Non-immune fetal hydrops: Are we doing the appropriate tests each time?

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Summary

Non-immune fetal hydrops is diagnosed when there is fluid accumulation in more than one extravascular space. A long list of etiologies has been found in association with non-immune hydrops. Thorough investigations are needed to be able to identify an underlying cause. There are many recent reports indicating that non-immune hydrops can be an extreme presentation of a number of metabolic disorders, mostly lysosomal storage diseases. The fetal hydrops associated with metabolic disorders is usually severe with very thick skin, massive ascitis, other feature could be seen such as contracture deformities, skeletal abnormalities, hepatosplenomegaly, renal abnormalities, and enlarged nuchal translucency. The diagnosis of a metabolic disorder can be done by a variety of different tests: measuring the level of the specific enzyme or metabolite, histological examination of different organs, or mutation identification. An index case is usually needed to confirm the diagnosis. In-utero diagnosis of a metabolic disorder in the absence of an index case is difficult and only available in selected laboratories around the world. In populations with high consanguinity, these diseases are much more commonly present than what we might think. Routine screening for metabolic diseases especially lysosomal storage diseases should be considered in these populations, and definitely in cases of recurrent hydrops in the same family. More efforts should be spent on identifying causative mutations in different ethnic groups. Every effort should be made to identify the etiology in an index case in the family, as this might be the best opportunity for improving future care.

Introduction

Non-immune fetal hydrops is a condition easily diagnosed by antenatal ultrasound. The diagnosis is reached when there is fluid accumulation in more than one extravascular space, this includes soft tissue edema in the skin or scalp, or fluid in body cavities such as ascites pleural effusion, pericardial effusion, or hydrocele. Non-immune fetal hydrops is a clinical phenotype and not a diagnosis. It is associated with a broad spectrum of causes. The identification of hydrops by ultrasound is very frustrating to the family and physicians because it requires extensive search for the etiology, which include a wide variety of diseases and pathologies. Even after undergoing a long list of testing, a good number of cases remain with no clear diagnosis. In addition, the prognosis has traditionally been reported as poor with perinatal loss of 70-90% (1, 2), more recent studies where more extensive work-up and in-utero treatment were utilized, better perinatal outcome was reported (3, 4).

Etiology of non-immune hydrops

A long list of etiologies has been found to be associated with non-immune hydrops. This includes fetal, maternal and placental/cord abnormalities. In previous reports, there were a large number of cases labeled as idiopathic. More recently, investigators have shown that with thorough investigations, an underlying cause can be identified in up to 84% of such fetuses. When hydrops fetalis is followed by intrauterine fetal death, the success rate for identifying an etiology for the hydrops drops to 40% (5).

Fetal causes include cardiac defects either structural defects such as (but not limited to) hypoplastic left or right heart, artioventricular septal defects, aortic stenosis or atresia, pulmonary stenosis or atresia, tetralogy of Fallot, premature closure of the ductus, or arrhythmias such as supraventricular tachycardia, atrial flutter, or heart block. Chromosomal abnormalities, skeletal dysplasia, feto-maternal hemorrhage and hematologic abnormalities are also important causes. Some structural fetal defects are associated with hydrops such as diaphragmatic hernia, intestinal or esophageal atresias, polycystic kidneys, bronchopulmonary sequestration, and congenital cystic adenomatoid malformation. Some fetal tumors can be associated with or can lead to hydrops, examples are neuroblastoma and sacrococcygeal teratoma. There are a number of genetic syndromes presenting with fetal hydrops including multiple pterygium, Noonan syndrome, Cornelia de Lange, tuberous sclerosis, myotonic dystrophy and Neu-Laxova syndrome.

Maternal disease include severe maternal anemia, diabetes and maternal indomethacin use. Placental/cord pathology include: chorioangioma, angiomyxoma of the cord, and chorionic vein thrombosis.

Metabolic disorders have been traditionally included in this long list, but as these diseases are very rare, routine

testing has not been part of the work-up list for non-immune hydrops.

