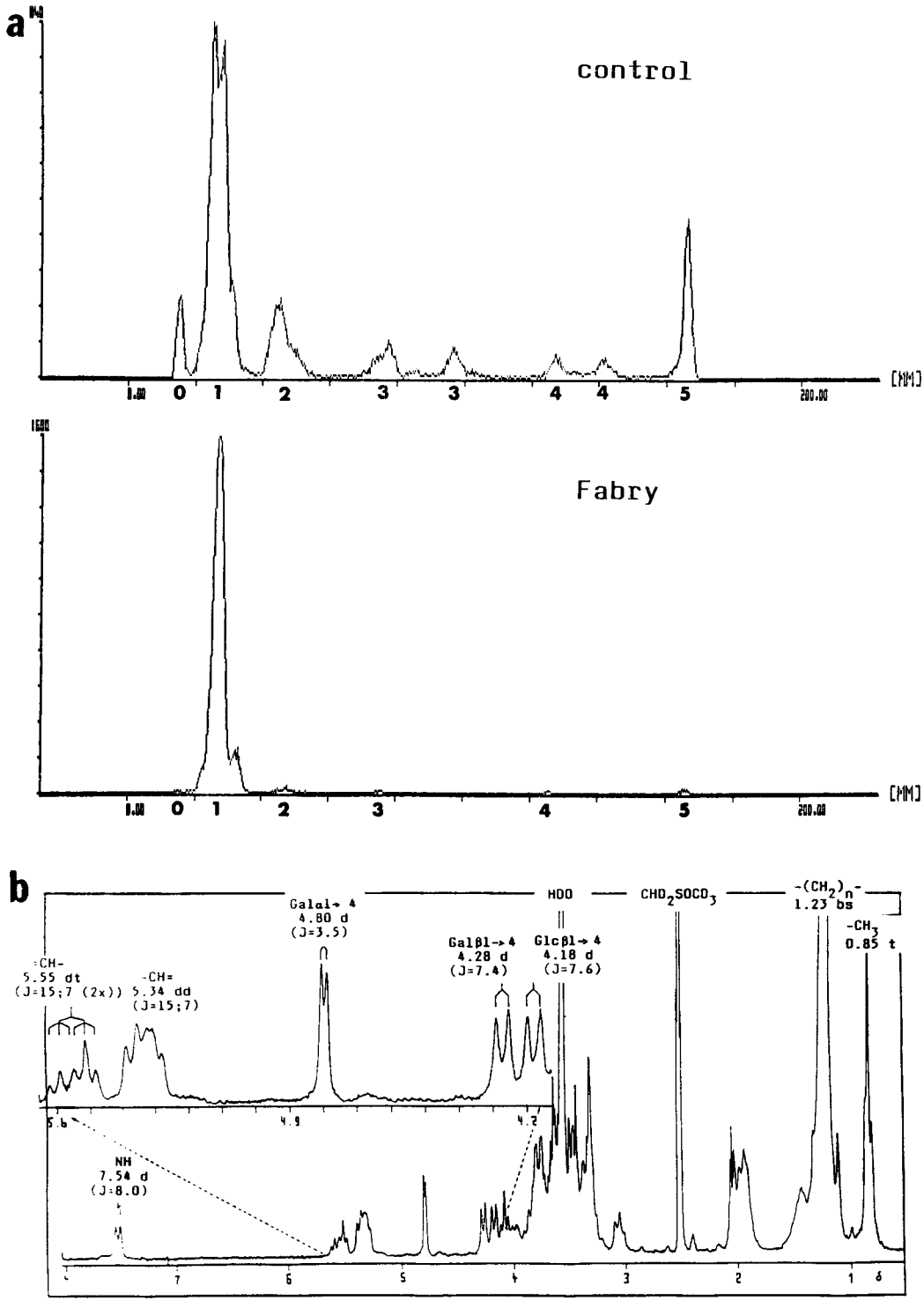

Fig. 3. Radio-TLC diagram (**a, b**) of control cultured fibroblasts (**a**) and reference Fabry mutant cells (**b**) fed with the labelled CTH isolated from the patient's myocardium (see Fig. 2b). The results show the stored CTH is a specific substrate for alpha-galactosidase. *0*, Origin from biosynthetic products (gangliosides?); *1*, remaining undegraded CTH; *2*, ceramide lactoside; *3*, glucosyl ceramides; *4*, ceramides; *5*, solvent front with further ceramide degradation products (fatty acids). All the spots had been compared with reference lipids. **c** ^{1}H NMR spectrum of the isolated CTH (see Fig. 2b) in $CD_3SOCD_3-D_2O$ (95:15)

