Klinične značilnosti in ledvična prizadetost bolnikov s tuberozno sklerozo v UKC Maribor

Clinical manifestations of renal disease in patients with tuberous sclerosis complex at University Medical Centre Maribor

Avtor / Author

Sonja Golob Jančič[1,2], Peter Gradišnik[1,2], Andreja Osterc Koprivšek[1,2], Albin Gačnik[3], Nataša Marčun Varda[1,2]

Ustanova / Institute

[1]Univerzitetni klinični center Maribor, Klinika za pediatrijo, Maribor, Slovenija; [2]Univerza v Mariboru, Medicinska fakulteta, Katedra za pediatrijo, Maribor, Slovenija; [3]Univerzitetni klinični center Maribor, Oddelek za nevrologijo, Maribor, Slovenija;

[1]University Medical Centre Maribor, Department of Paediatrics, Maribor, Slovenia; [2]University of Maribor, Faculty of Medicine, Department of Paediatrics, Maribor, Slovenia; [3]University Medical Centre Maribor, Department of neurologic diseases, Maribor, Slovenia;

Ključne besede:
tuberozna skleroza, ledvice, angiomiolipomi, ciste ledvic

Key words:
tuberous sclerosis, kidney, angiomyolipomas, kidney cysts

Članek prispel / Received
24. 9. 2020
Članek sprejet / Accepted
17. 5. 2022

Izvleček

Namen: *Tuberozna skleroza je avtosomno dominantni nevrokutani sindrom, ki prizadene približno 1/6.000–10.000 ljudi. Klinična slika se s starostjo spreminja, saj so pri različnih starostih prisotni različni klinični znaki. Ledvična prizadetost je prisotna pri 48–80 %, in sicer v obliki angiomiolipomov, ledvičnih cist ali ledvičnega karcinoma. Namen naše raziskave je bil pregled kliničnih manifestacij pri bolnikih s tuberozno sklerozo, obravnavanih znotraj Univerzitetnega kliničnega centra (UKC) Maribor v zadnjih desetih letih, in opredelitev števila tistih, ki imajo ledvično prizadetost.*

Metode: *Pregledali smo kartoteke bolnikov, ki so vodeni v UKC Maribor z diagnozo tuberozna skleroza (MKB – Q85.1). Iz medicinskih zapisov smo razbrali njihove antropometrične meritve, starost ob diagnozi, laboratorijske*

Abstract

Purpose: *Tuberous sclerosis is an autosomal dominant neurocutaneous syndrome that affects approximately 1/6000–10,000 people. The clinical presentation varies and is dependent on patient age. Renal manifestations, most often angiomyolipomas, cystic renal disease, and renal carcinoma, are present in 48%–80% of patients with tuberous sclerosis. The aim of our study was to determine the clinical characteristics and extent of renal impairment in patients with tuberous sclerosis who were followed at the University Medical Centre Maribor.*

Methods: *We reviewed the medical records of patients with tuberous sclerosis (ICD Q85.1) who received care at the University Medical Centre Maribor. The medical history, clinical characteristics, laboratory results, imaging studies, and current treatment were highlighted. In*

https://doi.org/10.18690/actabiomed.229, CC BY 4.0

Naslov za dopisovanje / Correspondence
Asist. Sonja Golob Jančič, dr. med.
Klinika za pediatrijo Univerzitetni klinični center Maribor
Ljubljanska ulica 5, 2000 Maribor
Telefon: +386 23212176
Fax: +386 23312393
E-pošta: sonja.golobjancic@ukc-mb.si

izvide, slikovne preiskave in morebitne rezultate genetskega testiranja ter trenutni režim zdravljenja.

Rezultati: *V naši kohorti je 13 bolnikov s tuberozno sklerozo, starih od 7 do 71 let, mediana starost je 16 let, povprečje 25,2 (14,6; 35,9). 92 % (12) ima kožno simptomatiko, ledvična prizadetost je prisotna pri 60 % naših bolnikov. 46 % ima angiomiolipome, 23 % ledvične ciste. Pomembnejše prizadetosti ledvične funkcije nimajo. Sistemsko terapijo z everolimusom prejemata dva bolnika, dva imata predpisan topični everolimus za kožne lezije. Genetsko testiranje je bilo opravljeno pri 7 bolnikih, pri 5 je bilo pozitivno.*

Zaključek: *Rezultati potrjujejo pogosto prizadetost ledvic pri bolnikih s tuberozno sklerozo v naši kohorti, primerljivo z literaturo. Ker je kohorta sestavljena predvsem iz pediatričnih bolnikov, je ledvična funkcija dobra, zdravljenje pa redko nujno. Redno spremljanje in multidisciplinarna obravnava sta ključna za dolgoročno blaginjo bolnikov.*

addition, the results of genetic analysis were reviewed.

