Case Report

Urology, Nephrology and Andrology International
Volume 2 Number 1, January-June 2017

Tuberous Sclerosis Complex: Report of Two Intrafamilial Cases, Both in Father and Daughter

Limesh M.*, Renuka S., Prashanth G. Kedalaya*****

Author Affiliation:
*Assistant Professor, **Professor and Head, ***Professor, Department of Nephrology, St Johns Medical college, Bengaluru, Karnataka, India.

Reprint Request:
Limesh M.,
Assistant Professor,
Department of Nephrology,
St. John's Medical College,
Bengaluru, Karnataka 560034.
E-mail:
limijay_2007@yaoo.co.in

Received on: 02.05.2017
Accepted on: 16.05.2017

Abstract

Tuberous sclerosis complex (TSC) is a multisystem syndrome characterized by neurological symptoms and tumors in multiple organs including kidney, brain, skin, eyes, heart and lung. Kidney and brain are the two most frequently affected organs in TSC. TSC is an autosomal disorder with extensive clinical variability. We describe a case of TSC in a family with father and daughter being affected. We emphasize the importance of Computed Tomography in the discovery of some asymptomatic organic involvement as bilateral renal angiolipoma in the father.

Keywords: Tuberous Sclerosis; Hamartoma; Angiofibroma.

Introduction

Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disorder characterized -by presence of hamartomas in almost every organ, most notably in the skin, brain, kidney, heart and eyes [1]. The condition was described by von Recklinghausen in 1862 [2]. In 1880, Bourneville described the pathologic features of the sclerotic tubers found post mortem in patients with epilepsy and mental retardation and coined the term "sclerose tubereuse" [1]. The term "tuberous sclerosis" refers specifically to the presence of multiple sclerotic masses scattered throughout the cerebrum. The diagnosis of TSC is based on the identification of hamartomas in more than one organ system. A hamartoma is a benign tumor composed of an overgrowth of mature cells and tissues that normally occur in the affected tissue, but often with one predominating element. The kidney and brain are two of the most frequently affected organs in TSC [3]. The disease is an autosomal dominant disorder with extensive clinical variability. The presence of hamartomas in two different organ systems is considered by some clinicians to be sufficient for the diagnosis [4].

Case Report

We describe here two cases of patients belonging to the same family, a father (case no. 1), aged 54-year-old and his daughter (case no. 2), aged 11, both displaying cutaneous TSC – suggesting lesions on their faces. Moreover, the father informed us that his daughter has been suffering from infantile seizures since she was 3-year-old. He had consulted many specialists and was recommended a CT examination. Apart from this, the girl is well developed physically and intellectually, according to her age. The father is apparently in complete health condition, without any subjective signs of neurological, renal, pulmonary or digestive affections. The family history shows that all the other family members are apparently healthy, with normal intellect.

General clinical examination was performed within normal limits for both the father (case no. 1) and his daughter (case no. 2). During dermatologic examination, both father and daughter presented pink to red small nodules of 1–5 mm diameter symmetrically distributed in the nasolabial folds, cheeks and nose. Most of the nodules were yellowish and firm, others were telangiectasic and soft, with a glossy smooth surface (Figure 1). Besides, the father had some small pulpous bud-like proliferations emerging from peri-nail folds (Figure 2) at fingers and toes and numerous confetti, hypopigmented macules on the trunk and lower extremities.

Laboratory investigations of the father showed : Hemoglobin 90 gm/l, total count :5.3x 10^9/L, platelet count : 160x 10^9 /L, blood Urea :8 µmol/l ,Serum creatinine : 185 µmol/l ,serum sodium :140 mmol/l, potassium 4.9 mmol/l,liver enzymes were normal. Urine analysis showed trace proteinuria with no RBCs or WBCs. Urine culture was sterile. Daughter's laboratory investigations were unremarkable.

