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CASE REPORT

Beyond polycystic kidney disease

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SUMMARY

Tuberous sclerosis(TS) is an autosomal dominant disease caused by mutations in *TSC1* and *TSC2* genes. *TSC2* gene is located in chromosome 16p13.3, adjacent to *PKD1* gene, responsible for the autosomal dominant polycystic kidney disease. In a rare subgroup of patients, the presence of a deletion which simultaneously affects the *TSC2* and *PKD1* genes has been confirmed. TSC2/PKD1-Contiguous Gene Syndrome is characterised by the early appearance of autosomal dominant polycystic kidney disease in combination with several phenotypic manifestations of TS. We present a 13-year-old girl with bilateral renal cysts detected at the age of 9 months. At the age of 13, she was referred to the Dermatology Outpatients Clinic due to a facial cutaneous eruption. She presented with facial erythema, fibroadenomas with malar distribution and disseminated hypomelanotic macules, meeting the criteria for TS. TSC2/PKD1 Contiguous Gene Syndrome deletion was suspected, being later confirmed by genetic testing.

BACKGROUND

Tuberous sclerosis (TS) is a neurocutaneous autosomal dominant disease with complete penetrance but with a broad intrafamilial and interfamilial phenotypic variability. However, it is estimated that over 60% of all cases are caused by new mutations.[1] Its incidence is up to 1/6000 to 1/10 000 live births, with a population prevalence of around 1/20 000.[1–3] It is caused by mutations in the *TSC1* gene, located in the long arm of chromosome 9 (9q34), which is responsible for the codification of the protein hamartin, or in the *TSC2* gene, located in the short arm of chromosome 16 (16p13), encoding for tuberin. Inactivation of the *TSC1* or *TSC2* gene causes uncontrolled cellular cycle progression with proliferation of hamartomas in multiple organs and systems.[2–4] TSC2 mutation is frequently associated with a more severe phenotype. However, there are reports of milder forms caused by TSC2 mutations.[5]

TS is a multisystemic disorder, characterised by the formation of hamartomas in the central nervous system, skin, eye, kidney, lung, heart, liver, musculoskeletal and gastrointestinal system. Neurological manifestations are extremely heterogeneous, ranging from normal cognitive function without seizures to mental retardation and epilepsy refractory to treatment. The more common dermatological manifestations are hypomelanotic macules and facial angiofibromas (75% of patients with TS). Shagreen patch is present in the lumbar sacral region in 20%–30% of patients and ungual and periungual fibromas (Koënen tumours) are present in 20% of cases, being more common in adults and teenagers.[6 7] The most frequent renal manifestations are angiomyolipomas and renal cysts. Renal cysts may be single or multiple and appear in younger ages than angiomyolipomas. According to the literature, renal cysts appear earlier and in greater number in patients with TSC2 mutation.[8] Other manifestations may be found: subependymal giant cell astrocytomas, cardiac rhabdomyomas, lymphangioleiomyomatosis and multifocal micronodular pneumocyte hyperplasia.[7 9]

Polycystic kidney disease (PKD) may have either recessive or dominant autosomal transmission. Recessive disease appears, in most cases, during the first year of life, usually with serious impairment of the renal function. Autosomal dominant PKD incidence is up to 1/1000 individuals. In 85% of cases, it results from *PKD1* gene mutation, with the remaining 15% being caused by *PKD2* gene mutation. It is characterised by bilateral renal cysts and progression to end-stage kidney failure.[8 9] Other possible manifestations are hepatic and pancreatic cysts, aortic and cerebral aneurysms, hepatic fibrosis, intestinal diverticula and heart valve defects.

Although PKD and TS are two different genetic diseases, there is a rare subgroup of patients where the association between both entities is well established—the so called TSC2/PKD1 Contiguous Gene Syndrome. This syndrome occurs due to a large deletion involving the genes responsible for both diseases, the *TSC2*/*PKD1* genes.[8 9]

CASE PRESENTATION

We present a 13-year-old girl, with unremarkable family history and without consanguinity. She was delivered at 38 weeks without antenatal or perinatal complications, namely prenatal ultrasonographic alterations. At the age of 9 months, she was referred to the paediatric nephrology due to bilateral polycystic kidneys found on ultrasound, performed for evaluation of a left flank palpable mass. Screening of family members for kidney and hepatic cysts was negative. She has normal body growth and psychomotor development. Ultrasounds revealed large kidneys with multiple cysts (figure 1). Kidney function, blood pressure and microalbuminuria remained within normal range. At the age of 10, she was referred to the paediatric dermatology due to the appearance of a cutaneous eruption on the face. She presented with facial erythema and angiofibromas with malar

