Journal of Clinical Neuroscience 21 (2014) 1180–1187

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

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

Clinical Study

Managing tuberous sclerosis in the Asia-Pacific region: Refining practice and the role of targeted therapy

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ARTICLE INFO

Article history:
Received 24 December 2012
Accepted 24 June 2013

Keywords:
Asia-Pacific
Management
mTOR inhibitor
TSC
Tuberous sclerosis

ABSTRACT

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder, with heterogeneous manifestations that pose major diagnostic and management challenges and incur considerable chronic disease burden on patients, their caregivers and healthcare systems. This survey of clinical practice in the Asia-Pacific region highlights priorities for improving TSC management in the region. The prevalence of TSC in non-Caucasians is uncertain and more data are needed to assess its impact and health-economic burden. There are unmet needs for access to genetic testing and earlier diagnosis and intervention. TSC management is multidisciplinary and largely based on experience, backed by international guidelines; however, physicians in the Asia-Pacific region feel isolated and lack local or regional guidance and support structures to implement best-practice. Raising awareness of TSC and increasing trans-regional collaboration are particular priorities. Understanding of TSC pathophysiology has enabled the development of targeted therapies. Encouraging data indicate that mammalian target of rapamycin (mTOR) inhibitors can ameliorate TSC-related lesions and may potentially change the treatment paradigm. Ultimately, improving outcomes for TSC patients in the region requires greater collaboration and a holistic, patient-focused, continuum of care that is maintained through the transition from pediatric to adult care.

1. Context

1.1. Pathophysiology

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with heterogeneous manifestations that affect multiple organs and systems. The classic clinical presentation includes epilepsy, skin lesions and intellectual impairment [1]; however, only 29% of TSC patients have all these symptoms and 6% have none of them [2].

TSC results from mutations in *TSC1*, which encodes hamartin, or *TSC2*, encoding tuberin [1]. The hamartin-tuberin heterodimer stabilizes tuberin, which in turn inactivates the protein Ras homolog enriched in brain (Rheb) that activates the mammalian target of rapamycin (mTOR) (Fig. 1). Consequently, *TSC* expression downregulates aberrant and potentially oncogenic and epileptogenic mTOR-driven cell growth, proliferation and protein synthesis [3–5]. *TSC* mutations account for approximately 85% of diagnosed TSC patients; two-thirds of which are due to new mutations [1]. *TSC* mutations exhibit variable expression; some affected patients remain asymptomatic, whereas others have life-threatening complications [6,7]. Mutations in *TSC2* appear to cause more severe

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http://dx.doi.org/10.1016/j.jocn.2013.06.029
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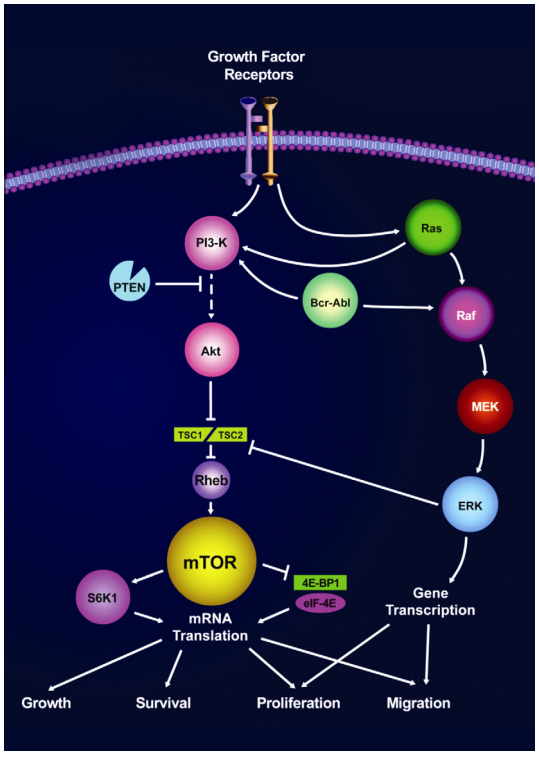

Fig. 1. Mammalian target of rapamycin (mTOR) integrates signaling pathways involved in cell growth and proliferation. Abl = Abelson, Bcr = break point cluster, ERK = extracellular signal-regulated kinases, MEk = mitogen-activated protein kinase, PI3K = phosphoinositide 3-kinase, PTEN = phosphatase and tensin homolog, Rheb = Ras homolog enriched in brain, TSC = tuberous sclerosis complex, TSC1 = hamartin, TSC2 = tuberin.

disease than those in *TSC1* [8,9], being associated with greater likelihood of severe epilepsy and intellectual disability [10].