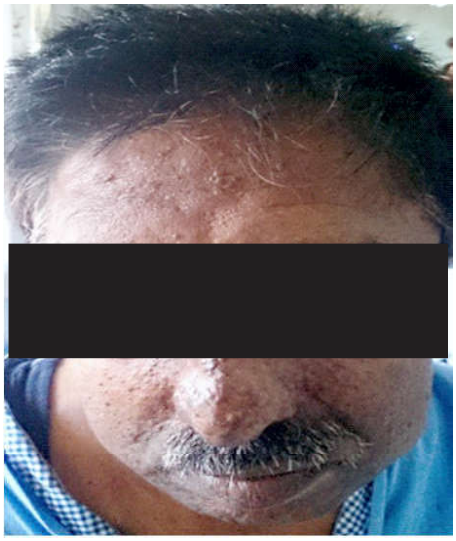

Fig. 1: Patient with Adenoma Sebaceum

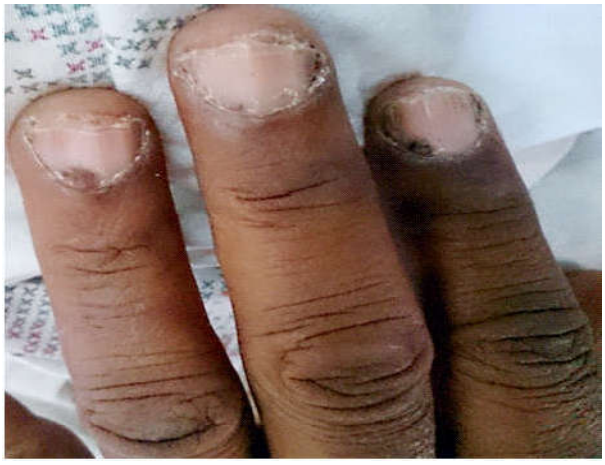

Fig. 2: Periungal and ungal fibroma

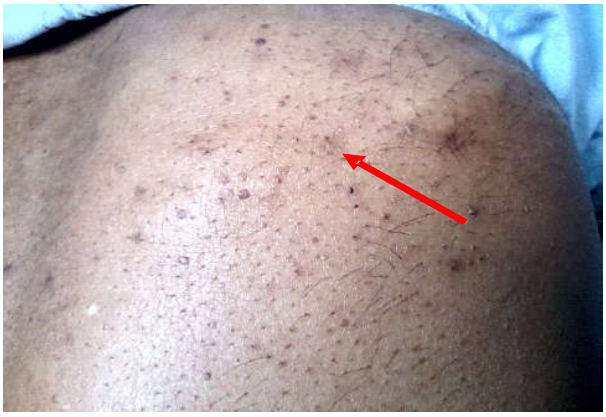

Fig. 3: Shagreen patches

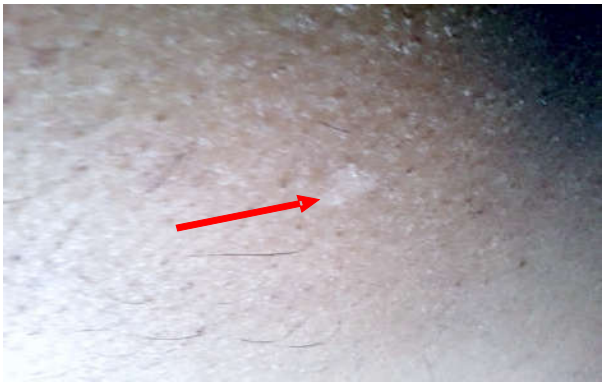

Fig. 4: Hypomelanotic macules or '' ash leaf spots"

