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Review

Non-immune hydrops fetalis

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Abstract

Non-immune hydrops fetalis (NIHF) refers to hydrops in the absence of maternal circulating red-cell antibodies, and constitutes up to 90% of all described hydrops fetalis cases.

One-third of hydropic fetuses are discovered incidentally during prenatal sonography in the first or second trimester of gestation. Although hydrops is a fetal condition, in many cases there are associated maternal findings, such as preeclampsia, polyhydramnios, and mirror syndrome (generalized maternal edema, that 'mirrors' the edema of the hydropic fetus and placenta). NIHF should be seen as a symptom or clinical phenotype rather than as a disorder, and considered as a non-specific, end-stage status of a wide variety of disorders. Numerous disorders including fetal disorders, maternal diseases (e.g., severe maternal anemia, diabetes and maternal indomethacin use) and placental/cord abnormalities have been associated with NIHF. Despite extensive investigations, the etiology on NIHF may remain unknown in 15% to 25% of patients, even after an autopsy has been performed. Chromosomal abnormalities are the cause of NIHF in 25-70% of the cases. Therefore, fetal or neonatal chromosome analysis is indicated in all cases of NIHF. Abnormalities of the cardiovascular system are responsible for as many as 40% of cases of NIHF. Thoracic abnormalities increase intrathoracic pressure and can obstruct venous return to the heart, leading to peripheral venous congestion, or they may obstruct the lymphatic duct, resulting in lymphedema.

Fetal anemia accounts for 10-27% of hydrops. To evaluate the risk of fetal anemia, Doppler measurement of the middle cerebral artery peak systolic velocity should be performed in all hydropic fetuses after 16 weeks of gestation. Parvovirus B19 is the most common infectious agent associated with hydrops. Even in persistent severe anemia, the prognosis is generally good if the fetus is supported by intrauterine fetal transfusions. The development of hydrops in fetuses with a TORCH infection is a poor prognostic indicator. Although hypoproteinemia is frequently proposed as

one of the causes of hydrops fetalis, recent studies show that hypoalbuminemia is unlikely to cause the initial development of hydrops. However, it seems to occur as a secondary effect in the cascade of hydrops, and might be the trigger for mild hydrops to evolve into severe hydrops. In addition, not all infants with hypoproteinemia become hydropic, and hydrops fetalis is uncommon in congenital nephrotic syndrome and congenital analbuminemia. In the pathogenesis, inherited metabolic disorders, especially lysosomal storage diseases, are more common than previously thought. Inherited metabolic disorders must be always thought when investigating cases of recurrent NIHF in the same family. It is very important to examine the placenta carefully in cases where hydrops or ascites are present at birth or detected by ultrasound, especially in the transient form. Even if a family does not agree to autopsy, placental examination may be done.

Keywords

Non-immune hydrops fetalis, evaluation, pathogenesis, chromosomal disorders, inborn errors of metabolism, placental examination.

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Introduction

Hydrops fetalis is defined as subcutaneous edema, accompanied by effusions in two or more serous cavities, including pericardial or pleural effusions, and ascites. Non-immune hydrops fetalis (NIHF) refers to hydrops in the absence of maternal circulating red-cell antibodies. In the past, immune hydrops fetalis was caused by Rhesus iso-immunization. However, since the 1970s, the introduction of widespread immunoprophylaxis for red cell alloimmunization and the use of *in utero* transfusions for immune hydrops therapy have led to a significant decline in the prevalence of immune hydrops. Currently, NIHF constitutes up to 90% of all described hydrops fetalis cases [1, 2].

The reported incidence is around 3 per 10,000 births; however, the incidence is much higher at the first- and second-trimester ultrasounds because of higher fetal deaths. Wide variations in reported incidence (ranges from 1/1,500 to 1/3,800 births) are due to differences in definitions, populations, and thoroughness of evaluation, as well as whether late pregnancy terminations were included [1, 2].

Prenatal diagnosis

Up to 35% of hydropic fetuses are discovered incidentally during prenatal sonography in the first or second trimester of gestation. The prenatal ultrasonographic findings of hydrops are (a) ascites, pleural effusions, pericardial effusions (visualization of pericardial fluid up to 2 mm is common and should not be regarded as pathologic, and even fluid up to 7 mm may be benign); (b) skin edema (pathologic skin edema has been defined as subcutaneous tissue thickness on the chest or scalp greater than 5 mm) [3].

Polyhydramnios or placental thickness are often associated. Polyhydramnios is present in 40% to 75% of pregnancies complicated by NIHF. Increased placental thickness or placentomegaly may occur due to intravillous edema. A placental thickness greater than 6 cm is considered abnormal. On the other hand, massive polyhydramnios can cause the placenta to appear thinned or compressed [1, 2].