of ceramide trihexoside. The observed fragmentation indicates the presence of fatty acid residues with 18, 22 and 24 carbon in chain. The NMR spectrum of native CTH dissolved in $CDCl_3+CD_3OD$ (1:1) showed a better resolution of ceramide protons. However, only one anomeric proton of the trisaccharide part could be observed (Fig. 3c). The others were obscured by residual signal from the solvent. Repeated measurement in the solvent mixture of $CD_3SOCD_3+D_2O$ (95:5) allowed us to detect all the three anomeric trisaccharide moiety

Table 2. Enzyme activities in peripheral leucocytes in patient's family members

	Enzyme activities (nmol[a]/mg protein/h)		
	α-Galactosidase	β-Galactosidase	β-Hexosaminidase
P.J., daughter	29.2	186	796
M.R., daughter	20.0	178	1243
J.B., daughter	29.3	192	1147
L.D., daughter	18.1	205	1618
V.M., sister	26.5	165.8	1363
M.R., sister	43.5	165	1268
Controls	46.6 ± 2.6 SD ($n=25$)	183 ± 9 SD ($n=30$)	1281 ± 52 SD ($n=30$)

[a] Methylumbelliferon released from MU glycosides used as substrates

protons (Fig. 3b). The chemical shifts and coupling constant values corresponded to the ^1H NMR data of globotriaosylceramide (Dabrowski et al. 1980).

Enzyme activities in peripheral leucocytes of consanguineous female members of the family including four daughters are shown in Table 2. Except for O.S. (patient's sister) all the values suggested heterozygosity and, indirectly, the hemizygous alpha – galactosidase – deficient state in the patient.

The stored CTH, tritium-labelled in the ceramide moiety was found to be degraded by enzyme preparations from various normal cells (leucocytes, about 5%; fibroblasts, about 2.5% degradation) as two additional peaks of radioactivity appeared which co-migrated with authentic lactosyl ceramide and glucosyl ceramide. After incubation with enzyme preparations from reference Fabry cells, no distinct additional peaks of radioactivity were released from the substrate peak (less than 0.5% degradation). In the cell culture loading experiment 9% and 12% of the CTH-bound radioactivity was incorporated in the control and Fabry fibroblasts, respectively. The controls cells metabolized 46% of the incorporated CTH while the Fabry cells degraded only 8% of the critical lipid (Fig. 3a, b).

Discussion

There are two peculiar features of the present case which warrant discussion. Firstly, the restriction of the storage process to cardiocytes is in stark contrast to the generalized pattern of storage in the classical Fabry phenotype (Desnick and Bishop 1989). An intriguing feature was the intensity of the cardiocyte lipid storage which matched that in classical generalized cases (see Table 1) having the same detrimental effect on the heart function. While the rest of the tissues in this hemizygote are protected against storage, the consequences of the deficient enzyme function are manifested only in the cardiocytes. The extramyocardial "protection" from storage may be explained by some residual catalytic activity of the mutant enzyme (described in similar cases; see Hübner et al. 1988; Mall et al. 1985), leading for some unknown reason, to a functional deficit solely in cardiocytes, perhaps due to high glycolipid turnover. The nature of the fibrillar non-lipid deposits is also unknown. The second peculiar feature of the present case is the marked cardiac hypertrophy, and its pattern. The weight of the heart in our case exceeded that of the cases reported so far which ranged from 430 g (Machinami 1972) to 890 g (Bannwart 1982). In some cases the storage hypertrophy was compounded by functional hypertrophy due to valvular dysfunction (also storage induced; see Desnick et al. 1976) and/or hypertension (Bannwart 1982; Becker et al. 1975; and others). The usual pattern of cardiac hypertrophy in classical Fabry's disease is a non-specific eccentric one which bears some resemblance to dilatative (congestive) CMP (Wynne and Braunwald 1988). A pattern of hypertrophic CMP associated or unassociated with the left outflow tract obstruction has been reported (Bannwart 1982; Colucci et al. 1982; Cohen et al. 1983; Frentzel et al. 1983; Fritz et al. 1978; Sakuraba et al. 1986). Among the most interesting group of living Fabry hemizygotes with myocardial restricted storage, two were of the hypertrophic CMP type (Mall et al. 1985); in one the degree of heart hypertrophy was not specified (Hübner et al. 1988). In one postmortem case the heart hypertrophy was borderline degree (Ogawa et al. 1985) contrasting with massive CTH storage. It should be pointed out that the heart restricted storage with hypertrophic CMP may occur even in heterozygous females (Sakuraba et al. 1986; Yokoyama et al. 1987).

