INTRODUCTION

Healthy hair is a sign of general well-being and youth. Unlike other animals, the function of hair in human beings is being debated. Nevertheless, hair serves as a great aesthetic tool and means of nonverbal communication. Hair color and style can significantly alter the physical appearance of a person and thus alter his/her body image. As graying of hair is perceived as a sign of old age, premature graying of hair (PGH) can bear an adverse effect on the self-esteem of the individual.

Graying of hair also called canities or achromotrichia occurs with normal aging. However, the age at which it occurs varies in different races. PGH is defined as graying of hair before the age of 20 years in Caucasians and before 30 years in African American population. It can severely affect the self-esteem of an individual. The exact etiopathogenesis remains unknown, although it has been associated with premature aging disorders, atopy, and autoimmune diseases. Patients, who present with PGH, should be assessed for syndromes and metabolism diseases. Hair dyes remain the main modality of the treatment for cosmetic concerns after nutritional supplementation.

ABSTRACT

Premature graying of hair (PGH) is defined as graying of hair before the age of 20 years in Caucasians and before 30 years in African American population. It can severely affect the self-esteem of an individual. The exact etiopathogenesis remains unknown, although it has been associated with premature aging disorders, atopy, and autoimmune diseases. Patients, who present with PGH, should be assessed for syndromes and metabolism diseases. Hair dyes remain the main modality of the treatment for cosmetic concerns after nutritional supplementation.

Key words: Canities, premature gray hair, white hair

PIGMENTATION OF HAIR

Hair pigmentation is one of the most unique features in humans ranging from black, brown, and blonde to red. The color of human hair is due to pigment melanin produced by melanocytes which are neural crest derivatives. Human hair follicles contain two types of melanin as follows: eumelanin and pheomelanin. The diversity of hair color arises mostly from the quantity and ratio of black-brown eumelanin and reddish-brown pheomelanin. It has been hypothesized that the pH and cysteine level of melanosomes influences the phenotype of hair. As pH reduces, there is a progressive reduction in tyrosinase activity leading to increased pheomelanin and reddish or blonde hair. A mutation in melanocortin-1 receptor (MC1R) gene causes auburn or red color of hair. This mutation is seen usually in individuals of Northern Europe with less sun exposure. A study in 2012 showed a recessive mutation in tyrosinase-related protein 1 (TYRP1) in people with blonde hair. There are various differences between pigmentation in the skin and that of hair. Each melanocyte is associated with five keratinocytes in the hair bulb forming a “hair follicle-melanin unit.” In contrast, each melanocyte in

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kumar AB, Shamim H, Nagaraju U. Premature graying of hair: Review with updates. Int J Trichol 2018;10:198-203.
The pigmentary unit is a pear-shaped black structure at the tip of dermal papilla in pigmented hair.\(^1\) In gray hair, the pigmentary unit becomes fuzzy, the melanocytes become few and rounded, and lightly pigmented oligodendritic melanocytes become visible in the proximal hair bulb.\(^12\) During anagen, there is a marked reduction in the number of melanocytes in the hair follicles through autophagolysosomal degeneration leading to pigment loss. This is thought to be central in the pathogenesis of graying.\(^13\) Defective melanosomal transfer to cortical keratinocytes or melanin incontinence due to melanocyte degeneration contributes to graying. Degenerative changes within the hair follicle are associated with an increase in dendritic cells in the hair follicle.\(^1\) Eventually, there are no melanogenic melanocytes in the hair bulb.

