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Premature Greying of Hair (Premature Canities): A Concern for Parent and Child

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Abstract

Hair goes grey with chronological aging. Premature hair greying may have significant adverse effects on the appearance, self-esteem, and socio-cultural acceptance of the affected individual. The exact aetiopathogenetic mechanism causing premature greying is still not clear and much speculative. Premature canities may appear alone as an autosomal dominant trait or it may occur in association with certain other disorders. The genes Pax3 and MITE play an important role in melanocyte stem cell maintenance and differentiation. Defective melanosomal transfer to the cortical keratinocytes or melanin incontinence due to melanocyte degeneration is also believed to contribute to greying. Despite the extensive molecular research being carried out to understand the pathogenesis of canities, treatment options still remain far from satisfactory and no effective therapy is available. Premature greying is a feature in a number of well recognised syndromes. A number of other conditions have also been observed to be associated with premature greying of hair.

Keywords: Premature greying; Canities; Aetiopathogenesis; Associations; New targets

Introduction

Hair plays a significant role in people's physical appearance. Hair goes grey with chronological aging and about half the population have a significant amount of grey hair by age of 50 years [1]. Typically, white people start going grey in their mid-30s, Asians in their late 30s, and African-Americans in their mid-40s [2]. Premature hair greying (canities) may have a significant adverse effect on the appearance, self-esteem, and socio-cultural acceptance of the affected individual. Racial variations exist as greying has an earlier onset in Caucasoids [1]. Also, premature hair greying is less frequent in certain ethnic groups, notably blacks, who also tend to have higher testosterone levels in both sexes [3]. It is observed that grey hairs tend to be thicker and longer than pigmented ones. Typically, grey hair first develops at age 34.2 ± 9.6 years in Caucasians while for Black people the average age of onset is 43.9 ± 10.3 years [4]. Both sexes are equally affected [5]. Greying of hair appearing in a white person by age 20 years; grey before 25 years for Asians and 30 years for African-Americans are considered to be prematurely grey [6].

Aetiopathogenesis

The exact aetiopathogenetic mechanism causing premature greying is still unclear and largely speculative. Follicular melanogenesis occurs effectively up to 40 years of age in an individual [7]. Fewer melanosome due to reduced melanocyte activity, defective melanosomal transfers to cortical keratinocytes and melanin incontinence due to melanocyte degeneration are believed to be factors resulting in greying of hair. The tyrosinase enzyme is necessary for the initial stages of melanin synthesis. The hair bulb tyrosinase activity gradually peaks at middle age and the bulbs of grey or white hairs appear to lack or be deficient in tyrosinase [8]. Repetitive oxidative stress causes apoptosis of hair follicle melanocytes, resulting in normal hair greying and premature greying is related to exhaustion and poor sustenance of the melanocyte stem cell pool [9]. The genes Pax-3 and MITE play an important role in melanocyte stem cell maintenance and differentiation [10]. Electron microscopy of grey hairs has revealed a normal number of melanocytes but with incompletely melanized melanosomes, whereas white hairs show reduced or absent melanocytes [11]. The follicles of grey hairs still have melanocytes placed normally over the dermal papilla, but the cytoplasm may contain large vacuoles and the melanosomes may be only lightly melanized. The follicles of fully white hairs may completely lack melanocytes. However, among grey or white hairs, there may be a few normal bulbs producing dark hairs [8]. In grey hair, the pigmentary unit becomes fuzzy, melanocytes are few and rounded, and lightly pigmented oligodendritic melanocytes become detectable in the proximal hair bulb below Auber's line [9]. The resultant pigment loss in greying hair follicles due to a marked reduction in melanogenically active melanocytes in the hair bulb of grey anagen hair follicles is central to the pathogenesis of greying [12]. Defective melanosomal transfer to the cortical keratinocytes or melanin incontinence due to melanocyte degeneration is also believed to contribute to greying. It has been suggested that loss of melanocyte stem cells can be observed and temporarily precedes the loss of differentiated melanocytes in the hair matrix [10]. This incomplete maintenance of melanocyte stem cells appears to cause physiologic hair greying through loss of differentiated progeny with aging [10].

