TUBEROUS SCLEROSIS AND KIDNEY FAILURE - A CASE REPORT

Boban Labovic[1], Violeta Rabrenovic[2]*, Milorad Rabrenovic[3], Milica Petrovic[2], Dragan Dulovic[4], Aleksandar Rakonjac[4], Dejan Pilcevic[2], Marijana Petrovic[2]* and Jelena Tadic[2]

[1]Military Medical Academy, Clinic of Neurology, Belgrade, Serbia
[2]Military Medical Academy, Clinic of Nephrology, Belgrade, Serbia
[3]Military Medical Academy, Center for Hyperbaric Medicine, Belgrade, Serbia
[4]Military Medical Academy, Institute of Radiology, Belgrade, Serbia
**University of Defense, Military Medical Academy, Faculty of Medicine, Belgrade, Serbia*

Labović Boban i Rabrenović Violeta contribute equally to the work

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Corresponding author:

Violeta Rabrenovic

Clinic of Nephrology, Military Medical Academy
Crnotravska 17, Belgrade, Serbia

Phone: +381 64 846 7172
E-mail: violettarab@gmail.com

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ABSTRACT

Tuberous sclerosis (TS) is a rare systemic autosomal-dominant genetic disease in which multiple hamartomatous lesions occur in many organs and tissues. Kidney involvement of TS usually includes angiomyolipomas, cysts, rarely kidney tumors, but there is not much description of other kidney involvement (proteinuria, hematuria, advanced kidney failure). We present a patient with preterminal renal failure who is diagnosed with tuberous sclerosis. A 52-year-old female was admitted to the hospital, due to decreased kidney function with worsening of the general condition and crises of consciousness. During the examination, cutaneous lesions -facial angiofibrolipomas were noticed, the patient was dehydrated and pale. Laboratory analyzes showed elevated parameters of nonspecific inflammation, anemic syndrome, azotemia (Cr 578umol / l, urea 50.1mmol / l, CKD e GFR 10 ml / min / 73m^2), leukocyturia, microerythrocyturia, proteinuria 1.5 g / 24h. MSCT of the abdomen indicated hemangiomas of the liver, enlarged kidneys with several hypodense and hyperdense changes - angiomyolipomas. Due to the crisis of consciousness, MSCT of the head was performed, on which cysts and calcifications of the brain were observed. During the treatment, there was a confusing state, agitation, and epilepsy seizure. MRI brain showed multi locular brain cysts with ependymal and subependymal calcified nodules in the lateral ventricles.The applied treatment resulted in a partial recovery of kidney function (CKDeGFR 17 mil / min / 1.73 m2, and further approach in the monitoring and treatment of this patient was multidisciplinary. Chronic renal failure of 4 stages was maintained for a further six-month follow-up. We underline the importance of a multidisciplinary approach in the treatment of patients, bearing in mind that, as in our patient, a rare genetic disease - tuberous sclerosis can be manifested by kidney failure of preterminal rank.

***Keywords**: Tuberous sclerosis, angiomyolipomas, renal failure.*

INTRODUCTION

Tuberous sclerosis (TS), or tuberous sclerosis complex as it is also called, is a multisystem genetic disease in which multiple tumors are formed in many organs and tissues (brain, skin, kidneys, liver, heart, lungs, eyes). The frequency of this disease is 1: 6000-1: 10/000 newborns, in the general population 1: 20.000 (1, 2). The underlying disorder is thought to be a mutation in the TSC1 gene on chromosome 9 or the TSC2 gene on chromosome 16, which encode hamartin and tuberin and represent tumor suppressor genes (3,4). Renal lesions are described in a large number of cases (57.5%) and manifest as angiomyolipoma (85.4%), cyst (44.8%), rarely renal cell carcinoma (4.2%), however, a small number of authors describe the occurrence of renal failure of preterminal rank and proteinuria (5, 6).

