

Head and neck dermatitis, a subtype of atopic dermatitis induced by *Malassezia* spp: Clinical aspects and treatment outcomes in adolescent and adult patients

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Abstract

Background and objectives: Head and neck dermatitis (HND) is a clinical variant of atopic dermatitis (AD), presenting in adolescence or adulthood and characterized by involvement of the head, neck, and superior part of the trunk. The role of *Malassezia* spp has been advocated in the pathogenesis of HND, and antifungal agents represent the treatment of choice.

Methods: A retrospective single-center study was performed to define the clinical features and treatment response of HND among adolescent and adult patients.

Results: Thirty-one patients were identified, 17 with "adolescent-onset" and 14 with "adult-onset" HND. Adolescent-onset HND positively correlated with a past history of AD and presented with exclusive head and neck involvement ($P < .05$). Adult-onset HND was associated with concomitant widespread atopic eczema, involving the flexural areas of the upper and lower limbs, trunk, nipples, or hands ($P < .05$). A positive response to itraconazole in combination with topical treatments was observed in both groups.

Conclusions: This study delineates two HND clinical phenotypes: adolescent vs adult onset. Different characteristics were observed in terms of relationship to AD and eczema localization. A history of AD in childhood and presentation with exclusive involvement of head and neck regions was observed predominantly in the adolescent-onset form, while adult-onset HND often occurred in association with diffuse dermatitis and a past history of AD was less frequent than in the adolescent group. The study is limited by the single-center retrospective nature, which may lead to diagnostic and selection biases, and the small cohort of patients.

KEYWORDS

atopic dermatitis, infection-fungal, pharmacology

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic, immune-mediated, inflammatory skin disease.¹ The prevalence in children is 10%-25%, whereas it ranges from 1% to 3% in adults.¹⁻³ Disease onset is variable, with the peak age

of presentation between 3 and 6 months of age; less is known about the late-onset forms.^{3,4} A wide spectrum of clinical presentations has been reported in both adolescents and adults.⁵⁻⁷ This includes chronic hand eczema, generalized eczema, nummular eczema, prurigo nodularis, psoriasiform dermatitis, secondary erythroderma, and head and

neck dermatitis.⁵⁻¹⁰ Head and neck dermatitis (HND) is a peculiar form of AD that targets the body's seborrheic areas, including the head, face (with a marked predilection for eyelids and lips), neck, and upper trunk.⁹ The etiology of HND is still debated, with involvement of *Malassezia* spp. being a proposed factor.¹¹ The principal differential diagnosis is seborrheic dermatitis (SD). Indeed, both conditions show the involvement of seborrheic areas and *Malassezia* colonization.

Head and neck dermatitis is characterized by eczematous plaques consistently affecting the forehead, eyelids, perioral region, and neck. In severe Head and neck dermatitis cases, the eczema might involve the entire face, leading to the so-called "red face" variant. Eczema and lichenification of the neck represent clinical hallmarks of HND. While SD of the face presents with erythematous scaling patches characteristically distributed along the hairline, within the eyebrows, on the nasolabial folds, in the ear canals, and in males on the beard and mustache areas, the "red face" variant and neck involvement represent exceptional findings in this condition.

The genus *Malassezia* comprises lipophilic yeasts that are part of the normal skin microbiota, with a high affinity for sebum-bearing regions. In HND, a defective skin barrier promotes close contact between *Malassezia* spp. and the cutaneous immune system, causing humoral and cell-mediated immune responses.^{5,8,11-15} HND is usually recalcitrant to conventional therapies for AD but responds well to systemic antifungal drugs such as itraconazole, decreasing the *Malassezia* colonization of seborrheic areas.^{16,17} However, there is not an extensive literature regarding the clinical hallmarks and treatment response in HND. We performed a retrospective, single-center, cross-sectional study to assess two cohorts' clinical features and treatment outcomes of HND treated with systemic antifungal medication in combination with topical therapies.

2 | MATERIALS AND METHODS

The clinical records of patients diagnosed with HND from January 1, 2005, to January 1, 2020, were retrieved. A 6-month wash-out from systemic treatments (including cyclosporine or systemic steroids), refractory response to conventional topical corticosteroids and calcineurin inhibitors, and at least 6-month follow-up from the initiation of oral itraconazole were set as inclusion criteria. A cutoff age of 18 years for HND onset was used to divide the patients into two cohorts: adolescent- vs adult-onset HND.

