ELSEVIER

Brain & Development 36 (2014) 306–314

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Wide spectrum of clinical manifestations in children with tuberous sclerosis complex – Follow-up of 20 children

Roland R. Mettin [a], Andreas Merkenschlager [a], Matthias K. Bernhard [a], Heidrun Elix [b], Wolfgang Hirsch [c], Wieland Kiess [a], Steffen Syrbe [a,*]

[a] *Department of Women and Child Health, Hospital for Children and Adolescents, University of Leipzig, Germany*
[b] *Clinic for Paediatrics and Adolescent Medicine, Klinikum Chemnitz gGmbH, Germany*
[c] *Department of Imaging and Radiotherapy, Section Paediatric Radiology, University of Leipzig, Germany*

Received 24 January 2013; received in revised form 10 May 2013; accepted 13 May 2013

Abstract

TSC is a multisystem genetic disorder predisposing to multiple organ manifestations and developmental problems. Clinical follow-up of patients remains a challenge for the caring paediatrician. *Methods:* We performed a retrospective analysis of clinical manifestations, diagnostic and therapeutic data in 20 children with the diagnosis of tuberous sclerosis complex (TSC) to answer the following questions: are the clinical guidelines and imaging strategies appropriate to discover complications, are there significant early predictors of long-term prognosis, what is the age range for signs and symptoms to occur. *Results:* Cardiac rhabdomyoma were present in 18 children and occurred as earliest manifestation. 8 of these exhibited associated arrhythmia or congenital cardiac anomalies. Seizures combined with cortical tubers and subependymal nodules occurred in 18 patients and were most likely to start in infancy, which was associated with later cognitive impairment. Cutaneous manifestations (15 children) occurred in late childhood and school age, whilst renal angiomyolipomas (11) developed in puberty. *Discussion:* The clinical course and imaging strategies are compared with data from previous studies. A review of TSC in regard to the multiple manifestations is provided.

Keywords: Tuberous sclerosis complex; Subependymal giant cell astrocytoma; Rhabdomyoma; Epilepsy

1. Introduction

Second only to neurofibromatosis type 1, tuberous sclerosis complex (TSC; tuberous sclerosis, Bourneville–Pringle's Disease) is the most common phakomatosis [1]. TSC is a multisystem genetic, autosomal-dominant disorder (OMIM 191100) which occurs in 1 in 6000 to 1 in 10,000 live births. In general, two-thirds of individuals are sporadic cases [2,3]. Mutations in two gene-loci have been identified as the cause for TSC. Mutations in the TSC2 gene (OMIM 191092; 16p13.3) are more common than mutations in the TSC1 gene (OMIM 605284; 9q34) [4–6]. TSC1 and TSC2 are tumour suppressor genes and their protein products form a complex. By inhibiting Ras homologue enriched in brain (RHEB) this complex modifies the mammalian target of rapamycin (mTOR) pathway, which regulates essential parts of protein translation and cell growth [7,8]. There is no strict genotype–phenotype-correlation, however individuals with TSC2 mutations experience more severe disease symptoms [9,10]. The penetrance is approximately 95%; but clinical manifestations vary from minor to severe disease [10]. In 1998 the current clinical diagnostic criteria were established by the Tuberous Sclerosis Complex Consensus

* Corresponding author. Address: Hospital for Children and Adolescents, University Hospitals, University of Leipzig, Liebigstr. 20a, D-04103 Leipzig, Germany. Tel.: +49 341 9726077; fax: +49 341 9726269.
E-mail address: steffen.syrbe@medizin.uni-leipzig.de (S. Syrbe).

0387-7604/$ - see front matter © 2013 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.braindev.2013.05.006

Conference (TSCCC) and distinguish between major and minor features [11]. This was followed by publishing surveillance protocols and recommendations for diagnostic evaluation of affected individuals [12,13]. TSC may cause multiple hamartomatous lesions of almost all organs with preference on skin, CNS, kidneys, heart, lungs and eyes [11,14–16]. CNS complications of TSC include seizures, cognitive impairment, behavioural problems and autistic spectrum disorder [2]. Morphologically these symptoms are attributed to multiple cerebral manifestations such as cortical tubers, subependymal nodules (SEN) or giant cell astrocytomas (SEGA), and cerebral white-matter radial migration lines (CRML) [17]. Based on the presence of major and minor features, a possible, probable or definite TSC diagnosis is to be established [11].