There is earlier terminal differentiation of pigmented hair than nonpigmented hair. The growth rate, diameter of medulla, and average diameter of nonpigmented hair are higher than its pigmented counterpart.\(^14\)\(^16\)

Genetic and environmental elements influence the hair follicle stem cells and melanocytes. Telomere shortening, decrease in cell numbers, and certain transcription factors have all been implicated in this process of aging. In turn, these molecular alterations lead to structural modifications of the hair fiber, decrease melanin production, and lengthen of the telogen phase of the hair cycle.\(^17\)

At the molecular level, various genes and signaling pathways that influence hair pigmentation are being studied. Receptors for bone morphogenetic protein and activins that are Bmpr2 and Acvr2a are known to influence hair pigmentation. The reduced activity of Bmpr2 and Acvr2 can cause early graying in experimental mice.\(^18\) The Notch signaling pathway influences various biological processes. Notch 1 and Notch 2 signaling pathways were reported to have a role in maintenance of hair pigmentation.\(^19\) Stem cell factor (SCF) is a cytokine involved in many physiological processes such as hematopoiesis. Recently, SCF and its receptor (kit) are shown to have a role in melanogenesis during anagen phase.\(^20\)

**POSSIBLE ETIOPATHOGENESIS OF GRAYING**

Till date, the exact etiopathogenesis of graying remains incompletely understood. PGH can occur as an autosomal dominant primary disease. Graying can also occur with premature aging disorders such as progeria and pangeria. Association with atopic diathesis and autoimmune diseases has also been reported.\(^21\)

Perhaps the role of reactive oxygen species (ROS) on graying of hair is most studied. During active growth phase, i.e., anagen phase there is active melanogenesis in the hair follicle. This involves hydroxylation of tyrosine and oxidation of dihydroxyphenylalanine to melanin causing enormous accumulative oxidative stress. The failure of antioxidant effect could damage melanocytes leading to decreased pigmentation.\(^12\)\(^22\) Wood et al. demonstrated that the accumulation of hydrogen peroxide in hair follicles and absent expression of antioxidants such as catalase and methionine sulfoxide reductase in gray hair follicles. Their experiment supported the theory of prooxidant role in graying of hair.\(^23\) Oxidative stress can also be a result of ultraviolet (UV) rays, pollution, emotional factors, or inflammatory causes. Experiments have shown melanocyte apoptosis and oxidative damage in graying hair follicles. Furthermore, exogenous oxidative stress showed increased graying in the hair follicles.\(^12\)

An experiment on mice demonstrated that UV radiation could cause oxidative damage on hair follicles causing hair graying. They also demonstrated that the protective effect of an antioxidant superoxide dismutase.\(^24\) Numerous studies have demonstrated increased oxidative load due to psychological stress implying that even emotional factors play a role in premature graying.\(^25\)\(^26\) A recent study on young adults in Turkey revealed that PGH is closely related to factors causing oxidative stress such as emotional stress, alcohol consumption, and chronic diseases in genetically predisposed men and women.\(^27\) Daulatabad et al. made an attempt to measure oxidative stress load in PGH. They demonstrated an increase in prooxidants such as serum malonaldehyde, whole blood reduced glutathione, and serum ferric reducing antioxidant potential and decrease in antioxidants.\(^28\) Shi et al. demonstrated compromised antioxidant activity in gray hair follicles. Their experiments revealed that catalase protein expression and hydroxyl radical scavenging activities are strongly repressed in unpigmented hair follicles.\(^29\)

Progeroid syndromes are associated with defective repair of DNA. Thus, DNA is more susceptible to oxidative stress.\(^30\) Vitiligo is another condition with early graying of hair. Melanocytes in patients with vitiligo are more
sensitive to oxidative stress. ROS damage to melanocytes leads to ectopic differentiation of stem cells and apoptosis of differentiated melanocytes.\[31\]

Vitamin B12 deficiency can cause PGH through unknown mechanism. About 55% of patients with pernicious anemia had graying before 50 years as compared to 30% in the control group.\[32\] Decreased thyroid hormones cause premature graying, alopecia, and changes in hair morphology. Thyroid hormones T3 and T4 act on hair follicles directly to increase melanogenesis.\[33\]

Certain chemotherapeutic drugs and antimalarials can cause PGH. These drugs are thought to inhibit the receptor tyrosine kinase c-kit found in melanocytes reducing melanogenesis. Chloroquine preferentially reduces pheomelanin production by unknown mechanism.\[34-37\]

