Thai Journal of Obstetrics and Gynaecology
October 2020, Vol. 28, No. 4, pp. 192-197

SPECIAL ARTICLE

The Systematic Work Up to Identify Etiology of Non-immune Hydrops Fetalis: A perspective view of pathologist

Patou Tantbirojn, M.D.*

** Division of Gynecologic Pathology, and Placental Related Diseases Research Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

ABSTRACT

Non-immune hydrops (NIH) is an important condition in health service. Many etiologies of NIH have been described, but the definite cause of NIH in many cases is still reported as "unknown". This finding may be partly explained by the inadequate investigation. The article summarized the possible etiology of NIH and the needed investigation to establish cause of NIH from the view of pathologist.

Keywords: Hydrops fetalis, non-immune hydrops fetalis, etiology

Correspondence to: *Patou Tantbirojn, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Rama IV Road, Pathumwan, Bangkok, Thailand, Email: two_devil@hotmail.com*

Received: 9 September 2020, **Revised:** 29 September 2020, **Accepted:** 30 September 2020

Introduction

Hydrops fetalis is the condition with excessive fluid accumulation in two or more fetal compartments. The accumulation of fluid can occur in tissue such as fetal subcutaneous tissue or in body cavities such as pericardial effusion, pleural effusion, and ascites[1]. The reported overall incidence of hydrops fetalis is 1 in 1,500 to 4,000 pregnancies. However, this number may be lower than the actual incidence because hydrops fetalis can spontaneously resolve in some cases[2, 3].

Etiology

There are two categories of hydrops fetalis: immune and non-immune. Immune hydrops fetalis is due to red blood cell alloimmunization in which Rhesus (Rh) D antibody is the most common cause. At the present, the blood test of red blood cells antibodies is routinely performed in antenatal care and anti-D immunoglobulin is also widely available, so the incidence of immune hydrops fetalis is much lower and accounts in only 10% of overall hydrops fetalis. The incidence is also varied among population because Rh-negative is found in up to 15% of Caucasian population, while less than 1% of Asian population are Rh-negative[4-7].

Non-immune hydrops (NIH) is much more common than immune hydrops and there are many etiologies that cause this condition. The prevalence and etiologies are different among countries, depends on the ethnic which is prone to hemoglobinopathy and

genetic disorders as well as endemic area of some infectious disease. The etiologies can be divided into four groups: maternal, fetal, placental, and idiopathic; which can be overlapping between groups. However, it is easier to classify by structures and pathophysiology as follows:

Cardiovascular abnormalities

This category is considered to be the most common cause of NIH in many studies, especially from western countries, and accounts for 17-35%[8, 9]. The abnormalities can be structural malformation which is the majority of cases; or other less common conditions such as arrhythmia, tumor, physical dysfunction from infection, inflammation, cardiomyopathy, and vascular anomaly. The common reported cardiac malformation in NIH are hypoplastic left heart and endocardial cushion defect[9, 10]. Cardiac or intrathoracic vascular malformation leads to increased venous pressure, resulting in volume overload and finally causes heart failure. The prognosis of NIH due to structural cardiac malformation is very poor with high rate of intrauterine fetal death. In contrast, fetal tachyarrhythmia is the most treatable cardiac cause by transplacental medical therapy[9].

Chromosomal abnormalities

Chromosomal abnormalities in NIH are varies among the studies, depending on the availability of investigation and financial resources. The reported prevalence is ranging from less than 10% and up to 70% in some series[8, 9, 11]. The most common reported cases are Turner syndrome (45,X) and Down syndrome (trisomy 21). Other common aneuploidies include trisomy 13, trisomy 18, and triploidy. The mechanism of hydrops in this group is explained by the increased rate of cardiovascular malformation, lymphatic dysplasia (e.g. cystic hygroma), and abnormal myelopoiesis in such cases.