Results: *Our cohort consisted of 13 patients with tuberous sclerosis (age range, 7–71 years; median age, 16 years; average age, 25.2 [14.6-35.9] years). Cutaneous pathology was noted in 12 (92%) patients. Renal manifestations were present in 6 (60%) of the patients; 46% had angiomyolipomas and 23% had renal cysts. No significant renal function impairment was demonstrated. Two patients were treated with systemic everolimus and two patients were treated with topical everolimus for skin lesions. Genetic analysis was performed in seven patients, five of whom were positive and two of whom were negative.*

Conclusion: *In agreement with literature reports, our results confirmed that renal impairment frequently occurs in tuberous sclerosis patients; however, because most of our patients were children, renal function was stable and treatment was rarely needed. Regular screening and follow-up evaluations in the multidisciplinary team are essential for good long-term outcomes.*

INTRODUCTION

Tuberous sclerosis complex (TSC) is a hereditary neurocutaneous syndrome that affects 1/6000–10,000 people. TSC is an autosomal dominant trait and often presents de novo (1). In 85% of patients, TSC is caused by mutations in the TSC1 or TSC2 gene. Currently, TSC–associated renal disease pathogenesis dogma holds that a somatic mutation of the functional copy at the affected TSC locus results in clonal proliferation of cells lacking TSC–mediated regulation of the mammalian target of rapamycin complex 1 (mTORC1) pathway (2). Major features of the disease include tumours of the brain, skin, heart, lungs, and kidneys, seizures, and TSC-associated neuropsychiatric disorders (TANDs), which include autism spectrum disorder and cognitive disability (3). There is no strict genotype-phenotype correlation; however, individuals with TSC2 mutations have more severe disease symptoms (4). Penetrance is approximately 95%, but clinical manifestations vary from minor-to-severe disease and are age-dependent. The Tuberous Sclerosis Complex Consensus Conference (TSCCC) published diagnostic criteria in 1998, which were revised in 2012, followed by publishing surveillance protocols and recommendations for diagnostic evaluation of affected individuals (5,6). The diagnosis of TSC relies on the presence of defined clinical features, each of which has a distinct timing

of onset. Renal manifestations are the second most significant cause of morbidity and mortality in patients with TSC, and include renal cysts, angiomyolipomas, fat-poor lesions, and malignant tumours (7). For the purpose of comprehensive surveillance, we have a Tuberous Sclerosis Centre in our University Medical Centre, the aim of which is to meet twice annually and discuss patient status and follow-up evaluations.

The aim of this study was to define the clinical characteristics of our cohort of patients with tuberous sclerosis and the associated renal impairment.

METHODS

A retrospective analysis of patients with tuberous sclerosis complex (ICD – Q85.1) was done by reviewing patient files. Our search included 13 patients with TSC who were under medical care in the Departments of Paediatrics and Neurologic Diseases at the University Medical Centre Maribor for the last 10 years. The history, clinical characteristics, including renal manifestations, laboratory tests, and treatments were highlighted. In addition, the results of genetic analysis were reviewed. All patients agreed to anonymized data collection and further analysis.

RESULTS

Our cohort of patients consisted of paediatric and adult patients (age range, 7-71 years; median age, 16 years; average age, 25.2 years [95% CI, 14.6-35.9]). Cutaneous manifestations in the form of angiofibromas, fibrous cephalic plaques, or hypomelanotic macules were present in 12 of 13 patients (92.2%). Eleven of 13 patients (84.6%) had neurologic symptoms or psychiatric disorders. Renal manifestations were present in 6 of 10 patients (60%), but three patients had missing ultrasound data. One patient had chronic kidney disease (CKD [stage II]); none of the other 12 patients had renal disease. Eye and heart abnormalities in the form of multiple retinal nodular hamartomas and cardiac rhabdomyomas were diagnosed in 3 of 10 (30%) and 3 of 9 patients (33%), respectively. Systemic everolimus was used in two patients for angiomyolipomas and astrocytomas (one patient each); embolization was performed due to renal haemorrhage in the patient with angiomyolipomas. Topical everolimus was prescribed in two patients for skin lesions. Genetic analysis was performed in seven patients, and was positive in five and negative in two patients (Table 1).

This was a retrospective study of medical records, therefore missing data was the main shortcoming of this study. In addition, because TSC is a rare disease, the sample size was small. Not all data are included in the medical records at our centre, such as dental health records.

