Non-immunological hydrops fetalis

A case report

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Summary

A case of hydrops fetalis which was not due to iso-immunization is presented. The condition was diagnosed antenatally by means of ultrasonography and the infant was delivered at 32 weeks' gestation. He required intensive care, but survived and is well at 18 months of age. The causation, diagnosis and management of this problem are discussed.

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Case report

A 22-year-old White primigravida first attended the antenatal clinic at Addington Hospital on 11 March 1980 when she was 18 weeks pregnant by dates. She felt well, and no abnormality was found on clinical examination, although the fundal height corresponded only to a 14-week pregnancy. She had previously had rubella, but otherwise no significant past medical history was obtained. The haemoglobin value was 13,1 g/dl, the Wassermann reaction was negative, the rubella haemagglutination inhibition (HAI) titre was 1:16 (indicative of the previous infection reported), and the blood group was O Rh-positive with no atypical antibodies. A routine ultrasound examination was performed when she was almost 24 weeks pregnant by dates. This revealed an apparently normal fetus and placenta, although the biparietal diameter corresponded to that of a 19-week fetus, confirming the clinical impression that the duration of the pregnancy was 1 month less than indicated by dates.

The patient attended the clinic regularly and uneventfully until her 9th visit, when she was found to have mild pre-eclampsia, with ankle oedema, a blood pressure of 130/90 mmHg, and weight gain of 4 kg over 10 days. At this time she was 35 weeks pregnant by both dates and fundal height, but only 31 weeks by extrapolation from earlier examination and ultrasound findings. She was admitted to hospital and a further ultrasound scan was performed. This demonstrated a biparietal diameter of 83 mm, correlating well with the first measurement. The fetal abdominal circumference was 32 cm, which is above the 95th percentile for 31 weeks' gestation. Gross fetal ascites was evident. Oedema of the head, trunk and limbs was also observed. The placenta was 6,5 cm thick and had a pattern characteristic of oedema. On these grounds the diagnosis of hydrops fetalis was made. There was no evidence of polyhydramnios on ultrasono-

graphy. The fetal heart tracing was examined and no obvious abnormality was detected.

Over the next few days of bed rest in hospital the patient's signs of pre-eclampsia settled. The serum oestriol level (88 ng/ml) was within normal limits, but the human placental lactogen level (11,1 μg/ml) was very high for a singleton pregnancy. A repeat ultrasound examination (Figs 1 and 2) showed the hydropic appearance of the fetus to be worsening. Amniocentesis was therefore performed, and 20 ml of liquor heavily stained
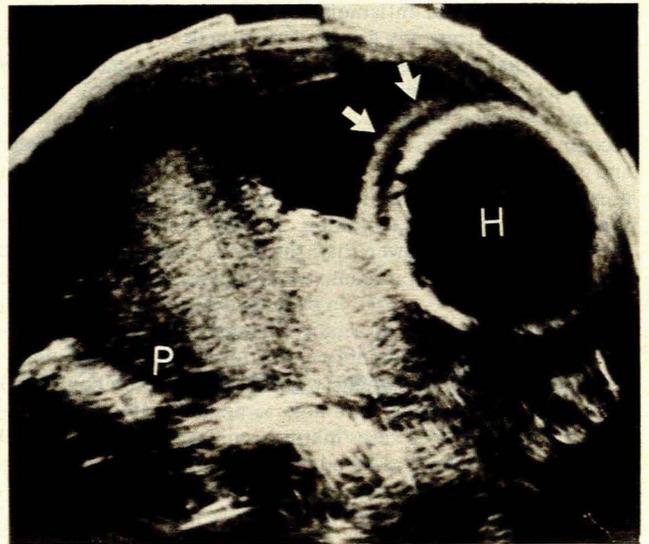

Fig. 1. Transverse scan through the fetal head (H) showing scalp oedema (arrowed) and the large oedematous placenta (P).

