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In-utero diagnosis of mucopolysaccharidosis type VII in a fetus with an enlarged nuchal translucency

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ABSTRACT

Mucopolysaccharidosis type VII was diagnosed prenatally during the first pregnancy of a Turkish consanguineous couple, following diagnostic work-up of an increased nuchal translucency detected by ultrasound at 13 weeks of gestation. Mucopolysaccharidosis type VII (MPS VII) or Sly syndrome is a rare autosomal recessive lysosomal storage disease, caused by the deficiency of the enzyme β-glucuronidase. The most severe form of MPS VII manifests itself by non-immune fetal hydrops. Tests for the diagnosis of metabolic disorders, especially lysosomal diseases, are essential when the major causes of hydrops fetalis have been excluded. The presence of a β-glucosidase deficiency, Gaucher's disease, in the infant of the patient's sister emphasizes the importance of a complete family history in consanguineous couples and the risk for several recessive diseases in some families.

INTRODUCTION

Mucopolysaccharidosis type VII (MPS VII) or Sly syndrome is a rare autosomal recessive storage disease caused by the deficiency of the enzyme β-glucuronidase. The first case was reported in 1973[1]. Various phenotypes of this metabolic disorder have been described[2,3]. The most severe form of MPS VII, non-immune fetal hydrops, has been reported in several fetuses[4–10]. Clinical signs at birth or within the first years of life are coarsened faces, hepatosplenomegaly, corneal clouding, frequent respiratory infections, umbilical or additional inguinal herniae, leukocyte inclusions, short stature and developmental retardation. Another mild phenotype becomes manifest in the second decade of life and presents with mild bony changes (X-ray), mild facial coarsening, normal growth and normal mental development.

Diagnosis of MPS VII is established by demonstrating β-glucuronidase deficiency in tissues, fibroblasts, leukocytes or serum. This enables reliable prenatal diagnosis by chorionic villus sampling[10] or amniocentesis. The β-glucuronidase gene has been mapped to 7q21.2-q22[11]. Analysis of the β-glucuronidase gene of MPS VII patients has revealed a broad mutational heterogeneity[3,12].

A case of MPS VII diagnosed during the first pregnancy of a consanguineous couple is presented.

CASE REPORT

A 21-year-old primigravida was referred to our Division of Prenatal Diagnosis because of increased nuchal translucency, detected at 13 weeks of gestation, based on the first day of the last menstrual period. She was admitted simultaneously due to hyperemesis. The family history initially revealed no abnormalities. The parents were consanguineous (first cousins) and of Turkish ancestry. Ultrasound examination (HDI 3000; Advanced Technical Laboratories (ATL), Bothell, Washington, USA) revealed a nuchal translucency of 5.7 mm and generalized skin edema. Chorionic villus sampling demonstrated a normal female karyotype.

Ultrasound examination was repeated at 15 weeks of gestation (Figure 1). In addition to generalized edema, a hydrothorax and echodense bowel were present. There were no other (cardiovascular) abnormalities that could explain the fetal hydrops. Maternal serum titers indicated no recent infection (cytomegalovirus, rubellavirus, parvovirus B19, toxoplasmosis). The maternal blood group was A rhesus positive. A maternal hemoglobinopathy was already excluded before the pregnancy, thus ruling out the most common causes of fetal hydrops. Based on the presence of fetal hydrops and parental consanguinity an autosomal recessive metabolic disorder was suspected. Amniocentesis was carried out at 17 weeks of gestation to screen for a series of metabolic disorders (Table 1; fetus 1).

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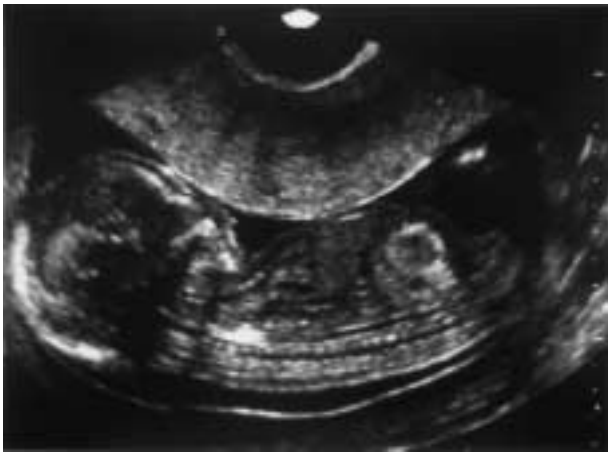

Figure 1 Fetus 1 at 15 weeks of gestation. Note the pronounced nuchal translucency, generalized skin edema and echogenic bowel.

