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Mini Review

Are Alopecias Non-Communicable Degenerative Diseases?

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ABSTRACT

The incidence of androgenic and areata alopecia appears to be increasing in some areas. While genetic factors have been identified, the relatively low level of heritability indicates the importance of external and epigenetic factors. Many of these are included in or driven by dietary shift, which thereby impacts on multiple aspects of the hair follicle environment. Various potential pharmaconutritional interventions are outlined.

Keywords: Endocrine; Hair loss; Epidemiology; Alopecia areata

INTRODUCTION

While the global epidemiology of hair loss is not well documented, there is evidence that the overall incidence may be rising in some regions, likely due to average earlier onset and partly linked to endocrine and immunological issues. This mini-review focuses on primarily on androgenic alopecia and female pattern hair loss, with reference also to alopecia areata, and sets them in the context of dietary shift and lifestyle changes.

LITERATURE REVIEW

In 1998 a community-based study in the USA found Male Pattern Hair Loss (MPHL) affecting 42% of the male population, ranging from 16% of males aged 18-29 to 53% of males aged 40-49 [1]. A 2000 Norwegian community study of males aged 25-50 reported 63% with hair loss, a quarter of whom reported moderate to severe loss [2]. In 2010, a large China community study found MPHL in 21.3% of males aged 18-59, a figure significantly lower than Caucasians and similar to Koreans at that time [3]. Since that time hair loss of all types is reported to have increased in China [4-6], as it has in South Korea [7-9], in both cases particularly affecting younger adults. In South Korea the growing problem of hair loss in young adults has even recently become an election issue [10].

A 2018 Chinese survey of male and female university students aged 18-24 recorded slightly over 60% with some degree of hair loss [4-6], and a 2015 Turkish study of alopecia in high school students aged 12-18 reported incidence of hair thinning in 37% [11]. If the reports of earlier onset and increased incidence are substantiated, a number of variables might be considered as potential contributory factors.

1. The incidence of autoimmune diseases has increased [12], several of which are associated with a higher risk of developing alopecia areata [13-15].
2. While PCOS is linked to hirsutism of the face and chest and to acanthosis nigricans, it also increases the risk of female pattern hair loss and androgenic alopecia [16]. The increasing incidence of PCOS among females in some regions may therefore be contributing to overall alopecia figures [17].
3. Average age of puberty has fallen in both sexes [18,19], which would be expected to advance the onset of androgenic alopecia.
4. Exposure to endocrine-disrupting chemicals (EDC's) has increased [20]. There appears to be a relationship between EDC exposure and advanced age of puberty, but it is a highly complex one [21,22]; the effects are gender- and compound-specific, and depend on the exposure window.
5. There may also be a link between EDC exposure and PCOS. EDC's bind to and alter hormone receptors including estrogen, progesterone, androgen, and glucocorticoid receptors [23,24]; and there is evidence that pre-natal exposure may predispose to PCOS in later life [25].
6. EDC's are routinely found in hair and urine samples, even in children [20]; and occur in a significant number of hair products [26], which deliver high concentrations of these compounds directly to the scalp. There may therefore be localized as well as systemic effects [27].

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7. Chronic low-grade inflammation is thought to be involved in hair loss in both sexes [28-34], and is likely exacerbated by recent dietary shifts which have shifted the balance of anti-and pro-inflammatory dietary factors in favour of the latter [35-38].
8. Falling intakes and/or reduced bio-functionality of iodine [39,40], and selenium [41-43], have likely contributed to rising rates of hypothyroidism [44,45], which is linked to FPHL via telogen effluvium.
9. Diabetes and its metabolic constituents have been linked to increased central scalp hair loss in women [46,47], and to androgenic alopecia [48-51]. The remarkable increase in NIDDM may therefore be another driver of alopecia.
10. Significant phenotypical (hair volume) differences between monozygotic male twins with androgenic alopecia [52], indicate a role for external [53], and epigenetic [54], factors involving histone modification [55,56].
11. Histone methylation and acetylation rates are affected by the availability of dietary methyl groups and intakes of prebiotic fiber respectively, and by ancillary dietary compounds including isothiocyanates, polyphenols, carotenoids, omega 3 HUFA's, vitamin D and others which impact mRNA expression [57].
12. Post-transitional dietary shift from basic produce to ultra-processed foods has reduced dietary intakes of all the above compounds; the phytonutrient density of ultra-processed foods is reduced by inter alia dilution with sugars, other simple carbohydrates and plant oils [58].

DISCUSSION

Current treatments

The limitations and adverse effects of the two pharmaceutical staples, minoxidil and finasteride, are well known and need not be repeated here. The most recent oral treatment for alopecia areata Olumiant (baricitinib), a JAK inhibitor originally designated for the treatment of RA, comes with a boxed warning for serious infections, mortality, malignancy, major adverse cardiovascular events and thrombosis. While these adverse effects may be a reasonable trade-off against a painful and crippling disorder such as severe RA, they seem excessive in the context of hair loss.

Nutritional remedies for hair loss include various B vitamins, vitamin D, trace elements, amino acids, garlic gel, marine proteins, capsaicin, melatonin and onion juice. All have some evidential support, albeit weak [59], but the vitamins, trace elements and amino acids presumably only rectify deficiency states. Herbal remedies with some evidence include *Curcuma aeruginosa*, *Trifolium pratense*, *Panax ginseng* and *Serenoa repens*. All of these are thought to act primarily via the inhibition of 5α-reductase [60], with all the limitations that this mechanism entails.

