Review Article

Premature Graying of Hair: A Comprehensive Review and Recent Insights

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Abstract

Background: Hair symbolizes well-being and self-expression, with graying occurring naturally among different racial groups at varying ages. Premature graying has psychological and societal impacts, influencing self-esteem and quality of life. Gray hair usually advances gradually and is permanent, with occasional reports of natural repigmentation. Premature graying of hair (PMGH) results from a complex interplay of genetic, environmental, and cellular factors. **Materials and Methods:** Studies exploring links between gray hair and conditions such as osteopenia, hearing loss, smoking, obesity, dyslipidemia, and cardiovascular disease have yielded mixed results. Despite continuous research into the causes of gray hair, effective, evidence-based treatments are lacking and still need to be improved. **Conclusion:** Herein, we reviewed the causes, mechanisms, risk factors, psychosocial effects, and emerging therapies for PMGH.

Keywords: *Canities, genetic, graying, oxidative stress, premature, treatment*

Introduction

Hair symbolizes well-being and plays a vital role in social communication, significantly shaping one's physical appearance and self-perception. Graying of hair, or canities, is a natural aging process that occurs at different ages depending on racial backgrounds. On average, Caucasians start graying at around 34 years, while in Blacks, it begins at around 43.9 years. Graying of hair may be labeled as premature in Caucasians when it takes place before the age of 20 years, while in individuals of Black descent, the defined age may be before 30 years. There is no well-defined threshold for premature graying of hair (PMGH) in the Asian population.[1,2]

PMGH has several psychological and sociocultural consequences, affecting self-esteem, body image, and overall quality of life due to society associating gray hair with aging and compromised health. This phenomenon challenges our understanding of hair biology, genetics, and aging processes.[3,4] In this review, we explore the various aspects of PMGH, including its causes, mechanisms, potential risk factors, psychosocial effects, and emerging treatments.

Clinical presentation of gray hair:

Canities, or hair whitening, primarily results from an optical phenomenon. As a result of the reflection or refraction of the incident light, the pale-yellow keratin appears white.[5] Gray hair retains some color due to scattered melanosomes. However, white hair lacks them entirely. Compared to pigmented hair, gray hair tends to be thicker, rigid, and more challenging to manage. Gray hair also grows faster and thickens more noticeably.[6] Gray hair is particularly susceptible to damage from UV radiation, necessitating increased photoprotection.[7] In addition, structural alterations in the hair fiber make it challenging for gray hair to maintain artificial color.[8]

Graying of hair differs between the genders. In women, it typically begins along the hairline boundaries, whereas in men, it first becomes noticeable at the temples and sideburns before spreading to the entire scalp and eventually the occiput.[9] The rate of graying varies across different parts of the body. Scalp hair is usually affected first, followed by facial hair and, subsequently, body hair. Pubic, axillary, and chest hair retain pigmentation for a longer duration. This pattern may be attributed to discrepancies in the dispensing of melanocyte precursors during melanoblast migrations in embryonic development.[10]

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Access this article online

Website: https://journals.lww.com/idoj

DOI: 10.4103/idoj.idoj_807_23

Quick Response Code:

How to cite this article: Poonia K, Bhalla M. Premature graying of hair: A comprehensive review and recent insights. Indian Dermatol Online J 2024;15:721-31.

Received: 25-Oct-2023. **Revised:** 27-Jan-2024. **Accepted:** 25-Mar-2024. **Published:** 30-Aug-2024.

Hair follicular pigmentary unit and melanogenesis

Immature melanoblasts, originating from the neural crest, migrate into the skin during embryogenesis to give rise to melanocytes in both the epidermal and follicular melanin units. As hair follicles mature, melanoblast/melanocyte descendants, referred to as "transit" or "transient-amplifying" melanocytes, proliferate in the epidermis and then migrate into the developing hair follicle. Within the follicle, these melanocytes can either remain dopa-oxidase-positive cells (actively expressing tyrosinase) or persist as dopa-oxidase-negative cells, depending on their specific follicular location.[11]

The hair follicular melanin unit synthesis involves specialized cell types, molecular pathways, and cellular organelles. It resides within the immune-privileged proximal hair bulb influenced by DP (dermal papilla) fibroblasts.[12] The ratio of melanocytes to keratinocytes in the hair bulb is approximately 1:5, while the basal epidermal layer adjacent to the DP maintains an almost equal 1:1 ratio. In contrast, the epidermal melanin unit has a 1:36 ratio.[13]