Metabolic disorders as a cause of non-immune hydrops

It has been recognized that a number of cases of non-immune hydrops were found to be secondary to lysosomal storage diseases and other metabolic disorders (6, 7). This include mucopolysacccharidosis type VII (Sly disease) and IVA (Morquio A syndrome), Gaucher disease type 2, sialidosis, GM1 gangliosidosis, galactosialidosis, Niemann-Pick disease type C, disseminated lipogranulomatosis (Farber disease), infantile free sialic acid storage (ISSD), and mucolipidosis II (I-cell disease).
There are many reports coming up in the literature indicating that non-immune hydrops can be an extreme presentation of a number of metabolic disorders, usually recurrent in the same family (8-11). Most of the recent reports are reporting antenatal ultrasound findings and prenatal or postnatal diagnosis. The association of lysosomal storage diseases with hydrops is not new phenomena, the pediatrics literature has reported this association in the postnatal period many years earlier (12).
Although lysosomal storage diseases are rare disorders, the combined incidence is around 1 in 1-500 births (13), with clear ethnic variations. Consanguinity is an important contributor to the increase risk for these disorders in these ethnic groups.

Diagnosis of a metabolic disorder in cases of non-immune hydrops

To reach a diagnosis for the underlying cause of a metabolic disease for non-immune hydrops, a high index of suspicion is required. The risk is higher if the hydrops is recurrent for the same couple, or if a family history is positive for a metabolic disease or non-immune hydrops.
Ultrasound can give a clue for the suspicion. The fetal hydrops associated with metabolic disorders is usually severe hydrops with massive ascites, and very thick skin. Other feature includes course faces (which might be difficult to see with the massive skin edema), contracture deformities, skeletal abnormalities, hepatosplenomegaly (5, 14), and renal abnormalities.
The diagnosis of a metabolic disorder can be done by a variety of different tests. The classic diagnosis is usually done by measuring the level of the specific enzyme. Different lysosomal storage diseases are associated with different enzyme deficiency. Examples include beta-glucuronidase deficiency in Mucopolysaccharidosis type VII, beta-galactosidase deficiency in GM1 gangliosidosis.
Other methods of diagnosis include histological examination of different organs such as liver, spleen, lungs, bone marrow, or placenta (15, 16). Mutation identification is not available for all diseases, and in some diseases the parents might not be carrying the common mutation for that particular disorder, which could limit the possibility of prenatal diagnosis (17).
Another difficulty that is faced in some diseases is that there are cases of pseudodeficiency in the enzyme which might be common in a particular disease (example include metachromatic leucodystrophy). In these cases it is important to know the enzyme level in the parents and the index case, or the mutation in the family before prenatal diagnosis can be offered (18). Because of these issues, In-utero diagnosis of a metabolic disorder in the absence of an index case is difficult and only available in selected laboratories around the world.
Few numbers of cases of Mucopolysaccharidosis type VII have been reported with prenatal diagnosis, by either amniocentesis or chorionic villus sampling, most of which there was a previously affected child in the family (10, 19, 20).
It is therefore of ultimate importance to try to identify the cause of non-immune hydrops in the index case, if not antenatal, then postnatal. This will be helpful when dealing with these families preconception, in order to provide them with appropriate counseling and options for next pregnancy.
Screening for metabolic abnormalities should be considered in any work-up for non-immune hydrops fetalis, but with repeat hydrops it should be mandatory.

Large nuchal translucency and metabolic disorders

Nuchal translucency, which is a measurement of the fluid accumulation in the back of the fetal neck has been found to be increased not only in fetuses with chromosomal abnormalities, but also in a variety of fetal abnormalities including structural fetal defects and genetic diseases (21). Since that time, many reports came out to indicate that metabolic disorders can be suspected if increased nuchal translucency is diagnosed in the first trimester. Many metabolic diseases have been found to have this association including Zellweger syndrome (22-24), mucopolysaccharidosis type VII (25, 26). Obviously, not all lysosomal storage diseases present with enlarged nuchal translucency, a recent study by De Biasio et al demonstrated that nuchal translucency could be normal in these fetuses (27).

Conclusions

Metabolic disorders, although uncommon, must be always thought of when investigating cases of non-immune hydrops, and enlarged nuchal translucency. Depending on the population managed, these diseases are much more commonly present than what we might think. Routine screening for metabolic diseases especially lysosomal storage diseases should be considered in at risk population, and definitely in cases of recurrent hydrops in the same family. More efforts should be spent on identifying causative mutations in different ethnic groups. Every effort should be made to identify the etiology in an index case in the family as this might be the best opportunity for improving future care.

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