Smoking has been studied as an etiological agent in early-onset achromotrichia. Studies revealed that there was a significant correlation between smoking and premature hair graying. The possible explanation to this is the prooxidant effect of smoking on the body leading to increased ROS damage to hair follicle melanocytes.\[38-41\]

Reversible hypopigmentation of the hair can be seen in nutritional deficiencies protein-energy malnutrition and diseases of chronic loss of protein. Copper and iron deficiency also can cause graying of hair. A study reported significantly lower levels of copper in patients with PGH when compared to the control group. The study, however, did not report lower levels of zinc or iron in the affected population.\[42\] A newer study of young Indian population reported lesser serum levels of ferritin, calcium, and Vitamin D3 levels in subjects prone to PGH.\[43\] Another study highlighted the association of PGH with lower high-density lipoprotein cholesterol (HDL-C) levels in Indian patients aged <25 years. They also reported that lower serum Vitamin B12 levels and Vitamin D levels in PGH.\[44\] Further studies on Vitamin D3 and HDL-C levels in PGH would be worthwhile. There have been occasional reports of zinc deficiency and PGH.\[45\] Copper, iron, calcium, and zinc have all been thought to influence melanogenesis and thus influence hair pigmentation.

PRESENTATION OF GRAYING

The white of canities is because of an optical illusion. The pale yellow of keratin appears white due to reflection or refraction of incident light.\[1\] Gray hair has some color with sparsely distributed melanosomes; however, white hair is completely deprived of melanosomes and color. White hair occurs only on the scalp.\[46\] Gray hair is coarser, stiffer, and harder to manage than darker hair.\[47\] The rate of growth and thickness of nonpigmented hair are significantly greater than dark hair.\[14-16\] Gray beard hair can grow up to four times faster than pigmented hair.\[48\] Not only is gray hair more sensitive to weathering but also more prone to damage by UV radiation.\[49\] Gray hair demands increased photoprotection and are less likely to hold artificial color due to structural changes in hair fiber.\[50,51\] Furthermore, the removal of gray and white facial hair by laser is challenging as it lacks melanin chromophore.\[49\]

The rule of thumb states that by the age of 50 years, 50% of the population would have 50% of their hair turned gray. A recent study, however, reported a far less percentage of affected population.\[52\] In men, graying first occurs in the temples and sideburns. It spreads to the vertex and rest of the scalp involving the occiput the last. In women, graying is first noticed at the boundaries of the scalp. The rate of progression of graying is determined by various factors, though mainly genetic. Furthermore, the rate of graying could vary in different areas on the scalp.\[53\] A study on Korean population revealed interesting clinical findings. Temporal and occipital areas were more affected in men than women. Furthermore, graying started in frontal area in women in contrast to the temporal area in men. Those with the onset of graying before 40 years, the parietal and temporal areas were affected more. Those who noticed the onset of graying after 40 years had more graying in the frontal area. Interestingly, the early onset of graying did not correlate with rapid progression. Regardless of the age of the onset, there was a rapid progression of graying in the fifth decade.\[58\]

PROBABLE ASSOCIATIONS OF PREMATURE GRAYING

Several studies have tried to assess the relationship between PGH and other diseases. The Copenhagen City Heart study found an increased risk of myocardial infarction in men with gray hair than those without gray hair. At the same time, they did not see an association between PGH and early mortality.\[51,52\] Two other studies also reported the association of PGH and cardiovascular diseases;\[53,54\] however, Glasser found no association between the two.\[55\] Aggarwal et al. found that PGH was a significant risk factor for cardiovascular disease among smokers.\[56\] PGH was reported as a risk factor for low bone mineral density by some studies. However, newer studies conflict this association.\[57,58\] A newer study tried to explore the
relationship between hearing loss and PGH. Patients with premature hair graying had hearing impairment at extended high frequencies. They concluded that PGH may be an important risk factor for hearing loss. These associations deserve further in-depth exploration.

