Published in final edited form as:

J Am Acad Dermatol. 2018 April ; 78(4): 717–724. doi:10.1016/j.jaad.2017.12.027.

Fibrous Cephalic Plaques in Tuberous Sclerosis Complex

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Abstract

Background: Fibrous cephalic plaques (FCPs) stereotypically develop on the forehead of tuberous sclerosis complex (TSC) patients. They constitute a major feature for TSC diagnosis, and may present before other TSC-related cutaneous hamartomas.

Objective: To describe the clinical characteristics of FCPs in TSC.

Methods: 113 patients with TSC were enrolled in an observational cohort study. Retrospective analysis of medical records and skin photography was performed. FCPs were categorized per anatomic location and size.

Results: FCPs were observed in 36% (41/113) of patients. Of 62 total lesions, 58% were 1 to <5 cm, 13% 5 cm, and 29% unknown size mostly due to prior excision. The distribution of lesions was 39% forehead, 27% face (non-forehead), 3% neck, and 31% scalp. Fourteen patients had similar lesions less than 1cm in diameter. Histopathologically, FCPs displayed dermal collagenosis, decreased elastic fibers, and features of angiofibromas or fibrofolliculomas.

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DISCLAIMER:

The opinions and assertions expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Uniformed Services University, the Department of Defense or the National Institutes of Health.

IRB Approval status: Patients were consented to protocols 00-H-0051, 95-H-0186 and/or 82-H-0032 approved by the National Heart, Lung, and Blood Institute Institutional Review Board

Conflicts of Interest: No conflict of interest reported

Statement on any prior presentation:

Presented at the National Medical Association Annual Convention and Scientific Assembly, Dermatology Symposium. Philadelphia, Pennsylvania, July 31, 2017.

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Limitations: Men were underrepresented since the cohort was enriched for TSC patients with lymphangioleiomyomatosis, which occurs in adult women.

Conclusion: Two-fifths of FCPs presented on the forehead, with most of the remainder in other locations on the face and scalp. Better recognition of these lesions may lead to earlier diagnosis of TSC.

Keywords

Tuberous sclerosis complex; Fibrous cephalic plaques; Cutaneous Manifestations of Tuberous Sclerosis; Histology of Fibrous Cephalic Plaque; Diagnosis of Tuberous Sclerosis; Forehead Plaque; Scalp Fibroma

INTRODUCTION

Tuberous sclerosis complex (TSC) has wide phenotypic variability characterized by the formation of benign tumors in multiple organs [1, 2]. TSC results from an inactivating mutation in either *TSC1* or *TSC2* leading to aberrant activation of the mechanistic target of rapamycin (mTOR) signaling cascade in tumors [3]. The two most commonly affected organs are the brain and skin. Brain involvement is usually discovered when a child presents with seizures [1]. Nearly all TSC patients develop dermatologic lesions such as facial angiofibromas, hypomelanotic macules, shagreen patches, ungual fibromas, and fibrous cephalic plaques (FCPs) [4]. These lesions are included in the major diagnostic criteria from the 2012 International Tuberous Sclerosis Complex Consensus Conference [5].

The use of clinical diagnostic criteria and genetic testing promotes timely and accurate diagnosis. However, diagnostic delay is not uncommon, with TSC diagnosed in some individuals decades after the appearance of characteristic skin lesions [6]. Nearly 12% of TSC patients are not diagnosed until adulthood, usually after an affected child receives the diagnosis [7]. One contributing factor for delayed diagnosis may be failure to consider TSC in those lacking seizures; up to 15% of patients do not report history of seizures [8]. Another factor may be poor recognition of characteristic skin lesions, including FCPs.

