OPEN ACCESS Freely available online

Hair Therapy & Transplantation

ISSN: 2167-0951

Mini-Review

Scalp and Hair Anomalies in Congenital Ichthyosis

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ABSTRACT

Congenital ichthyoses are characterized by diffuse scaling, often associated with skin inflammation. Given the chronic nature of the disease, the absence of curative treatment, social stigmatization and different complications, congenital ichthyosis usually have a major impact on quality of life. Among those complications impacting quality of life, alopecia and scalp anomalies are major influencing factors. Our objective, in this mini-review, was to describe the characteristics of hair/scalp anomalies in congenital ichthyosis and their management.

Keywords: Congenital ichthyosis; Scalp; Hair; Alopecia; Scales; Ulceration

INTRODUCTION

Congenital ichthyosis

Congenital Ichthyoses (CI) are primarily monogenic genetic disorders with more than 60 causal genes identified to date, all leading to a defective skin barrier [1]. A new classification based on a 2024 international expert consensus is in progress, but currently the different forms of CI are classified into two subgroups syndromic or non-syndromic CI [2]. The syndromic forms are sub-classified according to the most prominent anomalies (e.g. neurological anomalies, fatal disease course or hair anomalies (Netherton Syndrome (NS) or Trichothiodystrophie (TTD)). The non-syndromic forms include the group of Autosomal Recessive Congenital Ichthyosis (ARCI) and the group of Keratinopathic Ichthyosis (KI) [2]. CI typically present at birth or during early infancy and are characterized by varying degrees of skin thickening and/or scaling, often associated with skin inflammation. Skin lesions are generally widespread, also involving the scalp. The natural history of CI is chronic, with episodic flares occurring without well-identified triggers. CI is a skin disease but many non-cutaneous complications are usually seen, comprising eye and Ear-Nose-Throat (ENT) anomalies, pruritus, pain, recurrent cutaneous infections, growth failure and nutritional deficiency, reaction to hot and cold climates, physical limitations, and hair/scalp anomalies. These hair/scalp issues are seen not only in those with syndromic forms with prominent hair abnormalities but also in those with non-syndromic CI. CI require lifelong treatment; however, there are no curative therapies among the various available symptomatic conventional treatment options [3]. Topical agents include emollients, keratolytics and retinoids. Emollients are the first-line treatment for almost all patients, but these are time-consuming and often expensive, not reimbursed, adding to the disease burden [4,5]. Systemic therapy may be considered if topical therapies are insufficient, or if patients need a respite from excessive topical treatment. Systemic therapy for CI is primarily based on oral retinoids (mainly acitretin (the only one approved by the European medical agency for CI) but also alitretinoin and isotretinoin) [5]. Oral retinoids help reducing scaling/skin thickening and skin discomfort but usually have minimal effect on skin inflammation and pruritus. Some patients with inflammatory forms of CI, notably NS, may benefit from the repurposing of biologic drugs used in other inflammatory diseases such as atopic dermatitis or psoriasis (inhibitors of Interleukins *IL-12/23, IL-4/13*, or *IL-17*)(Mazereeuw-Hautier et al., manuscript in preparation). However, the outcomes are variable, often mild, sometimes transient, and worsening is also possible. Given the chronic nature, complications, absence of curative treatment, and social stigmatization, CI usually have a major impact on Quality of Life (QoL) [6]. Hair/scalp anomalies have a strong impact on QoL in CI.

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Received: 10-Jun-2024, Manuscript No. HTT-24-31935; **Editor assigned:** 13-Jun-2024, PreQC No. HTT-24-31935 (PQ); **Reviewed:** 28-Jun-2024, QC No. HTT-24-31935; **Revised:** 05-Jul-2024, Manuscript No. HTT-24-31935 (R); **Published:** 12-Jul-2024, DOI: 10.35248/2167-0951.24.14.247

Citation: Mazereeuw-Hautier J, Gostynski A, Severino-Freire M, Granier Tournier C, Hernandez-Martin A (2024) Scalp and Hair Anomalies in Congenital Ichthyosis. J Hair Ther Transplant. 14:247.

