CASE REPORT

JIACM 2019; 20(3-4): 238-41

Tuberous Sclerosis with Autosomal Dominant Polycystic Kidney Disease

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Abstract

Tuberous sclerosis is an autosomal dominant/sporadic condition characterised by the presence of multiple hamartomas in various organ systems of the body. The kidneys are affected in 80% of patients, in the form of renal angiomyolipoma, renal cysts or renal cell carcinoma. Tuberous sclerosis and Polycystic kidney disease (PCKD) are two different genetic diseases. The association of the two is well recognised, even though the incidence is rare. The association involves large deletion of both PKD-1 and TSC-2 genes on chromosome 16. This is also known as TSC-2/PKD-1 contiguous gene syndrome. We are reporting a case of a 22-year-old male patient of Tuberous sclerosis who presented with epilepsy, mental retardation and pain abdomen. He had other classical features of Tuberous sclerosis with USG abdomen revealing polycystic kidneys which was consistent with the diagnosis of PCKD.

Key words: Tuberous sclerosis, polycystic kidney disease, epilepsy, mental retardation.

Introduction

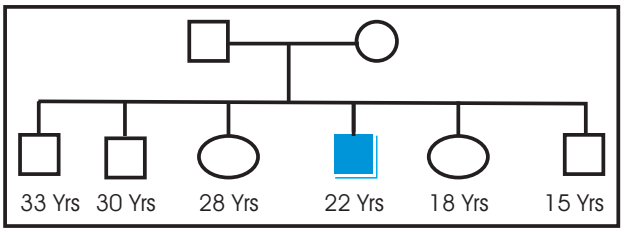
Tuberous sclerosis (TS) also known as Bourneville-disease or Bourneville-Pringle disease, is an autosomal dominant/ sporadic condition caused by mutations in a gene or genes that may occur spontaneously (sporadically) for unknown reasons or be inherited[1]. It has an estimated incidence of 1 in 5,000 live births[2,3]. It is a distinct clinical entity first described by Desiree Maglorie Bourneville in 1880. It results from a mutation of either TSC1 or TSC2 gene; TSC1 gene codes for hamartin and is located on chromosome 9q34 while TSC2 gene codes for tuberin and is located on chromosome 16p13. These mutations lead to multiple, uncontrolled proliferations/hamartomatous growths in the brain, skin, heart, lungs and kidneys[4]. Neurological manifestations include epilepsy, mental retardation and autism. Major dermatological features are facial angiofibroma (adenoma sebaceum), periungual fibromas, shagreen patches and hypopigmented macules. Common renal manifestations of TS include angiomyolipoma (85.4%), cysts (44.8%) and renal cell carcinomas (4.2%)[5,6].

Autosomal dominant polycystic kidney disease (ADPKD) is rarely seen; it is found in less than 2% of patients with TS[7]. Mutations of two genes are known to cause ADPKD; these are polycystic kidney disease (PKD) 1, located on chromosome 16p13.3 coding for polycystin 1, and PKD2, located on chromosome 4q21 - q23 coding for the protein polycystin 2[8]. Association of ADPKD in TS makes patients more are prone to renal failure and malignancy at earlier age.

Case report

A 22-year-old male was admitted in our medical ward with a history of generalised tonic-clonic seizures (GTCS) for last 15 years and pain abdomen for last 2 years. These episodes of GTCS happened 1 - 2 times per month and he was on antiepileptic drugs for last 15 years, with partial control. Patient also complained of intermittent episodes of pain abdomen and passing red colour urine. His mother also noticed delay in all milestones in his early childhood. He started schooling at age of 7 years, but because of his poor scholastic performance and onset of seizure, he discontinued school at age of 8 years. On further inquiry we came to know that this patient was born of a consanguineous marriage and full term vaginal delivery at home. He had 3 brothers and 2 sisters, no other family member had similar illness.

