Original Research

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Alopecia patterns and trichoscopic findings in patients with autosomal recessive congenital ichthyosis

Anissa Zaouak, MD[a,*], Wafa Jouini, MD[a], Ghaith Abdessalem, PhD[b], Sonia Abdelhak, PhD[b], Houda Hammami, MD[a], Cherine Charfeddine, PhD[b], Samy Fenniche, MD[a]

Background: Autosomal recessive congenital ichthyosis (ARCI) is a rare genodermatosis categorized among nonsyndromic ichthyoses. While ARCI patients often manifest hair abnormalities, their impact on the quality of life remains underreported in the literature.

Objective: This study aims to comprehensively characterize the clinical and trichoscopic findings of alopecia in ARCI patients.

Methods: A prospective study spanning from January 2019 to December 2021 (3 years) was conducted at the Dermatology Department of Habib Thameur Hospital, Tunis, Tunisia. Clinical and trichoscopic examinations were performed on the hair of the participants, with molecular studies conducted on 15 patients.

Results: The study included 30 patients, predominantly female (male/female = 0.58), with a mean age of 20 years. Twenty-eight patients were born from consanguineous marriages. Lamellar ichthyosis was observed in 22 cases, while congenital ichthyosiform erythroderma and bathing suit ichthyosis were each present in 4 cases. The ARCI severity score, assessed using the Visual Index For Ichthyosis Severity scale, had a mean value of 15 (4–28). Alopecia emerged as a prominent finding in 11 patients, presenting as hairline recession (13%), multiple patchy alopecia (27%), and alopecia of the eyebrows (13%). Trichoscopic findings included interfollicular and perifollicular scaling, perifollicular lamellar hyperkeratosis, peripilar casts, interfollicular erythema, loss of hair openings, predominance of single hair follicles, broken hair, vellus hair, anisotrichosis, pili torti, dystrophic hair, and comma hair. Several trichoscopic findings showed statistically significant associations with the severity of ARCI.

Limitations: In our study, we only included 30 patients due to the rarity of this genodermatosis.

Conclusion: Contrary to previous perceptions, alopecia is a notable finding in ARCI, particularly in patients with a severe form. This study provides a detailed characterization of alopecia in ARCI, shedding light on its prevalence and associated trichoscopic features, thereby enhancing our understanding of this dermatological condition.

Keywords: alopecia, hair, ichthyosis

Introduction

Autosomal recessive congenital ichthyosis (ARCI) stands as a rare genodermatosis within the spectrum of nonsyndromic congenital ichthyoses.[1] This heterogeneous group of monogenic disorders, characterized by autosomal recessive transmission, exhibits a higher prevalence in regions marked by elevated consanguinity rates, such as Tunisia. ARCI manifests as disorders of cornification,[2] leading to dry skin adorned with varying degrees of scales, sometimes accompanied by erythroderma.[3] In 2009, Oji et al.[4] introduced a new classification of hereditary ichthyosis, delineating 2 subtypes of ARCI: major forms encompassing Harlequin ichthyosis, lamellar ichthyosis (LI), and congenital ichthyosiform erythroderma (CIE); and minor forms including self-healing collodion baby, acral self-healing collodion baby, and bathing suit ichthyosis (BSI).

While skin involvement in ARCI has been extensively documented, the focus on hair involvement remains disproportionately limited. Alopecia, a term often imprecisely used, dominates the discourse on hair abnormalities in ARCI. Traupe and Happle[5] pioneered the exploration of hair involvement in ARCI in 1983, introducing the term "alopecia ichthyotica." Subsequent studies on ARCI have primarily touched upon hairline recession[6–9] and the presence of scaling.[10–13] In 2019, Gavazzoni Dias et al.[9] presented the first comprehensive article on trichoscopic features in ARCI patients; however, the study only included 4 patients with ichthyosis. Moreover, few studies have investigated the correlation between hair involvement and the severity of ARCI.

Recognizing the substantial impact of alopecia and other hair abnormalities on patients' quality of life potentially leads to social isolation, diminished self-esteem, and depression.[14] Our study aims to address this research gap. We endeavor to elucidate the clinical and trichoscopic aspects of hair involvement in ARCI, exploring its association with disease severity and genetic mutations. This investigation seeks to enhance our comprehension of the intricacies of hair-related manifestations in ARCI, ultimately contributing to improved patient care and well-informed clinical management.