FCPs may present at birth and commonly become noticeable in early childhood [9]. Seminal reports documented these plaques on the scalp or face of patients with TSC, and described histopathologic similarities to angiofibromas [10, 11]. Concepts and terminologies have varied, with some authors grouping lesions on the face or scalp, some discussing them separately as forehead plaques and scalp fibromas, and others using the term forehead plaque to include all lesions on the face and scalp. This makes it challenging to assess the literature with regards to frequencies of these lesions, reported as 19-36% for forehead plaques [9, 12], 13-30% for scalp fibromas [13, 14], and 46% overall [15]. A potential source of variability is that forehead plaques are more common in patients with mutations in *TSC2* than *TSC1* (40% vs. 10%) [12]. It is also likely that small lesions, especially if covered by hair on the scalp, are easily missed.

Our goal was to describe the clinical and histopathologic characteristics of FCPs in TSC. Herein we report the full scope and less classic presentations of FCPs to improve recognition of this diagnostic feature.

PATIENTS AND METHODS

A total of 113 adult TSC patients were examined at the National Institutes of Health (NIH) in Bethesda, Maryland from 1998 to 2016. Each provided written informed consent per protocols 00-H-0051, 95-H-0186 and/or 82-H-0032, which were approved by the National Heart, Lung, and Blood Institute Institutional Review Board. All patients met the revised diagnostic criteria of the 2012 International Tuberous Sclerosis Complex Consensus. The cohort was enriched for those with pulmonary lymphangioleiomyomatosis (LAM) and therefore consisted mostly of women [16]. Patients were evaluated for the presence or absence of FCPs and queried regarding the age of onset of lesion(s). Paired samples of FCP and normal skin were obtained from 11 patients and sections stained with routine haematoxylin and eosin.

Pictures were taken. Lesions were classified according to size based on the length of the major axis: 1 to <5 cm, and ≥5 cm (large FCPs). These categories were arbitrarily selected to provide information on size distribution in this population. Anatomic location was mapped onto a 3D mannequin head, and subsequently outlined on a representative head using Adobe Illustrator. Similar appearing lesions less than 1 cm in diameter, and clinically distinct from classic angiofibromas, were also mapped. Lesions were classified as left, right, or midline. Statistical analysis of lesion lateralization was conducted using Wilcoxon signed rank test.

RESULTS

Fibrous Cephalic Plaques

Frequency—The 113 adult patients with TSC were comprised of 108 women and 5 men ranging in age from 30 to 72 (median age 46) (Table I). Forty one patients (36%) had a FCP, one of whom was male. A total of 62 lesions were categorized by size into 36 “typical” FCPs (1 to <5 cm), 8 large FCPs (≥5 cm), 16 of unknown size that were excised, and 2 FCPs whose size could not be accurately determined from photos or medical records (Table II). Twenty-nine patients (71%) had a solitary lesion and 12 patients (29%) had multiple.

Clinical Features—FCPs appeared as rubbery to firm, smooth to bumpy, skin-colored, pink, red, or brown plaques (Fig 1A). Patients with more darkly pigmented skin tended to have much darker lesions relative to surrounding skin than did patients with lightly pigmented skin (Fig 1B). FCPs on the scalp were associated with decreased hair density in the location of the lesion (Fig 1C). Twenty patients (49%) reported onset of FCP at birth or during the first year of life (Table I). Many patients were unable to recall an age of onset, often because the lesions were unnoticed and asymptomatic. Fourteen patients had excisions of 16 lesions, primarily for cosmetic reasons and rarely for bleeding or pain in the scalp. Lesions did not recur except for one patient who reported thickening and pain near the scar. TSC diagnosis was frequently delayed even in those having their lesions excised. The

median delay in years from onset of FCP to TSC diagnosis was 16 years (range -12 to 52, n=28).

Location—The distribution of lesions was 24 (39%) on the forehead, 17 (27%) face (non-forehead), 2 (3%) neck, and 19 (31%) scalp. The outlines of these lesions are shown in Figure 2, excluding the 18 that could not be accurately mapped due to excision (7 forehead, 6 non-forehead face, and 3 scalp) or inadequate documentation (1 forehead and 1 scalp). FCPs were more common on the left side, with 38 left-sided lesions (67%) and 19 right-sided (33%), (significantly different from 50% expected, $p=0.024$, excluding 3 midline FCPs previously excised and 1 lesion with unknown laterality).

