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Original Article

Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference☆

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ABSTRACT

BACKGROUND: Tuberous sclerosis complex is a genetic disorder affecting every organ system, but disease manifestations vary significantly among affected individuals. The diverse and varied presentations and progression can be life-threatening with significant impact on cost and quality of life. Current surveillance and management practices are highly variable among region and country, reflective of the fact that last consensus recommendations occurred in 1998 and an updated, comprehensive standard is lacking that incorporates the latest scientific evidence and current best clinical practices. **METHODS:** The 2012 International Tuberous Sclerosis Complex Consensus Group, comprising 79 specialists from 14 countries, was organized into 12 separate subcommittees, each led by a clinician with advanced expertise in tuberous sclerosis complex and the relevant medical subspecialty. Each subcommittee focused on a specific disease area with important clinical management implications and was charged with formulating key clinical questions to address within its focus area, reviewing relevant literature, evaluating the strength of data, and providing a recommendation accordingly. **RESULTS:** The updated consensus recommendations for clinical surveillance and management in tuberous sclerosis complex are summarized here. The recommendations are relevant to the entire lifespan of the patient, from infancy to adulthood, including both individuals where the diagnosis is newly made as well as individuals where the diagnosis already is established. **CONCLUSIONS:** The 2012 International Tuberous Sclerosis Complex Consensus Recommendations provide an evidence-based, standardized approach for optimal clinical care provided for individuals with tuberous sclerosis complex.

Keywords: tuberous sclerosis, surveillance, treatment, management, guideline

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Introduction

The clinical manifestations of tuberous sclerosis complex (TSC) are highly diverse in both organ system involvement and severity. Any organ system can be involved, with some more prevalent during infancy and childhood and others more likely to affect individuals as adults.[1] Birth incidence is estimated to be 1:5800.[2] Many manifestations can be life-threatening and appropriate surveillance and management is necessary to limit morbidity and mortality in this disease. Appropriate management is also crucial for optimal quality of life of affected individuals and requires coordination of care among medical specialties and from childhood to adulthood on a regular basis and especially during the critical transition from pediatric to adult health care services.

In 1998, the National Institutes of Health sponsored the first Tuberous Sclerosis Complex Consensus Conference to develop recommendations for diagnosis and clinical management of patients affected by TSC.[3,4] At

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that time, the two known genes responsible for TSC cases had been identified but their function and molecular role were not yet known.[5,6] We now know that the *TSC1* and *TSC2* genes encode for hamartin (TSC1) and tuberin (TSC2), which form a regulatory complex responsible for limiting the activity of an important intracellular regulator of cell growth and metabolism known as mammalian target of rapamycin complex 1 (mTORC1) via inhibition of the small GTPase ras homolog enriched in brain (Rheb).[7] The functional relationship between TSC1/TSC2 and mTORC1 has led to important clinical advances in the use of mTORC1 inhibitors for the treatment of several clinical manifestations of TSC, including cerebral subependymal giant cell astrocytoma,[8-11] renal angiomyolipomas,[8,12,13] and pulmonary lymphangioleiomyomatosis (LAM).[8,13-15] Significant advances in imaging, surgery, interventional radiology, medical, and behavioral therapies have transformed TSC management since 1998.

The extent of medical advances in TSC and the need to standardize and optimize clinical care for individuals with TSC necessitated updating the diagnostic criteria and clinical management guidelines from 1998. In 2011, the International Tuberous Sclerosis Complex Consensus Conference was organized and sponsored by the Tuberous Sclerosis Alliance, a nonprofit patient advocacy group and member of Tuberous Sclerosis Complex International (TSCi). Identification of disease focus areas, participating clinical expert contributors, clinical questions to address, literature review process, and draft recommendations followed. On June 14-15, 2012, 79 experts from 14 countries convened in Washington, DC, to finalize diagnostic, surveillance, and management recommendations for patients with TSC. Finishing work and editing continued into early 2013. A summary report of revised diagnostic criteria for TSC is provided separately.[16] Here we summarize the updated surveillance and management recommendations for the standardized, optimal clinical management of patients with TSC.

