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A Rare Case of Tuberous Sclerosis with Autosomal Dominant Polycystic Kidney Disease with Renal Osteodystrophy

KEYWORDS: tuberous sclerosis, polycystic kidney disease, contiguous gene

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ABSTRACT *Although different diseases, Tuberous Sclerosis Complex (TSC) and Autosomal Dominant Polycystic Kidney Disease (ADPKD) have been seen in association, the molecular basis of this being the proximity of tuberous sclerosis complex 2 and polycystic kidney disease 1 genes on the same chromosome(16p13.3) Therefore, the classic autosomal dominant polycystic kidney disease renal phenotype may occur in the context of tuberous sclerosis complex disease as a result of large deletions involving both the polycystic kidney disease 1 and tuberous sclerosis complex 2 genes. This is known as the tuberous sclerosis complex 2/autosomal dominant polycystic kidney disease 1 contiguous gene syndrome (1) We report a case of a 30 year old female presenting with lower limb weakness as a result of renal osteodystrophy due to severe polycystic kidney disease in association with tuberous sclerosis but without evidence of neurological involvement which is the most common presentation of tuberous sclerosis.*

Introduction
Tuberous sclerosis [Latin *tuber* (swelling) and the Greek *skleros* (hard)] or tuberous sclerosis complex (TSC) is a rare multi-system genetic disease. Tubers were first described by Désiré-Magloire Bourneville in 1880 therefore also known as Bourneville's disease.

Renal involvement has a vital importance on the course of TSC because of the relentless progression of chronic kidney disease (CKD) .The classic tuberous sclerosis complex 2/autosomal dominant polycystic kidney disease 1 contiguous gene syndrome occurs due to large deletions on TSC2/PKD1 gene. The criteria for this condition are fulfilled when renal lesions typical for classic autosomal dominant polycystic kidney disease phenotype are associated with tuberous sclerosis complex phenotype.

Case Report
30 year old female was admitted with complaints of weakness in lower limbs which was gradually progressive over the last 3 months with difficulty in getting up from sitting position. She also had skin lesions which were brownish maculopapular predominantly on nose and cheeks since childhood and had gradually increased in size. There was no significant past or family history. She has two children who are normal.

On clinical examination BP was 140/94 mm Hg, she had pallor and brownish maculopapular lesions predominantly on nose and cheeks resembling adenoma sebaceum (Image 1) Therefore we also looked for other markers of tuberous sclerosis. She had leathery skin patch on lower back resembling Shagreen patch and fibrous growth at base of nail of right hand middle finger resembling Subungual fibroma (Image 2) CNS examination revealed proximal lower limb weakness with preserved reflexes and bowel, bladder function. Funduscopy was normal. Per abdomen examination revealed bilaterally palpable kidneys, rest of the examination was normal.

Investigations revealed Hemoglobin 7.4gm% microcytic, hypochromic anemia, Urine-1+albumin, Serum Creatinine 6.63 mg% BUL 103 mg% Serum Electrolytes –normal

Serum Calcium 6.1 mg% Corrected Calcium 6.74 mg% Serum Phosphorus 2.72 mg%

Serum PTH-798 pg/dl (raised), CPK-Total 80, Thyroid function test-normal, 2DEcho - normal

USG Abdomen (Image 3) multiple solid lesions in liver –likely multiple tiny hemangiomas and enlarged multi-cystic dysplastic kidneys Right – 17 x 9 cm, Left – 16.5 x 7.2 cm

In view of a raised PTH with hypocalcemia, Skeletal Scintigraphy with Three Phase Bone Scan was done which revealed Multiple Skeletal Fractures with Rib involvement suggestive of metabolic bone disease. MRI Brain – Multiple cortical tubers and calcified sub-ependymal nodules were seen(Image 4)

The diagnosis of tuberous sclerosis complex in this patient was established on the presence of major and minor features using Roach criteria (2) (Our patient had 4 major criteria and 1 minor criterion) and the diagnosis of ADPKD was based on the presence of numerous large roundish renal cysts. Molecular analysis could not be performed because of economic constraints. Diagnosis of Definite Tuberous Sclerosis with Autosomal Dominant Polycystic Kidney Disease with Renal Osteodystrophy was made.

She was treated with calcium and vitamin D supplements, low dose of antihypertensive, hematinics. She responded well and was suggested regular follow up for monitoring renal parameters and explained further need for renal replacement therapy.

Discussion
Tuberous sclerosis (TSC) is the 2nd most common neurocutaneous syndrome, inherited as an autosomal dominant trait characterized by the development of hamartomatous growths in many organs and recognized particularly for its neurological and dermatological manifestations. The live-birth prevalence is estimated to be between 10 and 16 cases per 100,000. It is characterised by triad of Mental retardation, Adenoma sebaceum, and Seizures. 96% have dermatologi-

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cal manifestations.

