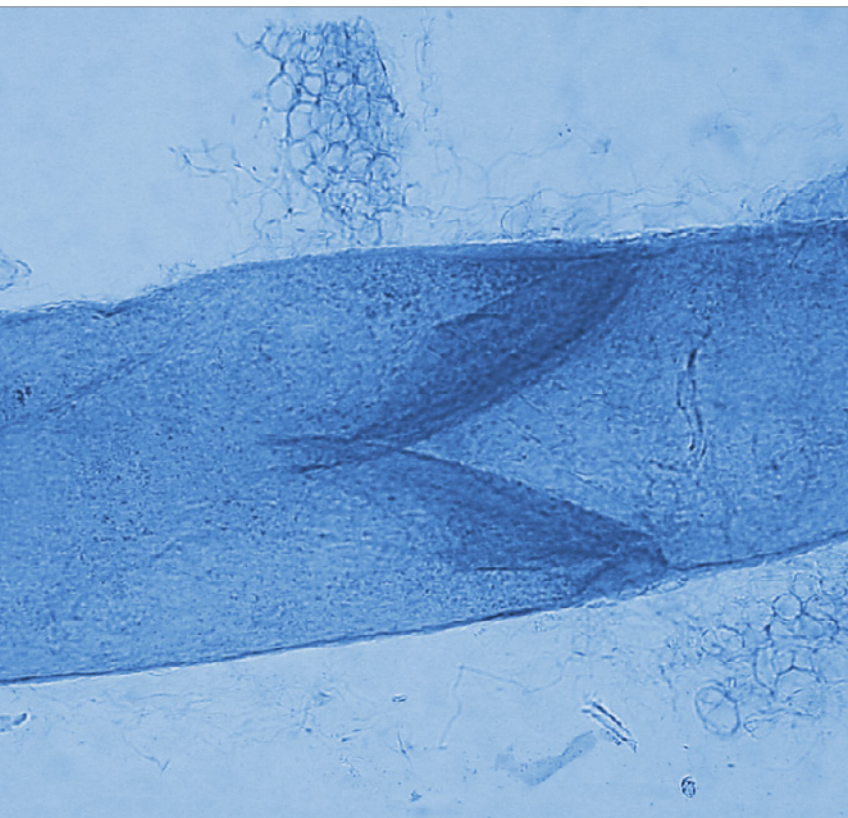


Non-immune hydrops
fetalis and congenital
hypothyroidism: coincidence
or causality?

October 2017



Hydrops fetalis describes excessive fluid collections within fetal extravascular compartments and serous cavities, characterized by skin edema, ascites, pleural and pericardial effusions. Non-immune hydrops fetalis (NIHF) refers to the subgroup of cases not caused by red cell alloimmunization and nowadays is responsible for more than 85% of all hydrops cases (1).

Many disease processes can cause dysregulation in fetal fluid homeostasis resulting in increased capillary permeability, increased central venous pressure, decreased oncotic pressure or reduced lymph flow, thus leading to NIHF (2). Apart from placental and maternal causes, the most frequent fetal pathologies leading to NIHF are cardiovascular disorders, twin-to-twin transfusion syndrome, congenital anomalies, lymphatic dysplasia, hematologic disorders and infections. In about 15% of cases, no etiology can be established (1, 3, 4). Mortality varies depending on the underlying pathology, gestational age at onset and gestational age at delivery; it is highest (> 50%) among neonates with congenital anomalies (3).

We report the case of a newborn baby with congenital hypothyroidism and NIHF, which resolved rapidly after starting a thyroid hormone replacement therapy. To the best of our knowledge, only one similar case has been described in the literature so far (5).

CASE REPORT

This 3770 g female infant was born after 38 weeks of gestation to a healthy 39-year-old G3/P2 mother. Pregnancy had been uneventful and prenatal ultrasound examinations unremarkable. Twenty-four hours before delivery, the mother noticed decreased fetal movements. Fetal heart rate monitoring showed reduced variability and the baby was delivered by Caesarean section.