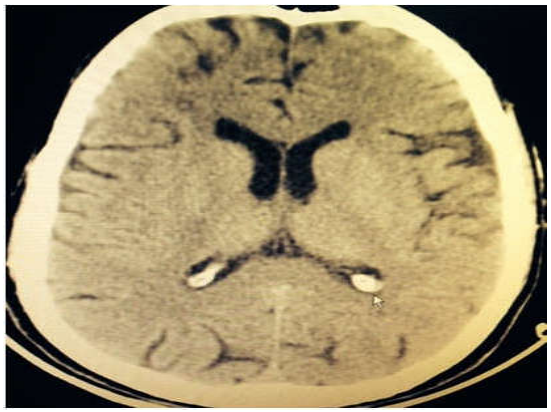

Fig. 5: CT scan brain showing calcifications in Lateral ventricles

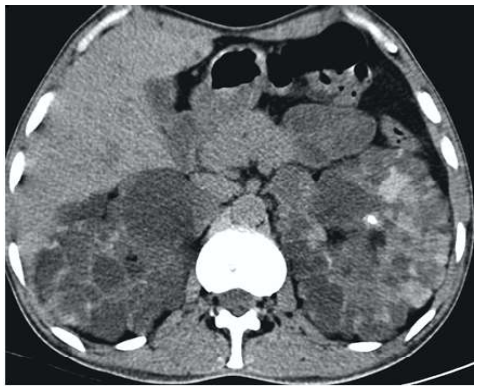

Fig. 6: CT abdomen showing bilateral renal angiomyolipoma and cysts

Computed tomography (CT) of father showed calcified subependymal nodule periventricular – IVth ventricle (Figure 5), and along the lateral border of temporal horn of right lateral. CT of abdomen showed bilateral renal angiomyolipoma and multiple cysts both in father and daughter. There was no evidence of cyst in the liver.

Discussion

Tuberous Sclerosis Complex (TSC) is an autosomal dominant disorder characterized by hamartomas in many organs [5]. It is an inherited disease with almost complete penetrance but variable expressivity [6,7]. Two-thirds (65%) of cases are sporadic and are thought to represent new mutation [5,8,9]. Two genes associated with TSC have been cloned: TSC1 located on the long arm of chromosome 9 (9q34) and TSC2 located on the short arm of chromosome 16 (16p 13.3). TSC 1 encodes hamartin and TSC2 encodes the protein tuberin. TSC is caused by mutations affecting either of the presumed tumor suppressor genes, TSC1 and TSC 2. Both appear to function as tumor suppressors, because somatic loss or intragenic mutation of the corresponding wild-type allele is seen in the associated hamartomas [5]. The expressivity is not determined by the specific gene mutation, because different manifestations can develop in affected members of the same family [10]. This disorder affects about 1 per 100 000 individuals in the USA and Western Europe. It has a worldwide distribution and involves both sexes.

Clinical presentation: The disease has protean manifestations and affects every organ, even though the classic features are mental deficiency, epilepsy and adenoma sebaceum. Four types of skin lesions are pathognomonic:

1. Adenoma sebaceum (Pringle) or facial angiofibroma is rarely present at birth but usually appears around the age of 5 to 6-year-old. The lesions increase in size and number until puberty and remain stationary thereafter. They are pink to red nodules with a smooth, glistening surface [11], symmetrically distributed in the nasolabial folds, cheeks, and nose in a butterfly pattern. The upper lip is notably spared [11]. The chin, ears, forehead, and eyelids may be involved. The lesions are usually discrete, but occasionally they may coalesce. Facial angiofibromas are comprised of vascular and connective tissue elements and are found in approximately 75% of patients with TSC [6]. Forehead plaque, a variant of angiofibroma, is seen in approximately 20% of patients with TSC [6,12]. These lesions appear in early childhood, grow very slowly, and present as firm, elevated plaques that are yellow-brown to flesh-colored [6].
2. Hypomelanotic macules or "ash leaf spots" named after the European mountain ash tree [12] are usually present at birth and almost all lesions are evident within the first two years of life [6]. Typically, the macules are rounded at one end and tapered of the other. These macules are found in more than 90% of patients with TSC [6]. In fair-skinned individuals, Wood's light helps in their detection [11]. They may be the only cutaneous sign of tuberous sclerosis and that is why they are of great diagnostic importance.
3. The shagreen or "leather" patch is an irregularly shaped plaque of thickened skin, slightly elevated, with a "peau d'orange" surface. Characteristically, the patch is in lumbosacral region and is the result of an accumulation of collagen. Occasionally, a central patch may have smaller satellite lesions around [11]. The shagreen patch is found in 20% to 30% of patients with TSC [13].
4. Periungual and ungual fibromas (Köenen tumors) are found in approximately 20% of unselected patients with TSC and are more common in adolescents and adults than in young children [13]. These tumors appear as smooth buds at the base of the nail or subungually and may reach a size sufficient to disrupt the nail bed [11]. They are flesh-colored, usually multiple, and may affect fingers and toes. The nails of toes are more commonly involved than those of the fingers [12,14]. These lesions occasionally develop subsequent to trauma [13].

