Seizure: European Journal of Epilepsy 60 (2018) 86–90

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Calcification in cerebral parenchyma affects pharmacoresistant epilepsy in tuberous sclerosis

Meng-Na Zhang[a], Li-Ping Zou[a,b,*], Yang-Yang Wang[a], Ling-Yu Pang[a], Shu-Fang Ma[a], Lu-Lu Huang[a,c], Yang Gao[a], Qian Lu[a,b], David Neal Franz[d,**]

[a] Department of Pediatrics, Chinese PLA General Hospital, Beijing, China
[b] Center for Brain Disorders Research, Capital Medical University, Beijing Institute for Brain Disorders, Beijing, China
[c] School of Medicine, Nankai University, Tianjin, China
[d] Department of Pediatrics and Neurology, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

ARTICLE INFO

Keywords:
Computed tomography(CT)
Tuberous sclerosis(TSC)
Cerebral parenchyma calcification
Pharmacoresistant epilepsy

ABSTRACT

Purpose: Tuberous sclerosis (TSC) is an autosomal dominant inherited disease caused by mutations in the *TSC1* or *TSC2* gene and results in the over-activation of the mammalian target of the rapamycin (mTOR) signaling pathway. Rapamycin, an mTOR inhibitor, is clinically used to treat hamartomatous lesionsas in TSC and its effect on controlling epilepsy is also reported in many studies. This study aims to evaluate the risk factors of pharmacoresistant epilepsy in patients with TSC receiving long-term rapamycin treatment.

Method: A total of 108 patients with TSC taking rapamycin for over 1 year were enrolled in this study. Factors that might influence seizure control were statistically analyzed by multiple factor analysis. A subgroup analysis was also conducted to access the relationship between calcified epileptic foci and pharmacoresistant epilepsy. (Clinical trial registration number: ChiCTR-OOB-15006535(2015-05-29)).

Results: Seizure was controlled in 53 patients but was not managed in 55 patients considered to be drug resistant. Logistic regression analysis showed that calcification in the cerebral parenchyma was a risk factor of pharmacoresistant epilepsy [P = 0.006, odds ratio (OR) = 4.831 (1.577, 14.795)]. Fifteen of 17 patients with calcified epileptic foci suffered from pharmacoresistant epilepsy (88.2%). Seizures in patients with calcified epileptic foci were probably pharmacoresistant (P = 0.010).

Conclusion: Calcification in epileptic foci strongly indicates pharmacoresistant epilepsy in patients with TSC even when treated with appropriate anti-epilepsy drugs (AEDs) and rapamycin. Calcification can be used to evaluate pharmacoresistant epilepsy in patients with TSC.

1. Introduction

Tuberous sclerosis (TSC) is an autosomal dominant inherited disease caused by mutations in the *TSC1* or *TSC2* gene and results in over-activation of the mammalian target of the rapamycin (mTOR) signaling pathway [1]. TSC produces hamartomatous lesions in the brain, kidney, skin, and other organs of the body. Epilepsy is observed in approximately 90% of patients with TSC, and approximately half of the patients have experienced infantile spasms (IS) and the majority are pharmacoresistant [2]. In children with TSC, uncontrolled seizure is associated with high risk of developmental delays and autism spectrum disorders [3].

New and old anti-epilepsy drugs (AEDs), such as valproic acid, carbamazepine, oxcarbazepine, topiramate, and vigabatrin (VGB), are used to control seizures in TSC; of which, VGB is the most effective [4]. VGB can stop seizures in up to 95% of patients with IS affected by TSC [5]. VGB can also effectively control partial seizures [6]. However, visual-field loss caused by VGB is irreversible, and its risk rises with increasing dosage and treatment duration [7].

In recent years, mTOR inhibitors, such as rapamycin and everolimus, have been clinically used to treat various manifestations of TSC. They can reduce the volume of sub-ependymal giant-cell astrocytoma (SEGA) and renal angiomyolipoma (AML); improve or stabilize pulmonary function in lympangioleiomyomatosis; and improve skin

Abbreviations: TSC, tuberous sclerosis; CT, computerized tomographic; EEG, electroencephalogram; mTOR, the mammalian target of rapamycin; IS, infantile spasms; AEDs, anti epilepsy drugs; VGB, vigabatrin; SEGA, subependymal giantcell astrocytoma; AML, angiomyolipoma; ILAE, international league against epilepsy; CI, confidence intervals; OR, odds ratio

* Corresponding author at: Department of Pediatrics, Chinese PLA General Hospital; Center of Epilepsy, Beijing Institute for Brain Disorders, 100853, Beijing, China.
** Corresponding author at: Cincinnati Children's Hospital Medical Center, MLC 2015, 3333 Burnet Avenue, Cincinnati, OH, 45229, USA.
E-mail addresses: zouliping21@hotmail.com (L.-P. Zou), franz@tsdev.org (D.N. Franz).

https://doi.org/10.1016/j.seizure.2018.06.011
Received 27 February 2018; Received in revised form 22 May 2018; Accepted 13 June 2018

lesions [8,9]. Open-label and double-blinded, placebo-controlled studies reported that everolimus was effective on treating TSC-related epilepsy [10–12]. A case series [13] and our previous observational study [14] indicated that rapamycin can be administered to effectively decrease seizures. However, pharmacoresistant epilepsy remains a challenge even when mTOR inhibitors are used.

Surgery is an option for patients with TSC and intractable epilepsy. Although tubers are multiple, epileptogenic activity can often be localized to one or two tubers [15]. Many neuroimaging technologies, such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET), are clinically used to locate epileptogenic tubers and associated epileptogenic regions. Surgery can stop seizures in 57% of drug-resistant patients [4], but convergent clinical, video electroencephalographic, MRI, and ancillary testing data are needed to select candidate patients for surgery.