Family-tree



Patient was examined thoroughly and found to be anaemic, and malnourished with height of 160 cm and weight of 40

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kg and BMI of 15.62 kg/m^2. Multiple well-defined reddish-brown sessile nodular growths were noted on forehead, cheeks, nose with characteristic butterfly-pattern (adenoma sebaceum) as shown in Fig. 1 and there were few papules around the nails suggestive of periungal fibroma. A well defined roughened hypermelanotic patch over back (shagreen patch) was seen.

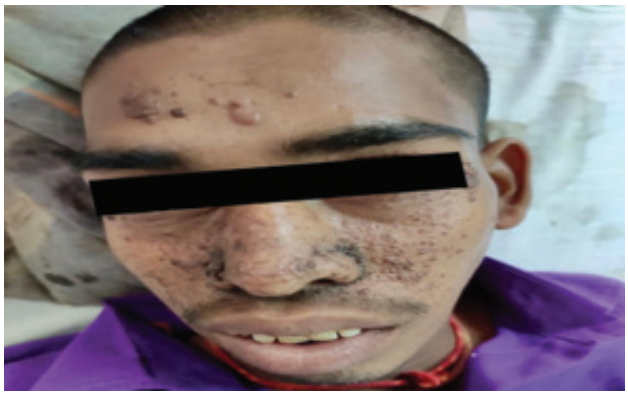

Fig. 1: *Multiple well defined reddish-brown sessile nodular growths on forehead, cheeks, nose, butterfly-pattern (Adenoma Sebaceum).*

He underwent detailed systemic examination and was found to have abnormal mental function in form of not being able to perform simple calculation, impaired judgement, partial impairment in memory and IQ of 55. His speech was slurred. Abdominal examination revealed both the kidneys were palpable and ballotable.

With this history and clinical examination, we put our physical diagnosis as epilepsy low IQ with adenoma sebaceum (EPILOIA) with bilateral palpable kidneys possibly tuberous sclerosis with polycystic kidney. For confirmation, patient was extensively investigated and found anemic (Hb 8 g/dl), ESR 30 mm at 1 hour. His renal functions were mildly deranged (urea 62 mg/dl, creatinine 2.4 mg/dl, uric acid 7.8 mg/dl) but liver function test, serum electrolytes, autoimmune profile, chest X-ray, ECG were found normal. USG abdomen was done which showed multiple variable sized cysts in both kidneys suggestive of polycystic kidney disease (Fig. 2). MRI brain showed multiple tubers distributed in cortical region and periventricular area suggestive of