Although hydrops is a fetal condition, in many cases there are associated maternal findings, such as theca lutein cysts, preeclampsia, anemia, preterm labor/delivery, birth trauma, retained placenta, and postpartum hemorrhage. Mirror syndrome (Ballantynes syndrome) refers to a condition of generalized maternal edema, often with pulmonary involvement, that 'mirrors' the edema of the hydropic fetus and placenta. Although usually associated with NIHF, it can also occur with immune-mediated hydrops. The pathogenesis is unknown. Mirror syndrome can occur at any time during the antepartum period and may persist postpartum. Clinical findings are similar to that of severe preeclampsia. In contrast to preeclampsia, the maternal hematocrit is often low due to hemodilution and amniotic fluid volume is often high (polyhydramnios) rather than low (oligohydramnios). Delivery or interventions that result in reversal of fetal hydrops is usually required to induce remission of maternal symptoms and findings. Spontaneous resolution of mirror syndrome has also been described after spontaneous

resolution of fetal hydrops related to parvovirus infection and after fetal death [3].

Disorders associated with hydrops

NIHF should be seen as a symptom or clinical phenotype rather than as a disorder, and considered as a non-specific, end-stage status of a wide variety of disorders [1, 4].

Fetal hydrops is the end result of one or more of the following abnormalities: (a) increased venous pressure due to myocardial failure (e.g., heart defects or anemia), or obstructed venous return to the heart; (b) increased capillary permeability (e.g., infection); obstructed lymphatic drainage in the thoracic and abdominal cavities (e.g., congenital anomaly, neoplasm); (c) reduction in osmotic pressure – hypoproteinemia (e.g., liver disease, nephropathy, non-immune mediated anemia). In addition to the three basic mechanisms, fetal hydrops has a causal relationship with a variety of structural abnormalities that interfere with the fetoplacental circulation [3].

Numerous disorders have been associated with NIHF. These include fetal disorders (presented below), maternal diseases (e.g., severe maternal anemia, diabetes and maternal indomethacin use) and placental/cord abnormalities (e.g., chorioangioma, angiomyxoma of the cord, and chorionic vein thrombosis). A growing number of conditions can result in NIHF. A systematic review has recently analyzed a total of 225 articles describing 5,437 cases. All cases were classified as cardiovascular disorders (21.7%), chromosome imbalances (13.4%), hematologic abnormalities (10.4%), infections (6.7%), intra-thoracic masses (6.0%), lymph vessel dysplasias (5.7%), twin-to-twin transfusion syndrome and placental causes (5.6%), syndromes (4.4%), urinary tract malformations (2.3%), inborn errors of metabolism (1.1%), extra-thoracic tumors (0.7%), gastrointestinal disorders (0.5%), miscellaneous causes (3.7%), and idiopathic cases (17.8%) [4].

Despite extensive investigations, the etiology on NIHF may remain unknown in 15% to 25% of patients. The cause of hydrops can be determined antenatally in 50% to 85% of cases; most of the remaining cases are determined postnatally, although 5% to 8% are classified as idiopathic, even after an autopsy has been performed [3].

Chromosomal abnormalities

The most common genetic etiology of hydrops is aneuploidy. Chromosomal abnormalities (aneuploidy, deletion, duplication, genetic mutation) are the cause of NIHF in 25% to 70% of cases. Aneuploidy is responsible for approximately 10% of NIHF cases [2]. The most common chromosomal cause of NIHF is monosomy X, which accounts for 42% to 67% of cases [5]. Other aneuploidies associated with hydrops are trisomy 21 (23% to 30% of cases), other forms of aneuploidy including trisomy 13, 18, and 12 (10% of cases), tetraploidy and triploidy, and rare deletions and duplications [5, 6]. NIHF prior to 24 weeks of gestation is usually related to an aneuploidy, while cardiac (structural defects and rhythm disturbances), pulmonary, and infectious etiologies account for the majority of cases after 24 weeks [7].

The mechanism for fluid accumulation in these fetuses may involve obstruction or incomplete formation of the lymphatic system in the neck (cystic hygroma) or abdomen, leading to lymphatic dysplasia. Other mechanisms include cardiac failure related to congenital heart disease (present in 15% to 25% of aneuploid fetuses) and Down syndrome associated congenital leukemia [3].

The risk of fetal aneuploidy is higher when identified earlier in gestation or when structural anomalies are seen. Therefore standard fetal chromosome analysis is indicated in all cases of NIHF. Genetic microassay molecular testing should also be considered in all NIHF cases. By this technique genetic smaller chromosomal anomalies are detected in 7% of fetuses with congenital anomalies and standard normal karyotype [8].

