Congenital ascites in newborns

Zhubi, Genta

Master's thesis / Diplomski rad

2018

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:071122

Rights / Prava: In copyright / Zaštićeno autorskim pravom.

Download date / Datum preuzimanja: **2024-04-20**

Repository / Repozitorij:

Dr Med - University of Zagreb School of Medicine Digital Repository

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Genta Zhubi

Congenital Ascites in Newborns

GRADUATE THESIS

Zagreb, 2018

This graduate thesis was made at the University Hospital Center Zagreb - Department of Pediatrics mentored by Associate Professor Jurica Vuković, M.D., Ph.D. and was submitted for evaluation in 2017/2018.

ABBREVIATIONS

ACE:	Angiotensin converting enzyme inhibitors
ARPKD:	Autosomal recessive polycystic kidney disease
CHF:	Congestive heart failure
CMV:	Cytomegalovirus
HF:	Hydrops fetalis
IDA:	Iminodiacetic acid
IEM:	Inborn errors of metabolism
ISSD:	Infantile free sialic acid storage disease
LSD:	Lysosomal storage diseases
MCA-PSV:	Middle cerebral artery peak systolic velocity
MRI:	Magnetic resonance imaging
MPS:	Mucopolysaccharidosis
NICU:	Neonatal intensive care unit
NIHF:	Non-immune hydrops fetalis
NPA:	Neimann Pick A disease
NPC:	Neimann Pick C disease
PKHD:	Polycystic kidney and hepatic disease
SAAG:	Serum ascites albumin gradient
TORCH:	Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes

TABLE OF CONTENTS

Summary……

Sažetak……

Introduction……. 1

Case Reports…… 4

Discussion……11

Conclusion……17

Acknowledgements……...18

References…….19

Biography……. 21

SUMMARY

Title: Congenital Ascites in Newborns

Author: Genta Zhubi

Congenital ascites occurs when there is increased fluid build-up in the peritoneal cavity of the fetus. It can occur in the setting of non-immune hydrops fetalis (NIHF) or be isolated. HF develops when fluid accumulates in extra-vascular areas and cavities of the fetal body. Examples of HF include a pericardial effusion, pleural effusion, ascites, placental growth and uniform skin thickening or skin edema. Congenital ascites can be diagnosed prenatally by an ultrasound exam, through which we are also able to find the cause of some cases of ascites. Biochemical and cytological laboratory analysis have been used in addition to the ultrasound exam, as these methods are more successful in identifying etiologies of congenital ascites. In this review paper, I will discuss several cases of congenital ascites in newborns, which have different etiological origin. In the first case, a neonate presents with congenital chylous ascites and cholelithiasis due to maldevelopment of the lymphatic system. Next, a discussion of four cases will follow in which all neonates present with congenital ascites due to different lysosomal storage diseases. In the third case, a neonate presents with severe congenital ascites and is simultaneously diagnosed with autosomal recessive polycystic kidney disease (ARPKD). The final discussion will focus on a series of 100 cases of congenital ascites for which biochemical and cytological testing were performed to identify the causes of ascites.

Key words: congenital ascites, non-immune hydrops fetalis, lysosomal storage diseases

SAŽETAK

Naslov: Kongenitalni Ascites u Novorođenčadi

Autor: Genta Zhubi

Kongenitalni ascites se javlja kada se tekućina nagomilava u peritonealnoj šupljini fetusa. Može se javiti u okviru neimunskog fetalnog hidropsa (NIHF) ili može biti izoliran. Fetalni hidrops (FH) se javlja kada se tekućina nakuplja u ekstravaskularnom prostoru i u šupljinama fetalnog tijela. Primjeri fetalnog hidropsa su perikardijalni izljev, pleuralni izljev, ascites, prekomjerni porast placente i generalizirani edemi cijelog tijela. Kongenitalni ascites se može diagnosticirati prenatalno ultrazvučnim pregledom, i pomoću ultrazvuka u nekim slučajevima se može ustanoviti uzrok kongenitalnog ascitesa. Osim ultrazvuka, razne biokemijske i citološke laboratorijske analize korisne su u razlučivanju etiologije kongenitalnog ascitesa. U ovom preglednom članku razmotrit ću nekoliko slučaja kongenitalnog ascitesa sa različitom etiologijom u novorođenčadi. U prvom slučaju riječ je o novorođenčetu sa kongenitalnim hiloznim ascitesom i kolelitijazom zbog poremećaja u razvoju limfatičnog sistema. Sljedeća su četiri novorođenčeta sa kongenitalnom ascitesom čiji uzrok su bile lizosomske bolesti nakupljanja. Treći slučaj je novorođenče sa teškim kongenitalnim ascitesom koje je imalo autosomno recesivnu policističnu bolest bubrega. Na kraju analiziramo seriju od 100 objavljenih bolesnika sa kongenitalnim ascitesom koji su obrađeni temeljem biokemijske i citološke analize za otkrivanje uzroka ascitesa.

