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Review Article

Tuberous sclerosis complex: an update

結節性硬化症的最新發展

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Tuberous sclerosis complex (TSC), a rare autosomal dominant neurocutaneous syndrome, may be caused by mutations of either the *TSC1* or *TSC2* gene encoding hamartin and tuberin respectively. It is characterised by cutaneous changes, neurologic conditions and the formation of hamartomas in multiple organ systems leading to morbidity and mortality. Until recently, the mainstay of management of TSC is supportive and treatment of complications. Recent studies have revealed that mammalian target of rapamycin (mTOR) inhibitors are promising in the treatment of this condition.This paper reviews the literature to provide a current understanding of the disease.

結節性硬化症是一種較爲罕見的，自體顯性遺傳的神經皮膚症候群，可由分別製造錯構素和馬鈴薯球蛋白的 *TSC1* 或 *TSC2* 基因突變所造成。此病的特徵爲皮膚和神經系統出現病變；並在身體不同系統及器官，長出錯構瘤，導致疾病及死亡個案的發生。直至最近爲止，其主要治療方案仍然是支持性治療以及處理其引起的併發症。最新的研究顯示，哺乳動物雷帕霉素靶蛋白抑制劑對此病的療效令人鼓舞，具有很大的發展潛力。本文將審視當代文獻，總結現今對此病的最新認識。

Keywords: mTOR inhibitor, rapamycin, TSC, tuberous sclerosis complex

關鍵詞：哺乳動物雷帕霉素靶蛋白抑制劑，雷帕霉素， TSC ，結節性硬化症

Introduction

Tuberous sclerosis complex (TSC), also known as Bourneville's disease, is an autosomal dominant neurocutaneous syndrome. It is characterised by neuropsychological manifestations, such as seizures, autism and cognitive disability and the formation of hamartomas in various sites throughout the body, e.g. angiofibromas on the face which might cause disfigurement and much distress to the patients. The management of this condition comprises observation for and symptomatic treatment of complications. Elucidation of the molecular basis of TSC and recent exciting advances with emerging targeted therapy with mTOR (mammalian target of rapamycin) inhibitors, however, have brought hope to us in the management of this condition. This review highlights some of the salient features and recent advances in the management of TSC.

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Epidemiology

The estimated prevalence of TSC is around one case for every 10000 to 25000 in Caucasian population.[1,2] A study in Taiwan revealed that the prevalence of TSC was estimated to be 1:95,136 and the prevalence for cases less that six years of age was 1:14,608.[3] The study also showed that only 15% of patients in the study had a family history of TSC. As for local data, a study which consisted of 44 cases over a 12-month period (January-December 2003) determined the period prevalence rate of tuberous sclerosis complex for children and adolescents younger than 20 years to be 3.5 per 10,000 (on Hong Kong Island excluding the eastern region with 125,100 younger than 20 years in 2003).[4]

Pathogenesis

TSC is caused by mutations of either the *TSC1* gene on chromosome 9q34 encoding hamartin or the *TSC2* gene on chromosome 16p13 encoding tuberin.[5] The tuberous sclerosis gene products, hamartin and tuberin, form a tumour suppressor complex which drives Rheb (Ras homologue enriched in brain) into the inactive guanosine diphosphate–bound state. When Rheb is in the guanosine triphosphate–bound active state, it stimulates the mammalian target of rapamycin (mTOR), an evolutionarily conserved protein kinase and a major effector of cell growth. Therefore, mutations in either *TSC1* or *TSC2* result in constitutive mTOR activation leading to formation of hamartomas in the brain, kidney, heart, lung and other organs of the body.[5] A large proportion of TSC patients, ranging from 50% to 80%, are caused by spontaneous mutations.[6] In a study of 325 individuals with TSC, 17% of the mutations were found in the *TSC1* gene, 50% in the *TSC2* gene, 4% unclassified variants and 29% with no mutation identified (NMI).[7] This is in agreement with the finding that the ratio of *TSC2*:*TSC1* mutations was 3.4:1 in a previous study.[8]