Hematologic abnormalities

Any hematologic abnormality causing fetal anemia can lead to hydrops. The most common etiology in this category is hemoglobinopathy which is inherited transmission. Alpha thalassemia or hemoglobin Bart hydrops are frequently found in Southeast Asia countries and considered to be the most common etiology of overall hydrops in this region[12, 13]. Other less common causes in this group consist of hemolysis, massive fetomaternal hemorrhage, abnormal in red blood cells productivity, and infection (e.g. parvovirus B19).

Infectious diseases

Intrauterine infection is a common cause of NIH and accounts for 4-15%. The hydrops can be occurred from viral, bacterial, or parasitic infection. The frequently identified diseases are parvovirus B19, cytomegalovirus, syphilis, and toxoplasmosis[14, 15]. The pathogenesis of hydrops in cases with intrauterine fetal infection is associated with several mechanisms including endothelial cell damage, increased capillary permeability, anoxia, myocarditis, and anemia. In western countries, parvovirus is the most commonly reported infectious cause of NIH. However, syphilis is more commonly found than parvovirus in Asian countries[16-19].

Thoracic abnormalities

This category comprises of multiple conditions, particularly involving with mass effect in thoracic cage either directly compress by lesion or complication such as effusion that impairs venous return and cardiac output. The examples of diseases in this group include congenital cystic adenomatoid malformation (CCAM), vena caval obstruction, brochopulmonary sequestration, mediastinal tumor, and congenital hydrothorax. Among of these etiologies, chylothorax is the most common cause of isolated effusion that leads to NIH, occurring from lymphatic obstruction[20, 21].

Urinary tract abnormalities

Structural urinary tract malformation is quite rare to be etiology of NIH. Huge intraabdominal tumor can cause NIH by the mass effect that interferes with venous return. Congenital nephritic syndrome has also been reported as a cause of NIH due to hypoproteinemia[22].

Hepatobiliary and Gastrointestinal tract abnormalities

The examples of abnormality in this group are diaphragmatic hernia, small bowel volvulus, gut obstruction, intestinal malrotation, liver tumor, biliary atresia, and meconium peritonitis. The mechanism of hydrops is varied depends on the etiology. The cause of NIH in cases with intraabdominal masses is explained

by obstruction the venous return. In contrast, NIH in cases of gut obstruction is due to decreased osmotic pressure from protein loss, while arteriovenous shunting is the main mechanism of high cardiac output failure in case with hepatic hemangioma[23].

Placental and cord lesions

The reported associated conditions with NIH include chorangioma, umbilical arterial aneurysm, umbilical venous thrombosis, angiomyxoma of cord, and amniotic bands[24]. Small chorangioma is identified in approximately 1% of pregnancies and does not have clinical significance. Therefore, the lesion that is larger than 5 cm can cause fetal hydrops due to high arteriovenous shunt[25].

Inborn errors of metabolism and other genetic conditions

This group has been occasionally reported in the past and account for only 1-2% of NIH. The most well known example is lysosomal storage disease[26]. However, the recent studies showed increased prevalence of lysosomal storage disease if a comprehensive workup for this condition was performed[27, 28]. The proposed pathogeneses are visceromegaly leading to decrease or obstruction of venous return; decreased erythropoiesis; and hypoproteinemia.

Workup of nonimmune hydrops fetalis[29, 30]

There are several guidelines, but the completion of every step is controversial and limited by the available resources of each center. Autopsy is still considered as a necessary procedure and strongly recommended in all cases of fetal death or termination of pregnancy that diagnosis is unknown prenatally[30]. Pathologist has an important role in summarizing the evidence and establish the final diagnosis. However, most cases were submitted for pathologic examination without adequate clinical information including the results of previous investigations. In order to accurately identify the cause of NIH, collaboration between obstetrician and pathologist is needed. The investigations that should be performed are as follows:

Clinical evaluation

Detailed maternal history is very important and should be informed the pathologist prior to autopsy examination. The history that should be focused includes ethnicity, consanguinity, maternal past history and reproductive history, previous hydrops or fetal death, infectious disease exposure, traveling, use of medication, and 3-generation pedigree.

