



Clinical and Dermoscopic Approaches to Diagnosis of Frontal Fibrosing Alopecia: Results From a Multicenter Study of the International Dermoscopy Society

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ABSTRACT **Introduction:** Frontal fibrosing alopecia (FFA) is a form of primary lymphocytic scarring alopecia characterized by a progressive recession of the fronto-temporal hairline. Although the clinical presentation of FFA is very typical, biopsy for histopathological examination is still recommended to confirm the diagnosis. Currently, a growing number of skin and mucosal inflammatory diseases are diagnosed with modern noninvasive techniques such as dermoscopy without the necessity of a biopsy.

Objectives: The International Dermoscopy Society (IDS) aimed to test the ability of its members to diagnose classic FFA through clinical and dermoscopic parameters and to compare acquired data to the largest cohort studies published since 1994.

Methods: This is an observational, cross-sectional study describing patient demographics, clinical presentation and diagnostic tools used in a sample of FFA patients collected by IDS members. A literature search was then performed using Pubmed to review studies reporting more than 100 cases.

Results: IDS members submitted 188 cases demonstrating a predominant female population (98.4%). In 71.8% of the cases, the clinical presentation and the trichoscopic findings allowed for the diagnosis. Out of 24 revised studies, 13 showed that clinical and trichoscopic features were decisive for the diagnosis in almost all cases.

Conclusions: Demographic and clinical data of our cohort were mostly comparable to previous reported data on FFA. The relevant role of the clinical and trichoscopic features in diagnosing FFA was confirmed by our study and the reviewed literature. Trichoscopy could be considered a worldwide-acknowledged non-invasive technique for the diagnosis of FFA.

Introduction

Frontal fibrosing alopecia (FFA), first described by Kossard in 1994 [1,2] is a form of primary lymphocytic scarring alopecia characterized by a progressive band-like recession of the fronto-temporal hairline and, in 50-75% of cases, by a partial or complete alopecia of the eyebrows. Whether FFA is only a form of lichen planopilaris (LPP) or a more complex disorder is still a matter of debate [3-5].

Thousands of cases have been described to date, with increasing incidence of the disease worldwide. Postmenopausal women are still those primarily affected, but women with childbearing potential and males can also present with this disease [6-8]. Scalp FFA can also present in atypical forms such as linear, diffuse, zig-zag, and pseudo-fringe patterns [9]. Hair follicles on the occipital scalp and sideburns can also be involved as well as eyelashes, beard, axillae, limbs and pubis [10-12]. Lichen planus pigmentosus, facial papules and facial erythema have also been described in patients with FFA indicating that this is not necessarily a disease limited to the scalp and eyebrows [13-15].

The real incidence of FFA is unknown, but the important increase in the reported cases in recent years has led some authors to refer to it as an epidemic disease [16]. The etio-pathogenesis and the reason for the increasing incidence of FFA are still unknown. The fact that FFA develops later in life suggests that triggering environmental factors might play a role in the development of the disease. A genetic basis has also been hypothesized since FFA has been diagnosed in siblings and members of the same family [17, 18]. Although FFA is thought to be a variant of LPP, there is no reported association with HLA-DR1. A recent genome-wide association study showed

that FFA correlates with the HLA-B*07:02 allele [19]. Lastly, it has been speculated that the disease was present even before Kossard's first description, but somehow passed unnoticed [20].

Due to the lack of randomized clinical trials and lack of a control group in previous clinical studies, treatment of FFA is not evidence-based [21]. Lack of evidence doesn't mean, however, lack of effectiveness. Disease control might be achieved with topical, intralesional and oral treatments, often combined together. The treatment aim is always to stop disease progression [22].

At present, although the clinical picture of FFA is very typical in most cases, a biopsy for histopathological confirmation is still recommended to administer the correct treatment [23]. In cases not involving the scalp, a biopsy is mandatory. Scarring might be subtle and the fibrous tracts so thin that the loss of follicular ostia might be missed. Thus, FFA can be mistaken for a nonscarring alopecia, particularly alopecia areata (AA) and androgenic alopecia (AGA). Moreover, due to the presence of the disease in cosmetically sensitive areas, patients do not always accept biopsy even if it is a 2-mm punch biopsy [24]. For these reasons, modern noninvasive techniques including dermoscopy [25-27], reflectance confocal microscopy [28] and optical coherence tomography [29] are increasingly used to diagnose several skin and mucosal inflammatory diseases. The goal is to perform a diagnosis without the necessity of a biopsy and to reserve it only for early stages, doubtful cases and/or uncommon presentations.