Other less pathognomonic lesions are multiple skin tags of the neck and axillae, "café au lait" spots in up 30% of patients with TSC [6], confetti lesions (stippled hypopigmentation), polyosis (a white patch or forelock) and thumbprint macules [13,15].

Neurological manifestations are often the presenting feature and major cause of morbidity/mortality. Symptoms of cortical tubers may include seizures, mental retardation, learning disabilities, and abnormal behavior. Seizures have a focal or multifocal origin, this clinical feature depending on the localization of the cortical tubers [16]. The most common types of seizures are infantile spasm, partial motor seizures, and generalized tonic clonic seizures [15,16]. Infantile spasms are most common during infancy. Epilepsy associated with TSC is often

intractable, but seizure control has benefited from the introduction of the new antiepileptic drugs. Mental retardation occurs in approximately 50% of patients with TSC. Almost all mentally retarded children will have seizures. Conversely, many patients with TSC have seizures, but not mental retardation [15]. In general, the earlier the onset of the seizures is particularly infantile spasms, the greater the risk of mental retardation, cognitive impairment, and behavioral disorders [18,20]. The intracranial abnormalities include tubers, subependymal nodules and subependymal giant cell astrocytomas [21]. No correlation was found between the number of subependymal lesions and the clinical severity of TSC. Computed tomography (CT) and magnetic resonance (MR) features of the brain lesions in patients TSC were an important support for diagnostic. CT clearly demonstrates calcified subependymal nodules. MR imaging more clearly demonstrates cortical and white matter lesions than CT, since MR imaging provides an excellent image. Contrast between various normal structures and high sensitivity in detecting pathological states due to intrinsic differences in proton density and in particular, in proton relaxation times of tissues [22].

Renal manifestations of TSC are a very significant cause of morbidity and mortality [23]. Three types of tumors occur in TSC kidneys: (1) angiomyolipomas, which are benign tumors composed of smooth muscle, fat and vessels; (2) epithelial cysts; and (3) malignant tumors [3]. Angiomyolipomas are the most common renal lesions. They are found in as many as 75–80% of the affected children older than 10 years [13] and must be distinguished from multiple renal cysts that occur less commonly. Females are more often affected, in a female to male ratio of 3 to 4:1 [24]. The facts that they are rarely diagnosed before puberty in patient without tuberous sclerosis, that large ones are more common in women that men and that they occasionally grow rapidly during pregnancy suggest that hormones may play a role in stimulating the growth of angiomyolipomas [25]. Angiomyolipomas are benign tumors composed of blood vessels with thickened walls, immature smooth muscle cells, and adipose tissue [7]. The lesions are often multiple and bilateral and grow in size and number with age [7,13]. Typical angiomyolipomas are benign but may have alarming properties: nuclear pleomorphism and mitotic activity, extension in the vena cava, and spread to regional lymph nodes, without malignant progression [25]. Smaller angiomyolipomas usually do not cause symptoms, but lesions larger than 4 cm in diameter are associated to an increased risk of serious hemorrhage [7,13]. Epithelioid angiomyolipoma is a recognized variant with malignant potential.