Ključne riječi: kongenitalni ascites, neimunskog fetalnog hidropsa, lizosomske bolesti nakupljanja

INTRODUCTION

Hydrops fetalis (HF) has been acknowledged throughout time as a condition with pre-natal and congenital presentations. It occurs when there is increased fluid build-up in extra-vascular areas and cavities of the fetal body. In the fetus, a pericardial effusion, pleural effusion, ascites, placental growth, uniform skin thickening of more than 5 mm or skin edema are distinguishing for HF (2,6,8). Two forms of hydrops fetalis are possible, the immunological and non-immunological forms. At the time when immunization of Rh negative mothers was inexistent, erythroblastosis caused by Rh alloimmunization was a source of an immunological form of hydrops fetalis. This was the most common kind of HF. Nowadays, causes of hydrops fetalis vary and since erythroblastosis is no longer common, the phrase non-immune hydrops fetalis (NIHF) is used when referring to this condition. Up to 90% of reported events of HF are due to NIHF (11).

HF normally includes fetal or congenital ascites as the main component of the clinical presentation (11). Ascites appears when there is excessive fluid present in the peritoneal cavity of the fetus (2, 5, 6, 8). As a cause of different congenital diseases, fetal ascites may also occur as a separate entity without any fluid gathering in other body cavities. However, the etiologies of primary congenital ascites are not well known. One likely, but quite rare explanation of congenital ascites is termed chylous ascites. Congenital lymphatic dysplasia or anomalous lymphatic drainage are two elements contributing to the cause of chylous ascites. (NOSE) More precisely it is due to faulty development of the fetal lymphatic system, such as intestinal lymphangiectasia and agenesis or hypoplasia of lymph nodes. This form of ascites is responsible for approximately 4% of cases of congenital ascites. Other etiologies of congenital ascites that should be considered include: congenital malformations, chromosomal aberrations, and

infectious diseases (5). Lysosomal storage diseases (LSD) are also included in the etiological spectrum of congenital ascites. LSD make up most of inborn errors of metabolism (IEM). Up to date, about 14 of such diseases are connected with NIHF and congenital ascites. It is speculated that HF and fluid build-up in the peritoneal space develop in patients with LSD due to a blockage of venous blood flow back to the heart. This hindrance may occur because of an enlargement of visceral organs which was initially caused by aggregation of storage substances. Ascites may also be provoked by anemia. The mechanism involved is either decreased erythropoiesis or hypersplenism, due to an increased number of storage cells. Additional events that may lead to ascites in LSD include congestive heart failure, hypoproteinemia, and liver impairment (10, 11).

This case review will investigate various cases of different anomalies or diseases diagnosed in newborns either congenitally or subsequently in the postnatal period, in which congenital ascites was a major component of the clinical picture. It will focus on the possibility of these diseases or conditions having etiological factors on congenital ascites.

In the first case, authors Siahanidou et al. describe a case of a newborn who presented with congenital chylous ascites and a ball-like formation in the gallbladder which later developed into gallstones (9). Next, discussion will follow on four cases of inborn errors of metabolism in which hydrops fetalis and specifically congenital ascites were seen in the clinical picture, presented by authors Whybra et al. (11). Another case report that will be discussed below is by authors Ling et al, in which a newborn with autosomal recessive polycystic kidney disease (ARPKD) presents with severe congenital ascites (7). Finally, diagnostic methods of congenital ascites will be described through a series of 100 cases presented by authors Dreux et al. Ascites can be diagnosed using an ultrasound exam. However, due to its many and different causes, authors Dreux et al,, looked into alternate ways to diagnose this condition. Their investigation

was focused on biochemical and cytological methods of examining the fetal ascites fluid and their efficacy in determining possible etiologies (5).