Methods

Twelve subcommittees, each led by a clinician with advanced expertise in TSC and the relevant medical subspecialty, were organized to focus on specific disease focus topics that have important clinical management implications in TSC: (1) dermatology and dentistry; (2) nephrology; (3) pulmonology; (4) cardiology; (5) ophthalmology; (6) gastroenterology; (7) endocrinology; (8) genetics; (9) epilepsy; (10) TSC-associated neuropsychiatric disorders; (11) brain structure, tubers, and tumors; and (12) coordination of clinical care. Each subcommittee was charged with formulating key clinical questions to address within its focus area, reviewing relevant literature, evaluating the strength of data, and providing a recommendation based on evaluated literature or, if data were lacking, an expert opinion based on experience or case studies or other appropriate method. If no recommendation could be provided because there was no consensus or conflicting evidence was found of equal value or weight, the subcommittee was to provide recommendations for future research that would help resolve the conflict.

A centralized literature search was performed on March 12, 2012, for all consensus group subcommittees to use. This search used PUBMED and SCOPUS databases of all articles published between 1997 (year before last consensus conference) and 2012 (current), regardless of language. Search terms for PUBMED consisted of "tuberous sclerosis" and "humans" and "diagnosis OR therapy." Search terms for SCOPUS consisted of "tuberous sclerosis" and "diagnosis OR treatment." A total of 2692 articles were identified with this approach. Each consensus group subcommittee was then able to determine additional terms pertinent to its organ system or disease focus area to further refine articles to be reviewed and evaluated. Additional literature searches, if deemed necessary by individual subcommittees to address key clinical questions not captured by the central literature search, could be performed as needed (e.g., epilepsy surgery or organ transplantation guidelines relevant but not specific to TSC).

The evidence-based framework based on the approach of the National Comprehensive Cancer Network (NCCN) Clinical Guidelines[17] was used to grade strength of evidence and resulting recommendations. The NCCN framework allows recommendations based on all classes of evidence by categorizing recommendations with regard to the type and strength of evidence used to support the recommendation and is well-suited for application across many organ systems and specialties for a rare disease such as TSC with multisystem involvement. NCCN Clinical Guidelines category 1 recommendations are based on high-level evidence and uniform consensus, whereas category 2 recommendations are based on lower-level evidence and either uniform consensus or consensus. Category 3 recommendations are those for which a consensus cannot be reached, regardless of evidence. Additional details regarding this framework, including definitions for high- and low-level evidence, are provided in Table 1.

For the purposes of this summary document, the 2012 International Tuberous Sclerosis Complex Consensus Group surveillance and management recommendations are organized into two sections: (1) recommendations applicable at the time of initial diagnosis and (2) recommendations applicable to follow-up health care. There is some overlap with this approach because some features discovered upon initial diagnosis may require immediate intervention, additional workup, or specialist referral. By necessity, discussion in this summary is limited to the most relevant and salient points. More detailed discussion of specific recommendations for the different TSC disease focus areas, supporting evidence thereof, and other special considerations will be published separately by each International Tuberous Sclerosis Consensus Complex Group subcommittee.

Surveillance and management recommendations for individuals with newly suspected or newly diagnosed TSC

TSC is usually first suspected in individuals when one or more clinical diagnostic criteria are identified (Table 2). The purposes of initial diagnostic studies are to confirm the diagnosis in individuals with "possible" TSC and to determine the extent of disease and organ involvement in individuals with "definite" TSC. Baseline studies are also important in guiding treatment decisions should additional disease manifestations emerge in later years.

Genetics

All individuals should have a three-generation family history obtained to determine if additional family members are at risk of diagnosis. Gene testing is recommended for genetic counseling purposes or when the diagnosis of TSC is suspected or in question but cannot be clinically confirmed (Category 1).

Brain

All individuals suspected of having TSC, regardless of age, should undergo magnetic resonance imaging (MRI) of the brain with and without gadolinium to assess for the presence of cortical/subcortical tubers, subependymal nodules (SEN), other types of neuronal migration defects, and subependymal giant cell astrocytomas (SEGA). If MRI is not