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Hydrops Fetalis (An Analysis of 34 Autopsy Cases)

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= Abstract =We have collected 34 cases of hydrops fetalis from the autopsy file of Department of Pathology of Seoul National University Hospital. The examination period was 26 years from 1962 to 1987. Major associated conditions were analyzed and classified. Among 34 cases 24 were deadborns and the remaining 9 cases survived from a few minutes to 5 days. There were 11 males and 23 females.

Immune hemolytic anemia was seen in 4 cases, comprising of 2 cases of Rh erythroblastosis and 2 cases of ABO erythroblastosis. Among non-immune hemolytic anemia group, cystic lymphangioma and pulmonary hypoplasia were commonly associated both in liveborns and deadborns. There were 8 cases of cystic lymphangioma and 8 cases of pulmonary hypoplasia. Besides, congenital heart disease, vascular malformation, infection or chromosomal anomalies were associated. There were 2 cases that showed no specific pathological conditions.

Kew words: ***Hydrops Fetalis, Anasarca, Generalized edema, Cystic hygroma, Fetal death, Stillborn***

INTRODUCTION

Hydrops fetalis refers to an excessive accumulation of fluid by the fetus. Although it ranges from mild peripheral edema to massive anasarca, hydrops fetalis usually indicates fairly considerable generalized edema. Hydrops usually develops in utero, but an infant born without edema may develop it during the first few hours (Rudolph 1987).

The cause of hydrops is not fully elucidated. There were many clinical or pathologic conditions that are reported to be associated with hydrops. Three mechanisms have been suggested in the literature; (1) increased capillary permeability to fluid and proteins secondary to anemia and tissue hypoxia; (2) low colloid osmotic pressure from decreased synthesis of albumin; (3) hypervolemia and elevated capillary hydrostatic pressure from high-output congestive heart failure secondary to anemia (Davidson 1944; Rudolph 1987).

MATERIALS AND METHODS

For the definition of hydrops fetalis, we have set the following criteria. (1) Significant degree of generalized edema in deadborn fetuses. (2) Peripheral edema as well as ascites and hydrothorax in liveborns at the time of birth or within several hours after birth. (3) History of generalized edema or immediately after for the babies more than 1 day of age.

Using above criteria we collected 34 cases of hydrops fetalis from the autopsy file of Department of Pathology of Seoul National University Hospital (1962 to 1985) and Seoul National University Children's Hospital (1986-1987). Since the diagnosis of generalized edema can sometimes be omitted in the front sheet of autopsy protocol, we have reviewed all the lantern slides of deadborn autopsies and cases with pulmonary hypoplasia or cystic lymphangioma.

Gross and microscopic descriptions and lantern slides were reviewed. When needed, microscopic slides were reviewed to confirm the associated conditions. We were particularly concerned to find any systemic abnormalities associated with the hydrops in terms of vascular structure.

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Table 1. Conditions associated with hydrops fetalis

Immune hemolytic anemia		4
Rh erythroblastosis	(2)	
ABO erythroblastosis	(2)	
Lymphatic malformation		8
Cystic lymphangioma	(7)	
Cavernous lymphangioma	(1)**	
Respiratory system abnormalities		12(2)
Laryngeal atresia	(1)*	
Lung hypoplasia	(8)**	
Cystic adenomatoid malformation	(3)	
Congenital heart disease		5
Atrial septal defect	(1)	
Ventricular septal defect	(1)*	
Truncus arteriosus	(1)	
Left ventricle hypoplasia	(1)	
Univentricular heart	(1)	
Vascular malformation		1
Cerebral arteriovenous fistula	(1)	
Infections		1
Syphilis	(1)	
Chromosomal anomaly		1
Trisomy 21	(1)	
Others		2
Urethral obstruction	(1)	
Sepsis	(1)	
Idiopathic		2
Total		36(2)

※indicates associated anomalies

RESULTS

1. Relative frequency of hydrops fetalis

There were 34 cases that fit the criteria of hydrops fetalis. Eleven cases were males and 23 cases were female. The female male ratio was approximately 2:1.