DISCUSSION

The diagnosis of TSC is established based on a thorough clinical examination and is supported by selective organ imaging and laboratory testing, including a genetic evaluation (6). Our patient cohort was most often affected by skin manifestations, followed by neurologic manifestations, which is consistent with the literature in which 80%–90% of patients have skin and neurological involvement (8). Indeed, skin and neurologic symptoms are the predominant clinical features and are therefore essential for diagnosis along with a complete medical history and thorough clinical examination.

Renal manifestations in TSC occur with a high frequency and a wide range of severity (7). Estimated rates of involvement range from 48%-80% (9,10) with at least two large studies reporting an incidence between 60% and 75% (11,12). Renal manifestations were present in two-thirds of our patients, with slightly fewer angiomyolipomas and renal cysts. A strong association between age, angiomyolipoma size, and CKD has been reported; patients with a higher CKD stage tend to be older and have more advanced angiomyolipomas (12). There were no patients who had undergone a nephrectomy or with end stage renal disease in our cohort, but the median age was low and paediatric patients were predominant.

The same explanation accounted for the lack of patients with lymphangioleiomyomatosis in our cohort because

Table 1. *Patient characteristics and clinical manifestations of tuberous sclerosis in our patients; ESRD - end stage renal disease, EEG - electroencefalogram.*

Patient's characteristics	Results
Male / Female [Number, %]	6/7, 46.2/53.8
Age (median/ average /min/max/) [years]	16/25.2/7/71
Age when patient is diagnosed with TS (median/min/max) [years]	2 /0.08/16.1
Family history of TSC 1 yes/no [%]	23.1/76.9
Genetic verified disease positive/negative/not done [%]	38.5/15.4/46.1
Cutaneous manifestations	
Angiofibroma or fibrous cephalic plaques yes/no [%]	69.2/30.8
Hypomelanotic cutaneous macules. yes/no [%]	53.8/46.2
Confetti skin lesion yes/no [%]	0/100
Renal manifestations	
Renal angiomyolipoma yes/no/ no data [%]	46.1/30.8/23.1
Multiple renal cysts yes/no/ no data [%]	23.1/61.5/15.4
ESRD yes/no [%]	0/100
Nephrectomy yes/no [%]	0/100
Neurological manifestations	
Subependymal astrocytoma yes/no/ no data [%]	23.1/69.2/7.7
Subependymal nodules yes/no [%]	69.2/30.8
Epileptic seizures verified by EEG yes/no [%]	61.5/38.5
Cognitive disorder yes/no [%]	46.1/53.9
Psychiatric disorder yes/no [%]	30.7/69.3
Cardiac rhabdomyoma yes/no/ no data [%]	23.1/46.1/30.8
Lymphangioleiomyomatosis yes/no [%]	0/100
Multiple retinal nodular hamartomas yes/no/ no data [%]	23.1/53.8/23.1
Intraoral fibroma yes/no [%]	0/100
Nonrenal hamartomas yes/no/ no data [%]	23.1/69.2/7.7
Therapy	
Everolimus systemic/topical/no [%]	15.4/15.4/69.2
Antiepileptic therapy yes/no [%]	61.5/38.5
Psychiatric therapy yes/no [%]	15.4/84.6

Table 2. *Protocol for patient evaluation and follow–up in our University Medical Centre Maribor, summarized from (6)*

Procedure or investigation	Newly diagnosed	Surveillance	Comments
Genetic testing	✓	/	Offer genetic testing for family counselling or when TSC diagnosis is in question but cannot be clinically confirmed
MRI brain	✓	Obtain MRI of the brain every 1–3 yr in asymptomatic TSC patients younger than age 25 yr to monitor for new occurrence of SEGA	More frequently in big or symptomatic SEGA
Neuropsychiatric testing	✓	Evaluation for TAND at key developmental time points: infancy (0 –3 yr), preschool (3 –6 yr), pre –middle school (6 –9 yr), adolescence (12 –16 yr), early adulthood (18 –25 yr), and as needed thereafter	
EEG	✓	Obtain routine EEG in individuals with known or suspected seizure activity	Prolonged video EEG if needed
MRI of the abdomen	✓	Every 1 –3 yr, to assess for the progression of angiomyolipoma and renal cystic disease	Frequently in older than 11 yr or growing more than 2 cm/yr or >5 lesions
Kidney US	✓	Once a yr	When MRI of abdomen is not available
Hypertension screening	✓	Once a yr	
Renal function evaluation	✓	Once a yr	
Pulmonary function testing	/	Once a yr	
HRCT of the lungs	✓	If symptomatic	In all females 18 yr or older
Clinical dermatologic inspection	✓	Once a yr	
Panoramic radiographs	/	By age 7 yr, if not performed	
Echocardiogram	✓	Every 1 –3 yr in asymptomatic paediatric patients until regression of cardiac rhabdomyomas is documented	
ECG	✓	Every 3 –5 yr in asymptomatic patients of all ages to monitor for conduction defects	
Ophthalmologic evaluation	✓	Once a yr	