Sonographic examination

Besides of determining the structural malformation; several etiologies can be confirmed or excluded by targeted ultrasound examination such as cardiac arrhythmia and fetal anemia. Middle cerebral artery Doppler study is essential to assess fetal anemia. Arterial Doppler is also important as it reflects the redistribution of fetal cardiac output to the blood flow in descending aorta and umbilical artery. However, changes in umbilical artery Doppler occur later than venous Doppler and cardiac function alteration. Absent or reversed end diastolic blood flow in the umbilical artery is associated with increased cardiac afterload and frequently seen in cases with poor prognosis[10].

Testing for hemoglobinopathy and other hematologic abnormalities

Routine maternal blood tests include complete blood count (CBC), ABO blood type, and antigen status. Hemoglobin electrophoresis and glucose-6-phosphate dehydrogenase (G6PD) deficiency screening are depending on the ethnic origin. Antibody screening can be done by indirect Coombs test. If fetal bradyarrhythmia is present, SS-A, SS-B antibodies should also be performed. Kleihauer-Betke smear is useful in cases that suspected of fetomaternal hemorrhage.

Investigation for fetal infection

There are several laboratory tests for infectious diseases that associated with fetal hydrops. Nowadays, two main categories are performed; serologic test and infectious agent detection[14, 31]. Serology is sensitive, but rather non-specific because it often cannot determine the definite time of infection. Classically, immunoglobulin (Ig) G and IgM are measured in which two samples from different period are required to determine seroconversion or rising in titer. IgM reflects a recent infection, but it may persist for a long time in some cases. In the other hand, IgM can also not be

detected at the time of fetal hydrops because seroconversion was rapidly occurred earlier. Maternal toxoplasmosis, rubella, cytomegalovirus, herpes simplex (TORCH), and parvovirus B19 serologic test are generally done one time when hydrops was diagnosed in which the interpretation of laboratory result may be limited. It will be more useful if prior immune status of these infectious diseases is tested as baseline since the first trimester. If available, more sensitive molecular methods (such as polymerase chain reaction (PCR) or reverse transcription polymerase chain reaction (RT-PCR)) to detect infectious agents are recommended, but the procedure to collect specimen is much more invasive than routine maternal serologic test.

Karyotype and genetic studies

As some chromosomal abnormalities may not have obvious structural malformation; fetal chromosomal analysis should be offered in all cases whether the anomalies are detected or not by sonography[32]. The prenatal diagnosis can be done by classic karyotype, fluorescence in situ hybridization (FISH), or chromosomal microarray analysis via chorionic villus sampling, amniocentesis, placental biopsy, or fetal blood sampling. Therefore, screening non-invasive prenatal testing can detect only some chromosomal abnormalities, so it is not considered as an adequate testing in cases of fetal hydrops.

Studies of inborn errors of metabolism

Although inherited metabolic disorders (such as lysosomal storage diseases, Gaucher disease, and Niemann-Pick disease) are rare, but it is critical because of the high recurrence due to autosomal recessive inheritance. In such cases, the pathologist should be informed in order to careful histologic examine of the placenta, liver, spleen, and bone marrow. Panels of causative storage diseases can be tested in only few specialized laboratories. However, this condition should be concerned in cases of NIH that cannot find any cause of hydrops or cases that have recurrent hydrops in a family[27, 28].

Placental pathologic examination

Placental examination should be performed in all cases of fetal hydrops. Some common infectious disease can be demonstrated in the placenta, but it is quite non-specific in most cases. Clinical information is needed to be evaluated at the time of examination to determine whether the pathologic feature is compatible with suspected condition or not. Additional immunohistochemical study may have a role in detection of infectious agent, but it is expensive and available in only some laboratories.