Histopathology—Of the 11 FCPs that were biopsied and histopathologically analyzed, all had thickened, disorganized bundles of reticular collagen in the dermis with decreased elastic fibers compared to unaffected skin (Fig 3A). Many lesions exhibited increased dilated vessels as observed in angiofibromas (Fig 3B). Others showed involvement of hair follicles ranging from distorted hair follicles with extensive perifollicular fibroplasia to bundles of collagen surrounding cords of abnormal epithelium emanating from the infundibular portions of the hair follicles, similar to fibrofolliculomas (Fig 3C). In addition, some samples exhibited fibrosis around eccrine glands.

Lesions <1cm

Fourteen patients (12%) had lesions similar to FCPs that were less than 1cm in diameter (Fig 1D). Five of these 14 patients did not have an accompanying FCP. There were a total of 23 lesions <1cm and the median number of lesions per patient was 1 (range 1-5). Five patients (36%) had multiple lesions while nine patients (64%) had solitary lesions. These lesions were skin-colored, pink, red or brown papules. The majority of lesions <1cm had an unknown age of onset. They were outside typical locations for angiofibromas, often in the scalp or lateral face, and did not arise from a confluence of angiofibromas. Of the twenty-three smaller lesions, 11 were located on the scalp (48%), 7 on the forehead (30%), and 5 on the face (22%) (Fig 2). There were 13 (57%) left-sided, 9 (39%) right-sided, and 1 (4%) previously excised midline lesion; a trend toward lesions on the left was not statistical significant ($p=0.54$). Eight of the lesions <1cm in size were histopathologically analyzed and showed features similar to FCPs, including thickened dermal collagen bundles and decreased elastic fibers. Some of the lesions additionally showed vascular changes similar to angiofibromas, as well as perifollicular fibroplasia.

DISCUSSION

Fibrous cephalic plaques were present in 36% of our cohort with TSC, within the range of 19-46% reported in previous studies [9, 12, 15]. Onset was commonly in infancy or early childhood. Lesions were significant enough to be excised in 34%. Despite this, TSC diagnosis was often delayed until late teens or adulthood, highlighting the need for improved recognition of this cutaneous manifestation of TSC.

The stereotypical location for FCP is the forehead, but only two-fifths were located on the forehead in our study. They occurred just as commonly on the non-forehead face and scalp,

and more rarely on the neck. Most FCPs occurred as a solitary plaque, generally measuring 1 to 5 cm along the longest axis. In our experience, FCPs have a characteristic appearance, particularly when large, with few lesions displaying similar features. The differential diagnosis may include melanocytic nevi, keloids, cutaneous lymphomas, neurocristic cutaneous hamartomas, and granuloma faciale. These entities can be excluded based on history and appearance, or biopsy if required. The differential diagnosis may also include the folliculocystic and collagen hamartoma associated with TSC. Two TSC patients have been described with folliculocystic and collagen hamartomas on the scalp. In contrast to FCPs these hamartomas show comedo-like openings that may drain a purulent material, and may also occur on the trunk [17], [18]. The presence of a FCP or multiple facial angiofibromas is a major feature for diagnosis of TSC; one additional major feature is sufficient for a clinical diagnosis [5]. A child with a FCP has possible TSC and should have a thorough diagnostic evaluation regardless of documented seizures [19].