The following demographics, historical, clinical, and serological data were collected: patient age, sex, HND onset, AD distribution (exclusive HND vs diffuse AD including HND involvement), past medical history of AD or atopy (personal or family), IgE serum levels, and clinical response to itraconazole and topical treatment. All the patients received 100 mg oral itraconazole administered daily for one month and then tapered to a maintenance dose of 100 mg once a week for an additional month. Topical treatments included corticosteroids and/or calcineurin inhibitors.

For all reported factors, statistical correlations of their frequencies among pubertal vs adult subjects, expressed as dichotomous

variables, were performed. The categorical variables were assessed using the Fisher exact test, calculated on contingency tables. The numerical variables were compared by the *t* test for independent means. Proportions were estimated with a 95% exact confidence interval based on the binomial distribution. Statistical tests were two-sided, and *P* < .05 was considered to be statistically significant. All analyses were performed using SPSS for Mac v22.0 (IBM Corp, Armonk, NY). All examinations were conducted in accordance with the Helsinki principles of medical ethics.

3 | RESULTS

Thirty-one patients were considered eligible for this study and were assigned either to the adolescent (17/31, 54.8%) or adult (11/31, 45.2%) cohort according to their age at HND onset (Table 1).

The adolescent group consisted of 9 females and 8 males, with a mean age of 16.5 years. The adult cohort was made up of 6 females and 8 males, mean age 38.4 years (Figure 1).

Both adult and adolescent patients were treated with 100 mg oral itraconazole administered daily for 1 month and then tapered to a maintenance dose of 100 mg once a week for an additional month. Concomitantly, dermatitis on the "head and neck" area was treated with topical corticosteroid application in 4/31 patients and with calcineurin inhibitor application in 20/31 patients. A short course of topical corticosteroids preceded the use of calcineurin inhibitors in 7/31 cases. In patients who achieved complete clearance of rash (11/31), treatment with topical calcineurin inhibitors was maintained twice weekly as preventive therapy. In the case of concomitant diffuse dermatitis, other sites were treated with topical corticosteroids (Table 2).

The adolescent group demonstrated the following features: 10/17 (58.8%) cases presented with an exclusive head and neck localization, while 7/17 (41.2%) had concomitant involvement of at least one of the following areas: upper limbs, lower limbs, trunk, nipples, hands, or flexural sites. A personal history of atopic dermatitis was reported in 100% of cases. Five cases (29.4%) experienced complete remission of AD during childhood and subsequently relapsed with HND after puberty, while twelve patients suffered from recalcitrant moderate-to-severe AD throughout childhood. The adult patients had the following features: 2/14 (14.3%) presented with exclusive head and neck involvement, while 12/14 (85.7%) had diffuse dermatitis at presentation. Among the adult cohort, 6/14 (42.9%) had a positive past history of AD, one of whom subsequently presented with exclusive head and neck localization, while 5/6 presented with diffuse dermatitis in combination with HND.

In summary, the adolescent-onset HND cohort was significantly more likely to have dermatitis limited to the head and neck at presentation and a past medical history of AD of the classic type (*P* < .05), whereas the adult group was significantly more likely to present with dermatitis in a diffuse distribution in combination with HND (*P* < .05).

TABLE 1 Demographic, historical, clinical, and serological data of the studied population

Parameters	Adolescent-onset HND	Adult-onset HND
Sex	8 M 9 F	8 M 6 F
Age (y)	Mean: 16.53[*] (Range 11-21; SD 3.04)	Mean: 38.4[*] (Range 23-62; SD 12.66)
Exclusive HND (pts)	10/17[*]	2/14
HND associated with flexural areas, trunk, nipples or hand eczema(pts)	7/17	12/14[*]
AD history (pts)	17/17	6/14
Age at AD onset (m)	13.3 mean; (Range 1-36; SD 8.33)	12.2 mean; (Range 1-24; SD: 9.80)
HND onset age (y)	14.6 mean; (Range 11-18; SD: 2.03)[*]	35 mean; (Range 19-62; SD: 12.09)[*]
IgE elevation >100 IU/mL (pts)	11/17 Mean: 821.45 (Range: 135-3000 IU/mL; SD: 1098.28)	11/14 Mean 1327.64 (Range: 110-7000 IU/mL; SD: 2018.76)
History of asthma, food allergy, allergic rhinitis and/or conjunctivitis (pts)	P: 9/17 Asthma: 6/9 pts; Food allergy: 4/9; Allergic rhinitis, conjunctivitis: 7/9	P: 10/14 Asthma: 4/10; Food allergy: 2/10; Allergic rhinitis, conjunctivitis: 6/10 pts
Familial history atopy (pts)	6/17	7/14
Itraconazole + topical steroids and/or calcineurin inhibitors treatment outcome (pts)	NR: 2/17 CR/PR: 15/17	NR: 4/14 CR/PR: 8/pts (2 responses limited to the "head and neck area," with no responses on other sites)

Note: P-values were computed using Fisher exact test and Student's *t* test for independent means, respectively, for categorical and ordinal variables. Significant features are in bold.

