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NONIMMUNOLOGIC FETAL HYDROPS AND CHROMOSOMAL DISORDER: TWO CASES OF DOWN SYNDROME ASSOCIATED WITH HEMATOPOIETIC ABNORMALITIES

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We investigated 6 neonates with nonimmunologic fetal hydrops admitted to Shimane Medical University Hospital between 1979 and 1996. Chromosome analysis revealed that two of these neonates (33%) had trisomy 21 (Down syndrome). Our data may suggest the importance of chromosomal analysis of the fetus and the neonate with nonimmunologic fetal hydrops. It was revealed that each of the two neonates with Down syndrome had hematopoietic disorders including pancytopenia and transient abnormal myelopoiesis. Although nonimmunologic fetal hydrops in Down syndrome has often been attributed to the cardiac diseases, hematopoietic disorders should also be considered to be a cause of the fetal hydrops in Down syndrome.

Key words : Fetal hydrops / Down syndrome / Pancytopenia / Transient abnormal myelopoiesis (TAM)

Fetal hydrops is divided into immunologic and nonimmunologic categories. As hemolytic disease of the newborn due to Rh incompatibility has markedly diminished recently, nonimmunologic fetal hydrops has become a more common type.

We came across 6 neonates with nonimmunologic fetal hydrops in Shimane Medical University Hospital between 1979 and 1996 as shown in Table 1. Five of the 6 neonates were male. Four of the 6 neonates died from the hydrops or its complications. All of the cases were preterm neonates, and all these neonates except for case 4 were heavy-for-dates. Chromosome analysis performed in all cases revealed that two (33%) of the 6 cases had trisomy 21 (Down syndrome). We report two cases of Down syndrome with nonimmunologic fetal hydrops that were likely caused by hematopoietic abnormality.

CASE REPORTS

CASE 1 was a Japanese male neonate, born to unrelated parents. His mother was a 29-year-old woman, primigravida and was transferred to our hospital for evaluation of fetal hydrops diagnosed upon the routine sonographic examination at 31 weeks' gestation. She had no special medical history nor other complications in the pregnancy.

Ultrasound examination at 31 weeks' gestation revealed moderate fetal ascites and hydramnion. In tests of umbilical blood sampled at 34 weeks' gestation was as follows: the fetal red blood cell count (RBC) was $0.42\times10^6/\mu l$, hemoglobin 1.5g/dl, hematocrit 4.3%, white blood cell count (WBC) $3,200/\mu l$, and serum total protein (TP) was 1.2g/dl (albumin 0.7g/dl). At 36 weeks' gestation, the fetal RBC was $1.12\times10^6/\mu l$, hemoglobin 4.8g/dl, hematocrit 14.1%, WBC $7,600/\mu l$, platelet count (PLT) $128\times10^3/\mu l$, and TP 4.4g/dl (albumin 2.9g/dl). Although fetal exchange transfusion through the umbilical cord, aspiration of fetal ascites and intraperitoneal infusion of albumin were performed at 36 weeks' gestation, the caesarean section was conducted because of fetal distress.

The birth weight of the infant was 3,180g and the Apgar scores were 1 and 5 at 1 min and 5 min, respectively. Immediately, mechanical ventilation was required for the respiratory distress. Furthermore, exchange transfusion, transfusion of fresh frozen plasma, concentrated red blood cell and platelets were carried out. Consequently, the condition of the neonate improved gradually and he was successfully extubated at 7th day after birth. Chromosome analysis on the neonate showed 47,XY,+21(Down syndrome). The peripheral blood tests at birth revealed pancytopenia; WBC $5,400/\mu l$, RBC $1.13\times10^6/\mu l$, hemoglobin 4.1g/dl, hematocrit 12.2%, and PLT $16\times10^3/\mu l$. The bone marrow cell count was $23\times10^3/\mu l$, the blood cell morphology was normal,

Table 1. 6 Cases of nonimmunologic fetal hydrops

Case	Sex	Birth weight (g)	Birth age (wk)	Genotypic diagnosis	Phenotypic characteristics	Outcome
1	M	3180	36	47,XY+21	Pancytopenia	Alive
2	M	3898	34	47,XY+21	TR, ASD, VSD, TAM	Death 2 hours
3	M	3470	35	46,XY	TR, MR	Alive
4	F	2344	33	46,XX	Infection, Anal atresia, Urinary tract anomaly	Death 36 hours
5	M	3045	33	46,XY	HLHS	Death 56 hours
6	M	1942	30	46,XY	TAPVC, PS, DORV, AVSD, Asplenia	Death 4 hours

M; male: F; female: TR; tricuspid valve regurgitation: ASD; atrial septal defect: VSD; ventricular septal defect: TAM; transient abnormal myelopoiesis: MR; mitral valve regurgitation: HLHS; hypoplastic left heart syndrome: TAPVC; total anomalous pulmonary venous connection: PS; pulmonary stenosis: DORV; double outlet right ventricle: AVSD; atrio-ventricular septal defect.