Any discussion on the divergent cardiocyte reaction to the common stimulus of lysosomal storage is hampered by lack of detailed knowledge of the mechanism of both the storage-induced hypertrophy and of CMP in general (reviewed by Wynne and Braunwald 1988) best demonstrable by the independence of the heart hypertrophy on the storage intensity (see Table 1).

This Fabry phenotype may represent a novel variant to be added to the spectrum of the disease. Similar variants suggesting storage restriction to the kidney have been described (case 1 in Clarke et al. 1971; reported also by Romeo et al. 1975). It should be borne in mind that the diagnosis of these oligosymptomatic or monosymptomatic disease variants may be extremely difficult due to the absence of storage in the usual bioptic sites such as the skin, or kidney. It also explains why all the previous cases of this novel monosymptomatic phenotype were diagnosed accidentally during routine endomyocardial biopsy examination (Hübner et al. 1988; Mall et al. 1985) or some time after autopsy. In all instances the microscopic discovery of the selective cardiocyte lipid storage directed the diagnostic process from CMP to that of a storage disease.

Cardiac symptomatology in the Fabry phenotype includes this monosymptomatic, purely cardiac, variant of Fabry disease. The disease patterns described so far include that of hypertrophic CMP both in hemizygotes (Mall et al. 1985; and the present case) and heterozy-

gotes (Sakuraba et al. 1986; Yokoyama et al. 1987). A quite mild heart affection with nonspecific (Hübner et al. 1988) or minimal clinical signs (Ogawa et al. 1985; Abe et al. 1988) has also been described. In the generalized classical variant with poly/oligo symptomatic a clinical picture in which heart dysfunction is manifested in about 30% (Mossard et al. 1972) is characteristic. In most instances the heart disease shows a pattern of eccentric hypertrophy, resembly dilatative (congestive) CMP. It may present as hypertrophic, obstructive or non-obstructive CMP (Colucci et al. 1982; Frenzel et al. 1983; Fritz et al. 1978; Sakuraba et al. 1986).

The real incidence of the monosymptomatic Fabry variant presenting as isolated primary heart disease is difficult to estimate, as endomyocardial biopsy is difficult to perform on a mass scale. Screening using an alpha-galactosidase activity assay in peripheral leucocytes, particularly in the CMP group, may prove useful. Some of these cases may represent an atypical monosymptomatic variant of the Fabry's disease.

References

Abe T, Ogawa K, Fujiwara Y, Sugamata K, Nagashima K (1988) Specific accumulation of Gb Cer in cardiac tissues in novel cases of Fabry's disease. Proceedings of the Third International Conference on the Biomedical Significance of Glycolipids, September 1988, Tokyo

Bannwart F (1982) Licht- und elektronenmikroskopischer Herzbefund 12 Jahre nach erfolgreicher Nierentransplantation. Schweiz Med Wochenschr 112:1742–1747

Becker AE, Schoorl R, Balk AG, Heide RM van der (1975) Cardiac manifestation of Fabry's disease. Report of a case with mitral insufficiency and electrocardiographic evidence of myocardial infarction. Am J Cardiol 36:829–835

Cohen IS, Fluri-Lundeen J, Wharton TP (1983) Two dimensional echocardiographic similarity of Fabry's disease to cardiac amyloidosis: a function of ultrastructural analogy? J Clin Ultrasound 11:437–441

Colucci WS, Lorell BH, Schoen FJ, Warhol MJ, Grossman W (1982) Hypertrophic obstructive cardiomyopathy due to Fabry's disease. N Engl J Med 307:926–928

Dabrowski J, Hanfland P, Egge H (1980) Structural analysis of glycosphingolipids by high resolution H nuclear magnetic resonance. Biochemistry 19:5652–5658