Fig. 2. Transverse scan through the fetal trunk showing ascites (A), the umbilical vein (U), more clearly seen than usual within the abdominal cavity because of the ascites, and oedema (arrowed).

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with bilirubin was obtained. A foam test on this was negative, but the lecithin/sphingomyelin (L/S) ratio was 2,1. Examination of the liquor for bilirubin revealed an optical density of 0,70, which is high in the upper zone shown by Liley[1] to be indicative of severe haemolysis.

It was therefore assumed that the fetus was suffering from hydrops fetalis due to a severe haemolytic process of unknown causation. In view of rapidly worsening condition of the fetus, the fact that it appeared normal otherwise and the adequate L/S ratio suggesting lung maturity it was decided to perform immediate caesarean section. A live hydropic male infant weighing 1800 g was delivered, with a large, oedematous and very friable placenta. His estimated gestational age was 32 weeks.

The infant was severely asphyxiated and required intubation and intermittent positive-pressure ventilation (IPPV) because of gross abdominal distension with ascites causing respiratory embarrassment. Abdominal paracentesis yielded 200 ml straw-coloured fluid with a protein content of 16 g/l and 400 lympho-cytes per microlitre. Thereafter a 2 cm firm hepatomegaly and a 3,5 cm splenomegaly became evident. A chest radiograph revealed a normal-sized heart, with no evidence of pulmonary congestion. The cord bilirubin level was 35 μmol/l and rose rapidly to 70 μmol/l in 1 hour. The infant's blood group was O Rh-positive and the direct Coombs test was negative. He was anaemic, with a haemoglobin concentration of 11,4 g/dl; the smear showed polychromasia 3+, microspherocytes +, aniso-cytes 3+, and 186 nucleated red cells per 100 white cells. The corrected white cell count was low at 5,4 x 10^9/l, with 50% polymorphs, 36% lymphocytes, 10% monocytes, 2% myelocytes and 2% blast cells. The platelet count was very low, the blood sugar level was 1,3 mmol/l, the total serum protein level was 24 g/l (normal 44-63 g/l), and the albumin level was 13 g/l (normal 33-45 g/l). There was no proteinuria.

An exchange transfusion was performed 4 hours after delivery because of worsening jaundice, anaemia and hypoproteinaemia. Over the succeeding days a further partial exchange transfusion and albumin and packed cell infusions were given. It was neces-sary to continue peritoneal drainage for 7 days and endotracheal intubation and respiratory support were required for 6 days. The infant received vitamin K on alternate days, and was treated with broad-spectrum antibiotics. Gastric feeding with expressed breast-milk was started on day 3 and was well tolerated. Cultures of blood and ascitic fluid were sterile, and serological tests for syphilis, toxoplasmosis and hepatitis B were negative. Cytome-galovirus, herpes simplex complement fixation and rubella HAI titres paralleled those in the mother's serum. Unfortunately no other viral studies were performed, and a Kleihauer test on the mother's blood to exclude fetomaternal haemorrhage was not carried out.

A liver biopsy on day 15 showed moderate intraductal, intra-canalicular and intracellular cholestasis, mild haemosiderosis, occasional binucleate hepatocytes and a tendency to pseudo-glandular arrangement of hepatocytes. This was suggestive of regeneration, but no giant cells were present; furthermore, a minimal number of neutrophils were found in the portal areas. These changes were thought to be the result of an intra-uterine hepatic insult, probably infective, but there was no active hepa-titis or residual fibrosis.

A slow rise in the serum protein level indicated gradual improvement in the patient's condition. On day 18 the serum albumin level was 26 g/l, and on day 118 the albumin level was 39 g/l and the total protein level 59 g/l. His platelet count also gradually improved from 14 x 10^9/l on day 2 to 134 x 10^9/l on day 37. The haemoglobin value remained low for the first 2 months, and he required packed-cell transfusions on several occasions before this improved.

