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Review Article

Update of Treatment for Children of tuberous sclerosis complex

Fuyong Jiao*[1], Li Wei[1], Bilal Hiader Shamsi[2]

[1]Childrens Hospital Shaanxi Provincial People's Hospital, Xi'an Jiao tong University, Xi'an China.
[2]Department of pediatrics, Shenmu County Hospital Shaanxi Province, China

Abstract

The children of tuberous sclerosis complex were also named Bourneville disease, and its neural symptoms and pathological change was firstly described by Bourneville in 1908. Heinrich Vogt pointed out the three main symptoms, namely epilepsy, mental retardation and facial angiofibromas. It is an autosomal dominant disease. It is an important cause of epilepsy, autism, and renal and pulmonary disease in children and adults. The appropriate therapy and prognosis for TSC patients are often different than that for individuals with epilepsy, renal tumors, or interstitial lung disease from other causes. In recent years, certain progress have been made in management of tuberous sclerosis, inhibitors of the mammalian target of rapamycin (mTOR) have demonstrated regression of astrocytomas, angiofibromas, and angiomyoliomas, as well as improved pulmonary function in persons with TSC. This article reviews the current therapeutic recommendations for medical and surgical management of neurologic, renal, and pulmonary manifestations of TSC.

Key words: Children of tuberous sclerosis complex; Treatment; Progress.

***Corresponding Author: Fuyong Jiao**, Department of Pediatrics, Shaanxi Provincial People's Hospital of Xi'an Jiao tong University, Xi'an China.

1. Introduction

Tuberous Sclerosis (Tuberous Sclerosis Complex, TSC) is an autosomal dominant genetic disease involving multiple systems, appears in the body a variety of tissues and organs hamartoma is characterized hyperplasia, occurs in the brain, skin, heart, kidney [1]. VonRecklinghauson first described the disease in 1862, 1880 Bourneville first name, so the disease is also called the Bourneville disease. TSC phenotypic variation is very big, even within the same family. Epidemiological investigation of western people speculated that TSC birth rates for 1:6000-1 to 000, roughly 2:3 cases for distributing, prompt the high spontaneous mutation rate. The disease has a genetic heterogeneity, pathogenic gene contains TSCl and TSC2 gene, was cloned in 1993 and 1993 [2]. Tuberous sclerosis complex is often associated with refractory epilepsy secondary to cortical

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tubers. Previous research has found a link between early epilepsy, often severe convulsions may increase intelligence damage. Early effective control epilepsy can improve intelligence level. For patients with intractable epilepsy surgery has been shown to reduce and even eliminate the influence of epileptic seizures and it's related. So far, epilepsy surgery has not been widely used in tuberous sclerosis patients [3].

1 The drugs

1.1 mTOR inhibitors- Rapamycin

1.1.1 Introduction - Rapamycin (Rapamune RAPA), also known as Sirolimus (Sirolimus), belongs to the large ring lactone class compound, its first found in Easter island soil samples bibulous Streptomyces product, rapamycin which gets its name from the vision of the Easter island name - ray island. RAPA from Streptomyces water imbibitions (Streptomyces hygroslopicus) are extracted from the fermented liquid of a large ring lactone class compounds (Molecular Formula: $C_{51}H_{79}NO_{13}$, relative molecular mass: 914.2), and another kind of immunosuppressant FK506 structure is similar to [1], soluble in ethanol, chloroform, acetone and other organic solvents, very slightly soluble in water. It is the American Home Products company research and development of new drug of renal transplant rejection, approved by the FDA of United States in September 1999.

mTOR is a highly conserved serine/threonine kinase, having 289 KD, belonging to the PI3K related kinase family, the cell's metabolism, growth, proliferation, survival, and biological processes such as cytoskeleton movement regulation plays an important role in regulation. The study found that mTOR signaling pathways involved in the formation of tumor, angiogenesis, insulin resistance, and T lymphocyte activation process [4]. Rapamycin is a kind of mammals rapamycin target protein (mammalian target of rapamycin mTOR) inhibitors, as a result of TSC and TSC protein involved in regulating mTOR kinase activity, when the TSC or TSC mutations mTOR kinase activity of the abnormal increase in TSC, so consider use of rapamycin for TSC rapamycin for inhibiting mTOR activity involved in regulating cell growth can also be used for antifungal therapy in organ transplantation also as immunomodulatory drug application, through the inhibition of interleukin - 2 to hinder the activation of T cells and B cells to suppress the immune.