Genetic syndromes

A number of other inherited syndromes may be associated with hydrops fetalis [2]. Genetic syndromes causing fetal akinesia may result in hydrops. These include multiple pterygium syndrome, arthrogryposis multiplex congenita, and congenital myotonic dystrophy. Pathogenesis may involve decreasing lymphatic flow and increasing intrathoracic pressure secondary to diaphragmatic paralysis. Skeletal dysplasias involving the thorax, such as campomelic dysplasia, short rib polydactyly syndromes, lethal chondrodysplasia, thanatophoric dysplasia, and homozygous achondroplasia, cause NIFH secondary to altered venous return and cardiac tamponade. Single gene defects in which there is a prominent cystic hygroma and lymphatic dysplasia are associated with NIHF and include familial nuchal bleb,

Noonan's syndrome, acrocephalopolydactylous dysplasia, thoracoabdominal syndrome and lymphedema distichiasis syndrome [3].

Cardiovascular abnormalities

Abnormalities of the cardiovascular system are responsible for as many as 40% of cases of NIHF [6]. Numerous cardiac lesions have been implicated, the three major subgroups are structural anomalies, arrhythmias, and vascular abnormalities. The most commonly encountered cardiac structural anomalies associated with hydrops are atrioventricular septal defect, hypoplastic left and right heart, and isolated ventricular or atrial septal defects. Other less common anomalies include tetralogy of Fallot and premature closure of the ductus arteriosus. Many of these lesions are also associated with aneuploidy. Fetal cardiac tumors are rare, but are often associated with hydrops, ventricular obstruction, and/or arrhythmia [9].

Most cardiac structural lesions cause early-onset hydrops, and their prognosis is poor, with a mortality rate close to 100% [10].

Both tachyarrhythmias and bradyarrhythmias can lead to hydrops. The mechanism is believed to be high output cardiac failure with progressive venous congestion in the former, and low cardiac output in the latter. Arteriovenous and venous malformations may also cause NIHF. Chorioangiomas of the placenta greater than 4 to 5 cm in diameter may lead to NIHF due to high output heart failure from arteriovenous shunting. Hydrops can also result from arteriovenous fistulas in other locations (e.g., sacrococcygeal teratoma, neuroblastoma), large hemangiomas, umbilical cord aneurysms, or obstruction of the vena cava, portal vein, or femoral vessels [3].

Thoracic abnormalities

Thoracic abnormalities account for up to 10% of hydrops. These lesions increase intrathoracic pressure and can obstruct venous return to the heart, leading to peripheral venous congestion, or they may obstruct the lymphatic duct, resulting in lymphedema.

Large pleural effusions may reduce venous and lymphatic obstruction and allow hydrops. Fetal pleural effusions may be isolated or associated with hydrops, which confers a worse prognosis. The overall prognosis depends, in part, upon the gestational age at the time the lung lesion developed. The presence of persistent pleural effusions prior to 20 weeks of gestation can compromise lung growth and function. In fetuses with large pleural effusions, placement of a pleuroamniotic shunt may alleviate the increased intrathoracic pressure, thereby reducing the risk of pulmonary hypoplasia. Needle aspiration of pleural effusions is generally not recommended, because the fluid usually reaccumulates within 48 hours [11].

One small study of pleurodesis in 45 hydropic fetuses reported it was less effective than shunting [12].

Anemia

Fetal anemia accounts for 10% to 27% of hydrops [6]. To evaluate the risk of fetal anemia, Doppler measurement of the middle cerebral artery (MCA) peak systolic velocity should be performed in all hydropic fetuses after 16 weeks of gestation. This is an accurate noninvasive tool for predicting fetal anemia of any etiology [13, 14]. In case of suspected fetal anemia, fetal blood sampling is obtained by umbilical vein sampling, and the fetal hemoglobin level should be determined to exclude anemia as a cause of hydrops [2]. In all reported cases with anemia and NIHF, hemoglobin values are less than 5 g/dL [13]. The mechanism for hydrops is thought to be high output cardiac failure.

Alpha-thalassemia major is the most common cause of NIHF among Southeast Asians. The fetus may be severely anemic, and a peripheral slide will show nucleated red cells and target cells. Profound acidosis, hypoxia and hydrops develop early in the midtrimester, followed by intrauterine fetal loss. Definite diagnosis can be made with hemoglobin electrophoresis.