According to a study on therapeutic difficulties, hair/scalp anomalies were among the top 10 clinical concerns of patients [7]. Indeed, the Ichthyosis-specific QoL questionnaire (IQoL-32) includes one question dedicated to hair/scalp anomalies ("Has your scalp bothered you because of your ichthyosis (e.g. combing, hair care, skin scaling or itching)?", emphasizing the impact of this anomaly [8].

LITERATURE REVIEW

In order to describe these hair/scalp anomalies in CI, this mini-review will be divided in 2 parts: Description and management of 1-Scalp anomalies (scaling and ulceration), 2-Hair anomalies (seen in syndromic or non-syndromic CI).

Scalp anomalies in congenital ichthyosis

Scaling: Scales on the scalp are seen in almost all types of CI, even in forms with relative mild involvement such as X-linked recessive ichthyosis. They may be adherent and thick, leading to an unsightly appearance (Figure 1), leaving loose scales on the shoulders and environment (Figure 1). The scaling tends to be thinner and non-adherent in milder forms (Figure 2). Pruritus, bad odor and recurrent episodes of scalp bacterial infections are not uncommon. Removing/reducing the scales with topical therapy is often difficult, especially if thick scales [5]. Foams, solutions, and shampoos are cosmetically more acceptable than gels and ointments but may be less effective. Scales may require regular applications of a layer of emollient or keratolytic (washable preparation), possibly under plastic occlusion to enhance efficacy. In such cases, caution should be exercised due to the potential for transfollicular penetration of active substances (i.e. salicylic acid), particularly in young children in whom they are contra indicated. A steam hot helmet, if available, may be useful under the supervision of a nurse to help remove adherent scales. After shampooing, scales must be gently removed with a fine comb. In CI with fragile skin or brittle hair, gentler procedures are recommended. Some patients may benefit from systemic treatment with oral retinoids to help reduce scaling [5].

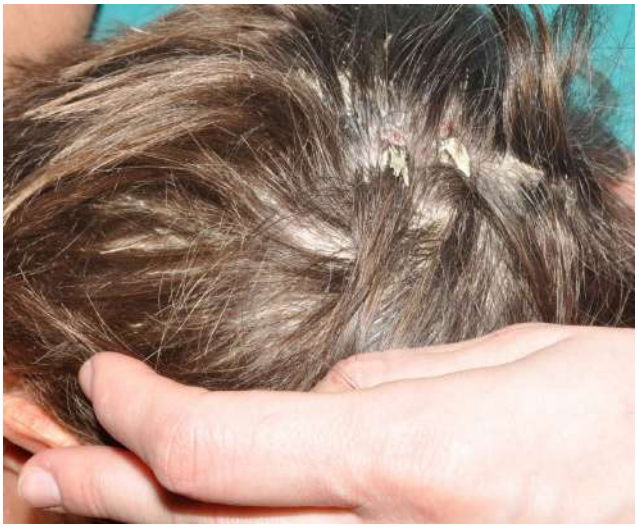

Figure 1: Severe scaling on the scalp.

Figure 2: Mild scaling on the scalp.

Other scalp anomalies: Chronic ulcerations (in association with crusts) have been reported in 5 patients including a series of 4 females patients with ARCI (due to *TGM1* or *ABCA12* variants) or KI (due to *KRT10* variants) [9]. Scalp ulcerations were localized in areas of total baldness. These areas were atrophic and covered by erythematous patches, small erosions and crusts (Figure 3). All patients reported intermittent surrounding pustular lesions. The ulcerations appeared during childhood or adulthood, with no apparent trigger factor, and were chronic with transient periods of improvement. In some cases, bacterial swabs revealed abundant *Staphylococcus aureus*. Histological examination of the ulcerations revealed a nonspecific inflammatory ulceration. A second biopsy taken from one patient also revealed *in situ* squamous cell carcinoma. Topical or intralesional steroids improved the ulceration in the reported cases but did not promote complete recovery. The etiology of such ulceration is unknown: Skin barrier defects, disturbed microflora (Hair anomalies), selective expression of antigenic proteins by hair follicles, repeated trauma/maceration from wearing a wig or scarf and or chronic scratching have been proposed a potential triggering factors, as well as long-term retinoid therapy. The risk of subsequent malignancy due to chronic inflammation is unknown and patients necessitate a close follow-up.