Therefore, the International Dermoscopy Society (IDS) aimed to test the ability of its members to diagnose typical or classic FFA through clinical and dermoscopic parameters and compare the acquired data to the largest cohort studies published since 1994.

Methods

The study was launched by the IDS via an online call for contributions published on the IDS website (www.dermoscopy-ids.org). From March 2018 to March 2020, IDS members were invited to submit cases of FFA. High quality clinical and dermoscopic images of the clinical presentations were mandatory. Information on patient demographics and lesion characteristics were also required including age, gender, involved skin/scalp areas, time at onset, subjective symptoms and trichoscopic features. Furthermore, information regarding the diagnostic methodologies were also mandatory. The study was conducted in accordance with ethical guidelines, and IRB approval was obtained. All data were collected and analyzed.

A literature search for “frontal fibrosing alopecia” was then performed on PubMed and returned 502 items (April 2021). Only papers reporting more than 100 cases were considered and revised. For each paper the year of publication, the number of patients, the origin of the population, the type of diagnostic methodology was collected.

Results

After the initial call, 206 FFA cases from 10 different centres were collected, but 18 cases were excluded from analysis due to misdiagnosis (8.7%). The clinical and trichoscopic data of all 188 included cases are presented in Table 1. The mean age of the studied population was 62 years (range 40–84) with a predominant female population (98.4%) and only 3 male patients. The great majority of the female population were post-menopausal (88.1%) with an average age of climacteric onset at 44.3 years. The mean age at onset of the disease was 58.6 years, on average 11.2 years after menopause. However, the disease was diagnosed up to 35 years after menopause. Regarding the degree of disease at diagnosis, 51.6% of the patients already showed grade 2 disease at that timepoint. When the frontal scalp was involved, the mean recession of the hairline was 2.35 cm (0-10 cm) and the distance between the glabella and the forehead was 7.57 cm (range 5-15 cm). FFA also affected the parietal regions in 70.2% of cases (132/188), while the occipital region was involved in 11.7% of cases (22/188). The sideburns were not affected in any of the patients.

Reduction or complete loss of eyebrows was reported in 85.6% of patients with partial loss in 104 patients (55.3%) and total loss in 56 patients (29.8%). The beard was involved only in one male patient, whereas involvement of eyelashes, armpits and pubis were reported in 52 (27.6%), 80 (42.5%) and 68 (36.1%) patients, respectively. In all cases with an extra-scalp involvement, the eyebrows were also compromised at the same time. Non-inflammatory facial papules were observed in 56 patients (29.8%). In 48 patients, they

Table 1. Clinical and Trichoscopy Data from 188 Patients Affected by FFA and Collected Through the International Dermoscopy Society Online Call

Characteristics	
Age (range)	62 (40-84) years
Female patients	98.4% (185/188)
Post-menopausal patients	88.1% (163/185)
Menopause onset, mean age (range)	44.3 (40-61) years
FFA family history	10.1% (19/188)
AGA family history	42% (79/188)
AGA personal history	38.8% (73/188)
FFA onset, mean age (range)	58.6 (15-84) years
Disease duration, mean (range)	4.4 (2 months – 30 years) years
Clinical Severity	
Grade 1	37 (19.6%)
Grade 2	97 (51.6%)
Grade 3	45 (23.9%)
Grade 4	7 (3.7%)
Grade 5	2 (1%)
Clinical Data	
Recession	2.35 (0-10) cm
Glabella-hairline distance	7.57 (5-15)
Occipital area involvement	11.7% (22/188)
Parietal area involvement	70.2% (132/188)
Eyebrows involvement	85.6% (161/188)
Eyelashes involvement	27.6% (52/188)
Body hairs involvement	47.3% (89/188)
Armpits hairs involvement	42.5% (80/188)
Pubis hairs involvement	36.1% (68/188)
Beard (*men only*)	33.3% (1/3)
Facial papules	29.8% (56/188)
Scalp symptoms	
Pruritus	65.9% (124/188)
Trichodynia	22.9% (43/188)
Trichoscopy	
Empty follicles	93.6% (176/188)
Absence of follicular ostia	92% (173/188)
Perifollicular erythema	63.8% (129/188)
Follicular hyperkeratosis	60.1% (113/188)
Lonely hairs	54.8% (103/188)
Clinical associations	
AGA	38.8% (73/188)
Lichen planopilaris	18.6% (35/188)
Lichen planus (skin/mucosae/nails)	5.3% (10/188)
Diagnostic methods	
Dermoscopy	71.8% (135/188)
Biopsy	28.2% (53/188)

