What do we know about Mirror Syndrome? – a comprehensive review

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Abstract

Mirror syndrome is a rare disease associated with a high fetal mortality of up to 67.2%. It is thought to be underdiagnosed and is often mistaken for preeclampsia. Mirror syndrome is characterized by 'triple edema': generalized maternal, placental, and fetal edema. A comprehensive search of several databaseswas conducted. Mirror syndrome is associated with high fetal morbidity and mortality; it is an important differential diagnosis with pre-eclampsia and thought to be currently underdiagnosed. Minimal is known about its pathogenesis. Maternal symptoms usually regress with resolution of pregnancy and management is dependent on the cause of fetal hydrops.

Introduction

In 1892 John W. Ballantyne described the 'Ballantyne syndrome'[1]: the association of fetal, placental and maternal edema with Rhesus isoimmunization. Later, other manifestations such as progressive weight gain, elevated arterial pressure and albuminuria were incorporated into the definition. Over the years, different pathologies resulting in fetal hydrops were associated with this syndome[2], leading to the proposal of different nomenclatures, including maternal hydrops syndrome, triple edema, and preeclampsia-like disease. The current name, mirror syndrome, was introduced in 1956 by O'Driscoll[3].

Mirror syndrome is a rare which is likely underdiagnosed disorder with undetermined incidence. It is characterized as a dramatic complication of fetal hydrops and likely reversible in the mother when the underlying factors are controlled. Mirror syndrome has been associated with high rate (up to 67.2%) of fetal mortality[4]. The etiology and pathogenesis of this syndrome is yet to be completely elucidated, but some hypotheses are under investigation. The purpose of the present study is to perform a comprehensive review of the pathogenesis, diagnosis, management and future directions related to mirror syndrome.

Methods

A comprehensive search of several databases from each database's inception to May 7th, 2020, any language, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for mirror syndrome in pregnancy. The actual strategy listing all search terms used and how they are combined is available in the**Appendix** .

Etiology and pathogenesis

The exact etiology of Mirror syndrome remains unclear but it is thought to be secondary to fetal hydrops[5]. To broaden the analysis, we review fetal hydrops‘ mechanisms and causes. Then, taking into account Mirror syndrome‘s similarities with preeclampsia (PE), we compare the pathophysiology of both diseases to aid the comprehension of Mirror syndrome.

Fetal hydrops is defined as the accumulation of fluid in at least two of the four fetal cavities (pleura, pericardium, peritoneum or skin). It is a multifactorial condition and is the result of several physiological conditions of the fetus. The fetal weight is 90-95% water at 8-weeks and gradually decreases to 70% in a full-term. This greater water ratio is possible because the amino acid and bicarbonate concentrations in the fetal blood are higher than in the mother, therefore, drawing water from the maternal to the fetal circulation. The newly formed endothelium has a thin layer of glycocalyx, increasing its permeability. In addition, the fetal interstitial space is highly compliant, meaning that it doesn't alter much of its hydrostatic pressure when it absorbs water[6].It has been hypothesized that some aquaporins may play a role in the control of ion homeostasis, water balance and angiogenesis in the human placenta[7]. This might indicate that disturbed aquaporin functioning could also lead to hydrops formation. All these physiological factors make the fetus more prone to develop edema in some decompensations.

Since the prevention of Rhesus immunization started in 1970, the prevalence of immune fetal hydrops lowered to about 10%[8]. A systematic review of non-immune fetal hydrops showed the following primary causes: 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 (17.8%)[8]. These primary conditions can lead to increased central venous pressure, reduced lymph flow or low oncotic pressure and, due to the singular physiological characteristics previously discussed; the fetus can develop fetal hydrops. Sacrococcygeal teratoma is the most common congenital tumor (incidence of 1 in 35,000 births) and has been shown to cause fetal hydrops due to a high output failure, caused by anemia or tumor hemorrhage and/or an arteriovenous shunt in a low resistance, rapidly growing tumor[9]. The fluid dynamics between vascular and interstitial spaces is then altered by cardiac failure and the resulting imbalance of interstitial fluid production and lymphatic return eventually leads to fetal hydrops [10].

A comparison between cases of fetal hydrops associated with Mirror syndrome and cases of non- Mirror syndrome fetal hydrops suggested that 29% of fetal hydrops cases developed Mirror syndrome. Additionally, those associated with Mirror syndrome showed an earlier onset and significantly lower levels of serum hemoglobin and albumin[11]. Not much is known of why some cases of fetal hydrops evolve to Mirror syndrome and others do not. There have been no animal models that successfully reproduce the disease and its rare nature makes understanding the mechanism of the disease that much harder.

