Cutaneous white spots in a child with polycystic kidneys: a clue to TSC2/PKD1 gene mutation

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disease with a prevalence of 1–2/1000 [5]. In rare cases (<1%) ADPKD can be associated with tuberous sclerosis (TS) as a result of a large single deletion on chromosome 16 affecting the adjacent genes PKD1 and TSC2 [2].

Case report

A 2.5-year-old female infant with a history of polycystic kidney disease was admitted to our unit because of newly diagnosed arterial hypertension. Polycystic kidneys had been identified on occasion of a hip screening ultrasonography at 6 weeks of age. Multiple renal cysts up to 60 mm in diameter were present in both kidneys, the large size of the cysts suggesting ADPKD rather than autosomal recessive polycystic kidney disease (Figure 1).

On admission the patient presented with normal renal function (serum creatinine: 0.3 mg/dl) and a normal liver ultrasound with no evidence of cystic or fibrotic changes as typical for the autosomal recessive form of PKD. There was no history of seizures or mental retardation, nor was there a family history of polycystic kidney disease or tuberous sclerosis. On examination the patient displayed five hypopigmented macules of different size and shape (diameter 3 to 15 mm) unequally distributed over the body (Figure 2). In addition, a few small fibromas (diameter 2 mm) were found in the dorsal neck region covered by the patient’s hair (Figure 2). The abdominal examination revealed two large bilateral masses consistent with enlarged kidneys. The cardiac, pulmonary and neurological status was normal. The developmental status was appropriate for age. Blood pressure on admission was 140/90 mmHg (i.e. ~25 mmHg above 95th percentile).

Alerted by the cutaneous signs of tuberous sclerosis, we screened for other manifestations of this disease. An echocardiography showed normal cardiac structure and function. Funduscopy disclosed no retinal changes, and an EEG showed no abnormalities. However, cerebral magnetic resonance imaging (MRI) revealed subependymal hamartomas (diameter ≤3 mm) and several cortical tubera (diameter ≤20 mm), establishing the diagnosis of tuberous sclerosis (Figure 3).

The coexistence of polycystic kidney disease of the ADPKD type and tuberous sclerosis suggested a contiguous PKD1/TSC2 gene mutation in this child. Fluorescence in situ hybridization (FISH) analysis confirmed a deletion affecting the adjacent genes on chromosome 16 (Figure 4). FISH investigations on both parents did not reveal a deletion in parental lymphocytes.

Discussion

The association of ADPKD and TS has recently been shown to belong to the heterogeneous ‘contiguous gene syndromes’. This term was first introduced by David Smith and describes the damage of two adjacent genes caused by a single gene mutation [8].

In ADPKD mutations in two genes, PKD1 on chromosome 16 and PKD2 on chromosome 4, have been identified to cause ADPKD [6]. Two dysfunc-
tional genes are responsible for TS, TSC1 and TSC2 on chromosome 9 and 16 respectively [7]. Genetic analysis on chromosome 16 revealed that TSC2 lies immediately adjacent to PKD1, separated by only a few base pairs [10,11]. The hypothesis that the association of ADPKD and TS could be caused by deletions in the transitional zone between PKD1 and TSC2 was proven by Brook-Carter et al., who demonstrated submicroscopic deletions at chromosome 16p13.3 involving both the TSC2 and the PKD1 gene in 6 affected patients [2]. The high prevalence of the contiguous gene syndrome was confirmed by Sampson et al. who observed the TSC2/PKD1 deletion in 22 of 27 patients with ADPKD and TS [9].

The clinical course in patients suffering from ADPKD and TS is highly variable for TS, ranging from early onset of seizures and severe mental retardation to the persistent absence of obvious signs of TS. In the patient presented here only several hypopigmented macules and a few small-sized fibromas raised the suspicion that we dealt with TS. Hypopigmented macules ('white spots') are a hallmark of TS. They are found in 80–90% of TS patients and may be the earliest indicator of the disorder in affected individuals. The prevalence of hypopigmented macules in individuals without TS is estimated to be 0.6–5%. The sign is reasonably specific for TS if patients with three or more hypopigmented macules are considered. Of 9737
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Fig. 3. Cerebral MRI showing a subependymal nodule in the anterior left ventricle (white arrow, left side) and a cortical tuber (white arrow, right side).

Infants examined by Debard and Richardet at age 1–18 months, 0.73% had any hypopigmented macules [4]. However, only 0.03% (three patients) had three or more hypopigmented macules, one child having neurofibromatosis and two having TS.

The course of renal function tends to be more adverse in patients with TSC2/PKD1 mutations than in the presence of PKD1 or PKD2 mutations alone. In the series studied by Sampson et al. patients with the combined mutation tended to reach end-stage renal failure much earlier than reported in patients with ADPKD alone [5,9]. This poor outcome in TSC2/PKD1 patients may be due to the additional renal lesions associated with tuberous sclerosis (angiomylipomatosis, cysts), which per se may lead to chronic renal failure [1,3]. Also, arterial hypertension may be aggravated, resulting in an accelerated progression of renal failure.

Our patient presented initially with enlarged kidneys without any features of TS. She had no family history of cystic kidney disease and showed no extrarenal cysts. The multiple large cysts visible in early infancy, the marked arterial hypertension and the negative family history did not favour the diagnosis of either ARPKD and ADPKD. Hence, this case illustrates the importance to consider the possibility of the contiguous TSC2/PKD1 gene mutation in young patients with unusual presentation of polycystic kidney disease.

Teaching point

Patients with polycystic kidney disease presenting with cutaneous lesions suspicious of tuberous sclerosis
should be further investigated by cerebral MRI, echocardiography, funduscopy and genetic analysis (FISH analysis) in order to identify a possible association of ADPKD with tuberous sclerosis.

References