CASE REPORTS

Newborn with congenital chylous ascites and cholelithiasis

A woman on the 18th week of pregnancy had an ultrasound exam which identified isolated fetal ascites. The TORCH infections were excluded after amniotic fluid was analyzed. C-section was performed as per mother's wish. A male baby was delivered who weighed 3900 grams. He followed with normal feeding by mouth for several days postnatally. He was admitted on day 8 after birth, where he presented with a bloated abdomen and bilateral hydroceles. Lab work up for a complete blood count, electrolytes, total protein and albumin levels and kidney function showed normal results. Peritoneal ascites was established upon performing an ultrasound on the abdomen. About 250 ml of fluid in the peritoneum were identified along with a ball-like formation in the gallbladder. 20 ml of ascitic fluid were withdrawn by paracentesis and analyzed. White blood cell count showed a number of 3.8 x 10^9/L and triglycerides were found in the amount of 2.1 g/L. Cytological analysis, Gram staining and culture did not show any abnormal results. The newborn was diagnosed with chylous ascites. He began treatment with medium-chain triglycerides, given orally. Ascitic fluid decreased to about 60 ml after three weeks of therapy. After several sequential ultrasounds were performed, small gallstones were developing from the previous ball-like formation in the gallbladder. Therapy with ursodeoxycholic acid was initiated with a dosage of 20 mg/kg/day. Several imaging techniques were performed in an attempt to find the etiology of chylous ascites. An MRI of the abdomen and thorax showed no abnormal findings. Intestinal malrotation was excluded by an abdominal x-ray. No lymphatic pathology or abnormal tracer uptake of inguinal and iliac lymph nodes were found, based on lymphoscintigraphy. However, paraaortic lymph

nodes were unable to be viewed. The etiology of gallstones was investigated and lab analysis excluded several hemolytic diseases, sepsis and malabsorption of the intestine, as the cause. The results of liver biochemical analysis were within the normal range. At the time the article was written, the baby was at the age of 8 months. An ultrasound exam showed that he still contained about 50 ml of fluid in the peritoneal cavity. Additionally, three small gallstones were viewed of less than half of a centimeter in diameter, even though the baby continues the ursodeoxycholic medication. He had normal white and red blood cell counts (9).

Four cases of congenital ascites in the presence of lysosomal storage disease

A weight of 3250 g., length of 48 cm. and head circumference of 36 cm. were recorded for a male baby who was delivered on term. During the 24th week of pregnancy, the fetal ultrasound showed fetal hydrops along with ascites. Fetal blood samples were used to eliminate prenatal infections or immunological etiologies. Chromosomal karyotyping for a male was normal after amniocentesis. The baby was breathing normally after delivery. Slight hepatosplenomegaly, bilateral inguinal hernia, and a usual outside appearance were noted, without pleural effusion or ascites. The neonate had cholestasis and jaundice, including increased levels of direct bilirubin. A Hepato-IDA-scintigraphy revealed open biliary ducts outside of the liver. Foamy cells were present upon liver biopsy, which coincided with Niemann Pick disease. Enzymatic tests were performed to eliminate various LSDs such as, Neimann Pick disease (NPC), Gaucher disease and Wolman disease. Ursodeoxycholic acid was used as therapy for cholestasis, which later cleared on its own. Necrosis of the femoral head on both hips, almost normal neurological progress, and slight joint contractures were seen on the male

infant. Due to this a slowly developing kind of NPC was considered. At the age of 8, the child was given a trial therapy of substrate reduction of NPC, which resulted in the exclusion of diagnosis for this disease. Finally, a diagnosis of mucopolysacchardidosis (MPS) II was reached after the presence if corneal clouding, hip dysplasia, and deficiency of the β-glucuronidase enzyme (11).

In the second case, fetal hydrops and extensive hydrothorax were present in the 22nd week of pregnancy. After two weeks, the fluid was drained from the intrapleural place, under the assistance of ultrasound guided feto-amniotic shunting. The female baby was delivered by C-section with weight, height, and head circumference of 3560 g., 52 cm, and 35 cm., respectively. A day after, the neonate presented with bradycardia and acrocyanosis at the neonatology ward where she was admitted. A heart ultrasound and an ECG eliminated heart problems and infections were excluded. The patient's walk was unsteady with weakness of quadriceps femoris and signs of kyphoscoliosis, at the age of three. A diagnosis of MPS IVA was confirmed after decreased levels of N-acetyl-glucosamin-g-sulfat sulfatase were found (11).