Abbreviations: A, absent; AD, atopic dermatitis; CR, complete response; CR, complete response; F, female; HND, Head and neck dermatitis; M, male; m, months; NA, not available; P, present; PR, partial response; pts, patients; y, years.

*Significant ($P < .05$).

FIGURE 1 A young adult with head and neck dermatitis. Clinical examination showed diffuse and severe eczema characterized by prevalent involvement of the face (A), shoulders and superior part of the trunk and flexural involvement of upper limbs (B)



Increased serum IgE level (>100 IU/mL) was detected in 11/17 (65%) adolescents and 11/14 (78%) adult patients. Specific IgE antibodies and patch test to *Malassezia* were not available.

No differences were observed between the two groups in terms of AD family history or personal atopy history, including asthma, food allergy, allergic rhinitis, or conjunctivitis.

TABLE 2 Details of topical therapy administered in combination with itraconazole and treatment outcome (patients with adolescent-onset of HND are in shaded rows)

Pt	Sex	Age	Age at HND onset (years)	Topical treatments administered in combination with itraconazole	Treatment outcome (systemic itraconazole + topical therapies)
Patients with eczema exclusively on "head and neck" area					
1	F	11	11	HN: MpA QD × 7 d, then Tacr 0.03% BID until remission.	R
2	F	11	11	HN: Pim QD until remission. PT: Pim BIW.	R
3	M	14	14	HN: MpA QD × 14 d, then Pim BID until remission.	R
4	M	14	12	HN: MpA QD × 14 d, then Pim BID until remission.	R
5	M	16	15	HN: FlutPr QD until remission. PT: Tacr 0.03% BID	R
6	F	17	17	HN: MpA 0.1% QD × 7 d, then Tacr 0.03% QD until remission.	R
7	M	18	16	HN: MpA 0.1% QD until remission. PT: Tacr 0.03% BIW.	R
8	F	19	16	HN: FlutPr 0.05% QD until remission. PT: Tacr 0.03% BIW.	R
9	F	19	16	HN: Pimecrolimus 1% BID for 10 days, then QD until remission.	R
10	F	21	18	HN: FlutPr 0.05% QD until remission. PT: Tacr 0.03% twice weekly.	R
11	M	32	27	HN: MpA 0.1% QD × 7d, then Tacr 0.1% BID until remission. PT: Tacr 0.1% BIW	R
12	F	40	35	HN: Tacr 0.1% QD until remission.	R
Patients with diffuse eczema: "head and neck" area and flexural aspect of upper and lower limbs, trunk, nipple and/or hands					
13	F	13	13	HN: MpA QD × 7 d, then Tacr BID until remission. NON-HN: MpA QD until remission.	R
14	M	16	16	HN: Pim BID. NON-HN: MpA QD	NR
15	M	17	13	HN: Pim QD until remission. NON-HN: MpA QD until remission, then PT: MpA BIW	R
16	F	18	15	HN: Pim BID until remission NON-HN: MpA QD until remission	R
17	F	18	15	HN: Pim BID NON-HN: MpA once daily	NR
18	M	18	15	HN: Pim BID until remission NON-HN: FlutPr QD until remission	R
19	M	21	16	HN: Pim BID until remission NON-HN: MpA QD until remission	R
20	F	23	22	HN: Pim BID until remission NON-HN: MpA QD	R on "head and neck area," but NR on other sites
21	F	26	24	HN: Pim BID until remission NON-HN: MpA QD until remission	R
22	F	27	24	HN: Pim BID NON-HN: FlutPr QD	NR
23	M	27	27	HN: MpA × 7d, then Tacr 0.03% BID until remission. NON-HN: FlutPr QD until remission.	R
24	F	31	26	HN: Pim BID NON-HN: FlutPr QD	NR
25	M	32	28	HN: Pim BID until remission. PT: Tacr 0.1% BIW NON-HN: MpA QD	R on "head and neck area," but NR on other sites
26	M	37	35	HN: Pim BID NON-HN: MpA QD	NR
27	M	40	39	HN: Pim BID until remission. PT: Tacr 0.1% BIW NON-HN: MpA QD until remission	R
28	F	49	47	HN: Pim BID until remission. PT: Tacr 0.1% BIW NON-HN: FlutPr QD until remission	R
29	M	55	50	HN: Pim 1% BID until remission. PT: Tacr 0.1% BIW NON-HN: MpA QD, until remission	R
30	M	57	55	HN: Pim BID until remission. PT: Tacr 0.1% BIW NON-HN: FlutPr QD until remission	R
31	M	62	54	HN: Pim twice daily NON-HN: MpA qd	NR

