Cyberspace Chat

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Beyond genetics part III: evidence that lifestyle choices may impact hair loss in androgenetic alopecia

In the previous two parts of "Beyond Genetics," the goal has been to review possible accelerating factors for hair loss in AGA beyond the known risks portended by an individual's genome. In part one, evidence was presented of identical genotypes in mice with pathologically different phenotypes based on dietary manipulation effecting epigenetic cellular controls. These controls determine whether a gene is silenced or activated and explains why identical genetics are not always equally expressed. The identical twin surveys that identified variant rates and patterns of hair loss suggest that AGA genetics may be influenced by external factors or epigenetic controls. Increased rates of hair loss were associated with lifestyle factors such as stress, being widowed or divorced, cigarette smoking, heavy alcohol consumption, and sunlight exposure.[1] Given these survey findings, I asked some of our peers if anyone believed there were accelerants for AGA? If so, was anyone counseling patients with AGA about lifestyle risks as a means to curtail or retard further hair loss—in addition to usual medical therapy with finasteride or minoxidil? Following are some of their responses.

Dr. Richard Shiell had this to share: There is certainly a common belief amongst some doctors and members of the public that there are factors that can accelerate hair loss, but in 50 years I have searched in vain for anything remotely "scientific." "Stress" is about the only lifestyle factor that I have observed from time to time, but I have not seen scientific proof and cannot even precisely define "stress." (One man's stressful life is just good fun for someone else—all in a day's work.) I did have a pair of 25-year-old "identical" twins, where one had lost significantly more hair than the other. When I spoke to the more hirsute twin, he laughed and said it was because his brother was married with a child and mortgage—and had more stress!

Dr. Mike Beehner remarked: One thing that comes up occasionally is the too frequent use of hair coloring, particularly those with ammonia and peroxide as ingredients. When patients color their own hair without the help of a salon professional, they almost always re-color the ends of all the hairs, thus rendering them somewhat brittle and subject to breakage. This can then translate into decreased hair mass and a thinner look. I think this vulnerability varies tremendously from one patient to another and doesn't affect everyone.

A similar issue with the potentially adverse effects of chemical hair treatments was pointed out by Dr. Marcelo Gandelman: Here in Brazil many men and women have curly hair and use chemical hair straighteners. These products contain ammonium thioglycolate and hydroxides to relax the curls and break the chemical bonds between the hair amino acids. However, we get frequent reports of improper use of hair straighteners, with serious damage such as scalp burns, partial or total hair loss, and more. Some beauty salons and hairdressers are unscrupulously using irregular products, adulterated by adding illegal and toxic formaldehyde, in chocolate and coffee perm formulas. The continuous damage from these chemicals causes hair loss and scarring alopecia. The advice that I offer—use only ready-made products of well-known brands and avoid homemade formulas!

Discussion

It seems most of us do not counsel patients in regard to potential accelerants for AGA suggested by the twin surveys. Dr. Shiell succinctly identified a likely reason for this—despite the sense that accelerants occur, in the past there was a lack of medical evidence to prove this. The premise of non-genetic factors influencing AGA, as noted, stems from the findings of the monozygotic twin surveys, where genetics were identical and included AGA, but rates of hair loss were not. If we determine that accelerants exist, are they controllable or treatable? Do these factors determine or impede the efficacy of current therapies such as finasteride or minoxidil? Among the potential accelerants cited in the twin studies were stress and marital status (specifically divorce or death of a spouse), cigarette smoking, unprotected sunlight exposure, and heavy alcohol consumption. Other lifestyle factors that have been observed among our peers to have an association with advancing hair loss are chemical treatments and hair dyes. Updated molecular evidence in the form of animal studies, human models, and epidemiologic surveys to review each of these factors and their affect on hair growth/loss will follow.

There is now a growing volume of molecular science to support the role of physiologic and psychoemotional stress in causing hair loss. Two murine model studies support the presence of a hair follicle–brain axis and convincingly show this relationship on a molecular level. In the first, mice were subjected to sonic stress, and neuropeptides, neurohormones, and nerurotransmitters were monitored for their role in mediating and modulating the systemic stress response. A major neuropeptide involved in this response is Substance P, which can activate T cells, macrophages, and mast cells. In mice, this molecule has been shown to modulate hair growth; in humans, it has been associated with the hair loss of alopecia areata following a stressful life event. In the study, an injection of Substance P was able to produce intrafollicular apoptosis, which was subsequently ameliorated by administration of a Substance P receptor antagonist, clearly documenting the impact of stress and Substance P as a modulator of hair growth in mice.[2] To establish the relevance of this study in human hair follicles, the same researchers were able to prove that Substance P receptors are expressed in human scalp and hair follicles in association with their proximity to follicular nerves, felt to be part of the psychoemotional response to stress that can trigger hair loss in some patients.[3] These researchers point out a Substance P inhibitor, called aprepitant (brand name