1.1.2 Mechanism of rapamycin with TSC and TSC protein involved in regulating mTOR kinase activity, when the TSC or TSC mutations mTOR kinase activity of the abnormal increase in TSC, so consider use of rapamycin for TSC rapamycin for inhibiting mTOR activity involved in regulating cell growth can also be used for antifungal therapy in organ transplantation also as immunomodulatory drug application, through the inhibition of interleukin - 2 to hinder the activation of T cells and B cells to suppress the immune, suggests a new study by different cytokines receptors RAPA block signaling, blocking the T cell and other cell from G1 phase to S phase process, thereby immunosuppressive effect into full play. Since RAPA listed, quickly became the world transplant the commonly used oral immune inhibitors. Preclinical and clinical studies have shown that rapamycin could shrink subependymal giant cell renal angiomyolipomas star cell tumor or tumor volume of lung lymphatic fibroid disease

can be used in the treatment of TSC [5], a new study shows that a rapamycin analogues and gamma interferon can reduce mouse model of TSC kidney disease severity [6]. Research shows that in accordance with the dimensional moss can narrow subependymal giant cell star cell tumor, in some cases of TSC, it can be used as surgical treatment outside another choice [7]. Other research reports, sirolimus can reduce the SEGA tumor size, an average of 65% volume four patients to avoid surgery [8]. According to the dimension of therapy in treatment of 27 patients, 21 cases of SEGA volume reduced by more than 30% (75%), 9 patients (32%), SEGA volume reduced more than 50%, curative effect lasts for up to 24 months [9].

1.1.3 Usage and Dosage of Rapamycin
Dosage: starting dose weight 50 kg, > < 2 mg/d, weight 50 kg, 1 mg/d, and follow-up every time all need to check blood drug concentration, the effective blood drug concentration range 5-15 ng/ml, the recommended blood drug concentration range 5-10 ng/ml.

1.1.4 Adverse reaction : oral ulcer and elevated blood lipids common, need to pay attention to adverse drug reactions are of rare: interstitial pneumonia and affect wound healing. Other common adverse reactions: respiratory tract and urinary tract infections, pain, menstrual abnormalities, leukopenia, and diarrhea. Other rare adverse reactions are cancer risk, high blood pressure, uterine bleeding, proteinuria, hypokalemia, and so on.

1.2 Antiepileptic therapy

Early control seizures can help prevent damage infant spasm secondary epilepsy encephalopathy and cognitive behavior. xi bao ning recommended individualized treatment regimen (ammonia hexene acid) is the treatment of TSC merger infant spasm first-line drugs, studies have shown that ammonia hexane acid of 73% of the patients with TSC infant spasm effective but it can happen to reduce the side effects, such as vision applications need to be closely observed. When normal parathyroid function, corticosteroids can be used as an alternative treatment. Carbamazepine, oqa xiping and phenytoin can lead to the deterioration of epileptic seizures, especially in young children and infants, these drugs can increase the baby convulsion, therefore is not recommended used in the treatment of infant spasm TSC merger [10].

1.2.1 The treatment of infant spasm
In infant spasm is a clinical manifestation of TSC [11], affecting 30% of TSC patients, can appear in the first month after birth, but in most cases appears before the age of 1. Ammonia acid, is a kind of GABA transaminase inhibitor, can cause inhibitory neurotransmitter GABA levels increase, the current has been proven in the treatment of TSC merger infant spasm very effective [12, 13]. Other traditional antiepileptic drugs (AEDs), including Phenobarbital, Benzodiazepines drugs, Valproic acid and Topiramate, Curative effect is not obvious or completely invalid [14, 15]. Carbamazepine, oqa xiping and phenytoin can lead to the deterioration of epileptic seizures, especially in young children and infants, [15]. These drugs can increase the baby convulsion, therefore is not recommended used in the treatment of infant spasm TSC merger [16]. Other treatments, such as muscle injection of adrenocorticotropic hormone (ACTH) or oral corticosteroids, can be used as second-line therapy, the curative effect of relatively poor ammonia hexene acid [12]. But while ammonia hexene acid was

proved to be effective, but its potential treatment-related side effects of visual field loss are limiting its widely accepted, have been reported in 30-40% of adults and children (17-20). This effect can reduce the minimum duration and dose not yet known. However, in most cases, this side effect is mild, with precision ophthalmic assessment tools and equipment can be monitored. Given the high probability of permanent nerve damage and early life infant spasm out of control, ammonia hexene acid is still the TSC merger infant spasm first-line treatment scheme, despite these potential risks [21, 22].

1.2.2 The treatment of partial convulsions First-line treatment: Xi bao ning are the preferred drug in the treatment of one-year-old attacks, research shows that children with ammonia hexene acid on TSC refractory children with partial onset seizures is a safe and effective treatment [38]. A year later, choose other boost GABA inhibitors, such as topiramate and carbamazepine. Second line plan: surgical treatment, the success rate is associated with epilepsy lesions in place. Third line treatment: ketogenic diet, nerve stimulation therapy and other antiepileptic drugs for the treatment of limited attack.

1.2.3 Cognitive and Behavioral Therapy studies have shown that behavior, cognition, and the most common mental disorders in patients with TSC, although its occurrence, anxiety disorders 5-56%, 4-43% emotional disorders, cognitive impairment, 1-43% (23-27), we should not be underestimated or ignored. Ehninger etc. Studies have shown that mTOR inhibitors may offer a unique nerve in patients with TSC cognitive and behavioral science benefits [28]. In intractable epilepsy patients with TSC, according to the dimension of therapy may be a good choice, it can improve the patient's behavior and the quality of life [29]. In Recent research and analysis, 3 cases with sirolimus or in accordance with the dimension of therapy to treat SEGA or other related TSC performance were found, there is no other subsequent adjustment of psychotropic drugs, have been found mental symptoms stable or improved. Although this result is very promising, still need to further research and evaluate the potential clinical treatment for mental illness, especially in patients with TSC.