FFA=frontal fibrosing alopecia; AGA= androgenetic alopecia

were localized on the face, in 6 patients on the limbs and in 2 patients simultaneously on the face, limbs and trunk.

Concomitant signs of LPP on the scalp were present in 35 patients (18.6%). Five of them showed diffuse hair thinning in the crown area associated with trichoscopic and histopathological features of LPP and were diagnosed with fibrosing alopecia in a pattern distribution (FAPD). Ten out of 188 patients (5.3%) had lichenoid changes on the skin, mucous membranes and/or nails. The concomitant presence of AGA was found in 73 patients (38.8%).

A family history of FFA was reported in 19 patients (10.1%) with a mean age of onset at 56.4 years, while it was 59.6 years in patients without a family history ($P = 0.9$).

Trichoscopy reports showed signs of cicatricial alopecia in all patients, with empty follicles in 93.6% of cases and absence of follicular ostia in 92% of cases. The presence of inflammatory signs such as perifollicular erythema and perifollicular hyperkeratosis were present in 129 (63.8%) and 113 (60.1%) of the patients, respectively. One hundred and three patients (54.8%) presented lonely hairs. Trichoscopic signs were not associated with the degree of disease, but clinical signs of inflammation such as perifollicular erythema and perifollicular hyperkeratosis were associated with the presence of pruritus ($P = 0.049$). Indeed, 124 patients (65.9%) complained of itching and 43 (22.9%) reported concomitant trichodynia.

In most cases (71.8%), the characteristic clinical presentation (Figure 1) and the typical trichoscopic findings (Figure 2) made it possible to make the diagnosis of FFA without resorting to the use of invasive diagnostic techniques. Only 53 patients required a histopathological diagnosis.



Figure 1. Clinical presentation of a female with frontal fibrosing alopecia.



Figure 2. Trichoscopy of a female affected by frontal fibrosing alopecia.

The literature search identified a total of 24 papers (all published between 2014 and 2021) with more than 100 included cases (Table 2) [19, 25-27, 30-49]. During 2014, 2015, and 2016 only one study was published per year [25,48,49]. Two and 5 studies were published in 2017 and

Table 2. Data of Published Studies on FFA Reporting more than 100 Cases

	Number of patients	Sex M/F	Population	Type of diagnosis	Data collected
Pindado-Ortega C et al 2021 [30]	224	2/222	Spain	Clinical (histopathological when needed)	Retrospective observational study on effectiveness of dutasteride in FFA
Muller Ramos P et al 2021 [31]	451	18/433	Brazil	NA	Multicenter case-control study on risk factors for FFA
Grassi S et al 2021 [32]	119	8/111	Italy	NA	Retrospective observational monocentric study on epidemiology, clinical and trichoscopic features and comorbidities in FFA patients
Trager MH et al 2021 [33]	173	14/159	Colombia and USA	Clinical and histopathological	Retrospective cohort study on medical comorbidities and gender distribution among patients with LPP and FFA
McSweeney SM et al 2020 [34]	711	0/711	UK	Clinical (histopathological when needed)	Descriptive cross-sectional study on clinical phenotype in women from FFA UK GWAS cohort

Table 2 continues

Table 2. Data of Published Studies on FFA Reporting more than 100 Cases (*continued*).