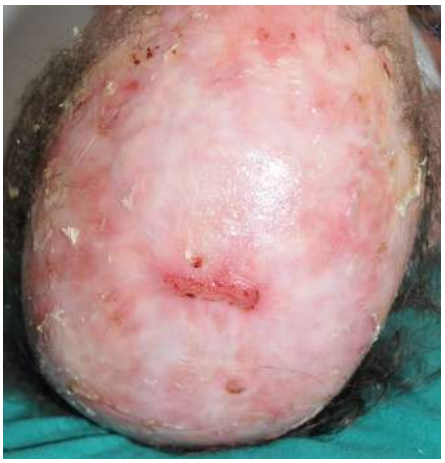

Figure 3: Chronic ulceration in a female patient with autosomal recessive ichthyosis (Harlequin ichthyosis due to *ABCA12* variants).

Hair anomalies in congenital ichthyosis

Syndromic ichthyosis: There are two syndromic forms involving hair fragility due to shaft hair dysplasia and pathognomonic hair microscopic analysis: NS (due to *SPINK5* pathogenic variants) and TTD (due to various pathogenic variants including *ERCC2, ERCC3, GTF2H5, MPLKIP, RNF113A, GTF2E2, TARS1, AARS1* and *MARS1*). In NS, patients present with dry, lusterless, easily fractured, sparse, and short hair. Under light microscopy or dermoscopy, trichorrhexis invaginata looks like a peculiar intussusception or telescope-like invagination along the hair shaft, which microscopically resembles the ball-and-cup joints of bamboo (Figure 4). In TTD, patients present with sparse and brittle hair (Figure 5) exhibit alternating light/dark bands under polarized light ("tiger tail banding") and present with low cysteine content in amino acid analysis. No therapies are available for these shaft hair anomalies, but some authors have reported enhanced hair growth in NS with biologic therapy, Mazereeuw-Hautier et al., manuscript in preparation, but such therapy should not be used for this indication alone [9].

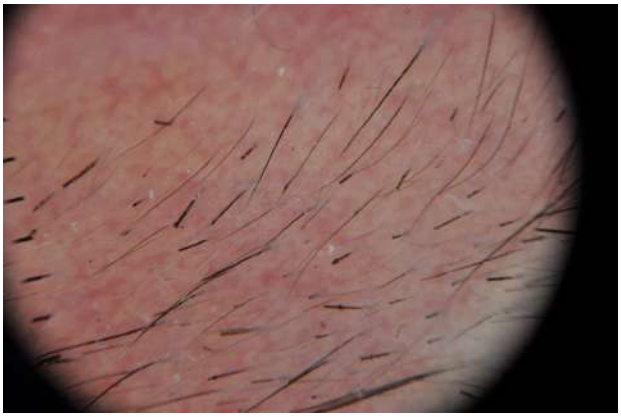

Figure 4: Trichorrhexis invaginata visible on dermoscopy in a patient with Netherton syndrome.

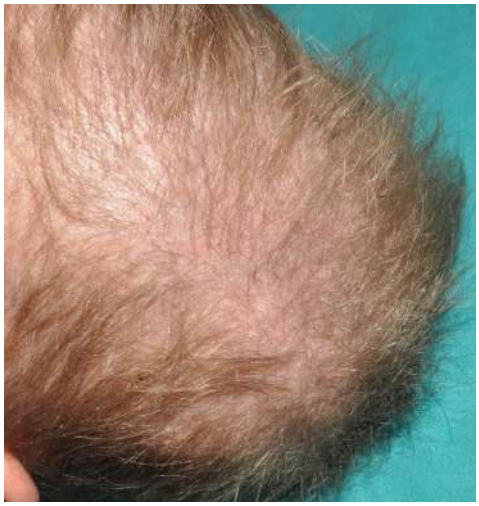

Figure 5: Sparse hair in a young patient with trichothiodystrophie.

Other syndromic forms of CI may show hypotrichosis (sparse hair) without shaft hair anomalies. These include ichthyosis with hypotrichosis syndrome, ichthyosis-hypotrichosis with sclerosing cholangitis syndrome, and Ichthyosis Follicularis Atrichia Photophobia syndrome (IFAP). Keratitis-Ichthyosis-Deafness (KID) syndrome is also often associated with hypotrichosis and even alopecia. Patients with peeling skin disease type I (*CDSN* variants) may present with easy plugging. Patients with ichthyosis en-confetti may present with thick and abundant hair [10]. Also, although not included in the current classification of congenital ichthyosis, desmosomal disorders with or without palmoplantar keratoderma may display prominent hair anomalies including woolly hair hypotrichosis [11].