In this clinical report, the spectrum of clinical manifestations of 20 individuals with TSC is described and compared with current data in the literature with regard to frequency and age-dependence. An overview of TSC is presented by analysing diagnostic as well as therapeutic aspects, clinical course and usefulness of clinical diagnostic criteria and recommendations for diagnostic evaluation with regard to complications in a hospital-based cohort.

2. Subjects and methods

The children who were enrolled in this clinical report had been under medical attendance at the Department of Paediatrics of the University of Leipzig and at the paediatric department of one related teaching hospital between 1988 and 2012. All patients, who had been diagnosed with tuberous sclerosis complex in infancy, childhood and adolescence up to an age of 18 years, were evaluated by using standardised computer databases and written files.

According to Roach et al. and Hyman et al. the diverse clinical manifestations subdivided in major and minor, as well as the diagnostics and surveillance were documented in a patient sheet [11–13]. The patients were characterised as having a definite, probable or possible diagnosis and were systematically analysed related to age, gender, initial manifestation, clinical diagnosis, genetic diagnosis, inheritance, period of attendance and therapy with particular interest on seizure control. Seizure control was defined as complete, partial or refractory. Mental retardation, neuropsychiatric problems and autistic spectrum disorder were assumed, when having been examined with special tests or documented repetitively by neuropaediatricians. Assessment of mental retardation was based upon educational performance. All the clinical data were descriptively and statistically analysed using SPSS and compared with current literature. Written informed consent was obtained from the families and where appropriate from the patients themselves.

3. Results

3.1. Biographic and diagnostic characterisation of patients affected by TSC (Table 1)

A total of 20 individuals from 20 families with the definite diagnosis of TSC were identified. Female patients accounted for 11 of 20 patients (55%). The periods of medical follow-up varied from 8 months to 18 4/12 years (median period 5 11/12 years). The median age at initial clinical manifestation was 3 months and differed from median age of clinical diagnosis (1 8/12 years) with a median latency of 2.5 months.

Initial clinical manifestations were seizures (12 of 20; 60%) and cardiac rhabdomyomas (8 of 20; 40%). In 3 cases, the antenatal diagnosis of cardiac rhabdomyomas led to an immediate postnatal definite diagnosis of TSC. The median age of initial clinical manifestation, clinical diagnosis and latency was lower in individuals with rhabdomyomas as an initial symptom (0.6, 2.2 and 0 months) than in individuals with seizures (4, 29.5 and 8.5 months). MRI scan, abdominal ultrasonography and echocardiography were carried out in all patients. In infancy 2 patients were diagnosed by cranial ultrasonography, displaying multiple tubers and SEN. These findings were reproduced by MRI scan in the second year of life (Fig. 1).

Genetic analyses were performed in 8 of the 20 affected individuals with identification of two TSC2 mutations and one TSC2-PKD1 deletion syndrome. In the remaining 5 cases mutations in neither TSC1 nor TSC2 gene were identified. Genetic analysis was performed by multiplex ligation probe amplification and by sequencing the coding exons 3–23 of TSC1 and the exons 2–42 of TSC2. Amongst our patient group 3 definite familial (15%) versus 11 sporadic cases (55%) were identified. In 6 cases (30%) clinical or genetic data from relatives were not complete.

3.2. Clinical manifestations

3.2.1. Cutaneous manifestations (Tables 2 and 3)

Hypomelanotic macules were diagnosed in 15 of the 20 patients (75%) at a median age of 4 1/12 years. Bilateral facial angiofibromas were present in 9 of the 20 individuals (45%) with an age of diagnosis between 12 months and 13 2/12 years (median age 5 9/12 years) and in 9 of the 18 patients older than 5 years (50.0%). Fibrous forehead plaques were seen in 5 patients (25%) at median age of 13 years. Shagreen patches, found on the lumbosacral flank, upper legs and anterior trunk, were diagnosed in 5 individuals (25%) between 14 months and 18 11/12 years (median age 17 2/12 years). Ungual and subungual fibromas were noted in 2 patients at 16 7/12 and 19 6/12 years.