FCPs may present before other manifestations of TSC, as an isolated skin finding or with hypomelanotic macules, the most common cutaneous manifestation of TSC in infancy [9], [20]. FCPs can be disfiguring, leading to stigmatization and low self-esteem. In our study, fourteen patients had lesions excised primarily for cosmetic reasons. Alternatives to surgical excision include vascular laser therapy for erythematous lesions or ablation with a CO₂ laser [4, 21]. A combination of pinpoint electrosurgery, pulsed dye laser, and ablative fractional resurfacing was shown to flatten and soften an FCP in one patient [22]. The potential for treating these lesions using an mTOR inhibitor was suggested by studies showing that fibroblast-like cells grown from FCPs show activation of mTOR signaling due to biallelic mutations in *TSC2*, and treatment responses observed in xenograft and conditional knockout models [23-25]. Recently, topical 1% sirolimus cream was shown to improve the appearance of FCPs in 9 of 16 patients after 3 to 9 months of treatment [26].

Interestingly, FCPs were more common on the left side in our cohort. It appears that large shagreen patches in TSC patients also predominate on the left [27]. This may be spurious but a potential biological explanation can be postulated based on the role of the primary cilium in lateralization. Loss of *Tsc1* or *Tsc2* leads to aberrations in the length of the primary cilium in mouse embryonic fibroblasts [28, 29], and morpholino knockdown of *tsc1a* in zebrafish causes ciliary dysfunction and left-right asymmetry defects [30]. The manner in which abnormalities in the primary cilium might impact embryonic development and subsequent tumor localization is unknown. Further studies are warranted to confirm possible lateralization.

Histopathologic examination of FCPs revealed thickened bundles of reticular collagen with decreased or absent elastic fibers. In addition to these features, with similarities to the shagreen patch of TSC, lesions frequently showed focal areas that were histopathologically similar to angiofibroma, perifollicular fibroma, fibrofolliculoma, or combination thereof. Angiofibromatous changes have been documented previously in forehead plaques [9] and a scalp fibroma [31]. Multiple fibrofolliculomas are classic for Birt-Hogg-Dubé (BHD) syndrome, but a facial fibrofolliculoma was previously reported in a patient with TSC [32]. Our observations indicating variable stromal and epithelial findings in FCPs, with a histopathologic spectrum varying from angiofibroma to fibrofolliculoma, support the

proposition that cutaneous hamartomas in TSC and BHD syndrome share a common histogenesis [33].

In addition to FCPs, 12% of our cohort presented with lesions similar in clinical and histopathologic appearance to FCPs but measured <1cm in diameter. These lesions do not fulfill diagnostic criteria. Clinical diagnostic certainty is less for these small lesions than for large FCPs. In the absence of other TSC-related skin findings, confirmation with a skin biopsy is necessary. Patients with histopathologically confirmed, small FCP-like lesions should be questioned for a personal or family history suggestive for TSC, closely examined for additional mucocutaneous features of TSC, and considered for complete diagnostic evaluation. This presentation and work-up is analogous to small collagenomas <1cm diameter that do not meet criteria for shagreen patch [27].

Limitations of this study include the retrospective design, use of patient-reported onset of FCPs, and the small sample size for histopathologic analysis. Ages of onset were by patient or parent recollection and a prospective study is needed to define when these lesions appear. Our cohort was comprised mainly of adult women due to enrichment for those with pulmonary lymphangioleiomyomatosis, which occurs almost exclusively in women. It is possible that our results are not generalizable to men with TSC. However, one study found no significant difference in frequency of fibrous forehead plaques in men compared to women [34]. We did not observe the evolution of these lesions from early childhood, although FCPs in adulthood remained stable over time. FCPs in children have been observed to grow slowly and become raised [9].

CONCLUSIONS

Only about two-fifths of FCPs present on the classic location of the forehead, with the remainder split between other locations on the face, neck, or scalp. In addition to thickened collagen and decreased elastic fibers, FCPs frequently show stromal and epithelial changes that fall on a spectrum between angiofibromas of TSC and fibrofolliculomas of BHD syndrome. Better recognition of these lesions by clinicians may help to ensure prompt diagnosis, early treatment initiation and appropriate referral for follow-up of other TSC-related sequelae.