Non-syndromic ichthyosis: Scarring alopecia have been reported in some non-syndromic CI. According to the series by Putterman et al., and Challamel et al., such alopecia is only seen in ARCI (Autosomal Recessive Congenital Ichthyoses) due to *TGM1(Transglutaminase 1)* or *ABCA12* variants, and KI due to *KRT1* or *KRT10* variants [12,13]. The severity of this alopecia has been demonstrated to correlate with the severity of ichthyosis [12]. The pattern displayed by ARCI patients with *TGM1* variants was well described in the series of 28 patients by Challamel et al., who showed a particular pattern of alopecia consisting of a recession of the hairline leaving a band of atrophic and shiny skin (Figure 6) [13]. The frontotemporal and retro-auricular hairlines were involved for all patients. The occiput or the vertex was also involved for some patients. Trichoscopy revealed erythematous areas and diffuse thick scales more pronounced on perifollicular areas, hair of variable size, often miniaturized, single hair per hair unit, and isolated hairs. Skin inflammation, together with a disturbed intrafollicular microflora, could contribute to this ARCI-related alopecia. The microbiote of patients with CI was recently studied using metagenomics sequencing analysis, in different samples including scalp ones [14]. Taxonomic profiling showed significant shifts in bacterial abundance in patients with ichthyosis CI compared to healthy controls, with a loss of lipophilic microbes such as *Malassezia globosa*, most pronounced on the scalp, which is a sebaceous gland-enriched body site. Moreover, the analysis showed a reduced contribution of fungi, particularly on the scalp. There is no treatment to prevent or limit the progression of this scaring alopecia, and the benefit of intensive and early treatment of scalp scaling is unknown.

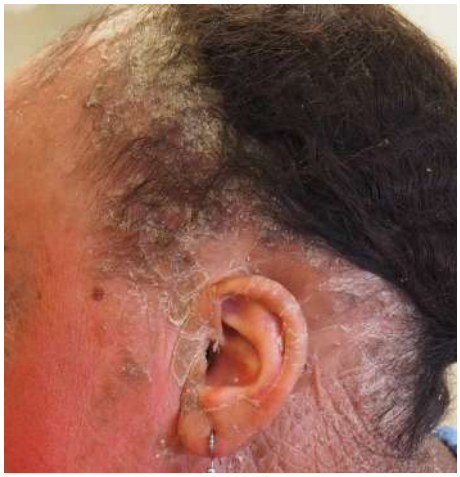

Figure 6: Alopecia consisting of a recession of the hairline leaving a band of atrophic and shiny skin in a female patient with autosomal recessive ichthyosis due to *TGM1* variants.

Finally, patients with both syndromic and non-syndromic CI may also be affected by other common forms of alopecia not specifically related to CI, such as androgenetic alopecia or telogen effluvium. Importantly, alopecia may also be related to the use of oral retinoids, which can cause hair loss. Among the commonly used oral retinoids, acitretin seems to cause hair loss most often than isotretinoin or alitretinoin. Aggravating factors of alopecia should also be checked (e.g., for deficiency of iron, zinc, vitamin D or vitamin B12, thyroid dysfunction, drugs) [15]. Patients with pronounced alopecia should be offered a wig; while the cost is usually not fully covered by the health system, country-specific charitable agencies may aid patients in getting wigs.

DISCUSSION

Scalp and hair anomalies are frequent in CI and can be a part of the distinctive features of some forms, providing helpful elements for diagnosis. Scalp/hair anomalies usually have a significant impact on QoL due to troublesome symptoms, unsightly appearance and loss of scales. The management of these anomalies remains challenging due to the absence of effective treatments. A better understanding of the pathophysiology of these anomalies should help to potential treatment, ideally targeted to be administrated, notably before the occurrence of a cicatricial alopecia.

CONCLUSION

With this mini-review, we provide the characteristics and management strategies for scalp and hair anomalies in CI. However, a better understanding of the pathophysiology of these anomalies should help in designing more effective treatments than those that currently exist.

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