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PREMATURE HAIR GRAYING: INTEGRATING MECHANISMS, RISK FACTORS, AND THERAPEUTIC APPROACHES

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ABSTRACT

Premature graying of hair (PMGH) is a phenomenon resulting from the interaction of genetic, metabolic, and environmental factors, leading to melanocyte dysfunction in the hair follicle. This article discusses the key etiopathogenic mechanisms of PMGH, with particular emphasis on the roles of oxidative stress, micronutrient deficiencies, autoimmune processes, hormonal disorders, and metabolic alterations. Population data indicate that gender and ethnicity influence both the incidence and course of PMGH, while clinical observations suggest that it may serve as an early marker of endocrine, autoimmune, hematological, or cardiovascular disorders. Although the psychosocial burden varies, in many young individuals graying negatively affects their sense of attractiveness and overall mental well-being. Current therapeutic strategies include optimizing nutritional status, antioxidant supplementation, modulation of α-MSH pathways, as well as selected pharmacological treatments and phototherapy. Case reports confirm the possibility of partial or complete repigmentation. Despite a growing body of evidence, the pathogenesis of PMGH remains incompletely understood, highlighting the need for further research into the mechanisms underlying the reversibility of this process and the development of effective, targeted therapies.

KEYWORDS

Premature Hair Graying, Melanocyte Stem Cells, Oxidative Stress, Risk Factors, Repigmentation

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1. Introduction

1.1. Definition of graying hair

Hair graying is a natural part of the aging process and results from the progressive decline of active melanogenesis in the hair follicle, leading to a gradual loss of pigment within the hair shaft. The key mechanism of this process is a marked decrease in the number of melanocytes capable of producing melanin in the hair bulb during the anagen phase [1]. Hair color is determined by the process of melanogenesis, i.e., the synthesis of melanin and its transfer from melanocytes to keratinocytes. This mechanism is genetically regulated at many levels, which means that individual differences in pigmentation have a strong hereditary basis [2].

1.2. Premature graying - differences and age criteria

Premature graying of hair (PMGH) is defined as the appearance of visible pigment loss at an age significantly earlier than that typical for physiological aging [3]. Although the general definition of premature graying is uniform, its application in research varies depending on the ethnic group, which is due to different typical age ranges for the appearance of the first gray hairs [4]. Premature graying is defined as the appearance of gray hair before the age of 20 in Caucasians, before the age of 25 in Asians, and before the age of 30 in people of African descent [5]. There are also reports of PMGH occurring in children and adolescents, which highlights its distinctiveness from physiological graying, which typically begins only in the third or fourth decade of life, with Caucasians averaging around their mid-30s, in Asians in their late 30s, and in people of African descent in their mid-40s [2], [5], [6].

1.3. Epidemiology - population data, ethnic and gender differences

Although the frequency of graying is similar in women and men, its distribution on the scalp is not the same [7]. In men, the first changes usually appear around the temples, while in women they are most prevalent in the frontal area, with the occipital area remaining the least affected by graying [7]. Epidemiological data from population studies involving more than 4,000 people from different ethnic groups have shown that graying is a common phenomenon, the frequency of which increases with age [8]. In the 45–65 age group,

gray hair was found in 74% of respondents, with an average intensity of 27%, while after the age of 60, almost the entire study population (91%) showed signs of graying, with the average degree of graying increasing to around 40% [8]. Furthermore, the lowest intensity of graying has been described in African and Asian groups, while the highest intensity has been observed in people with light hair, including Poles, Scots, Russians, Danes, and other Caucasian groups [8].

1.4. Clinical and psychosocial significance of the problem

Premature graying of hair, although not a disease in itself, can be an important sign of systemic disorders. Population studies indicate that it is more often associated with deficiencies of certain micronutrients, especially copper, as well as metabolic and endocrine disorders [7], [9]. In addition, it may appear as part of the clinical picture of accelerated aging syndromes, such as progeria [2]. Due to the important role of hair in social communication, premature graying can have significant negative psychosocial consequences. In many cultures, premature graying is also a source of stigmatization and social judgment, and in extreme cases can contribute to discrimination or difficulties in interpersonal relationships [2]. For this reason, PMGH should be considered not only as a dermatological problem, but also from a psychosocial and psychological perspective, which justifies the need for a holistic approach to diagnosis and patient care. The aim of this review is to provide a comprehensive analysis of the current state of knowledge on the biological mechanisms, risk factors, and psychosocial consequences of premature graying.