ACKNOWLEDGEMENTS:

We thank Sorana Raiciulescu, M. Sc. (Uniformed Services University) for statistical analysis. This work was supported by NIH R01AR062080 and the Intramural Research Program of the National Institutes of Health, National Heart, Lung, and Blood Institute. This research was also made possible through the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation, the American Association for Dental Research, the Colgate- Palmolive Company, Genentech, and other private donors. For a complete list, visit the foundation website at <http://www.fnih.org>.

ABBREVIATIONS AND ACRONYM LIST

(FCP)	Fibrous cephalic plaque
(TSC)	Tuberous sclerosis complex

(mTOR)	Mechanistic target of rapamycin
(LAM)	Lymphangioleiomyomatosis
(BHD)	Birt Hogg Dube

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CAPSULE SUMMARY

- Fibrous cephalic plaques present early in life and are a characteristic manifestation of tuberous sclerosis complex
- Lesions classically occur on the forehead but are frequent elsewhere on the face or scalp
- Identification of fibrous cephalic plaques may promote earlier diagnosis of tuberous sclerosis complex

Figure 1. Tuberous Sclerosis Complex. Clinical Appearance of Fibrous Cephalic Plaques (FCP) and FCP-like lesions <1cm in size. (A) FCP on the forehead of a lightly pigmented individual. (B) Two lesions on the forehead of a darkly pigmented individual. (C) Scalp FCP exhibiting decreased hair follicle density. (D) Lesion <1cm on the forehead, with onset at birth prior to the development of multiple facial angiofibromas.

Figure 2.

Tuberous Sclerosis Complex. Locations and sizes of fibrous cephalic plaques. FCPs 1cm to < 5 cm in red, large FCPs ≥ 5cm in yellow. Also shown are lesions similar to FCPs <1cm in blue. A: Front face. B: Left face. C: Right face. D: Back of head. E: Top of head.

Figure 3.

Tuberous Sclerosis Complex. Histopathologic features of FCPs. A: FCP from scalp. Two abnormally shaped hair follicles partially surrounded by sclerotic collagen and separated by thickened bundles of reticular dermal collagen fibers (4x). B: FCP from forehead. There is increased vascularity characteristic of an angiofibroma (40x). C: FCP from cheek. Cords of squamous epithelium emanate from the infundibular portion of hair follicles. The hair follicle is surrounded by sclerotic collagen that is focally arranged perpendicularly to the follicular epithelium (20X).

Table I:

Characteristics of individuals with TSC

		No. (%) of patients
Sex		
	Female	108(96)
	Male	5 (4)
Race		
	White, not Hispanic	91 (81)
	Black, not Hispanic	8 (7)
	Asian or Pacific Islander	3 (3)
	Hispanic	9 (8)
	Other or unknown	2 (2)
Fibrous Cephalic Plaque		
	Yes	41 (36)
	No	72 (64)
Age of onset per patient report		
	0-<2 year	20 (49)
	2-<5 years	2 (5)
	5-<10 years	3 (7)
	10-<15 years	2 (5)
	15-<18 years	0 (0)
	18 years	1 (2)
	unknown	13 (32)

Table II:

Size and Distribution of FCPs in TSC

		No.	%
All Locations		62	
	FCPs < 5cm	8	13
	FCPs 1- 5cm	36	58
	FCPs with prior excision	16	26
	FCPs with size not documented	2	3
Forehead		24	39
	1-<5cm on forehead	14	58
	5cm on forehead	2	8
	Unknown size	8	33
Face (non-forehead)		17	27
	1-<5cm on face	9	53
	5cm on face	2	12
	Unknown size	6	35
Neck:		2	3
	1-<5cm on neck	0	0
	5cm on neck	2	100
	Unknown size	0	0
Scalp:		19	31
	1-<5cm on scalp	13	68
	5cm on scalp	2	11
	Unknown size	4	21