In the third case, a child was born to parents of common ancestry. Spontaneous abortion occurred in two pregnancies of the mother, prior to this one. Intrauterine fetal hydrops was apparent. The baby was delivered by C-section, before term, on the 29th week of gestation. At birth he weighed 1550 g., had a length of 41 cm., and a head circumference of 27.5 cm. The patient was able to walk at the age of 1 year and 8 months, but slight mental retardation was present. Kyphoscoliosis was also seen around this time. After four years passed, the child was diagnosed with MPS IVA due to low levels of N-acetyl-glucosamin-6-sulfat sulfatase. This diagnosis was reached as the child was not showing any increase in length (remained below 3rd percentile) and skeletal anomalies were present (11).

In the fourth case, ascites was found on the 30th week of pregnancy. There were no fetal infections or immunological causes of ascites in this male fetus. Chromosomal karyotyping was normal as shown by amniocentesis. The baby was delivered on term on the 36th week of pregnancy. The small amount of ascites that was present at birth cleared within the first couple of weeks. Neonatal jaundice and a slight increase in enzyme levels of a cholestatic liver continued for eight weeks. A year after. a periodic check-up of the child revealed hepatosplenomegaly. There were high levels of the chitotriosidase enzyme, which led to a possibility of NPC. NPC was then confirmed due to the presence of storage cells from a bone marrow biopsy. Additionally, a Filipin staining was positive and mutations were present on the NPC1 gene, further explained the diagnosis (11).

Severe congenital ascites in the presence of autosomal recessive polycystic kidney disease

A newborn female born on the 36th week of pregnancy with a weight of 2,700 grams. She presented with slight, right spontaneous pneumothorax and was taken into the NICU. An ultrasound exam done around the 28th week of pregnancy showed an increased size of both kidneys and oligohydramnios. The baby was experiencing respiratory distress and the increased size of kidneys was noted upon palpation. The pneumothorax subsided after administration of oxygen. Polycystic kidney disease of the infantile type was diagnosed after both kidneys appeared larger than normal size and echogenic during an ultrasound exam. Both kidneys contained several cysts and calcifications appeared on parenchymal tissue. Doppler ultrasound of the heart showed pulmonary hypertension, regurgitation through the tricuspid valve with a gradient of 58 mmHg. This cleared on its own, a week after birth. The infant also presented with congenital hypothyroidism approximately 6 weeks after birth and was treated with

levothyroxine. On day five after birth, the newborn became hypertensive; the systolic blood pressure was 90 mmHg. Administration of hydralazine, captopril (ACE inhibitor) and propranolol (B-blocker) did not show complete success in lowering the blood pressure. Plasma renin activity was 4.66 ng/mL/hour and aldosterone levels were >120 ng/dL. These values coincided with normal levels of a premature infant. The amount of urine produced was 0.6-1.0 mL/kg/hour. Analysis of electrolyte levels showed hyponatremia with a sodium low of 123 mEq/L. Ascites was apparent 2 weeks after birth, with moderate expansion of the abdomen. Paracentesis followed, and the fluid that was collected appeared clear, in an amount of 250 mL. Albumin levels in the blood were 2.6 g/dL. Portal hypertension was determined by the serum-ascites albumin concentration gradient (SAAG) which was 1.9g/dL. This value determined portal hypertension. An ultrasound of the abdomen was done before paracentesis but it did not indicate portal hypertension or obstruction of hepatic veins. Three months after birth, twisted and enlarged bile ductules and an elevated number of bile ducts were seen upon liver biopsy. The diagnosis of congenital hepatic fibrosis corresponded to these findings. Genetic analysis was performed to check for mutations of the *PKHD1* gene, by taking the infant's peripheral blood. There was a deletion on the maternal allele and a missense mutation on the paternal allele of the *PKHD1* gene. The treatment plan for the baby included: propranolol in the amount of 3mg/kg/day, furosemide, spironolactone, amlodipine, and captopril. A percutaneous gastrostomy was performed and the tube was kept for 12 months until the baby was able to consume adequate amounts of food on her own. At the time when the article was written, the child is 6 years and 8 months old. At the present time, she had hypertension which was managed with ramipril and propranolol and stage IV chronic kidney disease. Additional medications and supplements that the child takes include: levothyroxine, growth hormone, sodium bicarbonate,

and supplements of vitamin D, α-D3, and calcium. Also, at this time, the girl's weight was 17.7 kg and she was 107 cm tall. These measurements both lied below the 5th percentile. At the age of 6 years and 7 months, the child experienced bleeding from the upper gastrointestinal tracts, casing her hemoglobin levels to fall to 4g/dL Hypertensive gastropathy and esophageal varices were found after performing gastroscopy. This followed with ligation treatment of the varices and there was no reappearance of ascites (7).