This enabled the detection of mucopolysaccharidosis type VII by demonstrating a β-glucuronidase deficiency. Following counseling, the parents opted for termination of pregnancy, which was carried out at 20 weeks of gestation. Post-mortem investigation was not permitted.

Additional information on the family history was revealed at the time of enzyme analysis of fetus 1. It appeared that the patient's sister had a previous stillbirth (Figure 2; fetus 2) at 22 weeks of gestation of a severely hydropic fetus. Gaucher's disease was suspected by the finding of large, atypical histiocytes in many organs at post-mortem investigation. A β-glucosidase deficiency (Table 1; fetus 2) established the diagnosis of Gaucher's disease and subsequent mutation analysis showed homozygosity for a null mutation in the glucocerebrosidase gene[13].

The second pregnancy of our patient (Figure 2; fetus 3) revealed normal activity of β-glucuronidase and β-glucosidase in chorionic villi. A healthy infant was born at term.

DISCUSSION

Non-immune fetal hydrops occurred in each of the previously reported perinatal cases of MPS VII, but different pathways led to the diagnosis[4–10].

The first in-utero diagnosis of MPS VII was reported in 1992[6]. Two previous hydropic infants of a consanguineous couple were stillborn at 35 and 28 weeks of gestation, respectively. β-Glucuronidase deficiency was diagnosed in both infants. The origin of fetal hydrops in a subsequent pregnancy, diagnosed at 18 weeks of gestation, remained unclear. A normal fetal karyotype was present; intrauterine infections and Rhesus iso-immunization were excluded. Repeated albumin transfusions were administered to the fetus until β-glucuronidase deficiency was diagnosed in cultured amniotic cells and lymphoblasts. Fetal death occurred in the third trimester of pregnancy.

A similar case of parental consanguinity and two previous stillborn infants with ascites was described by Nelson et al.[7]. Post-mortem examination was not permitted. In a subsequent pregnancy fetal hydrops was demonstrated at 22 weeks and fetal death was diagnosed 6 weeks later. In this case, placental histology provided an important clue to the diagnosis. The presence of pronounced foamy cytoplasmic changes in the villous Hofbauer cells of the placenta raised the possibility of a lysosomal storage disorder. The parents were shown to have β-glucuronidase activity in the heterozygous range in leukocyte and fibroblasts, which suggested that the nonimmune hydrops was caused by MPS VII.

In another case MPS VII was suspected on the basis of histopathologic examination[8]. Finely vacuolated interstitial foamy cells were present in many organs, especially in the spleen, lung, myocardium, bowel mucosa and bone marrow. The placenta showed vacuolation of villus Hofbauer cells. The diagnosis of MPS VII was confirmed by quantification of enzyme activity in cultured fibroblasts.

In a further case of parental consanguinity and nonimmune hydrops, fetal death occured at 26 weeks of gestation[5]. Again the fetal karyotype was normal, intrauterine infections were excluded but post-mortem examination was not permitted. A skin biopsy of the infant was taken and β-glucuronidase deficiency was diagnosed in the cultured fibroblasts.

Three cases of MPS VII were reported from different, non-consanguineous families[4,9,10]. In the first case lysosomal overloading in the fetal kidneys, liver and spleen was seen by light and electron microscopy. Deficiency of β-glucuronidase was diagnosed in cultured amniotic cells and fetal plasma.

In the second case a Cesarean section was carried out at 32 weeks of gestation because of fetal hydrops, first diagnosed at 22 weeks. The major causes of fetal hydrops had been excluded. Cultured skin fibroblasts revealed a deficiency of β-glucuronidase activity. The infant died at 7 months of age. Intra-uterine growth acceleration (birth

Table 1 Enzyme activities in amniocytes (fetus 1) and fibroblasts (fetus 2)

Enzyme	*Metabolic disorder*	*Fetus 1*	*Controls amniocytes*	*Fetus 2*	*Controls fibroblasts*
β-glucuronidase	MPS VII/Sly syndrome	0.5	139; 207		
β-glucosidase	Gaucher disease	116	159; 174	0.5	130–400
β-galactosidase	GM1-Gangliosidosis	943	652; 1580	332	450–1250
α-fucosidase	Fucosidosis	287	244; 364		
α-mannosidase	α-Mannosidosis	110	108; 165		
β-mannosidase	β-Mannosidosis	76	81; 103		
β-hexosaminidase	Sandhoff disease	6630	3800; 5280		