Infectious diseases

Infections are responsible for 8% of NIHF [15]. Parvovirus B19 is the most common infectious agent associated with hydrops accounting for about 15% of cases. Parvovirus B19 attacks red blood cells, hepatocytes, and myocardial cells causing transient anemia, hepatitis, and myocarditis [16]. In these cases, hydrops may resolve spontaneously. Even in persistent severe anemia, the prognosis is generally good if the fetus is supported by intrauterine fetal transfusions. Platelets should be available at the time of blood

sampling and transfusion since some fetuses may also be profoundly thrombocytopenic [3].

Other infections that have been associated with NIHF include TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes virus), and varicella, adenovirus, coxsackievirus infections. Not all fetuses with these infections develop hydrops. The development of hydrops in fetuses with a TORCH infection is a poor prognostic indicator which reflects multisystem failure. Sonographic signs that suggest *in utero* infection include microcephaly, calcifications of the brain, cerebral ventriculomegaly, hepatosplenomegaly, and growth restriction.

Rethinking pathophysiology

Water, lipophilic solutes (e.g., gases such as O_2 and CO_2), and other small solutes are able to pass between endothelial cells or through them by receptor-mediated transcytosis (transcellular transport). Small proteins can also pass through inter-endothelial cell junctions (intercellular transport). Opening of the inter-endothelial junctions (i.e., adherens junctions and tight junctions) is mediated by the retraction of actomyosin, which results in a marked increase in permeability. Plasma proteins such as albumin are too large to pass between intact endothelial cells. Transcellular transport of albumin can occur through caveolae (small cytoplasmic vesicles), vesiculo-vacuolar organelles (grape-like clusters comprised of hundreds of cytoplasmic vesicles) and/or transcellular channels [17-22].

Some agents secreted form perivascular cells, as angiopoietin-1 or fibroblast growth factor, and sphingosine 1-phosphate produce potent barrier enhancement and decrease vascular permeability via actin and junctional protein rearrangement and resultant cytoskeletal changes. Permeability-increasing agents or inflammatory mediators (e.g., histamine, thrombin, and bradykinin, serotonin, platelet activating factor) cause in a rapid but self-limited (complete by 20-30 min) increase in vascular permeability. Vascular endothelial growth factor (VEGF-A) induces vascular permeability. Chronic hyperpermeability of pathological angiogenesis is found in tumors, healing wounds, and chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, cellular immunity, etc. [17-22].

Atrial and brain natriuretic peptides (ANP and BNP, respectively) are cardiac hormones released into the bloodstream in response to hypervolemia. The actions of both peptides include natriuresis and diuresis, a decrease in systemic blood pressure, and inhibition of the renin-angiotensin-aldosterone system. Further, ANP and BNP elicit increases in blood microvessel permeability sufficient to cause protein and fluid extravasation into the interstitium to reduce the vascular volume [23]. However, ANP and BNP also increase collecting lymphatic permeability, oppose the absorptive function of the lymphatic capillaries, and aid in the retention of protein and fluid in the interstitial space to counteract volume expansion [24].

Modified Starling's principle

The fundamental principle governing fluid shifts across the endothelium was introduced by the British physiologist Ernest Starling in 1896. Starling proposed that the walls of capillaries are semipermeable membranes. Fluid movement across the walls of capillaries is passive and dependent on pressure gradients between opposing hydrostatic and colloid (protein) osmotic pressures across the endothelium. Since hydrostatic pressure decreases along a capillary, filtration occurs at the arterial end of capillaries and reabsorption at the venous end of capillaries, and formally comply with the low rates of lymphatic flow. Increased capillary hydrostatic pressure, increased capillary permeability to fluid or plasma proteins, decreased plasma oncotic pressure, decreased lymphatic flow and increased negative pressure within the interstitial space cause edema [25].

Almost 90 years later, however, this model has been challenged [26]. According to the classic Starling principle there is a linear relationship between capillary pressure and transcapillary fluid flux. However capillary hydrostatic pressure activates signaling pathways that increase endothelial permeability resulting in nonlinear dynamics and a higher water flux than would be predicted by the summation of net Starling forces. This deviation from the classic Starling relationship is due to glycocalyx on the endothelial surface [25].

Vascular endothelium is coated by a great variety of transmembrane and membrane-bound molecules, which together constitute the endothelial glycocalyx with a thickness of around 1 μm. The glycocalyx is a complex layer of proteoglycans, glycosaminoglycans (mostly heparan sulfate, chondroitin sulfate, and hyaluronan), and glycolipids [20], and plays a major role in the development of capillary leakage [27]. An intact glycocalyx limits

water and protein flux into the cell-cell junction by forming a molecular filter over the junctional orifice, and provides plasma/interstitial fluid balance and solute exchange [25].