Retrospective study on 100 cases of congenital ascites

A cohort study was conducted on 100 pregnant women, in which the fetuses were identified with ascites. Ascites fluid was collected and they were sampled in the period between 2006-2010. The volume of amniotic fluid, presence of HF, and presence of related abnormalities were investigated by an ultrasound exam. Fetal chromosomal karyotyping was performed by amniocentesis. In this study, ascites was noted as a separate entity if no other malformations of the fetus existed. If HF was present, it was treated as a more serious form of ascites and not as an isolated condition. Lab exams were performed on three different samples: maternal blood, amniotic fluid, and ascites fluid. Maternal blood was checked for blood group, agglutinin, blood count, and TORCH infections (syphilis, toxoplasmosis, rubella, herpes simplex, cytomegalovirus, parvovirus B19, and toxoplasmosis. Using cytological testing, centrifugation of an ascites fluid sample was done, using cytopsin. Cell counting was done to check for the number of monocytes or macrophages, polymorphonuclear leukocytes, lymphocytes, and mesothelial cells. In addition, the amount of cytoplasmic vacuoles in lymphocytes was analyzed. These specific organelles were a sign of metabolic disease. Using biochemistry methods,

centrifugation was again performed on ascites fluid. The supernatant was collected and stored at a freezing temperature. Seven markers were to be identified using biochemistry investigations on the supernatant. These markers included: total protein, β_2 - microglobulin, total IgM, gamma-glutamyl transpeptidase, aspartate aminotransferase, aminopeptidase M, and total alkaline phosphatase and its three isoenzymes. During the time the study was done, 48 mothers aborted their pregnancy because of the presence of serious fetal abnormalities. Twelve mothers experienced a miscarriage. Forty mothers delivered a baby and those babies were investigated postnatally. In 31 of the fetuses there was a relation between ascites and HF. Possible etiologies of ascites were categorized in eleven groups. The most repetitive causes included obstruction of the urinary tract and urogenital malformations. When observing the outcomes of biochemical markers, it was found that total protein and digestive enzyme activities showed decreased levels in ascites arising from urinary problems. On the other hand, very high digestive enzyme activity levels were seen in ascites stemming from digestive abnormalities such as in peritonitis with perforation of the digestive tract. Ascites caused by CMV and parvovirus infections showed increased numbers in β_2 - microglobulin. High counts of lymphocytes were observed in chylous ascites and increased numbers of vacuoles were found in ascites caused by LSD such as sialidosis, Niemann–Pick disease type C, MPS VII, GM1 gangliosidosis, and galactosialidosis (5).

DISCUSSION

In the patient with chylous ascites, lymphoscintigraphy showed that faulty development of the lymphatic system was the cause of ascites in this case. Congenital chylous ascites is most often caused by such maldevelopment. The inability to visualize the paraortic lymph nodes in scintigraphy, was exhibitive of lymphatic dysplasia in that region. It can be presumed that this dysplasia causes a disturbance in the small lymphatic vessels which in turn influences the flow of lymph into the peritoneal space. Common causes of cholelithiasis in newborns such as: hemolytic disorders, congenital anomalies of the biliary tree, prematurity, infection were not present in this baby. As per authors' knowledge, there was no previous case of a newborn presenting with both chylous ascites and gallstones. A theory could be possible as to why the two conditions occurred simultaneously. The paraaortic lymph nodes are the last lymph nodes which drain lymph into the gallbladder. If a disruption is existent within them, it could lead to an interruption of normal lymphatic flow within the gallbladder and development of gallstones. Still, the possibility of these two conditions occurring only by chance should also be considered. In this patient both chylous ascites and gallstones were handled conservatively. Octreotide medication which is known to restrict secretion of lymph was not used in this patient because of the possibility of causing gallstones, which the patient already had. Ursodeoxycholic acid was not successful in the separation of gallstones. A possible reason could be that this medication is not effective on black pigment bilirubinate gallstones, which is the most common composition of gallstones in children, compared to cholesterol ones which are present in adults. At the time the article was written the patient remained asymptomatic but, in the future, he may need surgical treatment for chylous ascites or cholelithiasis or both (9).