Premature canities may appear alone as an autosomal dominant trait or it may occur in association with certain organ-specific autoimmune disorders like pernicious anemia, hyper- or hypo-thyroidism or as part of various premature aging syndromes and atopic diathesis [13]. A number of theories have been postulated but there are not too much evidence proving any of the theories, besides heredity. Premature greying of hairs may be induced by ectopic differentiation of melanocyte stem cells in the niche and or their death because of

deficiencies in stemness-related genes with subsequent hair greying [14]. A genome-wide association study has found a susceptibility variant for vitiligo/Non-segmental vitiligo (NSV) in the tyrosinase gene (TYR) in European whites, rarely found in patients with melanoma [15], which suggests a genetic dysregulation of immune-surveillance against the melanocytic system.

The association between premature greying and certain organ specific autoimmune diseases is well recognized. Autoimmunity has been proposed as the cause because of the higher frequency (about 50%) of greying in patients with pernicious anemia, a known autoimmune disease [16]. In a controlled study of 125 patients with pernicious anaemia, 11% had premature greying, defined as onset before the age of 20, compared with 2% in the control group [16]. In a recent Latent class analysis of a series of 717 patients with NSV an early age onset (prepubertal onset) class vitiligo was significantly more associated with premature greying as compared to late age onset of vitiligo [17]. Strikingly, in patients with early-onset disease, a higher proportion of familial history of premature hair greying (PHG) was also observed. Thus, a subset of PHG might be reconsidered as an immune process targeting inappropriately the hair follicle melanocytic compartment.

The hair appearance is known to change in childhood protein deficiency states and in inborn errors of amino-acid metabolism [18]. Patients with phenylketonuria have abnormally high phenylalanine content in their imperfectly pigmented hair [19] and patients with kwashiorkor have a deficiency in the number of melanosomes in the cornified hair [20] and a reduction in the amount of sulphur-containing protein with corresponding depigmentation [21]. Although, there is no known association between premature greying of the hair and the subsequent diagnosis of adult coeliac disease, Hill observed reversal of premature hair greying in adult coeliac disease after starting a gluten-free diet [22]. Although the mechanism of the hair colour changes in his cases is not clear, its connection with gluten sensitivity is undoubted. The amino-acid content of 17 standard amino-acids in dark and light zones of hair in their patient was similar and within normal ranges. Hill hypothesised that perhaps this type of premature greying is either the presenting sign of adult coeliac disease or is a coincidental predictor of its later occurrence.

Besides these, reactive oxygen species (ROS) generated in melanin synthesis places melanocytes under a higher oxidative stress load. Impairment of antioxidant system with age probably leads to accumulation of ROS and oxidative stress that damages the melanocyte [23]. Catalase and methionine reductase A and B expression and functional loss of methionine sulfoxide repair mechanism in the grey hair follicle have also been demonstrated [24]. Oxidative stress generated outside hair follicle melanocytes by exogenous factors, for example, by pollution, UV light, psycho-emotional or inflammatory stress, may add to this endogenous oxidative stress and overwhelm the hair follicle melanocyte antioxidant capacity resulting in enhanced terminal damage in the aging hair follicle [25,26].

Apart from oxidative stress, other factors may also contribute to the process of greying. Insufficient neuroendocrine stimulation of hair follicle melanogenesis by locally synthesized agents, such as adrenocorticotrophic hormone, α-MSH and β-endorphin, has also been hypothesized as a possible mechanism for hair greying [27,28]. Cervical and lumbar sympathectomy of long duration has also been shown to retard the normal greying of scalp and pubic hair, respectively, in two patients, suggesting that sympathetic denervation somehow slows or prevents the normal greying of hair with increasing age [29,30].

Smoking was reported to be significantly associated with hair greying, and impairment of stem cell regenerative capacity with substance abuse was postulated to lead to greying of hair [31,32].

A connection has been suggested between premature greying and lower bone density later in life. Premature greying may be a weak marker for reduced bone mineral density (BMD) in women with a history of Graves' disease, but it is not a marker in normal women [33]. But later studies showed no such link [34].

Extensive research in the field of premature greying of hair is underway at the molecular level. Bmpr-2, a known receptor for bone morphogenetic proteins (Bmps) and Acvr2a, a known receptor for Bmps and activins, are individually redundant but together essential for multiple follicular traits [35]. Reduced Bmpr2/Acvr2, a function in melanocytes in mutant mice was recently shown to result in grey hair due to aberrant hair shaft and melanosomes' differentiation [36]. Stem cell factor (SCF) and its receptor (KIT) were shown to have an important role in signalling in the maintenance of human hair follicle melanogenesis during the anagen cycle and in physiological aging of the hair follicle pigmentary unit [37].