The second most frequent renal manifestation is a renal cyst. The tubule cysts in this disease are lined by a distinct, perhaps unique epithelium of marked hypertrophic and hyperplastic cells with prominent eosinophilic cytoplasm, bearing some resemblance to that of proximal tubule [26]. The combination of cystic kidneys and angiolipomas has been said to be virtually pathognomonic for tuberous sclerosis [13]. The cysts may be large and renal impairment, although relatively uncommon, may occur before other evidence of the syndrome [27-29]. Renal cysts are identified in children younger than those with present angiomyolipomas [30]. Cysts greater than 4 cm in diameter are more likely to be symptomatic and might present with flank pain or gross hematuria or as a tender mass [24]. Hypertension is also a major manifestation of the renal abnormality. ADPKD will develop in patients with a contiguous deletion of PKDi gene, which is associated with flank pain, hypertension, pyelonephritis and progressive renal failure [31]. Renal carcinomas are rare and tend to grow more slowly in patients with TSC than in those found in the general population. The average age in patients with TSC is of 28-year-old, compared to 53-year-old in patients with renal carcinomas in the general population [7]. Ultrasonography, CT and arteriography are important in distinguishing multiple renal cysts from the more common angiomyolipomas in this disease.

Other organs are also involved. Cardiac rhabdomyomas are present in two thirds of newborn infants with TSC and are usually multiple [13] and asymptomatic [14]. They frequently develop between 22 to 26 weeks of gestation, are of maximal size, and cause the most clinical symptomatology during intrauterine life or early infancy [31]. The lesions often regress over the first few years of life [13].

Retinal hamartomas occur in 40% to 50% of patients with TSC and are bilateral in a third of cases [30,31]. Most lesions are asymptomatic. Three types of retinal lesions have been described including classic "mulberry" lesions adjacent to optic disc, plaque-like hamartomas, and "punched-out" areas of retinal hypopigmentation [13].

Oral manifestations include enamel pitting in the permanent teeth [31], fibrous hyperplasia, hemangioma, bifid uvula, cleft lip and palate, high-arched palate, macroglossia, thickening of the alveolar bone and pseudocystic lesions of the mandible [1,32].

Pulmonary involvement is uncommon and its symptoms include dyspnea, hemoptysis, and

recurrent spontaneous pneumothorax [11]. The classic pulmonary lesion is lymphangioleiomyomatosis, a progressive lung disease [10].

Bone involvements is evident in 80% of patients with tuberous sclerosis and include bone cysts found mainly in the phalanges of the hands and feet, sclerotic lesions, and periosteal new bone formation [33].

Gastrointestinal manifestations may also be present. Hamartomatous polyps in the gastrointestinal tract, especially in the rectum, usually asymptomatic, are common [12]. Papillomas in the gastrointestinal tract were also reported [2].

According to National Institute of Health (NIH) Consensus Conference, a permanent diagnosis of TSC can be made when two major features or one major feature plus two minor characteristics are demonstrated (Table 1) [34]. Additional diagnostic categories include probable TSC when one major feature plus one minor one are present, and possible TSC when either one major feature or two or more minor characteristics are present [34].

Table 1: Diagnostic criteria of TSC

Major features	Minor Feature
Facial angiofibromas or forehead plaque; Nontraumatic ungual or periungual fibroma Hypomelanotic macules – more than three Shagreen patch (connective tissue nevus); Cortical tuber Subependymal nodule Subependymal giant cell astrocytoma Multiple retinal nodular hamartomas Lymphangiomyomatosis; Renal angiomyolipomas. Cardiac rhabdomyoma, single or multiple	Multiple randomly distributed pits in dental enamel Hamartomatous rectal polyps; Bone cysts Cerebral white-matter "migration tracts"; Gingival fibromas Nonrenal hamartoma Retinal achromic patch Multiple renal cysts "Confetti" skin lesions;

*Definite TSC – either two major features or one major feature plus two minor features; **Probable TSC – one major and one minor features; ***Possible TSC – either one major feature or two or more minor features.

