Teaching Point
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A child with polycystic kidney disease: do we have to care about associated malformations?

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Introduction

A large number of associations between cystic kidneys and other clinical features has been described in the literature. Among these are syndromes that most clinicians will readily think of when kidney cysts are a major symptom. These include autosomal dominant and recessive polycystic kidney disease. In other syndromes kidney cysts can represent a less prominent clinical feature that might be overlooked initially, i.e. in tuberous sclerosis, Ehler–Danlos syndrome or Meckel–Gruber syndrome.

A syndrome with prominent skeletal features that in its original description was not linked to cystic kidneys is Hajdu–Cheney syndrome. It was first described by Hajdu and Kauntze in 1948 as a cranioskeletal dysplasia with peripheral dysostosis and spinal osteoporosis [1]. Harnasch first used the term acro-osteolysis to describe bilateral destructive bone lesions in the distal phalanges [2]. In 1965, Cheney reported acro-osteolysis in a family [3], most of whose symptoms (short stature, short neck, high palate, early loss of teeth, acro-osteolysis, broad, stubby fingers, prominent occiput, and basilar impression) have become the hallmark of the disease. Herrmann et al. [4], emphasized that osteolysis in the terminal phalanges of the affected patients is a disorder of defective bone development rather than destruction of bone already formed; it was thus a 'pseudo-osteolysis'.

It was concluded that the Hajdu–Cheney syndrome was distinct from other forms of acro-osteolysis syndromes by the presence of a generalized skeletal dysplasia and the fact that acro-osteolysis was usually not present in early childhood [5,6]. While the patho- aetiology of Hajdu–Cheney syndrome is still unknown, Brown et al. [5] concluded that it was inherited as an autosomal dominant trait, often occurring spontaneously. As possible causes an abnormality of osteoblastic function was suggested [5] as well as a neurovascular dysfunction [7] or a local factor produced by mast cells promoting osteolysis [8]. Over 40 patients with Hajdu–Cheney syndrome have been described so far, the youngest of whom was presenting acro-osteolytic bone changes by the age of 3.5 years [9].

In addition to the main features of the disease that were found in a majority of patients (acro-osteolysis, short neck, coarse face, short stature, dental anomalies, and normal intelligence) several additional manifestations have been documented: congenital heart disease [10–15], hydrocephalus [10,12–14,16,17], syringomyelia [18,19], cleft palate [14,16], hepatosplenomegaly [4,10,16], respiratory problems [20,21], hypoplastic kidneys [22], and cystic kidneys [12–14, 16,20,21,23].

We report on a patient with this syndrome, in whom short stature and polycystic kidneys were the initial presenting symptoms. These clinical findings are compatible with many known syndromal disorders that have to be carefully evaluated to reach the correct diagnosis. In 1984, Zerres et al. [24] presented an overview of the different types of cystic changes in many of these syndromes, demonstrating the heterogeneous morphology of cystic kidney changes to be yet another tool of differential diagnosis.
Clinical report

We report the case of a 10-year-old boy, the second child of unrelated parents. The family history was unremarkable except for a partial nephrectomy of unknown cause and an insulin-dependent diabetes mellitus in the father. The patient was spontaneously delivered at term after an uneventful pregnancy, with a birth weight of 3600 g and a body length of 55 cm. His further development was unremarkable until the age of 6 years when his parents increasingly noted his short stature.

Endocrinological studies at that time did not show a growth hormone deficiency, a 6-months trial of growth hormone treatment (dosage unclear) was unsuccessful. Further clinical and laboratory tests initiated at this point revealed renal insufficiency and hepatomegaly with liver function impairment. A liver biopsy demonstrated chronically active inflammation and liver fibrosis. These findings, combined with the ultrasonographic appearance of the patient’s kidneys (multiple small cysts, brilliant echoes, hyperechogenicity with diminished corticomедullary differentiation), led to the diagnosis of autosomal recessive polycystic kidney disease (ARPKD). The boy received steroid treatment for the chronic liver inflammation over 2 years, while cholestasis therapy consisted of ursodesoxycholic acid, barbiturates, cholestyramine, and vitamins. The chronic renal failure was treated conservatively with bicarbonate, calcium, and vitamins until peritoneal dialysis was started in 1998 at an age of 9.5 years. At that point the patient was presented at our hospital to be evaluated for a possible combined liver and kidney transplantation.