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and no blast cells were present. Coombs test, TORCH titers, parvovirus B19 serologies, and immunoglobulin M titers were all negative. Echocardiography showed no abnormalities.

CASE 2 was a Japanese male neonate, born to unrelated parents. His mother was a 41-year-old woman, gravida 5, para 1 and was transferred to our hospital for evaluation of fetal hydrops, that was suspected based on the routine sonographic examination at 32 weeks' gestation. No other complications were noted.

Ultrasound examination at 34 weeks of gestation revealed moderate fetal ascites and hydrothoraxes in the fetus. Laboratory findings of the umbilical blood sampled at 34 weeks' gestation were as follows: the fetal RBC was $3.53\times10^6/\mu l$, hemoglobin 14.3g/dl, hematocrit 41.9%, WBC 43,000/μl, PLT $840\times10^3/\mu l$, and TP 2.8g/dl (albumin 1.7g/dl). Aspiration of fetal ascites and pleural effusions were carried out at 34 weeks' gestation, nevertheless caesarean section was eventually conducted because of fetal distress.

The neonate weighed 3,898g at birth and had severe asphyxia with Apgar score of 1 at 1 min. Mechanical ventilation and aspiration of pleural effusions were immediately required for the respiratory distress. The neonate, however, became worse due to pulmonary hypoplasia and died at 2 hours after birth. Chromosome analysis revealed 47,XY,+21(Down syndrome). The peripheral WBC was 47,700/μl (blast 20%), RBC $3.54\times10^6/\mu l$, hemoglobin 14.7g/dl, hematocrit 45%, and PLT $102\times10^3/\mu l$ at birth. Coombs test, TORCH titers, parvovirus B19 serologies, and immunoglobulin M titers were all negative. Echocardiography revealed that he had tricuspid valve regurgitation (TR), atrial septal defect (ASD) and ventricular septal defect (VSD). At autopsy, marked extramedullary hematopoiesis in the liver, spleen, pancreas and lymphonode were noted. The bone marrow was hypercellular without morphologic abnormalities. These findings were likely consistent with transient abnormal myelopoiesis (TAM).

DISCUSSION

Of the six neonates with nonimmunologic fetal hydrops that we investigated in this study, two cases had Down syndrome. Only one (case 4) of the 6 cases was an appropriate-for-dates infant, presenting with oligohydramnios as a result of urinary tract anomaly.

According to previous reports, the incidence of the chromosomal disorder in nonimmunologic fetal hydrops is around 6-7% (1,2), but two of 6 cases were Down syndrome in this study. It was reported that Down syndrome and Turner syndrome (monosomy X) were the most commonly identified chromosomal disorders related to nonimmunologic fetal hydrops (3). Unfortunately, because of the acute presentation and poor prognosis of nonimmunologic fetal hydrops, data collection is often incomplete. Furthermore, their features are often distorted by edema, thus obscuring the phenotypic characteristics of the chromosomal disorders. Our data may suggest the importance of chromosomal analysis in nonimmunologic fetal hydrops.

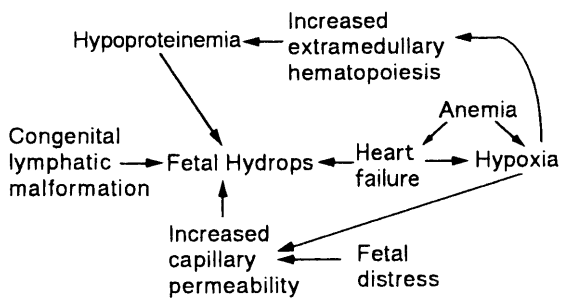

Fig. 1. The pathophysiology of fetal hydrops.

It is generally assumed that the edema in nonimmunologic fetal hydrops is caused by heart failure due to some of congenital cardiovascular anomalies, anemia or hypoxia due to hematologic disorders, hypoproteinemia according to extramedullary hematopoiesis, congenital lymphatic malformations or fetal distress (1,3) as illustrated in Fig.1.

Associated anomalies, specifically cardiovascular abnormalities in Down syndrome have been often thought to be the causative factor in the development for the fetal hydrops (3). Although cardiovascular abnormalities have been noted in some cases, many of fetal hydrops with Down syndrome were structurally normal (1). On the other hand, a variety of blood diseases have been described in neonates with Down syndrome (4,5).

In our cases, each of the two neonates with Down syndrome had hemotopoietic disorders. Case 1 had pancytopenia and case 2 had TAM. Extramedullary hematopoiesis due to these diseases may compress the intrahepatic vessels, producing venous stasis with portal hypertention, hepatocellular dysfunction and decreased albumin synthesis. There is a report that TAM was prenatally observed but spontaneously disappeared within 5 weeks (6), therefore, it should be considered the possibility that hematopoietic abnormalities occured transiently in a time of the fetal period of Down syndrome even if no hematologic abnormalities were observed at birth.

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