2. Materials and Methods

A literature review was conducted using the PubMed, Scopus, and Web of Science databases, covering articles published up to November 2025. Keywords used included “premature hair graying,” “PMGH,” “melanocyte stem cells,” “oxidative stress,” and “hair repigmentation.” The aim of this review was to collect comprehensive and up-to-date information on the biological mechanisms, clinical significance, and therapeutic strategies related to premature hair graying. Relevant studies, including original research articles, reviews, case reports, and clinical trials, were included to provide a comprehensive overview of current evidence.

3. Hair biology and the role of oxidative stress in premature graying

3.1. Hair structure and the role of melanocytes

Hair is a biomaterial composed mainly of keratin and consists of three layers: the cuticle, the cortex, and the medulla [10]. The medulla is a loosely packed region within the fiber, surrounded by the cortex, which constitutes most of its mass, while the outer protection is provided by the cuticle composed of overlapping dead cells [10]. The individual layers are interconnected by the cell membrane complex [10]. Hair fibers are characterized by a hierarchical structure typical of keratin materials, and their chemical properties are primarily determined by the presence of α-keratin [11]. Within the hair follicle, melanocytes play a key role in pigmentation. They produce melanin in melanosomes and transfer it to keratinocytes that form the hair shaft [12]. Mature melanocytes located in the matrix are responsible for the pigmentation of the growing hair, while pigmentation continuity is ensured by melanocyte stem cells (McSCs) present in the bulge–subbulge area [12]. These cells act as a reservoir and, during the anagen phase, supply precursors that differentiate into melanocytes producing melanin [12].

3.2. Oxidative stress

A growing number of studies confirm that oxidative stress is one of the key mechanisms of aging, as excessive accumulation of reactive oxygen species causes cellular damage, including damage to mitochondrial DNA and mitochondrial structures in particular [13]. With age, there is both increased production of free radicals and a gradual weakening of the body's endogenous antioxidant systems [14]. Although this system includes numerous enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants, including glutathione, vitamin C, vitamin E, and ubiquinone, its ability to neutralize free radicals decreases with age [15]. The oxidative imbalance that builds up over time leads to the gradual degradation of cellular structures, which disrupts the process of melanogenesis and promotes the development of graying hair [15], [16].

4. Risk factors for premature graying

4.1. Genetic factors

Genetic factors play an important role in both the regulation of hair pigmentation and the predisposition to premature graying [7]. Population and genetic studies indicate that certain variants of genes associated with melanocyte function and the process of melanogenesis may increase susceptibility to early pigment loss [7]. A wide range of genes are involved in pigmentation, including TYR, TYRP1, TYRP2, MITF, Pax3, Sox10, MC1R, c-Kit, Pmel17, and MET, whose polymorphisms explain the differences in hair color observed between populations [7]. BCL-2 and MITF are of particular importance, as they are key to maintaining the pool of melanocyte stem cells (McSC) [17], [18] Disturbances in the expression of MITF and the transcription factors Pax3 and Sox10 can lead to McSC depletion and thus promote premature graying [19], [20] In addition, studies in animal models have shown that critical telomere shortening disrupts the functioning of highly proliferating tissues, including skin and hair follicles, which manifests itself, among other things, in premature graying [21]. Clinical observations regarding the familial occurrence of graying are consistent with the findings of molecular studies, which indicate a strong genetic basis for this phenomenon. In a study conducted among young adults in Indonesia, a positive family history was found in 39% of participants with premature graying, most often involving the father (26%), less often the mother (10%), and in 3% of cases both parents [22]. The analysis also showed a statistically significant relationship between the number of gray hairs and the presence of familial graying [22]. Another study conducted in Korea, involving 6,390 young men, confirmed that family history is one of the strongest factors associated with premature graying [23] Among people with PMGH, graying was most commonly reported on the father's side (33.3%), less commonly on the mother's side (11.2%), and in 4.6% of cases on both sides [23]. Risk analysis showed that the influence of family history is significantly stronger on the paternal side; graying in the father increased the likelihood of PMGH almost 15-fold, while graying in the mother was associated with an approximately 3-fold increase in risk [23].