Both Notch 1 and Notch 2 signalling pathways are required for the maintenance of melanoblasts and melanocyte stem cells and are essential for proper hair pigmentation in mice [38]. Premature greying of hair has been shown to significantly predispose one for CAD less than 35 years of age [39]. Aggarwal et al also reported a significant association of premature greying of hair and baldness in patients with young CAD [40].

Premature Greying Hair Syndromes and Hypomelanotic Hair Disorders

Premature Greying of hair is usually familial and may occur alone as an autosomal dominant trait or in association with various autoimmune or early aging syndromes. Premature greying is a feature in a number of well recognised syndromes. A number of other conditions have also been observed to be associated with premature greying of hair. Besides these, isolated syndromic presentation has also been reported.

Waardenburg's Syndrome

Waardenburg's syndrome (WS) is a rare autosomal-dominant condition caused by mutations in the PAX3 gene, MITF gene, SOX10, endothelin-3/EDNR3 gene PSX3 or SNAI2 genes [41,42]. In Waardenburg's syndrome premature greying may develop with or without a congenital white forelock similar to that seen in Piebaldism [43-49]. These mutations affects neural crest cells and impair the ability of melanoblasts to reach their final target sites (inner ear, eye, skin) during embryogenesis. There is lateral displacement of the medial canthi (dystopia canthorum), a hypertrophic nasal root, deafness, and partial or total heterochromia of the iris [44]. WS accounts for 2% to 5% of all congenital deafness cases [45]. Skin histopathology reveals an absence of melanocytes [44]. The irregular depigmented patches of WS patients can be treated cosmetically with topical pigmenting agents such as self-tanning products or with skin grafting [44]. Nearly all patients require ophthalmologic referral with appropriate management.

Werner's Syndrome (Adult Progeria, Pangeria)

Werner's syndrome is a rare autosomal recessive premature aging disorder due to biallelic inactivating mutations in WRN gene on 8p12–p11.2 encoding a RecQ DNA helicase/exonuclease involved in DNA replication and repair [46]. Its prominent features include premature ageing, "bird-like" facies, scleroderma-like skin changes, bilateral cataracts, subcutaneous calcification, short stature, premature arteriosclerosis, diabetes mellitus, and premature greying of scalp hair [47] and a predisposition to malignancy [48].

Ataxia Telangiectasia (Louis–Bar Syndrome)

Ataxia telangiectasia is an autosomal-recessive disorder due to mutations in a single gene on chromosome 11 (ATM) localized to chromosome 11q22.3 [49]. It is a DNA repair disorders characterized by progressive cerebellar ataxia, oculocutaneous telangiectasiae, variable immunodeficiency and an increased risk of lymphoid malignancy [50]. The clinical features of the patients are progressive ocular and cutaneous telangiectasias, premature aging, and progressive neurodegeneration. The characteristic skin changes comprise cutaneous non-infectious granulomas (which can be ulcerative and painful), loss of subcutaneous fat, premature grey hair, large irregular café-au-lait spots, vitiligo, seborrheic dermatitis. Hypomelanotic macules accompany premature greying in ataxia-telangiectasia; there are signs of immunodeficiency and an increased risk for malignancy. Ataxia and cerebellar signs are always present and neurological degeneration is progressive. Cellular and humoral immunodeficiency affects 60–80% of cases, with low levels of IgA, IgG2 [51].