At birth, the infant presented with massive generalized edema, a distended abdomen and severe respiratory failure, necessitating cardiopulmonary resuscitation, catecholamine support and mechanical ventilation. Apgar scores were 1, 1 and 1 at 1, 5 and 10 minutes, respectively; the venous umbilical cord pH value was 7.24. Following resuscitation, venous blood gas analysis at 30 minutes of life confirmed severe perinatal asphyxia with a pH of 6.86 and a base excess of -10 mmol/l. Neurological examination was consistent with severe hypoxic-ischemic encephalopathy (HIE). The infant was transferred to our NICU and therapeutic hypothermia was started per national guidelines.

Physical examination on admission revealed generalized edema, decreased breath and heart sounds and grotesque abdominal distension. In addition, some dysmorphic features (hypertelorism, long philtrum, single palmar creases) raised suspicion of an underlying syndrome. Additionally, a singular umbilical artery was observed.

A chest X-ray showed bilateral pleural effusions (Fig. 1) and chest drains were inserted: more than 100 ml of xanthochrome fluid was drained from both pleural cavities and identified as chylous with a high quantity of lymphocytes and chylomicrons. No bacteria or virus could be isolated. Ultrasonography confirmed the diagnosis of a hydrops fetalis with bilateral pleural effusions, ascites, subcutaneous edema and a small pericardial effusion (Fig. 2–4).

To find a possible cause for the hydrops fetalis additional laboratory tests and diagnostic procedures were performed:

- 1) Immune hydrops fetalis was unlikely because of the blood group constellation (mother: 0 positive, infant: 0 negative) and a negative indirect Coombs test; also, there was no evidence of hemolysis or hyperbilirubinemia.
- 2) Chromosomal analysis showed a normal karyotype, a chromosomal microarray identified no abnormalities and additional genetic analyses could not link the mild dysmorphic features to a distinct syndrome causing NIHF such as Noonan-Syndrome, Costello-Syndrome or velo-cardio-facial syndromes.
- 3) Echocardiography showed a small pericardial effusion, a small muscular ventricular septal defect and a persistent foramen ovale but no major malformations. Arrhythmias were never documented. The initially reduced cardiac contractility was interpreted within the context of cardiopulmonary resus-

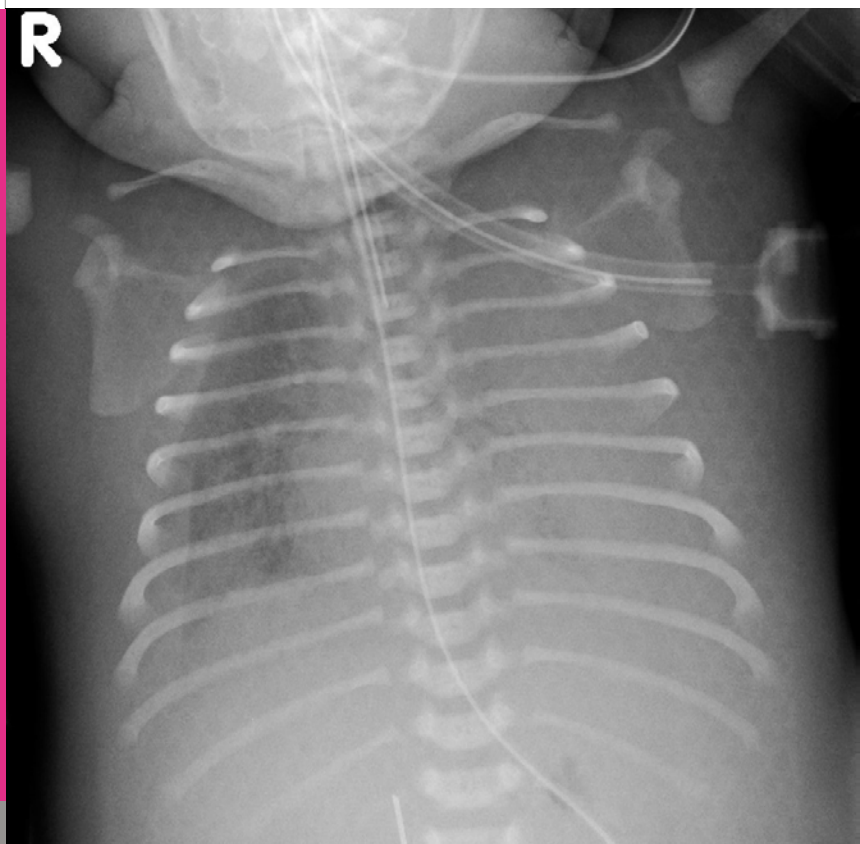
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Fig. 1

Chest X-ray after admission to the NICU: bilateral pleural effusions.

