Diagnosis and Treatment of Tuberous Sclerosis Manifestations in Children: A Multicenter Study

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Abstract

Tuberous sclerosis complex (TSC) is a genetic disease with a significant morbidity and mortality. We conducted a retrospective analysis of two cohorts (Vall d’Hebron University Hospital [HVH], Barcelona, Spain, 1982–2015, and at Saarland University Medical Center [UKS], Homburg, Germany, 1998–2015) to assess prevalence and treatment of TSC associated manifestations and to evaluate if the follow-up was in line with published recommendations. This was considered if more than 15% of patients did not receive adequate examination with regard to potential organ involvement. A definite diagnosis was made in 52 patients (96%), and a possible diagnosis was made in 2 patients (4%). Thirty-four (63%) patients were from HVH and 20 (37%) from UKS. Median age at first presentation was 6 months (interquartile range: 0–38 months), and median time of follow-up was 6 years (interquartile range: 2–13 years). Clinical symptoms that led to a diagnosis of TSC were cardiac rhabdomyoma (22/54), epilepsy (20/54), and cutaneous manifestations (4/54). Assessment of neuropsychiatric, renal, and ocular manifestations was inadequate in both hospitals, whereas cutaneous manifestation was inadequate at UKS only. Our data demonstrate insufficient examinations in a substantial number of TSC patients with regard to neuropsychiatric, renal, ocular, and cutaneous manifestations. The recently published guidelines may prove valuable in establishing a more comprehensive approach.

Keywords

► mTOR
► everolimus
► SEG A
► angiomyolipoma
► rhabdomyoma
► epilepsy

Introduction

Tuberous sclerosis complex (TSC) is a genetic disease often with in utero onset, which is characterized by benign tumors affecting multiple organs including the heart, central nervous system, skin, kidney, and lungs.1–3 The broad range of clinical manifestations was first described in the late 19th century and has consequently led to the publication of several consensus

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The occurrence of epilepsy, in particular infantile spasms and treatment with antiepileptic drugs (AEDs), was assessed. Refractory epilepsy was defined if seizures persisted despite treatment with ≥3 AEDs. Adequate seizure control was defined as a seizure-free period of at least 12 months upon last follow-up. A patient was considered to have developmental delay in case of an abnormal age-appropriate neurodevelopmental test or an intelligence quotient test of ≤85, or if the patient experienced a delay in two out of four domains of normal development. Neuropsychiatric manifestation was determined based on neuropsychiatric testing or whenever a diagnosis of autism spectrum disorder or attention deficit/hyperactive disorder syndrome was documented. Ophthalmological and dermatological examinations were considered adequate if results from these examinations were documented in written form in the medical charts.

Results

General Demographics

Initially, 58 patients were identified, 4 of whom were excluded because of inappropriate medical records or not meeting diagnostic criteria for TSC. A definite diagnosis was made in 52 (96%) patients and a possible diagnosis was made in 2 (4%) patients (29 [54%] males and 23 [46%] females; 34 [63%] patients in HVH and 20 [37%] patients in UKS). The median age at first presentation was 6 months (interquartile range: 0–38 months), and the median time of follow-up was 6 years (interquartile range: 2–13 years) (~Supplementary Fig. S1). There was no statistical difference in terms of patient distributions and prevalence of symptoms between the two hospitals.

Results of molecular analysis were available in 31/54 (57%) patients: 23/31 (74%) patients demonstrated mutations in the TSC2 gene, 5/31 (16%) patients demonstrated mutations in TSC1 gene, and 3/31 (10%) patients were without TSC1/TSC2 gene mutation.

mTOR inhibitors were given to 12/54 (22%) patients (11 everolimus, 1 sirolimus) at an average age of 10 years (standard deviation: 6.9; range 0–24). Patients were treated on average for 28 months (range: 6–50 months).
TSC Nonneurologic Manifestations, Treatment, and Response

- Figs. 1 and 2 summarize the main clinical symptoms.

The most frequent manifestation that led to a diagnosis of TSC was the presence of cardiac rhabdomyoma (22/54 [41%] patients, 16 of whom were diagnosed by prenatal ultrasound). Overall, cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac arrhythmias were seen in 3/54 (6%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits. Cardiac rhabdomyomas were diagnosed in 38/54 (70%) patients. In 9/38 (24%) patients, involution of rhabdomyomas was noted during follow-up visits.

The presence of cardiac rhabdomyoma (22/54 [41%] patients), and dental pits (1 patient). A statistically significant difference was found between patients with and without neuropsychiatric pathologies.

- Fig. 5 and Supplementary Table S1 summarize the examinations performed in our cohort. In summary, the following examinations were insufficiently performed and/or documented: neuropsychiatric evaluation in 41/54 (76%) patients, renal imaging studies (ultrasound/MRI) in 11/54 (20%) patients, ophthalmological examination in 15/54 patients (28%), and dermatological examination in 11/54 (20%) patients. Similar results were found between the study periods (Supplementary Table S2) as well as between both hospitals, except for inadequate dermatological assessment, which was only seen at UKS (p = 0.006).
Discussion

In our study, all patients fulfilled the current diagnostic criteria for TSC or possible TSC. Due to the retrospective nature of our study, it was only possible to assess whether TSC1 or TSC2 mutations existed with regard to their pathogenicity, thus contributing to establishing a diagnosis of TSC in all affected patients. Of note, in all but two patients, a diagnosis of TSC could be established using clinical criteria only.