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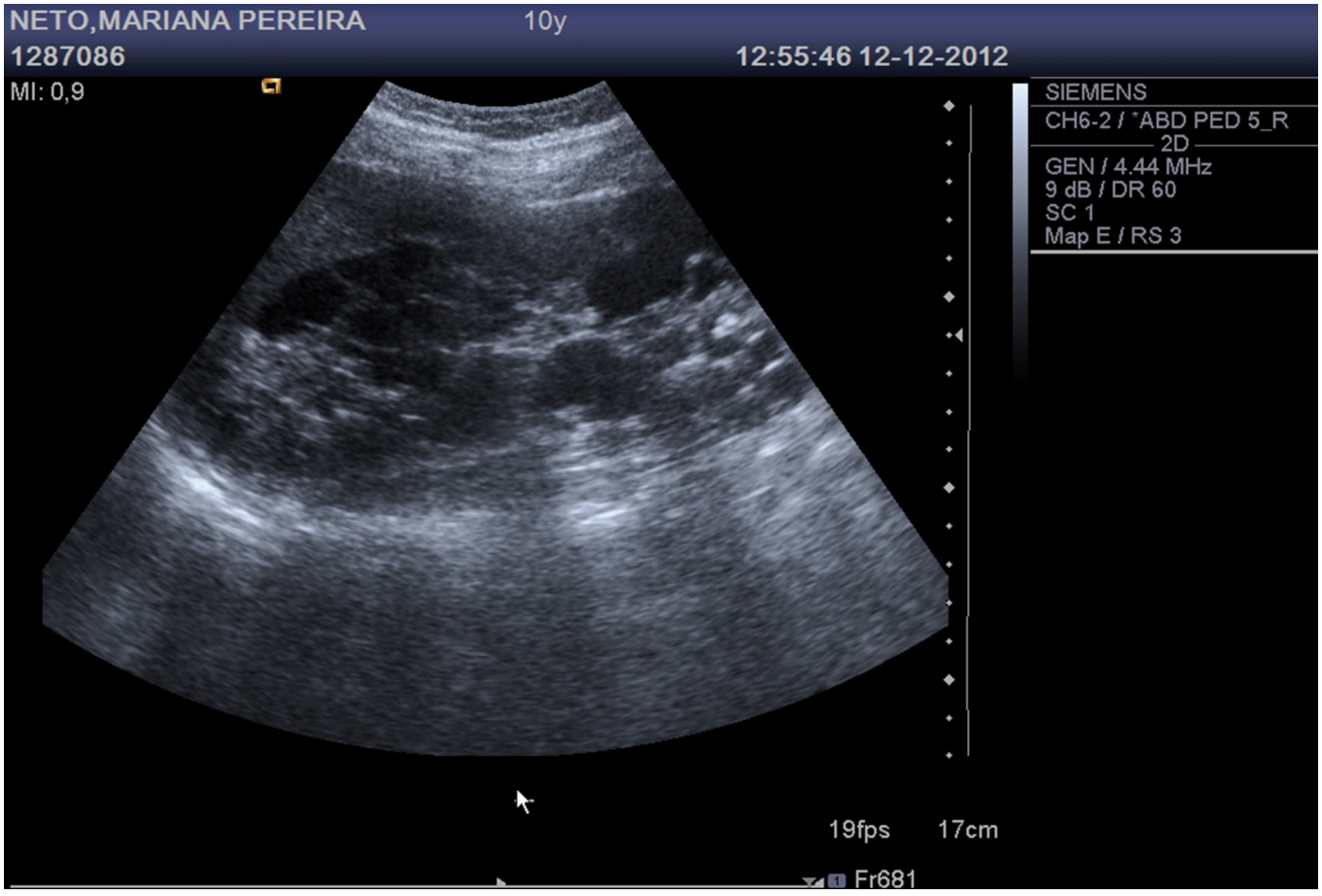

Figure 1 Renal ultrasonographic: enlarged kidneys with multiple cystic formations.

distribution (figure 2) and various hypopigmented maculas in the upper body, arms and legs, meeting the criteria for TS. Afterwards, parents mentioned that some lesions were already present in the first years of age. Repeat ultrasound (at 10 years old) identified two nodules, suggestive of angiomyolipomas, in the left kidney. Diagnostic hypothesis of TSC2/PKD1 Contiguous Gene Syndrome was placed, which was confirmed by the genetic testing.