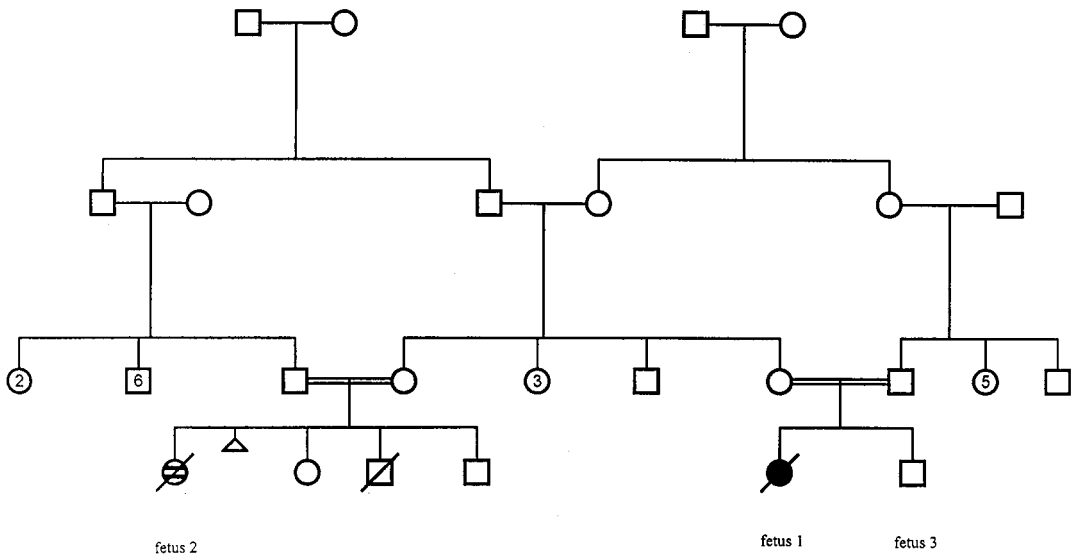

Figure 2 Pedigree of family with pregnancies affected with mucopolysaccharidosis type vii (fetus 1) and β-glucosidase deficiency, Gaucher's disease (fetus 2).

length, femur length and thoracic spine length) and bone maturation were reported in this infant with MPS VII associated with fetal hydrops[9].

In the third case enzyme analysis of fibroblasts cultured from the skin of a second hydropic, stillborn infant revealed a deficiency of β-glucuronidase[10]. In the next pregnancy a transcervical chorion villus sampling was carried out at 11 weeks of gestation and β-glucuronidase activity in the villi appeared deficient. Aspirotomy was performed and histo-pathological examination demonstrated edematous fetal parts.

In our case, the patient obviously did not acknowledge the importance of her sister's infant with Gaucher's disease since this was not mentioned at the first visit for ultrasound examination. When this diagnosis became clear we expected to find a β-glucosidase deficiency in fetus 1 rather than a β-glucuronidase deficiency.

This case report emphasizes the importance of the family history and the importance of paying attention to family members being at risk when counseling a (consanguineous) couple. The patient and her sister are both potentially at risk for two autosomal recessive diseases in their offspring.

Analysis of the β-glucuronidase gene of MPS VII patients has revealed extensive genetic heterogeneity, even in a group of patients presenting with fetal hydrops[3,12].

Mucopolysaccharidosis type VII is a rare disorder. Between 1985 and 1996, six cases of MPS VII, all associated with fetal hydrops, were diagnosed in the Netherlands[14]. This suggests a prevalence of 1 : 417 000 live births, giving a 5% prevalence for the whole group of mucopolysaccharidoses (1 : 22,000 [14,15]) and 1.7% for the combined prevalence of all lysosomal storage disorders (1 : 7100[14] and 1 : 7700[15]) recently been established in the Netherlands[14] and Australia[15], respectively. It seems likely that the prevalence of fetal hydrops due to lysosomal enzyme defects has been underestimated as enzyme investigations have not routinely been performed in such cases. Diagnosing a metabolic disorder is important because of the high risk of recurrence and the possibility of early diagnosis, for example by chorionic villus sampling[16]. Tests for the diagnosis of metabolic disorders should be performed when major causes of hydrops fetalis have been excluded.

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