Regarding the cases associated with LSD, a matter of doubt still exists of whether LSD are frequent in NIHF and congenital ascites. Metabolic diseases can be a cause of many unidentified cases of NIHF and congenital ascites. For some LSD, if HF exists, it means that the most serious form of the disease is present. Twelve types of LSD which are associated with NIHF include: MPS IVA, MPS VII, GM1-gangliosidosis, type 2 Gaucher disease, NPA, NPC, Farber disease, Wolman disease, Sialidosis, Infantile sialic and storage disease, type II Mucolipidosis, and Sialidosis Galactosialidosis (11). Congenital ascites is often included as part of the clinical picture of LSD. There are a lot of arguments in various studies about what stimulates the build-up of excessive fluid in the peritoneum in newborns with LSD. Factors that may lead to the presence of congenital ascites include anemia due to hypersplenism or decreased erythropoiesis. Additionally, liver abnormalities may lead to decreased protein production which in turn leads to ascites. Also, congestive heart failure and cirrhosis of the liver may cause ascites. Many times, a newborn presenting with ascites and who is later diagnosed with an LSD may have older siblings who are ill but were not diagnosed with the disease. LSD should always be investigated as a possible cause, if NIHF runs in families. An LSD is assumed if physical features such as facial dysmorphism, epiphyseal abnormalities, and coarse trabeculations of long bones exist together with congenital ascites (10). The prevalence of LSD in those babies affected with ascites was measured to be 1.4% in a broad cohort study (3). LSD was investigated in 28 fetuses in utero who were identified to have NIHF, and 5 newborns who had HF. Five patients among these were diagnosed with an LSD, which included I-cell disease, Niemann-Pick type A, galactosialidosis, sialidosis, and MPS IVA. Only MPS IVA was diagnosed after birth, while the others were diagnosed in utero (4). Patients affected with type 2 Gaucher disease in the presence of congenital ascites often have very low levels of the glucocerebrosidase enzyme.

The disease can also present with joint contractures. It is one of the most infrequent and serious of the LSD. Detailed investigation of the placenta is e key element when dealing with cases of ascites present in utero or postnatally. Histological analysis of the placenta plays a great role in providing evidence for early diagnosis of LSD. Upon histological testing, if cells that contain numerous vacuoles or storage cells are identified, this is a hint to proceed with enzymatic testing for LSD. Placental histological analysis has been able to detect GM1 gangliosidosis, MPS VII, ISSD, Gaucher disease, galactosialidosis, and Fabry disease (10).

The case of ARPKD is also linked with portal hypertension. When portal hypertension occurs in the liver, it is usually the first sign that ascites may follow. One of the required criteria for portal hypertension is a portal pressure of 12 mmHg or more. Those patients who become symptomatic due to portal hypertension with show a deterioration in vascular and biochemical functions. The patient in the case with ARPKD presented with slight pulmonary hypertension and tricuspid regurgitation which cleared at the end of the first postnatal week. Due to the ascitic fluid showing high SAAG levels, infections, intestinal obstruction, and chyle obstruction were excluded as causes of ascites. Ling et al. point out the likelihood of primary sodium retention as a cause of ascites. This is linked to hypertension which is a prevalent symptom in the first few years in patients with ARPKD. Such a setting is possible even though serum creatinine levels appear normal. Mutations in the recessive allele of the *PKHD1* gene are often seen in those affected with congestive heart failure (CHF). A syndrome of ciliopathies exists in which CHF as well as biliary, hepatic, and kidney abnormalities are involved. A transgenic *PKHD1* gene was synthesized from mice who just like humans showed abnormalities of the pancreas, liver, and kidney. This case is quite infrequent in the spectrum of etiologies of congenital ascites.

Nevertheless, if a newborn presents with ascites, CHF and ARPKD should be included in the differential diagnosis (7).