Melanocytes in the hair bulb are distinct from epidermal ones in size, dendritic structure, rough endoplasmic reticulum and Golgi activity, and the production of larger melanosomes. Unlike epidermal melanocytes, where melanin granules disintegrate in differentiating keratinocytes, granules transferred to follicular cortical keratinocytes undergo minimal digestion, contributing to hair pigmentation's distinct appearance and longevity.[14]

In adult hair follicles, the pigmentation process encompasses an interface among follicular melanocytes, cortical/medullary keratinocytes, and DP fibroblasts. This process comprises melanogenesis in hair bulb melanocytes, then pigmented granules pass on to cortical and medullary keratinocytes and the development of pigmented hair shafts.[15,16]

Unlike continuous epidermal melanogenesis, follicular melanogenesis is synchronized with the hair growth cycle, occurring during the anagen phase, stopping during catagen, and remaining dormant in telogen.[15] Anagen typically lasts 3–5 years, with a monthly hair growth rate of approximately 1 cm. Immature melanocytes re-differentiate during early anagen, likely recruited from an emerging reservoir in the upper layer of the outer root sheath. Active melanogenesis begins during anagen III, with tyrosinase activity becoming evident. Pigment transfer to cortical keratinocytes starts in anagen IV and continues through anagen V and VI. As anagen VI concludes, hair follicle regression begins, primarily affecting the hair follicle pigmentary unit with melanocyte dendrite retraction and reduced melanogenic activity while keratinocyte multiplication persists. Hence, the hair shaft closest to the scalp remains non-pigmented.[17,18]

This segregation of melanocyte subpopulations during skin development has significant implications for understanding the melanocyte replenishment during the hair cycle, the function of melanocyte stem reservoirs, and the aging-related changes in pigmentation, including the depletion of functional melanocytes contributing to the graying process.[16]

Aging of the follicular melanin unit

A hair follicle goes through various stages throughout the life span, resulting in different hair types. Fine, unpigmented lanugo hair appears in fetal development, which later transforms into shorter vellus hair, still lacking pigmentation. Subsequently, this vellus hair progresses to intermediate hair with subtle pigmentation, eventually forming long, thick terminal hair in adulthood.[10]

The pigmentary unit of hair follicles is particularly susceptible to age-related alterations. Typically, hair color begins in its lightest shade during early childhood and gradually darkens even before puberty begins. This darkening trend continues through adolescence and young adulthood until it eventually culminates in the onset of gray hair or canities. Hormones, particularly androgens and estrogens, significantly influence this process.[19]

Etiopathogenesis of PMGH

The etiopathogenesis of premature canities involves a complex interaction of genetic, environmental, cellular, and biochemical factors. While our understanding of this phenomenon continues to evolve, several key mechanisms that contribute to the premature loss of hair pigmentation have been identified.[20]

Role of reactive oxygen species in PMGH

Reactive oxygen species (ROS) and their role in premature hair graying are a significant research focus, providing insights into the underlying mechanisms. During the active growth phase known as anagen, robust melanogenesis occurs within hair follicles, involving the synthesis of melanin through the oxidation of tyrosine and dihydroxyphenylalanine. However, this melanogenesis process generates ROS as by-products, disrupting normal cellular functions and leading to oxidative stress in melanocytes.[21,22]

Antioxidant defense mechanisms in the body, for example, enzymatic antioxidants such as superoxide dismutase and catalase, play a central part in neutralizing free radicals and protecting melanocytes from damage.[23] Nevertheless, with aging, a decline in antioxidant activity and increased oxidative species production create an imbalance, contributing to oxidative stress-related melanocyte dysfunction. These findings assist the theory that oxidative stress has a role in hair graying.[24]

Oxidative stress triggers changes in gene expression, affecting genes such as B-cell lymphoma 2 (BCL-2),

TRP-2, TRP1, microphthalmia-associated transcription factor (MITF), and PAX 3. BCL-2, important for regulating and countering cell death in oxidative stress-prone environments, gains significance in graying. *In vivo* mouse models (with bcl-2−/− phenotype) have demonstrated faulty melanogenesis and enhanced apoptosis, including reduced MITF expression, suggesting BCL-2's role in hair graying.[25,26]

Elevated oxidative stress reduces BCL-2 expression, leading to cell death and decreased active hair follicles. In addition, ROS negatively affects BCL-2 levels.[27] Similarly, Shi *et al*.[28] conducted a study on premature hair graying, analyzing pigmented and gray hair from a similar Chinese population (n = 9). Their Western blot findings revealed distinct gene expression levels for melanogenesis genes (TRP1, MITF, and PAX3), notably higher in pigmented hair follicles.