4.2. Systemic disorders and premature graying

4.2.1. Thyroid dysfunction

Thyroid dysfunction is one of the most frequently reported endocrine causes of premature graying [7]. In one study, an abnormal thyroid profile was found in 14% of patients with PMGH [24]. In addition, it has been shown that people with premature graying have significantly higher TSH concentrations compared to the healthy population, suggesting a link between hypothyroidism and weakened melanocyte activity and accelerated pigment loss [25]. Cases of repigmentation of gray hair under the influence of high doses of triiodothyronine (T3) have also been described; in two patients, complete and permanent pigment recovery was achieved, which was explained by stimulation of hair follicle melanocytes and acceleration of hair entry into the anagen phase [26].

4.2.2. Autoimmune diseases

Like thyroid diseases, vitiligo can also affect the graying process [27]. Leukotrichia, or the presence of completely discolored hair within vitiligo lesions, results from the loss of follicular melanocytes and leads to a complete lack of pigment in the hair [28]. This is an unfavorable prognostic factor, as vitiligo areas with leukotrichia rarely respond to treatment with repigmentation [29].

4.2.3. Hematological diseases

Pernicious anemia may also contribute to premature graying. Studies have shown that more than half of patients with this disease had gray hair before the age of 50, while in the control group this percentage was about one-third [30]. There are isolated cases in the literature indicating that pernicious anemia may be associated with premature graying, and in some patients, hair repigmentation even occurred after treatment with vitamin B_{12} [31].

4.2.4. Progeroid syndrome

Werner syndrome (WS), caused by mutations in the Werner gene (WRN), leads to accelerated aging of the body, an early symptom of which is premature graying and thinning of the hair [32]. These disorders result from damage to DNA repair mechanisms and cellular instability, which cause cells to lose their ability to function properly more quickly [33]. The literature emphasizes that in patients with WS, graying and hair loss occur as early as the third decade of life, and mutations leading to WRN loss of function promote accelerated cellular senescence and increase the tendency of cells to undergo malignant transformation [34], [35].

4.2.5 Metabolic and cardiovascular diseases

People with premature graying are more likely to have higher blood pressure, larger waist circumference, elevated blood sugar, and lower high-density lipoprotein (HDL) levels [36]. Early graying has also been shown

to be associated with an unfavorable metabolic profile and subclinical atherosclerosis, as reflected in metabolic differences between groups with varying degrees of graying and increased carotid intima-media thickness (CIMT) [37]. In addition, the results of a large cohort study confirm that graying correlates with an increased risk of heart attack, suggesting its importance as an external marker of systemic degenerative processes involving the cardiovascular system [38]. Premature graying often coexists with systemic disorders, therefore in clinical practice it should prompt a broader differential diagnosis [39].

4.3. Lifestyle

4.3.1. Smoking

Smoking is one of the best-documented environmental factors associated with premature graying of hair. This mechanism is linked to oxidative stress induced by smoking, which can lead to damage to follicular melanocytes and melanogenesis disorders [14]. Several studies have shown that smokers are more likely to have PMGH and are characterized by an earlier age of onset of the first gray hairs [23], [40], [41]. In a study by Zayed et al., smokers accounted for 40.2% of the group with premature graying, compared to 24.7% in the control group, and the average age of onset of graying was significantly lower in smokers. Multivariate analysis in this study showed that smoking increases the risk of premature graying by 2.5 times, making it one of the strongest modifiable risk factors for PMGH [40]. A large analysis of 6,390 young men found that exposure to tobacco smoke, expressed as ≥5 pack-years, was independently associated with the occurrence of premature graying [23]. Another study found a clear positive correlation between tobacco use and the incidence of gray hair [41].

