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Hydrops fetalis: manifestation in lysosomal storage diseases including Farber disease

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Abstract The authors describe a case of disseminated lipogranulomatosis (Farber disease) presenting as non-immune hydrops fetalis. This is the tenth lysosomal storage disease which can show this clinical manifestation. The literature is reviewed for all hydrops cases associated with lysosomal storage diseases.

Conclusion Although rare, the lysosomal storage diseases collectively are significant causes of non-immune hydrops and appropriate investigations are required in all cases of unexplained hydrops fetalis.

Key words Lipogranulomatosis · Farber disease · Hydrops fetalis · Lysosomal storage diseases

Abbreviations *NIH* nonimmune hydrops fetalis

Introduction

Nonimmune hydrops fetalis (NIH) has many causes [19, 26] and it is interesting that inborn errors of metabolism, including lysosomal storage diseases, are present in 1%–2% of all NIH cases [19, 26, 44]. We here report on the first case of disseminated lipogranulomatosis (Farber disease) presenting with hydrops fetalis.

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Case report

The second pregnancy of non-consanguineous parents (who had experienced early abortion of undetermined origin in the first pregnancy) had an uneventful course until the 26 th gestational week. Ultrasonic examinations then showed hydrops fetalis with excessive hepatosplenomegaly. Chromosomal, haematological and virological studies in fetal umbilical cord blood gave negative results.

An extremely hydropic infant was delivered by Caesarian section with APGAR score 2/2/5, umbilical artery pH 7.15, and birth weight 1920 g. Primary intubation was necessary and pleural effusions were drained immediately. After endotracheal administration of surfactant, ventilation was uncomplicated. During the 2nd day renal failure, disseminated intravascular coagulation, intra-abdominal haemorrhage and cerebral convulsions developed. The latter proved resistant to therapy and intensive care treatment was reduced. The child died 3 days after birth.

Abnormal laboratory findings at birth were severe hypoproteinaemia, mild thrombocytopenia, extreme elevations of lactate dehydrogenase and aspartate aminotransferase activities. On autopsy the general organ immaturity corresponded to the indicated gestational age. Generalised cutaneous and soft tissue oedema were evident. The enlarged abdomen was filled with haemorrhagic ascites. Hepatosplenomegaly was present with the following organ weights: liver 116 g (mean nominal value 49 g), spleen 24 g (mean 4 g). Multiple, pinhead sized, white nodules on the peritoneal surface of liver, spleen and visceral pleura, hyperplasia of suprarenal glands, thyroid and parotid glands were found. Microscopically, micronodular conglomerates of storage macrophages were found in the reticulo-endothelial system compartments of interstitial spaces in liver, spleen, bone marrow, lymph nodes, thymus, thyroid gland, parotid gland (not pancreas) and adrenal medulla. The thesaurocytes showed a finely meshed, only slightly PAS-positive or scarcely stainable broad cytoplasm and vesicle-like, normal nuclei. The macroscopic granulomas described on liver, spleen and pleura surfaces microscopically contained polypous, pediculated, micronodular foci of concentrically arranged storage macrophages along with fibrosis. The liver structure was severely impaired by the hyperplastic reticulo-endothelial system, extramedullary haematopoesis and proliferation of portal duct epithelia. The brain showed oedema and progressive changes of the glial cells, but storage macrophages were both macroscopically and microscopically undetectable in brain and meninges.

Total lipid extract of splenic tissue was studied by thin-layer chromatography. A less polar lipid fraction was greatly increased and could be identified as ceramide ([24] FAR in the lipid data). The other lipids were essentially free of pathological changes.

Cultured fibroblasts were fed radioactive glucosylceramide and accumulated large amounts of radioactivity in the released ceramide . Corresponding to this result only little radioactivity was found in the other metabolites of ceramide ([24] Patient no 4 in the sphingolipid loading data). In addition, ceramidase activitiy was profoundly reduced (Table 1). This provided the biochemical confirmation of Farber disease.

Table 1 Acid ceramidase activity in cultured skin fibroblasts. (pmol lauroyl sphingosine* degraded /h/mg protein).