Neurological symptoms of TSC tend to be the most obvious and problematic; epilepsy affects up to 80% of patients, most commonly presenting before the age of 1 year. Early-onset epilepsy often presages drug-resistant epilepsy and mental retardation [11]. Subependymal giant cell astrocytomas (SEGA) affect 10% to 20% of TSC patients and cause major morbidity [5,7]. Untreated SEGA may lead to serious complications associated with intracranial hypertension [6,7]. Hypopigmented macules are usually present at birth, with most children developing facial angiofibromas by age 5 [1]. The most common renal manifestation of TSC is angiomyolipoma (AML), which usually develops in later childhood and adolescence [1]. Renal AML occur in 55% to 75% of TSC patients and are a leading cause of death [6,7,12]. Pulmonary lymphangioleiomyomatosis (LAM) is an uncommon, but potentially fatal, manifestation, predominantly affecting premenopausal adult women [1,6,7].

1.2. Epidemiology

Global incidence of TSC is approximately 1 per 6–10,000 live births (~1.5 million people) [6]. There are few epidemiology data from the Asia-Pacific region; however, Taiwanese TSC patients have similar distributions of phenotypes and mutations to those reported in Caucasians [8]. Managing TSC incurs substantial treatment costs [13]; however, the exact health-economic burden remains little studied and, consequently, uncertain.

1.3. Diagnosis

TSC is diagnosed according to defined clinical and imaging criteria (Table 1) [1,14]. Common presenting symptoms include: seizures, including infantile spasms; family history of TSC; cardiac rhabdomyomas detected antenatally; and hypopigmented macules [10]. However, many patients have subtle manifestations that elude immediate diagnosis; renal, cardiac and dermatologic features are those most commonly overlooked [10]. Furthermore, the standard diagnostic criteria may not be useful in infants, because most features become evident only after the age of 3 [12]. Genetic tests may help to confirm a suspected TSC diagnosis, especially in infants, or inform reproductive decision-making [1,6,12]; however, these are expensive, time-consuming [6,15], and not easily accessible in some countries or regions.

1.4. Conventional management

Given its heterogeneous manifestations, TSC management must be individualized. Even asymptomatic patients should be monitored regularly. Despite internationally accepted monitoring guidelines [16], implementation is variable and especially poor in adults with TSC [17]. Until recently, treatment options for TSC have been limited and primarily reliant on clinical monitoring and symptom management, rather than addressing the underlying pathology [5,6]. More severe neurological symptoms potentially require multiple therapeutic strategies.

1.4.1. Epilepsy

Seizures are primarily treated with antiepileptic drugs (AED) but often remain poorly-controlled, despite multiple trials of medications. Two-thirds of TSC patients in a large clinic series had intractable epilepsy, with a median age of onset of 7 months [18]. Early seizure control with active epilepsy management may prevent subsequent encephalopathy and reduce consequent cognitive and behavioral problems [19]. Corticosteroids have traditionally been the mainstay of treatment for infantile spasms, but vigabatrin has greater efficacy in TSC [1]. In one retrospective series, prophylactic AED treatment of 14 infants with TSC whose electroencephalograms showed active pre-clinical epileptic discharges reduced the incidence of intractable epilepsy and improved neurodevelopmental outcomes [11]. Unfortunately, vigabatrin treatment may cause loss of peripheral vision and requires monitoring [1,12]. There are no data on the relative efficacy of anticonvulsants in other forms of TSC-related epilepsy. The ketogenic diet and surgery can be highly effective alternatives in selected patients where medications fail; a systematic review of 25 surgical series showed a seizure-free outcome in 57% after a median follow-up of 3.7 years [20].

1.4.2. SEGA

Standard management for SEGA is surveillance neuroimaging and resection of SEGA that exhibit significant growth and/or clinical signs of intracranial hypertension [16,21].

1.4.3. AML

Early identification of renal AML allows timely intervention; tumors larger than 40 mm in diameter have an increased probability of becoming symptomatic and are conventionally managed with selective arterial embolization, radiofrequency ablation or partial nephrectomy [10]. Renal tissues should ideally be preserved [1,12].

1.4.4. LAM

No effective medical treatments for LAM exist; in addition to symptomatic treatment, progesterone has been trialed, with varying success [22].