Dean KJ, Sweeley CC (1977) Fabry disease. In: Glew RH, Peters SP (eds) Practical enzymology of sphingolipidoses. Liss, New York, pp 173–216

Desnick RJ, Bishop DF (1989) Fabry Disease: alpha-galactosidase deficiency; Schindler disease: alpha-N-acetylgalactosaminidase deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic basis of inherited disease. McGraw-Hill, New York, pp 1751–1796

Desnick RJ, Blieden LC, Sharp HL, Hofschire PJ, Moller JH (1976) Cardiac valvular anomalies in Fabry disease. Clinical, morphologic, and biochemical studies. Circulation 54:818–825

Elleder M (1977) Lipid histochemistry – a critical survey. Acta Histochem (Jena) [Suppl] 19:239–265

Elleder M, Šmíd F (1977) Lysosomal non-lipid component of Gaucher's cells. Virchows Arch [B] 26:133–138

Esselman WJ, Laine RA, Sweeley CC (1972) Isolation and characterization of glycosphingolipids. In: Ginsburg V (ed) Methods in enzymology, vol XXVIII. Complex carbohydrates, part B. Academic Press, New York, pp 141–156

Frenzel H, Kuhn H, Hort W (1983) Die diagnostische Bedeutung der Endomyokardialbiopsie (EMcB) bei hypertrophischer nicht obstruktiver Kardiomyopathie (CMP) (abstract): Z Kardiol 72 [Suppl 1]:8

Fritz P, Schneider H, Heimburg P, Wegner G (1978) Sekundare hypertrophe obstruktive Kardiomyopathie bei Morbus Fabry. Med Welt 29:1851–1854

Hübner G, Gokel JM, Erdmann E, Scheidt W von, Christomanou H (1988) Isolierter Morbus Fabry des Herzens. Eine bisher unbekannte Variante des alpha-Galactosidasemangels A. Verh Dtsch Ges Pathol 72:580

Jensen E (1966) On the pathology of angiokeratoma corporis diffusum (Fabry). Acta Pathol Microbiol Scand 68:313–331

Kobayashi T, Kira J, Shinnoh N, Goto I, Yoshigoro K (1985) Fabry's disease with partially deficient hydrolysis of ceramid trihexoside. J Neurol Sci 67:179–185

Lou HOC (1966) A biochemical investigation of angiokeratoma coprporis diffusum. Acta Pathol Microbiol Scand 68:332–342

Machinami R (1972) Autopsy case of Fabry's disease. Acta Pathol Jpn 22:409–426

Mall G, Schwarz F, Zebe H, Kubler W (1985) Herzhypertrophie: Differential Diagnose an Endomokardialbiopsien. In: Mall G, Otto HF (eds) Herzhypertrophie. Springer, Berlin Heidelberg New York, pp 196–199

Mossard JM, Jossot G, Wolfe LS, Batzen-Schlager A, Stoebner P, Metzger H (1972) La coeur dans la maladie de Fabry. Arch Mal Coeur 65:495

Nilsson O, Svennerholm L (1982) Characterization and quantitative determination of gangliosides and neutral glycosphingolipids in human liver. J Lipid Res 23:327–334

Ogawa K, Abe T, Yoshimura K, Nagashima K, Nagashima T (1985) Cardiac accumulation of trihexosyl ceramide in a case with amyotrophic lateral sclerosis. Jpn J Exp Med 55:123–127

Romeo G, D'Urso M, Pisacane A, Blum E, DeFalco A, Ruffilli A (1975) Residual activity of alpha-galactosidase in Fabry's disease. Biochem Genet 13:615–628

Sakuraba H, Yanagawa Y, Igarashi T, Suzuki Y, Suzuki T, Watanabe T, Ieki K, Shimoda K, Yamanaka T (1986) Cardiovascular manifestations in Fabry's disease. Clin Genet 29:276–283

Yokoyama A, Yamazoe M, Shibata A (1987) A case of heterozygous Fabry's disease with a short PR interval and giant negative T waves. Br Heart J 57:296–299

Wynne J, Braunwald E (1988) The cardiomyopathies and myocarditides. In: Braunwald W (ed) Heart disease, 3rd edn. A textbook of cardiovascular medicine. Saunders, Philadelphia, p 1410