PE is characterized by abnormal placentation during the second trophoblastic invasion stage. Cytotrophoblasts fail to form an invasive endothelial subtype and remodel the spiral uterine arteries. This leads to narrow maternal vessels and relative placental ischemia. Histological evaluation of placentas with PE show decidual vasculopathy characterized by acute atherosclerotic lesions, loose edematous endothelium, medial hypertrophy, and perivascular lymphocytes[12]. In this scenario, there is an oxidative stress that leads to an overproduction of reactive oxygen species (ROS) and a consequent imbalance of oxidants and antioxidants. In response, there is the transcription of antiangiogenic factors, such as soluble FMS-like tyrosine kinase 1 (sFlT-1) and soluble endoglobin (sENG), thus, these factors' serum concentration is highly predictive of PE[13]. They bind to angiogenic factors, such as PlGF, VEGF and TGF-β1, that are necessary to maintain endothelial homeostasis, especially of fenestrated endothelium found in kidneys, liver and brain[12]. This leads to protein loss from these capillaries resulting in proteinuria and loss of oncotic blood pressure, with resultant interstitial edema and hemoconcentration.

Knockout models have been used to reproduce hypertension and proteinuria, hallmarks of PE and are used to explain the pathophysiology. However, none have been able to reproduce severe complications such as

HELLP syndrome (characterized by hemolysis, elevated liver enzymes and low platelet count) putting the full applicability of these models into question[12].A rodent model study by Moffett-King et al.[14] suggests that dysfunctional uterine natural killer lymphocytes (uNK) fail to remodel the spiral arterioli of the decidua and lead to a dysfunctional placenta and reproduce PE symptoms, therefore suggesting an immunological component to the disease. Obesity, hypertension, diabetes mellitus and renal disease are some of the risk factors, suggesting the role of systemic inflammation and previous vasculopathy in the placental ischemia[12]. Other rodent models show the role of heme oxygenase on of ROS clearance in the uterine microenvironment[15]. Therefore, the many explanations for the pathogenesis of PE suggest it is a multifactorial disease.

A case report by Hobson et al.[3] analyzed Mirror syndrome secondary to twin-to-twin transfusion syndrome (TTTS). Hematocrit and serial concentration of factors that are increased in PE[12] such as sFlT, endothelin I (ET-1), follistatin, von Willebrand Factor (vWF), activin A, vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1(ICAM) and hemoglobin were drawn. It was observed that inflammatory markers (sFlT, ET-1, ICAM-1 and vWF) were higher during the onset of symptoms and lowered after pregnancy resolution. In this study, PE was ruled out due postnatal placental histopathology. The high levels of these factors suggest a PE-like systemic pathogenesis. The case-control study conducted by Espinoza et al compared the blood levels of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), an antiangiogenic factor, in mirror syndrome patients (n=4) and in normal pregnancies (n=40). The levels of sVEGFR-1 were elevated in all cases. In this case, microscopic view revealed immature intermediate villi with edematous changes increased syncytial knots, increased intervillous fibrin, and multifocal villous calcifications[14].These findings are also seen in PE. Thus, Mirror syndrome and PE share a similar pathogenesis. A case report about Mirror syndrome secondary to Ebstein abnormality showed high levels of hCG[16]. Some hypothesize that placentomegaly results in an overproduction of hCG that leads to ischemia. Because of this, there is an overproduction of renin and activation of the renin-angiotensin-aldosterone system (RAAS) leading to hypertension. However, it cannot be concluded whether the rise in hCG is cause or consequence of Mirror syndrome.

Since placental increase in expression of placental growth factor (PlGF) and soluble Fms-like tyrosine kinase 1 (sFlt-1) are hypothesized to be involved in the development of Mirror syndrome, these have been studied as markers that may aid diagnosis. It has been proposed that noticeable increase in sFlt-1 levels[17, 18] and decrease in the sFlt-1: PlGF ratio[19] could point to a diagnosis of Mirror syndrome; still, further investigation on this matter is needed to allow for significant conclusions.

Diagnosis

It is commonly expected to simultaneously identify maternal and fetal findings to diagnose Mirror syndrome. However, described cases in the literature show that this is not always the case and fetal findings may predate maternal presentation and vice-versa. This pattern needs to be kept in mind to allow for diagnostic accuracy and inclusion of Mirror syndrome in differentials.

Maternal presentation in Mirror syndrome is significantly similar to that of PE; both include elevated arterial pressure, edema, weight gain and proteinuria, which makes differentiating between the two one of the biggest diagnostic challenges in patients with this symptomatology. The unique features of Mirror syndrome include younger gestational age at diagnosis (Mirror syndrome has an earlier onset with more than 50% of cases diagnosed between 26.5 and 27.5 weeks[4]) and maternal presence of hemodilution (decrease in hematocrit and hemoglobin).

Fetal presentation of hydrops fetalis is also a differentiating factor; it is characterized by excessive fluid accumulation within the fetal extravascular components and body cavities. It can have different etiologies and determining the exact cause is important for management of Mirror syndrome.