At the age of $3^1/_2$ months the patient had normal incubated osmotic fragility and glucose-6-phosphate dehydrogenase acti-vity, and the direct Coombs test was negative. Alkali denatura-

tion was 21%, and no abnormal haemoglobins were present on electrophoresis. There was no evidence of cataract, retinitis or retrolental fibroplasia at 4 months. At 11 months audiometry showed his hearing to be normal. At 13 months his weight, length and head circumference were on the 50th percentile, and liver function tests were normal. He has achieved normal deve-lopmental milestones.

Discussion

This patient presented with hydrops fetalis, and apparently suf-fered severe intra-uterine haemolysis as evidenced by a high amniotic fluid bilirubin level, anaemia, and a high level of bili-rubin in the cord blood. There was no evidence to suggest an immune basis for the haemolysis, but the liver biopsy suggested infection as a possible cause. The relatively rapid resolution of the haemolysis after delivery suggests a transient intra-uterine red cell insult rather than an inherent red cell abnormality, and no evidence of such inherent abnormality was found.

The term hydrops fetalis means generalized oedema of the fetus, and it can be associated with a wide range of pathological processes. Giacoia[2] lists 47 known associations, including infec-tions, chronic anaemias, cardiac diseases (including tachyar-rhythmias), renal diseases, malformations and congenital tumours. Use of anti-D immunoglobulin in Rh-negative mothers has resulted in a fall in the number of cases of rhesus iso-immunization seen in developed countries. Non-immuno-logical hydrops fetalis (NIHF) is therefore becoming relatively more common, although the overall incidence has probably decreased. The incidence of NIHF has been estimated at 1/2 566 - 3 975.[3-5]

The pathophysiological mechanism responsible for general-ized fetal oedema is obscure, but it usually seems to be due to one or more of three interrelated factors: (i) anaemia, which may be severe; (ii) hypoproteinaemia, which may be due to decreased protein production (e.g. in liver damage) or increased loss, as in the congenital nephrotic syndrome; and (iii) heart failure, secon-dary to anaemia, cardiac abnormality or a high-output state. In our case, the oedema was associated with gross hypoproteinae-mia, suggesting that decreased plasma oncotic pressure played a part in its genesis.

Infection *in utero* is well known, and hepatitis can result from syphilis, listerosis, varicella, and infection with the TORCH group (toxoplasmosis, rubella, cytomegalovirus and herpes sim-plex virus) and Coxsackie virus. Danks *et al.*[6] have suggested that transplacental infection by one of the many agents capable of damaging the liver may occur in as many as 5 - 10% of pregnan-cies, but that only fetuses with some further problem are in general predisposed to develop overt disease. We were unable to demonstrate the cause of the intra-uterine hepatic insult in our patient. His hypoproteinaemia was almost certainly due to decreased hepatic protein production, as no renal loss of protein or immune haemolysis was demonstrated. The high number of white cells in the ascitic fluid is suggestive of 'aseptic peritonitis'. The relatively rapid spontaneous recovery with only supportive therapy is in keeping with the histological picture.

Unlike the position in rhesus disease, the diagnosis of NIHF presents considerable problems because there is usually little to alert suspicion of the fetal disease until after the child has died. There are few maternal associations to point out those at high risk. In Thailand, homozygous α-thalassaemia is the most com-mon cause of hydrops,[7] but this is uncommon in other parts of the world. There seems to be an association between hydrops and pre-eclampsia,[8] but of course the vast majority of pre-eclamptic mothers do not have hydropic infants. There is also an associa-tion with hydramnios, thought to be due to obstruction to fetal swallowing from peri-oral oedema.[8] Nevertheless, most hydrops occurs without hydramnios. The obstetric history rarely pro-vides any clues, as most cases of NIHF are isolated events.