Among 34 cases, 10 cases (29.4%) were liveborn. Twenty four deadborns ranged in gestational age from 21 weeks to 40 weeks. The gestational period belonged to the second trimester in 8 cases and the third trimester in 4 cases. There were no cases in the first trimester.

2. Conditions associated with hydrops fetalis (Table 1)

Major pathological conditions that were found in fetuses or infants with hydrops fetalis were classified and tabulated in Table 1. They were grouped arbitrarily into nine categories. Thirty two out of 34 cases of hydrops fetalis had only one major condition. There were two cases that had two major conditions together. In one case cavernous lymphangioma was associated with pulmonary hypoplasia, and the other case was combination of laryngeal atresia and ventricular septal defect.

(1) Immune hemolytic anemia

This was the group that anasarca was associated with any kind of immunological mechanism involved. There were 2 males and 2 females. Rh incompability was the cause in 2 cases and ABO incompatibility in 2 cases. One case (A80-2) of Rh erythroblastosis was also associated with kernicterus, and showed hypoproteinemia (4.1 gm/dl) and hypoalbuminemia (2.6 gm/dl). The protein content in ascites was 3.18 gm/dl. One case (A65-6) of ABO isoimmunization showed a marked edema that was the cause of dystocia. And the placenta was severely edematous weighing 1600 gm. Trophoblastic villi were also hydropic.

The edema seen in this immune hemolytic anemia group was generalized particularly involving subcutaneous tissue of face and trunk.

(2) Lymphatic malformation

Cystic lymphangioma was seen in 7 cases, accounting for 10 per cent of hydrops fetalis. Cystic lymphangioma was found in the neck in all cases, and consisted of 2 to 6 locules, with varying thickness of septum. They were bilateral in all cases and affected 2 males and 5 females. All of these were deadborns. The cystic content was serosanguineous in macerated fetuses probably because of exudation of blood pigment. The edema was excessive particularly in neck, face although trunk and extremities were also involved. Anasarcaa in deadborn was sometimes difficult to distinguish from advanced maceration. In this situation observation of joint areas was very helpful because this area was not involved in swelling in hydrops, while in advanced maceration, the swelling affected the joint area as well. Involved fetuses or newborns did not show associated lymphangiomatous change in abdominal or thoracic organs. The heart was not particularly enlarged and the anomalies of vascular system were not seen. Although degree of congestion could not be easily assessed in macerated fetuses no remarkable changes that could be interpreted as signs of congestive heart failure could be found.

The cystic cavities of lymphangioma were lined

by a single layer of attenuated endothelial cell resting upon edematous fibromuscular wall. Surrounding tissue was also edematous. The locules were separated by connective tissue and were not interconnected. The locules ranged in size from 2 to 7 cm in diameter. And the number ranged from 2 to 6. Lateral neck and posterior neck were the sites of involvement in all cases.

There was a case of cavernous lymphangioma that was associated with hydrops. This was a deadborn fetus terminated at 34 weeks of gestation. A large well defined cavernous lymphagnioma, measuring 10 cm in diameter, was seen in the left neck. This case was also associated with a severe lung hypoplasia.

(3) Respiratory system abnormalitis

As a group, respiratory system was the most commonly affected system associated with hydrops fetalis, accounting for 35%. Twelve cases of respiratory anomalies could be broken down into 8 cases of lung hypoplasia, 3 cases of cystic adenomatoid malformation and 1 case of laryngeal atresia. Pulmonary hypoplasia was seen in 8 cases, thus accounting for 23.5 per cent of the total cases. There were 3 males and 5 females. There were 7 deadborns and one liveborn.

The hypoplasia of the lung always involved both lungs, and varied in degree considerably. Grossly the hypoplasia was easily recognized by finding that the lower margin of the lung was above the level of the cardiac apex. In other words the hypoplastic lungs were obviously smaller than the heart in volume. Accordingly the thoracic cavities of the involved fetuses was filled with fluid instead of the lung parenchyme. Combined weight of the lungs ranged from 4.5 gm to 16.7 gm.

