ON THE DIAGNOSES OF FABRY'S DISEASE

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Abstract. Fabry's disease is a recessive X-linked inborn error of metabolism due to deficiency of the lysosomal enzyme α-galactosidase. The large variety of symptoms may make the diagnosis difficult. A severely afflicted female patient is presented. For several years she had been treated under the diagnosis polyarteritis nodosa until the characteristic cutaneous lesions of Fabry's disease were recognized. Enzymatic studies and electronmicroscopic examinations confirmed the diagnosis. A symptomatic effect of corticosteroid treatment was proven. The grave prognosis, the recent attempts at enzyme substitution therapy and the possibility of preventing new cases by prenatal diagnosis should stimulate the efforts of the clinician to diagnose the disease.

Key words: Fabry's disease; Angiokeratoma; α-galactosidase; Sphingolipidoses

CASE REPORT

The patient is a 28-year-old woman. She has been admitted several times to different hospitals in Denmark and Sweden during the last 7 years under the diagnosis of collagen disease.

At the age of 13 (1959) pin-head sized red spots gradually appeared on the skin of the lower abdomen. However, these lesions remained unnoticed until March 1974. At the age of 17 she developed recurrent, severe, left-sided facial pain and at the age of 19 attacks of severe, burning pain in the muscles of the neck, shoulders and extremities. These attacks were usually provoked by physical activity, fever or heat. Progressive fatigue, excessive need for sleep, headaches and recurrent episodes of unexplained fever, with extremity pains, hypersensitivity to touch, and paresthesia occurred; no motor defects were observed.

During the period 1966-73 she was admitted about 25 times to different hospitals because of these symptoms. Corneal opacities were demonstrated as early as 1967. The patient complained of periodically blurred vision, but visual acuity was unimpaired, and no defects in the visual field were demonstrable. The diagnoses considered were rheumatic fever, atypical facial pains, polyarthritis rheumatica, and polyarteritis nodosa. The latter diagnosis was based on a biopsy from a subcutaneous swelling that showed pronounced fibrinoid necrosis in the vessel walls surrounded by granulation tissue densely infiltrated by polymorphonuclear granulocytes, whereas eosinophils and lymphocytes were sparse. All biopsies from skeletal muscles have shown normal histology.

Treatment with systemic corticosteroids was initiated in 1971. In a few months the patient developed a pronounced cushingoid appearance. Attempts to reduce the dosage of steroid failed because of a concomitant flare-up of the fever and muscle pains.

In March 1974 the patient was admitted to the Medical Department TA, Rigshospital. She was in no acute distress, and there was no evidence of musculoskeletal or neural involvement. Her blood pressure was slightly elevated (150/100 mmHg), and the creatinine clearance was slightly decreased (1.0 ml/sec), but no other signs of renal involvement were observed. She was referred to the Department of Dermatology because of pityriasis versicolor, but, in addition, multiple pin-head sized haemangiomas were found on the lower part of the abdomen and on the upper thighs (Fig. 1), and the diagnosis of Fabry's disease was suggested. Light
microscopy of biopsy material from a haemangioma revealed dilated capillaries just below the epithelium, but no intra-epithelial lakes containing erythrocytes. No pronounced hyperkeratosis was seen, and no lipid deposits could be demonstrated by lipid staining methods or by polariscope examination. The diagnosis was subsequently confirmed by the demonstration of decreased α-galactosidase activity in serum (50% of normal level) and in leucocytes (30% of normal) (5). Electronmicroscopy of biopsy material from the haemangiomas revealed the diagnostic lamellar osmiophilic granules (Fig. 2).

A second investigation of the family history revealed that the patient belonged to family I described in Lou’s monograph (7) on Fabry’s disease.

As soon as the diagnosis was established, corticosteroid treatment was tapered off to zero. This immediately caused a severe acute exacerbation, and reinstitution of prednisone was necessary. The patient left for the USA shortly after the diagnosis of Fabry’s disease was established and was therefore referred to Brady’s group at the NIH, where clinical trials of enzyme replacement therapy for this disorder are in progress (1). Prenatal examination of enzyme activity in desquamated foetal cells in connection with future pregnancies has been recommended.

COMMENTS

Because Fabry’s disease is considered to be inherited as a recessive X-linked trait, it may be overlooked that the disease may be manifest in females. In most cases a related male will be suffering from the disease, so that a careful family history will give rise to a suspicion of Fabry’s disease. Corneal opacities constitute the most common symptom in heterozygous females suffering from the disease, while skin manifestations are not a constant finding. The patient reported here had a typical family history, corneal opacities and skin manifestations. Nevertheless, the diagnosis was not considered until the typical skin lesions were recognized.

The diagnosis may be confirmed by biopsy from the angiokeratomas which show intracellular vacuolization and PAS-positive granules in frozen sections, with double-refractile lipid material (4). Di- and trihexosceramide and lipid-containing cells are often present in the urine. Demonstration of a decreased activity of α-galactosidase establishes the diagnosis.

Electron microscopic examination of the PAS-positive granules is also of diagnostic value. The granules consist of a lamellar system with alternating electron-opaque and light areas with a periodicity of 42-62 Å. They closely resemble the lamellar

Fig. 1. Lesions of angiokeratoma corporis diffusum, present particularly on the lower torso (arrow). The lesions are dark red, telangiectatic macules or papules; no overlying hyperkeratosis is present.

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osmiophilic structures in other sphingolipidoses (Tay-Sachs, Niemann-Pick), but differ from these in ultrastructural details (4, 9). To our knowledge, these typical granules have not been described previously in a heterozygous female patient.

The multiplicity and severity of symptoms in our patient is of interest. Heterozygotes with a residual enzyme activity of only 20–25% may be completely healthy, and after kidney transplantation, which restored the enzyme activity in a hemizygote to 5–20% of normal values, biochemical improvement and disappearance of clinical symptoms were observed (10). Analysis of serum and leukocytes from our patient disclosed an α-galactosidase activity which was 30–50% of normal, indicating that the severity of the clinical symptoms cannot be deduced from the results of these laboratory studies. Systemic corticosteroid treatment had a proven effect in our patient, since discontinuation of prednisone on several occasions was associated with severe exacerbation of symptoms, with remissions occurring less than 24 hours after reinstitution of treatment. The patient was discharged on a dosage of 7.5 mg of prednisone daily.

A male patient with Fabry’s disease followed-up at the Rigshospital likewise cannot be tapered down to less than 7.5 mg of prednisone daily (E. Christensen, personal communication).

Rational trials on enzyme substitution are in progress (1, 8, 10), and prenatal diagnosis in the offspring of female carriers is possible (2). These facts should stimulate careful evaluation for Fabry’s
disease in patients with suspect or obscure symptoms with or without concomitant skin lesions. Suspicion should be aroused if one or more related males have died before the age of 40 because of cardiac or renal failure or a cerebrovascular attack. When a new case is diagnosed the relatives should be examined, and α-galactosidase activity should be determined. The detection of heterozygous females makes genetic counselling possible, including prenatal diagnosis by which further cases can be prevented.

REFERENCES

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