Genetic factors: Several genes play essential roles in normal hair pigmentation, including BCL-2, TRP-2, TRP1, MITF, and telomerase. Among these, BCL-2 and MITF are crucial for preserving melanocyte stem cells (MSCs) and serve as indicative markers of MSCs. MITF deficiency and Pax 3 and Sox 10 genes directly contribute to PMGH development.[25,26] MITF-mutant mice experience progressive hair graying due to reduced melanocyte numbers, eventually leading to widespread depigmentation. Harris *et al*.[29] unveiled a novel role for MITF in suppressing innate immune gene expression, thereby impeding hair graying. Their findings demonstrated that artificially enhancing the innate immune response in animals resulted in substantial melanocyte stem cell loss and an increased prevalence of gray hair. In addition, telomerase has a notable role in PMGH, supported by observations that telomerase-deficient mice exhibit a higher proportion of gray hair than control mice.[30]

Several syndromes can lead to PMGH, either directly or indirectly, often associated with impaired DNA repair mechanisms, rendering individuals more susceptible to oxidative stress.

External factors

External factors can be categorized as physical and chemical influences. Physical factors involve exposure to ultraviolet (UV) radiation, smoking, chronic alcoholism, chronic illness, a sedentary lifestyle, and psychological stress. In contrast, chemical factors encompass the utilization of synthetic dyes and pharmaceutical drugs.[31]

1. **Drugs:** Certain chemotherapeutic drugs (tyrosine kinase inhibitors (sunitinib, pazopanib, dasatinib)), antiepileptics (phenytoin and phenobarbital), antiandrogen (tamoxifen), immunomodulators (interferon), and antimalarials (chloroquine and hydroxychloroquine) can trigger PMGH by inhibiting c-kit receptor activity in melanocytes, reducing melanin production. Although its mechanism is not fully understood, chloroquine specifically seems to decrease pheomelanin production.[20]
2. **Smoking:** Smoking and PMGH are linked through the production of substantial ROS, which accelerates hair follicle aging. Unfortunately, smoking also causes hair loss apart from graying. Testing on DP cells of balding individuals revealed higher markers of oxidative stress and DNA damage.[32]
3. **UV radiation:** UV radiation plays a significant role in PMGH by inducing oxidative stress through the production of ROS. This oxidative stress can harm melanocytes, disrupt melanin production, and trigger cellular responses, contributing to hair graying. UVA can cause biochemical damage, resulting in changes to hair color, while UVB leads to protein depletion, causing structural damage to the hair shaft's cuticle.[33]
4. **Nutritional:** Hair can undergo reversible hypopigmentation due to a deficiency of various nutritional factors. In the context of premature graying, one study found significantly lower zinc levels in individuals with PMGH compared to a control group.[34] A recent study on a youthful Indian population noted reduced serum levels of ferritin, calcium, and hemoglobin in those predisposed to PMGH.[35] Another study identified a correlation between lower serum vitamin B12 levels in individuals with PMGH.[36] Similarly, Sonthalia *et al*.[37] established a strong link between PMGH, family history, vitamin B12 deficiency, and hypothyroidism. In a study involving 35 students, Bhat *et al*.[38] examined various hematological parameters, including serum ferritin, hemoglobin, calcium, total iron-binding capacity, iron, vitamin D3, and vitamin B12, confirming the significant role of vitamin D3 deficiency in PMGH. Fatemi Naieni *et al*.[39] emphasized the importance of metal ions, especially copper ions, which are essential for tyrosinase activity and normal hair coloration. They observed lower levels of these metal ions in serum samples from individuals with PMGH.