The involved lungs were small and doughy without evidence of aeration in both deadborns and liveborns. In average the degree of hypoplasia was more severe among deadborns. However, the trachea and main bronchi were not particularly smaller or hypoplastic. The lungs showed microscopically a poor development of respiratory structure. In general the development pattern of the lungs were at least 4 weeks less mature than that expected in the corresponding gestational weeks.

Congenital cystic adenomatoid malformation of the lung was encountered in 3 cases. Two of these rare anomalies were seen in deadborns and the remaining one case survived for 2 hours. All of the cases were female. One case (CHA87-81) was diagnosed in utero by ultrasonography at gestational age of 22 weeks, and the pregnancy was terminated. The lesion was involving the right lung and formed a large mass (6 × 5 × 3.5 cm), compressing the mediastinal structure contralaterally. The left lung was hypoplastic. This case showed massive edema of face and ascites. However, extremities were relatively mild in swelling. The second case (A82-70) of the adenomatoid malformation was a cotwin deadborn after 30 weeks of gestation. Maternal hydramnios was complicated. She weighed 2.1 kg and showed severe generalized edema. The mass was in the right lower lobe and measured 3.5 × 3.0 × 2.0 cm. This mass was compressing the heart and superior vena cava. The third case was a female who died 45 minutes after birth. The lesion involved the right lung and measured 8 × 7 × 5 cm. This case was also complicated by maternal hydramnios. No other anomalies were seen.

Laryngeal atresia was seen in one case. This case (A87-7) was a female liveborn who died of respiratory difficulty in two hours. The atresia was of infraglottic type. She showed massive facial edema and ascites. The lungs were also markedly edematous. The left persistent superior vena cava, ventricular septal defect and spina bifida were also noted at autopsy.

(4) Congenital heart disease

There were 5 cases of various congenital heart anomalies who presented with hydrops. They were 2 males and 3 females. One of these 5 cases was deadborn and the remainder was liveborns. One case (A81-18) with truncus arteriosus was associated with ventricular septal defect, ectopic kidney and bony anomalies. The edema was generalized and survived for 2 days. The second case (A81-17) was one of twins and was complicated by maternal hydramnios. This case had a large atrial septal defect of ostium II type. This deadborn case showed edema on face and massive ascites and relatively mild extremity edema. The third case (A85-10) had severe left ventricular hypoplasia, patent ductus arteriosus and mitral cleft. She had polysplenia syndrome. The fourth case (A83-119) had univentricular heart and was a female. The edema was generalized. One case of ventricular septal defect was associated with laryngeal atresia, and this case was already described in respiratory system anomaly.

(5) Vascular malformation

One case of arteriovenous aneurysm of the great vein of Galen was associated with generalized edema in a newborn baby. This baby was born after 38 weeks of gestation and showed a marked edema and cyanosis immediately after birth and died 3 hours later. The aneurysm was of 2.8 cm in diameter in the Galen vein and was fed by pericallosal branch of the anterior cerebral artery, central branches of the middle crebral artery, posterior cerebral artery and superior cerebellar artery. The brain showed hydrocephalus. The heart was enlarged, particularly the right atrium and ventricle. Both carotid arteries and veins were dilated. This baby showed findings of congestive heart failure, including hepatomegaly.

(6) Infection

A case of congenital syphilis presented as fetal hydrops. It was a male deadborn who had generalized edema and hepatosplenomegaly. Fetal liver and lung demonstrated spirochetal organisms. The edema was moderate in degree and generalized. There was no pleural effusion. Microscopical examination of the organs confirmed fibrosis and plasma cell infiltration in all organs.