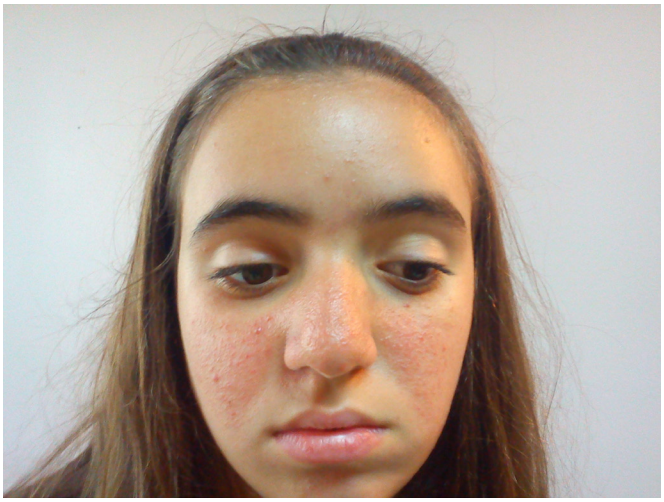

Figure 2 Facial erythema and angiofibromas with malar distribution.

INVESTIGATIONS

Laboratory investigations, including routine haematological and biochemical workup, were normal. At the age of 13, microalbuminuria (52.00 µg/mL) was detected, with normal blood pressure. Brain MRI showed multiple corticosubcortical lesions involving both cerebral hemispheres, hypointense on T1-weighted images and hyperintense on T2-weighted images, with morphological characteristics compatible with cortical tubers (figure 3), as well as multiple calcified subependymal nodules. Echocardiogram was normal, and ophthalmologic evaluation showed no hamartomas or other alterations. The genetic testing revealed a heterozygous deletion which included the *TSC2* genes (exon 37) and the terminal portion of the *PKD1* gene.

OUTCOME AND FOLLOW-UP

At 13 years of age, patient continued to be seizure free; she had normal cognitive functions and an unremarkable neurological examination. She had persistent hypopigmented maculas in the upper body, arms and legs, without Shagreen patch or Koënen tumours. Facial lesions significantly improved with topical sirolimus.

During follow-up, her renal function and blood pressure remained within normal limits. Cardiac and ophthalmological evaluations remained unremarkable. Patient was started on enalapril 10 mg once daily for microalbuminuria, with subsequent improvement.

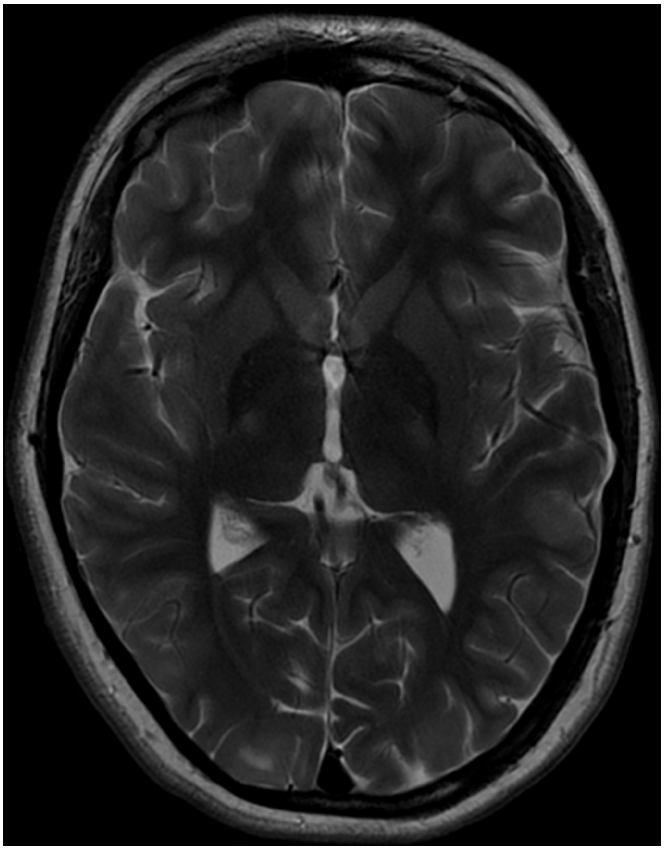

Figure 3 Tuber cortical.

