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1. Aktuelle Fachinformation TREMFYA®.
2. Reich K et al. Lancet 2019;394(10201):831–839.
3. Griffiths CEM et al. J Dermatol Treat (2020) https://doi.org/10.1080/09546634.2020.1782817

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Daher ist es wichtig, jeden Verdacht auf Nebenwirkungen in Verbindung mit diesem Arzneimittel zu melden.

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JDDG
Journal of the German Society of Dermatology

Minireview

Submitted: 13.3.2017
Accepted: 21.4.2017
Conflict of interest
None.

DOI: 10.1111/ddg.13264

Dermatological manifestations of tuberous sclerosis complex (TSC)

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Summary

Tuberous sclerosis complex (TSC) is a genetic multisystem disorder with prominent skin involvement that frequently occurs in early childhood. Dermatologic manifestations include facial angiofibromas, hypomelanotic macules, fibrous cephalic plaques, shagreen patches, and ungual fibromas. The International TSC Consensus Conference in 2012 provided guidelines for standardized baseline evaluation and follow-up. Detailed clinical dermatological evaluation at the time of diagnosis and annual skin examination is recommended for both pediatric and adult populations. The onset of dermatological manifestations is clearly age-related. However, dermatologists also have to assess for clinical manifestations beyond their own specialty. With advances in genetics and the advent of mTORC1 inhibitors, new specific therapeutic options have become available for TSC patients with skin manifestations. Early intervention is commonly recommended for symptomatic, rapidly evolving, disfiguring, or debilitating lesions. The consensus guidelines recommend "treatment as appropriate for the lesion and clinical context" and suggest the use of surgical excision, laser therapy, or topical mTORC1 inhibitors. Topical mTORC1 inhibitors present a useful option for TSC-associated skin lesions, particularly in medically complex patients. They may prevent or reduce the risks of subsequent surgeries and permanent scarring.

Introduction

Tuberous sclerosis complex (TSC) is a genetic multisystem disease that occurs with a frequency of about 1 : 5,800 to 1 : 12,300 births [1, 2]. It shows an estimated prevalence of 6.8–12.4/100,000 [3], equally distributed among all ethnic groups and both genders [4]. First descriptions of the disease date back to the 19th century when *von Recklinghausen* and later *Bourneville* documented key pathological findings in a small number of affected individuals [5, 6]. The British dermatologist *Pringle* reported *congenital adenoma sebaceum* as facial lesions frequently observed in individuals with intellectual disability, linking the dermatological manifestations to cognitive deficits seen in TSC patients [7]. Later, the German pediatric neurologist *Vogt* proposed a diagnostic triad consisting of seizures, intellectual disability, and facial angiofibromas [8]. Vogt's triad defined the clinical spectrum of TSC over the next 60 years, until *Gómez* published a monograph describing the full clinical spectrum of TSC for the first time [9]. The most common non-dermatological manifestations concern the central nervous system, heart, kidneys, lungs, and less frequently other abdominal organs, as well as retina, gingiva, or bones [2, 10]. Penetrance and expressivity are highly variable, ranging from mild dermatological symptoms with normal life expectancy to persistent epilepsy and severe intellectual disability. Benign hamartomas are the hallmark of this disease. They may develop in any of the aforementioned organs, showing variability with regard to their number, distribution, and size. In recent years, the discovery of the genetic cause of TSC has allowed a detailed delineation of the molecular biology behind many disease manifestations and offers – for the first time – the possibility of a targeted therapy that not only ameliorates symptoms but might eventually prevent or reverse some of the most disabling manifestations.

The objective of this review is to summarize the dermatological manifestations of TSC and provide an overview

of current diagnostic and therapeutic approaches with a particular emphasis on TSC-related skin lesions.

Pathophysiology and genetics

Despite the fact that TSC is inherited in an autosomal dominant manner, 70 % of cases are due to sporadic mutations. Loss-of-function mutations in the *TSC1* or *TSC2* genes are the root cause of TSC. *TSC1* on chromosome 9q34 and *TSC2* on 16p13 as well as their respective protein product (Tsc1 or hamartin and Tsc2 or tuberin) are critical regulators of the mTORC1 (mechanistic target of rapamycin complex 1) pathway [10]. The mTORC1 pathway is a key signaling pathway that controls cell growth, metabolism, and autophagy [11]. A pathogenic mutation in either *TSC1* or *TSC2* as detected by genetic analysis represents a separate diagnostic criterion and is sufficient for a definitive diagnosis regardless of clinical findings [12]. Many pathogenic mutations have been identified, summarized by the Tuberous Sclerosis Complex Variation Database (www.lovd.nl/TSC1, www.lovd.nl/TSC2). However, negative genetic testing does not rule out TSC, given that no mutation in *TSC1* or *TSC2* is identified by conventional genetic testing in a substantial subset of patients (~10–15 %) [12]. Remarkably, in 85 % of NMI (no mutation identified) patients, mutations can be found using next-generation-sequencing (mostly in introns or mosaic) [13].