Recent studies show that the interstitial protein concentration, in contrast to Starlings classical concept, does not play a major role in the fluid shift. The endothelial glycocalyx rather appears to act as a molecular filter, actively retaining plasma proteins, increasing the oncotic pressure within the glycocalyx. A small space beneath the protein-loaded endothelial glycocalyx but still at the luminal side of the anatomical vessel wall is almost protein-free. Accordingly, transcapillary fluid loss actually seems to be limited by an oncotic pressure gradient across the endothelial glycocalyx, and not across the whole anatomical vessel wall. Recent findings relocate the inwardly directed oncotic gradient from the interstitial space (as suggested by Ernest Starling) to the luminal side of the anatomical vessel wall, across the endothelial glycocalyx [27, 28]. In addition, the postulated high reabsorption of interstitial fluid in the venular segments of the microcirculation was shown not to exist. Also, filtration across the vascular barrier surprisingly remains largely independent of the bulk colloid concentration surrounding the vessel [28].

Abnormal glycocalyx causes increased capillary transendothelial permeability. Shedding of the glycocalyx induced by the inflammatory cytokine TNF-α or by ischemia-reperfusion causes a substantial increase in vascular permeability to both plasma and colloids [20]. During inflammation, proteases degrade the glycocalyx, and breakdown of the glycocalyx is associated with increased vascular permeability due to loss of the junctional barrier and opening of the intracellular junction, as evidenced by increased water and protein flux through the junction into the interstitium, and resultant tissue edema. The generalized destruction of the glycocalyx could also be a trigger for generalized leucocyte adhesion. Polymorphonuclear leukocytes release mediators (oxidants, proteases) that disrupt inter-endothelial junctions and so increase paracellular permeability [20, 27]. Loss of glycocalyx could be prevented by either antithrombin III or hydrocortisone [20].

Systemic capillary leak syndrome: acquired hydrops?

Systemic capillary leak syndrome (Clarkson disease) is a rare and often fatal idiopathic disorder, characterized by transient spontaneous episodes of macromolecular hyperpermeability with increased capillary leakage and pronounced shifts of plasma from the intravascular to the extravascular space. Hypotension and hemoconcentration are characteristic in pediatric patients. Attacks vary in intensity, duration, and frequency, and swelling all over the body can be misdiagnosed as due to sepsis. Non-infectious causes of recurrent hypovolemic shock with general edema (anaphylaxis, C1-esterase inhibitor deficiency, nephrotic syndrome, adrenal insufficiency, systemic mastocytosis) are excluded by relevant investigations. The precise mechanism of the syndrome remains unclear; increased permeability in the capillary bed of skeletal muscles could be related to classic pathway complement activation, low-grade overstimulation of arachidonic acid metabolism, or cytokine-induced retraction of vascular endothelial cells [29]. G-CSF (granulocyte colony-stimulating factor) is responsible for the pathogenesis of systemic capillary leak syndrome, irrespective of whether the serum level increases idiopathically or after therapeutic administration. Infusions of interleukin (IL)-2, IL-4, tumor necrosis factor, GM-CSF (granulocyte macrophage colony-stimulating factor) may also result in systemic capillary leak syndrome [30, 31].

Fetal predisposition

The fetus is at risk of interstitial fluid accumulation (i.e., hydrops) owing to increased capillary permeability, increased compliance of the fetal interstitial space and the marked influence of lymphatic return by venous pressure [32]. Newly formed vessels during angiogenesis have a thinner glycocalyx layer, and are therefore more permeable [33].

Compliance of the fetal interstitial space is increased to approximately 10 times the adult value. During fetal life lymph flow is five times greater than in the adult per kilogram of body weight to cope with increased fluid in the interstitium [34]. If capillary filtration is higher than the lymphatic fluid removal capacity, the fetal interstitial space readily expands and causes to progressive fetal edema and hydrops [1].

Prenatally, congestive cardiac failure does not lead to pulmonary edema like it would in the newborn. Fetal lungs are collapsed, thereby increasing intra-thoracic pressure and impeding extravasation into the alveoli. The foramen ovale is crucial in regulating changes in central

venous pressure. Conditions characterized by closed or restrictive atrial foramen associated with anatomical or functional obstruction of left atrial pressure dramatically affect fetal pulmonary circulation, leading to pulmonary lymphedema, hydrothorax and hydrops [18].

Fetal renal regulation of fluid excretion is still unknown. Although both renal function impairment and elevated angiotensin levels may play a significant role in the etiology and pathogenesis of NIHF, hydrops can also occur without any significant renal damage and with normal urine production [1].

Hypoalbuminemia: a cause of fetal hydrops?

Hypoproteinemia with decreased colloid osmotic pressure is frequently proposed as one of the causes of hydrops fetalis. Although it has been reported low serum albumin levels in severely anemic neonates with hydrops, a recent study show that most fetuses with immune hydrops have an albumin concentration within the normal range; it suggests that hypoalbuminemia is unlikely to cause the initial development of immune hydrops [35, 36].

