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RESEARCH ARTICLE

Neurological manifestations of tuberous sclerosis are more common in patients with earlier stages than in the end stage of the chronic kidney disease: Multicentric study from South-Eastern Europe countries

Vladimir Prelevic[1], Ivana Juric[2], Hrvoje Bilic[3], Danilo Radunovic[1], Igor Zabic[4], Branka Gledovic[1], Tanja Antunovic[5], Nikolina Basic-Jukic[2]

[1] Clinic for Nephrology, Clinical Centre of Montenegro, Podgorica, Montenegro, [2] Department for nephrology, arterial, hypertension, dialysis and kidney transplantation, University Hospital Center Zagreb, Croatia, [3] Clinic for Neurology, University Hospital Centre Zagreb, [4] Department for Internal Medicine, General Hospital Koprivnica, Croatia, [5] Centre for Laboratory Diagnostics, Clinical Centre of Montenegro, Podgorica, Montenegro

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Background

Tuberous sclerosis is a rare, genetic disease with the various clinical presentations with most frequent clinical presentation which includes epileptic seizures and cognitive disorders. The main cause of mortality in those group of patients is renal impairment., and in some cases, neurological and renal clinical manifestation can be followed, but can also be the main therapeutic aim of mTOR inhibitors. Here, we aimed to correlate neurological symptoms with different stages of chronic kidney disease.

Methods

This multicentric retrospective study included 51 patients from clinical centres from seven South-Eastern Europe countries We included patients older then 18 years with possible or definitive diagnosis of TSC. Data were collected from nephrological and neurological registries form clinical centres.

Results

Study enrolled 51 patients with a median age of 32.3 years and predominant female gender. Neurological symptoms represented with epiletic sizures were more common in patients in earlier stages of CKD (nonESRD patients) then in patients in the end-stage renal disease.

Conclusion

Results of this study have shown that neurological manifestation in analyzed cohort correlate with renal lesions in early stage of chronic kidney disease.

Introduction

Tuberous sclerosis (TSC) is rare, genetic disease with autosomal-dominant model of inheritance which is presented with various clinical manifestations. Some epidemiological studies in USA shown that the incidence of tuberous sclerosis is 0.28–0.56 per 100 000 newborns.[1]

The main genetic mechanism includes mutations in tuberous sclerosis 1 and 2 genes (TSC1 and TSC2) gene locus responsible for encoding hamartin and tuberin protein, what leads to overactivation of mTOR pathway and finally leads to the growth of hamartomas in multiple organs, what is main pathological base of clinical presentations.[2]

The main clinical presentations include different neurological symptoms usually presented with cognitive and behavioural disorders. Epilepsy is the most prevalent and clinically important manifestation of tuberous sclerosis, with wide range of clinical presentation from infantile spasms to refractory epilepsy. On the other side the first symptoms of tuberous sclerosis can be disorders form autism spectrum.[3]

The first clinical manifestations can also be cutaneous manifestations and newborns can be presented with hypomelanotic lesions and „confetti"-skin lesions in aproximately 90% of patients. Neurological symptoms are usually accompanied with opthamological and pulmonary lessions.[4]

Renal failure is one of the leading cause of mortality and morbidity in adult patients then 30 years. Angiomyolipomas (AMLs) are the main renal lessions, but renal lessions can be presented with renal cysts and renal cell carcinoma. For a long period of time frequent embolisations and hemoorrhage in AMLs were main cause of renal failure.[5] Revolution in treatmant and better control of progression to end stage of renal disease corelate with usage of mTOR inhibitors. As a results of two clinical studies EXIST-1 and EXIST-2 mTOR inhibitors found crucial place in treatmant of those patients. Main mechanism of those drugs include inhbition of angiogenesis. It can be used for the successful treatment not only for renal angymolipomas, but also for different types of brain tumors.[6]

There is a small number of studies where corellation between CKD and neurological manifestation of tuberous sclerosis is found. Particullary, there is no reasarchs where corellation between different stages of CKD and ESRD where made with neurological manifestations of TSC event the common pathways of mTOR inhibitors signaling.

The aim of this study was to correlate neurological manifestations with different stages of chronic kidney disease (CKD). Our hypothesis was that neurological manifestations are more common in end-stage renal disease (ESRD) patients than to CKD patients in earlier stages of CKD

Methods

This multicentric retrospective study included 51 patients from clinical centres from seven South-Eastern Europe countries (Albania, Bosnia and Herzegovina, Croatia, Greece, Montenegro, Serbia and Slovenia), in the period from February to April 2020.

We included patients older then 18 years with possible or definitive diagnosis of TSC. Data were collected from nephrological and neurological registries form clinical centres form mentioned countries in accordance to national and local Ethical committees' guidelines. Research was performed in accordance of Helsinki Declaration. All patients accepted voluntary to participate and signed informed consent.

Table 1. Patients' characteristics and renal disease characteristics.