DISCUSSION

Brook-Carter *et al* first described the TSC2/PKD1 Contiguous Gene Syndrome in 1994. It is caused by a deletion that affects *TSC2* and *PKD1* genes, both are located on chromosome 16 at position 16p13.3, separated by only a few nucleotides. It is characterised by the presence of major bilateral kidney cysts, usually present at birth or appearing in the first years of life.[4 8 10] Diagnosis is established by genetic testing, using the multiplex ligation-dependent probe amplification technique.[8 11 12] Years later, Sampson *et al* studied 27 patients with TS and multiple bilateral renal cysts and found contiguous deletions of TSC2 and PKD1 in 22 patients.[1–3] Since then, a few other case reports were published. In 2014, Ismail *et al* described two novel gross deletions of TSC2 gene in two Malaysian patients with TS complex and TSC2/PKD1 contiguous gene deletion syndromes, respectively. One deletion involved exons 26–31, and the other deletion involved exons 32–41 which is contiguous into adjacent *PKD1*.[13]

Kidney cysts may be found in both TS and autosomal dominant PKD, and the contribution of each gene to its appearance is unknown. However, it is estimated that 2% to 3% of patients with TS have the contiguous deletion of *TSC2*/*PKD1* gene, causing a more severe phenotype of polycystic kidney with frequent progression to kidney failure within first or second decade of life.[4 12 14–16] Pathophysiology of renal cysts is unknown, but it is believed that the complete inactivation of the *PKD1* gene may be implicated. In the series published by Sampson *et al*, 22 patients had contiguous deletions of *TSC2* and *PKD1*. In 17 patients with constitutional deletions, cystic disease was severe, with early renal insufficiency. Fourteen patients were diagnosed with renal cysts in the first year of life, and three evolved to terminal kidney failure by the age of 20.[2 3]

Although clinical or imaging findings of TSC may not manifest early in life, radiological findings can be the first to suggest a diagnosis of TSC2/ADPKD1 contiguous gene syndrome and prompt investigation in search of TSC lesions, namely imaging and directed skin examination. Renal imaging findings in TSC2/ADPKD1 contiguous gene syndrome progress over time and demonstrate a specific pattern of renal disease different from typical TS complex. During infancy and early childhood, there are multiple renal cysts, with progressive enlargement of the kidneys and of the renal cysts. Recognition of this pattern by the radiologist may prompt further screening for TSC phenotype and help in early diagnosis. Histopathological features of skin lesions in TSC2/PKD1 contiguous deletion syndrome are similar to those encountered in TS. Hence, clinical awareness and appropriate molecular investigation of TSC2/PKD1 contiguous gene syndrome are essential in all patients with a typical phenotype of TSC in early years of life because of the severity of the renal alterations in these patients.[17] One should consider the TSC2/PKD1 Contiguous Gene Syndrome in patients with TS who present with congenital or early age appearing bilateral renal cysts, without family history of autosomal dominant or autosomal recessive PKD. TSC2/PKD1 Contiguous Gene Syndrome should also be considered in children less than 2 years of age with renal cysts and no family history of autosomal dominant or autosomal recessive PKD. The additional finding of renal angiomyolipomas in this setting is virtually pathognomonic of TSC. Patients who will require renal transplantation in the future may benefit from mTOR inhibitors, which are immunosuppressive agents that reduce the size of benign tumours in TS as well as the risk of rupture and bleeding.[18] Most cases described in the literature refer to patients diagnosed with TS in which, during the follow-up of their disease, bilateral kidney cysts are detected. In our patient, the chronological order was different: there was a follow-up for PKD without family history or genetic study, and the latter detection of cutaneous lesions led to suspicion of TS.

Although patients with TS complex exhibit a high rate of epilepsy and cognitive problems, our patient had a normal cognitive development with no seizures. In the study published by Kassiri *et al*, a cohort of 24 patients with TS complex underwent brain MRI, electroencephalogram and neuropsychological evaluation. The study reported a negative correlation between number of cortical tubers an IQ score.[19]

Microalbuminuria was the only abnormality in renal function that the patient had at the time of diagnosis. Since she has the described mutation, and the combination of mutations of *TSC2* and *PKD1* genes is associated with severe kidney lesion, it is expected that in the future she will evolve to chronic kidney failure.

Authors also consider that this case illustrates the relevance of a detailed physical examination, significance of the cutaneous

Learning points

- The TSC2/PKD1 contiguous gene syndrome is characterised by the early appearance of manifestations of polycystic kidney disease in combination with varied phenotypic expressions of Tuberous sclerosis (TS).
- This diagnosis should be considered in patients with manifestations of kidney polyscystosis and stigmas of TS.
- Because prognosis of renal and neurological functions is worse in this subgroup of patients, earlier detection and treatment may help preventing kidney and neurological deterioration.

manifestations (which are sometimes unnoticed or unvalued) in children with polycystic renal disease, as well as pertinence of the multidisciplinary collaboration between paediatrics and dermatology in the diagnosis of TSC2/PKD1 contiguous gene syndrome.

Contributors SFS: involved in preparation of the manuscript and bibliographic research. TF, AIC and MJãPL: involved with the patient's care in management and bibliographic research. MJãPL: discussed planning and help on conception and design, acquisition of data or analysis and interpretation of data and so on.

Competing interests None declared.

Patient consent Guardian consent obtained.

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