(7) Chromosomal anomalies

A case of Down's syndrome was associated with generalized edema. This case (A82-107) was a female deadborn of Trisomy 21. She showed moderate facial and truncal edema. All external stigmata of Down syndrome were found. Internal examination showed ventricular septal defect of the heart. No other associated anomalies could be detected.

(8) Others

There was a case of neonatal sepsis and a case of urethral obstruction. The sepsis case (CHA87--97) showed edema soon after the birth and survived for 10 days. The other case (A72-26) showed urethral obstruction and severe hydronephrosis at autopsy as well as generalized edema. It was a deadborn at 35 weeks of gestation. The lungs were unremarkable in both cases.

(9) Idiopathic

There were two cases that we could find no significant pathological change at autopsy. One case (A86-59) was a deadborn at 30 weeks of gestation. She showed advanced maceration. She weighed only 900 gms indicating growth retardation. The lungs were also smaller than expected. The other case (A84-39) was also a deadborn female who weighed 1900 gm. Maternal hydramnios was complicated. She showed a short neck without webbing and club foot. No other internal anomalies were seen. The edema was moderate and generalized.

Table 2. Major associated conditions of hydrops fetalis in deadborns

Condition	Male	Female	Total
Immune hemolytic anemia	·	1	1
Congenital heart disease	1	·	1
Cystic hygroma	2	5	7
Lung hypoplasia	3*(1)	4	7
Adenomatoid malformation	·	2	2
Cavernous lymphangioma	1	·	1
Cerebral AVM	1	·	1
Trisomy 21	·	1	1
Syphilis	1	·	1
Urethral obstruction	·	1	1
Unknown	·	2	2
Total	9(1)	16	25(1)

3. Hydrops fetalis in deadborns (Table 2)

It was encountered in 24 cases. There were 8 males and 16 females. The major conditions associated with hydrops among deadborns were slightly different from those of liveborns in terms of proportion of the associated conditions. Cystic lymphangioma and pulmonary hypoplasia were particularly prevalent among the deadborn group. Cystic lymphangioma was occurring entirely in deadborns, and 7 out of 8 cases of lung hypoplasia were also deadborns. Accordingly these two conditions together accounted for 14 out of 24 cases of fetal hydrops died in utero. Immune hemolytic anemia was encountered in only one case.

When deadborns were grouped according to gestational weeks at the time of delivery, cystic lymphangioma was common among those of the second trimester, whereas among those of the third trimester, pulmonary hypoplasia was more common, suggesting that cystic lymphangioma could be the cause of early fetal death in utero.

4. Hydrops fetalis in liveborns (Table 3).

Ten cases of fetal hydrops were alive at birth. They survived 40 minutes to 10 days. The great majority of them died within 3 days of life. There were 3 males and 7 females.

Table 3. Major association conditions of hydrops fetalis in liveborns

Conditions	Male	Female	Total
ABO erythroblastosis	1	1	2
Rh erythroblastosis	1	·	1
Congenital heart disease	1	3*(1)	4(1)
Laryngeal atresia	·	1	1
Hypoplasia of lung	·	1	1
Cystic adenomatoid malformation	·	1	1
Sepsis	·	1	1
Total	3	8(1)	11(1)

The major associated conditions were immune hemolytic anemia and congenital heart disease. Two cases of ABO erythroblastosis and one case of Rh erythroblastosis were seen among liveborns. In other words 3 out of 4 cases of immune hemolytic anemia were alive. Cystic lymphangioma that was so common among deadborns was not encountered, and the lung hypoplasia was seen in only one case. One case of cystic adenomatoid malformation of the lung survived only 2 hours after birth.

Among liveborns immune hemolytic anemia and non-immune hydrops were equally divided.

DISCUSSION

It was the common practice that immune hemolytic anemia should be firstly considered when we enounter a case of hydrops fetalis. However, this study clearly showed that diverse pathological findings could be associated with hydrops. Obviously immune hemolytic anemia took minor proportion (11.7%) among the associated conditions. This was particularly true among deadborns that only one case out of 24 was associated with immune hemolytic anemia. Therefore one should keep in mind particularly in deadborns that non-immune hemolytic anemia group is much more commonly associated. However, one should also keep in mind that among liveborns immune hemolytic anemia is still accounting for 30% of hydrops fetalis.