[a] Dermatology Department, Habib Thameur Hospital, Tunis, Tunisia
[b] Biomedical Genomics and Oncogenetics Laboratory, Institut Pasteur de Tunis, Tunis, Tunisia

* Corresponding author.

E-mail address: anissa_zaouak@yahoo.fr (A. Zaouak).

International Journal of Women's Dermatology (2024) 10:e175

Received: 5 February 2024; Accepted 21 July 2024

Published online 21 August 2024

DOI: 10.1097/JW9.0000000000000175

What is known about this subject in regard to women and their families?

- In Tunisia, the prevalence of autosomal recessive congenital ichthyosis (ARCI) is notably influenced by a high rate of consanguinity, contributing to the increased expression of this genetic condition.
- ARCI is a severe disease that significantly impacts the psychological and emotional well-being of affected women, particularly when accompanied by alopecia. The associated psychological burden underscores the need for comprehensive care and support.
- Despite its severity, alopecia in ARCI has received limited attention in the literature. There is a scarcity of studies addressing alopecia patterns and trichoscopic features in patients dealing with this rare genodermatosis, highlighting the importance of further research in this area.

What is new from this article as messages for women and their families?

- This article reveals a noteworthy female predominance of ARCI in Tunisia, shedding light on gender-specific aspects of the condition that may influence its manifestation and impact on women.
- Unique insights into alopecia patterns associated with ARCI are provided, including prevalent patterns such as multiple patchy alopecia, hairline recession, and eyebrow alopecia. This information enhances our understanding of the condition's dermatological features in affected women.
- The study indicates that patients with a severe form of ARCI also exhibit a severe form of alopecia, underscoring the correlation between the severity of the underlying genetic condition and its dermatological manifestations.
- An important message from the study is the acknowledgment of the burden of alopecia in females, revealing that many affected women choose to wear veils as a means to conceal their severe alopecia, even from a young age. This insight highlights the social and cultural aspects that add an additional layer of complexity to the experience of women with ARCI.

Materials and methods

Study population

This single-center, cross-sectional, and prospective study took place at the Dermatology Department of Habib Thameur Hospital, Tunis, Tunisia, a tertiary referral center, spanning from January 2019 to December 2021. Participants were exclusively individuals diagnosed with ARCI based on the Sorèze classification, with syndromic ichthyosis cases excluded.[4]

Clinical data

Clinical and demographic data encompassed age, gender, ARCI type and severity (assessed via Visual Index for Ichthyosis Severity score), and detailed information on hair involvement and abnormalities. Two dermatologists conducted clinical and trichoscopic assessments using the Dermlite DL4 dermatoscope. Additionally, clinical and dermatoscopic photographs of the patients' hair were systematically recorded.

Molecular study

For 15 consenting patients, a molecular investigation was performed. DNA was extracted from peripheral blood using established chloroform standard procedures. Hotspot mutation screening of *TGM1* exons 5 and 6 was conducted employing standard molecular biology techniques. Polymerase chain reaction amplification of the targeted region was accomplished using the "AmpliTaq Gold_360 Master Mix" kit from Applied Biosystems (Foster City, California). Subsequent DNA sequencing, according to the Sanger method, was carried out utilizing the "BigDye_Terminator v3.1 Cycle Sequencing" kit from the same company. Electropherograms were meticulously analyzed using BioEdit.

Statistical analysis

IBM SPSS Statistics 23 (version 23.0, SPSS Inc., Chicago, Illinois) was utilized for the comprehensive analysis of patient data. A significance level of $P < .05$ was considered statistically significant.

Ethical consideration

Informed consent was diligently obtained from all participants. This study received ethical approval from the committee at Habib Thameur Hospital, Tunis, Tunisia (reference: HTHEC-2021-31).

Results

Between January 2019 and December 2021, a total of 30 patients diagnosed with ARCI were meticulously examined, revealing the following phenotypes: LI (74%), CIE (13%), and BSI (13%). The cohort exhibited a mean age of 20 years (1–48) with a notable female predominance (sex ratio male/female = 0.58).