	Number of patients	Sex M/F	Population	Type of diagnosis	Data collected
Anzai A et al 2019 [27]	151	0/151	Brazil/Italy	Histopathological	Retrospective and prospective study on trichoscopic findings of FFA of the eyebrows
Papanikou S et al 2019 [35]	100	0/100	Greece	NA	Observational study on the influence of social status on the prognosis of FFA in female patients
Mulinari Brenner F et al 2019 [36]	227	NA	Brazil	NA	Observational study on reported cases of FFA in a tertiary center
Vañó-Galván et al 2019 [37]	306	NA	Australia, Brazil, Chile, Colombia, Italy, Mexico, Norway, Poland, Portugal, South Africa, Spain, Switzerland, USA and UK	NA	Retrospective multicenter study on frequencies of alopecia types at 22 specialized hair clinics
Kanti V et al 2019 [38]	490	25/465	France and Germany	Clinical (histopathological when needed)	Observational cross-sectional descriptive study on demographic and clinical characteristics associated with the severity of FFA
Moreno-Arrones OM et al 2019 [39]	278	0/278	Spain	Clinical (histopathological when needed)	Multicenter cross-sectional study on factors influencing FFA severity
Tziotzios C et al 2019 [19]	1016	0/1016	Greece and UK	NA	Genome-wide association study on FFA
Moreno-Arrones OM et al 2019 [40]	335	20/315	Spain	NA	Multicenter case-control study on risk factors associated with FFA
Cranwell WC et al 2019 [41]	130	0/130	Australia	NA	Case-control questionnaire study on exposure to sunscreen or facial skin care products and their association with FFA
Buendia-Castano D et al 2018 [42]	104	0/104	Spain	Clinical (histopathological when needed)	Case-control study on hormonal and gynecological risk factors for FFA
Imhof RL et al 2018 [43]	148	0/148	USA	Clinical (histopathological when needed)	Retrospective study on clinicopathological findings, comorbidities and treatment outcomes in women with FFA
Saceda-Corralo D et al 2018 [44]	103	0/103	Spain	Clinical (histopathological when needed)	Descriptive cross-sectional study on patients diagnosed with both FFA and LPP
Cervantes J et al 2018 [26]	108	NA	USA	Clinical (histopathological when needed)	Retrospective study on trichoscopic features of sideburns in FFA compared to fronto-temporal scalp
Pindado Ortega C et al 2018 [45]	103	0/103	Spain	Clinical (histopathological when needed)	Descriptive cross-sectional study on relationship between FFA and rosacea
Donati A et al 2017 [46]	149	NA	France	Clinical (histopathological when needed)	Retrospective analysis on the use of direct immunofluorescence in FFA

Table 2 continues

Table 2. Data of Published Studies on FFA Reporting more than 100 Cases (continued).

	Number of patients	Sex M/F	Population	Type of diagnosis	Data collected
Moreno Arrones OM et al 2017 [47]	242	0/242	Spain	Clinical (histopathological when needed)	Retrospective single-centre observational study on clinical and prognostic classification of FFA
Aldoori N et al 2016 [48]	105	0/105	UK	Clinical	Case-control study on the role of leave-on facial skin care products and sunscreen in FFA
Fernandez-Crehuet P et al 2015 [25]	249	11/238	Spain	Clinical and histopathological	Descriptive retrospective observational multicenter study on trichoscopic features of FFA
Vañó-Galván et al 2014 [49]	355	12/343	Spain	Clinical (histopathological when needed)	Retrospective multicenter study on epidemiology, comorbidities, clinical presentation, diagnostic findings, and therapeutic choices in FFA

FFA = frontal fibrosing alopecia; F = females; M = males; NA=not applicable.

2018, respectively [26,42-47]. Nine studies were released in 2019 [19,27,35-41] and 5 studies were published in 2020 and 2021 [30-34]. In 13 studies, clinical and trichoscopic features were decisive for the diagnosis in almost all FFA cases [26,30,34,39,42-49]. Invasive biopsies for histopathological examinations were reserved for doubtful cases and confirmed the diagnosis in all cases.

Conclusions

Since its first description in 1994, FFA has shown a significant increase in incidence all over the world. In 2014, Vañó-Galván et al published the first large cohort of patients diagnosed with FFA [49]. Subsequently, as confirmed by our review of the literature, the number of published large cohort studies have increased over time, in particular during the last 3 years. Of note, Tziotzios et al published the largest cohort study in 2019, reporting more than 1,000 patients from Greece and UK [19]. Here, we report an additional large cohort of patients diagnosed with FFA collected through IDS members who responded to our online call.

The mean age at onset of the disease in our sample was 58.6 years, which is comparable to the previously reported data on FFA. The results support the current theory that the disease mainly affects postmenopausal women (88.1%), but also documents that it can be found in younger women (11.9%). The youngest patient was 15 years old at the onset of symptoms. Our sample also included 3 male subjects supporting the fact that FFA can affect males as well. Cases of FFA within multiple members of the same family have been reported in 5-8% of the cases [49, 50], a result that is a very similar to the percentage observed in our study (10.1%).