In the two cases of patients, belonging to the same family whom we presented above, we can find out two major criteria necessary for TSC diagnosis. However, we must underline the importance of their imagistic investigations, respectively CT, to discover any organic alteration, which most of the time evolves asymptomatically during long periods, but undergoes major complications. In case no. 1 (the father's case), following imagistic investigations, there was discovered a significant renal affectation – the presence of angiomyolipoma. They are generally benign, but may lead to serious complications. On the other hand, a cranial affection was discovered at the father's daughter. Children seem to develop subependymal giant cell astrocytomas, possibly more frequently than adults do. These tumors are histologically benign but are locally invasive and may cause hydrocephalus because of their typical occurrence in the anterior lateral ventricle. Early identification of an enlarging giant cell tumor enables it to be removed before symptoms development and before it becomes locally invasive, probably reducing the likelihood of tumor residual or recurrence. It is recommended for the children to undergo periodic cranial imaging with either CT or MRI scans every one to three years, depending on the level of clinical suspicion in a given child. It is also necessary an examination of the other family members who do not have any clinical obvious TSC manifestation, CT being the most preferred test. MRI may be more sensitive than CT, but it often detects lesions that are not so specific to TSC.

Conclusions

Clinical and histopathological examinations are essential because many of the major features of TSC are cutaneous, and these lesions often herald the diagnosis. Imaging evaluation plays an important role in the assessment of patients with tuberous sclerosis complex. In newly diagnosed patients, they help both to confirm the diagnosis of TSC and to identify clinically significant complications. For patients with a well-established TSC diagnosis, sometimes we can identify treatable complications in early stage. These investigations sometimes also provide evidence of TSC in asymptomatic patients with TSC.