Clinical data

The assessment of ARCI severity, utilizing the Visual Index for Ichthyosis Severity scale, yielded a mean score of 15 (4–28). Clinical scrutiny of patients' hair unveiled prevalent findings, including scales in 27 patients, thin and brittle hair in 13 patients, and alopecia in 11 patients. Alopecia of the scalp manifested in 2 primary forms: multiple alopecic patches in 7 patients (Fig. 1A) and hairline recession in 4 patients (Fig. 1B–D). The latter presented circumferentially, with or without the persistence of some locks of hair in 2 patients, involving the posterior scalp in one patient, and the anterior scalp in another. Additionally, 4 patients exhibited alopecia of the eyebrows (Fig. 2A). Hair involvement demonstrated a statistically significant association with the severity of ARCI, including alopecia ($P = .009$), scales ($P = .01$), and thin and brittle hair ($P < .001$). Detailed clinical findings are summarized in Table 1.

Trichoscopy

The clinical evaluations were complemented by trichoscopic examinations, revealing prevalent features such as interfollicular and perifollicular scaling (30 and 27 patients, respectively) (Fig. 2B), interfollicular erythema (27 patients), perifollicular lamellar hyperkeratosis (Fig. 2C), predominance of single hair follicles, broken hair, vellus hair, anisotrichia, pili torti (Fig. 2D), dystrophic hair, comma hair (12 patients each), loss of hair openings (10 patients), peripilar casts (9 patients), and transparent proximal hair shaft emergence (4 cases) (Fig. 2E). Several trichoscopic features exhibited statistically significant associations with the severity of ARCI, notably anisotrichia, black dots, broken hair, vellus hair, and dystrophic hair ($P < 0.001$ each). A comprehensive summary of trichoscopic findings is presented in Table 2.

Genetic study

Fifteen patients underwent molecular studies, revealing *TGM1* gene mutations in 13 cases. In 2 cases, mutations in the *PNLPA1* gene were identified.

Discussion

Our study provides a comprehensive exploration of various clinical and trichoscopic patterns of alopecia in 30 Tunisian patients with ARCI. LI emerged as the predominant phenotype in our cohort, with hair involvement observed in 27 patients. Notably, alopecia was the most prominent finding, affecting 11 patients and manifesting in 3 primary aspects: multiple alopecic patches (27%), alopecia of the eyebrows (13%), and hairline recession (13%). The latter exhibited diverse patterns, including circumferential recession with or without persistent hairlocks, posterior scalp involvement, and anterior scalp recession.

Clinical examinations unveiled additional features such as scales (90%) and thin, brittle hair (34%). Importantly, hair involvement was statistically associated with the severity of ARCI. Trichoscopic evaluation highlighted various signs, including interfollicular and perifollicular scaling, perifollicular lamellar hyperkeratosis, peripilar casts, interfollicular erythema, loss of hair openings, predominance of single hair follicles, broken hair, vellus hair, anisotrichia, pili torti, dystrophic hair, and comma hair. Some trichoscopic findings exhibited statistically significant associations with the severity of ARCI.

Molecular analysis, performed on 15 patients, consistently revealed mutations in the *TGM1* gene in 13 patients. Limited studies have previously reported hair involvement in ARCI, with a predominant focus on rare forms of syndromic ichthyosis[15] where hair abnormalities serve as diagnostic clues. In contrast,