Association of PMGH with systemic diseases

Several studies have investigated the link between PMGH and various health conditions. The Copenhagen City Heart study observed an increased likelihood of heart attack in men with non-pigmented hair compared to those with pigmented hair, but it did not find a connection between PMGH and early mortality.[40] Similarly, further studies also reported associations between PMGH and cardiovascular diseases, while Glasser's study did not find such a link.[41-43] A recent study showed elevated levels of IL-6 and TNF-α in patients with premature canities and stated that these could be useful markers to assess the risk of adverse cardiovascular events.[44] Aggarwal *et al*.[45] identified PMGH as a substantial indicator of cardiovascular disease in smokers.

Some studies have suggested that PMGH is associated with low bone mineral density, although more recent research contradicts this association.[46,47] A recent study explored the correlation between hearing loss and PMGH, explaining that patients with PMGH experienced hearing impairment at higher frequencies. This suggests that PMGH is a noteworthy risk factor and warrants further investigation.[48] Another study correlated family history and obesity not only with the prevalence but also with the severity of PMGH.[32] Obesity has been independently linked to systemic oxidative stress, with many detrimental effects attributed to this increased oxidative burden. Furthermore, obesity seems to influence melanogenesis through hormonal pathways.[49] It has been proposed by Morpurgo *et al*.[50] that leptin resistance in obese individuals elevates melanocyte-stimulating hormone antagonists, leading to reduced melanogenesis and a diminished ability for melanocyte DNA repair.

Paik *et al*.[51] and Sharma *et al*.[52] found decreased HDL-cholesterol levels in PMGH patients, while Kocaman *et al*.[53] identified hyperlipidemia as an independent predictor of PMGH. Similarly, Chakrabarty *et al*.[54] observed raised LDL and lower HDL levels in PMGH cases compared to controls. However, these differences, although statistically significant, had minimal clinical relevance.

Differential diagnosis

Distinguishing gray hair from other hypopigmented hair disorders is essential [Table 1]. The latter can occur in localized or diffuse patterns. Conditions characterized by reduced pigment include oculocutaneous albinism, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Tietz syndrome. Syndromes related to disrupted melanosomal transfer, such as Griscelli, Elejalde, and Chediak-Higashi syndromes, can result in distinct silver hair. In Menke's syndrome, hair is scanty, light in color, and has a texture resembling steel wool, often accompanied by structural abnormalities. Metabolic disorders such as phenylketonuria, histidinemia, and homocystinuria can also lead to light-colored hair. Oasthouse disease, linked to methionine metabolism, is characterized by light hair and recurring edema.[55]

Localized gray hair, also called poliosis, can occur in conditions such as vitiligo, piebaldism, Wardenburg syndrome, Woolf's syndrome, Ziprkowski-Margolis syndrome, and tuberous sclerosis.[56] If a specific area of hair suddenly turns white, clinicians should investigate the possibility of depigmentation in the underlying skin to rule out vitiligo. Reports of abrupt overnight graying of hair (canities subita) have been associated with vitiligo, telogen effluvium, and alopecia areata.[57-60]

Table 1: Differentiating features from various differential diagnoses

Differential diagnosis	Distinguishing features of Premature Graying Hair
Diffuse gray hair causes	
Oculocutaneous albinism	Lack of pigmentation in skin, hair, and eyes; commonly involves vision impairment
Hermansky-Pudlak syndrome	Albinism, bleeding tendencies, and lung fibrosis; platelet dysfunction may also be present.
Chediak-Higashi syndrome	Albinism, recurrent bacterial infections, and giant granules in white blood cells; immunodeficiency.
Tietz syndrome	Albinism affecting skin and hair; hearing loss may be associated.
Griscelli syndrome	Silver hair due to pigmentary dilution; immunodeficiency and neurological abnormalities in some types.
Elejalde syndrome	Characterized by silvery-gray hair; associated with developmental delays, intellectual disability, and facial dysmorphism.
Menke's syndrome	Sparse, light-colored hair with a texture resembling steel wool; often accompanied by hair shaft abnormalities.
Metabolic disorders	Phenylketonuria, histidinemia, and homocystinuria may lead to light-colored hair. Associated with metabolic abnormalities
Oasthouse disease	Linked to methionine metabolism; characterized by light hair and recurring edema
Localized causes of gray hair (Poliosis)	
Vitiligo	Depigmented skin patches. Autoimmune condition where melanocytes are destroyed.
Piebaldism	Congenital pigmentary disorder. Characterized by depigmented and hyperpigmented skin areas and localized white patches of hair
Wardenburg Syndrome	Genetic disorder with sensorineural deafness, pigmentary disturbances, and often heterochromia iridis (different-colored irises).
Woolf Syndrome	Rare genetic condition with hypopigmentation, hair abnormalities, and hearing loss.
Ziprkowski Margolis syndrome	Syndrome involving localized poliosis, ocular abnormalities, and hearing loss; a rare and poorly understood condition.
Tuberous sclerosis	Neurocutaneous disorder with skin lesions, intellectual disabilities, and the development of benign tumors in various organs.
Sudden graying of hair (canities subita)	Vitiligo, telogen effluvium, and alopecia areata