Present patient		
	1st determination	22
	2nd determination	27
Known Farber disease infant		
	1st determination	19
	2nd determination	35
Control cells (n = 18)		
	mean	481
	Standard deviation	250
	Range	190–950

*Lauroyl sphingosine (^{14}C labelled in the lauroyl moiety) was a gift from Dr. Y. Kishimoto (UCSD, La Jolla). 1 mmol was incubated for 60 min at pH 4.0 in the presence of Triton X-100 and ca. 80 μg fibroblast proteins. Released lauroic acid was determined radiochemically

Discussion

We describe the first case of dissiminated lipogranulomatosis (Farber disease) presenting as hydrops fetalis. The infant was extraordinary because of her severe, generalised oedema and extreme enlargement of liver and spleen. Similar findings were described in other cases of hydrops fetalis associated with a thesaurismosis. Table 2 shows nine lysosomal storage diseases in which the manifestation as fetal or neonatal hydrops - in some cases with familial occurrence - has been observed. One more case of mucopolysaccharidosis without a subtype diagnosis was described by Mahony et al. [28]. Hurler disease, as well as I-cell disease associated with NIH are cited by Norton [36] without the detailed referrence. Sometimes ascites with moderate oedema is the predominant clinical feature which can already be demonstrated in utero by ultrasonic examination. This manifestation of lysosomal storage diseases has been reviewed by Gillan et al. [12].

The mechanism of the development of hydrops in storage diseases may involve an obstruction of the venous blood stream due to visceromegaly [16]. Storage substances accumulate in many organs, particularly those of the reticuloendothelial system, and therefore, their mass may cause local circulatory problems. Hydrops fetalis may result from anaemia as a consequence of hypersplenism and reduction of erythropoetic bone marrow stem cells by the infiltration with storage cells [14]. Hypoproteinaemia as a result of liver dysfunction may be another cause of hydrops in these diseases [35].

Our hydropic infant had normal haemoglobin levels despite the accumulation of storage macrophages in the interstitial spaces of bone marrow. However, there was a severe hypoproteinaemia as an obvious result of liver dysfunction. Histopathologically, the liver had a severely impaired structure.

Farber disease (disseminated lipogranulomatosis), first described in 1952 [10], is a disorder of the sphingolipid metabolism resulting from a deficiency in lysosomal acid ceramidase with consecutive deposition of ceramide in tissues. Characteristic of this disease is the clustering of ceramide storing histiocytes and macrophages which form granulomas ubiquitously. These on their part may lead to progressive, painful arthropathy with subcutaneous juxta-articular nodules. Nodules are also encountered in mechanically strained cutaneous areas and in the larynx, where they induce progressive hoarseness. If the brain is involved, variable neurological disorders result. Clinically and phenotypically Moser [32] differentiated two groups and six types. Cases of group I with unfavourable prognosis, often show hepato- or, less frequently, splenomegaly in the neonatal period, and death usually occurs within the first 14

Table 2 Published cases of hydrops fetalis associated with lysosomal storage diseases

Disease	Biochemical defect	Hepato-and/or splenomegaly	Number of cases	References
Mucopolysaccharidosis IV Morquio A	galactose-6-sulphatase deficiency	++	1	[2]
Mucopolysaccharidosis VII Sly	β-glucuronidase deficiency	+	10	[6, 18, 21, 25, 33, 34, 40, 45, 46]
Sialidosis II (congenital form)	neuraminidase deficiency	++	10	[3, 4, 5, 12, 20, 22, 38, 43]
Galactosialidosis	cathepsin A,β-galactosidase and neuraminidase deficiency	+	10	[7, 23, 38]
Niemann-Pick disease type C	cellular trafficking of exogenous cholesterol	++	7	[27, 29, 30, 31, 37]
Gaucher disease type II	acid β-glucosidase deficiency	+	11	[8, 12, 13, 14, 17, 30, 39, 42]
GM1 gangliosidosis	β-galactosidase deficiency	++	4	[1, 12]
Mucopolysaccharidosis I Hurler	α-L-iduronidase deficiency	++		Cited by Norton [36]
Mucolipidosis II I-cell disease	phosphotransferase deficiency	++		Cited by Norton [36]
Disseminated lipogranulomatosis Farber	ceramidase deficiency	++	this observation	

months of life. Cases of group II with a less severe course of the disease show less visceral involvement and only slight affection of the brain. The diagnosis is made by demonstrating the ceramidase deficiency (Table 1) in vitro [9, 11] or by evidence of ceramide accumulation in different tissues and of impaired ceramide turnover within living cells in situ [24].

Although lysosomal storage conditions are rather rare causes of NIH they are collectively significant, and appropriate investigations are necessary in all cases of unexplained hydrops fetalis [15, 41]. In particular familial NIH is highly suspicious of lysosomal or other inborn errors of metabolism. Several manifestations in siblings and late diagnoses have been described [13, 17, 34]. The diagnosis can be established when cultured cells (skin fibroblasts, amniotic fluid cells or chorionic villus tissue) are assayed for the specific metabolic parameters. Amniotic fluid or urine can be tested for specific metabolites by electrophoresis and chromatography. A definite diagnosis is of great importance for genetic counselling as all diseases listed in Table 2 are autosomal recessively inherited. Prenatal diagnosis is feasible in all of them except in some families with Niemann-Pick type C.

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