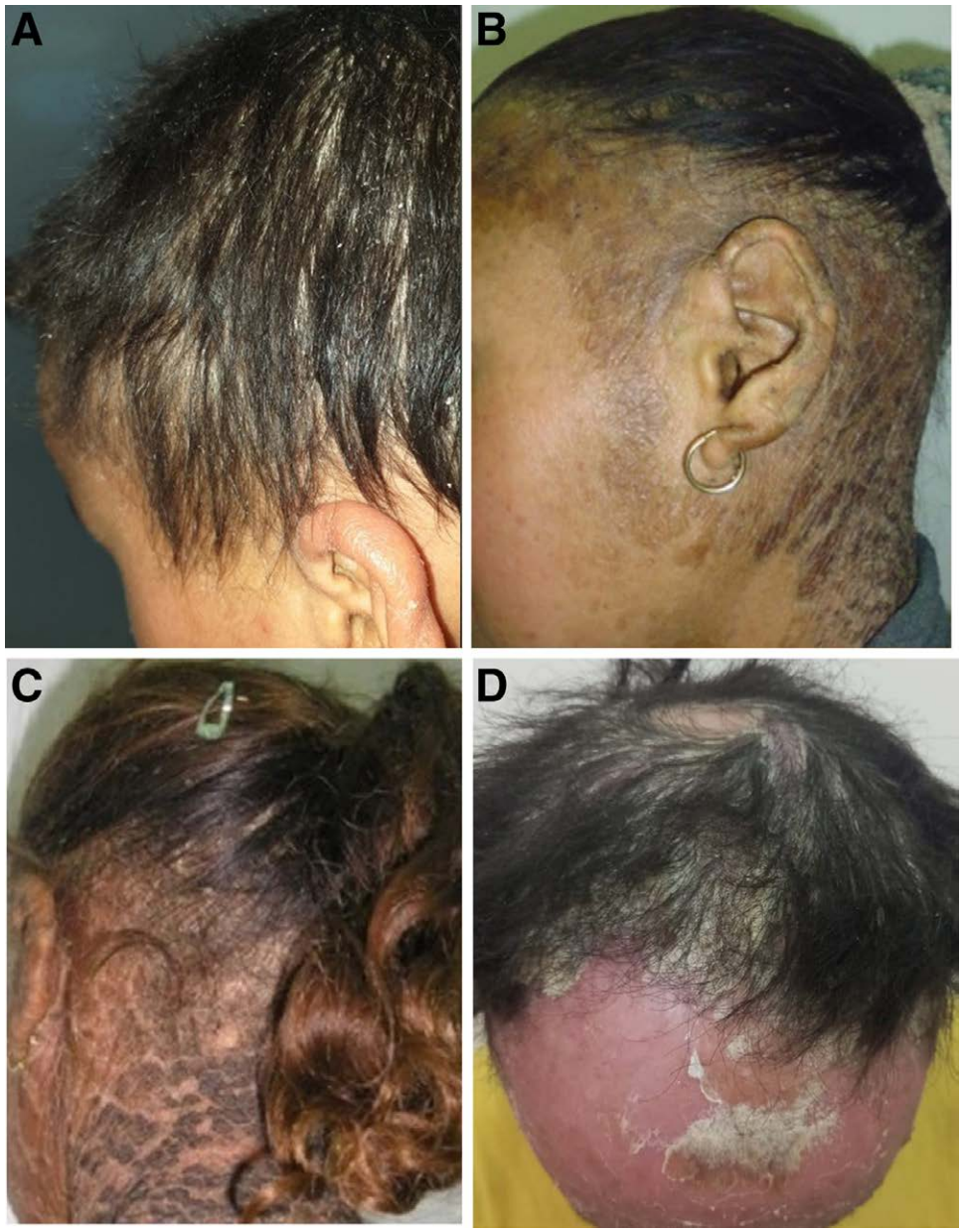

Fig. 1. (A) Multiple alopecic patches of the scalp associated with diffuse scaling and thin and brittle hair. (B) Circumferential hairline recession associated with brown lamellar scales on the scalp. (C) Hairline recession of the posterior scalp associated with brown lamellar scales. (D) Hair line recession of the frontal scalp associated with yellow scales.