Scoring for PMGH

There is currently no standardized scoring system to evaluate the severity of PMGH, which is particularly important for monitoring the response to therapy and assessing the efficacy of drugs.[61] Various scoring systems

have been used in different studies [Table 2], but none is standardized or universally accepted as yet. A commonly used scoring system in different studies is the hair whitening score (HWS), wherein gray/white hair is used to determine the percentage of hair whitening:

1. Trace: <25%
2. Mild: 25%–50%
3. Moderate: 50%–75%
4. Manifest: 75%–100%
5. Complete: 100%

Approach to a patient with PMGH: Flowchart

Though PMGH is a condition of cosmetic concern, it may need a detailed history and evaluation to exclude other associated conditions. Some baseline investigations may help not only in delineating the underlying cause but also in counseling the patient [Figure 1].

Management: Despite extensive molecular research, effective treatments for canities still need to be discovered. Oral therapies have been attempted with inconsistent outcomes, often supported only by anecdotal reports rather than robust clinical trials. It is alarming that the number of patients seeking treatment for PMGH and its significant psychological and social impact.[69] Consequently, patients are frequently prescribed supplements comprising multivitamins, antioxidants, and minerals such as biotin, calcium pantothenate, zinc, copper, and selenium on an empirical basis.[70] However, it is crucial to acknowledge that the systematic evidence supporting their efficacy remains relatively weak.