Emend), is currently available as a novel therapy for depression in humans. They further suggest since hair loss can exacerbate stress and cause depression, this therapy may be useful to treat both. No studies in humans are yet published to test this hypothesis, however. In a more recent study investigating the stress–hair response, bald mice experiencing chronic stress from over expression of Corticotropin Releasing Factor (CRF) experienced hair regrowth when treated with a CRF receptor antagonist, astressin-B.[4] Evidence that human hair follicles are a target for corticotrophin releasing hormone (CRH) suggests a similar response may occur in human hair.[5]

It is pertinent to note that in addition to "stress" as a contributing factor for hair loss, the twin survey also identified divorce or loss of a spouse. Based on the role of life events and their contribution to the human physiologic response to stress as defined in the Holmes-Rahe readjustment life events scale, among the 43 most stressful life events likely to cause illness, death of a spouse was highest, with divorce a close second.[6] Therefore, the twin study identified an accelerant of AGA mediated by strong "life event" psychoemotional stressors. Although studies to document molecular stress effects of divorce and spousal death on hair loss were not found, there have been studies establishing the relationship of these life events with physiologic stress and the immune response.[7] One survey of 1,500 men in Taiwan found that policemen had a 2 times greater risk for developing AGA compared to the general population, and the conclusion of the surveyors was that obesity at a young age and sunlight exposure may have been contributing factors.[8] Notably absent from their assessment was the associated stress with that occupation. This brings us, however, to another accelerant mentioned in the twin study.

In addition to the previously mentioned policemen survey, in the twin survey, men in particular who did not wear hats or use other head protection when outdoors experienced significantly greater hair loss. One proposed mechanism of hair follicle injury from ultra violet light refers to Propionibacterium sp. in the pilosebaceous duct, which undergoes photoactivation of porphyrins leading to oxidative stress in tissue, and has been implicated in follicular microinflammation.[9] A recent *in vitro* study using a human hair model documented oxidative damage to mitochondrial DNA and follicular apoptosis in response to 20J of ultra violet radiation.[10] The suggestion from the twin studies that exposure to ultra violet light is an AGA accelerant along with in vitro and epidemiologic support, makes it reasonable to recommend UV protection for hair—via hats or sunscreens, for patients with AGA. Particularly since as hair loss progresses, skin has greater exposure to known UV toxicity as well.

The general toxicity of cigarette smoking to human tissues, and skin in particular, are well documented. The role of cigarette smoke as an accelerant in AGA may have been suspected, however, there is now further epidemiologic and scientific support for this assumption.[11] A population survey in Taiwan was performed among 740 men with AGA, which found a statistically significant association between cigarette smoking and early onset of and greater severity in Norwood pattern for participants who smoked >20 cigarettes/day.[12] One possible mechanism for this observation is suggested by the lifestyle and serum androgen survey among European men that found that current smokers had higher mean concentrations of testosterone and androstandione by 13% and 15%, respectively.[13] However, more toxic mechanisms are suggested by a murine study where mice were exposed to a whole body mixture of cigarette smoke. After 3 months most of the exposed mice developed areas of alopecia and gray hair, compared to the control mice who were not exposed. Cell apoptosis was observed along the edge of hair loss, along with atrophy of the epidermis and reduced thickness of subcutaneous skin. Other mechanisms by which smoking may contribute to hair loss are likely related to the effect of nicotine on the microvasculature, as well as genotoxicants that damage DNA of the hair follicle. Of considerable interest, however, is the fact that exposed mice who received the supplement N-acetylcysteine (NAC)—an antioxidant used to treat a variety of physiologic conditions, including trichotillomania—did not develop lesions.[14] NAC has been studied and used as a potent antioxidant, though some researchers point out this action depends on its cellular environment. NAC can also prevent apoptosis and promote cell survival by activating an extracellular signal-regulated kinase pathway.[15] Although the precise mechanism of action for NAC's affects in this setting were not described, it appears as though oxidative stress may have been a factor for hair loss that was prevented by administration of NAC. Finally, in a follow-up study, researchers studied L-cystine and vitamin B6 in mice exposed to environmental smoke and these also were effective preventive treatments.[16] The evidence to support cigarette smoking as an accelerant to AGA is suggested by twin studies, and supported by a separate epidemiologic study, as well as the mouse model. Although NAC may be helpful to prevent this type of hair loss, smoking cessation is a healthier option.