Hypoalbuminemia thus seems to occur as a secondary effect in the cascade of hydrops (e.g., because of a reduced re-uptake of albumin from the interstitial compartment). Hypoalbuminemia might even be the trigger for mild hydrops to evolve into severe hydrops. In the chain of events that leads to hydrops, other mechanisms (such as cardiac failure and lymphatic flow obstruction) are likely to be more important.

Not all infants with hypoproteinemia and decreased colloid osmotic pressure become hydropic. Colloid osmotic pressures in babies with erythroblastosis was found to be low, but similar in both hydropic and nonhydropic erythroblastotic infants [37]. In addition, a reduction of plasma protein and colloid osmotic pressure of a short duration do not affect the body water content of fetal sheep. If this degree of hypoproteinemia and decreased colloid osmotic pressure increases the rate of transvascular fluid filtration, then for body water content not to be increased, the fetal hypoproteinemia must lead to a decrease in or a reversal of the net rate of fluid transfer from the maternal to the fetal compartment, or the lymphatic system must effectively return the excess filtered fluid to the fetal vascular space [38].

In alloimmunized fetuses that received a first intrauterine transfusion, there is a significant relation between total blood volume per kilogram of body weight and hydrops; however, there is no relation with severity of anemia. Therefore in nonhydropic fetus with severe hemolytic anemia, total blood volume is maintained, and the decrease in red blood cell volume is compensated by an increase in plasma volume. In hydropic fetuses, however, total blood volume seems to be increased. This is in accordance with the hypothesis that congestive heart failure plays a role in the pathophysiology of hydrops in anemic fetuses [39].

Hydrops fetalis is uncommon in congenital nephrotic syndrome (CNS). The most common CNS is the Finnish-type (CNF), an autosomal recessively inherited disease characterized by intrauterine onset of massive proteinuria and a large placenta [40]. Studies have shown that hypoalbuminemia is not a likely cause of edema formation in most nephrotic patients. A major advance in our understanding of the pathophysiologic basis of edema formation in the nephrotic syndrome is the discovery that proteinuria can cause primary renal sodium retention through ENaC (epithelial sodium channel) activation [41].

Hydrops is also uncommon in infants with congenital analbuminemia, an autosomal recessive disorder characterized by very low, or absent, serum albumin with relatively asymptomatic or remarkably mild signs and symptoms at all ages. Although albumin normally contributes 80% to the colloid osmotic blood pressure, congenital analbuminemia is usually not associated with systemic edema. In the absence of serum albumin, the osmotic pressure gradient is maintained by the compensatory increase in the biosynthesis of non-albumin plasma proteins in liver, as well as by increased transcapillary fluid filtration and lymph drainage, and the reduced hydrostatic pressure gradient is achieved by lowered capillary blood pressure and increased interstitial hydrostatic pressures. The hydrostatic and oncotic pressure differences may affect placental function and/or integrity, and create a suboptimal *in utero* environment. The large edematous placentas and frequent SGA (small for gestational age) infants in the case series support this hypothesis [42-44].

Lymphatic vascular system

Lymphatic vascular system maintains fluid homeostasis by absorbing water and

macromolecules from the interstitium. Lymphatic capillary endothelial cells are connected by buttonlike junctions. Interstitial components penetrate lymphatic capillaries via openings among endothelial cells. Free overlapping endothelial cell edges anchored on each side by these junctions form "flap valves". These specialized structures prevent the return of lymph back to the interstitium through which fluid flows unidirectionally into the capillary lumen.

Malfunctioning of the lymphatic vasculature results in lymphedema formation and compromises immune function. Hereditary lymphedema is a rare genetic disorder, which can develop *in utero*, neonatally, or more frequently, years or decades after birth. One of the hereditary lymphedema syndromes is primary congenital pulmonary lymphangiectasis, which results from thoracic duct obstruction, and leads to hydrops by reducing venous return or cardiac tamponade [45]. Secondary congenital pulmonary lymphangiectasis is a consequence of thoracic masses or congenital heart defects or a component of one of the syndromes [46].

Generalized lymphangiectasis syndrome results from systemic lymphatic vessel ectasia and causes subcutaneous and visceral lymphedema with chylothorax. Hydrops results from gastrointestinal protein loss, chylothorax and diffuse lymphatic leak [47].