Clinical diagnostic criteria

Diagnostic criteria as shown in Table 1 are grouped into major and minor features. The occurrence of two major features or one major feature with ≥ two minor features definitively confirms the clinical diagnosis of TSC. A possible diagnosis

Table 1 Diagnostic criteria according to the International Tuberous Sclerosis Complex Consensus Conference [12].

Definite diagnosis: Two major features or one major feature with ≥ two minor features **Possible diagnosis: Either one major feature or ≥ two minor features**		
Dermatology / dental medicine	Major feature: ▸ Hypomelanotic macules (n ≥ 3, ≥ 5 mm in diameter) ▸ Angiofibromas (n ≥ 3) or fibrous cephalic plaque ▸ Ungual fibromas (n ≥ 2) ▸ Shagreen patch	Minor feature: ▸ "Confetti" skin lesions ▸ Dental enamel pits (n > 3) ▸ Intraoral fibromas (n ≥ 2)
Neurology	Major feature: ▸ Cortical dysplasias (includes tubers and cerebral white matter radial migration lines) ▸ Subependymal nodules (SEN) ▸ Subependymal giant cell astrocytoma (SEGA)	
Ophthalmology	Major feature: ▸ Multiple retinal hamartomas	Minor feature: ▸ Retinal achromic patch
Cardiology	Major feature: ▸ Cardiac rhabdomyoma	
Pulmonology	Major feature: ▸ Lymphangioleiomyomatosis (LAM)[1]	
Nephrology	Major feature: ▸ Angiomyolipomas (n ≥ 2)[1,2]	Minor feature: ▸ Multiple renal cysts
Other organs		Minor feature: ▸ Nonrenal hamartomas
Genetics	Identification of a pathogenic mutation of either *TSC1* or *TSC2*[3] in DNA from normal tissue is sufficient to make a definite diagnosis	

[1]A combination of the two major clinical features (lymphangioleiomyomatosis and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.
[2]Anatomic location may include the liver or other organ systems.
[3]A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins, prevents protein synthesis or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd.nl/TSC2).

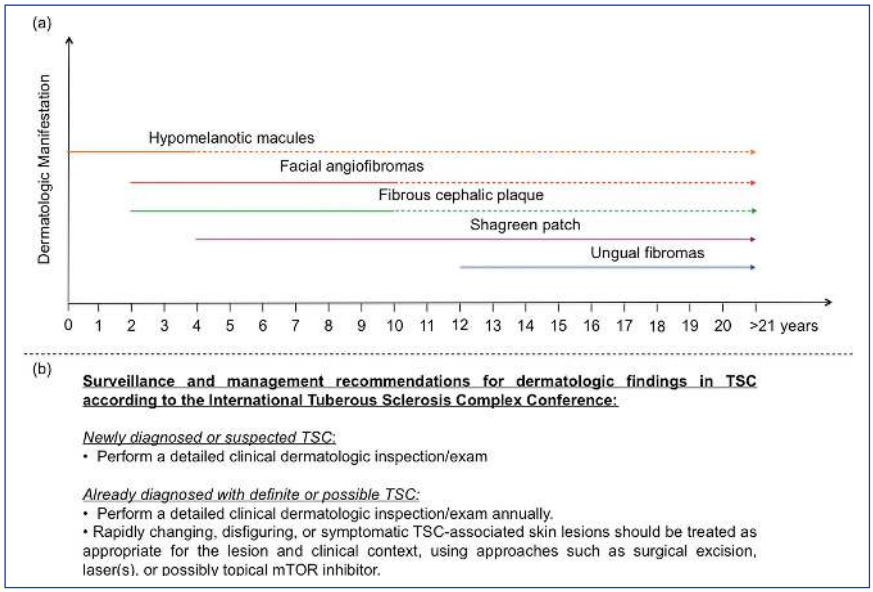

Figure 1 Estimated age at onset of symptoms (solid lines indicate the approximate age of onset, whereas dashed lines indicate continued symptoms) (a). Surveillance and management recommendations for dermatological findings in TSC according to the International Tuberous Sclerosis Complex Conference (b) [16].

is defined as either one major feature or ≥ two minor features [12]. The diversity of possible organ involvement highlights the fact that TSC is a multidisciplinary disease. In this context, dermatologists also have to look for clinical manifestations beyond their own specialty.

