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Review Article

Clinical manifestations of tuberous sclerosis complex

Ahmet Engin Atay[a,*], Halit Akbas[b], Nafi Sakar[c], Semir Pasa[d], Seyhmus Ari[e], Nazim Ekin[f]

[a]*Department of Internal Medicine, Government Hospital, Silvan, Diyarbakir, Turkey*
[b]*Department of Medical Biology and Genetics, Medical School of Harran University, Sanlıurfa, Turkey*
[c]*Department of Obstetrics and Gynecology, Family Medical Center, Diyarbakir, Turkey*
[d]*Department of Internal Medicine, Damla Hospital, Elazıg, Turkey*
[e]*Department of Ophthalmology, Medical School of Dicle University, Diyarbakır, Turkey*
[f]*Department of Internal Medicine, Medical School of Dicle University, Diyarbakır, Turkey*

Abstract: Tuberous sclerosis complex (TSC) is an autosomal dominant syndrome or in sporadic form characterized by hamartamatous lesions in multiple organs. It affects several sites such as skin, kidney, lung, heart, central nervous system and liver in diferent stages of disease. TSC is caused by mutations on either chromosome 9 (*9q34, the TSC1 gene*) or chromosome 16 (*16p13, TSC2 gene*). TSC1 and TSC2 genes encode proteins called tuberin and hamartin; respectively. Although the pathogenetic mechanism is exactly unknown, a possible mechanism is a GTPase-activating protein against Rheb (Ras homolog enriched in brain), which regulates mTOR (mammalian target of rapamycin) signaling. The mammalian target of rapamycin (mTOR), is a serine-threonine kinase that increases cell proliferation and growth. We aimed to review the clinical manifestations and their predictive role on the course of disease.

Key words: Tuberous Sclerosis, autosomal dominant

1. Introduction

Tuberous sclerosis complex (TSC), also known as Bourneville–Pringle disease, is an autosomal dominant disorder with equal gender incidence and variable expression (1). Overall incidence of TSC is approximately 1/6000 however varies between 1/10000 and 1/100000 (1,2). TSC is first described in depth by Bourneville in 1880 and in 1908, Vogt proposed a triad (facial angiofibromas, mental retardation and intractable epilepsy) typical for TSC (3,4) (Figure 1).

*Correspondence: Ahmet Engin ATAY
Gevran Cad. Yucel Apt. No:12
Diyarbakir, Turkey
Gsm: +90532 6536736
E-mail: aeatay@hotmail.com
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However less than 40% of patients with TSC have all three features (5) Diagnostic criterias for TSC were recently established at the Tuberous Sclerosis Complex Consensus Conference in 1998 (Table 1) (6).

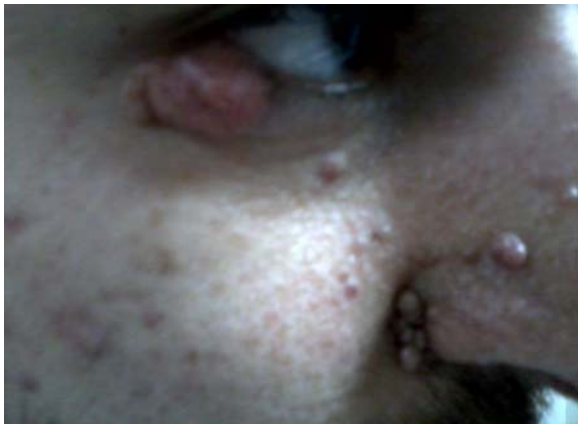

Fig. 1. Characteristical facial angiofibromas (with permission of M.D.)

Table 1. Major and minor diagnostic criterias for Tuberous Sclerosis Complex (TSC)

Major Criterias		Minor Criterias	
-facial angiofibroma	- subependymal nodule	-multiple pits in dental enamel	- bone cysts
-ungual fibroma	- retinal hamartoma	-hamartomatous rectal polyps	- gingival fibromas
-shagreen patch	-cardiac rhabdomyoma	-cerebral white- matter radial migration lines	
-hypomelanotic macule	-lymphangiomyomatosis	-retinal acromic patch,	
-cortical tuber	-renal angiomyolipoma	-confetti skin lesions	
-subependymal giant-cell tumor		-multiple renal cysts	