Genotype-Phenotype correlation

In one study, patients with a *TSC2* mutation were diagnosed nine years earlier than the patients with a *TSC1* mutation and 11 years earlier than those with NMI.[9] This finding implied that the patients with a *TSC2* mutation have more severe symptoms than those with a *TSC1* mutation and NMI. Dabora et el found that sporadic patients with *TSC1* mutations had, on average, milder disease in comparison with patients with *TSC2* mutations.[10] It was found that despite overlap in the spectrum of many clinical features of patients with *TSC1* and *TSC2* mutations; grade 2 to grade 4 kidney cysts or angiomyolipomas, forehead plaques, retinal hamartomas and liver angiomyolipomas were very rare or even absent in *TSC1* patients. Au et al also found that patients with mutations in *TSC2* had more severe symptoms and that patients with *TSC2* mutations had significantly more hypomelanotic macules and learning disability in contrast to those with *TSC1* mutations.[7] These findings in human beings are in agreement with animal studies.[11]

Diagnosis and investigations

TSC is characterised by the formation of hamartomas in various organs, e.g. the brain, heart, lung, kidneys and skin and the revised criteria of diagnosis of TSC is listed in Table 1.[12] Some manifestations of TSC including seizures, subependymal giant cell astrocytoma (SEGA), renal failure and lymphangioleiomyomatosis (LAM) lead to morbidity and mortality. While hypopigmented macules, facial angiofibromas or forehead plaque, shagreen patch and ungual or periungual fibroma are included in the major features, confetti skin lesions are classified as minor features in the diagnostic criteria of the diagnosis of TSC. It is important to make an early diagnosis of TSC so that lifelong monitoring, early recognition of complications and proactive treatment can lower the morbidity and mortality rates. Appropriate investigations as dictated by

the symptoms and recommended by guidelines are integral parts of the management once diagnosis is established. These investigations include electrocardiography as a baseline investigation and to be repeated as necessary to exclude cardiac conduction defects and arrhythmias; echocardiography in patients with cardiac symptoms; renal ultrasonography at diagnosis for detection of polycystic kidney disease associated with contiguous gene deletions of the *TSC2* and *PKD1* genes; follow-up renal ultrasound scans every one to three years; electroencephalography for the evaluation of seizures; cranial computed tomography or magnetic resonance imaging at diagnosis and to be repeated every one to three years.[13] Additional investigations include molecular genetic testing, neurodevelopmental and behavioural assessment, ophthalmic examination and chest computed tomography for female patients at adulthood and when there are pulmonary symptoms to evaluate for LAM and genotyping. Evaluation of other family members, genetic counselling, family planning and prenatal diagnosis are other integral elements of the evaluation process.

Table 1. Diagnostic criteria for TSC

Major features
Facial angiofibromas or forehead plaque
Nontraumatic ungual or periungual fibroma
Hypomelanotic macules (>3)
Shagreen patch (connective tissue naevus)
Cortical tuber
Subependymal nodule
Subependymal giant cell astrocytoma
Multiple retinal nodular hamartomas
Cardiac rhabdomyoma, single or multiple
Lymphangiomyomatosis
Renal angiomyolipoma
Minor features
Multiple randomly distributed pits in dental enamel
Hamartomatous rectal polyps
Bone cysts
Cerebral white matter migration tracts
Gingival fibromas
Nonrenal hamartoma
Retinal achromic patch
Confetti skin lesions
Multiple renal cysts
Definite TSC:
2 major features or
1 major feature + 2 minor features
Probable TSC:
1 major feature + 1 minor feature
Possible TSC:
1 major feature or
≧ 2 minor features

Adapted from Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998;13:624-8.[12]

Presenting symptoms and signs

The most common presenting symptoms and signs are those related to the central nervous system, e.g. seizures and infantile spasms.[9] This is illustrated by a recent longitudinal study of 125 children, in which 62% of the patients presented with seizures.[14] Patients with TSC might have a delay in the diagnosis as some findings might be unrecognised during childhood by medical practitioners and some disease manifestations may not occur until adulthood. In the study of Seibert et al, 56% of the patients were diagnosed in adulthood and two-thirds of these patients had symptoms in childhood.[15] Hence, many parents are found to have TSC only after their children are diagnosed to have the condition. While seizures or skin lesions might not be present in many adult patients with TSC, serious pulmonary and renal complications can occur. Though Webb found skin signs to be present in 96% of patients with TSC,[16] dermatologic features were found to be presenting signs in only 6% of patients with TSC in one study.[14]

