

### Clinical history

26 years G3P2 woman, blood group type O negative but with blood group negative antibody screen and negative TORCH screen had a 17 weeks USG showing 49 mm septated nuchal cystic hygroma of neck, generalized hydrops and anhydramnios; followed by amniocentesis (karyotype 46,XY) and termination of pregnancy at 18 weeks.

### Autopsy findings

Nonmacerated hydropic male foetus, 75gm/17cm, weights and measurements consistent with gestational age of 18 weeks. 75% of the integument showed fluid-filled blisters (asymmetrical hydrops). Features of oligohydramnios sequence were present (Potter's face, micrognathia, bell-shape chest, clubbed feet, and pulmonary hypoplasia).

Microscopically, the lungs and skin, but not gastrointestinal tract, showed extensive lymphangiectasia. Both kidneys were small for gestational age and microscopically showed absence of proximal tubules (H&E, CD10, EMA, dPAS) and focal intratubular calcifications. The liver showed confluent necrosis, haemorrhage, intracanalicular cholestasis, calcifications and minimal hemosiderosis. Meconium in the intestinal lumen was also focally calcified. The placenta was hydropic, with convoluted outlines of chorionic villi and intravillous trophoblastic pseudo-inclusions, extensive mineralisation of basement membranes of chorionic villi (positive for iron and phosphates), and amnion nodosum. Immunohistochemistry for parvovirus B19 was negative.

Differential diagnosis: Immune hydrops, nonimmune hydrops, generalized lymphangiectasia, Hennekam syndrome, hereditary and acquired renal tubular dysgenesis (RTD)

### Discussion

As there were no cardiovascular malformations, the TORCH screen, serology and immunohistochemistry for parvovirus were negative, by exclusion, the generalized lymphangiectasia (1) was regarded responsible for hydropic look of the fetus. Asymmetric nonimmune hydrops fetalis, facial dysmorphic features, congenital hydrothorax, intestinal lymphangiectasia, and congenital pulmonary lymphangiectasia are the features of the Hennekam syndrome (2), however, in this case abnormal facial features were rather of the Potter's face than the Hennekam dysmorphism and there was no intestinal lymphangiectasia or polyhydramnios. The interesting finding was absence/paucity of proximal renal tubules, associated with increased renin expression by immunohistochemistry. RTD associated with hydrops and trisomy 21 has been reported in two cases [3,4], but this foetus had normal male karyotype. In 3 of 17 cases (17.6%) of foetal hydrops a marked decrease of proximal tubules was reported [5]. Usually, however, RTD is associated with severe oligohydramnios (as in this case), postnatal anuria, hypotension and respiratory insufficiency leading to early neonatal demise [6,7], but not foetal hydrops. Only exceptionally patients with RTD survive the neonatal period [8]. Hypoxia (indomethacin, donor twin in twin transfusion syndrome), foetal heart failure in foetal hydrops [8], accumulation of renin (hypoperfusion, ACE inhibitors) with vasoconstriction may lead to secondary damage to proximal tubules. A familial association between renal tubular dysgenesis and congenital neonatal iron storage disease

suggest either a genetic link, or a common in utero insult, or renal hypoperfusion due to hepatic necrosis [10]. Since proximal tubules are responsible for renal water resorption, excessive fluid retention in their absence suggests that the occurrence of foetal hydrops and renal tubular dysgenesis in one individual is coincidental [4], but RTD may aggravate the postnatal outcome. Mineralization of basement membranes of chorionic villi is associated with foetal chromosomal abnormalities and foetal hydrops and may be associated with abnormal placental iron storage and transport or defects in foetal excretion not only of iron, but also of calcium [4]. In this case some abnormality of storage and transport of iron and calcium was present (mineralisation of basement membranes of chorionic villi, calcifications of kidneys, liver and meconium). Skull ossification defects (hypocalvaria), or thickened arcuate or afferent arteries which were observed by others in renal tubular dysgenesis [11,12], were not observed, perhaps because of the early gestational age in our patient. In summary, this is a case of lymphangiectasia and cystic hygroma-associated foetal hydrops of unknown aetiology, with RTD most probably secondary to foetal hydrops. Foetal heart failure may be responsible for RTD in foetal hydrops [2]. However, since the mother was not treated in pregnancy with angiotensin converting enzyme (ACE) inhibitors or indomethacin, the inherited RTD is also a possibility as increased renin expression in mesangium, juxtaglomerular apparatus and arterioles away from glomeruli was found by immunohistochemistry [13], also in this case. However, we were unable to prove or disprove this possibility by genetic analysis and molecular biology studies because of poor mother's compliance (imprisoned, unsure about paternity).

Diagnosis: Lymphangiectasia-associated foetal hydrops with renal tubular dysgenesis and disturbed mineral homeostasis

#### References

1. Machin GA. Hydrops, cystic hygroma, hydrothorax, pericardial effusions, and fetal ascites. In Potter's Pathology of the fetus, infant and Child. Gilbert-Barness E (ed). St. Louis: Mosby, 2007: 333-354
2. Bellini C, Mazzella M, Arioni C et al. Hennekam syndrome presenting as nonimmune hydrops fetalis, congenital hydrothorax, and congenital pulmonary lymphangiectasia. *Am J Med Genet* 2003;120A:92-96.
3. Genest DR and Lage JM. Absence of normal-appearing proximal tubules in the fetal and neonatal kidney: prevalence and significance. *Hum Pathol* 1991;22:147-153
4. Jain V and Beneck D. Renal tubular dysgenesis in a hydropic foetus with trisomy 21: a case report with literature review. *Pediatr Dev Pathol* 2003;6:568-572
5. Endo H and Oka T. Renal tubular abnormalities in hydrops fetalis: a histological and immunohistochemical study. *Early Hum Dev* 1997;48:11-21
6. Querfeld U, Orfmann M, Vierzig et al. Renal tubular dysgenesis: a report of two cases. *J Perinatol* 1996;16:498-500.
7. Kriegsmann J, Coerdt W, Kommos F et al. Renal tubular dysgenesis (RTD) – an important cause of the oligohydramnion-sequence. Report of 3 cases and review of the literature. *Pathol Res Pract* 2000;196:861-865

8. Zingg-Schenk A, Cacchetta J, Corvol P et al. Inherited renal tubular dysgenesis: the first patients surviving the neonatal period. *Eur J Pediatr* 2008;167:311-316
9. Genest DR and Lage JM. Absence of normal-appearing proximal tubules in the fetal and neonatal kidney: prevalence and significance. *Hum Pathol* 1991;22:147-153
10. Bale PM, Kan AE and Dorney SF. Renal proximal tubular dysgenesis associated with severe neonatal hemosiderotic liver disease. *Pediatr Pathol* 1994;14:479-489.
11. Gribouval O, Gonzales M, Neuhaus T et al. Mutations in genes in the renin-angiotensin system are associated with autosomal recessive renal tubular dysgenesis. *Nature Genet* 2005;37:964-968
12. Lacoste M, Cai Y, Guicharnaud et al. Renal tubular dysgenesis, a not uncommon autosomal recessive disorder leading to oligohydramnios: role of the renin-angiotensin system. *J Am Soc Nephrol* 2006;17:2253-2263
13. Ben Amar H, Gargouri A, Makni S et al. Dysgénésie tubulaire rénale autosomique récessive: étude morphologique et génétique de 2 nouveau cas. *Arch Pediatr* 2007;14:1088-109