2 major or 1 major plus 2 minor features are required for definite diagnosis, 1 major and 1 minor feature are required for probable diagnosis

2. Molecular Analysis

Molecular genetic studies have defined at least two loci for TSC. TSC-1 gene; localized on the long arm of chromosome 9 (9q34) encodes a protein, called hamartin. In TSC-2, the gene abnormalities are on chromosome 16p13 and encodes a guanosine triphosphatase-activating protein called tuberin. Spesific function of the TSC gene products is not entirely known however they regulate the integration of cellular sensory input, such as growth factors, genomic integrity, cellular energy supply, and growth substrate availability (7). Tuberin and hamartin are considered to act as tumor suppressors by forming a complex that regulates cellular proliferation (8). The mammalian target of rapamycin (mTOR) is a controller of cell growth and proliferation and TSC genes supress mTOR (9). Fifteen to 20% of patients with TSC have no identifiable mutations and generally have milder clinical disease such as lower incidence of mental retardation, seizures, and dermatologie signs (7-10).

3. Central Nervous System (CNS)

Seizure is the most common manifestation however mental retardation, epilepsy, learning difficulties, behavioral problems, autism, and obstructive hydrocephaly are also frequently seen (11). These findings are approximately seen in 80% of patients (12). Twenty to 30 percent of patients with TSC experience infantile spasms characterized by mental retardation and a poor neurologic prognosis and, well responds to vigabatrin; an inhibitor of γ-aminobutyric acid transaminase, (13) Subependymal giant-cell tumor (SGCT) leading to obstruction of cerebrospinal fluid flow and hydrocephalus is seen in 10% of patients. Brain lesions in TSC include cortical tubers, subependymal nodules and subependymal giant cell astrocytomas (SGCA) with variable appearance on magnetic resonance imaging (MRI) in different age groups (14,15) (Figure 2). The incidence of cortical and subcortical tubers may be as high as 90% and may be seen as earlier as 20th week of gestation on MRI examination (16-18). They usually located in supratentorial area however vary in location as well as size and number (19). Cortical tubers cause epilepsy, intellectual disability, and autism in 85% of patients (17-20). The bigger size and large number of tubers are associated with poor cognitive outcome and drug-resistant epilepsy with early onset (21,22). Patients with TSC had significantly worse scores on attention/concentration, behaviour/ disorganization, academic and emotional behaviours (23). Boer et al. (14) indicate a persistent and complex activation of inflammatory pathways in cortical tubers and SGCT. Tubers and infantile spasms explain less than 50% of the IQ variance among patients with TSC. Crino et al. (24) recommend annual MRI of the brain until patients are at least 21 years of age and then every 2 to 3 years.

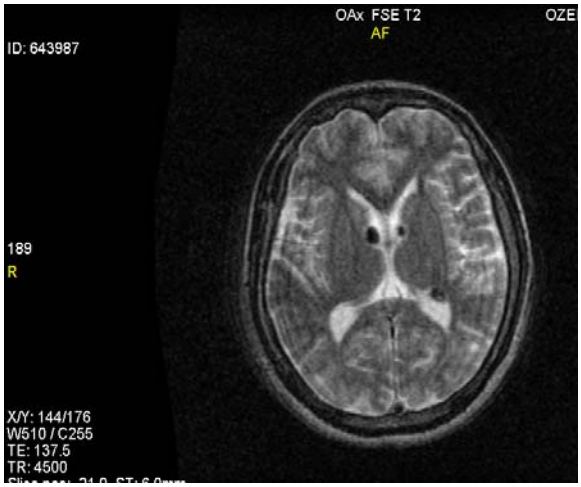

Fig. 2. Cranial hamartomas in supratentorial area are shown (with permission E.M)

4. Cutaneous Involvement

Ninety percent of patients with TSC have one or more cutaneous lesions (25). Hypomelanic macules, facial angiofibromas, fibrotic plaques, periungual fibromas are most common features of skin involvement (26). Hypopigmented macules are the first ones to develop and the most prevalant (27). These lesions are observed mainly on trunk and limbs before puberty or even at birth (28). They usually increase in size and number in earlier ages however tend to become smaller and pigmented in latter ages. Angiofibromas; consisting of vascular and interstitial cells, usually observed in late infancy (29). Usual location for angiofibromas are facial areas, especially proliferate to involve the nose and cheeks. Periungual fibromas; also called Koenen Tumor, are common in females and generally involve nails of toes (30). They tend to increase in size and become larger with age. Forehead fibrotic plaques are skin coloured or brown lesions. Fibrotic plaques are infrequent however considered pathognomic for TSC (27). Treatment of these lesions vary from removal with surgical blade to dermoabrasion, CO_2 or argon laser and radiofrequency ablation (31). Also topical rapamycin seems to be an theraupeutic choice for facial angiofibromas (25). Although cutaneous lesions of TSC do not have life-threating aspect, they pose a serious cosmotical problem which adversely affect the social life of patients with TSC.