yr – year/s, SEGA - subependymal giant cell astrocytoma, TAND - TSC-associated neuropsychiatric disorders, MRI - magnetic resonance imaging, US - ultrasound, HRCT-high-resolution computed tomography, EEG - electroencephalograph, ECG - electrocardiogram

it is known to affect women > 18 years of age (13).

TAND is a new term that was proposed to describe the interrelated functional and clinical manifestations of brain dysfunction, which is common in patients with TSC, including aggressive behaviours, autism spectrum disorders, intellectual disabilities, psychiatric disorders, neuropsychological deficits, and school and occupational difficulties (14). Although our cohort was relatively young, nearly one-half of the patients already had cognitive or psychiatric manifestations of the disease and 15% were receiving psychiatric therapy. We do not have additional information on the type of disorders. According to the literature, the most common psychiatric disorders observed in association with TSC include neurodevelopmental disorders, such as autism spectrum disorders (25%–50%) and attention deficit hyperactivity disorder (ADHD; 30%–50%), as well as depressive and anxiety disorders [30%–60%] (14).

Nearly one-third of our patients were treated with everolimus (topical and systemic, two patients each) and two-thirds were receiving antiepileptic therapy. Most of the patients in our cohort did not meet the criteria for everolimus treatment, presumably due to their age, and epileptic seizures were mostly controlled with antiepileptic therapy.

Genetic testing was performed in greater than one-half of our patients, 15% of whom were negative despite meeting the diagnostic criteria for TSC, which is consistent with the literature (15). Because TSC has most often been diagnosed based on clinical findings until recently, older patients did not have genetic testing performed. Nevertheless, we intend to perform genetic testing if the patients will submit to diagnostic testing in the future, which is not always possible because of their health status.

Currently we are following the guidelines of the International Tuberous Sclerosis Complex Consensus Conference in 2012 (ITSCCC2012) to follow our patients with TSC (6). According to the protocol, patients are invited for annual visits depending on their symptoms and receive diagnostic evaluation according to the plan described in Table 2. We provide our specialists with a protocol to ensure consistent follow-up. In addition, we have multidisciplinary teams to discuss patients among the various specialists.

CONCLUSION

Tuberous sclerosis is a rare disease with symptoms pertaining to different specialities. Renal impairment is an important role in mortality and renal involvement is often present. We confirmed that the incidence of renal impairment in our patients is consistent with the literature, although CKD was not common in our patients due to young age.

REFERENCES

1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med. 2006;355(13):1345–56.
2. Bissler JJ, Kingswood JC. Renal manifestation of tuberous sclerosis complex. Am J Med Genet C Semin Med Genet. 2018;178(3):338–47.
3. Henske EP, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016;2:16035.
4. Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, Delgado MR et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. Genet Med. 2007;9(2):88–100.
5. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. J Child Neurol. 1999;14(6):401–7.
6. Krueger DA, Northrup H, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management:

recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):255–65.
7. 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.
8. Budde K, Gaedeke J. Tuberous sclerosis complex-associated angiomyolipomas: focus on mTOR inhibition. Am J Kidney Dis. 2012;59(2):276–83.
9. Ewalt DH, Sheffield E, Sparagana SP, Delgado MR, Roach ES. Renal lesion growth in children with tuberous sclerosis complex. J Urol. 1998;160(1):141–5.
10. Zimmerhackl LB, Rehm M, Kaufmehl K, Kurlemann G, Brandis M. Renal involvement in tuberous sclerosis complex: a retrospective survey. Pediatr Nephrol. 1994;8(4):451–7.
11. Cook JA, Oliver K, Mueller RF, Sampson J. A cross sectional study of renal involvement in tuberous sclerosis. J Med Genet. 1996;33(6):480–4.
12. O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP. An epidemiological study of renal pathology in tuberous sclerosis complex. BJU Int. 2004;94(6):853–7.
13. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372(9639):657–68.
14. de Vries PJ, Whittemore VH, Leclezio L, Byars AW, Dunn D, Ess KC et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND checklist. Pediatr Neurol. 2015;52(1):25–35.
15. Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet. 2001;68(1):64–80.