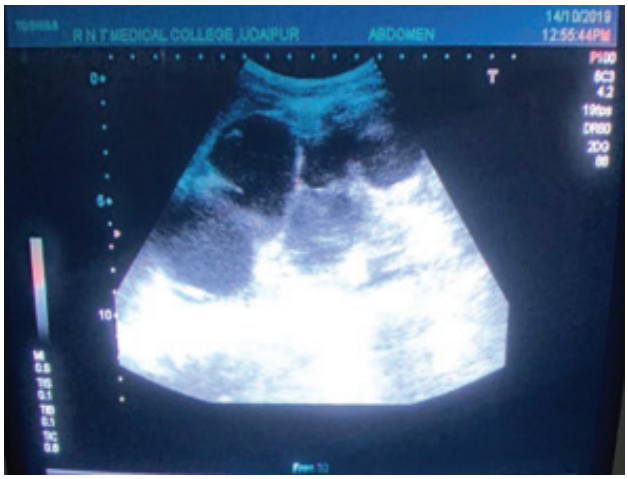

Fig. 2: *USG abdomen of patient showing multiple renal cysts of variable size.*

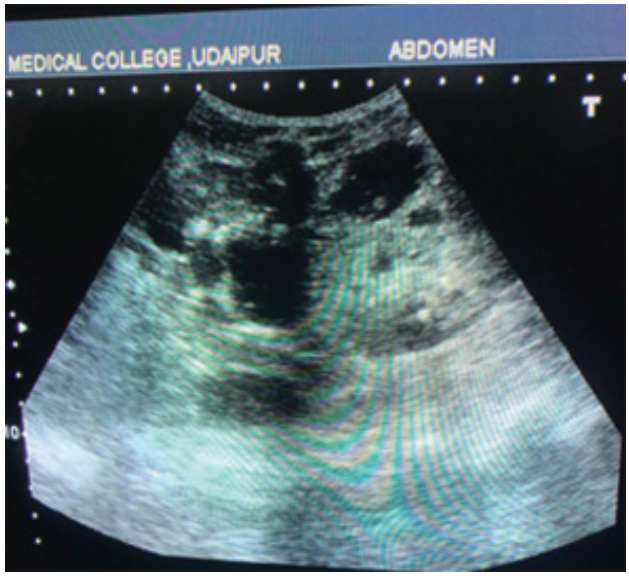

Fig. 3: *USG abdomen of patient's father showing multiple renal cysts of variable size.*

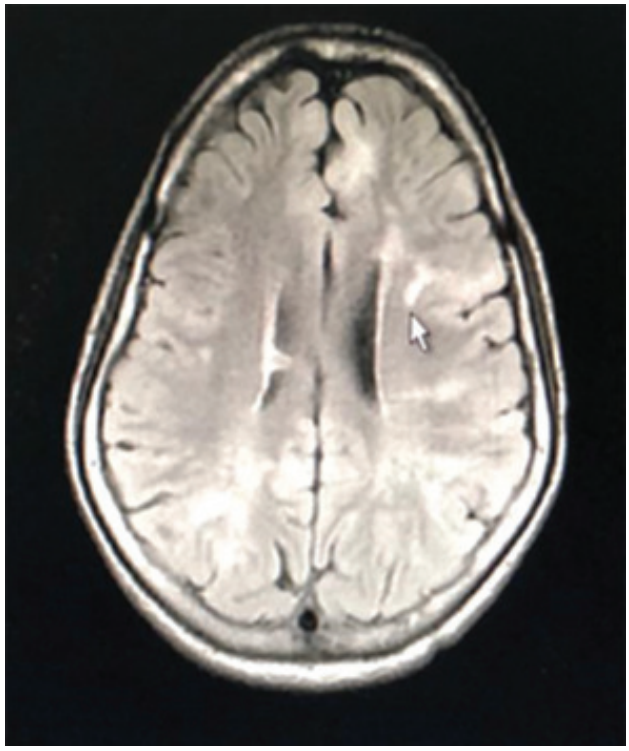

Fig. 4a: *MRI brain (axial section) showing multiple cortical tubers*

tuberous sclerosis (Figs. 4a, 4b).

Suspected to be ADPKD, other family members were screened with ultrasonographic imaging and his father and one elder brother had bilateral polycystic kidneys (Fig. 3). Genetic analysis was not done as patient's parents did not give consent for the same.