CASE REPORT

Due to the worsening of the general condition with the development of renal failure and previous data on the disorder of consciousness, a 52-year-old patient was admitted to the Nephrology Clinic. During the examination, cutaneous lesions in the form of facial angiofibrolipomas were noticed and the patient was dehydrated and pale. The other finding was normal. In laboratory analyzes with elevated parameters of nonspecific inflammation (ESR 115 mm/h, CRP 41.45mg/l, anemic syndrome (Hb 79g / l), azotemia (Cre. 578umol / l, urea 50.1mmol / l, hyperkalemia 5.3, CKD and GFR 10 mil/min/73m^2), were observed in the urine leukocyturia, microerythrocyturia, proteinuria 1.5g / 24h. Due to the crisis of consciousness, the patient was examined by a neurologist, and MSCT of the head was performed, on which cysts and calcifications of the brain were observed. Abdominal ultrasound showed hemangiomas of the liver, renal cysts (up to 21 mm) with numerous lipomatous changes. MSCT of the abdomen indicated hemangiomas of the liver, kidneys about 16.5 cm in diameter, irregular structure without corticomedullary border with multiple hypodense and hyperdense changes (Figure 1). During the treatment, confusion, agitation, and then epilepsy seizures were treated in consultation with a neurologist and psychiatrist. Neurological examinations, EEG, which was within physiological limits, and MR of the head having confirmed multilocular cystic changes in the brain with ependymal and subependymal calcified nodules in the lateral ventricles (Figures 2 and 3). Examination by an ophthalmologist revealed a whitish irregular change in the fundus which may correspond to a typical change by tuberous sclerosis. The diagnosis of tuberous sclerosis was made based on typical brain changes, skin changes of the face, renal lesions (amgiomyolipomas and cysts). The applied rehydration, diuretic antibiotic, and other symptomatic therapy resulted in partial recovery of kidney function (Cre 305 umol / l) CKDeGFR 17 mil/min / 1.73 m^2, and a further approach in monitoring and treatment of this patient was multidisciplinary.

Figure 1. CT image demonstrates irregular kidney structure without corticomedullary border with multiple hypodense and hyperdense changes - angiomyolipomas

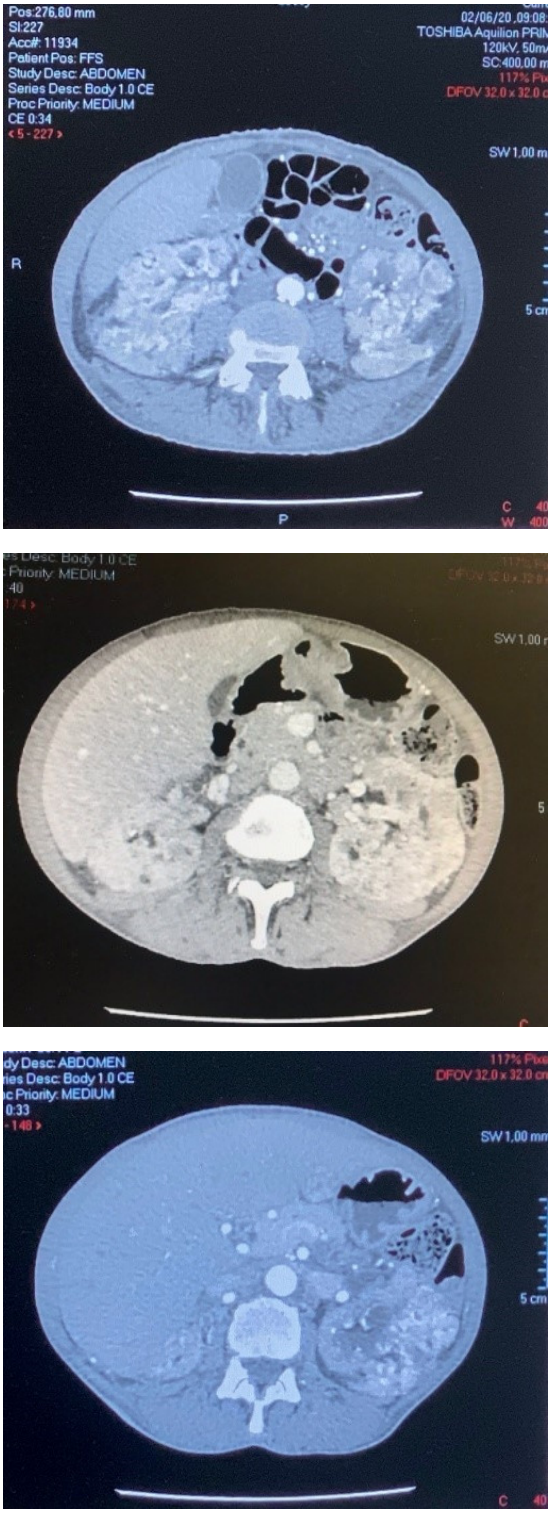


Figure 2. MR of the head having confirmed multilocular cystic changes in the brain with ependymal and subependymal calcified nodules in the lateral ventricles