Cardiac manifestations and management

Around two thirds of newborns with TSC have cardiac rhabdomyomas which are often multiple but shrink over time. Yates et al reported that the detection of abnormalities, the bulk of which were cardiac rhabdomyoma, in routine antenatal ultrasound examination had become the second commonest mode of presentation of TSC.[14] The authors reported that cardiac rhabdomyomas were detected in 61% of children under 5 years of age and in 36% of older children.[14] However, before their regression, medical and surgical treatment of the cardiac rhabdomyomas might be necessary if clinically significant ventricular inflow and outflow obstruction, arrhythmia or heart failure occurs. Apart from the conventional therapies, treatment with mTOR inhibitor seems to be promising in the treatment of this condition as evidenced by the description by Tiberio et al on the success of everolimus, an mTOR inhibitor, in the treatment of a 7-year-old boy born with TSC and a large left ventricular tumour which showed significant regression.[17] Everolimus was originally approved in March 2009 for the treatment of adult patients with advanced renal cell carcinoma resistant to treatment with sunitinib or sorafenib.

Pulmonary/renal manifestations and management

Pulmonary and renal manifestations of TSC include pulmonary LAM, renal cysts and angiomyolipomas (AMLs). LAM, a condition with proliferation of abnormal smooth muscle cells and cystic changes in the lungs, affects around 30% of women with TSC[18] and the treatment is supportive. AML which are benign renal tumours affect 55 to 75% of patients with TSC by adolescence. Renal complications including haemorrhage, pain, haematuria and renal insufficiency might occur and necessitate surgical intervention. Bissler et al administered sirolimus (rapamycin), an mTOR inhibitor, to patients with AMLs and found that there was a significant reduction in the mean AML volume.[19] Rapamycin, an antibiotic derived from the bacterium, *Streptomyces hygroscopicus*, was approved by the FDA for use in renal transplant patients in 1999. Moreover, improvement in lung function was observed in patients receiving rapamycin who had concurrent LAM. The MILES (Multicentre International LAM Efficacy of Sirolimus) study, a double blind, multicentre study with 89 patients confirmed that sirolimus was effective in reducing the decline in lung function.[20] The TESSTAL (Trial of Efficacy and Safety of Sirolimus in Tuberous Sclerosis and LAM) study in the UK showed sustained regression of renal AMLs in 16 patients with TSC or sporadic LAM receiving two years of sirolimus treatment.[21]

Neurologic manifestations and management

Neurologic symptoms and complications due to the development of cortical tubers, subependymal nodules and subependymal giant cell astrocytomas (SEGA) are common in patients with TSC. The mainstay of management of these neurologic complications has been surgical intervention. In 2006, Franz reported that administration of sirolimus to four patients with SEGAs and one with pilocytic astrocytoma resulted in the regression of all tumours.[22] Recently, Krueger et al administered everolimus to 28 patients with SEGA and a clinically meaningful reduction in the volume of the tumours from 30% to 50% was found.[23] The reduction occurred within three months and was sustained. Shortly after this study, FDA has granted accelerated approval to everolimus for patients with SEGA associated with TSC who require therapy but are not candidates for surgical resection.

Individuals with TSC exhibit epilepsy, cognitive disabilities and autism spectrum disorders. The mainstay of treatment of seizures in TSC is

anticonvulsant supplemented by epilepsy surgery. In the study by Krueger et al, it was observed that there was a decrease in seizure frequency in the patients with SEGA who received everolimus.[23] Moreover, improvement in the mean score on the validated Quality of Life in Childhood Epilepsy questionnaire was noted. Neurocognitive monitoring in the TESSTAL study showed that recall memory improved in seven of eight patients with tuberous sclerosis treated with sirolimus.[21]