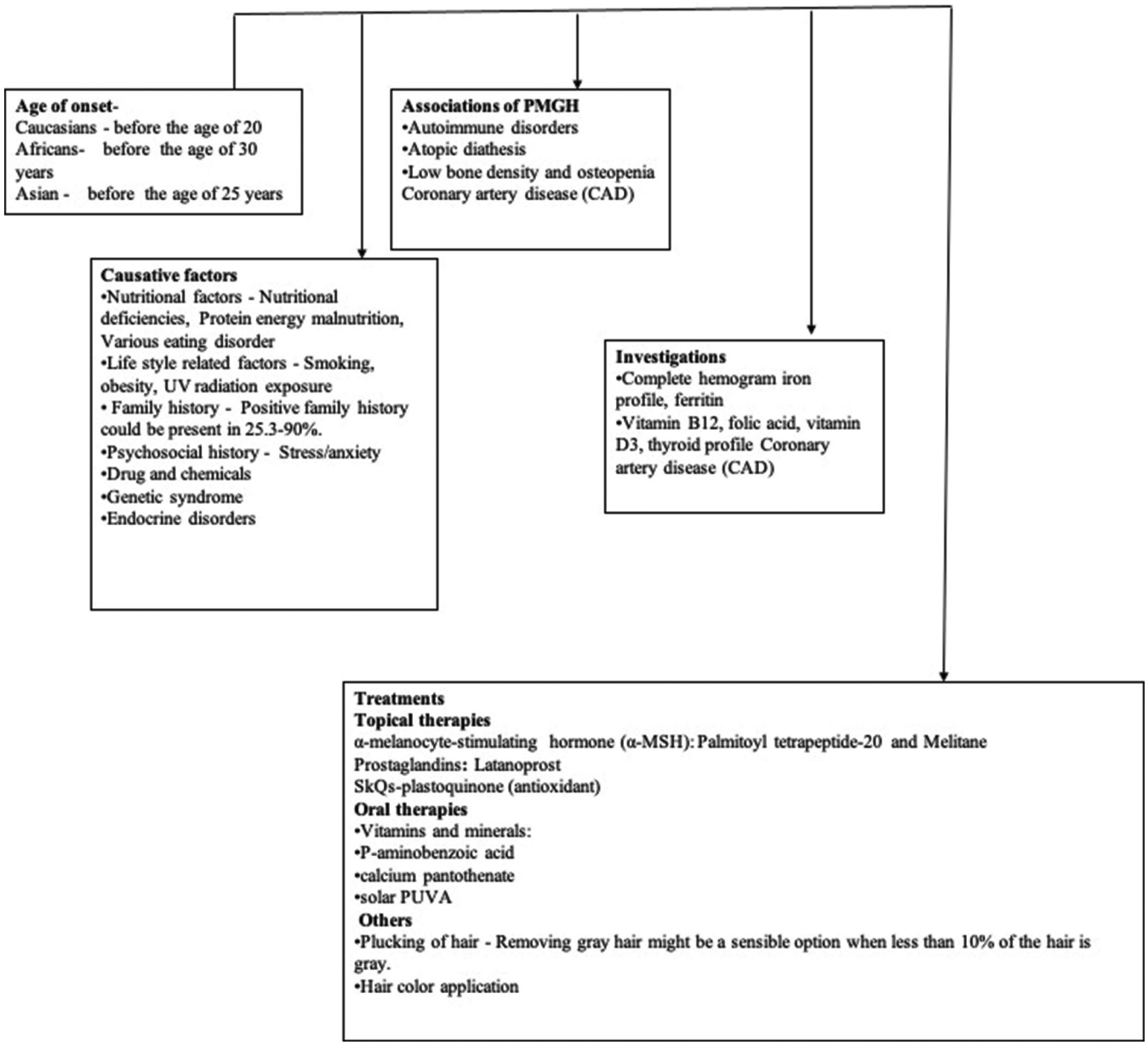

Figure 1: Approach to a patient with PMGH

Table 2: Scoring system used in different studies for grading of severity of premature graying of hair

Authors	Year	Scoring system used	Place of study
Jo *et al*.[9]	2012	Grade 1: <20% Grade 2: 20%–40% Grade 3: 40%–60% Grade 4: 60%–80% Grade 5: >80%	Korea
Bhat *et al*.[38]	2013	Mild: <50 gray hair Moderate: 50–100 Severe: >100	India
Erdoğan *et al*.[62]	2013	Hair whitening score (HWS) 1 (Trace): <25% 2 (Mild): 25%–50% 3 (Moderate): 50%–75% 4 (Manifest): 75%–100% 5 (Complete): 100%	Turkey
Kocaman *et al*.[53]	2013	Hair whitening score (HWS): defined according to the percentage of gray/white hairs 1: pure black 2: black > white 3: black=white 4: white > black 5: pure white A gray/white-hair scale was used to determine the percentage of hair whitening. 1 (Trace): <25% 2 (Mild): 25%–50% 3 (Moderate): 50%–75% 4 (Manifest): 75%–100% 5 (Complete): 100%	Turkey
Shin *et al*.[32]	2014	Severity was based on the number of gray hairs on a self-reported basis. No gray hair Mild: <10 gray hair Moderate: 10–100 gray hair Severe: >100 gray hair	Korea
Singal *et al*.[61]	2016	Score 1: assigned to under 10% gray hair/cm^2 Score 2: 10%–30% gray hair/cm^2 Score 3: >30% gray hair/cm^2	India
El-Sheikh *et al*.[63]	2018	Hair whitening score (HWS) 1 (Trace): <25% 2 (Mild): 25%–50% 3 (Moderate): 50%–75% 4 (Manifest): 75%–100% 5 (Complete): 100% Texture and diameter of gray hair fibers were also assessed	Egypt
Sharma *et al*.[64]	2018	0 gray hair Mild: <10 gray hair Moderate: 10–100 gray hair Severe: >100 gray hair	India
Thompson *et al*.[65]	2019	severity of graying (0, 1–10, 11–100, and >100 self-reported gray hairs)	United States
Kiafar *et al*.[66]	2020	The number of gray hair/100 hair was used for grading	Iran

Contd...

Table 2: Contd...