4.3.2. Diet and micronutrient deficiencies (copper, iron, zinc)

A study by Acer et al. showed that people with premature graying were more likely to follow a vegetarian diet than the control group, suggesting a possible role for nutritional factors in the development of PMHG [42]. Patients with PMGH often have disturbances in the levels of key micronutrients [43]. Chakrabarty et al. showed significantly lower ferritin and vitamin B12 concentrations in these individuals compared to the control group [44]. Another study showed significantly reduced zinc levels in patients with PMHG compared to the control group [9]. El-Sheikh et al. reported lower concentrations of iron, copper, and calcium in individuals with premature graying and a negative correlation between iron and calcium levels and the severity of depigmentation [43].

4.3.3. Stress

Studies show that stress can accelerate the appearance of gray hair. In a study by Acer et al., people with premature graying had higher levels of emotional stress and more signs of oxidative stress in their blood [45]. A second study found that people who felt more work pressure and stress also had more oxidative stress-related DNA damage [46]. These results suggest that stress, both mental and physical, can intensify cell-damaging processes, which over time can accelerate hair pigment loss.

5. The psychological and social dimensions of graying

Population-based data indicate that premature graying may affect the emotional and social functioning of young people, although the extent of this impact varies [47] In a study conducted among students in Thailand, more than half of the participants with PMHG did not report significant psychological consequences (67.31%), but some experienced significant psychosocial distress: 25% of respondents reported reduced self-confidence, and 7.69% experienced stigmatization due to their gray hair [47]. Another study conducted among students in Pakistan found that although premature graying affected their socio-cultural functioning, it was not associated with a decrease in self-esteem as measured by the Rosenberg scale, confirming that its psychological impact may be moderate and varied [48]. These results emphasize that although graying does not cause serious psychological difficulties in most young people, it can be a source of emotional discomfort and negative social experiences for some.

6. Therapeutic strategies

6.1. Prevention and supplementation

Prevention of graying is mainly based on reducing oxidative stress and protecting melanocytes. A diet rich in antioxidants and an adequate supply of copper, zinc, and B vitamins, especially B12 and folates, are key [49]. It is important to avoid factors that increase ROS production, such as smoking, excessive alcohol consumption, and UV radiation [49]. Reducing mental stress and gentle care with antioxidant preparations further support the protection of hair follicles and may slow down pigment loss [49]. The importance of correcting deficiencies is confirmed by a case report in which iron supplementation in a patient with iron deficiency led to partial repigmentation of the hair, indicating the possibility of reversible melanogenesis disorders in the course of micronutrient deficiencies [50].

6.2. Therapies modulating melanocyte activity - α-MSH agonists

Studies on palmitoyl tetrapeptide-20 have shown that this ingredient stimulates hair pigment production and reduces oxidative stress, which helps protect the cells responsible for pigmentation [51]. A similar effect has been described with Greyverse 2% therapy, used twice daily in a patient with premature graying. The first improvement was noticed after just three months, and after five months, over 90% repigmentation was achieved, which persisted even after the end of treatment [52]. In another case study, Melitane 5% used with supplementation led to over 95% hair color recovery after 24 months [53]. α-MSH agonists are therefore a promising group of substances aimed at supporting the hair pigmentation process [51]

6.3. Medications causing repigmentation as a side effect

Although some drugs are not designed as repigmentation therapies, there are cases where they stimulate melanogenesis as a side effect [54], [55]. A case has been reported of a 65-year-old female patient who, after several years of using latanoprost to treat glaucoma, experienced gradual repigmentation of her hair, even though it had been completely white for over 20 years [54]. This phenomenon was considered analogous to the well-described effect of $PGF_2\alpha$ analogues on eyelashes and the iris [56]. A similar effect was reported in a patient treated with acitretin, who experienced not only gradual darkening of the hair, but also a change in its structure in the form of twisting; The authors emphasized that the mechanism of repigmentation remains unknown, while the change in texture may result from the effect of retinoids on keratinization and the inner sheath of the hair [55]. Interesting results were also obtained with PUVASOL phototherapy: in a group of 37 patients with premature graying, complete repigmentation was achieved in 17 patients, partial repigmentation in 7, and no improvement was observed in 8 [57]. A historical series of cases also showed that some patients receiving very high doses (6–24 g per day) of para-aminobenzoic acid (PABA) experienced a marked darkening of previously gray hair, although the response was inconsistent and many patients showed no change [58]. The author noted that despite the observed cases of repigmentation, PABA should not be used solely for the purpose of darkening hair [58].

