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Original Article

Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

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ABSTRACT

BACKGROUND: Tuberous sclerosis complex is highly variable in clinical presentation and findings. Disease manifestations continue to develop over the lifetime of an affected individual. Accurate diagnosis is fundamental to implementation of appropriate medical surveillance and treatment. Although significant advances have been made in the past 15 years in the understanding and treatment of tuberous sclerosis complex, current clinical diagnostic criteria have not been critically evaluated or updated since the last clinical consensus conference in 1998. **METHODS:** The 2012 International Tuberous Sclerosis Complex Consensus Group, comprising 79 specialists from 14 countries, was organized into 12 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 diagnostic implications and was charged with reviewing prevalence and specificity of disease-associated clinical findings and their impact on suspecting and confirming the diagnosis of tuberous sclerosis complex. **RESULTS:** Clinical features of tuberous sclerosis complex continue to be a principal means of diagnosis. Key changes compared with 1998 criteria are the new inclusion of genetic testing results and reducing diagnostic classes from three (possible, probable, and definite) to two (possible, definite). Additional minor changes to specific criterion were made for additional clarification and simplification. **CONCLUSIONS:** The 2012 International Tuberous Sclerosis Complex Diagnostic Criteria provide current, updated means using best available evidence to establish diagnosis of tuberous sclerosis complex in affected individuals.

Keywords: diagnostic criteria, clinical features, tuberous sclerosis

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Introduction

Tuberous sclerosis complex (TSC) was initially described approximately 150 years ago by von Recklinghausen in 1862.[1] TSC is an extremely variable disease that can affect virtually any organ in the body. The most common findings are benign tumors in the skin, brain, kidneys, lung, and heart that lead to organ dysfunction as the normal parenchyma is replaced by a variety of cell types.[2] Disease manifestations in different organ systems can vary widely between even closely related individuals and the protean nature of the condition can make clinical diagnosis challenging. TSC was underdiagnosed until the 1980s when individuals with less severe manifestations of the disease began to be recognized. Before the 1980s, incidence rates for TSC were quoted at between 1/100,000 and 1/200,000.[3,4] Recent studies estimate a frequency of 1/6000 to 1/10,000 live births and a population prevalence of around 1 in 20,000.[5,6] Although TSC was recognized to be a genetic disease more than 100 years ago,[7] the underlying molecular etiology was not unraveled until the discovery of the two causative genes, *TSC1* and *TSC2*.[8,9]

The second International Tuberous Sclerosis Complex Consensus Conference was held June 13-14, 2012, in Washington, DC. Seventy-nine experts (Appendix) from 14

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TABLE.
Updated diagnostic criteria for tuberous sclerosis complex 2012

A. Genetic diagnostic criteria

The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

B. Clinical diagnostic criteria

Major features

1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)†
11. Angiomyolipomas (≥2)†

Minor features

1. "Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥2 minor features

Possible diagnosis: Either one major feature or ≥2 minor features

* Includes tubers and cerebral white matter radial migration lines.

† A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

countries convened to finalize diagnostic, surveillance, and management recommendations for patients with TSC. A summary report of the current, updated surveillance and management recommendations for the standardized, optimal clinical management of patients with TSC is provided separately.[10] One of the major goals of the conference was to revisit the clinical diagnostic criteria published subsequent to the first International TSC Consensus Conference in 1998.[11] Since 1998, one additional manuscript regarding the diagnostic criteria has been published that was designed to provide more guidance to practitioners by including pictures of the major and minor findings.[12] At the 2012 meeting, the most significant change recommended to the diagnostic criteria was the incorporation of genetic testing. Although the *TSC1* and *TSC2* genes were discovered before the 1998 conference, molecular testing was not widely available at that time. Molecular testing of the *TSC1* and *TSC2* genes yields a positive mutation result for 75-90% of TSC-affected individuals categorized as "definite" by the 1998 Consensus Conference Clinical Diagnostic Criteria.[2] The use of molecular testing in medicine has expanded greatly since the 1990s, becoming widely accepted as invaluable in the diagnosis of diseases with a genetic basis. Utilization of genetic testing for TSC was addressed along with refinement of clinical criteria.

Genetic diagnostic criteria

Comprehensive and reliable screens for *TSC1* and *TSC2* mutations are well-established, and many pathogenic mutations have been identified (www.lovd.nl/TSC1, www.lovd/TSC2). The recommendation of the Genetics Panel was to make identification of a pathogenic mutation in *TSC1* or *TSC2* an independent diagnostic criterion, sufficient for the diagnosis or prediction of TSC regardless of the clinical findings (Table part A). This will facilitate the diagnosis of TSC in some, particularly young individuals, allowing earlier implementation of surveillance and treatment with potential for better clinical outcomes. A "pathogenic" mutation was defined as a mutation that clearly prevents protein synthesis and/or inactivates the function of the TSC1 or TSC2 proteins (e.g., nonsense mutation or frameshift mutations, large genomic deletions) or is a missense mutation whose effect on protein function has been established by functional assessment.[13,14] *TSC1* and *TSC2* genetic variants whose functional effect is less certain are not definitely pathogenic and would not be considered a major diagnostic criterion. A significant fraction (10-25%) of TSC patients have no mutation identified by conventional genetic testing. Therefore, a normal result does not exclude TSC. Nonetheless, if the mutation in an affected relative is known, testing for that mutation has very high predictive value for family members. Assembled experts at the Consensus Conference agreed with the recommendation that identification of a pathogenic mutation in *TSC1* or *TSC2* is an independent diagnostic criterion.

Clinical diagnostic criteria

In addition to diagnosis by genetic analysis, the clinical diagnostic criteria used to establish the diagnosis of TSC were also reviewed at the conference. Special attention was