Dermatologic manifestations and management

Cutaneous manifestations are common in TSC patients and a careful skin examination of patients suspected to have TSC is mandatory. As revealed in the study of Jozwiak et al, the frequencies of patients with hypopigmented macules, facial angiofibromas, forehead or scalp plaque, shagreen patch and periungual fibroma were 97%, 75%, 48%, 19% and 15% respectively.[24] The appearance of dermatologic features is age dependent. Hypopigmented macules are the commonest skin lesions found in patients with TSC; they usually present at birth but they may occur at a later age. These lesions are generally a few millimetres to centimetres in size and can be found anywhere on the face, limbs or trunk. The shape is usually polygonal, but can be lance-ovate shaped like an ash leaf. Angiofibromas, previously known as adenoma sebaceum, are the next most common cutaneous lesions and are usually found at two to five years of age.[24] Forehead fibrous plaques, usually found on the forehead or scalp as yellowish-brown or skin-coloured plaques, can appear as early as in the neonatal period. The shagreen patches, a slightly elevated area of roughened skin, usually found on the lower back, commonly present after early infancy. Periungual fibromas, also known as Koenen's tumours, usually occur later in childhood and seldom appear before the age of five years. However, these may grow rapidly during puberty and lead to the diagnosis of TSC in adolescence. Confetti-like hypopigmented macules, 1 mm to 3 mm in size, usually distributed symmetrically on the limbs, can also be found in a proportion of patients of TSC. The frequency was quoted to be 2.8% in one study[24] and 28% in another.[16] Despite being easily recognisable, these dermatologic features were found to have been missed in 9% of patients.[9]

Facial angiofibromas and periungual fibromas, apart from being a source of cosmetic concern, cause symptoms such as bleeding and infection. Options for the treatment of symptomatic periungual fibroma include CO_2 laser, phenolisation and excision.[25,26] Angiofibromas cause disfigurement and thus a great negative impact on the psychology of the patients. Management options for facial angiofibromas include dermabrasion, surgical removal and laser therapy.[27] However, these procedures might cause complications e.g. scars and hyperpigmentation and the results may not be long lasting. In 2008, Hofbauer observed a significant improvement in the facial angiofibroma in a patient with TSC who underwent renal transplantation and treatment with rapamycin.[28] The patient received bilateral nephrectomy and renal transplantation because of recurrent life-threatening haemorrhage from both kidneys due to extensive AML formation. Haemel et al employed topical 1% rapamycin ointment on a 16-year-old girl to treat the facial angiofibromas.[29] She was noted to have improved skin texture shortly afterwards and decreased erythema at one week. At the 6-week follow-up visit, decreased facial erythema and a decrease in the number and size of the angiofibromas were observed. The improvement was maintained at the 12-week visit. Wataya-Kaneda et al conducted a left–right comparison study in nine patients with TSC who were given topical tacrolimus ointment with and without 0.2% rapamycin.[30] The authors reported that the combination of rapamycin and tacrolimus ointment was significantly more effective in all patients, with fewer side-effects, when compared with tacrolimus alone. These studies revealed that the improvement which could

not have been achieved by surgical procedures was accomplished by the application of rapamycin.

The way forward

Although symptomatic treatment has been the mainstay of management of TSC patients, we are embracing the era of targeted therapy. Evidence is accumulating to show that some mTOR inhibitors have become valuable additions to the armamaterium in the treatment of TSC. As discussed above, the mTOR inhibitors have been shown to be effective for facial angiofibromas, SEGAs, cardiac rhabdomyomas, LAM, AMLs and possibly epilepsy. It is envisaged that targeted therapy with mTOR inhibitors, such as rapamycin or everolimus, will play a more important role in the management of TSC in the future. Nonetheless, there are many unanswered questions and problems regarding the use of mTOR inhibitors, e.g. re-growth of AMLs was noted after cessation of mTOR inhibitor therapy.[19] What is the optimal timing for starting mTOR inhibitor and how long should it be continued? Is it effective in the prevention of occurrence of symptoms if it is started early? Should it be combined with other therapeutic agents? Hence, further research is warranted to elucidate a fuller picture of the pathogenesis, especially on the mTOR signalling pathway and the interplay of the signalling networks. Efforts to explore additional effective novel therapies for TSC would be other directions of future research work.

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