**DIFFERENTIAL DIAGNOSIS**

Premature gray hair has to be differentiated from other causes of hypomelanotic hair disorders some of which can be localized. Albinism which can cause white hair. White hair in children can be due to neurocutaneous disorders such as in Griscelli, Chediak–Higashi, and Elejalde syndromes. Cross syndrome, Angelman, and Prader–Willi syndromes are other causes of gray hair in childhood. Metabolic syndromes such as phenylketonuria, histidinemia, oasthous disease, and homocystinuria can cause light hair. Vitiligo is an important cause of localized white hair called poliosis. Poliosis is also seen in Piebaldism, Waardenburg syndrome, Woolf syndrome, and tuberous sclerosis. Canities subita is a rare condition in which the patient complains of overnight graying of hair. Canities subita has been associated with vitiligo, telogen effluvium, and alopecia areata and psychogenic causes.

**MANAGEMENT**

Graying is said to have occurred prematurely if seen before 20 years in Caucasians or before 30 years in Africans. Few authors have suggested that 25 years can be used as a cutoff for people in the Indian subcontinent. Canities is mainly a clinical diagnosis. Some authors suggest investigations involving serum Vitamin B12, folic acid, and thyroid levels to be conducted in individuals with no family history of premature graying. The role of trichoscopy in canities remains to be explored.

There is no single widely recognized standard scoring system to determine the severity of PGH. Attempts have been made to classify graying as mild, moderate, and severe based on percentage of hair involved, number of hair involved, or percentage of hair affected in various areas of the scalp. These grading systems used questionnaires and clinical examination to assess the severity of graying.

Although many patients visit dermatology outpatient for the treatment of PGH, very few treatment options are satisfactory. The treatment for PGH should be directed to address the cause. Vitamin B12 deficiency and hypothyroidism are reversed with vitamin and hormone replacement, respectively. Plucking of gray hair is an easy option for individuals with <10% affected the scalp hair. Most of the individuals must rely on hair colorants for restoration of hair color. Hair colors can be prepared from natural products or can be synthesized artificially. They can be temporary or permanent colorants. Commonly, natural hair dyes are prepared from Indian gooseberry (Emblica officinalis), false daisy (Eclipta alba), and lotus tree (Zizyphus spina-christi) and Henna (Lawsonia alba). The advantage of natural hair dyes is that they are hypoallergenic and nontoxic. Permanent hair dyes are most popular in the commercial market. There is a risk of damage to the hair shaft due to oxidation with permanent hair dyes. Temporary hair dyes do not penetrate the cuticle and wash out with shampooing. Hair dyes not only help camouflaging of gray hair but also protect gray hair from photodamage. Some individuals experience irritant dermatitis (commonly due to p-phenylenediamine) and hair loss due to hair coloring.

Although various vitamins and minerals such as biotin, calcium pantothenate, zinc, copper, and selenium are being prescribed, the results have not been promising. Calcium pantothenate is a commonly prescribed agent for PGH. Pasricha reported the cases of successful treatment of PGH in two adolescent girls treated with 200 mg of calcium pantothenate daily. They further investigated on 39 patients and concluded that high doses (200 mg/day) were beneficial for PGH. In addition, when combined with gray hair avulsion therapy, it yielded better results. Not all gray hair that were avulsed grew back as gray hair.

There have been anecdotal reports of temporary hair darkening with P-aminobenzoic acid (PABA). Sieve administered 200 mg PABA to 30 patients for 2 months and repigmentation was seen in all subjects. Zarafontes reported repigmentation of gray hair in patients who had received PABA for various indications. The authors, however, do not recommend the use of PABA for the sole purpose of darkening hair. Psoralen and UV A (PUVA)-sol was reported to be effective in PGH in one study. PUVA therapy stimulates melanocytes leading to pigmentation. However, repeated experiments failed to yield similar results. Topical prostaglandins have been used to stimulate melanogenesis. Bellandi reported repigmentation of gray hair after using Latanoprost for around 3 years.