Roach Criteria are used for diagnosis of tuberous sclerosis which include major and minor features;

Major Criteria 1. Facial angiofiromas (adenoma sebaceum) 2. Nontraumatic ungual or periungual fibromas 3. More than 3 hypomelanotic macules 4. Shagreen Patch (connective tissue nevus) 5. Cortical tuber, Subependymal nodule 6. Subependymal giant cell astrocytoma 7. Multiple retinal nodular hamartomas 8. Cardiac rhabdomyoma 9. Lymphangiomyomatosis 10. Renal angiomyolipoma

Minor Criteria 1. Multiple randomly distributed pits in dental enamel 2. Hamartomatous rectal polyps 3. Bone cysts 4. Cerebral white matter migration tracts 5. Gingival fibromas 6. Nonrenal hamartomas 7. Retinal acromic patch 8. Confetti Skin lesions 9. Multiple renal cysts

Definite TSC - 2 major or 1 major+ 2 minor criteria. Probable TSC-1 major +1 minor

Suspect TSC-1 major or 2 or more minor
Revised criteria for diagnosis on ultrasonography in ADPKD are presence of three(unilateral or bilateral) renal cysts in 15-39 years of age or two cysts in each kidney in 40-59 years of age and 4 or more cysts in each kidney in > 60 years of age.

Two thirds of TSC cases result from sporadic genetic mutations, not inheritance, but their offspring may inherit it from them. TSC is caused by a mutation of either of two genes, TSC1 and TSC2 .TSC1 encodes for the protein hamartin, is located on chromosome 9q34.

TSC2 encodes for the protein Tuberin, is located on chromosome 16 p13.3.Mutations at the TSC1 and TSC2 loci result in a loss of control of cell growth and cell division, and therefore a predisposition to forming tumors.

TSC2 is contiguous with PKD1.The TSC2 gene has been identified and characterized by European Chromosome 16 Tuberous Sclerosis Consortium in 1993(3). It lies immediately adjacent to PKD1, the major gene for ADPKD (European Polycystic Kidney Disease Consortium 1994), raising the possibility that PKD1 plays a role in the aetiology of renal cystic disease in tuberous sclerosis. A possible role for PKD1 in renal cystogenesis in tuberous sclerosis was suggested by Kandt et al. (1992) when TSC2 was mapped to the region of chromosome16 containing PKD1. Adjacent TSC and PKD1 genes are associated with severe and early onset polycystic phenotype, and account for 2% of TSC patients

Constitutional deletions involving the coding regions of both TSC2 and PKD1 are associated consistently with severe early onset renal cystic disease, with renal enlargement and radiological appearances similar to those with advanced ADPKD. Prognosis for renal function is poor in cases with constitutional deletions involving TSC2 and PKD1.Mosaicism for deletions involving TSC2 and PKD1 is associated with preserved renal function(4)

In contrast to the unpredictable nature of many complications of tuberous sclerosis, familial occurrence of renal cystic disease in tuberous sclerosis has been noted. Testing for deletions at the TSC2 and PKD1 loci prove useful during investigation of polycystic kidney disease detected in infancy (or even antenatally).

Cases without PKD1 involvement in which there is no evidence of structural disruption of PKD1 or large deletions involving TSC2 but not PKD1, have numerous angiomyolipomata and a small number of cysts, in each kidney.

The kidneys are affected in 80% of patients of tuberous sclerosis of which angiomyolipomata are the commonest whereas polycystic kidney disease is less common. Rarely Renal Clear Cell Carcinoma (RCC), Lymphangiomatous cysts, Oncocytoma (benign adenomatous hamartomas) and focal segmental glomerulosclerosis may be seen. Patients with TSC also are at risk for acute kidney injury that can include the use of anticonvulsant and nonsteroidal anti-inflammatory medications as well as rhabdomyolysis and hypoxia induced by prolonged seizures.

Renal cysts may present in the first year of life and may be the presenting manifestation of TSC. Children with TSC are almost universally born with normal kidneys, but cystic disease and angiomyolipomas develop with increasing age. Renal Cystic disease is usually asymptomatic and is not evident on imaging studies until adulthood. Renal cystic disease can also be microcystic and undetectable by imaging studies.

Rarely, renal cysts may be large and numerous, sometimes leading to End Stage Renal Disease(ESRD) and producing a clinical scenario that can be confused with ADPKD, especially if there are few other systemic manifestations of Tuberous Sclerosis. 60% of patients of ADPKD develop ESRD by age 70.

Management-
There is no specific treatment for tuberous sclerosis. Because the disease can differ from person to person, treatment is symptomatic.

Some seizures are controlled with medication (vigabatrin). Other children may need surgery.

Brain tumors can be treated with medicines called mTOR inhibitors (mTOR, mammalian target of rapamycin—so named because of its ability to bind to the immunosuppressant drug rapamycin (sirolimus, everolimus).

Small growths (adenoma sebaceum) on the face may be removed by dermabrasion or laser treatment. These growths tend to recur and repeat treatments will be needed.

Rhabdomyomas commonly disappear after puberty, so surgery to remove them is usually not needed.

In cases with renal disease, follow up scans should be performed at six monthly intervals. Regular blood pressure measurements and renal function tests should be performed if there is extensive renal involvement. Lipid-soluble antimicrobials such as trimethoprim-sulfamethoxazole and fluoroquinolones having good cyst penetration are the preferred therapy for infected kidney and liver cysts. Patients with renal cystic disease have a significant risk for nephrolithiasis related to distal tubular dysfunction. This leads to hypocitraturia and hypertension, which responds very well to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Vasopressin V2 receptor antagonists are being studied.