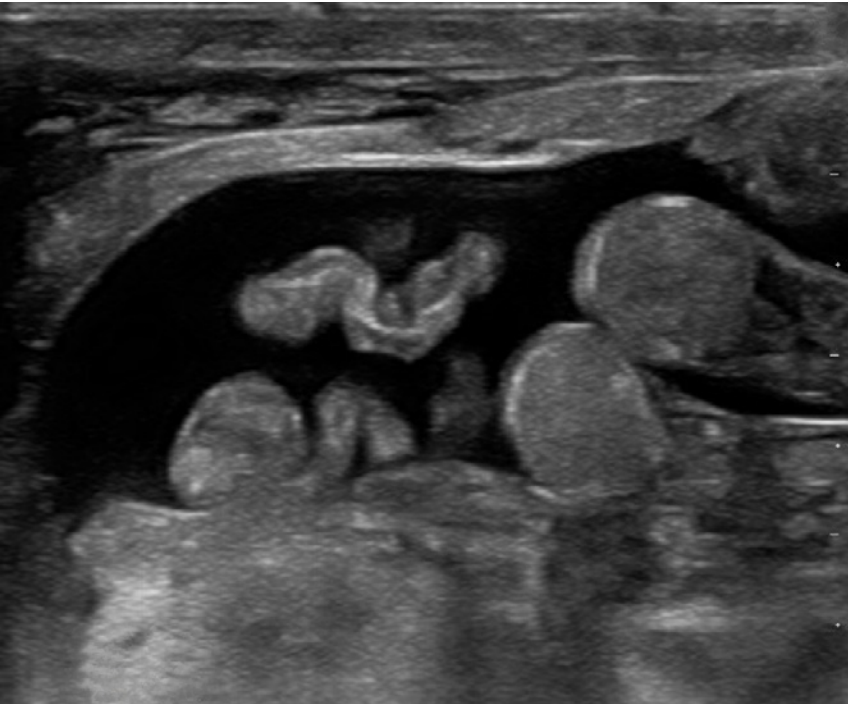


Fig. 2

Ultrasound examination of the abdomen showing ascites.