Navarro Belmonte et al reported that the age at onset of the disease in cases with relatives affected by FFA appears to be lower than in isolated cases [51]. Our study also showed an earlier onset of about 3 years in subjects with a positive family history. However, the difference between the two groups was not significant in our cases.

In accordance with other small studies [8,52], our study reported an association between FFA and LPP (18.6% of cases) including 5 patients with FAPD. This observation supports the theory that FFA could actually represent a clinical variant of LPP despite the different symptoms. Although this association was not reported in larger studies, it is possible that it is under-reported.

Consistent with previous studies [53,54], the presence of AGA was recorded in 38.8% of patients suggesting that AGA may be at the root of a fibrotic process leading to FFA or that FFA and AGA may have a similar underlying pathogenetic mechanism, for example a hormonal basis. The role of hormones is however still uncertain and debated as well as the link between FFA, LPP and AGA. One retrospective study associated FFA with androgen deficiency, while LPP was more frequently associated with androgen excess [54]. Furthermore, no association with Lupus and AA was reported in our group of patients.

Interestingly, the diagnosis of FFA in our cohort was made on average 4.4 years after the onset of the disease and in 51.6% of cases already presented as grade 2 of severity with a mean frontal hairline recession of 2.35 cm, which in some cases reached 10 cm. This underlines the importance of awareness and education on this disease, not only among patients but also among health professionals, in order to diagnose and treat FFA at an earlier stage to stop the scarring process.

Alopecia of the eyebrows, found in 85.6% of cases, was confirmed as the most frequent sign of the disease, while the loss of eyelashes and axillary, pubic and/or body hair was documented with a lower rate. Some authors have raised the doubt that the peripheral involvement of the disease could actually be simply a consequence of menopause and/or aging [55]. In this regard, we compared patients of childbearing age with menopausal patients and found overlapping percentages of body hair involvement in both age groups (86.4% versus 87.1%). Therefore, these observations seem to confirm the frequent involvement of various anatomical regions of FFA. In particular, eyebrow involvement could play a significant role in early diagnosis since, in many cases, thinning or loss of the eyebrows precedes the recession of the fronto-temporal hairline. Eyebrows and body hair reduction/loss are often confused with age-related loss and seldom reported by patients themselves. Thus, awareness of this sign possibly indicating FFA is important when considering differential diagnoses such as AA or aging [56]. Moreover, the finding of non-inflammatory facial papules was described in 29.8% of patients, suggesting that this sign should always be sought in cases of suspected FFA.

Even if the clinical diagnosis is most often easy to perform, trichoscopy is a valid aid in milder cases and in evaluation of facial/body hair loss. Trichoscopy is also a valid aid in the differential diagnosis with other diseases such as AGA, traction alopecia or AA in which there is no scarring. Interestingly, trichoscopic cicatricial signs were absent in a small percentage of patients, suggesting that FFA could likely begin as a non-scarring process. Consequently, early treatment could partially recover damaged follicles.

The presence of inflammatory signs such as perifollicular erythema and perifollicular hyperkeratosis were present in 63.8% and 60.1% of patients, respectively, and were associated with the presence of dysaesthetic sensations such as trichodynia and pruritus ($P = 0.049$). Previous studies report that up to one-third of patients with FFA may have itching and, less frequently, trichodynia. However, our series revealed higher percentages of symptomatic subjects with 65.9% of patients complaining of itching and 22.9% reporting concomitant trichodynia.

In most cases (71.8%) the characteristic clinical presentation and the typical trichoscopic findings allowed the diagnosis of FFA. The relevant role of the clinical and trichoscopic features in performing the diagnosis was also confirmed by the literature review. Indeed, in most studies they were decisive for the diagnosis confirming that trichoscopy is a worldwide-acknowledged non-invasive technique for the diagnosis of FFA. Further studies are necessary to evaluate the role of other in vivo non-invasive imaging techniques such as reflectance confocal microscopy, optical coherence tomography, diffuse reflection spectrophotometry and ultrasound in the

investigation of FFA to reduce the need of surgical biopsies and histopathological confirmation of the disease.

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