Recent advances include addition of antioxidants in shampoos such as Vitamins C and E. However, their efficacy has been questioned due to short contact period. Green tea extract, selenium, copper, phytoestrogens, and...
melatonin are being studied as attractive topical anti-aging compounds. Recombinant human growth hormone has resulted in improved hair thickness, growth, and even darkening of hair.[73] Skulachev et al. presented their work on preventing senescence in a recent article. A new type of compounds (SkQs) comprising plastoquinone SkQs, antioxidant has been shown to inhibit age-related changes such as canities, balding, retinopathy, cataract, etc. Thus, SkQs look promising for the treatment of senescence and age-related diseases.[70] Delivery of drugs through hair follicular route is an interesting novel concept. Current research focuses on topical liposome targeting for melanin, genes, and proteins in hair follicles. Liposomal delivery of melanin into hair follicles has resulted in darkening of hair follicles. Liposomes can be used to selectively target hair follicles in molecular therapy and gene therapy to restore hair color.[80]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tobin DJ, Paus R. Graying: Gerontobiology of the hair follicle pigmentedary unit. Exp Gerontol 2001;36:29-54.
2. Panhard S, Lozano I, Loussouarn G. Graying of the human hair: A worldwide survey, revisiting the ‘50’ rule of thumb. Br J Dermatol 2012;167:865-73.
3. Ito S, Wakamatsu K. Diversity of human hair pigmentation as studied by chemical analysis of eumelanin and pheomelanin. J Eur Acad Dermatol Venereol 2011;25:1369-80.
4. Aneans J, Tobin DJ, Hoogsluijt MJ, Smit NP, Wakamatsu K, Thody AJ, et al. Melanosomal pH controls rate of melanogenesis, eumelanin/pheomelanin ratio and melanosome maturation in melanocytes and melanoma cells. Exp Cell Res 2001;268:26-35.
5. Rees J. Plenty new under the sun. J Invest Dermatol 2006;126:1691-2.
6. Rees JL. The melanocortin 1 receptor (MC1R): More than just red hair. Pigment Cell Res 2000;13:135-40.
7. Kenny EE, Timpson NJ, Sikora M, Yee MC, Moreno-Estrada A, Eng C, et al. Melanin-based blond hair is caused by an amino acid change in TYRP1. Science 2012;336:554.
8. Slominski A, Wortsman J, Plonka PM, Schallreuter KU, Paus R, Tobin DJ. Hair follicle pigmentation. J Invest Dermatol 2005;124:13-21.
9. Fitzpatrick TB, Breathnach AS. The epidermal melanin unit system. Dermatol Wochenschr 1963;1:478-91.
10. Slominski A, Paus R. Melanogenesis is coupled to murine anagen: Toward new concepts for the role of melanocytes and the regulation of melanogenesis in hair growth. J Invest Dermatol 1993;101:908-78.
11. Peters EM, Imfeld D, Gräub R. Graying of the human hair follicle. J Cosmet Sci 2011;62:1215.
12. Arek PC, Overall R, Spatz K, Liezman C, Handijski B, Klapp BF, et al. Towards a “free radical theory of graying”: Melanocyte apoptosis in the aging human hair follicle is an indicator of oxidative stress induced tissue damage. FASEB J 2006;20:1567-9.
13. Horikawa T, Norris DA, Johnson TW, Zelman T, Danscomb N, Bennion SD, et al. DOPA-negative melanocytes in the outer root sheath of human hair follicles express premelanosomal antigens but not a melanosomal antigen or the melanosomal-associated glycoproteins tyrosinase, TRP-1, and TRP-2. J Invest Dermatol 1996;106:28-35.
14. Choi HI, Choi GI, Kim EK, Choi YJ, Sohn KC, Lee Y, et al. Hair greying is associated with active hair growth. Br J Dermatol 2011;165:1183-9.