Clinical management and outcomes

The treatment of choice depends on the etiology of the fetal hydrops, resolution of the fetal edema will lead to maternal recovery and it has also been shown to improve fetal survival[4, 20]. If the fetus cannot be

treated, maternal conditions can be improved by terminating the pregnancy. Induction of labor has also been associated with survival benefit in the fetus since intrauterine fetal death represents almost 60% of deaths by Mirror syndrome.[4]

Many case reports suggest benefit from fetal therapy approaches administered to improve fetal hydrops. Surgical intervention in cases of sacrococcygeal teratoma, specifically minimally invasive therapy such as interstitial laser ablation and radiofrequency ablation has proven to improve fetal survival[10, 21]. A pleuroamniotic shut placement has also shown to improve fetal hydrops and maternal edema, allowing patients to prolong their pregnancies[11, 22]. The use of intrauterine fetal transfusion is another option, proven effective in cases of Mirror syndrome caused by alloimmunization[23].

Clinical Data

A systematic review by Allarakia et al.[4] included 113 patients with Mirror Syndrome diagnosed between 1956 and 2016. They found that gestational age at presentation varied between 16 to 39 weeks with a mean of 27 weeks. In 46.0% of cases maternal and fetal findings were diagnosed simultaneously, in 41.0% fetal findings preceded any maternal alterations and in the remaining 13.0% maternal findings were first to appear. Most common maternal manifestation was weight gain or edema, present in 84.0% of cases, followed by hypertension in 60.1% and anemia or low hematocrit in 51.3%. The majority of fetuses presented with hydrops fetalis (94.7%) or placental edema (62.8%). Associated conditions were deemed to not influence overall fetal mortality, they were: fetal anemia (16.8%), Rh-isoimmunization (16.8%), multiple gestation pregnancy (16.8%), twin-to-twin transfusion (13.2%), viral infections (15.9%) and one case of metabolic disorder. Data analysis showed that procedural interventions to correct fetal hydrops (maternal blood transfusion, intrauterine transfusion, amniocentesis, laser ablation therapy, peritoneal-amniotic shunt, thoracoamniotic shunt and aortic valve dilation) were significantly associated with fetal survival, regardless the etiology of the disease; the only other intervention to improve survival was induction of labor. The overall survival rate of fetuses was 32.7% and no maternal mortality was reported. Maternal symptoms were found to be resolved in a median of 5.5 days after delivery; in 8 cases there was complete reversal of maternal symptoms before delivery, following supportive treatment or blood transfusion.

Future directions

An updated review of described cases is necessary to add to the body of evidence and improve the quality of data. In addition, further studies on the pathophysiology and possible markers are needed to better understand this disease.

There is also need for better reporting of available data, described cases should be thorough and include exams, interventions and both fetal and maternal outcomes. We highly recommend that in the suspicion of mirror syndrome, attending physicians request PlGF and sFlt-1 exams to help validate these tools as a diagnostic aid since currently there isn't enough evidence to qualify these markers and the diagnosis of Mirror syndrome remains a challenge.

Conclusion

Mirror syndrome is associated with high fetal morbidity and mortality; it is an important differential diagnosis with pre-eclampsia and thought to be currently underdiagnosed. Maternal symptoms usually regress with resolution of pregnancy; management of fetal hydrops to prolong the pregnancy and induction of labor are options to increase fetal survival. The management of mirror syndrome depends on the cause of fetal hydrops.

Contribution to authorship:

Conception and design: ATAT, RMC, AE, ERI, KN, RR; Data collection: ATAT, RMC; Data analysis and interpretation: ATAT, RMC; Drafting the article: ATAT, RMC, RR; Critical revision of the article: ATAT, RMC, AE, ERI, KN, RR; Final approval of the version to be published; ATAT, RMC, AE, ERI, KN, RR.

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Appendix

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials March 2020, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 1, 2020, Embase 1974 to 2020 May 06, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06, 2020 Search Strategy:

#	**Searches**
1	((hydrops and placenta* and (maternal* or mother*) and (edema* or oedema*)) or "Ballantyne syndrome*" or "mirro
2	(exp animals/ or exp nonhuman/) not exp humans/
3	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian o
4	1 not (2 or 3)
5	limit 4 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or commen
6	4 not 5
7	remove duplicates from 6

Scopus

1 TITLE-ABS-KEY((hydrops and placenta* and (maternal* or mother*) and (edema* or oedema*)) OR "Ballantyne syndrome*" OR "mirror syndrome*" OR "triple edema*" OR "triple oedema*")

2 TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR

drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans or patient or patients))

3 1 and not 2

4 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

5 3 and not 4

6 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)

7 5 and not 6