5. Renal Involvement

Vast majority of patients with TSC born with normal kidneys however renal complications develop inevitably (1). The incidence of angiomyolipoma (AML), cysts and renal cell carcinoma (RCC) are 85.4%, 44.8%, and 4.2%; respectively (32) (Figure 3,4). The frequency and number of renal lesions significantly correlated with age (16). Renal injury is attributed to rhabdomyolysis due to seizures or anticonvulsant therapy induced renal celular injury (33). Angiomyolipomas exhibit immunoreactivity to HMB-45, a melanocytic marker, and actin, a smooth muscle marker. These markers are helpful in differentiating atypical AMLs from RCC; as well as growth rate introduced by Patel et al (34). Large AMLs (> 5 mm) are under risk to develop aneurysms that may rupture and bleed excessively (35). AMLs may invade to adjacent normal renal tissue and deteriotes renal functions. Renal cystic disease is significantly associated with hypertension which well responds to angiotensin converting enzym inhibitors or angiotensin receptor blockers.

Patients with 16p13 (TSC-2) mutation is frequently associated with severe renal involvement than 9q34 (TSC-1) mutation and; AMLs or cysts are more common in this subgroup (32). The incidence of RCC in patients with TSC is similar to that of general population however mean age at the onset of RCC is significantly younger in patients with TSC (35).

Ultrasound scanning to detect renal complications of TSC is recommended in every 1-3 years and MRI study is beneficial in the suspicion of RCC (36,37).

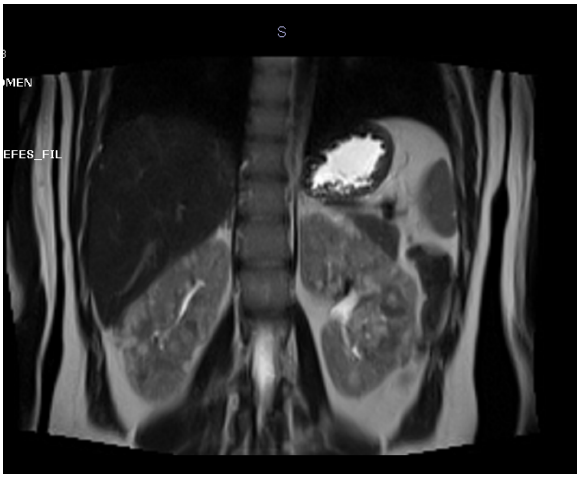

Fig. 3. Abdominal tomographic examination indicates the renal angiomyolipomas (with permission of M.D)

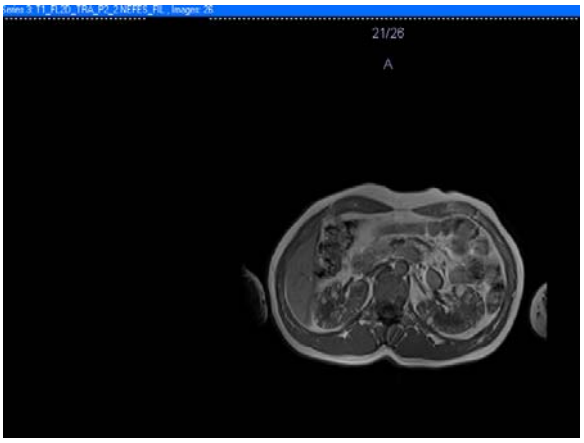

Fig. 4. Renal angiomyolipomas in axial tomographic examination are shown.