Based on the study 100 cases discussed by Dreux et al., it was determined that the general prognosis of congenital ascites was feeble due to fetal or neonatal death observed in 60% of these cases. It was shown in this study that laboratory analysis performed on the fetal ascitic fluid which was sampled in utero, succeeded in identifying 96% of causes of ascites that could not be identified by an ultrasound exam alone. Using biochemical tests, it was observed that quite low levels of protein existed in the ascites that stemmed from urinary or genitourinary malformations. Three quarters of the cases showed protein levels at less than 10 g/L. All ascitic cases which had a digestive cause displayed quite high levels of digestive enzyme activity. Ascitic fluid which had an infectious cause showed high β_2-microglobulin levels in all samples. Cell count investigations were utilized to determine the percentage of lymphocytes in the sample of ascitic fluid. Ascites of of chylous origin was assumed, if the amount of lymphocytes in a sample was 80% or more. Nevertheless, one cannot be based on this test to determine that lymphatic dysplasia is the cause of chylous ascites. Increased numbers of vacuoles in cells were seen in ten cases, which indicates that metabolic storage diseases could be the cause. Out of the ten cases, five different lysosomal storage diseases were found in five of the cases. These diagnoses were verified by performing different biochemical analysis on amniotic fluid (5).

In this study the presence of ascites was identified in all cases by an ultrasound exam. Furthermore, the ultrasound exam was successful in identifying ascites caused by cardiac abnormalities in 100% of the cases. In 92% of the cases it identified ascites caused by urinary and genitourinary abnormalities and ascites of digestive origin was caught in only 28% of the cases. HF was observed in 40% of the cases with lysosomal storage diseases. Moreover, a

relation with HF was seen in all of the etiologies of congenital ascites described in this study. Due to this, the presence of HF should indicate an extent of severity of ascites and not be linked with a certain cause of ascites. In 50% of the cases in this study, the ultrasound exam was unable to identify the etiology of ascites. In such an event, the ultrasound must be accompanied by a Doppler exam of the MCA-PSV and fetal anemia should be investigated. If there is serious fetal anemia present, in utero blood transfusion should be carried out. At this time percutaneous umbilical blood sampling (PUBS) can be done to perform cell counting. This sample can be analyzed for the present of stomatocytosis. Xerocytosis, a dehydrated form of stomatocytosis exists, which may cause HF. In most cases, fetal blood is not checked for this condition, which means that some etiologies of congenital ascites are undervalued. In this study infectious diseases as a cause of ascites were seen in 6% of the cases, demonstrating the importance of checking for TORCH infections (5). Fetal karyotyping is another key element when deducing the cause of ascites, as there have been cases of aneuploidy and congenital ascites seen in the same baby (1). Based on the results of this study, there is a plan that consists of two steps in controlling pregnancies. In the first step, there are three additional sub-steps. They include: performing an ultrasound exam which includes the Doppler and MCA-PSV, blood work of maternal blood, and fetal karyotyping. In the second step ascitic fluid is checked through biochemical and cytological testing. In 63% of the cases, the cause of ascites was identified by performing the procedures in the first step alone. When the procedures of the second step were added, the etiology of ascites was identified in 96% of the cases. There were four cases of ascites that were not identified by these methods and those were three cases of genetic syndromes and one case of pulmonary sequestration. One weakness of this study was the fact that it was retrospective. This way the medical personnel involved in the investigation chose

those cases of ascites that were most challenging to them and did not reveal all cases of NIHF (5).

CONCLUSION

Hydrops fetalis develops when there is increased fluid accumulation in extra-vascular areas and cavities of the fetal body. If noticed in utero, a pericardial effusion, pleural effusion, ascites, placental growth, uniform skin thickening of more than 5 mm or skin edema are distinguishing for HF. In this case review the focus was on the non-immunological form of HF. Congenital ascites is an important clinical sign of HF. Ascites appears when there is excessive fluid present in the peritoneal cavity of the fetus. The etiologies of congenital ascites are not always clear and acknowledged. The causes of congenital ascites as mentioned in the cases include maldevelopment of the lymphatic system causing chylous ascites, autosomal recessive polycystic kidney disease, and lysosomal storage diseases. Though ascites can be diagnosed prenatally by an ultrasound exam, biochemical and cytological investigations have shown to be more successful in the ability to diagnose more cases of congenital ascites than the ultrasound exam.