Despite the suggestion that excessive alcohol consumption is an AGA accelerant, there were no direct studies to evaluate this hypothesis. Evidence for the creation of oxidative stress from reactive oxygen species (ROS) from alcohol metabolism have been documented in liver tissues and in nerve tissue relative to peripheral neuropathy.[17,18] ROS can damage proteins and DNA or combine with other substances to create carcinogens. Furthermore, the metabolic by-product of alcohol metabolism is acetaldehyde, a known carcinogen, also capable of interfering with DNA replication and DNA repair.[19,20] No studies in hair follicles were found specifically related to ethanol ingestion. However, a nice review of the literature on oxidative stress relative to the ageing of hair as it pertains to graying and hair loss indicates this form of stress is detrimental to hair[21] and suggests a role for this association with ethanol consumption. The greatest hurdle in proving that alcohol consumption is an AGA accelerant is the potential for both genetic and epigenetic variability to influence toxicity. There are 4 major enzymes that control alcohol metabolism, and 10 genes subject to variation that control the enzyme variabilities influencing toxicities. Although the twin studies provide the opportunity to control for gene variation, our knowledge of epigenetic control over gene activation is a reminder how variable an individual's response may be even when the genome is identical. For example, it is believed that alcohol consumption itself may assist as part of the feedback mechanism to activate some of these genes.[19,20] Furthermore, despite known toxicities, alcohol consumption in moderation is known to have some health benefits. Perhaps the take away message from the twin surveys is that alcohol consumption beyond moderation may be an AGA accelerant in some people. More research is necessary to elucidate who is at

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risk. Meanwhile, it would be interesting to study whether the antioxidant NAC would be helpful to counteract oxidative stress in this setting as well.

At least one AGA hair loss accelerant not mentioned in the twin studies, and not addressed in epidemiologic surveys, but mentioned independently by two of our peers, Drs. Parsley and Gandelman, are chemical hair treatments, including straighteners and dyes. One component of hair dyes reported in current literature is p-phenylenediamine; in Europe the weighted prevalence of sensitivity to this chemical was 4.6% among 21,515 participants—a significant number most often caused by use of consumer hair dyes. This chemical is responsible for many published cases of severe contact dermatitis, which can cause hair thinning and presents a health risk to many patients.[22] Although the frequency of hair dye reactions was not identifiable in the literature, a murine model to identify the causative agents of contact dermatitis and hair loss was performed by applying dye to the dorsum of mice for 3 days. Combination components of the dye were studied in this fashion, and hydrogen peroxide and monoethanolamine were identified as the cause of hair loss and dermatitis. This was noted in all mice exposed. Histologic examination revealed oxidative stress as the likely cause of these reactions.[23] Antioxidants were not tested in this study to see if these would attenuate the reaction in mice.

Finally, an interesting epidemiologic survey in 242 Kenyan women who used scalp relaxers revealed that most of them had experienced an adverse reaction (67%)—including scalp burns, hair thinning or loss, and contact dermatitis—yet over half of those who experienced a side effect were still willing to subsequently use these products for their cosmetic results.[24] Counseling patients on the risk of permanent hair loss may help them to avoid this problem in the future.

Conclusion

In the past decade, advances in molecular science have provided evidence of the mechanisms involved in hair follicle growth modulation, and also for cellular stress revealing a hair follicle–brain connection. All of the accelerants reviewed have the end effect of causing cellular stress—either through the hypothalamus pituitary pathway or oxidative stress. The evidence establishes that factors, such as divorce, spousal death, cigarette smoke, and sunlight, that cause oxidative and psychosocial stress are potential accelerants for hair loss in AGA. To the extent that alcohol can cause oxidative stress, it has potential as an AGA accelerant as well but complexities in genetic and epigenetic variations in metabolism will make it difficult to identify who is at risk for this. Furthermore, as Dr. Shiell mentioned, one man's stress is another man's adventure, and variable physiologic stress responses to comparable stimuli are expected, and remain to be elucidated. Perhaps someday we will have a "physiologic stress panel" of lab tests to help guide therapy. The answer to the question of whether these accelerants impact the effectiveness of medical therapies is not yet known, but may be one reason for continued hair loss in some patients despite them. Acknowledging that AGA accelerants exist presents hair loss specialists an opportunity to counsel patients about lifestyle choices that may slow this process. Avoiding work and life stress is not always possible. However, along with advances in molecular biology are emerging molecular anti-stress therapies, including Substance P inhibitors (as noted above, one such therapy already available is aprepitant). Evidence for safety and efficacy as an adjunctive therapy for hair loss, however, is not yet available. A further adjunctive therapy may be NAC, an over-the-counter supplement, to counteract oxidative stress in patients who are exposed to UV light, ethanol, cigarette smoke, and even hair dye—when avoiding these factors is impossible or improbable. Other supplement options may be L-cystine and vitamin B6 to offset accelerants associated with oxidative stress. Studies to document the effect of these therapies in humans will be helpful, though there is little down side to recommending the nutritional supplements. The role of Substance P and CRF inhibitors are yet to be defined, but may have a place in AGA exacerbated by stress. Patients should also be encouraged to provide a chemical hair treatment history, and be counseled about potential risks of hair loss from these treatments when improperly performed or when sensitization occurs.

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