6. Respiratory System

Lymphangiomyomatosis (LAM) is a rare cystic lung disease also called Iymphangioleiomyomatosis, affecting women almost exclusively with an incidence of 26 to

39% in patients with TSC (38). Most of affected women are in childbearing age and asymptomatic (39). It is the 3rd most common cause of death after renal and brain lesions (9). TSC related LAM is 5 to 10 fold more common than sporadic LAM (39). LAM is characterized by cystic destruction of lung parenchyma and loss of respiratory function due to progressive infiltration of smooth muscle-like cells (38). AML usually predates the onset of pulmonary disease (37). Clinical presentation of LAM is exertional dyspnea, reccurent pneumothorax and less frequently cough, chest pain and hemoptysia. Lung cysts may be visualized in only one-third of patients on radiographic examination in the early stages of TSC however pleural effusion, pneunothorax and reticulonodular infiltrates may become evident in the latter stages (16). In contrast, high-resolution computed tomography reflects abnormalities such as several thin-walled cysts in patients with normal radiographic examination. Differential diagnosis of LAM includes leiomyoma, emphysema and histiocytosis (38). Non-malignant metastases of renal AML cells and migration of TSC-altered cells are two hypothesis to define the development of LAM (40). Gonadtropin-releasing hormone agonists and rapamycin are promising agents in the treatment of LAM (34). LAM almost inevitably progress to respiratory failure and cor pulmonale with a 5-year survival rate ranging from 50 to 97% (40). Computed tomography of lung is recommended in every 6-12 months for symptomatic patients (41).

7. Cardiovascular System

Cardiac rhabdomyomas are benign hamartomas and most common cardiac tumors in infants with TSC (50 to 70%) (12,42). Rhabdomyomas usually have favorable prognosis and silent course however rarely cause non-immune fetal hydrops, arrhythmia, or death (13). Parames et al. (42) suggest to perform echocardiography at any age whenever cardiac symptoms occur.

8. Liver Involvement

Similar to renal angiomyolipomas, AMLs may also observed in liver. Twenty three to 45 percent of patients with TSC have AMLs however hepatic AMLs are asymptomatic and grow more slowly than renal AMLs which does not lead to death (4).

9. Follow-up

Appropriate diagnosis and determining the involvement areas are first steps in the management of TSC. Dermatologic examination to observe skin lesions, fundoscopic examination to identify retinal hamartomas and echocardiographic examination to detect cardiac rhabdomyomas are initially recommended. However evaluation of central nervous system and renal involvement are complicated and differential diagnosis of lesions at these sites require detailed examination and closer follow-up. MRI or CT of the brain is indicated to identify tubers and subependymal giant-cell tumors (12). In the presence of AMLs or cysts, it is recommend to follow-up by ultrasound annually thereafter (35). In the suspicion of RCC, MRI for re-evaluation and follow-up imaging at six-month intervals is recommended (36). Tomographic examination of lungs is warranted to determine the presence of subclinical LAM. Once the diagnosis of LAM is confirmed, annually pulmonary function tests is crucial to determine the progress to respiratory failure

Monitoring the growth of lesions and indicating the probable development of complications are achieved by long-term and regular follow-up. The growth of angiomyolipomas or subependymal giant-cell tumors requires continued vigilance. Family members of patients with TSC require genetic counselling to determine the possible presence of TSC-related mutations (12).

10. Treatment

Rapamycin; an inhibitor of mTOR, has been identified as a potential therapeutic agent and normalize the upregulated pathway in TSC (4). It was indicated that rapamycin is beneficial in controlling the growth of angiomyolipomas and reducing the incidence of TSC-related tumors (43). Rapamycin therapy induces the regression of astrocytomas, angiomyolipomas and lymphangiomyomatosis (44, 45). Ljunberg et al. (43) demonstrated that administration of rapamycin have additional antiepileptic effect. Bissler et al. (46) stated that the mean angiomyolipoma volume decreased significantly subsequent to rapamycin therapy for 12 months. Also they observed significant increase in mean forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). However Wienecke et al. (47) emphasized to regrowth of angiomyolipomas after discontinution of rapamycin therapy.

11. Conclusion

Although TSC was firstly described more than a century ago, establishment of diagnostic

criterias is relatively recent. Each involvement site of the disorder requires specialized monitoring procedure because some have static and others have silent but progressive course. However follow-up procedure should be individualized. Regular follow-up has vital effect to detect probable complications and initiate appropriate therapy. The relationship between the complications of TSC still require further clinical and molecular evaluation.

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