15. Nagl W. Different growth rates of pigmented and white hair in the beard: Differentiation vs. proliferation? Br J Dermatol 1995;132:94-7.
16. Van Neste D.Thickness, modulation and growth rate of female scalp hair are subject to significant variation according to pigmentation and scalp location during ageing. Eur J Dermatol 2004;14:28-32.
17. Goodier M, Hordinsky M. Normal and aging hair biology and structure ‘aging and hair’. Curr Probl Dermatol 2016;47:1-9.
18. Han R, Beppu H, Lee YK, Georgopoulos K, Larué I, Li E, et al. A pair of transmembrane receptors essential for the retention and pigmentation of hair. Genes Dev 2012;26:783-800.
19. Selouwey K, Delmas V, Larué I, Zimber-Strobl U, Strobl LJ, Radtke F, et al. Notch1 and notch2 receptors influence progressive hair graying in a dose-dependent manner. Dev Dyn 2007;236:282-9.
20. Hachiya A, Sirligtanapont P, Kobayashi T, Nagasawa A, Yoshida H, Ohuchi A, et al. Stem cell factor-KIT signalling plays a pivotal role in regulating pigmentation in mammalian hair. J Pathol 2009;218:30-9.
21. Daulatabad D, Singal A, Grover C, Chhillar N. Profile of Indian patients with premature canities. Indian J Dermatol Venereol Leprol 2016;82:169-72.
22. Trieb RM. Oxidative stress in ageing of hair. Int J Trichology 2009;1:6-14.
23. Wood JM, Decker H, Hartmann H, Chavan B, Rokos H, Spencer JD, et al. Senile hair graying: H2O2-mediated oxidative stress affects human hair color by blunting methionine sulfoxide repair. FASEB J 2009;23:2065-75.
24. Emerit I, Filipe P, Freitas J, Vassy J. Protective effect of superoxide dismutase against hair graying in a mouse model. Photochem Photobiol 2004;80:579-82.
25. Irie M, Asami S, Nagata S, Miyata M, Kasai H. Relationships between perceived workload, stress and oxidative DNA damage. Int Arch Occup Environ Health 2001;74:153-7.
26. Eipel ES, Blaehlumph EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A 2004;101:17312-5.
27. Akin Belli A, Etnu F, Ozbaz Sok S, Kara B, Dogan G. Risk factors for premature hair greying in young Turkish adults. Pediatr Dermatol 2016;33:438-42.
28. Daulatabad D, Singal A, Grover C, Sharma SB, Chhillar N. Assessment of oxidative stress in patients with premature canities. Int J Trichology 2015;7:91-4.
29. Shi Y, Luo LF, Liu XM, Zhou Q, Xu SZ, Lei TC. Premature graying as a consequence of compromised antioxidant activity in hair bulb melanocytes and their precursors. PLoS One 2014;9:e83589.
30. Dominguez-Gerpe L, Araujo-Vilar D. Prematurely aged children: Molecular alterations leading to hutchinson-gilford progeria and werner syndromes. Curr Aging Sci 2008;1:202-12.
31. Jimbow K, Chen H, Park JS, Thomas PD. Increased sensitivity of melanocytes to oxidative stress and abnormal expression of tyrosinase-related protein in vitiligo. Br J Dermatol 2001;144:53-65.
32. Dauwe RP. Integumentary associations of pernicious anaemia. Br J Dermatol 1970;82:221-3.
33. van Beek N, Bodó E, Kromminga A, Gáspár E, Meyer K, Zmijewski MA, et al. Potential hair pigment loss due to theHelper T cell (CD4) deficiency. J Invest Dermatol 1992;100:441-6.
34. Hartmann JT, Kanz L. Sunlight and periodic hair depigmentation due to temporary c-KIT inhibition. Arch Dermatol 2008;144:1525-6.
35. Sideras K, Menecée ME, Burton JK, Etlichman C, Bible KC, Ivy SP. Profound hair and skin hypopigmentation in an African American woman treated with the multi-targeted tyrosine kinase inhibitor pazopanib. J Clin Oncol 2010;28:312-3.
Kumar, et al.: Premature gray hair