ACKNOWLEDGMENTS

I would like to show my gratitude to my mentor for this thesis paper, Associate Professor Jurica Vuković, M.D., Ph.D., at the Department of Pediatrics, University Hospital Center Zagreb. I am very thankful for his assistance and support, and his overall effort towards the success of this essay. In addition, I am truly grateful for the support and love with which my parents and brothers have provided me throughout my medical studies and the writing of this paper.

REFERENCES

1. Bellini, C., Hennekam, R., Fulcheri, E., Rutigliani, M., Morcaldi, G., Boccardo, F., & Bonioli, E. (2009). Etiology of nonimmune hydrops fetalis: A systematic review. *American Journal Of Medical Genetics Part A*, *149A*(5), 844-851. doi: 10.1002/ajmg.a.32655

2. Bellini C, Donarini G, Paladini D, Calevo MG, Bellini T, Ramenghi LA, Hennekam RC. (2015). Etiology of non-immune hydrops fetalis: An update. *Am J Med Genet A 167A*(5), 1082-8. doi: 10.1002/ajmg.a.36988

3. Bouvier R, Maire I. (1997). Diagnosis of lysosomal storage diseases with fetal presentation [in French]. *Ann Pathol 17*(4): 277–280.

4. Burin, M., Scholz, A., Gus, R., Sanseverino, M., Fritsh, A., & Magalhães, J. et al. (2004). Investigation of lysosomal storage diseases in nonimmune hydrops fetalis. *Prenatal Diagnosis*, *24*(8), 653-657. doi: 10.1002/pd.967

5. Dreux, S., Salomon, L. J., Rosenblatt, J., Favre, R., Houfflin-Debarge, V., Broussin, B., . . . Muller, F. (2014). Biochemical analysis of ascites fluid as an aid to etiological diagnosis: A series of 100 cases of nonimmune fetal ascites. *Prenatal Diagnosis,35*(3), 214-220. doi:10.1002/pd.4522

6. Favre, R., Dreux, S., Dommergues, M., Dumez, Y., Luton, D., & Oury, J. et al. (2004). Nonimmune fetal ascites: A series of 79 cases. *American Journal Of Obstetrics And Gynecology*, *190*(2), 407-412. doi: 10.1016/j.ajog.2003.09.016

7. Ling, G., Landau, D., Bergmann, C., Maor, E., & Yerushalmi, B. (2015). Neonatal ascites in autosomal recessive polycystic kidney disease (ARPKD). *Clinical Nephrology*, *83 (2015)*(05), 297-300. doi: 10.5414/cn108345

8. Nose, S., Usui, N., Soh, H., Kamiyama, M., Tani, G., Kanagawa, T., . . . Fukuzawa, M. (2011). The prognostic factors and the outcome of primary isolated fetal ascites. *Pediatric Surgery International,27*(8), 799-804. doi:10.1007/s00383-011-2855-y

9. Siahanidou, T., Mikou, C., Karra, P., Pappas, D., Zellos, A., & Mandyla, H. (2010). Cholelithiasis in a neonate with chylous ascites. *Journal of Perinatology, 30*(3), 227-230. doi:10.1038/jp.2009.128

10. Staretz-Chacham, O., Lang, T. C., LaMarca, M. E., Krasnewich, D., & Sidransky, E. (2009). Lysosomal Storage Disorders in the Newborn. *Pediatrics*, *123*(4), 1191–1207. http://doi.org/10.1542/peds.2008-0635

11. Whybra, C., Mengel, E., Russo, A., Bahlmann, F., Kampmann, C., Beck, M., . . . Mildenberger, E. (2012). 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 Journal of Rare Diseases, 7*(1), 86. doi:10.1186/1750-1172-7-86

BIOGRAPHY

Genta Zhubi was born in 1988 in Mitrovica, Kosovo. In 1999, her family immigrated to Detroit, Michigan. She studied at Wayne State University in Detroit, Michigan and graduated in 2011 with a Bachelor of Science in Biological Sciences. In 2012, she decided to move to Zagreb to pursue a medical degree at the University of Zagreb School of Medicine. After the sixth year of studies, Genta completed a two-month internship at the Department of Cardiac Surgery of American Hospital Kosova, in Prishtina, Kosovo. She is undecided about the field of medicine in which she would like to specialize, but her goal is to complete the USMLE exams and move back to the United States to pursue residency training.