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CASE REPORT

Familial Frontal Fibrosing Alopecia

Report of a case and systematic review of the literature

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abstract: Frontal fibrosing alopecia (FFA) is an emerging disease in Western countries. We present the cases of three sisters who were referred simultaneously to the Department of Dermatology, Hospital Universitario San Cecilio, Granada, Spain, in 2018. All patients suffered from at least partial frontotemporal hairline recession and eyebrow loss. Following trichoscopic examination, the three sisters were diagnosed with FFA. Only one of the sisters agreed to be treated; she was prescribed with topical clobetasol propionate solution and minoxidil and achieved disease control at the three-month follow-up. These patients represent a new case of familial FFA wherein three sisters as well as their mother were affected by FFA. A systematic review found a total of 24 cases of familial FFA, of which this report is the 25th. In the majority of families, only females were affected (88%) while in the remainder both males and females (8%) were affected; there was only one family where only males were affected (4%). The relationship between the affected individuals was predominately between sisters (56%) followed by mother and daughter (32%). The median age was 61 years old (range: 14–88 years) and the duration of the disease ranged between 3–360 months. Family groups of FFA are an infrequently described phenomenon with unknown prevalence.

Keywords: Alopecia; Dermatology; Hair Diseases; Case Report; Spain.

Frontal fibrosing alopecia (FFA) is a type of scarring alopecia described by Kossard in 1994.[1] Since then, the number of publications about this disease has been rising. It has been considered a variant of lichen planopilaris due to histological similarities between the diseases;[2] however, others consider it to be an independent disease among scarring alopecias due to the clinical peculiarities of FFA.[3–5] New diagnostic criteria have recently facilitated its identification.[6] In this case report, we report a case of familial FFA and perform a systematic review of the scientific evidence available in the literature.

Case Reports

Three sisters were referred simultaneously to the Department of Dermatology, Hospital Universitario San Cecilio, Granada, Spain, in 2018. The first patient was a 62-year-old female, who underwent menopause aged 52 and had a medical history of cutaneous lupus and breast cancer. She complained about frontotemporal hairline recession and partial eyebrow loss with a one year evolution [Figure 1A]. Trichoscopic examination showed erythema and follicular hyperkeratosis [Figure 1D]. Clinical and dermoscopic findings were consistent with the diagnosis of FFA. The patient claimed that her two sisters both presented with a similar type of alopecia as well as her mother, who died of breast cancer at the age of 55. Treatment with clobetasol propionate 0,1% solution and minoxidil 5% solution was established and achieved disease control at the scheduled three-month follow-up visit.

The second patient, who was the eldest sister, was a 67-year-old woman who had undergone menopause at the age of 53 and had no medical history of interest. A 10-year alopecia evolution presenting partial loss of eyebrows and slight involvement of frontotemporal hairline was noted with a slow progression [Figure 1B]. Dermoscopic signs were also consistent with the diagnosis of FFA. She refused any treatment.

The third patient, who was the youngest sister, was 59 years-old who underwent menopause at 50. She had a similar scarring alopecia with a three-year evolution but with a much more inflammatory pattern, accentuated perifollicular erythema, a higher recession of frontotemporal hairline and was overall more aggressive [Figure 1C]. Similar to her two sisters, her symptoms were in agreement with the diagnosis of FFA. Likewise, she rejected any therapeutic approach.

All patients provided consent to publish details and photographs of their case.

Discussion

In this article, we presented a case of familial FFA that adds to the body of literature on this condition. A systematic literature review was undertaken to determine the extent of available literature [Figure 2].

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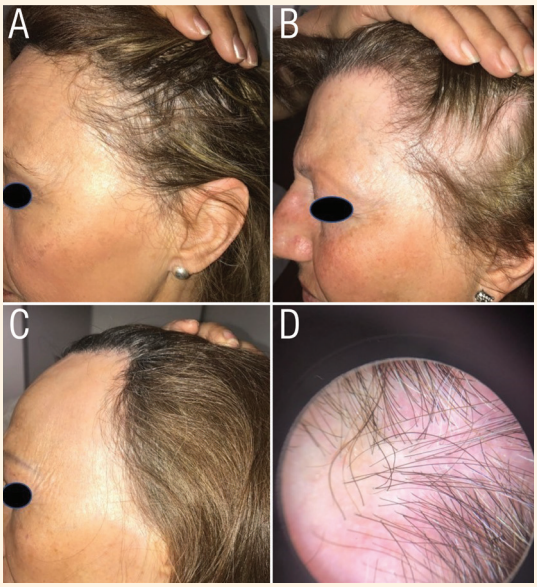

Figure 1: Photographs of the heads of three sisters. **A:** A 62-year-old woman with frontotemporal hairline recession and partial eyebrow loss. **B:** A 67-year-old woman with similar pattern and accentuated eyebrow loss. **C:** A 59-year-old woman with marked hairline recession and almost total loss of eyebrows. **D:** Trichoscopic examination photograph of the 62-year-old woman showing erythema and follicular hyperkeratosis.