1.3 Surgical Treatments

Once diagnosed SEGA, as long as patients without clinical symptoms, without the risk of acute hydrocephalus and judgment, clinicians can choose to continue to dynamic follow-up imaging studies, otherwise, will adopt surgical removal of lesion, this is at present a clear plan for the treatment of SEGA [30]. Cut of surgical treatment including focal cortical tubers, corpus callosum. Focal cortical tubers resection for most patients with TSC belongs to palliative rather than curative surgery; Corpus callosum cut can effectively reduce the loss of tension and tonic-closure seizures (i.e., the fall to), but for other attack effect is poor. A few patients with corpus callosum to cut off the postoperative epilepsy and no attack SEGAs hydrocephalus or obvious placeholder effect should be removed surgically, but likely to recur. Surgical treatment is the hemisphere or side hemisphere discharge of multifocal TS [31] good means.

Surgery usually adopts the method of the frontal or by the corpus callosum, the advantages and disadvantages of two kinds of scheme depends on the depth of the lesion and surrounding the key structure. The frontal method changed the

way into the lesions, thus increasing the possibility of a complete resection. However, a large number of normal functions of brain tissue during surgery may cause permanent nerve function defect removal [32]. The lesions may reduce with the use of balloon expansion technology; this technology reduces the reach lesions in the process of normal brain tissue damage [30]. This can also be avoided by using the method of the corpus callosum, but reaching the entire tumor is difficult sometimes, in some cases even impossible. This will make the residual tumor tissues inevitably continue to grow and require additional surgical operation. Preoperative and postoperative complications exists, it is influenced by tumor size and shape, and the experience of the neurosurgeon and processing tools, such as intraoperative magnetic resonance imaging (IMRI). Permanent nerve dysfunction, bleeding, cerebrospinal fluid circulation disorder, epilepsy and infection can also occur.

1.4 The Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) treatment can significantly reduce the TSC patients with simple part and complex partial seizure; About the vagus nerve stimulation current evidence is insufficient, but the related experimental data show that this treatment alone, almost no children can be exempt from seizure [33]. This treatment can be done and ketogenic diet, especially for those resistant and not suitable for surgical treatment of patients can be given. VNS for TSC complicated with refractory epilepsy provides another treatment option, studies have shown that treatment with 10 patients with TSC VNS for at least six months, including 9 cases of patients with epileptic seizure frequency reduced more than 50%, 5 cases were reduced by more than 90% [35]. A more recent studies evaluating VNS the effectiveness of the treatment in 19 patients with TSC, age range from 2-44 years old, average 4.9 years of follow-up, seizures decreased by 72% [36].

1.5 The Ketogenic Diet

Ketogenic diet, it is a 2:1, 3:1 and 4:1, or a higher proportion of fat content of protein and carbohydrates (antibiotic food). Ketogenic diet is applied to the treatment of refractory epilepsy has a history of more than 80 years, its effectiveness and safety has been internationally recognized. Recently by the ketogenic diet leader of the Johns Hopkins hospital Eric h. Kossoff professor presided over a ketogenic diet treatment of 12 cases of patients with tuberous sclerosis clinical research, the results show that at the time of 6 months, 92% of the patients can decrease The Times of the onset of > 50% 67% of the patients can reduce the onset of > 90%, 42% of the patients can complete control of seizures, only 1 patient had failed, in 67% of patients can reduce the use of antiepileptic drugs, patients with no symptoms of kidney stones, acidosis and hyperlipidemia. So in 2009 the international symposium on ketogenic diet, 26 experts agree: ketogenic diet is especially applicable to the treatment of patients with tuberous sclerosis. Research reports, with antiepileptic drugs had failed to control the seizures in 12 patients, after the ketogenic diet, 11 cases can reduce seizure frequency more than 50% (92%) of the [37]. Kossoff, says professor of tuberous sclerosis patients with refractory epilepsy, the ketogenic diet is a safe, effective and side effects of therapy. Compared with surgery and drug treatment, cost is not high, is worth promoting.

2. Conclusion

While TSC is a multiorgan disorder, abnormalities in the brain and the clinical consequences carry the most morbidity and mortality. So the treatment of TSC is very important. At present much progress has been made about the treatment of TSC. However, with advances come additional questions and new challenges. For example, when will mTOR inhibitors be best utilized for the treatment of TSC-associated disease manifestations? Will treatment safe and be well tolerated over time? Will new treatments appear that can augment or replace current mTOR inhibitors for even better safety and efficacy? Although advances in mTOR inhibitors research have provided hope for TSC patients and clinicians, the evaluation and optimization of other treatments and interventions that are available now and in the future must not be overlooked, as they may provide equal if not added benefit for affected individuals who are negatively impacted by TSC.

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