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CASE REPORT

A case of neonatal Jeune syndrome expanding the phenotype

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Key Clinical Message

We report the case of a premature, very low birth weight, newborn with stigmata of Jeune syndrome, a rare skeletal dysplasia, and marked renal involvement (i.e. remarkable prenatal oligohydramnios, histologic nephronophthisis-like pattern, macroscopic renal cysts, and renal failure), expanding the phenotype consistent with the continuum of syndromic ciliopathies.

Keywords

Asphyxiating thoracic dystrophy, ciliopathy, dwarphism, Jeune syndrome, nephronophthisis, oligohydramnios, renal cyst.

Research Letters

Dear Editor,

Jeune asphyxiating thoracic dystrophy (JATD, *MIM 208500*) is a rare autosomal recessive skeletal dysplasia characterized by a small and narrow chest, variable limb shortness, and typical radiographic signs [1, 2]. Associated congenital abnormalities are postaxial polydactyly of both hands and/or feet and renal, hepatic, pancreatic, and ocular complications occurring later in life [1, 2]. Respiratory symptoms widely vary from respiratory failure, leading to neonatal-infantile death in the 60–80% of cases, to a mild phenotype without respiratory symptoms [1, 2]. JATD is a genetically heterogeneous disorder and belongs to syndromic skeletal ciliopathies, a group of syndromes associated with mutations in genes encoding proteins participating in the formation or function of cilia [3].

The reported patient was a newborn male of non consanguineous Senegal parents. He was delivered prematurely at 29 + 5 gestation weeks by cesarean section due to severe intrauterine growth restriction and remarkable oligohydramnios. At birth the weight was of 1320 gr, the length was of 36 cm, and the cranial circumference was of 28 cm. The neonate showed a long, slight bell-shaped and narrow chest (thoracic circumference of 22 cm) with marked lung hypoplasia (Fig. 1A and B), mild shortened upper extremities, normal femur length for gestational age, postaxial polydactyly of both hands and of the left foot (Fig. 1C), and hepatomegaly. Oral cavity and face were normal and no signs of ectodermal dysplasia were detected. Pelvis radiography showed short squared iliac wings and a trident appearance of the pelvis due to the presence of spur-like projections at the lower margins of the sciatic notches (Fig. 1C). Renal ultrasound detected cortical cysts of the right kidney (Fig. 1D). Cardiac echography highlighted a normal heart anatomy, but the presence of pulmonary hypertension signs. Cerebral ultrasound was compatible with gestational age. In the first hours of life, the newborn showed an hyperkalemic status compatible with acute renal failure and severe respiratory distress that led to death at 7 days of life despite aggressive ventilatory care. Autopsy findings in the liver were characterized by edematous fibroplasia of periportal spaces associated with biliary duct proliferation and in the kidneys by nephronophthisis-like pattern and tubules dilatation.

The patient showed suggestive skeletal signs consistent with JATD phenotype. In the differential diagnosis, we have to consider Ellis-van Creveld syndrome (EvCS) and the others syndromic ciliopathies, which may also have small thorax, polydactyly, and pelvic abnormalities but the cardiac, ectodermal, and internal malformations asso-

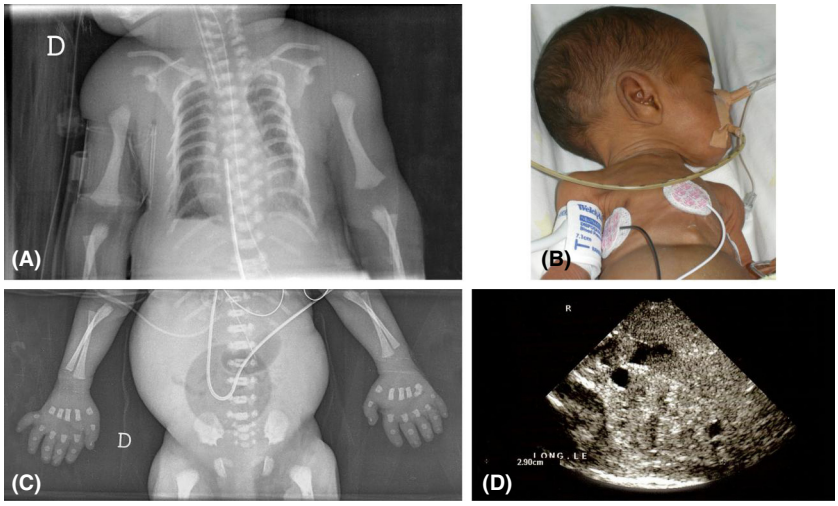

Figure 1. Clinical and radiological findings of the patient. (A and B). The narrow thorax with short ribs and hypoplastic lung. The arms long bones appear mildly shortened. (C) Postaxial hands polydactyly. At X-ray of the pelvis note the typical trident appearance of the acetabula. (D) Kidney ultrasound examination: note the cortical cysts, loss of cortico-medullary differentiation, and increased echogenicity.