36. Etienne G, Gory-Makhlouf P, Mahon FX. Imininib mesylate and gray hair. N Engl J Med 2002;347:446.
37. Di Giacomo TB, Valente NY, Nicos MM. Chloroquine-induced hair depigmentation. Lupus 2009;18:264-6.
38. Jo SJ, Paik SH, Choi JW, Lee JH, Cho S, Kim KH, et al. Hair graying pattern depends on gender, onset age and smoking habits. Acta Derm Venereol 2012;92:160-1.
39. Mosley JG, Gibbs AC. Premature grey hair and hair loss among smokers: A new opportunity for health education? BMJ 1996;313:1616.
40. Zayed AA, Shahid AD, Ayoub MN, Yousef AM. Smokers’ hair: Does smoking cause premature hair greying? Indian Dermatol Online J 2013;4:90-2.
41. Trüeb RM. Association between smoking and hair loss: Another opportunity for health education against smoking? Dermatology 2003;206:189-91.
42. Zarafonetis CJ. Darkening of gray hair during para-amino-benzoic acid therapy. J Invest Dermatol 1950;15:399-401.
43. Bhat RM, Sharma R, Pinto AC, Dandekar S, Maris J. Epidemiological and investigative study of premature graying of hair in higher secondary and pre-university school children. Int J Trichology 2013;5:17-21.
44. Chakrabarty S, Krishnappa PG, Gowda DG, Hiremath J. Factors associated with premature hair greying in a young Indian population. Int J Trichology 2016;8:14-4.
45. Vinay K, Yadav S, Handa S. Zinc deficiency and canities: An unusual opportunity. JAMA Dermatol 1950;15:1116-17.
46. Keogh EV, Walsh RJ. Rate of greying of human hair. Nature 1965;207:877-8.
47. Hollfelder B, Blankenburg G, Wolfram LJ, Hocker H. Chemical and physical properties of pigmented and non-pigmented hair (‘grey hair’). Int J Cosmet Sci 1995;17:87-9.
48. Gao T, Bedell A. Ultraviolet damage on natural gray hair and its photoprotection. J Invest Dermatol 2001;52:103-18.
49. Alijanpoor R, Poorsattar Bejeh Mir A, Mokmeli S. Successful white hair removal with combined coloring and intense pulsed light (IPL): A randomized clinical trial. Photomed Laser Surg 2011;29:773-9.
50. Tobar D. Aging of the hair follicle pigmentation system. Int J Trichology 2009;1:85-93.
51. Schnoor P, Lange P, Nyboe J, Appleyard M, Jensen G. Gray hair, baldness, and wrinkles in relation to myocardial infarction: The copenhagen city heart study. J Am Heart J 1995;130:1003-10.
52. Schnoor P, Nyboe J, Lange P, Jensen G. Longevity and gray hair, baldness, facial wrinkles, and arcus senilis in 13,000 men and women: The Copenhagen city heart study. J Gerontol A Biol Sci Med Sci 1998;53:M347-50.
53. Eisenstein I, Edelstein J. Gray hair in black males a possible risk factor for coronary artery disease. Angiology 1982;33:65-6.
54. Gould I, Reddy CV, Oh KC, Kim SG, Becker W. Premature hair greying: A probable coronary risk factor. Angiology 1978;52:300-3.
55. Glasser M. Is early onset of gray hair a risk factor? Med Hypotheses 1991;36:404-11.
56. Aggarwal A, Srivastava S, Agarwal MP, Dwivedi S. Premature greying of hair: An independent risk marker for coronary artery disease in smokers – A retrospective case control study. Ethiop J Health Sci 2015;25:123-8.
57. Morton DJ, Kritz-Silverstein D, Riley DJ, Barrett-Connor EL, Wingard DL. Premature greying, balding, and low bone mineral density in older women and men: The Rancho Bernardo Study. J Aging Health 2007;19:275-85.