6.4. Hair repigmentation during biological therapies

A growing number of clinical reports indicate that certain biological therapies may lead to partial or complete hair repigmentation. This phenomenon, although rare, is likely due to modulation of the immune environment of the hair follicle, normalization of melanocyte activity, and restoration of their microenvironment [59].

Hair repigmentation was reported in fourteen patients with non-small cell lung cancer treated with anti-PD-1/PD-L1 antibodies [60]. In thirteen patients, it took the form of diffuse darkening, while in one patient, black strands appeared among gray hair [60]. At the same time, most of these individuals responded well to immunotherapy, suggesting that repigmentation may be an external marker of a favorable response to treatment [60]. A similar effect was observed in a patient with advanced colorectal cancer and Hodgkin's lymphoma, who experienced generalized hair repigmentation throughout the body after starting nivolumab [61]. Cases of repigmentation have also been reported during therapy with TNF-α inhibitors. A patient treated with adalimumab showed a marked darkening of previously gray hair, and in the absence of other new clinical factors, this phenomenon was considered most likely to be related to biological therapy [62]. In a patient with psoriasis treated with secukinumab, both the appearance of new, darker-colored hair and repigmentation of existing hair were observed, which was explained by the removal of the inhibitory effect of IL-17 on melanocytes [63]. Another description concerns a patient with psoriasis treated with ustekinumab, who experienced significant darkening of gray hair after several months of treatment [59]. The authors emphasized

that this case indicates the significant role of cytokines in the microenvironment of the hair follicle and the possible involvement of the IL-23 axis in melanogenesis processes [59]. The accumulated observations indicate that repigmentation during biological therapy is rare but potentially clinically significant, and its analysis may help to understand the mechanisms responsible for melanogenesis and the graying process.

6.5. Cosmetology techniques

Hair dyeing remains the main aesthetic treatment for graying hair, constituting the basic form of masking gray hair after taking into account possible supplementation [64] The most lasting effects are achieved with oxidative dyes, which penetrate the cortex of the hair and lead to a permanent change in its color [65]. Semi-permanent and toning dyes mainly act on the surface and offer more delicate coverage of gray hair, but this is associated with a less lasting effect [65]. Natural plant dyes, although perceived as safer, have low coloring power and limited color durability, which poses a significant challenge to their wider use [66].

6.6. Prospects for research into the reversibility of graying

The latest data show that repigmentation of individual hairs is possible and can occur within a single anagen phase, as confirmed by high-resolution mapping of hair pigmentation patterns (HPPs) [67]. Proteomic analyses indicate reversible, stress-sensitive metabolic pathways, which explains the link between graying and psychological factors and suggests that this process may be a potential pharmacological target [67]. The development of topical therapies and physical methods that stimulate melanogenesis while maintaining and activating melanocyte stem cells is a promising future strategy for effective hair repigmentation [68].

7. Summary

Premature graying of hair is a complex phenomenon resulting from the interaction of genetic, metabolic, endocrine, and environmental factors, leading to the loss of melanocytes and melanogenesis disorders. Although it is not a disease in itself, it can be a marker of systemic disorders and generate a significant psychosocial burden. Current data indicate that PMGH is influenced by, among other things, oxidative stress, family predisposition, micronutrient deficiencies, smoking, autoimmune diseases, and metabolic disorders. The growing number of reports on therapy-induced repigmentation highlights the potential reversibility of the process and opens up prospects for new treatments aimed at protecting and activating melanocyte stem cells. Despite advances in research, graying remains a clinical challenge that requires further analysis of biological mechanisms and effective therapeutic strategies.

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