Rothmund–Thomson syndrome (Poikiloderma congenital, RTS)

RTS is a rare autosomal-recessive disorder due to compound heterozygous mutations in a DNA helicase gene, known as RECQL4, on chromosome 8q24.3, although in around 40% of patients, no mutations have been identified [52,53]. The skin appears normal at birth and then poikiloderma appears including atrophy, irregular pigmentation and telangiectasias beginning during the first 3–6 months of age. Plaques of erythema and oedema, or more transitory diffuse erythema, are succeeded by varying combinations of atrophy, telangiectasia, pigmentation and depigmentation. Characteristically, the arms and legs are affected, with sparing of the antecubital and popliteal fossae; palmoplantar hyperkeratosis; and sensitivity to sunlight. Scalp, hair eyebrows and eyelashes, and pubic and axillary hair are often sparse or absent. Premature greying of hair is frequently observed. Nails and teeth are often normal [54]. Cataracts occur in a small percentage of patients in childhood or young adult life. In many cases keratosis develop on exposed skin from adolescence onwards and large warty keratosis of hands, wrists, feet, ankles and elsewhere may restrict the patient's activities [55]. Squamous or basal cell carcinoma may develop in the keratosis or in the surrounding atrophic skin [56]. Skeletal abnormalities include short stature, saddle nose and radial ray defects or complete absence of the radius [57]. There is a recognized risk of osteosarcoma, especially in the bones of the lower leg, which can present in childhood [58-60].

Cri Du Chat Syndrome (Chromosome 5, Short-Arm Deletion Syndrome)

Cri du chat syndrome is a clinically heterogeneous syndrome. Characterised by mentally deficient microcephalics with a cat-like cry, pre-auricular skin tag and low-set malformed ears [61,62]. One-third of patients with cri du chat syndrome have prematurely grey hair [63].

Book's Syndrome

Book's syndrome is an autosomal dominantly inherited trait. The premature greying is associated with premolar hypodontia and palmoplantar hyperhidrosis [64].

Progeria (Hutchinson–Gilford Syndrome)

Progeria occurs due to de novo mutations of the lamin A gene (LMNA) which encodes for a major constituent of the inner membrane lamina [65]. Progeria is a rare disorder characterized by accelerated aging, dwarfism, alopecia, generalized atrophy of the skin and muscles, enlarged head with prominent scalp veins, and a high incidence of generalized atherosclerosis, usually fatal by the second decade. The large bald head and lack of eyebrows and eyelashes are distinctive. The skin is wrinkled, pigmented and atrophic. Generalized alopecia often begins in the first year of life. Premature greying may occur. The nails are thin and atrophic. Most patients lack subcutaneous fat, which produces the appearance of premature senility. There are usually sclerodermatous plaques on the extremities. The dentition is abnormal and delayed, and there may be skeletal abnormalities Sexual maturation is absent but intelligence is normal. Death usually occurs in the second decade as a result of severe, generalized atheroma [66]. The intelligence remains intact. Arteriosclerosis, anginal attacks, and hemiplegia may occur, followed by death from coronary heart disease at an early age. Mutations in LMNA and mosaicism have been identified [67]. In progeria, the child is often small but otherwise normal during the first year; thereafter, development is delayed. Scalp hair, eyebrows and eyelashes are lost and the skin assumes an increasingly senile appearance [68].

Fisch's Syndrome

Auditory-pigmentary syndromes are caused by physical absence of melanocytes from the skin, hair, eyes, or the stria vascularis of the cochlea. Dominantly inherited examples with patchy depigmentation are usually labelled Waardenburg syndrome (WS). Type I WS, characterised by dystopia canthorum, is caused by loss of function mutations in the PAX3 gene [69]. Klein-Waardenburg syndrome or Waardenburg syndrome type 3 (WS-III; MIM 148820) is characterized by the presence of musculoskeletal abnormalities in association with clinical features of Waardenburg syndrome type 1 (WS-I). Since the description of the first patient in 1947 [70], a few cases have been reported. Only occasional families have demonstrated autosomal-dominant inheritance of WS-III [71]. Fisch Syndrome is similar to Klein-Waardenburg syndrome, distinguished there from by the presence of early grey hair and congenital deafness.

Seckel's Syndrome (Microcephalic Primordial Dwarfism)

Seckel syndrome is an autosomal recessive [72] disorder caused by a mutation in the SCKL gene on chromosome 3 and 18 [73]. The

disease is characterized by growth retardation, dwarfism, microcephaly with mental retardation, and unique facial features such as narrow bird-like face with a beak-like nose, large eyes, and receding lower jaw [73,74]. Premature greying and blood abnormalities may be present [72,74].