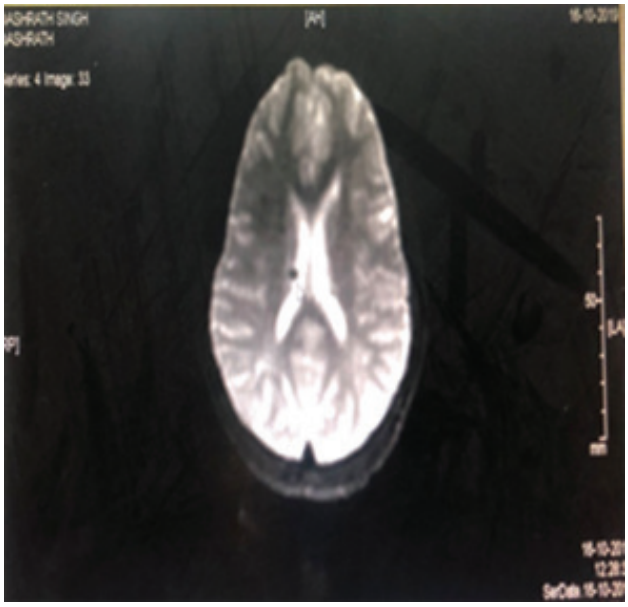

Fig. 4b: *Arrowhead showing periventricular tuber.*

Discussion

TS is an autosomal dominant/sporadic condition with multiple hamartomas in various organs of the body. Epilepsy and mental retardation, characteristic cutaneous manifestations, intracerebral hamartoma, renal angiomyolipoma and pulmonary lymphangioleiomyomatosis are among the major clinical features of TS[9]. The majority of patients (more than 80%) with TS develop some form of kidney disease during their lifetime[10]. Angiomyolipoma (85.4%) and cystic kidney diseases (44.8%) are among the common renal manifestations of TS, with rarely renal cell carcinoma (4.2%)[7]. The classic ADPKD renal phenotype may occur in the context of TS as a result of large deletions involving the PKD1 and TSC2 genes present on chromosome 16p13. This condition is also known as TSC2/ADPKD1 contiguous gene syndrome and is diagnosed when renal lesions typical for ADPKD phenotype are associated with TS phenotype. The concurrence of TS and ADPKD is rare with very few cases reported in the literature. Most of these cases belong to the paediatric age group with adult cases representing about one-fourth of the total[8]. Renal failure in TS is rare (1% of patients) though this is the second most common cause of mortality after central nervous system causes. Progression to end-stage renal disease (ESRD) has been noted in early ages, even as early as the third decade in some cases, and requires renal replacement therapy[11]. For diagnosis of TS, 2 major, or 1 major and 2 minor features are required. The major features such as angiofibroma on the face, angiomyolipoma of liver and kidney, calcified tubers in periventricular area of brain and hypomelanotic macules on extremities, and minor features such as multiple renal cysts. Our case also met 2 major and 1 minor criteria such as angiofibroma over face, periventricular tubers as major and multiple cysts in both the kidneys as minor criteria which confirms diagnosis as TS. In most cases, diagnosis is made by using clinical criteria but molecular genetic testing can be used for prenatal diagnosis, screening of family members or where diagnosis is not sure[12]. ADPKD is usually manifest in the 4th to 6th decade and renal failure may manifest in 6th decade but association with TS may have early presentation. ADPKD is usually associated with polycythaemia in the early stage due to increased erythropoietin (EPO) production but once renal function deteriorates or CKD sets in patient may have decreased haemoglobin and anemia as in our case[13,14]. In about 90% of these patients, an affected patient inherits mutation from one affected parent. In our case, ADPKD was diagnosed with USG abdomen which shows multiple cysts of variable size in both kidneys. The optimal surveillance protocols for renal imaging in TS are not well established, but it is recommended that USG should be done in all patients before 5 years of age. In the presence of angiomyolipoma or cysts, renal lesions should be followed closely with imaging every 1 - 2 years because aggressive treatment can prevent kidney failure[15]. Currently, there is a lack of definite therapy for ADPKD and TS, but use of tolvaptan which is a selective vasopressin receptor antagonist (V2 receptor) may be helpful in few patients as it delays increase in kidney volume, slows the decline in renal functions and reduces pain [16]. Recently, therapy with sirolimus (rapamycin), which is a macrolide acting as a potent inhibitor of the mammalian target of rapamycin complex (m-TOR), has been shown to be effective in ADPKD by slowing the progression of cyst size and angiomyolipomatosis[17].

Only few cases of tuberous sclerosis associated with polycystic kidney disease have been reported worldwide. Because of the rarity of this syndrome we are reporting this case. This case also emphasizes the importance of USG screening of kidneys in patients with TS to avoid late complications of chronic kidney disease.

Conclusion

Polycystic kidney disease, though infrequent, has a significant association with Tuberous Sclerosis. An early screening of kidneys with USG abdomen or genetic testing for PKD gene can help to establish diagnosis of PCKD and

use of renoprotective drugs with early referral to nephrologists to prevent kidney associated morbidity and mortality.

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