Case Report

Familial case study: a recurrent metabolic disease in a Tunisian family

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Abstract

We report a recurrent case of Sly syndrome in a Tunisian family. The mother was a 32-year old, parity three, five gestations, from a first-degree consanguineous marriage. Her first pregnancy ended in a miscarriage; the second pregnancy ended with the birth of a healthy child. The other three pregnancies were interrupted through medical intervention due to hydrops fetalis.

The histological placental examination of the first two fetuses found cytoplasmic vacuolization affecting the trophoblast and Hofbauer cells (Hale coloration). The prenatal diagnosis by amniocentesis of the third pregnancy revealed a high level of glycosaminoglycans with a predominance of chondroitin sulfates in electrophoresis, confirming the diagnosis of Sly disease.

In conclusion, the histological examination of the placenta is essential for the biological and genetic examination, as a basis for the diagnosis of Sly disease and for a further genetic counseling.

Key words

Hofbauer cells, hydrops fetalis, mucopolysaccharidosis VII, placenta, Sly syndrome.

Introduction

Lysosomal storage diseases are a group of 50 inherited monogenic diseases that are characterized by malfunctioning lysosomes and an accumulation of unprocessed biopolymers in various tissues and organs. The clinical symptoms progressively develop with a coarsening of facial features, bone, skin, and eye changes, organomegaly and a severe retardation in the neuropsychological development. Lysosomal storage diseases belong to the group of rare diseases. As separate diseases, they are extremely rare, but the incidence of the group as a whole is 1 in 5000-7000. The most common classification of lysosomal storage diseases is according to the type of metabolite accumulating in lysosomes mucopolysaccharidoses, glycoproteinoses, sphingolipidoses and glycogenoses [1].

Mucopolysaccharidoses are a large heterogenous group caused by a deficit of any of the eleven enzymes involved in the metabolism of these biopolymers [2, 3]. They are characterized by an intracellular accumulation and increased excretion of mucopolysaccharides (glycosaminoglycans, GAGs) [2, 3]. Mucopolysaccharidosis type VII (MPS VII), or Sly syndrome, is a rare lysosomal storage disorder first described by Sly et al. in 1973 [4]. MPS VII occurs in less than 1 out of 250,000 births. It is an autosomal recessive disease caused by a deficiency of the enzyme β-glucuronidase, leading to a lysosomal accumulation of heparan, dermatan and chondroitin sulphate [5, 6]. The gene for β-glucuronidase is mapped to be at 7q 21.2-22.

According to the clinical symptoms, MPS can be divided into four phenotypes: MPS which predominantly affects the skeleton and soft tissues; MPS which only affects the skeleton and soft tissues; MPS which affects the skeleton; MPS which predominantly affects the central nervous system [8]. The diagnosis of lysosomal storage diseases and, in particular, of MPS VII is based on the histopathologic discovery of an accumulation of metabolites and a confirmation of an enzyme deficiency by electrophoresis.

The clinical diagnosis is always difficult due to the polymorphism of clinical symp-