Nuchal translucency is a hypo-echoic region of subcutaneous fluid accumulation in the posterior neck at the level of the cervical spine between the skin and soft tissues found at 10-14 weeks gestation. This ultrasound finding is important because increased nuchal translucency measurements place the fetus at increased risk for chromosomal and structural abnormalities. The basis of nuchal edema is most likely multifactorial, a combination of delayed or disturbed lymphangiogenesis, cardiac and vascular abnormalities, and abnormal extracellular matrix components [48].

CD-31 is a platelet endothelial cell adhesion molecule-1 that is highly specific for lymphatic and blood endothelium. CD-34 is expressed by embryonic cells, including blood-vascular vessel endothelial cells. D2-40 (or Podoplanin) is a selective marker for lymphatic endothelium. D2-40 positive and CD-34 negative staining ecstatic vessels are lymphatic cells. SMA (smooth muscle actin) is highly positive in lymphangylodysplastic vessels, and scantly positive in lymphoid vessel ectasia [49]. An immunohistochemical study 18 aborted fetuses with increased nuchal translucency revealed that all cases were D2-40 positive, CD-31 positive, and CD-34 negative, suggesting the presence of nuchal lymph vessel ectasia; 2 cases were SMA staining positive and 6 cases were SMA negative, suggesting that 6 cases had nuchal cystic lymphangiectasia, whereas 12 had cystic hygromas [50]. Therefore, if there is a history of increased nuchal translucency and vascular ectasia in postmortem examination, immunohistochemical study should be performed using CD-31, CD-34, D2-40, and SMA.

Inherited metabolic disorders: much more common than previously thought

Inborn errors of metabolism (IEM), especially lysosomal storage disease (LSD), may cause NIHF. However, the precise incidence of NIHF is difficult to elucidate, because many cases are not detected prior to intrauterine fetal death and some cases may resolve spontaneously *in utero*. The incidence of LSD may be significantly higher in NIHF than the estimated 1% reported in previous studies. However, the higher incidence (e.g., 18%) could be due to an ascertainment bias, again due to referral to a specialized center for metabolic diseases. But, as also stated by some authors, the given low incidences, in contrast, could be the result of incomplete investigation of NIHF [51]. A mortality rate of 100% of IEM in association with a NIHF is assumed; however, transient NIHF with a good perinatal outcome has hardly been described [52].

Today, around 14 different LSD have been reported as being associated with NIHF and congenital ascites: mucopolysaccharidoses (mucopolysaccharidosis I [Hurler], mucopolysaccharidosis IVA [Morquio A], mucopolysaccharidosis VII [β-glucuronidase deficiency]), oligosaccharidoses (galactosialidosis, sialidosis, GM_1-gangliosidosis), sphingolipidoses (Gaucher type 2, Niemann-Pick A, Niemann-Pick C, lipogranulomatosis [Farber], Wolman), mucolipidoses (mucolipidosis II [I-cell disease], lysosomal transport defects (sialic acid storage disease) and multiple sulfatase deficiency. There are also non-lysosomal diseases causing hydrops fetalis: glycogenoses (glycogenosis type IV [Anderson disease]), fatty acid oxidation defects (long-chain hydroxyacyl CoA dehydrogenase deficiency), cholesterol biosynthesis defects (Smith-Lemli-Opitz syndrome, 3β-hydroxysterol-

Δ^{14}-reductase deficiency), congenital disorders of glycosylation (CDG Ix), others (citric acid cycle-defect, hereditary hemochromatosis) [53, 54].

The cause of the development of NIHF in storage diseases may involve the obstruction of venous blood return resulting from visceromegaly secondary to accumulation of storage material. Anemia may be a trigger, being caused by either hypersplenism or the reduction of erythropoietic stem cells caused by infiltrating storage cells. Other conditions that may trigger NIHF in storage diseases are myocardial damage, congestive heart failure, liver dysfunction, hypoalbuminemia, portal hypertension. There is no specific therapy in the antenatal period; *in utero* death usually occurs. It is important to make an accurate diagnosis and offer genetic counseling [54].

Inherited metabolic disorders must be always thought when investigating cases of recurrent NIHF in the same family or if a family history is positive for a IEM or NIHF.

Ultrasound can give a clue for the suspicion in the first trimester. Although not all LSD present with enlarged nuchal translucency, many IEM have been found to have this association. The fetal hydrops associated with inherited metabolic disorders is usually severe hydrops with massive ascites. Other features include facial dysmorphism, contracture deformities, irregularity of the epiphyses, coarse trabeculations of the long bones hepatosplenomegaly, and renal abnormalities [53].