Dermatological manifestations

Given that dermatological manifestations may occur in infancy or early childhood, they frequently prompt an initial evaluation for TSC. Nearly every TSC-affected individual has skin or dental findings [12], highlighting the importance of a thorough dermatological evaluation to detect skin lesions for early diagnosis, especially in family members or individuals with suspected TSC. The onset of dermatological manifestations is clearly age-related (Figure 1a) [14–16].

The main dermatological manifestations in TSC patients include hypomelanotic macules (ash-leaf spots), facial angiofibromas, shagreen patches, and ungual fibromas (Figure 2). Although these lesions usually do not give rise to severe medical complications, if prominent, they can be disfiguring and frequently cause severe psychological problems for TSC patients and their families [17]. There is a wide range of differential diagnoses of cutaneous lesions, including vitiligo, Alezzandrini's syndrome, Vogt-Koyanagi-Harada disease, scleroderma and other autoimmune diseases, Birt-Hogg-Dubé syndrome and multiple endocrine neoplasia type 1.

Hypomelanotic macules

Observed in about 90 % of TSC patients, hypomelanotic macules (ash-leaf spots) frequently appear in the first years of life [12, 18, 19]. They become less apparent in late adulthood. Current guidelines include the occurrence of at least three hypomelanotic macules, each with a diameter of at least 5 mm, as a major criterion. The term "confetti" lesions is used if they are smaller and more numerous. Given that many adults in the general population develop similar lesions as a consequence of chronic sun exposure, the usefulness of this finding is limited in adults [12]. A history of onset in early childhood is therefore more suggestive of TSC. Poliosis is considered a variant presentation of hypomelanosis and is included in the count of hypomelanotic macules [12]. The use of a Wood's lamp may assist in detecting subtle cases [15].

Angiofibromas

Historically, facial angiofibromas used to be called adenoma sebaceum [7]. They occur in about 75 % of TSC patients, usually between the ages of two and five [12, 14, 18]. Throughout adolescence, they increase in number and size and may become quite disfiguring [17]. Bilateral facial angiofibromas are hamartomatous nodules of vascular and connective tissue, distributed over the centrofacial areas with a butterfly pattern on the cheeks, nasolabial folds, and the chin [10]. In children, they are occasionally mistaken for acne [15]. As they can appear as isolated sporadic lesions in the general population, the presence of at least three facial angiofibromas is required to qualify as a major feature in TSC [12, 20]. The occurrence of multiple facial angiofibromas in adolescence is almost pathognomonic for TSC. However, if they appear in adulthood, they should be treated as a minor feature. The differential diagnosis should then include Birt-Hogg-Dubé syndrome and multiple endocrine neoplasia type 1 [12, 15, 21].

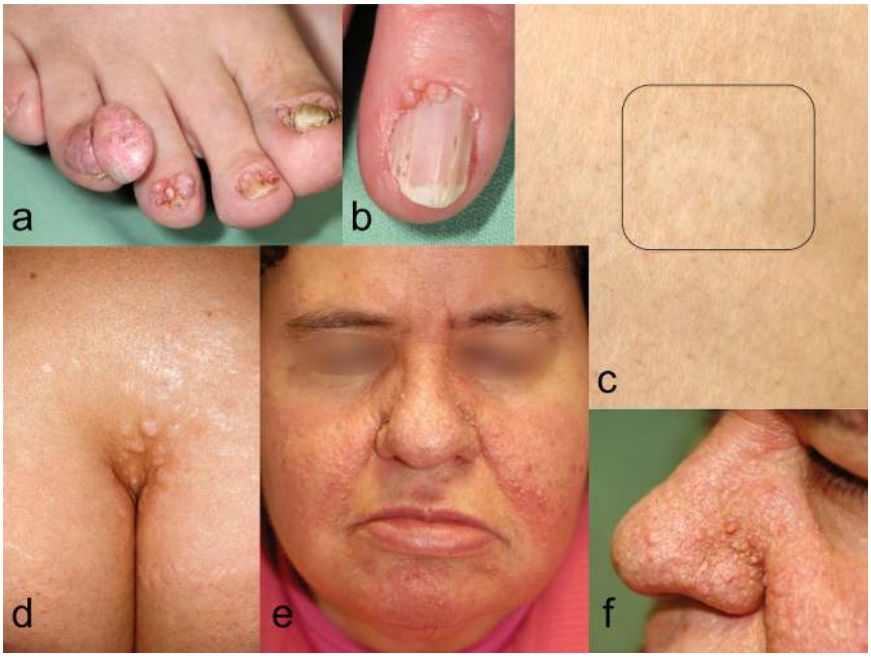

Figure 2 Clinical manifestations: ungual fibromas (a, b); hypomelanotic macule (c); shagreen patch (with kind permission by Professor Peter Altmeyer http://www.enzyklopaedie-dermatologie.de) (d); facial angiofibromas (e, f).