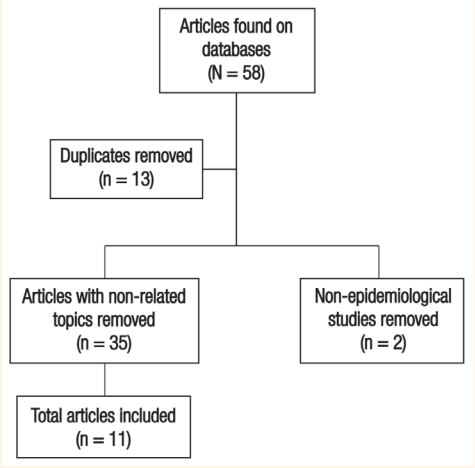

Figure 2: Flowchart showing the process of article selection for a literature review on frontal fibrosing alopecia.

MEDLINE® (National Library of Medicine, Bethesda, Maryland, USA) and EMBASE (Elsevier, Amsterdam, Netherlands) databases were searched on 11th February 2020 using the term "ALOPECIA AND (FRONTAL OR FIBROSING) AND FAMILIAL". Articles that were published in English, Spanish, French or German as well as articles published for at least one year on the databases were included. FFA epidemiological studies were included but narrative reviews were excluded. Subsequently, two independent reviewers checked the title and abstract of the articles obtained. The full text of the articles was reviewed as well as the bibliography that supported them to search for sources of additional information. Only the articles agreed upon by both reviewers in relation to the inclusion criteria were included in the final analysis. In the case of disagreement, a third reviewer analysed the article. A total of 11 articles were included in this review in which there are a total of 24 cases of familial FFA [Figure 2]. The current case represents the 25th and resulted in a total of 59 individual cases [Table 1].[4,7–16]

Most affected family members were women (88%) but some families had both men and women (8%) who were affected; only one family presented with only affected males (4%). Analysis of the familial relationships showed that the most common relationship was between sisters (56%) followed by mother and daughter (32%) and brother and sister (8%). Regarding ethnicity, the majority of families with a known ethnicity were Caucasian (83%) followed by Hispanic (11%) and Black (6%). The median age was 61 years old (range: 14–88 years) and the duration of the disease ranged between 3–360 months. Eyebrows were involved in 93% of patients. Among the comorbidities, there were autoimmune disorders such as rheumatoid arthritis, vitiligo, hypothyroidism, primary biliary cirrhosis or cutaneous lupus, several cardiovascular risk factors such as diabetes mellitus type 2, dyslipidaemia, high blood pressure or psoriasis, other hair disorders such as lichen planopilaris or alopecia areata, cancers such as colorectal and breast cancer and infectious diseases such as a case of hepatitis due to the hepatitis C virus. It should be noted that this literature review was subject to the limitation that it only included case reports.

There is still uncertainty about aetiopathogenesis of FFA. Based on the apparent increase in incidence in recent years, FFA has been related to environmental factors such as dioxins and dioxin-like chemicals.[7] The importance of hormonal factors has been posed too, due to the widespread prevalence in Caucasian postmenopausal women and the high effectiveness of anti-androgens compared with other treatments.[5] Genetic factors have also been linked to this disease, as family cases reported in the literature to date suggest.[4,7–19] Finally some authors have stated an autoimmune origin due to the inflammatory infiltrates in the bulb, the similarities to LPP and the association with other autoimmune diseases.[17]

Family groups of FFA are an infrequently described phenomenon, with unknown prevalence among all cases of FFA. From the genetic point of

Table 1: Epidemiologic and clinical characteristics of familial cases of FFA reported in the scientific literature.