DISCUSSION

Tuberous sclerosis is a genetic disease that usually manifests itself in the pediatric population, most often with disorders at the central nervous system (1-5). This is why these patients are usually diagnosed by neuropediatricians (53%), neurologists (17%), less often by other specialties among which nephrologists are represented in 4% of cases (6).

Bearing in mind that TS is characterized by disorders of many organs and systems for easier diagnosis, the recommendations of the International Tuberous Sclerosis Complex Consensus Group were adopted in 2012. when the recommendation for genetic tests was introduced (7). Diagnostic criteria are genetic and clinical, which are divided into major (hypopigmented macules ≥3, at least 5 mm in diameter, angiofibromas ≥3 or fibrous plaques, nail fibromas ≥2, shagreen skin, multiple retinal hamartomas, cortical dysplasias) subependymal astrocytomas of giant cells, cardiac rhabdomyomas, lymph angioleomiomas, angiomyolipomas ≥2. And in minor criteria: skin lesions "confetti", tooth erosions> 3, intraoral fibroids ≥2, retinal achromatic changes, multiple kidney cysts, non-renal hamartomas (7). Our patient had cortical tubers, subependymal nodules, renal angiomyolipomas, multiple renal cysts, and facial skin changes - multiple angiofibromas,

According to a large study that included 2093 patients with TS who ranged in age from 0-71 years (average age was 13 years), the most common manifestations were cortical tubers (82.2%) subependymal nodules (78.2%) hypomelanotic macules 66.8%, facial angiofibromas (57.3%), renal angiomyolipomas (47.2%) while other manifestations had a lower frequency (6).

Changes in the brain, skin, and kidneys dominated also in our case report, and in addition to these, changes were observed in the liver (hemangiomas) and the fundus. Epileptic seizures also occurred on a couple of occasions, with the control EEG being within the reference range.

According to the literature, the frequency of epileptic seizures in patients with TS is described in about 80% of cases, but this frequency is lower in the age group over 50 years (8,9). In a Japanese study of 166 patients with TS, 80% of patients were younger than 50 years, and in the group older than 50 years the most common brain lesions were subependymal nodules and autism, refractory epilepsy and subependymal astrocytomas were not observed (9). The frequency of epilepsy in general, refractory epilepsy, and intellectual disabilities in this study decrease with the age of the patients, i.e. they are more pronounced at a younger age, somewhat more common in male (9).

In addition to brain lesions, kidney lesions are often described within TS. Most studies have described the presence of kidney angiomyolipomas and cysts, a significantly lower percentage of cancers. Other kidney disorders, especially the progression of kidney failure, pathological urine sediment

(proteinuria, erythrocyturia) and arterial hypertension are described very rarely and are very serious complications whose early detection and treatment would be very important, especially in children (8). A study by Janssens et al, described the occurrence of arterial hypertension in 32% of cases, proteinuria in 16%, hyperfiltration in 25%, and terminal kidney failure in 7.5% (8). In our patient, kidney failure was initially observed (preterminal grade GFR 10-17mil / min / 1.73m2), and that was the reason she was admitted to the Nephrology Clinic. Among other disorders in the laboratory analysis, a pathological finding of urine in the form of proteinuria 1.5g / 24h and microerythrocyturia was observed. A favorable response to the applied treatment was manifested in a slight recovery of kidney function (Cre 305 umol / l , CKDeGFR 17 mil/min / 1.73 m2) , which was then maintained in a further six-month follow-up.