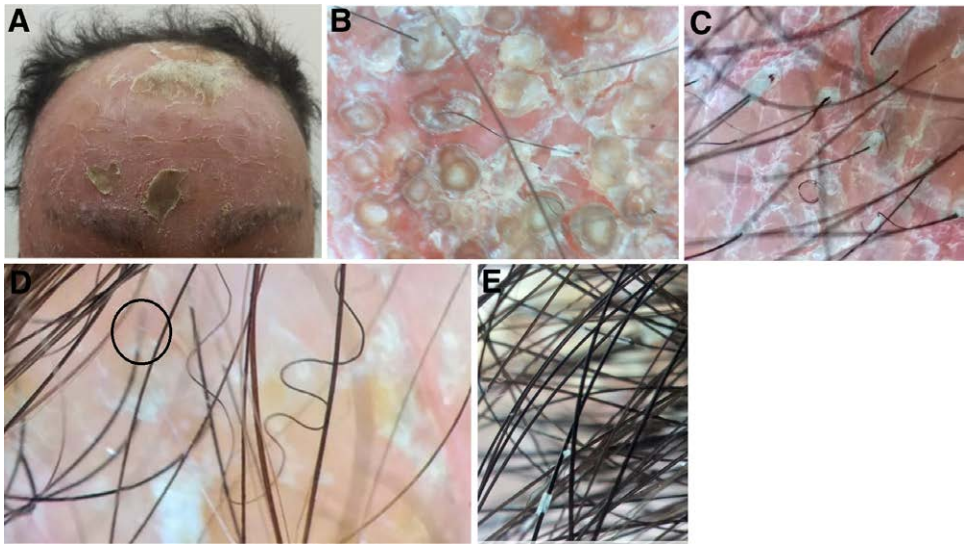

Fig. 2. (A) Alopecia of the eyebrows. (B) Fishing float keratotic plugs and 3D bubble yellow dots (Dermlite DL4 × 20). (C) Interfollicular erythema and interfollicular scales, and perifollicular lamellar keratosis (Dermlite DL4 × 20). (D) Transparent proximal hair shaft emergence (Dermlite DL4 × 20). (E) Peripilar casts (Dermlite DL4 × 20).

nonsyndromic ichthyosis, such as ARCI, often lacks detailed descriptions of hair abnormalities, as clinicians predominantly concentrate on cutaneous and genetic aspects.

The earliest recognition of hair involvement in ARCI dates back to Traupe and Happle in 1983,[5] who identified patchy or diffuse alopecia in 4 unrelated ARCI patients, coining the term "alopecia ichthyotica." Subsequent studies have sporadically delved into hair abnormalities in ARCI, with alopecia being the most commonly reported.[16,17] Notably, it predominantly occurs in LI and CIE,[13,18] often associated with specific genetic mutations (*TGM*1 and *ABCA12*).[19–21]

Our study aligns with existing literature, revealing alopecia in 11 patients, 10 of whom had LI and 1 with CIE. This finding correlated significantly with the severity of ARCI ($P = .009$). Patients with alopecia and *TGM1* gene mutations were notably consistent, mirroring findings by Putterman et al.,[22] who established a correlation between the severity of ichthyosis and alopecia, particularly in cases with *TGM1* and *ABCA12* mutations.

Hairline recession was described in the literature during ARCI. Several patterns were found: posterior scalp alopecia in a patient with BSI,[10] alopecia at the hair margins,[1,8] and frontotemporal hairline recession in LI.[9] Scarring alopecia at the hair margins during ARCI is secondary to the continuous tension of the skin.[2,8] It can be compared to traction alopecia, which also predominates at the periphery of the scalp, mainly in the frontotemporal region.[23] Following prolonged and significant traction forces, the chronic inflammation leads to the alteration of the hair follicle that impairs hair regrowth and thus, causes alopecia.[24] This long-lasting and initially nonscarring alopecia may evolve into a secondary scarring aspect.[25] Therefore, early treatment of ARCI could prevent the development of irreversible alopecia.

Eyebrow alopecia is frequently associated with hairline recession in frontal fibrosing alopecia (FFA)[26] and was also described in LI.[7,21] This abnormality was statistically associated with the severity of ARCI ($P < .001$).

During ARCI, and besides alopecia, patients usually suffer from more or less thick scalp desquamation[12,13] and dry and brittle hair.[9] Severe scalp scaling may explain the presence of multiple patches of cicatricial alopecia. In fact, initially, alopecia is not cicatricial, but due to severe scaling, follicular openings are progressively filled with compact keratotic

Table 1

Descriptive summary of ichthyosis subtypes and ichthyosis severity by hair change

Hair changes	Number of patients	LI	BSI	CIE	Severity: mean value (VIIS score)	Severity score: *P* value
Alopecia	11 (37%)	10/22	0/4	1/4	19,64	.009
Hairline recession	4 (13%)	3/22	0/4	1/4	25	<.001
Circumferential with or without the persistence of some locks of hair	2 (7%)	2/22	0/4	0/4	24	<.001
Hairline recession of the anterior scalp	1 (3%)	0/22	0/4	1/4	28	.082
Hairline recession of the posterior scalp	1 (3%)	1/22	0/4	0/4	24	.236
Multiple alopecic patches	7 (23%)	6/22	0/4	1/4	20,86	.018
A large and unique alopecic patch	2 (7%)	2/22	0/4	0/4	16,5	.509
Enlarged and alopecic median hairline with hair rarefaction	2 (7%)	2/22	0/4	0/4	18,3	.516
Alopecia of the eyebrows	4 (13%)	3/22	0/4	1/4	25	<.001
Scales	27 (90%)	19/22	4/4	4/4	16	.01
Thin and brittle hair	13 (43%)	10/22	0/4	3/4	20	<.001

BSI, bathing suit ichthyosis; CIE, congenital ichthyosiform erythroderma; LI, lamellar ichthyosis; VIIS score, Visual Index for Ichthyosis Severity score.

