

## Recurrent Non-immune Fetal Hydrops: A Case Report

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### Abstract

**Introduction:** Recurrent non-immune fetal hydrops (NIH) has been reported in the literature but is a rare entity, with fewer than 6 reported cases so far. It has been postulated to be related to a recessive gene. **Clinical Picture:** We report a case of recurrent fetal hydrops in a multigravida with no medical history of note. She presented in her current pregnancy with a significant history of having 4 (out of 7) previous pregnancies affected by hydrops. **Treatment:** All the affected pregnancies resulted in mid-trimester pregnancy termination (MTPT) following diagnosis in the second trimester. Previous investigations for hydrops did not yield any obvious cause. **Outcome:** Her most recent pregnancy was unaffected. We discuss the possible differential diagnoses and the likelihood of autosomal recessive metabolic diseases being the aetiological factor. **Conclusion:** Rare causes of fetal hydrops need to be excluded in cases of recurrent non-immune hydrops with no obvious aetiology following routine investigations.

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**Key words:** Hydrops fetalis, Lysosomal storage disorders, Non-immune, Thalassemia, Ultrasonography

### Introduction

The incidence of non-immune hydrops (NIH) has been reported to be 1/1000<sup>1</sup> and is associated with high perinatal morbidity and mortality at all gestational ages with an overall perinatal mortality rate (PNMR) of 86.6%.<sup>2</sup> If the diagnosis is made before 24 weeks' gestation, the PNMR is 95%, with 30% having an abnormal karyotype. In most countries with adequate anti-D and fetomaternal expertise, as well as low rhesus-negative rates in the population, non-immune causes are more prevalent. True incidence is regionally dependent and also varies seasonally (e.g., parvovirus B19 epidemics).<sup>3-5</sup> Alpha-thalassaemia is the most common cause in Southeast Asia.<sup>3,6</sup>

### Case Report

A 39-year-old Indian lady, gravida 8, para 3, booked at 13 weeks of amenorrhoea in her most recent pregnancy. She did not have a past medical or surgical history of note. Her marriage was non-consanguineous and she had no significant family history of note. None of her previous babies had neonatal jaundice.

Of her 7 previous pregnancies, 3 were successfully carried to term in 1986, 1993 and 1996. In each of these 3 pregnancies, the antenatal course was uneventful apart

from impaired glucose tolerance requiring dietary restriction in 1996. She required an emergency caesarean section for non-reassuring fetal status in 1986, but the 2 subsequent normal pregnancies in 1993 and 1996 were successfully delivered vaginally.

In the other 4 previous pregnancies, fetal hydrops was diagnosed at 20 weeks' gestation in 1988, and at 18 weeks' gestation in 1993, 1997 and 2000. All 4 cases were diagnosed on routine screening ultrasound scans in the second trimester.

Investigations for the aetiology of the fetal hydrops were carried out following the diagnosis of the condition in the affected pregnancies. Maternal blood investigations (a full blood count and renal, liver and thyroid function tests) were normal. Viral serology markers (parvovirus, toxoplasma, rubella, cytomegalovirus, herpes simplex virus and coxsackie) were negative for acute infection in the latter 2 pregnancies. She was positive for parvovirus and cytomegalovirus immunoglobulin G. An oral glucose tolerance test revealed impaired glucose tolerance but glycyated haemoglobin (HbA1C) was within the normal range. A Kleihauer-Betke test showed no evidence of fetomaternal haemorrhage. An immunological screen consisting of lupus anticoagulant, anti-nuclear antibodies

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and anti-Ro antibodies was negative. Both parents had normal mean corpuscular volumes and were of blood group O-positive with no abnormal antibodies.

Detailed ultrasound scans of each affected pregnancy revealed generalised hydrops with no other detectable abnormalities of the fetus, placenta and cord. No arrhythmias or abnormal blood flow patterns were present on fetal echocardiography, pulsed and colour Doppler studies. Invasive investigation was undertaken for the fourth affected pregnancy in 2000. Fetal full blood count, haemoglobin electrophoresis, blood typing and a Coombs test were performed following a cordocentesis. The couple had decided on a mid-trimester termination of pregnancy (MTPT) by then. The fetal haemoglobin was 11.2 g/dL; electrophoresis showed 100% Hb F; serology for acute phase-specific IgM for infection, culture and electron microscopy was done to exclude parvovirus, toxoplasma, rubella, cytomegalovirus and herpes simplex virus. The results were negative for acute infective serological markers.

Following the terminations, histology of the placenta and cord had villous changes consistent with hydrops, with no other remarkable findings. Karyotype for all the abortuses were normal. Postmortem examinations were performed for the first 3 abortuses. There was generalised oedema with bilateral pleural effusions, but no fetal anomalies. The couple declined a postmortem examination for the fourth affected fetus.

She was lost to follow-up until her most recent pregnancy in 2004 when she booked at 13 weeks of amenorrhoea with spontaneously conceived monochorionic diamniotic twins. This twin pregnancy was not complicated by fetal hydrops.