ciated with these syndromes allow them to be distinguished from JATD [1–3]. In particular, normal tubular bones can clinically exclude short rib polydactyly type III [4]. Although a differential diagnosis of JATD and EvC on the basis of radiology alone may not be possible, the absence of ectodermal signs (e.g. fingernail dysplasia or congenital teeth) and of congenital cardiac defects (i.e. defects of primary atrial septation) fairly excludes clinical EvCS diagnosis [3]. Furthermore, in EvCS developmental defects and dysplasia of kidneys and liver are occasional, and although hands polydactily is a constant feature, the feet are uncommonly affected [3]. Normal femur length allowed us to exclude short-limbed dwarfisms.

In our patient, renal ultrasound examination revealed uniformly increased echogenicity, poor cortico-medullary differentiation, and macroscopic cortical cysts. To our knowledge, grossly visible cysts were not previously reported in neonatal period and anyway before 2 years of life [1, 2]. Usually renal problems in JATD patients do not appear until after the second year of life and are characterized by tubular disorders and by histological findings, as previously described: atrophic and cystic dilatation of the tubules, diffuse interstitial fibrosis, periglomerular fibrosis, glomerular sclerosis (nephronophthisis) and, to a varying degree, microscopic cystic changes arising from dilation of the collecting ducts [1, 2]. Nephronophthisis, characterized by the loss of cortico-medullary differentiation and increased echogenicity at ultrasound, in most cases leads to end-stage renal failure during childhood or young adulthood [3, 5]. In our case, in addition to postnatal renal failure, a severe oligohydramnios, a finding not reported in literature and in despite of previously reported polyhydramnios [6, 7], was prenatally detected. We could speculate that the remarkable oligohydramnios could be due to the reduction in fetal urine production as a consequence of precocious fetus' kidneys damage as highlighted by the nephronophthisis pattern found at postmortem examination. In our patient, the fatal outcome was due to severe kidney involvement and to coexisting causes (i.e. extreme prematurity, very low birthweight, and lack of amniotic fluid flowing in and out of the fetal lung concurring to pulmonary hypoplasia) that damaged and precipitated the respiratory dynamic, in addition to marked chest narrowing.

The parents did not give the consent to carry out genetic tests. However, the diagnosis of JATD is primarily based on clinical and radiological findings due to genetic heterogeneity, or rather different mutations in different genes can cause JATD (i.e. *WDR19, DYNC2H1, TTC21B, IFT140* genes) [3]. Furthermore, in a part of analyzed patients, no mutation in these genes was found suggesting the hypothesis that other genes may also be implicated in the disease. Aside from gene causing mutations, JATD is transmitted in an autosomal recessive manner and the recurrence risk for a couple, after the birth of an affected child, is 25% for every pregnancy independently of the fetus sex. Molecular diagnosis must be confirmed in the proband before proposing prenatal molecular testing. Family counseling has to consider that mutations in the same gene can cause different disease phenotype. *WDR19* gene was found to be mutated in JATD, Sensenbrenner syndrome (also known cranioectodermal dysplasia, *MIM 614378*), and isolated nephronophthisis [5]. *DYNC2H1* gene mutations are associated with JATD and short rib

polydactyly type III (*MIM 263510*) [4, 8]. *TTC21B* gene mutations are associated with JATD and isolated nephronophthisis [9], and, finally, *IFT140* gene mutations were detected in JATD and Mainzer-Saldino syndrome *(MIM 266920*) [10].

If prenatal genetic analysis is not possible, only a careful antenatal ultrasound examination can detect the disease. For both prenatal and postnatal diagnosis and prognosis it is mandatory to bear in mind the variable expressivity occurring in JATD syndrome expressed to a different degree of severity.

Finally, we reported a case with JATD cardinal stigmata and new associated clinical features consistent with the phenotypic continuum of syndromic ciliopathies, characterized by variable expressivity and by phenotypic heterogeneity and probably due to the existence of modifier genes.

Conflict of Interest

The authors declare that they have no competing interests.

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