Variable	Values
Age (years)	32.3±13.7
Gender	60.45% females
Age at TS diagnosis (months)	25.5 (9.0-120.0)
Age at CKD diagnosis (years)	21.0 (2.6-32.7)
CKD	66.70%
Multiple renal cysts	42.6% of all patients
	34.4% of CKD patients
Renal angiomyiolipoma	76.6% of all patients
	84.4% of CKD patients
Nephrectomy	34.00%
Everolimus for systemic usage	37.5%
ESRD	39.6%
CKD stage of non ESRD patients	20.8% of all patients CKD stage I
	22.9% of all patients CKD stage II
	12.5% of all patients CKD stage III
	4.2% of all patients CKD stage IV
Renal replacement therapy	37.50%

TS-tuberous sclerosis, CKD-chronic kidney disease, ESRD-end-stage renal disease

For the classifications of patients with possible and definite diagnosis of TSC, we used current TSC updated guidelines 2021.[7]

Chronic kidney disease was defined regarding to KDIGO guidelines regarding the eGFR (less then 60ml/min/1.73m2), level of albuminuria (greater then 30mg) and ESRD was defined when eGFR was less then 15 ml/min/1.73m2.[8]

Categorical data were presented by absolute and relative frequencies. The normality of the distribution of continuous variables was tested by the Shapiro-Wilk test. Continuous data were described by the median and the limits of the interquartile range (IQR) and categorical variables were shown as relative or absolute frequencies. The level of significance was set at $P<0.05$. The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Results

This study enrolled 51 patients with a median age of 32.3 years (range, 18-46 years), and predominant female gender (60.45%).

The most prevalent renal lesions leading to CKD were AMLs in 76.6%. Nephrectomy was performed in 43% of patients, while the mTOR inhibitors were used in 18 patients (37.5%). Patients' characteristics are presented in Table 1.

Neurological manifestations of TSC were frequent, represented with epileptic seizures (68.80%) and cognitive disorders (43.80%).

Table 2. Extrarenal omplication of ESRD and nonESRD patients

		ESRD (number of patients)	nonESRD (number of patients)	P
Epileptic seizures	Yes	9	24	**p<0.05**
	No	5	10	
Cognitive disorders	Yes	5	16	**p<0.05**
	No	9	18	
Cardiac rhabdomyoma	Yes	1	4	p>0.05
	No	13	29	
Lymphangioleiomyomatosis	Yes	4	2	p>0.05
	No	10	32	
Multiple retinal nodular hamartomas	Yes	7	6	**p<0.05**
	No	7	27	
Angiofibromas or fibrous cephalic plaques	Yes	8	25	p>0.05
	No	6	9	
Hypomelanotic cutaneous macules	Yes	13	27	p>0.05
	No	1	7	
Subependymal astrocytoma	Yes	4	10	p>0.05
	No	10	23	
Subependymal nodules	Yes	7	17	p>0.05
	No	7	17	
"Confetti" skin lession	Yes	11	15	p>0.05
	No	3	19	
Intraoral fibromas	Yes	2	2	p>0.05
	No	12	32	
Non-renal hamartomas	Yes	4	8	p>0.05
	No	10	25	

ESRD- end stage renal disease

The majority of patients had cutaneous manifestations of TSC - 83.30% had hypomelanotic cutaneous lesions, and 68.80% had angiofibromas.

Those clinical presentation were followed by multiple renal nodal hamartomas (27.70%), lymphangioleiomyomatosis (12.50%), and cardiac rhabdomyoma (10.60%).

The percentage of patients with CKD diagnosis of the total number of patients was 66.90%, with ESRD development in 39.6%.

Neurological symptoms represented with epiletic sizures were more common in patients in earlier stages of CKD (nonESRD patients) then to patients in end-stage renal disease (ESRD) what is presented in table 2.

Discussion

The main finding of this study is that epileptic seizures and cognitive disabilities are more frequent in earlier stages of CKD.

In our cohort the middle age of patients was 32.3 what is older than mean age of patients in other studies. Vobret and al. reported mean age at the diagnosis of TSC 25, while Zöllner et al. have shown that the mean age at the diagnosis was 29.2 years.[9,10]

Early detection and better screening for this disease gave opportunity for better control of disease and better long-term outcome related to surveillance and quality of life.[11]

In analysed group of patients, neurological symptoms represented with epileptic seizures and cognitive disorders where more common in the group of patients in earlier stages of CKD then to patients in end-stage renal disease.

The most common clinical manifestation in out cohort were neurological manifestations (54%). Epilepsy was diagnosed in 68.80% and cognitive disorders in 43.80% of patients.

Those results correlate with the results of the the largest TOSCA registry which included data of 2093 patients, epilepsy was diagnosed in 1748 (83.5%), 451 (54.9%) had a cognitive disability and 1199 (57.3%).

Usage of m-tor inhibitors as a first line of therapy, reduced the size of hamarotma. It has been used to reduce not only renal AMLs but also to reduce subependimal astrocytoma and retinal hamartoma.[12]

Some studies have shown beneficial efects of usage of mTOR inhibitor not only in regression of volume of angyomilipoma in those group of patients but also in decrease of epileptic seizures

mTOR signaling pathway could also be involved in mechanisms of epileptogenesis. Abnormal cell growth and proliferation as a consequence of mTOR hyperactivation in TSC could indirectly promote excitability of neuronal circuits and promote seizures.[13]

In our cohort 37.50% of patients received a mTORi.

Possible correlation between renal angiomyolipoma, but especially of patients with polycistic renal damages and neurological manifestation represented with epileptic seizures can be the deletions of the *TSC2-PKD1* gene, because of close position of those two genes.[14]

This study has proven possible correlation between neurological and nephrological symptoms in TSC patients, what can be beneficial also from therapeutic approach.

The main limitiation of this study is small number of patients so further multicentric studies with large number of patients shuld be needed.

Conclusion

This study has shown that neurological manifestations in this cohort of patients represented with epileptic seizure and cognitive disabilities correlates with renal lessions in earlier stages of chronic kidney disease what is novel finding in the light of renal and neurological impairaments in TSC patients.

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