58. Beardsworth SA, Kearney CE, Steel SA, Newman J, Purdie DW. Premature greying of the hair is not associated with low bone mineral density. Osteoporos Int 1999;10:290-4.
59. Ozbay I, Kahirman C, Kucer C, Namdar ND, Ogahan F. Is there a relationship between premature hair greying and hearing impairment? J Laryngol Otol 2015;129:1097-100.
60. van Geel N, Speelkaert M, Cheviolet I, De Schepper S, Lapeere H, Boone B, et al. Hypomelanoses in children. J Cutan Aesthet Surg 2013;6:65-72.
61. Shah VV, Aldahan AS, Mlacker S, Alsaidan M, Nouri K. Canities subita: Sudden Blanching of the Hair in History and Literature. Int J Dermatol 2016;55:362-4.
62. Tan SP, Weller RB. Sudden whitening of the hair in an 82-year-old woman: The ‘overnight greying’ phenomenon. Clin Exp Dermatol 2012;37:458-9.
63. Helm F, Milgrom H. Can scalp hair suddenly turn white? A case of canities subita. Arch Dermatol 1970;102:102-3.
64. Hoffmann E. Sudden turning gray of the hair caused by fright, canities subita psychogena. Z Haut Geschlechtskr 1957;22:74-8.
65. Pandhi D, Khanna D. Premature greying of hair. Indian J Dermatol Venereol Leprol 2013;79:641-5.
66. Shin H, Ryu HH, Yoon J, Jo S, Jang S, Choi M, et al. Association of premature hair greying with family history, smoking, and obesity: A cross-sectional study. J Am Acad Dermatol 2015;72:321-7.
67. Erdogan T, Kocaman SA, Cetin M, Durakoglugil ME, Ugurlu Y, Sahin I, et al. Premature hair whitening is an independent predictor of carotid intima-media thickness in young and middle-aged men. Intern Med 2013;52:29-36.
68. Singal A, Daulatabad D, Grover C. Graying severity score: A useful tool for evaluation of premature canities. Indian Dermatol Online J 2016;7:164-7.
69. McDonald PH, Schwartz RA. Premature hair greying. Cutis 2012;89:161-5.
70. Dweek AC. Natural ingredients for colouring and styling. Int J Cosmet Sci 2002;24:287-302.
71. Morel OJ, Christie RM. Current trends in the chemistry of permanent hair dyeing. Chem Rev 2011;111:2537-61.
72. Pande CM, Albrecht L, Yang B. Hair photoprotection by dyes. J Cosmet Sci 2001;52:377-89.
73. Trüeb RM. Pharmacologic interventions in aging hair. Clin Interv Aging 2006;1:121-9.
74. Parthica JS. Effect of grey hair evasion on the response to calcium pantothenate in premature grey hairs. Indian J Dermatol Venereol Leprol 1985;52:77-80.
75. Sieve BE. Clinical achromotrichia. Science 1941;94:257-8.
76. Pavithran K. Puvasol therapy in premature greying of hair. Indian J Dermatol Venereol Leprol 1986;52:121-9.
77. Pasricha JS. Can puva darken grey hair. Indian J Dermatol Venereol Leprol 2013;79:641-5.
78. Skulachev VP, Erichev VP, Anisimov VN, Antonenko YN, Bakeeva LE, Chernyak BV, et al. Hair greying due to the therapeutic effects of 2′-deoxyadenosine in children. J Laryngol Otol 2015;5:362-4.
79. Berrilli S, Amato L, Cipollini EM, Antiga E, Brandini L, Fabbri P. Repigmentation of hair after latanoprost therapy. J Eur Acad Dermatol Venereol 2011;25:1485-7.
80. Skalachev VP, Anisimov VN, Antonenko YN, Bakeeva LE, Chernyak BV, Erichev VP, et al. An attempt to prevent senescence: A mitochondrial approach. Biochim Biophys Acta 2009;1787:437-61.
81. Hoffmann RM. Topical liposome targeting of dyes, melanins, genes, and proteins selectively to hair follicles. J Drug Target 1998;5:67-74.