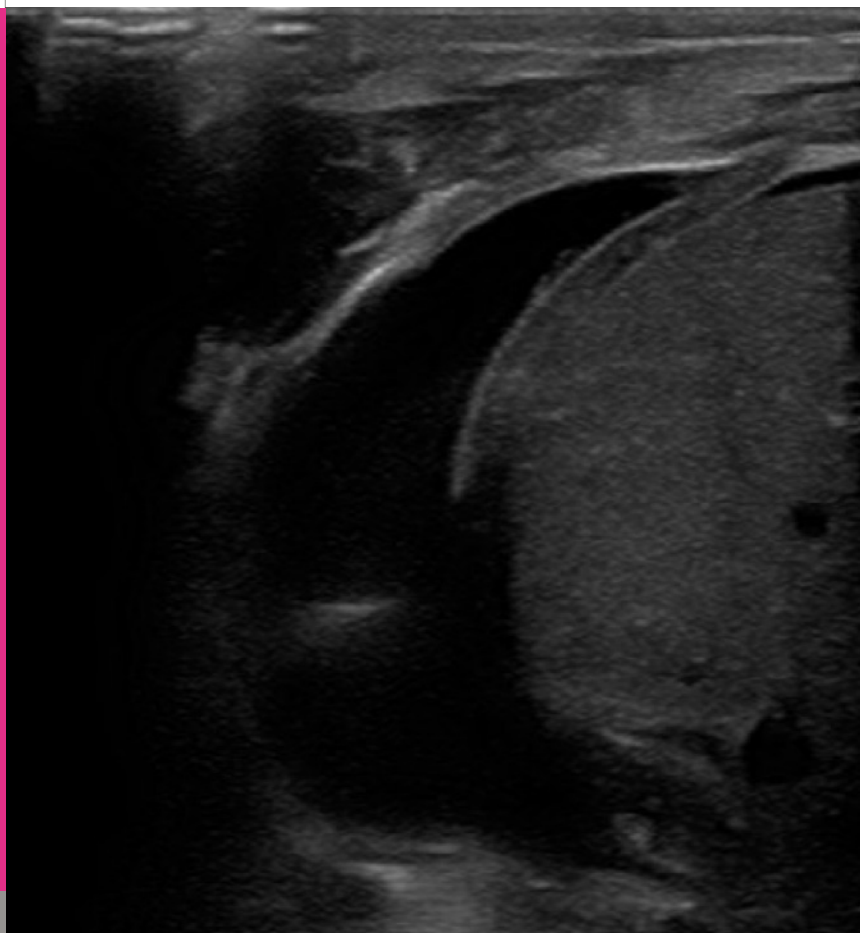


Fig. 3

Ultrasound of the chest showing pleural effusions.

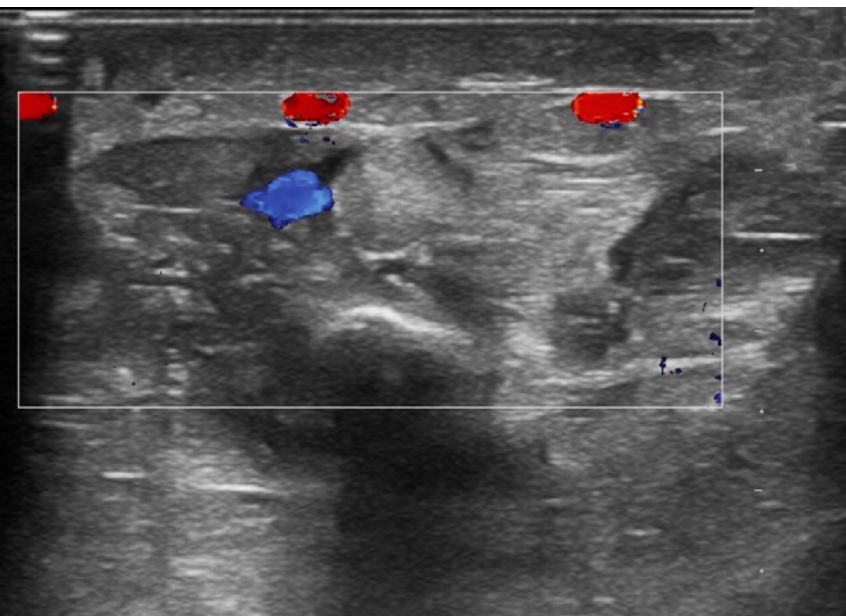


Fig. 4

Ultrasound of the right leg documenting distinct subcutaneous edema.



Fig. 5

X-ray of left knee joint: delayed bone age corresponding to a gestational age of 30 weeks (according to Pyle and Hoerr).

citation, perinatal asphyxia and therapeutic hypothermia.

- 4) There was no evidence for an infection at the time of birth, nor signs of infection during pregnancy (TORCH). Histopathologic examination of the placenta did not show signs of chorioamnionitis.
- 5) Newborn screening for metabolic diseases was normal and laboratory investigations revealed no evidence of an inborn error of metabolism.

Measurements of thyroid hormone concentrations on day of life two (DOL 2), triggered by an educated guess, showed a strongly elevated TSH with 584 mIU/l and a reduced fT4 with 4.2 pmol/l. When these values were again abnormal on a second blood sample obtained within 12 hours and an X-ray of the left knee showed a delayed bone age (Fig. 5), the diagnosis of severe congenital hypothyroidism was established. Thyroid hormone supplementation was initiated intravenously and serum thyroxin level normalized by DOL 7 (25.4 pmol/l). No thyroid autoantibodies were detected in the mother and on ultrasound a small orthotopic thyroid gland with normal morphology was identified in the infant.