No differences were found in terms of patients’ demographics between both hospitals. To assess if patients underwent an appropriate diagnostic work-up of the TSC-related manifestations, the published recommendations from 1999 as well as from 2013 were used. Contrary to previous reports, the first key symptom that led to the diagnosis of TSC in our cohort was, for both hospitals, the detection of cardiac rhabdomyoma, most often in utero, followed by epilepsy. Compared with previous reports, a higher rate of in utero detection of cardiac rhabdomyoma was seen in...
our two cohorts, indicating improved antenatal care.\textsuperscript{22} We found a lower percentage of patients with epileptic spasms (26\%) compared with other clinical studies (33–54\%) as well as higher percentage of patients with refractory epilepsy (54\%) compared with previous reports (34–44\%).\textsuperscript{23–27} This may be because of the use of different definitions of refractory epilepsy.\textsuperscript{18} According to other studies, valproate and vigabatrin are the most common AEDs used in TSC.\textsuperscript{28} Differences in the use of sulthiame between our two cohorts can be easily explained by a lack of availability of sulthiame in Spain.\textsuperscript{29}

In this study, we found a higher prevalence of SEGA compared with other series.\textsuperscript{17,23,25,30–33} This may also be because of differences in SEGA definitions and improvement of cerebral imaging studies, most importantly the widespread use of high-resolution MRI. We found a similar response rate of SEGA to everolimus as in previous reports.\textsuperscript{34} Of note, two patients underwent a neurosurgery procedure, both treated at UKS. This may have to do with differential experiences in the surgical treatment of TSC patients with SEGA.\textsuperscript{31,35} The percentage of patients with developmental delay was similar when compared with previous reports.\textsuperscript{23,25,33} As described previously, a positive correlation between epilepsy and neurodevelopmental delay could be established; however, and contrary to other reports, we also found an association between neurodevelopmental delay and SEGA.\textsuperscript{26,36} Possibly, this association may be indicative of the extent of further underlying CNS pathology, for example, the number of cortical tubers. Unfortunately, due to the retrospective nature of our study, it was not possible to quantify in full detail all CNS pathologies, including the number, size, and location of cortical tubers in our study cohorts.

Of note, this is the first multicenter and international comparison (Spain, Germany) that demonstrates that TSC patients were often not managed in accordance with the current guidelines for diagnosis and long-term treatment. This effect was most apparent with regard to inappropriate assessment of neuropsychiatric, renal, ophthalmological and dermatological manifestations. This pattern was found in both hospitals (HVH and UKS), except for inadequate skin examination, which was only seen at UKS. Of importance, a specific screening test for TSC-associated neuropsychiatric disorders has been published after data completion, thus potentially improving this shortcoming.\textsuperscript{37} We found a higher prevalence of renal AML compared with previous reports. This finding could be explained by neither population demographics nor different prevalence of TSC2 mutations,\textsuperscript{21,38} but may at least in part be also attributed to the use of more sophisticated and readily available imaging modalities (ultrasound). Conversely, a possible explanation for the inappropriate use and implementation of renal examinations may be the young age of our two cohorts: in clinical practice, renal ultrasound is first performed at school age since the occurrence of clinically relevant renal
angiomyolipoma is usually seen at a later age (school age and thereafter).\textsuperscript{21,38} The percentage of patients with unknown information about dermatological manifestation may also be age-related. However, and of note, hypomelanotic macules (white spots) along with cardiac rhabdomyoma are among the very early organ manifestation of TSC.\textsuperscript{3,39} The underuse of dermatological and ophthalmological examinations may be secondary to the fact that a diagnosis of TSC was often already established based on cerebral imaging or cardiac ultrasound. Therefore, a dermatological and ophthalmological diagnostic evaluation may have been deferred, although recent guidelines recommend repetitive skin assessment.\textsuperscript{9} At UKS, we have taken action with regard to the aforementioned shortcomings in treating TSC patients, providing comprehensive optimized care in patients with rare diseases at the Center for Rare Diseases (ZSEUKS) at UKS.\textsuperscript{40}

Undoubtedly, this study has several weaknesses. First, this is a retrospective analysis with all its inherent shortcomings. Second, given the rarity of this disease, the number of patients included is limited. Third, the inclusion period spans almost four decades with substantial changes in both diagnostic and therapeutic approaches over time. Moreover, as a reference for adequate patient management of TSC patients, we used the definition of Roach et al from 1999, and current surveillance and management recommendations (Krueger and Northrup) were only used in patients included after 2013.\textsuperscript{6,8} Fourth, the cutoff value for inadequate management of TSC patients was somewhat arbitrarily chosen at >15%.

In summary, this is the first multicenter and international study (Spain, Germany), which demonstrates that TSC patients were often not managed in accordance with current guidelines on diagnosis and long-term treatment. This effect was most relevant with regard to inappropriate assessment of neuropsychiatric, renal, ophthalmological and cutaneous manifestations. More widespread application/use of current guidelines on diagnosis and long-term management has the potential to improve the care of TSC patients.

Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

Conflict of Interest
Prof. Dr. Macaya-Ruiz reports other from Advisory board, outside the submitted work. All the other authors have no conflict of interest.

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