Vogt–Koyanagi–Harada Syndrome (Vkhs)

The VKHS is a cell-mediated autoimmune, condition with bilateral uveitis, labrynthine deafness, tinnitus, vitiligo, poliosis and alopecia areata [75,76]. The auto antigen(s) is supposed to be solely expressed in tyrosinase or tyrosinase-related protein or melanin-containing cells in the eyes, skin, inner ears, and central nervous system (CNS). Clinically, the features are meningismus, headaches, mental status changes, tinnitus, and dysacusis, uveitis, choroiditis, frontal non-cicatricial alopecia, vitiligo, poliosis and premature greying of the hair [75,77]. Sensorineural hearing loss, early greying, and essential tremor: Karmody et al. reported a syndrome composed of sensorineural hearing loss, early greying of scalp hair, and adult-onset essential tremor [78]. All individuals had blue eyes without heterochromia. Molecular genetic testing also suggested this is not a variant of Waardenburg syndrome.

Prolidase Deficiency

Prolidase deficiency, an autosomal-recessive inherited inborn error of metabolism, is characterised by dermatologic manifestations, mental deficiency and abnormal facies. Skin changes occur in about 85% of cases in the form of skin fragility; ulceration and scarring, mainly of the lower extremities. There may be photosensitivity, telangiectasia, poliosis, purpuric lesions, premature greying, and lymphoedema [79]. Antinuclear antibodies (ANA) and anti-ds-DNA may be positive [80].

Matzner Syndrome

Matzner et al. reported a case of primary hypo-parathyroidism in association with pernicious anemia, premature greying, reversible immunodeficiency and hypoadrenalism [81].

Other Conditions

Greying of hair is the main dermatologic manifestations along with glossitis and hyperpigmentation in Vitamin B12 deficiency. Kwashiorkor produces hair and skin changes, edema, impaired growth, and the characteristic potbelly. The hair is hypopigmented, varying in color from a reddish-yellow to grey or even white. Patients with HIV infection have recently been reported to develop rapid and premature greying (PMG) as well as androgenetic alopecia (AGA) as well as PMG has also been reported in patients with hyperthyroidism, hypothyroidism, cystic fibrosis, Hodgkin's lymphoma, myotonic dystrophy and acrodermatitis enteropathica-like dermatitis [82-85]. Interferon-alpha therapy has also been observed to cause canities [86].

Beral et al. [87] in their study of Cutaneous factors related to the risk of malignant melanoma observed that presence of red hair colour at age 5 years was associated with a tripling of risk of developing melanoma while the presence of premature greying of the hair was protective to the risk of developing malignant melanoma.

Can Anything Be Done?

Despite the extensive molecular research being carried out to understand the pathogenesis of canities, treatment options still remain far from satisfactory and no effective therapy is available. Few oral therapies including p-aminobenzoic acid (PABA), calcium pantothenate, nutritional supplements, (alone or in combination), Psoralen combined with solar ultraviolet light (PUVASOL) have been tried with rather inconsistent results. Prolonged (around 3 years) use of latanoprost, a PGF2 alpha eye drops has shown repigmentation of grey hair [88]. Hair darkening has also been described after X-ray irradiation and following electron beam therapy [89]. However, reports of successful treatment are anecdotal and have never been confirmed by other trials. Paucity of systemic or topical therapies in this condition has rendered camouflage techniques using hair colorants as the mainstay of therapy. Major types of hair colours currently used are: temporary (textile dyes), natural colouring (e.g. henna), semi-permanent and permanent [90]. The future of treatment options for premature canities lies with targeting genes and proteins involved in hair follicle melanocyte biology. There is an increasing interest in the hair follicular route for delivery of active compounds affecting the hair. Current research activities focus on topical liposome targeting for melanins, genes, and proteins selectively to hair follicles for therapeutic and cosmetic modification of hair [91]. Topical liposome selective delivery to hair follicles has demonstrated the ability to color hair with melanin [92]. The discovery of potential targets and the development of both selective and effective delivery systems following topical application indicate further rational strategies for maintenance of healthy hair and scalp in the young and old [93].

Conclusion

Premature canities may appear alone as an autosomal dominant trait or in association with certain organ-specific autoimmune disorders or as part of various premature aging syndromes and atopic diathesis and has always remained a cause of worry for parents and adolescents. A number of modalities have been tried to correct the problem but none has succeeded to full satisfaction. Targeting genes and proteins involved in hair follicle melanocyte biology and liposome selective drug delivery to hair follicles has created a lot of hope to repigment these hairs.

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