Table 2

Descriptive summary of ichthyosis subtypes and ichthyosis severity by trichoscopic findings

Trichoscopic findings	Number of patients	LI	BSI	EICS	Severity: mean value (VIIS score)	Severity score: *P* value
Follicular and interfollicular features						
Interfollicular scale	30 (100%)	20/22	4/4	4/4	15	.01
Interfollicular erythema	27 (90%)	19/22	4/4	4/4	15,78	.01
Perifollicular scale	27 (90%)	19/22	4/4	4/4	15,78	.01
Perifollicular lamellar hyperkeratosis	12 (40%)	10/22	0/4	2/4	20,5	<.001
Peripilar casts	9 (30%)	8/22	0/4	1/4	20,44	.008
Pinkish-white area	5 (17%)	4/22	0/4	1/4	21,6	.032
Transparent proximal hair shaft emergence	4 (13%)	4/22	0/4	0/4	19,75	.188
Honeycomb pattern	2 (7%)	2/22	0/4	0/4	19,5	.400
Perifollicular erythema	1 (3%)	1/22	0/4	0/4	18	.700
Follicular opening						
Predominance of single hair follicle	12 (40%)	10/22	0/4	2/4	19,08	.015
Anisotrichosis	12 (40%)	9/22	0/4	3/4	21,08	<.001
Loss of hair openings	10 (33%)	9/22	0/4	1/4	20,2	.006
Follicular plugging	5 (17%)	4/22	0/4	1/4	23	.008
Yellow dots	3 (10%)	3/22	0/4	0/4	21	.155
Fishing float keratotic plugs	2 (7%)	2/22	0/4	0/4	19,5	.4
3D bubble yellow dot	2 (7%)	2/22	0/4	0/4	19,5	.4
Truffled hair	3 (10%)	2/22	0/4	1/4	23	.054
Hair shaft						
Broken hair	15 (50%)	12/22	0/4	3/4	20,53	<.001
Vellus hair	14 (47%)	11/22	0/4	3/4	21	<.001
Pili torti	11 (37%)	10/22	0/4	1/4	19,64	.009
Black dots	11 (37%)	9/22	0/4	2/4	21,73	<.001
Comma hair	8 (27%)	7/22	0/4	1/4	20,13	.024
Dystrophic hair	8 (27%)	6/22	0/4	2/4	23,5	<.001
Trichoclasis	4 (13%)	3/22	0/4	1/4	22,75	.026
Exclamation mark hair	4 (13%)	4/22	0/4	0/4	21,75	.056
Pigtail hair	3 (10%)	2/22	0/4	1/4	22,33	.079
Trichoptilosis	2 (7%)	2/22	0/4	0/4	19	.456

BSI, bathing suit ichthyosis; CIE, congenital ichthyosiform erythroderma; LI, lamellar ichthyosis; VIIS score, Visual Index for Ichthyosis Severity score.

plugs that initially lead to reduced hair density and the onset of cicatricial alopecia. These findings are consistent with the results of our study. In fact, 27 patients had scalp scaling (19 cases of LI, 4 cases of EIC, and 4 cases of BSI) and 13 patients had dry and brittle hair. These abnormalities were statistically associated with the severity of ARCI (P = .01 and P < .001 subsequently).

Gavazzoni et al.[9] published in 2019 the only paper about trichoscopic findings in ARCI. It included only 3 patients with LI and the trichoscopic abnormalities were: inter and perifollicular scales, anisotrichosis, transparent proximal hair shaft emergence, and broken hair. Our study is the second and the largest study of trichoscopic findings in ARCI as it included 30 patients who underwent trichoscopic examination.

Interfollicular erythema and desquamation are nonspecific findings that are frequently found in various affections of the scalp including scarring[27] and no scarring alopecia.[28,29] They have been described in ARCI and more specifically LI.[9] They were found in 30 and 27 patients of our study, respectively. Interfollicular erythema was statistically associated with the severity of ARCI (P = .01). Perifollicular desquamation is also a common finding in scarring alopecia.[27] It is significantly associated with lichen planopilaris and marks the activity of the disease.[30] It reflects an inflammation around the hair follicle leading to the formation of scales, which can be lamellar.[31] The latter aspect was described in ARCI.[9]Twenty-seven patients in our study had perifollicular scaling on trichoscopy, which was lamellar in 12 cases. The presence of perifollicular scaling was statistically associated with the severity of ARCI (P = .01). Peripilar scaling can form peripilar casts that are frequently present in lichen planopilaris, FFA, and traction alopecia[32] but not in ARCI. They were found in 9 patients in our study with a statistically significant association with the severity of the affection (P = .008).