The greater availability of sensitive ultrasound equipment has provided a relatively reliable means of diagnosing NIHF antenatally. However, cases will continue to be missed unless every antenatal patient is scanned at regular intervals, which is unlikely to be feasible in most countries. The only way to increase the chance of discovering this problem antenatally is by a liberal policy of scanning patients with other problems, especially hydramnios. Antenatal diagnosis is important, since early delivery before fetal death occurs *in utero* will frequently be the only hope of the infant's surviving. Having discovered that a fetus is affected, it is also important to search for the underlying disorder antenatally for two reasons. Firstly, if a lesion is discovered which precludes viability, such as a severe malformation or a lethal neoplasm, a conservative policy can be adopted regarding the timing of delivery. Beischer *et al.*[9] commented on the almost 50% incidence of fetal malformations in NIHF, while incidences of between 30% and 40% have been reported by other authors.[4,10] Secondly, in a potentially viable fetus knowledge of any underlying lesions may be of great help in the care of the baby after delivery. Attention should be directed to cardiac defects, infections, neoplasms and local lesions within the fetal abdomen. Ultrasonography is the most effective means of showing structural abnormalities.

If an attempt is to be made to save the baby, the first major problem is to decide on the optimal time of delivery. This will usually require a compromise between the risks of worsening fetal condition, and the risks of premature delivery. At this point discussion should be held between obstetricians and the paediatricians and the parents. Fetal well-being can be assessed by the usual means, but the results of biochemical tests may be difficult to interpret. A raised amniotic fluid α-fetoprotein level may indicate congenital nephrotic syndrome. Fetal heart tracings may give clues to any cardiac anomalies, as well as the general condition of the baby. Ultrasonography is again probably the most useful technique available. It can be used to assess fetal growth (by measuring biparietal diameters serially) and to watch for increase of hepatomegaly and ascites by comparing biparietal diameter/abdominal circumference ratios. Placental thickness can be measured ultrasonically, and can also give some indication of the severity of the problem. The normal placenta has an average thickness of up to 4,5 cm, while in hydrops fetalis the thickness is often found to be more than 6 cm.[11]

Any attempt to save the baby is likely to involve premature delivery. The mode of delivery will depend on the degree of fetal compromise, the risk of this being worsened by labour, the state of the cervix, and the assessed risk of soft-tissue dystocia if the fetus has significant ascites.

Immediately after delivery the infant will require intensive paediatric care, and it must be delivered where such care is available. Severe depression at birth is almost universal; ventilation is likely to be required, and in the face of inadequate response to intubation and IPPV, abdominal paracentesis and even chest drainage in the delivery room may be life-saving. Transfusion or exchange transfusion may be needed for anaemia, worsening jaundice or disseminated intravascular coagulation immediately or during the first few days, and fresh packed cells cross-matched against the mother's serum should be available at delivery. Depending on the cause of the hydrops, other specific treatment may be required.

Series of cases of NIHF have been published by 6 authors, with a collective total of 90 patients.[3-5,8,10,12] Excluding a postmortem series of 17 patients,[12] the overall survival rate has been 20%. This varies, however, from Scott's[8] 1958 series (no survivors) to Etches and Lemons's[10] 1979 series (50% survival) and Spahr *et al.*'s[4] 1980 series (31% survival). This seems to suggest that there has been a trend towards improved survival with time. If so, this may reflect improved access to ultrasound examination, resulting in earlier diagnosis, and improvements in paediatric intensive care. However, as Etches and Lemons[10] point out, it may also partly reflect a biased population resulting from later referral to tertiary centres, which are never reached by some of the most seriously affected infants.

Unlike the situation with hydrops caused by iso-immunization, the prognosis for future pregnancies in mothers of patients with NIHF is good. A total of 5 cases of recurrent NIHF have now been reported, but in the vast majority of patients subsequent pregnancies are unaffected.

Conclusion

NIHF is an uncommon but serious problem, because at present most affected children die, often *in utero*. A significant proportion have basic lesions which are treatable if the child survives. The major problems are early diagnosis antenatally, timing of delivery, and care of the seriously ill infant after delivery. However, we tend to agree with Giacoia,[2] who concludes that 'The improved outlook for survival of infants with hydrops fetalis justifies aggressive support efforts'.

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