Kidney tumors are treated with surgery, or by reducing the blood supply using special x-ray techniques. mTOR inhibitors are being studied for the same. Bilateral nephrectomy should be considered in cystic disease before transplantation surgery because of risk of life threatening hemorrhage and development of RCC.

Complications of TSC include -Brain tumors (astrocytoma), Heart tumors (rhabdomyoma), severe mental retardation, Uncontrollable seizures

Summary
Tuberous sclerosis complex is a rare multi-system genetic disease with wide-ranging organ system involvement. Renal complications are the most common cause of death in adult TSC patients, thus renal involvement has a crucial importance on the course of this disease

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Regular follow-up and appropriate therapy are essential to determine renal complications of TSC in the earlier stages and to overcome the preventable complications including renal failure.

Image 1: Adenoma Sebaceum

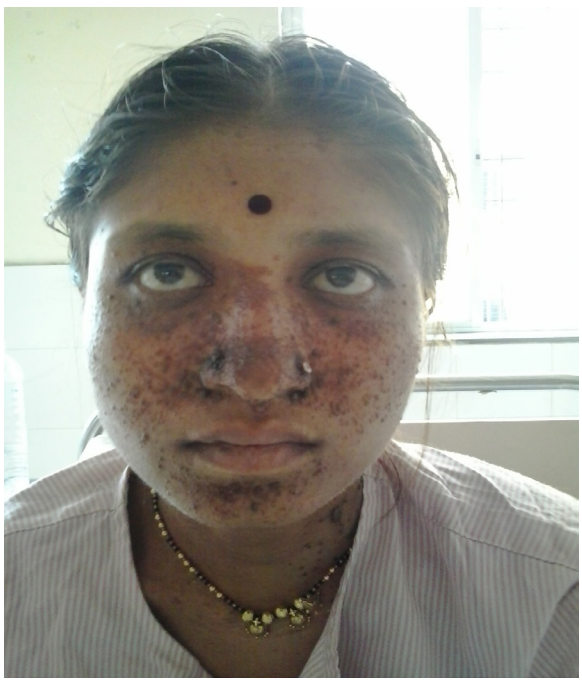


Image 2: Subungual Fibroma

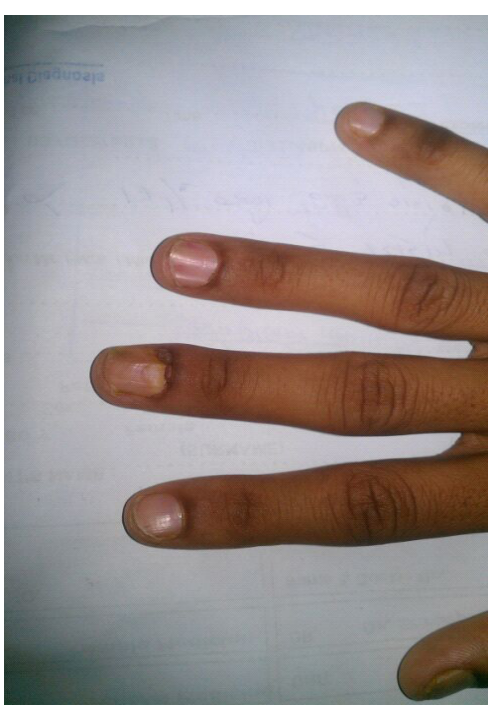


Image 3: Polycystic Kidneys

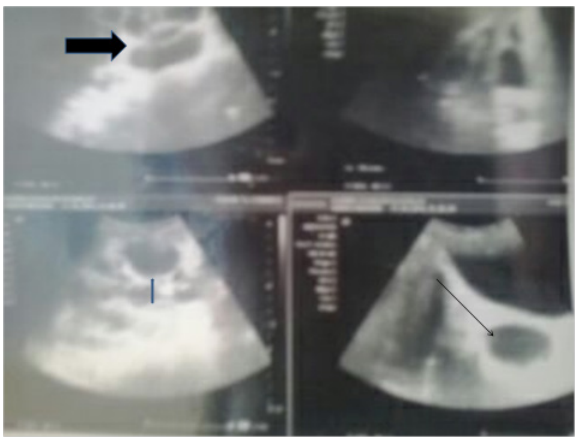
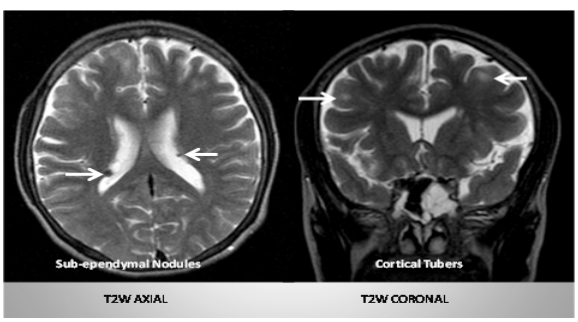


Image 4: Cortical tubers and subependymal nodules



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