Patients with ARCI may suffer from scarring alopecia.[8] The disappearance of the follicular openings is a major sign of scarring alopecia.[30] In the more advanced stage, we can find a pinkish-white area that marks significant tissue fibrosis.[30,31] Those 2 findings were found in, respectively, 10 and 5 patients in our study. They were statistically associated with the severity of ARCI (P = .006 and P = .032, respectively). Scarring alopecia can also be associated to acquired dystrophy of the hair shaft. This abnormality is due to peripilar fibrosis: the follicle continues to produce dystrophic hair before being completely destroyed.[33] This feature was found in 8 patients in our study and had a statistically significant association with the severity of ARCI (P < .001). Pili torti was a predominant finding in our study. It has as well been described during ARCI.[9] Eleven patients in our study had pili torti in trichoscopy, 10 of whom had IL. In the acquired form, pili torti is thought to be secondary to rotational forces due to perifollicular fibrosis.[34] This is consistent with our study as 10 patients with a pili torti had scarring alopecia. It was statistically associated with the severity of ARCI (P = .009). Transparent proximal hair shaft emergence is secondary to skin atrophy. It was mainly described during FFA but can be found in healthy subjects at the sideburns.[35] It was also found in ARCI.[9] This condition was found in 4 of our patients, who all had scarring alopecia.

We also identified various alterations of the follicular openings: keratotic plugs, which are mostly described in discoid lupus,[30] were found in 5 cases in our study and were statistically associated with the severity of ARCI (P = .008). Besides, we identified a new trichoscopic finding in ARCI: fishing float keratotic plugs. It is a large keratotic plug with a central hair shaft similar to the aspect of a fishing float. This aspect was found in 2 cases.

Chronic inflammation during ARCI can explain hair fragility and thus, multiple trichoscopic findings such as black dots.

Black dots can be secondary to mechanical forces as in trichotillomania and traction alopecia, or to inflammatory processes as in alopecia areata, tinea capitis, and scarring alopecia.[33,36] In our study, this aspect was found in 11 patients. It was statistically associated with the severity of ARCI ($P < .001$). Broken hair can also be secondary to mechanical forces or inflammation leading to increased hair fragility.[33,37] It was also described in ARCI.[9] Fifteen patients in our study had broken hair, which had a statistically significant association with the severity of ARCI ($P < .001$). Hair fragility may also lead to trichoptilosis and trichoclasis,[33] which were found subsequently in 2 and 4 patients in our study. Trichoclasis was statistically associated with the severity of ARCI ($P = .026$).

In our study, we tried to perform a molecular investigation to seek for a potential genotype-phenotype correlation. It appears that patients with severe ARCI had a severe form of alopecia and a mutation in the *TGM1* gene.

While our study provides valuable insights into the trichoscopic aspects of ARCI, the sample size is limited. Further investigations with larger cohorts and comprehensive genetic analyses are essential for elucidating genotype-phenotype correlations. Understanding the nuances of hair involvement in ARCI not only aids in diagnosis but also holds implications for the timely initiation of therapeutic interventions, potentially preventing irreversible alopecia and improving the overall management of ARCI patients.

Conclusion

In this investigation, we meticulously delineated the diverse facets of hair involvement observed in 30 individuals grappling with ARCI. Among the array of manifestations, alopecia emerged as the most notable, with hairline recession and patchy alopecia standing out as the prevailing abnormalities. This study's distinctive contribution lies in the incorporation of trichoscopy, a pivotal tool that has enriched our understanding of ARCI by unveiling a spectrum of polymorphous findings.

Our findings contribute valuable insights that can enhance the holistic comprehension of ARCI and, in turn, inform more comprehensive approaches to its diagnosis and management.

Conflicts of interest

None.

Funding

None.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

Author contributions

AZ and WJ wrote the manuscript; GA and CC performed the genetic investigation; HH revised the dermoscopic study; SA and SF revised the final version of the manuscript.

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