Future developments

PGD2: Recent research underpins the role of PGD2 and its receptors GPR44 and PTGDR in alopecia. PGD2, a pro-inflammatory mediator [61], increases hair loss in mice [62], is elevated in bald areas of the scalp in males with androgenic alopecia, and reduces anagenic hair lengthening [62]. The selective GPR44 receptor antagonist Septiprant was relatively ineffective as an anti-inflammatory agent in seasonal allergic rhinitis [63], and failed as a hair loss treatment [64]. However, an extract of Leea indica leaves with PGD2 synthase inhibitory activity showed enhanced hair growth in a pre-clinical model [65]. HairAgeVitae, an alkaloid-free extract of Ageratum conyzoides which blocks 5-alpha reductase and also inhibits PGD2 synthesis, generated positive results in males and females in two clinical trials [66,67], the second of which was reasonably robust.

Dysbiosis: Colonic dysbiosis plays a crucial role in many disease states, both within the gut and in almost all other tissues, to the extent that a fibre-depleted diet is associated with a 30% increased risk of early death [68]. Colonic and dermal dysbiosis alter systemic and local immune responses, and are suspected of promoting the development of skin diseases including atopic dermatitis, psoriasis, acne vulgaris, dandruff and skin cancer [69,70]. In some cases the mechanism linking colonic dysbiosis and hair loss is relatively well characterized. Colonic dysbiosis characterized by overgrowth of *Lactobacillus* murinus reduces biotin in the gut of mice, and causes alopecia [71]. Biotin deficiency causes alopecia in pre-clinical models [69], and humans [72], giving these findings coherency. Rectifying (human) colonic dysbiosis with blended prebiotics, which can improve biotin status [73] and at the same time exert systemic anti-inflammatory effects [74], may therefore provide some efficacy against hair loss. The dermal microbiotal population is also significant, and estimated at 10 to the 12th [59], is also significant; and dermal dysbiosis is emerging as another key variable involved in alopecia. The hair follicle environment contains stem cells, immune cells and a population of bacteria, fungi and bacteriophages, and the bulb and bulb regions are immune-privileged [75,76]. A healthy microbial profile in the follicle plays a role in setting appropriately low (physiological) levels of inflammatory stress, involved in homeostasis and innate immune defense [77,78]. Higher levels of pathogenic taxa in the hair follicle can disrupt local immune-privilege [79], contributing to a pro-inflammatory state in the scalp [79,80], which can damage or destroy the follicle [81]. These taxa are linked to alopecia areata [82,83], and there is evidence of an excessively inflammatory component in androgenic alopecia also [84,85]. Colonic dysbiosis, dermal dysbiosis and follicular health appear to be inter-linked. There is some evidence that colonic dysbiosis may, partly by inducing gastrointestinal and then systemic inflammation and also possibly *via* more direct gut-dermis connections, increase inflammatory stress in the hair follicle and damage hair growth [86-89]. Specific colonic species such as *Clostridum difficile* [87], and dermal species *Malassezia* [88] and *C. acnes* [89] have been implicated. Given their shared embryological origins, the structural/functional similarity of gut and skin and hand-mouth-skin microbial transfer, the possibility of a more direct relationship between colonic and dermal microbiota cannot be excluded [90,91]. This may provide another rationale for utilizing prebiotic fibers to re-establish a pre-transitional colonic microbiota.

Glycemic control: Diabetes and its metabolic components have been linked to an increased incidence of hair loss [46-51]. More recently, Type 2 diabetes was associated with significantly increased central-scalp hair loss in women [47], an association which was unaffected by diabetic treatment. Diabetes causes chronic inflammatory stress [92], immune dysfunction [93], and altered skin pH [94], providing several possible mechanistic links to alopecia. Here again, the role of prebiotic fibers in supporting glycemic control [95], may be relevant. Given the established use of non-medical tools (i.e., reduced intakes of digestible carbohydrate, increased levels of physical activity, weight loss) in improving and reversing Type 2 diabetes [96-101], with resulting normalisation of cardiovascular, metabolic and hepatic parameters [102,103], it is conceivable that these lifestyle strategies may impact positively on hair growth also.

Inflammatory stress: Dietary shift involving a move away from basic produce toward increasing consumption of ultra-processed foods [104-106], is associated with rising rates of most if not all of the non-communicable chronic degenerative diseases [107-112]. This shift has reduced intakes of key anti-inflammatory nutrients such as the polyphenols, omega 3 HUFA's and prebiotic fibers, contributing to wide-spread chronic inflammation [113,114] and to a situation where poor diet has become the leading cause of death world-wide from diseases with inflammatory components [115].

This excessively inflammatory background has been shown to impact adversely on immune-privileged processes in males and females [116,117], and it is reasonable to assume that similar effects may be present in the hair follicle also. This would be expected to increase the tendency to anagenic curtailment, androgenic alopecia and alopecia areata [118-123].

CONCLUSION

Alopecia has likely always been with us, as shown by the fact that various non-human primates may present with alopecia, and genome-wide association studies which have identified susceptibility loci accounting for roughly two fifths of the heritability of androgenic alopecia. However, a number of factors associated with the modern diet and lifestyle may be contributing to an increased incidence of androgenic alopecia and alopecia areata over and above the genetically disposed. This is hinted at in recent research. By inducing chronic inflammatory stress, dysbiosis, and metabolic and epigenetic disruption, the modern diet and lifestyle increase the incidence of many non-communicable degenerative conditions; and it may be useful to consider the alopecias within this context. A restoration of pre-transitional nutritional and therefore metabolic and epigenetic profiles will likely reduce the numbers of non-genetically determined cases.

CONFLICT OF INTEREST

The author has consulted with GenCor Pacific, the company which developed a standardized alkaloid-free extract of Ageratum conyzoides.

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