References

1. Barron R. P., Kainulainen V. T., Forrest C. R., Krafchik B., Mock D., Sandor G. K., Tuberous sclerosis: clinicopathologic features and review of the literature, J Craniomaxillofac Surg, 2002; 30(6):361–366.
2. Leung A. K. C., Robson W. L. M., Tuberous sclerosis complex: a review, J Pediatr Health Care, 2007; 21(2):108–114.
3. Neumann H. P., Schwarzkopf G., Henske E. P., Renal angiomyolipomas, cysts, and cancer in tuberous sclerosis complex, Semin Pediatr Neurol, 1998; 5(4):269–275.
4. O' Callaghan F. J., Osborne J. P., Advances in the understanding of tuberous sclerosis, Arch Dis Child, 2000;83(2):140–142.
5. Jones A. C., Shyamsunder M. M., Thomas M. W., Maynard J., Idziaszczyks S., Tomkins S., Sampson J. R., Cheadle J. P., Comprehensive mutation analysis of TSC1 and TSC2-and phenotypic correlations in 150 families with tuberous sclerosis, Am J Hum Genet, 1999;64(5):1305–1315.
6. Sweeney S. M., Pediatric dermatologic surgery: a surgical approach to the cutaneous features of tuberous sclerosis complex, Adv Dermatol, 2004; 20:117–135.
7. Henskee E. P., Tuberous sclerosis and the kidney: from mesenchyme to epithelium, and beyond, Pediatr Nephrol, 2005;20(7):854–857.
8. Narayanan V., Tuberous sclerosis complex: genetics to pathogenesis, Pediatr Neurol, 2003;29(5):404–409.
9. Menkes J. H., Tuberous sclerosis. In: Memkes J. H., Sarnath H.B. (eds), Child Neurology, 6th edition, Lippincott Williams & Wilkins, Philadelphia, 2000.
10. Sparangana S. P., Roach E. S., Tuberous sclerosis complex, Curr Opin Neurol, 2000;13(2):115–119.
11. Der Kaloustian V. ., Kurban A. K., Genetic diseases of the skin, Springer Verlag, Berlin, 1979;253–255.
12. Tsao H., Tuberous sclerosis. In: Bolognia J. L., Jorizzo J. L., Rapini R. P., Dermatology, Mosby, 2003.
13. Roach E. S., Sparagana S. P., Diagnosis of tuberous sclerosis complex, J Child Neurol, 2004;19(9):643–649.
14. Osborne J., Tuberous sclerosis. In: Burns T., Breathnachs S. M., COX N., Griffiths C. E. (eds), Rook's Textbook of Dermatology, 7th revised edition, Blackwell Publishing Ltd., 2006.
15. Kandt R. S., Tuberous sclerosis complex and neurofibromatosis type 1: the two most common neurocutaneous diseases, Neurol Clin, 2003; 21(4):983–1004.
16. Curatolo P., Neurological manifestations of tuberous sclerosis complex, Childs Nerv Syst, 1996; 12(9):515–521.
17. Roach E.S., Delgado M.R., Tuberous sclerosis, Dermatol Clin, 1995;13(1):151–161.
18. Curatolop, Porfirio M.C., Manzi B., Seri S., Autism in tuberous sclerosis, Eur J Paediatr Neurol, 2004, 8(6):327–332.
19. Zaroff C. M., Devinsky O., Miles D., Barr W.B., Cognitive and behavioral correlates of tuberous sclerosis complex, J Child Neurol, 2004;19(11): 847–852.
20. Prather P., De Vroes P. J., Behavioral and cognitive aspects of tuberous sclerosis complex, J Child Neurol, 2004;19(9):666–674.
21. Dimario F. J. JR., Brain abnormalities in tuberous sclerosis complex, J Child Neurol, 2004;19(9): 650–657.
22. Inouey., Nemotoy., Murata R., Tashiro T., Shakudo M., Kohno K., Matsouoka O., Mochizuki K., CT and MR imaging of cerebral tuberous sclerosis, Brain Dev, 1998;20(4):209–221.
23. O' Hagan A.R., Ellsworth R., Secic M., Rothner A. D., Brouhard B.H., Renal manifestations of tuberous sclerosis complex, Clin Pediatr (Phila), 1996; 35(10):483–489.
24. Cooper C.S., Elder J. S., Renal angiomyolipoma. In: Avner E.D., Harmon W.E., Niaudet P. (eds), Pediatric Nephrology, Lippincott Williams & Wilkins, 2004; 1120–1121.
25. Eble J. N., Angiomyolipoma of kidney, Semin Diagn Pathol, 1998;15(1):21–40.
26. Welling W.L., Pathogenesis of renal disease. In: Brenner B.M., Rector F. C., Brenner & Rector's the Kidney, W. B. Saunders Company, 1996.
27. Okada R. D., Platt M.A., Flesisman J., Chronic renal failure in patients with tuberous sclerosis. Association with renal cysts, Nephron, 1982; 30(1):85–88.
28. Stapleton F.B., Johnson D., Kaplan G.W., Griswold W., The cystic renal lesion in tuberous sclerosis, J Pediatr, 1980, 97(4):574–579.
29. Rosenberg J.C., Bernstein J., Roseenberg B., Renal cystic disease associated with tuberous sclerosis complex: renal failure treated by cadaveric kidney transplantation, Clin Nephrol, 1975; 4(3):109–112.
30. Lendvay T. S., Marshall F. F., The tuberous sclerosis complex and its highly variable manifestations, J Urol, 2003;169(5):1635–1642.
31. Franz D.N., Non-neurologic manifestations of tuberous sclerosis complex, J Child Neurol, 2004; 19(9):690–698.
32. Celenk P., Alkan A., Canger. M., Gunhan O., Fibrolipomatous hamartoma in a patient with tuberous sclerosis: report of a case, Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2005;99(2): 202–206.

33. Bernauer T.A., Mirowski G. W., Caldemeyer K.S., Tuberous sclerosis. Part II. Musculoskeletal and visceral findings, J Am Acad Dermatol, 2001; 45(3):450–452.

34. Hyman M.H., Whittemore V.H., National Institutes of Health Consensus Conference: tuberous sclerosis complex, Arch Neurol, 2000;57(5):662–665.