Abbreviations: BID, twice daily; BIW, twice weekly; d, days; F, female; FlutPr, fluticasone propionate 0.05% cream; HN, head and neck area; HND, head and neck dermatitis; M, male; MpA, methylprednisolone aceponate 0.1% cream; NON-HN, non-head and neck area (referring to flexural aspect of upper and lower limbs, trunk, nipple and/or hands); NR, non-responder to the treatment; P.T, Proactive therapy; Pim, pimecrolimus 1% cream; QD, once daily; R, responder to the treatment; Tacr, tacrolimus ointment.

Itraconazole in combination with topical therapy resulted in clearance of HND in 15/17 (88%) adolescent and 8/14 (57%) adult cases (Figure 2). Two adult patients (2/14, 14%) with widespread AD achieved complete clearance of dermatitis affecting the seborrheic areas but did not clear on the remaining body sites. No significant difference was found in terms of clinical outcomes between the two groups (P -value .097).

4 | DISCUSSION

Head and neck dermatitis is a variant of AD occurring during adolescence and adulthood.¹ During puberty, the increased sebaceous secretion favors *Malassezia* spp colonization of the skin.^{16,17} The constitutional defects of the epidermal barrier in AD associated with the changes of microbiota result in increased exposure of *Malassezia* antigens to the cutaneous immune system.¹⁴ This triggers the innate and adaptive immune responses. Keratinocytes secrete T-helper 2

cytokines (such as IL-4, IL-5, IL-10, and IL-13) and chemokines. T and NK cells interact with activated skin-resident antigen-presenting cells (APCs), enhancing production of pro-inflammatory cytokines. Finally, APCs and T-helper 2 cytokines activate B cells, leading to *Malassezia*-specific IgE production.¹⁷⁻²⁰ In line with the observation of Brodská et al,²¹ 65% of adolescents and 78% of adult patients in our series had a history of "extrinsic" (IgE-allergic) AD.

The involvement of the head, neck, and upper trunk delineates the clinical hallmarks of HND, although diffuse eczema may be associated. Resistance to topical corticosteroids and calcineurin inhibitors and the prompt response to antifungal treatment is a diagnostic clue to the presence of HND.^{5,17-22} In our patients, SD was ruled out clinically by the presence of eczema of the forehead, eyelids, lips, perioral region and neck, or by the presence of the "red face" variant. The sites classically affected in SD (hairline, eyebrows, nasolabial folds, ear canals, beard, and mustache area) were generally spared. The presence of eczema on typical sites of AD, such as the flexural areas of the upper and lower limbs, trunk, nipples, or hand eczema,



FIGURE 2 Treatment outcome after one month of 100 mg daily oral itraconazole and twice-daily pimecrolimus 1% cream in an adolescent female patient (A: before; B: after treatment) and in a young adult male patient (C: before; D: after treatment)

was observed in 19/31 patients. IgE elevation (22/31 patients), familial (13/31), and personal history for atopy, including AD (23/31), or asthma, food allergy, allergic rhinitis, or conjunctivitis (19/31) represented other factors that led to HND diagnosis.

This study demonstrates the presence of two clinical phenotypes of HND: adolescent-onset and adult-onset forms. Two patients in the adult group demonstrated a therapeutic response that was limited to the head and neck, with no response at sites of eczema beyond the seborrheic areas. This finding is very interesting since it is still debated whether *Malassezia* triggers the immune response in a dose-dependent or all-or-none process. Some studies suggest that *Malassezia* prevalence in the skin microbiota is not increased,^{14,23} while other papers found a higher carriage rate in severe forms of AD.²⁴ Whether the response of HND to treatment with systemic antifungal medication is due to a decreased fungal load or to itraconazole-driven anti-inflammatory activity²⁵ remains to be explained. Compared to adults, adolescents showed a better response, though not statistically significant (88% vs 57%), to the treatment regimen of systemic antifungal in combination with topical therapy proposed by Darabi et al.¹⁷

5 | CONCLUSION

Head and neck dermatitis is a clinical variant of AD that promptly responds to itraconazole in combination with topical steroids and/or calcineurin inhibitors. The clinical characteristics differ depending on whether the condition arises in adolescents or adults. *Malassezia*-driven immune dysregulation and defective epidermal barrier are considered the initiating factors of HND. However, the exact pathogenesis and the different response patterns to itraconazole therapy should be investigated in larger studies.

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