Authors	Year	Scoring system used	Place of study
Acer *et al*.[67]	2020	The number of graying hairs was classified as <10, 10–100, and >100 to determine the severity of PHG.	Turkey
Agarwal *et al*.[68]	2020	Hair whitening score (HWS) based on the extent of gray hair 1: pure black 2: black > white 3: black=white 4: white > black 5: pure white	India

Oral therapy

P-aminobenzoic acid and calcium pantothenate: Temporary hair darkening has been noted in individuals ingesting significant amounts of p-aminobenzoic acid (PABA), though the exact mechanism is unclear. A study of 460 patients with gray hair who took 100 mg of PABA three times a day led to pigment restoration within 2–4 months in 82% of patients. However, relapse occurred after discontinuation. Zarafonetis reported hair repigmentation with doses of 12–20 g of PABA.[71]

Pasricha *et al.* reported success with vitamin supplements such as 200 mg of daily calcium pantothenate (vitamin B5) in two young girls with PMGH hair. Over 29 and 13 months of follow-up, they witnessed the transformation of 300 and 1069 gray hair into pigmented hair respectively. The hair follicles displayed a pigmented base and a gray tip, termed "converted hair." In a separate study, they combined gray hair avulsion and supplementation, uprooting all gray hair during each 3-month follow-up and trimming any converted hair at the junction where it shifted from gray to black. Their results indicated that the combination was more effective than using supplements alone.[72]

However, Brandaleone *et al.* used 200 mg of PABA, 100 mg of calcium pantothenate, and 50 grams of brewer's yeast for 8 months in patients with non-pigmented hair with no success.[73] In addition, Pavithran *et al*.[74] reported that solar PUVA was useful in nearly two-thirds of patients with PMGH hair.

Topical solutions

Palmitoyl tetrapeptide-20 and Melitane

Palmitoyl tetrapeptide-20, an agonist for α-melanocyte-stimulating hormone (α-MSH), has been studied in labs and among 15 men with PMGH. In those with PMGH, it increased melanin production in pulled hair within 3 months.[75] An additional α-MSH agonist, melitane, a biomimetic peptide, has also been considered for reversing premature graying.[76] However, it is crucial to note that limited data regarding its effectiveness is available.

Prostaglandins

Prostaglandins are recognized as highly effective stimulants for melanocyte growth and melanin production. Latanoprost, an eye drop containing prostaglandin F2a (PGF2a), has been associated with the repigmentation of gray hair after long-term use. The repigmentation process typically begins at the hair's base and gradually extends along the entire length.[77]

Hair plucking: Removing gray hair might be a sensible option when less than 10% of the hair is gray. In addition, coloring, specifically the gray strands, could be contemplated, especially during the initial phases of graying, mainly when it is localized to the temples in men and the perimeter in women.[3]

Hair colorant: With no effective topical or oral treatments available, alternative approaches gain importance, such as plucking gray hair and using hair colorants to conceal it. Hair colorants come in two categories: natural and synthetic. Natural hair colors often contain ingredients such as Henna, Amla, and false daisy. They are commonly safe but require regular reapplication due to the weaker color retention by gray hair. Synthetic hair dyes fall into two main groups: oxidative and nonoxidative [Table 3]. Oxidative dyes, including permanent, semi-permanent, and auto-oxidative types, are favored for their longer-lasting color and ease of use. They effectively penetrate the hair cortex. In contrast, nonoxidative dyes adhere to keratin but do not penetrate the hair cortex.[78,79]

Anti-aging compounds: Anti-aging compounds for graying hair are continually being explored for their potential benefits. Some promising compounds include green tea polyphenols, selenium, copper, phytoestrogens, melatonin, and substances from traditional Chinese medicine (TCM) and Ayurvedic medicine. These compounds are of current interest in addressing the aging process of hair, particularly in relation to graying. Anti-aging compounds prove ineffective in shampoos due to water dilution and short contact time. Shampoos containing antioxidants such as vitamins C and E primarily safeguard the fatty substances within the shampoo from oxidation, rather than providing protection to the scalp.[3,76]

Future therapy

Stem cell approach: Melanocytes actively participating in melanin production express a complete set of enzymes and

