Foamy changes of placental cells in probable \( \beta \) glucuronidase deficiency associated with hydrops fetalis


Abstract
Mucopolysaccharidosis type VII (MPS VII, \( \beta \) 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 \( \beta \) glucuronidase activities in the heterozygous range in leucocytes and fibroblasts which suggested that the non-immune hydrops was caused by \( \beta \) glucuronidase deficiency.


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 I H (MPS I 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. 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, GM1 gangliosidosis, and sialic acid storage disease. A skin biopsy specimen was taken from the fetus at the time of delivery but it was

![Image](http://jcp.bmj.com/)
impossible to establish a successful fibroblast culture. As the presence of Hofbauer cells suggested a metabolic storage disorder, leuco-
cyte lysosomal enzyme studies were per-
formed on anticoagulated blood samples
taken from both parents. This gave inter-
mediate 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, gangli-
sidosis), β glucosidase (Gaucher’s disease)
and α iduronidase (Hurler’s syndrome) were
within the normal range. Serum β hexo-
saminidase, which is usually raised in carriers
for I-cell disease, was also normal in both
parents. The couple had a subsequent preg-
nancy 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 glucu-
ronidase deficiency in association with non-
immune hydrops fetalis and others have
emphasised how variable the clinical and bio-
chemical manifestations may be, with a defi-
cency of β glucuronidase being the only
consistent finding.1

Other inherited metabolic disorders such as
infantile Gaucher’s disease, GM, ganglio-
sidosis, 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
fetals or neonatal ascites.2-8,10 It is therefore
important to consider inborn errors of metab-
olism 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 pre-
sent in any of the affected pregnancies.

Prenatal diagnosis was performed by amnio-
centesis 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 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 histol-
ogy provided an important clue to the aetio-
logy 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 particu-
lar, with recurrent fetal hydrops strongly sug-
gests 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 bio-
chemical investigations can be performed.

Although metabolic storage disorders are a
rare cause of non-immune hydrops, they are
particularly important because of their gen-
etic basis and consequent high risk in future
pregnancies. Prenatal diagnosis is usually fea-
sible and should be offered in any subsequent
pregnancy provided the cause of the hydrops
has been established.

Mucopolysaccharidosis type VII is inher-
ited in an autosomal recessive manner and
prenatal diagnosis by chorionic villus biopsy
or amniocentesis should be possible. This was
depressed 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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