Both lymphatic malformation and respiratory system abnormalities together took a major portion (39%) in hydrops fetalis in both deadborns and liveborns. These two system anomalies were particularly important in deadborns, as these together accounted for 68 percent of hydrops fetalis found in this group. Among these, pulmonary hypoplasia and cystic lymphangioma of neck were two major anomalies.

The associated conditions that were mentioned in this study do not necessarily mean the cause of the hydrops. However, since these lesions were found as the only significant finding in the autopsy of that particular case, one has to consider causal relationship between two. Exact mechanism of hydrops is uncertain. There are three mechanisms that have been suggested in the literature; (1) increased capillary permeability to fluid and proteins secondary to anemia and tissue hypoxia; (2) low colloid osmotic pressure from decreased synthesis of albumin; (3) hypervolemia and elevated capillary hydrostatic pressure from high-output congestive heart failure secondary to anemia (Davidsohn 1944; John and Duncan 1964).

Perhaps all of these mechanisms play major or minor role in each case of hydrops, since the associated lesions are fairly different in nature. Mechanism (1) should be the most important playing at least some role if not entirely for developing hydrops in all cases. Mechanism (2) appears to be important in case of immune hemolytic anemia. The incidence of hydrops fetalis is estimated generally as one out of 3000 births. In erythroblastosis, hydrops fetalis occurs in 6.9% and once occurs the mortality rate is 100%.

The lung hypoplasia seems to be a single most common major condition associated with hydrops fetalis according to this study. Whether the hypoplasia of the lung is directly related to hydrops is not certain. Pulmonary hypoplasia is often associated with diaphragmatic hernia in deadborns or newborns. However, they are not always hydropic. We have collected all deadborns who showed at

least moderate degree of pulmonary hypoplasia. Approximately 80 percent of the cases had some degree of generalized edema, indicating that they are causally related. Cystic adenomatoid malformation (CAM) of the lung is a rare anomaly. We had 5 cases CMA in our autopsy file. Three of them showed hydrops (Ahn *et al.* 1969). The remaining 2 cases were of diffuse type without forming a mass to compress the adjacent structure. One of these two cases of diffuse variety had striated muscle heteroplasia (Chi and Shong 1982) and showed no evidence of edema. It appears reasonable therefore that anasarca in cases of CAM is probably related to compression of vena cava by the cystic mass and also to increase of intrathoracic pressure. Chin and Tang (1949) also observed that there is increased number of anasarca in CAM.

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= 국문초록 =

태아부종 (34부검증례 분석)

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지제근

태아부종은 재태기간중 혹은 출생직후에 전신부종을 나타내는 태아 및 신생아 사망의 중요한 원인이다. 그럼에도 불구하고 이것이 발생하는 기본병변 내지 발생기전에 관하여는 불명한점이 있다.

본 논문에서 저자는 1962년부터 1987년의 26년의 기간동안 서울의대 병리학교실에서 시행한 신생아 및 사산아 부검에중 태아부종을 나타내었던 34증례를 선택하여 이를 형태학적으로 분석하였다.

그결과 다음과 같은 성적을 얻었다. 즉 34예중 24예가 사산아였고 10예가 신생아였으며 11예는 남아 그리고 23예는 여아였다. 수반된 병변별로 보면 면역성 용혈성 빈혈은 4예 (Rh 적이구증 2예, ABO적아구증 2예) 뿐이었고 나머지는 면역기전과 무관한 것이었다. 이중에는 특히 낭성 림프관종과 폐형성부전증이 수종을 이루어 각각 8예씩 있었다. 그외에 선천성 심기형, 맥관기형, 감염 및 염색체 이상 증후군이 있었다. 34예중 원인이 분명치 않는 예는 2예 뿐이었다.