On admission we saw a dystrophic (weight 18.6 kg (4 kg below the 3rd centile)) and growth retarded (height 108 cm (20 cm below the 3rd centile)) boy aged 7 years, 9 months. While suffering from pruritus he did not exhibit any scratch marks on his skin, but pachydermia was noted as well as hyperkeratosis of his palms. Additionally, the shape of his hands was unusual, with short fingers and wide palms, and his neck appeared short. In addition to an unusual facies with a wide and rather short face, his ears were prominent. Except for the upper and lower medial incisors he had retained all his primary teeth.

Further clinical examination, including neurological assessment, was unremarkable except for a small umbilical hernia.

On abdominal ultrasound, a slight hepatomegaly was noted, with an increase in hepatic echogenicity and ascites in the abdominal cavity. Both kidneys demonstrated a hyperechogenic pattern with a loss of corticomедullary differentiation and one renal cyst at the right lower pole. Laboratory tests showed a serum creatinine of 298 μmol/l, serum urea of 21.4 mmol/l, serum albumin of 64 g/l, and an increase of cholesterol (8.9 mmol/l) and triglycerides (1.91 mmol/l). Hypokalaemia was present (3.1 mmol/l) as well as hyperphosphataemia (2.36 mmol/l). Proteinuria was 60 mg/l. Hepatic enzymes demonstrated a cholestasis pattern with significant increase of gamma glutamyl transferase (300 U/l) and alkaline phosphatase (1735 U/l), while lipoprotein X (0.57 g/l) and bile acids (22 μmol/l) showed a pattern of biliary obstruction. A classical growth-hormone deficiency was excluded by growth-hormone stimulation tests. Immunoglobulins as well as antinuclear antibodies and complement factors were within normal limits. A high serum level of vitamin A was noted (1602 μg/l) that was interpreted as a possible reason for the severe pruritus the patient was suffering from.

Urological, cardiological, and ophthalmological diagnostic tests were unremarkable. Skeletal X-rays of both hands (Figure 1, left hand) revealed an increased epiphyseal density of the distal phalanx, while the distal phalanx of the 2nd digit demonstrated a bilateral transverse split of the bone that is usually detectable in the acro-osteolysis process of Hajdu-Cheney syndrome. Further X-rays of chest, feet, elbow joint, and skull were unremarkable.

After completion of diagnostic procedures, the diagnosis of ARPKD was re-evaluated. Radiological findings in combination with a polycystic kidney disease, some of the reported clinical stigmata (short neck, rather coarse face, abdominal hernia) and a skeletal dysplasia that was not present in early childhood, led to the diagnosis of Hajdu-Cheney syndrome.

Fig. 1. Radiograph of the patient’s left hand. (A) Distal osteolysis with transverse splitting of the bone typical for acro-osteolysis type Hajdu-Cheney. (B) Separation of bony particles at the tip of the distal and medial phalanx of the 2nd digit (arrows).
syndrome. While some of the reported stigmata were not visible in this patient (vocal cord paralysis, hearing loss, osteoporosis or early eruption of permanent teeth), he did demonstrate an abnormal teething pattern, with a delayed eruption of the permanent teeth.

Discussion

Kaplan et al. [14] estimated that cystic kidneys are prevalent in Hajdu-Cheney syndrome in about 10% of cases, and concluded that they are an important component of the disorder. The discovery of renal disease in the patient described in this article was coincidental only after he presented with short stature, and further diagnostic tests revealed chronic renal failure. The incidence of renal cysts might be even higher in patients with Hajdu–Cheney disease than estimated, since ultrasonography is usually not performed as long as the patients are asymptomatic. *Vice-versa*, Hajdu–Cheney syndrome and other disorders associated with polycystic kidney disease are often not looked for in patients with polycystic kidneys, as was the case in our patient. It has been speculated by Kaplan *et al.*, that a connective-tissue disorder might be the underlying cause of Hajdu–Cheney syndrome [14]. The incidence of polycystic kidneys in connective tissue disorders like von Hippel-Lindau syndrome, tuberous sclerosis, oro-facial-digital type I syndrome and Ehlers–Danlos syndrome points to polycystic kidneys being part of a multi-system connective tissue dysfunction [23]. In 1993, Somlo et al. [25] reported the cosegregation of an overlap connective-tissue disorder with autosomal dominant polycystic kidney disease. A connective-tissue dysfunction might be a possible explanation for the renal and extrarenal manifestations present in Hajdu–Cheney syndrome.

Teaching points

(1) The case points out the necessity to look carefully for associated malformations and extrarenal manifestations in polycystic kidney disease, thus reaching the correct therapeutic and prognostic conclusions.

(2) Since cystic kidney lesions are associated with many syndromes primarily exhibiting extrarenal manifestations, an ultrasound examination of the kidneys should be performed in any case of a syndromic disorder of unknown classification.

References