During the postpartum period of this most recent pregnancy, she gave a history of hypothyroidism diagnosed in India in early 2002 and that she was on thyroxine replacement till December 2002. Her free thyroxine, thyroid-stimulating hormone, thyroglobulin, thyroid receptor antibody, thyroglobulin antibody and thyroid peroxidase antibody levels done before her discharge from hospital were all in the normal ranges. Subsequent follow-up with the physician showed her to be clinically and biochemically euthyroid.

## Discussion

Idiopathic NIH is sporadic in most instances and a diagnosis is made by excluding a variety of possible causes. Several causes of recurrent NIH have previously been reported in the literature. This has been postulated to be related to a recessive gene.<sup>7,8</sup>

The aetiology of the recurrent fetal hydrops in this case is still unknown, despite numerous investigations. The number of idiopathic NIH varies from 9% to 42%.<sup>8,9</sup> A recessive inheritance may be recognised by occurrence in

siblings of a family, which may represent a distinct, frequently unrecognised condition.<sup>10,11</sup> Other investigations that may have yielded significant results but were not done are parental G6PD and pyruvate kinase carrier status, maternal alpha-fetoprotein, fetal liver enzymes and serum albumin and white cell enzymes (Gaucher's disease, mucopolysaccharidosis). Ultrasonographic parameters such as fetal middle cerebral artery peak systolic velocity (MCA PSV) and umbilical vessel pressure may have been useful. In the management of non-immune hydrops, measurement of fetal MCA PSV can help identify the subgroup with fetal anaemia.<sup>12</sup> The finding of a normal umbilical venous pressure greatly reduces the likelihood of a cardiac cause for hydrops, even if there is co-existing heart malformation.<sup>13</sup>

Well recognised causes of recurrent NIH are homozygous alpha-thalassaemia and metabolic storage disorders (some types of mucopolysaccharidosis, Gaucher's, gangliosidosis, sialidosis).<sup>14</sup> Alpha thalassaemia is a common genetic disease in our population but was excluded in this case by normocytic erythrocytes in parental blood and absence of severe anaemia on cordocentesis. Beta-glucuronidase deficiency is a rare autosomal recessive condition, of which hydrops fetalis is a common form of presentation. Mutations in hydropic fetuses are widely scattered in the beta-glucuronidase gene.<sup>15-17</sup> Gaucher's disease is another rare metabolic storage disease that has given rise to cases of recurrent NIH.<sup>18</sup> Sialic acid storage disease is a rare metabolic disorder,<sup>19</sup> and its diagnosis is confirmed by enzymatic assay in cultured fibroblasts<sup>20</sup> or based on high levels of free sialic acid in amniotic fluid and fetal cell culture.<sup>21</sup>

Other rare causes of recurrent NIH include a chylous form with congenital malformation of the lymph vessels.<sup>22</sup> It has also been reported that in cases of idiopathic NIH, the proportion of parents sharing 4 or 5 HLA antigens increase significantly.<sup>23</sup> It has been reported that male fetuses are particularly affected by maternal alloimmunisation to D.<sup>24</sup> However, no similar preponderance in non-immune hydrops fetalis has been reported in the literature.<sup>25</sup> Dufke et al<sup>26</sup> reported a patient who had a female child with clinical signs of incontinentia pigmenti (IP) after consecutive miscarriages of 3 male fetuses due to hydrops. In that study, the diagnosis of IP in both the girl and her mother was confirmed by molecular genetic analysis. The inheritance of affected maternal X chromosome was demonstrated retrospectively in 2 fetuses by linkage analysis. Hence the maternal line should be investigated in cases of recurrent hydrops in male fetuses. In our case, the patient had no preponderance of gender in both her affected or normal pregnancies.

The diagnosis of Beckwith-Wiedemann syndrome should be considered, as an association with a inherited unbalanced translocation has been reported,<sup>27</sup> following retrospective fluorescent in-situ hybridisation analysis of abortuses

(termination for hydrops) showing similar translocations noted on the paternal chromosome. Lysosomal storage disorders can also present very early as hydrops fetalis.<sup>28</sup> Differential diagnoses of recurrent NIH, albeit even rarer, include carbohydrate-deficient glycoprotein syndrome,<sup>29</sup> familial perinatal haemochromatosis,<sup>30</sup> and congenital dyserythropoietic anaemia type III.<sup>31</sup>

There were several possible aetiologies in this patient which were not excluded. G6PD and pyruvate kinase carrier status were not done. More importantly, the white cell enzymes (Gaucher's disease or mucopolysaccharidosis) were not analysed. The fetal middle cerebral artery peak systolic velocity was not measured. The aetiology of recurrent fetal hydrops in this case is still unknown despite numerous investigations. The couple was not keen on further investigations. However, they are more amenable to an early diagnosis of hydrops and a termination of pregnancy if hydrops is diagnosed again.

In conclusion, the precise diagnosis of NIH is important for prenatal diagnosis, neonatal management and prognosis. Rare causes of fetal hydrops, especially inborn errors of metabolism, need to be excluded in cases of recurrent nonimmune hydrops with no obvious aetiology following routine investigations. Accurate diagnosis of inheritable diseases is important as it implies a high risk of recurrence, with genetic counselling and prenatal care being crucial in management.

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