Table 3: Comparison between different categories of hair colorant

Hair coloring agent	Properties	Pros	Cons
Permanent	a. Contains three agents: developer, coupler and oxidant hydrogen peroxide b. Reacts and forms color within the hair fiber c. Resists washing but may fade with time	a. Long lasting result b. Give intense color c. Provide full coverage	a. Contains ammonia and hydrogen peroxide, which damage hair quality b. Regrowth of new hair require touch-ups
Semi-permanent	a. Contains small molecules such as para dyes b. Penetrates the hair cortex c. Provide natural and with some variation d. Applied on wet shampooed hair and left for 10–40 minutes then rinsed e. Resist- 6–10 shampoos wash (last for 4–6 weeks)	a. Enhances natural color b. Low ammonia content c. Less damaging than permanent color	a. Fades gradually with each wash b. Limited coverage for gray hair (<30%)
Demi-permanent	a. Contains three agents: developer, coupler and oxidant. Instead of ammonia contains ethanolamine or sodium carbonate b. Reacts and forms color within the hair fiber c. Last up to 20–25 shampoos	a. More natural appearance b. Longer lasting than semi-permanent c. Require less frequent touch -ups	a. Damage hair quality, but less than permanent
Temporary	a. Contains large organic, water soluble molecules b. Remains on hair shaft, do not penetrate c. Applied on towel dried hair and left d. Washes out with next hair wash	a. Natural, safe b. Adds temporary vibrancy and highlights	a. Wash out easily, require regular reapplication b. May stain clothing and towels c. Suitable only for less extensive involvement (<15%)

proteins involved in melanin biosynthesis. Consequently, one potential long-term strategy for addressing PMHG is analyzing the gene-level expression of these proteins, particularly in stem cells.[80] Another study by Saha *et al*.[81] discusses the utilization of a placental extract rich in C18:0 sphingolipid to stimulate microphthalmia-associated transcription factor (MITF) and initiate the activity of dormant melanocyte stem cells in gray-haired mice. In addition, recent findings highlight the ability of flavonoids such as sterubin, luteolin, and hydroxygenkwanin, known for their antioxidant and anti-inflammatory properties, to scavenge free radicals and encourage melanogenesis through the Wnt signaling pathway.[82]

Laser: Improvement in hair pigmentation in a male-pattern hair-loss patient was observed when subjected to a combination treatment involving 1927-nm fractionated thulium laser therapy and intra-perifollicular polydeoxyribonucleotide injections (PRDN). After completing 12 sessions, there was a noticeable increase in pigmented hair follicles. This effect is attributed to the antioxidant properties of PRDN.[83] Nonetheless, these study findings pertain to a single individual and require validation in a larger population.

Drugs in development: The approach is to study the potential of neural-crest-derived stem cells, encouraging their differentiation into active melanocytes to rejuvenate the pigmentation of gray hair. A novel combination compound named RT1640 (comprising cyclosporin A, minoxidil, and a pigment-promoting drug) was used in a mouse model with gray hair and observed repigmentation. The increased pigmentation was linked to an 80% rise in melanocyte progenitor cell counts in hair bulbs. In addition, regrowth was observed with continued repigmentation even after discontinuing treatment and shaving the hair.[84]

Several medications have been identified as inducing repigmentation through diverse mechanisms. For instance, drugs with anti-inflammatory properties, including thalidomide, lenalidomide, adalimumab, acitretin, etretinate, prednisone, cyclosporin, cisplatinum, interferon-α, and psoralen, play a role in this process.[85] Certain drugs, such as latanoprost, erlotinib, imatinib, tamoxifen, and levodopa, stimulate melanogenesis.[86] In contrast, clofazimine accumulates within tissues, leading to repigmentation, while the mechanism of repigmentation induced by captopril remains unknown.[87] Notably, many of these medications have been widely used for various indications, yet only a minority of individuals have reported experiencing hair repigmentation. Furthermore, confirming drug-induced repigmentation is challenging as it typically requires the hair to return to its original color after the drug is discontinued. However, this is practically impossible in most cases as patients often continue the treatment. The observed complexity in the pathways involved in hair melanogenesis and repigmentation suggests a complex interplay. Therefore, targeting a single pathway may not be sufficient to reverse the process.[88]

A novel compound, designated as SkQs, consists of plastoquinone, a penetrating cation serving as an

antioxidant component that is designed to selectively target mitochondria. Its efficacy has been demonstrated in inhibiting the progression of age-related diseases, including cataracts, retinopathy, glaucoma, balding, canities, and osteoporosis in animal studies.[3]

Conclusions

PMGH is an interesting phenomenon of growing cosmetic concern, with more patients seeking a solution and treatment. There is a paucity of literature regarding all aspects of this condition. More epidemiological and experimental studies are required to unravel the mystery so that more treatment options can be offered for the management.

Acknowledgment

All authors have contributed to the preparation of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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