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Foamy changes of placental cells in probable β glucuronidase deficiency associated with hydrops fetalis

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Abstract

Mucopolysaccharidosis type VII (MPS VII, β glucuronidase deficiency) has been described in association with non-immune hydrops fetalis. Three consecutive pregnancies in an itinerant family, which resulted in stillbirths caused by non-immune hydrops are described. The parents were closely related and there was a strong family history of storage disorders. The main clue to the diagnosis, however, came from the presence of pronounced foamy cytoplasmic change in the villous Hofbauer cells of the placenta. This raised the possibility of an inherited metabolic storage disorder. The parents were subsequently shown to have β glucuronidase activities in the heterozygous range in leucocytes and fibroblasts which suggested that the non-immune hydrops was caused by β glucuronidase deficiency.

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Case report

The parents were healthy members of a large itinerant family and were closely related (their fathers were brothers and their mothers were first cousins). There is considerable intermarriage among the itinerant families in Northern Ireland and first cousin marriages are common. In the extended family there was a history of mucopolysaccharidosis type 1 H (MPS 1 H, Hurler's syndrome), mucolipidosis type II (I-cell disease), osteogenesis imperfecta type II, neural tube defects and mental retardation. The first pregnancy resulted in a spontaneous abortion at 12 weeks' gestation. The second and third each resulted in a macerated male stillbirth with gross ascites at 31 weeks' and 30 weeks' gestation, respectively. Consent was refused for post mortem examinations and biochemical investigations were not performed. In the fourth pregnancy an ultrasound scan at 22 weeks' gestation showed gross ascites, pleural effusions, and a pericardial effusion. The parents elected to continue with the pregnancy. A repeat ultrasound scan at 26 weeks showed no change. At 28 weeks intrauterine death was confirmed and a stillborn male infant was delivered.

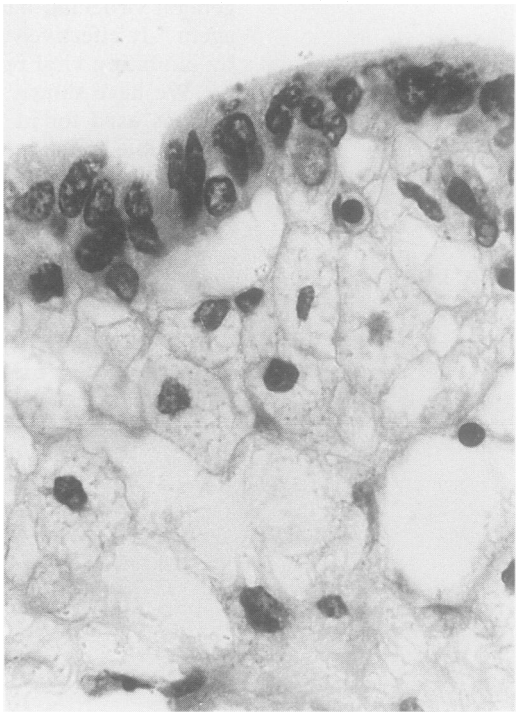
Pathological findings

Necropsy confirmed a grossly hydropic infant with blood stained pericardial, pleural, and peritoneal effusions. There was severe skin maceration and post mortem autolysis of the internal organs, especially the brain, liver, kidneys and adrenals but no evidence of congenital structural abnormality. The placenta was severely hydropic. The villi were generally swollen with oedematous stromal cores. In many there were conspicuous numbers of Hofbauer cells (placental macrophages) with abundant foamy or finely vacuolated cytoplasm (figure). This suggested the possibility of an inherited metabolic storage disorder.[1] The appearance of the trophoblastic cells was not striking and in particular, they did not show the vacuolated (foamy) change which has been described in I-cell disease,[2] GM_1 gangliosidosis,[3] and sialic acid storage disease.[4]

β glucuronidase (nmol/min/mg protein)

	Leucocytes	*Cultured skin fibroblasts*
Mother	3·27	1·22
Father	3·51	2·04
Controls	n = 61, mean (SD) 6·96 (1·56)	n = 10, mean (SD) 2·36 (0·78)

A skin biopsy specimen was taken from the fetus at the time of delivery but it was



High power magnification shows foamy cytoplasm of

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impossible to establish a successful fibroblast culture. As the presence of Hofbauer cells suggested a metabolic storage disorder, leucocyte lysosomal enzyme studies were performed on anticoagulated blood samples taken from both parents. This gave intermediate values for β glucuronidase consistent with both parents being heterozygotes for the β glucuronidase (MPS VII) gene. These results were confirmed by enzyme assay on fibroblasts (table).

Values for β galactosidase (GM_1 gangliosidosis), β glucosidase (Gaucher's disease) and α iduronidase (Hurler's syndrome) were within the normal range. Serum β hexosaminidase, which is usually raised in carriers for I-cell disease, was also normal in both parents. The couple had a subsequent pregnancy which resulted in a normal male infant whose leucocyte β glucuronidase values were also consistent with heterozygosity. A skeletal survey performed when he was 1 year 6 months old yielded normal results.

Discussion

Several authors have described β glucuronidase deficiency in association with non-immune hydrops fetalis[5 6] and others have emphasised how variable the clinical and biochemical manifestations may be, with a deficiency of β glucuronidase being the only consistent finding.[7]

Other inherited metabolic disorders such as infantile Gaucher's disease, GM_1 gangliosidosis, sialidosis (neuraminidase deficiency), mucopolysaccharidosis type IV A (Morquio's disease type A) and I-cell disease have been implicated as a cause of non-immune hydrops fetalis or neonatal ascites.[4 8–10] It is therefore important to consider inborn errors of metabolism in the aetiology of these conditions.

Several children with I-cell disease have been born into this extended family. They all presented in the first year of life with typical "Hurler-like" features. Hydrops was not present in any of the affected pregnancies. Prenatal diagnosis was performed by amniocentesis in one of the affected pregnancies by lysosomal enzyme studies on amniotic fluid cells. The pregnancy was terminated and fetal necropsy showed the typical placental changes of I-cell disease[2] with no evidence of fetal hydrops.

This report emphasises the importance of careful examination of the placenta in cases of hydrops fetalis when obvious causes such as blood group incompatibility, haemoglobin variants, and intrauterine infections have been excluded. In this case placental histology provided an important clue to the aetiology of the hydrops even though the fetus was grossly macerated and little was gained from examination of the fetal tissues.

Although Hofbauer cells may be present in a normal pregnancy and may be a common finding early in pregnancy, their presence in association with fetal hydrops and in particular, with recurrent fetal hydrops strongly suggests an inherited metabolic storage disorder as the cause of the hydrops.

It is important to attempt to establish a cell line in such a fetus so that appropriate biochemical investigations can be performed. Although metabolic storage disorders are a rare cause of non-immune hydrops, they are particularly important because of their genetic basis and consequent high risk in future pregnancies. Prenatal diagnosis is usually feasible and should be offered in any subsequent pregnancy provided the cause of the hydrops has been established.

Mucopolysaccharidosis type VII is inherited in an autosomal recessive manner and prenatal diagnosis by chorionic villus biopsy or amniocentesis should be possible. This was declined by the patient in her most recent pregnancy but no evidence of hydrops was apparent on ultrasound scan in the second trimester of that pregnancy which suggested correctly that the fetus was unaffected. In this family evidence of hydrops in an affected fetus is likely to be present on an ultrasound scan from 20 weeks' gestation onwards.

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