In utero diagnosis of a IEM in the absence of an index case is difficult. 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. Routine screening for IEM especially LSD should be considered in cases of recurrent hydrops in the same family in populations with high consanguinity [53, 54]. However, to analyze all 14 lysosomal diseases that may be causative of NIHF, a great amount of amniotic cells is necessary, and all these analyses are time consuming and expensive. Therefore, a fast and cost-effective protocol was designed by analyzing 7 of the most frequent described lysosomal pathologies that may cause NIHF, with only 5 different determinations, which make the analysis of NIHF fast, cost-effective and without need of too much amniotic fluid. In the proposed protocol, the presence of glycosaminoglycans in the supernatant, and the enzymatic activities of β-glucuronidase, β-glucocerebrosidase, β-galactosidase and total hexosaminidase are analyzed. The combination of the study of glycosaminoglycans in the supernatant and the enzymatic analyses allows studying 7 of the 14 LSDs that may cause NIHF: mucopolysaccharidosis type I and VII, multiple sulphatase deficiency, Gaucher disease, GM1 gangliosidosis, galactosialidosis and mucolipidosis II/III [55].

It is very important to examine the placenta carefully in cases where hydrops or ascites are present at birth or detected by ultrasound, especially in the transient form. Even if a family does not agree to autopsy, placental examination may be done. In some instances, examination of the placenta of a grossly macerated fetus may be more informative than that of the fetus. Placental histology can serve as an early diagnostic clue for a number of storage diseases. The presence of highly vacuolated cells or cells demonstrating storage should be followed up with enzymatic testing in patients [53, 56-61].

Prognosis

All patients with fetal hydrops should be referred promptly to a tertiary care center for evaluation. Prognosis depends upon the etiology, the gestational age at onset, and whether pleural effusions are present. In general, the earlier hydrops occurs, the poorer the prognosis.

In particular, pleural effusions and polyhydramnios prior to 20 weeks of gestation are poor prognostic signs because of increased risks of pulmonary hypoplasia and preterm labor/premature rupture of membranes, respectively. On the other hand, absence of aneuploidy and absence of major structural abnormalities confer a better prognosis [62, 63].

Fetal echocardiography and detailed ultrasonograpy are indicated in all cases. Fetal treatment for NIHF depends on the etiology and gestational age: intrauterine transfusion for anemia; repeated centesis or shunt insertion for pleural effusion, ascites, or thoracic cystic lesions; maternal treatment with anti-arrhythmic drugs to treat fetal tachyarrythmia, laser surgery for severe and early twin-to-twin transfusion syndrome with hydrops [2].

Fetuses with NIHF should be delivered after prenatal consultations with appropriate specialists including geneticist, neonatologist, pediatric cardiologists, and pediatric surgeons. Antenatal consultation also allows for parental counseling and

adequate preparation of the resuscitation team. At delivery, there is an increased risk of birth trauma due to soft tissue dystocia, postpartum hemorrhage, and retained placenta. *In utero* aspiration of the pleural fluid or ascites prior to delivery may reduce the risk of dystocia and facilitate neonatal resuscitation. Cesarean birth should be reserved for routine obstetrical indications; however, the high frequency of nonreassuring fetal heart rate patterns and dystocia increases the likelihood of cesarean delivery. Postnatal therapy begins with resuscitation including thoracentesis and/or paracentesis to establish adequate lung expansion. Depending on the etiology of NIHF, specific interventions to support the neonate may be indicated at delivery. For example, a fetus with a large pulmonary lesion, mediastinal shift, and hydrops may benefit from *ex utero* intrapartum therapy (EXIT) performed at cesarean delivery. In EXIT, the fetus is partially delivered and intubated without clamping the umbilical cord [64].

After stabilization and transfer to NICU, the cause of NIHF is evaluated extensively [25]. A flow-chart as a guide to both prenatal and postnatal diagnosis of the causes of NIHF has been suggested [32].

NIHF indicates significant fetal compromise and is associated with an overall perinatal mortality rate of 50% to 98% and high rates of neonatal morbidity [65]. Despite advances in fetal diagnosis and therapy, the mortality rate has not changed very much over the past 15 years [3]. After the death of the fetus or newborn with NIHF, it is mandatory to continue the investigation. Clinical photography and fetal X-rays should be obtained to evaluate the malformations including skeletal dysplasia. Placental examination is indicated [66].

Fetal blood, tissues, DNA, amniotic fluid supernatant should be collected and stored (-70ºC). Skin biopsy for cell cultures is also indicated for future biochemical or molecular genetic assays. Autopsy should be recommended in all cases [67].

The risk of recurrent NIHF depends upon the underlying etiology; therefore, every effort should be made to determine the cause of hydrops. In idiopathic cases, the risk of recurrence appears to be small. Some of these early reports preceded the availability of tools for postmortem diagnosis of metabolic disorders [68-70].

Declaration of interest

The Author declares that there is no conflict of interest.

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