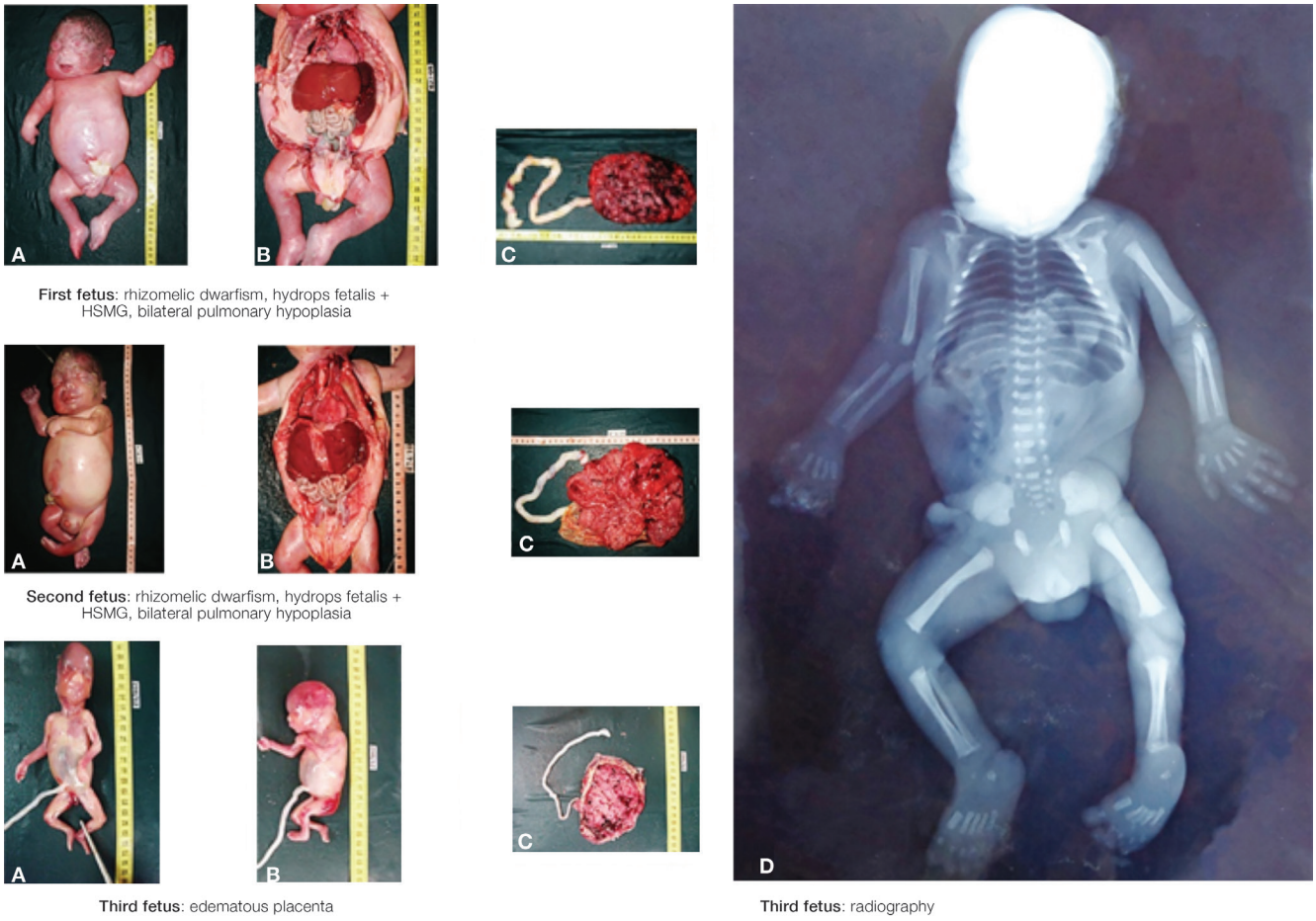

Figure 1. Macroscopic examination of the three fetuses and their placentas (left panel, A-C); radiography of the third fetus (right panel, D).

toms [7]. The genetic heterogeneity of lysosomal storage diseases limits the diagnostic and prognostic capabilities of a genomic analysis. The first ultrasound symptoms are always anasarca and a thickened nuchal fold in the first trimester, progressive ascites in the second trimester, and a pericephalical edema or a generalized edema of the body, often accompanied by ventriculomegaly. Facial dismorphia with an indentation of the middle level of the face was observed. There were also multiple hypertrophic epiphysal disostoses, fetal immobilization, vacuolated lymphocytes and anemia or thrombocytopenia.

Case presentation

We report a recurrent case of Sly syndrome in a Tunisian family and the treatment of this condition.

A 32-year old woman, parity three, five gestations, 0+ blood group from a first-degree consanguineous union. Her first pregnancy ended in a miscarriage; the second pregnancy ended with the birth of a healthy child (now a 6-year old daughter). The other three pregnancies were interrupted through medical intervention due to hydrops fetalis. The karyotypes of these three fetuses were normal. A fetal examination was performed in all three cases.

The three fetuses all had facial dismorphism – pericephalical edema in the first two fetuses and a thickened nuchal fold in the third fetus, hypertelorism and prominent infra-orbital folds, long philtrum, low-set and malformed ears (Figure 1A). All three fetuses had very short necks (Figure 1A).

In the three fetuses there were symptoms of multiple dysostosis, which in the first two fetuses was represented by a rhizomelic dwarfism (Figure 1A). The radiography of the third fetus shows multiple symptoms of dysostosis – shortened and thick proximal and distal ends of long bones, pes equinovarus and abnormalities of the vertebral bodies and arches. The epiphyses had a rugged contour (Figure 1D).