A study by Malaga-Dieguez et al, indicated that kidney disorders in the form of arterial hypertension (36% of cases) and lower GFR in 20% of patients were more pronounced in children and young adolescents with the TSC2 gene mutation (10). Similar data are confirmed by the Tuberous Sclerosis registry, which describes a statistically significantly higher prevalence of angiomyolipomas in TSC2 compared to patients with TSC1 mutation (59.2%; 33.3%) as well as a higher prevalence in females (11). The prevalence of multiple renal cysts is also linked to the TSC2 gene mutation and the ratio is 33.4% to 13.7% in the TSC1 mutation (11). In most patients, angiomyolipomas were asymptomatic (82%), and pain (6.1%), hematuria (5.0%), microscopic hematuria (4.3%), arterial hypertension (5.7%), and decreased kidney function were reported rarely (9%) (11). Our patient had bilateral angiomyoliposis and multiple renal cysts that were about 21 mm in size, with microerythrocyturia, proteinuria, and arterial hypertension, and kidney failure.

CONCLUSION

We underline the importance of a multidisciplinary approach in the treatment of patients, bearing in mind that, as in our patient, a rare genetic disease - tuberous sclerosis can be manifested by the kidney failure of preterminal rank.

REFERENCES

1. Mowrey K, Koenig MK, Szabo CA, Samuels J, Mulligan S, Pearson DA, Northrup H.wo different genetic etiologies for tuberous sclerosis complex (TSC) in a single family.Mol Genet Genomic Med 2020; 8(7) :e1296.
2. Morrison PJ, Shepherd CH, Stewart FJ, Nevin NC. Prevalence of tuberos sclerosis in UK. Lancet 1998; 352:318-9.
3. Mowrey K, Koenig MK, Szabo CA, Samuels J, Mulligan S, Pearson DA, Northrup H. Two different genetic etiologies for tuberous sclerosis complex (TSC) in a single family. Mol Genet Genomic Med 2020; l;8(7):e1296.
4. European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell 1993;75(7): 1305-15.
5. Rakowski SK, Winterkorn EB, Paul E, Steele DJR, Halpern EF, Thiele EA. Renal manifestations of tuberous sclerosis complex: Incidence, prognosis, and predictive factors. Kidney Int 2006;70(10):1777-82.
6. Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R, Cottin V, Curatolo P, Dahlin M, de Vries PJ, Feucht M, Fladrowski C, Gislimberti G, Hertzberg C, Jozwiak S, Lawson JA, Macaya A, Nabbout R, O'Callaghan F, Benedik MP, Qin J, Marques R, Sander V, Sauter M, Takahashi Y, Touraine R, Youroukos S, Zonnenberg B, Jansen AC; TOSCA consortium and TOSCA investigators. TuberOusSClerosis registry to increase disease Awareness (TOSCA) - baseline data on 2093 patients. Orphanet J Rare Dis 2017 ;12(1):2.
7. Northrup H, Krueger DA. International Tuberous Sclerosis Complex Consensus Group . Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49 (4):243-54.
8. Janssens P, Van Hoeve K, De Waele L, De Rechter S, Claes KJ, Van de Perre E, et al. Renal progression factors in young patients with tuberous sclerosis complex: a retrospective cohort study. Pediatric Nephrology 2018; 33 (11): 2085–93.
9. Wataya-Kaneda M, Tanaka M, Hamasaki T, Katayama I. Trends in the prevalence of tuberous sclerosis complex manifestations: an epidemiological study of 166 Japanese patients. PLoS One 2013; 8(5):e63910.
10. Malaga-Dieguez L, Spencer R, Pehrson LJ, Vento S, Menzer K, Devinsky O, Trachtman H. Early manifestations of renal disease in patients with tuberous sclerosis complex. Int J Nephrol Renovasc Dis2017;10:91-95.
11. Kingswood JC, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, Dahlin M, D' Amato L, d'Augères GB, de Vries PJ, Ferreira JC, Feucht M, Fladrowski C, Hertzberg C, Jozwiak S, Lawson JA, Macaya A, Marques R, Nabbout R, O'Callaghan F, Qin J, Sander V, Sauter M, Shah S, Takahashi Y, Touraine R, Youroukos S, Zonnenberg B, Jansen AC. Renal angiomyolipoma in patients with tuberous sclerosis complex: findings from the TuberOus Sclerosis registry to increase disease Awareness. Nephrol Dial Transplant 2019; 34 (3) : 502-8.