Author and year of publication	Family no.	No. and gender	Relationship	Age in years	Ethnicity	History of FFA in months	Eyebrow involvement	Comorbidities
Dlova *et al.*[7] (2013)	#1	3F	Sisters	55	Caucasian	12	Yes	None
				61		24	Yes	None
				73		-	Yes	None
	#2	1F	Sister	59	Caucasian	36	Yes	LPP
		1M	Brother	62		12	Yes	None
	#3	2F	Sisters	25	Hispanic	12	Yes	None
				21		3	Yes	None
	#4	3F	Mother	74	Black	24	No	Traction alopecia
			Daughter	50		12	No	Traction alopecia
			Cousin	44		12	Yes	Traction alopecia
Roche *et al.*[8] (2008)		1F	Sister	75	Non-specified	12	Yes	None
		1M	Brother	71		8	Yes	None
Junqueira Ribeiro Pereira *et al.*[13] (2010)		2F	Sisters	57	Caucasian	12	Yes	None
				59		12	Yes	Oophorectomy (at 32 years-old), colorectal adenocarcinoma (at 54 years-old) and HCV treated with IFN + ribavirin (at 55 years-old)
Miteva et al.[9] (2011)		2F	Twin sisters	67	Caucasian	12	Yes	Vitiligo
						6	Yes	Vitiligo
Cranwell and Sinclair[11] (2017)		2F	Mother	46	Non-specified	10	Yes	Rheumatoid arthritis, AA
			Daughter	-		Non specified	Yes	None
Chan *et al.*[12] (2014)		2F	Sisters	49	Caucasian	18	Yes	None
				63		24–36	Non-specified	None
Navarro-Belmonte *et al.*[4] (2015)	#1	2F	Mother	75	Non-specified	Non-specified	Yes	Hypothyroidism
			Daughter	47		18	Yes	Psoriasis, HBP, dyslipidaemia
	#2	2F	Mother	60	Non-specified	24	Yes	DM type 2, HBP
			Daughter	41		12	Yes	None
	#3	2F	Mother	63	Non-specified	24	Yes	Primary biliary cirrhosis
			Daughter	37		Non-specified	Yes	None
	#4	2F	Mother	62	Non-specified	Non-specified	Yes	None
			Daughter	33		Non-specified	Yes	None
Atarguine *et al.*[10] (2016)		2F	Twin sisters	14	Non-specified	108	Non-specified	Goitre (one sister)
Rocha *et al.*[14] (2020)		6F	Sisters	67	Hispanic	180	Yes	DM, Systemic arterial hypertension
				64		144	Yes	No
				62		24	No	No
				61		360	Yes	Allergic rhinitis
				52		24	Yes	Deep Vein Thrombosis
				51		24	Yes	No
Porriño-Bustamante *et al.*[16](2019)	#1	2F	Sisters	59	Caucasian	30	Yes	Non-specified
				66		108	Yes	Non-specified
	#2	3F	Mother	78	Caucasian	228	Yes	Non-specified
			1st Cousin of mother	68		144	Yes	Non-specified
			Daughter	50		36	Yes	Non-specified
	#3	2M	Brothers	44	Caucasian	48	Yes	Non-specified
				46		12	Yes	Non-specified
	#4	2F	Sisters	39	Caucasian	72	Yes	Non-specified
				42		24	Yes	Non-specified
	#5	3F	Sisters	88	Caucasian	24	Yes	Non-specified
				72		12	Yes	Non-specified
				64		48	Yes	Non-specified
	#6	2F	Sisters	53	Caucasian	96	Yes	Non-specified
				46		12	Yes	Non-specified
	#7	2F	Sisters	74	Caucasian	288	Yes	Non-specified
				72		240	Yes	Non-specified
	#8	2F	Sisters	77	Caucasian	204	Yes	Non-specified
				74		168	Yes	Non-specified
	#9	2F	Mother	70	Caucasian	144	Yes	Non-specified
			Daughter	44		24	Yes	Non-specified
Current case		3F	Sisters	62	Caucasian	12	Yes	Breast cancer, cutaneous lupus None
				67		120	Yes	None
				59		36	Yes	

F = female; M = male; LPP = lichen planopilaris; HCV = hepatitis C virus; IFN = interferon; AA = alopecia areata; HBP = high blood pressure; DM = diabetes mellitus.

view, genome-wide association studies in females from a UK cohort (comprising 844 cases and 3,760 controls) and a Spanish cohort (consisting of 172 cases and 385 controls) have been related to HLA-B*07:02; a genome-wide significant association with FFA was observed at four genomic loci (2p22.2, 6p21.1, 8q24.22 and 15q2.1).[20] Inheritance mode seems to follow an autosomal dominant pattern with incomplete penetrance which is in line with the current case.[21] Considering the findings of the present case and available scientific evidence, there are several phenotypic expression patterns of FFA which may be the result of epigenetic modulation or genic interaction mechanisms and give rise to the partial penetrance of the trait. Upon this genetic predisposition, some trigger factors may overlap. A decrease in serum oestrogen levels or traumatisms, setting off an inflammatory reaction at the level of the follicular bulge, leading to fibrosis and final loss of the follicular hair may be considered.

Conclusion

The cases of the three sisters highlights the need to carefully evaluate family aggregation patterns when examining patients, since on many occasions, unlike in our case, patients attend consultations alone. International collaboration between researchers is needed in order to perform epidemiological studies with larger sample sizes.

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