M. Elleder - H. Christomanou - B. Kustermann-Kuhn
K. Harzer

Leptomeningeal lipid storage patterns in Fabry disease

Received: 6 April 1994 / Revised, accepted: 18 July 1994

Abstract We found two patterns of leptomeningeal storage that reflect two basic visceral storage patterns in Fabry disease. (i) A generalized-type leptomeningeal storage pattern, affecting all main leptomeningeal cell types (external arachnoideal epithelium, fibroblasts, vessel wall elements), was a consistent finding in three cases of classical generalized visceral phenotype. (ii) A localized leptomeningeal storage pattern was expressed, to a high degree, solely in the external arachnoidal epithelium; this pattern was found in one case with the variant visceral-restricted-type storage (confined to the cardiocytes). Thus, the external arachnoidal epithelium may be particularly susceptible to Fabry lipid storage, probably caused by a distinctly larger sustained lysosomal lipid load as compared to other cell types.

Key words Fabry disease - Leptomeningeal storage External arachnoideal epithelium - Restricted type of visceral storage

Introduction

Fabry disease is a well-defined X-chromosome-linked lysosomal lipidosis caused by a deficiency of α-galactosidase A, leading to excessive storage of globotriaosyl ceramide (trihexosyl ceramide, THC) and dihexosyl ceramide (DHC). The THC/DHC ratio usually exceeds 1, but approaches this value in some tissues. The ensuing clinical phenotype, in its classical form, shows a complex of renal, cardiovascular, dermatological and neurological symptoms [4]. Atypical phenotypes with single organ (heart) affection have often been described [5, 15]. The peak area of the storage in Fabry disease is regularly found in cardiomyocytes and in the vessel wall elements. Although the brain is usually spared (as are neurons and glia), it is constantly affected by storage in the leptomeninges, including the ectomeningeal complex.

In this communication, we demonstrate a prominent storage in the external arachnoidal epithelium not only in the generalized, but also in the restricted (myocardial) Fabry phenotype, where other tissues are histochemically and ultrastructurally normal. The findings are discussed in relation to the peculiar anatomical organization of the ectomeningeal complex.

Material and methods

Superficial parts of formaldehyde-fixed brains with adjacent leptomeninges from four cases of Fabry hemizygotes were used for analysis. Three cases were of classical clinical phenotype; in the fourth the storage was restricted to the myocardium. The clinical picture of the latter case was that of the hypertrophic-obstructive cardiomyopathy, thus resembling cases recently described [5, 15]. The patient was relatively well for a number of years and died from a bile duct carcinoma aged 65 years. In repeated assays of his leukocytes α-galactosidase activity, the residual activity was less than 5% of the mean control activity. Histochemical and ultrastructural analysis showed massive storage in the cardiocytes (heart weight 750 g), but failed to disclose any storage in the heart capillaries and in the skin sample. There were occasional storage lysosomes in the kidney glomerular cells and questionable finding in the liver cells (modified by cholestasis). Brain structures were also negative (unpublished results).

Part of each specimen was embedded in gelatin, cut frozen and examined for birefringence and stained with PAS, with and without pre-extraction with chloroform-methanol 2:1 (v/v). Parts were postfixed with 1% OsO₄, dehydrated with ethanol and embedded in an Araldite-Epon mixture. Thick sections were stained with alkaline toluidine blue, and thin sections were double contrasted with lead citrate and uranyl acetate.

Biochemical analysis of lipids of tissue from the variant phenotype case was carried out according to Bradová et al. [2].
Results

We observed essentially two patterns of storage in the leptomeningeal tissue complex, which corresponded well to the extent of the visceral storage.

The generalized form was uniformly seen in all three cases with the classical generalized clinical phenotype. All cell types were found to be affected by storage of birefringent PAS-positive lipid droplets, consisting ultrastructurally of densely packed lipid membranes. The storage was expressed most strongly in the superficial arachnoideal layer, in the arachnoideal villi and in the vessel wall elements. It was less intensive and less constantly expressed in the fibroblast-like elements in the arachnoideal trabecules and in the pia mater.

The localized pattern was seen in the case with atypical clinical phenotype (see Material and methods). The storage was confined solely to the superficial arachnoideal layer and its derivatives, i.e., the arachnoideal villi and Pacchionian granulations. The cells in these areas were loaded to various degrees with lipid granules that had the same ultrastructural (Fig. 1) and histochemical features as those seen for the generalized storage pattern (Fig. 2 a–c). The storage cells were inter-connected with desmosomes.

Fig. 1 Present case with variant restricted (myocardial) type Fabry disease. Electronogram of the external arachnoid epithelial cell displaying high degree of lysosomal lipid storage. × 15 000

Fig. 2 a–c Present variant Fabry case. a Lipid storing external arachnoid epithelium is intensely birefringent (frozen section, gelatin embedded leptomeningeal, × 300 unstained. b Lipid storing superficial arachnoid epithelium (birefringent in a) stain dark with alkaline toluidine blue. The deeper parts of arachnoidea are fibrously thickened and free of storage (semithin section, toluidine blue, × 360). c Absence of storage in the arterial wall cells. The tiny granules (arrow) in the adventitial cell in lipofuscin (semithin section, toluidine blue, × 360)