Autopsy

Autopsy is strongly recommended for every case that the prenatal diagnosis is still unknown. Review of all clinical data and investigation is necessary for good planning of autopsy to collect specimen for further studies. Besides of routine autopsy examination, detailed photography should be taken for retrospective review of dysmorphic structures. Fetal X-rays are optional in cases that suspected of skeletal dysplasia. Fetal blood, tissue, deoxyribonucleic acid (DNA), and amniotic fluid supernatant should be collected and frozen at -70°C. In some centers, a potentially dividing fetal cell line (amniocytes, skin biopsy) is also collected for future biochemical or molecular genetic testing. Extensive sampling from various sources to test for tissue-specific enzymatic activity or gene expression should be considered in the indicated case[33].

Conclusion

NIH has several etiologies. In order to identify definite cause of NIH, it needs the collaboration between obstetricians and pathologists to combine the clinical information and plan of investigation.

Potential conflicts of interest

The author declares no conflict of interest.

References

1. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, Spong CY. Williams Obstetrics, 25 ed. New York: Mc Graw Hill Education; 2018.
2. Kajdy A, Materny A, Modzelewski J, Baszczeska J, Rabijewski M, Szymkiewicz-Dangel J. Spontaneous resolution of prenatally diagnosed isolated pleural effusion: An unusual early sign of a newborn disease. J Obstet Gynaecol Res 2019;45:2466-9.