After ending therapeutic hypothermia on DOL 4, the patient's condition improved steadily with ongoing mechanical ventilation, continuous pleural drainage, parenteral nutrition, repetitive albumin replacement and thyroid hormone supplementation. When a trial

of feeding with breast milk led to increased pleural drainage, formula feeding with added medium chain triglycerides (MTC) was introduced. On DOL 8, mechanical ventilation could be discontinued. Ultrasound examinations documented steady decreases of ascites and pleural effusions and complete resolution of pericardial effusion. On DOL 13 and 17, respectively, the chest tubes could be removed. MCT enriched formula was switched gradually to breast milk without reaccumulation of pleural effusions and our patient was discharged home fully breastfed on DOL 30.

Ultrasound examination of the brain on the first day of life had shown cerebral edema, and, on DOL 7, an MRI showed persistent cerebral edema with multiple subcortical ischemic lesions consistent with HIE secondary to severe perinatal asphyxia. At the age of 14 months, global developmental delay, most pronounced in the motor domain, was documented. Thyroid hormone supplementation is ongoing at a standard dose for permanent congenital hypothyroidism with regular endocrinological follow-up.

Our report describes a severe case of NIHF with pleural effusions, ascites, pericardial effusion and subcutaneous edema. Because the last antenatal ultrasound at 20 weeks of gestation had been inconspicuous and our infant did not show signs of pulmonary hypoplasia, which might develop in longer standing pleural effusions (6), the fetal hydrops most likely developed during the second half of pregnancy.

We performed comprehensive investigations to identify the etiology of the hydrops fetalis in our patient but could not detect any of the common causes. We did not find any structural abnormalities or malformations. Neither did we find evidence for infectious diseases or hemolytic anemia. Noonan syndrome or Costello syndrome, which can present with NIHF (1), were excluded. Finally, metabolic investigations did not reveal any inborn error of metabolism.

Hypothyroidism may cause pleural effusion, ascites, pericardial effusion and subcutaneous edema if left untreated (7–9). We therefore considered the possibility that congenital hypothyroidism could be the cause of NIHF in our patient. However, NIHF has been described in only one case of congenital hypothyroidism, and most infants with congenital hypothyroidism are completely asymptomatic at birth (5, 10, 11). Nevertheless, in their case report, Kessel and colleagues hypothesized that thyroid hormone deficiency can

reduce the adrenergic stimulation of the lymphatic system and thereby decreases lymphatic flow rate and lung liquid clearance leading to an increased intraluminal lymph volume and leakage of lymph into the pleural spaces (5).

Another possible mechanism that would link hypothyroidism to NIHF could be low-output cardiac failure. Cardiovascular signs of hypothyroidism include bradycardia, decreased cardiac contractility and arrhythmia (through prolongation of the QT interval), all of which can impair cardiac output (8). In adults, it is known that high venous pressure caused by low cardiac output increases capillary filtration and consequentially abdominal lymph production. Lymph flow in the thoracic duct can increase up to 12-fold above the normal rate, but the stiffness of the veno-lymphatic junction in the neck limits lymphatic flow causing engorgement of lymph vessels (12). At the same time, high pressure in the left subclavian vein reduces lymphatic drainage and causes fluid leakage into pleural and peritoneal cavities (13, 14). One case of severe congestive heart failure in the context of panhypopituitarism with resolution after treatment of central hypothyroidism and hypocortisolism has been published (15). Admittedly, congestive heart failure is not a usual presenting sign of congenital hypothyroidism in the absence of congenital heart defects. In our case, we attributed heart failure to perinatal asphyxia and therapeutic hypothermia,

and felt that an association with congenital hypothyroidism was unlikely.

In conclusion, we describe the second case of NIHF associated with congenital hypothyroidism. If the etiology of NIHF is unknown, it appears justified to rule out hypothyroidism as early as possible.

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