The three fetuses had hydrops, hepatosplenomegaly and bilateral pulmonary hypoplasia (Figure 1B). The brain examination found no neuropathological signs. The histological examination showed no abnormalities of the visceral organs in all autopsies. The macroscopic study found an edema of the placenta (Figure 1C). The microscopic

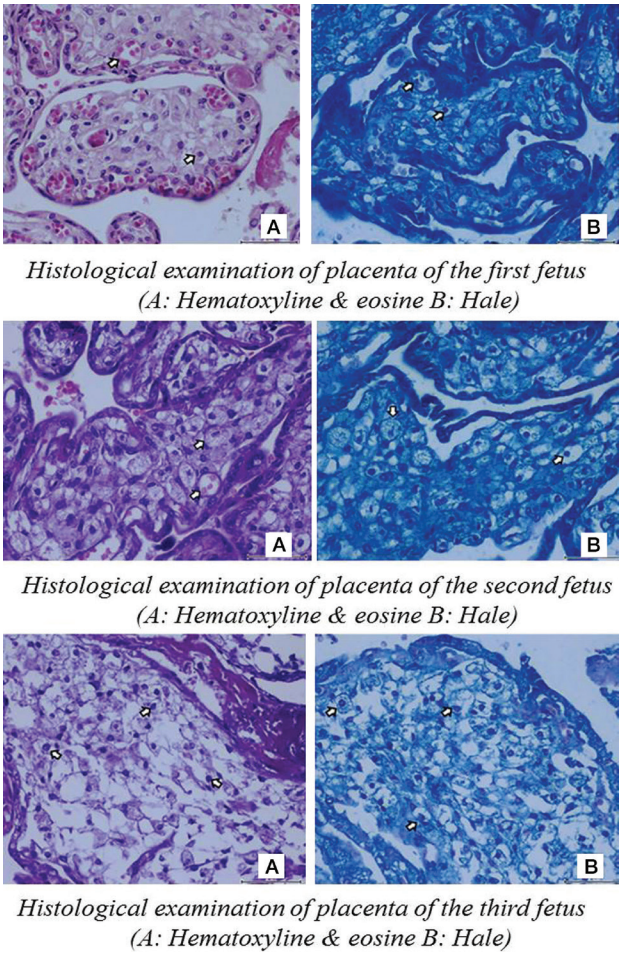

Figure 2. The histological examinations of the placentas.

examination of the placenta of the fetuses found evidence of accumulation-vacuolization of the Hofbauer cells.

The placenta of the second fetus had reproduced the same lesions and the Hale coloration showed cytoplasmic vacuolization affecting the trophoblast and Hofbauer cells-suggesting Sly syndrome (Figure 2).

The prenatal diagnosis by amniocentesis has been done for the third pregnancy. It revealed a high level of glycosaminoglycans with a predominance of chondroitin sulfates during the electrophoresis, confirming the diagnosis of Sly syndrome.

Conclusion

The association of hydrops fetalis, hepatosplenomegaly and multiple dysostosis with consanguinity is suggestive of a metabolic disease. The histological examination of the placenta is essential to diagnose Sly syndrome. The biological and genetic examinations confirm the diagnosis and may be used as a basis for counseling.

References

1. Maire I. Mucopolysaccharidose de type VII ou maladie de Sly. Encyclopédie Orphanet 1998.
2. Huynh HT, Grubb JH, Vogler C, Sly WS. Biochemical evidence for superior correction of neuronal storage by chemically modified enzyme in murine mucopolysaccharidosis VII. Proc Natl Acad Sci USA 2012;109(42):17022-7.
3. Rowan DJ, Tomatsu S, Grubb JH, Haupt B, Montaño AM, Oikawa H, Sosa AC, Chen A, Sly WS. Long circulating enzyme replacement therapy rescues bone pathology in mucopolysaccharidosis VII murine model. Mol Genet Metab 2012;107(1-2):161-72.
4. Rowan DJ, Tomatsu S, Grubb JH, Montaño AM, Sly WS. Assessment of bone dysplasia by micro-CT and glycosaminoglycan levels in mouse models for mucopolysaccharidosis type I, IIIA, IVA, and VII. J Inherit Metab Dis 2013;36(2):235-46.
5. Hytönen MK, Arumilli M, Lappalainen AK, Kallio H, Snellman M, Sainio K, Lohi H. A novel GUSB mutation in Brazilian terriers with severe skeletal abnormalities defines the disease as mucopolysaccharidosis VII. PLoS One 2012;7(7):e40281.
6. Huang YL, Li SY, Zhao XY, Fan LP, Lin WC, Zhou ZH, Cheng J, Liu L. Enzymatic diagnosis and clinical characteristics of 52 children with mucopolysaccharidosis. Zhongguo Dang Dai ErKeZaZhi 2012;14(7):510-4.
7. Beck M. Variable clinical presentation in lysosomal storage disease. J Inherit Metab Dis 2001;24(2);47-56.
8. Muenzer J. The mucopolysaccharidosis: a heterogeneouse group of disorders with variable pediatric presentation. J Pediatr 2004;144(5):S27-34.