3. Kiyota A, Tsukimori K, Yumoto Y, Hojo S, Morokuma S, Fukushima K, et al. Spontaneous resolution of cystic hygroma and hydrops in a fetus with Noonan's syndrome. Fetal Diagn Ther 2008;24:499-502.
4. Ismail KM, Martin WL, Ghosh S, Whittle MJ, Kilby MD. Etiology and outcome of hydrops fetalis. J Matern Fetal Med 2001;10:175-81.
5. Webb J, Delaney M. Red blood cell alloimmunization in the pregnant patient. Transfus Med Rev 2018;32: 213-9.
6. Karim F, Moiz B, Kamran N. Risk of maternal alloimmunization in Southern Pakistan - a study in a cohort of 1000 pregnant women. Transfus Apher Sci 2015;52:99-102.
7. Sankaralingam P, Jain A, Bagga R, Kumar P, Marwaha N. Red cell alloimmunization in RhD positive pregnant women and neonatal outcome. Transfus Apher Sci 2016;55:153-8.
8. Bellini C, Hennekam RC, Fulcheri E, Rutigliani M, Morcaldi G, Boccardo F, et al. Etiology of nonimmune hydrops fetalis: a systematic review. Am J Med Genet A 2009;149A:844-51.
9. Bellini C, Donarini G, Paladini D, Calevo MG, Bellini T, Ramenghi LA, et al. Etiology of non-immune hydrops fetalis: An update. Am J Med Genet A 2015;167A:1082-8.
10. Hofstaetter C, Hansmann M, Eik-Nes SH, Huhta JC, Luther SL. A cardiovascular profile score in the surveillance of fetal hydrops. J Matern Fetal Neonatal Med 2006;19:407-13.
11. Jauniaux E, Maldergem LV, Munter CD, Moscoso G, Gillerot Y. Nonimmune hydrops fetalis associated with genetic abnormalities. Obstet Gynecol 1990;75:568-72.
12. Taweevisit M, Thorner PS. Hydrops fetalis in the stillborn: a series from the central region of Thailand. Pediatr Dev Pathol 2010;13:369-74.
13. Ratanasiri T, Komwilaisak R, Sittivech A, Kleebkeaw P, Seejorn K. Incidence, causes and pregnancy outcomes of hydrops fetalis at Srinagarind Hospital, 1996-2005: a 10-year review. J Med Assoc Thai 2009;92:594-9.
14. Syridou G, Spanakis N, Konstantinidou A, Piperaki ET, Kafetzis D, Patsouris E, et al. Detection of cytomegalovirus, parvovirus B19 and herpes simplex viruses in cases of intrauterine fetal death: association with pathological findings. J Med Virol 2008;80:1776-82.
15. Al-Buhtori M, Moore L, Benbow EW, Cooper RJ. Viral detection in hydrops fetalis, spontaneous abortion, and unexplained fetal death in utero. J Med Virol 2011;83:679-84.
16. Carles G, Lochet S, Youssef M, El Guindi W, Helou G, Alassas N, Lambert V. Syphilis and pregnancy. J Gynecol Obstet Biol Reprod (Paris) 2008;37:353-7.
17. Chisaka H, Morita E, Yaegashi N, Sugamura K. Parvovirus B19 and the pathogenesis of anemia. Rev Med Virol 2003;13:347-59.
18. Enders M, Klingel K, Weidner A, Baisch C, Kandolf R, Schalasta G, et al. Risk of fetal hydrops and non-hydropic late intrauterine fetal death after gestational parvovirus B19 infection. J Clin Virol 2010;49:163-8.
19. Enders M, Weidner A, Zoellner I, Searle K, Enders G. Fetal morbidity and mortality after acute human parvovirus B19 infection in pregnancy: prospective evaluation of 1018 cases. Prenat Diagn 2004;24:513-8.
20. Attar MA, Donn SM. Congenital chylothorax. Semin Fetal Neonatal Med 2017;22:234-9.
21. Downie L, Sasi A, Malhotra A. Congenital chylothorax: associations and neonatal outcomes. J Paediatr Child Health 2014;50:234-8.
22. Fischbach H, Schwarz R, Müller WD, Kellner A. A new type of congenital nephrotic syndrome. Pathol Res Pract 1978;163:387-94.
23. Albano G, Pugliese A, Stabile M, Sirimarco F, Arsieri R. Hydrops foetalis caused by hepatic haemangioma. Acta Paediatr 1998;87:1307-9.
24. Sivasli E, Tekşam O, Haliloğlu M, Güçer S, Orhan D, Gürgey A, et al. Hydrops fetalis associated with chorioangioma and thrombosis of umbilical vein. Turk J Pediatr 2009;51:515-8.
25. Merry-Sperry AD, Chaffin DG, Denning KL, Shamma B, Massey C, Werthammer J. Placental chorioangioma with nonimmune hydrops fetalis. South Med J 2018;111:457-9.
26. Whybra C, Mengel E, Russo A, Bahlmann F, Kampmann C, Beck M, et al. Lysosomal storage disorder in non-immunological hydrops fetalis (NIHF): more common than assumed? Report of four cases with transient NIHF and a review of the literature. Orphanet J Rare Dis 2012;7:86.
27. Gimovsky AC, Luzi P, Berghella V. Lysomal storage diseases as an etiology of non-immune hydrops. Am J Obstet Gynecol 2015;212:281-90.
28. Gort L, Granell MR, Fernández G, Carreto P, Sanchez A, Coll MJ. Fast protocol for the diagnosis of lysosomal diseases in nonimmune hydrops fetalis. Prenat Diagn 2012;32:1139-42.
29. Society for Maternal-Fetal Medicine (SMFM); Norton ME, Chauhan SP, Dashe JS. Society for maternal-fetal medicine (SMFM) clinical guideline #7: nonimmune hydrops fetalis. Am J Obstet Gynecol 2015;212:127-39.
30. Désilets V, De Bie I, Audibert F. No. 363-Investigation and management of non-immune fetal hydrops. J Obstet Gynaecol Can 2018;40:1077-90.
31. Mendelson E, Aboudy Y, Smetana Z, Tepperberg M, Grossman Z. Laboratory assessment and diagnosis of congenital viral infections: Rubella, cytomegalovirus (CMV), varicella-zoster virus (VZV), herpes simplex virus (HSV), parvovirus B19 and human

immunodeficiency virus (HIV). Reprod Toxicol 2006;21:350-82.
32. Désilets V, Audibert F; Society of Obstetrician and Gynecologists of Canada. Investigation and management of non-immune fetal hydrops. J Obstet Gynaecol Can 2013;35:923-38.
33. Rodriguez MM, Bruce JH, Jimenez XF, Romaguera RL, Bancalari E, García OL, et al. Nonimmune hydrops fetalis in the liveborn: series of 32 autopsies. Pediatr Dev Pathol 2005;8:369-78.