Considering that remission of seizures is associated with high intelligence quotient (IQ) [2], we retrospectively analyzed risk factors affecting seizure control in patients with TSC taking rapamycin for over 1 year.

2. Results

The clinical characteristics of the patients are summarized in Table 1. A total of 108 patients, of which 55 were males, were enrolled in this study. The participants aged 3 months to 10 years old, with an average age of 2.2 years and median age of 1.4 years. Forty six patients had IS, 24 patients had partial seizures, and 38 patients had generalized seizures at enrolled time. Thirteen AEDs, including topiramate, valproic acid, vigabatrin, levetiracetam, and clonazepam, were used to control seizure onset. Two patients (partial seizures) given with rapamycin alone and without traditional AEDs achieved seizure free.

Fifty-three patients (49%) receiving AEDs and rapamycin for more than 1 year were declared seizure free. Logistic regression analysis showed that calcification in the cortex and other cerebral parenchyma was a risk factor of pharmacoresistant epilepsy [P = 0.006, OR = 4.831 (1.577, 14.795)]. Age, gender, genotype, seizure type, and family history were not considered risk factors of pharmacoresistant epilepsy in patients with TSC under long-term use of rapamycin (Table 1).

Seizure reduction ≥50% was observed in 23 of 75 patients without cerebral parenchyma calcification and in 9 of 33 patients with cortex and other cerebral parenchyma calcification. These patients have pharmacoresistant epilepsy according to the definition of drug-resistant epilepsy (ILAE, 2010) [16], which is failure of adequate trial of two drug schedules to achieve sustained seizure freedom.

A subgroup analysis was conducted in 33 patients with cortex and other cerebral parenchyma calcification. Seventeen patients showed calcification in epileptic foci, and 15 of them (88.2%) were considered pharmacoresistant. Of 16 patients with calcification unrelated to epileptiform discharge site, seven patients (43.8%) manifested pharmacoresistant epilepsy. Hence, seizures in patients with cerebral parenchyma calcification in epileptic discharge site were likely to be pharmacoresistant (P = 0.010). Calcification in the epileptic foci strongly suggested the presence of pharmacoresistant epilepsy in patients with TSC even when treated with appropriately selected AEDs and rapamycin.

Table 1
Clinical features of 108 patients and single factor analysis.

Risk factors	Total number N = 108	Seizure onset		P value
		Seizure free n = 53	Drug-resistant n = 55	
Male	55	24	31	0.123
Age				0.745[a]
< 1 year	34	17	17	
1 ~ 5 years	62	29	33	
> 5 years	12	7	5	
Seizure type				0.788
Infantile spasm	46	21	25	
Focal seizures	24	13	11	
Generalized seizures	38	19	19	
Cerebral parenchyma calcification	33	11	22	0.030
Genotype				0.204
TSC1	8	6	2	
TSC2	59	30	29	
Family history	20	10	10	0.927
AEDs				0.017[a]
0 ~ 1[b]	33	23	10	
2 ~ 4 AEDs	72	28	44	
≥5 AEDs	3	2	1	

[a] Age and AEDs were considered continuous variable.
[b] Two patients achieved seizure free only by rapamycin.

3. Discussion

3.1. Rapamycin and TSC

Rapamycin, also known as sirolimus, is a natural product isolated from soil bacteria. Open-label and double-blinded, placebo-controlled studies reported that everolimus, the analog or rapamycin, can effectively treat SEGA, AML, and other neurological and nonneurological manifestations in patients with TSC and epilepsy [8,9]. These effects of rapamycin were also described [13,14]. The evidence level of case series and observational study is lower than that of randomized controlled trials (RCT).However, the price of rapamycin is approximately half that of everolimus in China, and none of them was covered by medical insurance. Treatment with rapamycin can save approximately 1000 dollars a month for a child weighing 25 kg (everolimus 5 mg/m^2/day [11]). Moreover, sirolimus oral solution is suitable for infants and toddlers.

This work, which is part of an observational study using rapamycin for children with TSC, indicated that 53 patients (49%) became seizure free. Seizure reduction ≥ 50% was observed in 32 patients (29.6%), who were also considered to have pharmacoresistant epilepsy in this study. Among patients with TSC and epilepsy, 62.5% developed refractory epilepsy and 33.5% achieved epilepsy remission [3] prior to clinical use of mTOR inhibitors. RCTs on the use of everolimus are usually limited by sample size, and the total number of patients declared to be seizure free has not been calculated yet.

Seizure remission is associated with high IQ [2]; as such, risk factors of pharmacoresistant epilepsy were retrospectively analyzed in the present study. Logistic regression analysis showed that calcification in the cortex and other cerebral parenchyma was a risk factor of pharmacoresistant epilepsy (P = 0.006, OR = 4.831 [1.577, 14.795]). Age, gender, genotype, seizure type, and family history were not considered as risk factors of pharmacoresistant epilepsy in patients with TSC under long-term use of rapamycin. However, brain MRI data were not analyzed due to lack of digitized image.

3.2. Calcification in cerebral parenchyma

Calcification in cortical tubers occurs in 54% of patients with TSC, and its incidence increases with increasing age [17]. Gallagher et al. [18] reported a progressive calcified tuber in a young male with TSC, suggesting that tubers with calcification components are not necessarily static lesions. In the present study, rapamycin was found to less effective in controlling epilepsy in patients with cerebral cortical calcification.

Inflammation is found in tubers of TSC [19]. A histopathological study of TSC classified tubers into three types: 1) low density of giant cells or dysmorphic neurons; 2) high density of giant cells or dysmorphic neurons, and 3) giant cells, dysmorphic neurons, and