Fibrous cephalic plaques

A fibrous cephalic plaque may occur on the forehead or other craniofacial areas in about 25 % of TSC patients [12]. In the current diagnostic criteria, this feature is paired with angiofibromas. Fibrous cephalic plaques may represent the most specific skin finding. Histologically, they are similar to angiofibromas [12].

Ungual fibromas

Ungual fibromas (Koenen tumors), a term for periungual or subungual fibromas, show the latest onset of all dermatological manifestations as they predominantly occur during adolescence or sometimes even during adulthood [10, 12, 14, 15]. If they are located at the base of the nail, they can give rise to a groove [10]. While ungual fibromas can be found in 20 % of TSC patients, they may also be induced by trauma [12].

Shagreen patch

A large shagreen patch is a specific finding for TSC [15]. Usually located on the trunk, these lesions generally present as large plaques with an uneven surface [12]. Shagreen patches often appear in the first decade of life and are observed in about 50 % of TSC patients [12, 14].

Current management

Ideally, TSC patients should be referred to a specialized TSC clinic for interdisciplinary management, follow-up and support [16]. Recommendations for standardized baseline evaluation and follow-up have been provided by the International TSC Consensus Conference held in 2012 (Figure 1b) [12, 15, 16]. For most TSC patients, no skin biopsy is required; however, it may be appropriate if there is uncertainty regarding the clinical diagnosis [15]. Surveillance and management recommendations for dermatological findings in TSC according to the International TSC Conference include a detailed clinical dermatological exam for newly diagnosed or suspected TSC [15, 16]. If a definite/possible diagnosis of TSC has been established, annual inspection/exam is recommended [15, 16].

Therapeutic options

The activity of mTORC1 is sensitive to rapamycin and rapalogs (for example, everolimus). Results of the EXIST (examining everolimus in a study of TSC) studies led to the approval of everolimus by the FDA (U.S. Food and Drug Administration) and EMA (European Medicines Agency) for subependymal giant cell astrocytoma (September 2011) and renal angiomyolipoma (October 2012) [22, 23]. Remarkably, these studies also demonstrated the benefit of systemic mTORC1 inhibitors in treating dermatological manifestations of TSC. Skin response (secondary endpoint) rates were significantly higher than for placebo, with 58 % vs. 11 % in EXIST-1 and 26 % vs. 0 % in EXIST-2 [22, 23]. Based on results of the EXIST-3 study, everolimus has also been approved for adjunctive treatment of refractory partial-onset seizures, with or without secondary generalization, since January 2017 [24]. Reported adverse events of systemic therapy include. stomatitis, mouth

ulceration, hypercholesterolemia, hypertriglyceridemia, proteinuria, joint pain, bone marrow suppression, and infections [22, 23]. Case reports and small case series suggest that topical use of mTORC1 inhibitors represent a safe and effective treatment option for TSC-related cutaneous manifestations, however, long-term outcome data is pending [25–27]. Presently, no standard dose or formulation for topical use exists [15], although several formulations have been described in the literature and used with good effects [25–28]. It should be noted that long-term maintenance therapy is necessary to prevent the regrowth of facial lesions. To date, there has only been one randomized, controlled trial evaluating topical rapamycin therapy versus placebo [28]. Although subjects in the treatment arms reported greater subjective improvement in facial angiofibromas (73 %) compared to those in the placebo arm (38 %), this study did not reach statistical significance [28]. Indications for surgical treatment may include impaired function, irritation, pain, bleeding, and disfigurement [15]. While surgical approaches have been used for a long time, the benefits of invasive treatment options have to be weighed against the risk of scarring and the need for general anesthesia, especially in medically complex patients. Thus, the use of systemic (if indicated for other TSC manifestations) and topical mTORC1 inhibitors should always be considered in individuals with skin involvement, given that they are becoming the standard of care in most parts of the industrialized world. Topical mTORC1 inhibitors may prevent surgical procedures and reduce associated risks [15]. Nevertheless, selecting the best treatment approach depends on various aspects, including clinical presentation, comorbidities, and social stigmatization. In each individual, decisions should always be made on a case-by-case basis. Early intervention is commonly recommended for symptomatic, evolving, or disfiguring lesions. The consensus guidelines recommend "treatment as appropriate for the lesion and clinical context", and suggest the use of surgical excision, laser therapy, or topical mTORC1 inhibitors [15, 16].

Acknowledgments

We are very grateful to Professor Peter Altmeyer for kindly providing Figure 2 (d) (shagreen patch) for this publication.

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