Indian Journal of Dermatology

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Indian J Dermatol. 2017 May-Jun; 62(3): 304–308.
doi: 10.4103/ijd.IJD_221_17: 10.4103/ijd.IJD_221_17

PMCID: PMC5448266
PMID: 28584374

Demographic Characteristics and Association of Serum Vitamin B12, Ferritin and Thyroid Function with Premature Canities in Indian Patients from an Urban Skin Clinic of North India: A Retrospective Analysis of 71 Cases

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Received 2017 Apr; Accepted 2017 Apr.

Abstract

Background:

The incidence of self-reported premature hair graying (PHG) seems to be on the rise. PHG has a profound impact on the patient's quality of life. It remains an incompletely understood etiology with limited and modest treatment options.

Aim:

The evaluation of the demographic and clinical profile of patients with premature canities, and exploration of the association of this entity with certain systemic disorders suspected to be related to its etiology.

Methods:

Seventy-one cases of premature canities (onset noticed by patients before 25 years of age) presenting to an urban skin clinic in Gurugram, India, between September 2012 and September 2015 with this complaint were retrospectively analyzed. The patient records were retrieved that provided details of the onset, duration and pattern of involvement, history, and examina-

tion findings (scalp, cutis, and general physical). Since all these patients had been screened for anemia, thyroid disorder, fasting blood glucose, and Vitamin B12 levels at the time of presentation, these parameters were also available for analysis.

Results:

The mean age at onset of graying was 10.2 ± 3.6 years (range: 5–19 years), with an almost equal gender distribution. The earliest age of onset recorded was 5 years. A positive family history of PHG (at least one of the biological parents or siblings) was obtained in 64 (90.1%) of the cases. The temporal regions of the scalp (35.2%) were most commonly involved followed by the frontal region (18.3%). Hypovitaminosis B12 and hypothyroidism showed significant association with the disorder, whereas anemia, serum ferritin, and fasting blood glucose did not.

Conclusion:

The age of onset of hair graying can be as low as 5 years. Temporal and frontal areas are the most commonly involved sites. A strong family history, Vitamin B12 deficiency, and hypothyroidism are strongly associated with PHG. Larger case–control studies are mandated for discerning the correlation of these and other risk factors with PHG.

Keywords: *Canities*, *graying*, *hair*, *India*, *premature*

What was known?

- Premature graying of hair is a common condition of multifactorial etiology with significant psychosocial impact on patients
- Genetic predisposition and certain micronutrient deficiencies such as serum iron have been implicated in the pathogenesis.

Introduction

Graying of hair, also known as “canities,” is a physiological phenomenon associated with chronological aging. The age of normal occurrence of physiological graying of hair varies in different races; age of 34.2 ± 9.6 years in the white races, 43.9 ± 10.3 years in the blacks, and between the age of 30–39 years in the Japanese population.[1] There is no available reference age range for physiological graying for the Indian subcontinent. The pattern of graying over the scalp and that of the beard and moustache area is also different. The hair in beard and moustache areas tend to gray earlier than scalp or body hair.[2] When graying begins before the usual age of onset, it is termed premature hair graying (PHG) or premature canities. The age of graying varies with race and ethnicity. Hair has conventionally been considered to gray prematurely only if graying occurs before the age of 20 years in Whites, before 25 years in

Asians, and before 30 years in Africans.[3] Although an exact cutoff to define premature canities in the Indian-Asian population is lacking, a cutoff of 20 years was used in the study by Bhat *et al*. and 25 years was suggested by Pasricha and Verma.[4,5]

In recent times, the banality of this innocuous disorder has been capsized, especially in ethnic groups with predominantly dark-colored hair, including Indian population owing to the significant recusant impact on the self-esteem and sociocultural acceptance of the affected individual.[6] Our current understanding of the pathogenesis of PHG revolves around a robust genetic component with a speculated autosomal dominant pattern of inheritance, with additional role of various acquired and environmental factors, especially autoimmune disorders such as hypo- or hyper-thyroidism, atopic diathesis, pernicious anemia; nutritional deficiencies such as chronic protein loss and deficiency of iron, Vitamin B12 and copper; and HIV infection, cystic fibrosis, and Hodgkin's lymphoma.[7] Other causes implicated include stress, smoking, drugs like chloroquine, and application of topical agents such as dithranol and resorcin.[7,8]

There is paucity of epidemiological and investigative studies on PHG, especially from the Indian subcontinent. In view of this, we undertook this retrospective analysis to study the demographic and clinical profile of Indian patients with PHG and explore the association of this entity with certain systemic disorders and deficiencies suspected to be related to its etiology.

Methods

In this retrospective analysis, the records of all patients presenting with PHG to an urban skin clinic in Gurugram, India, between September 2012 and September 2015 were analyzed. The definition of PHG taken in the study was – onset (with at least 5 gray hair fibers) noticed by patients before 25 years of age. Although the cutoff of "at least 5 gray hairs" is purely arbitrary, this cut-off was adopted from the study by Bhat *et al*.,[4] for the sake of inter-study comparison. Patients with PHG associated with conditions such as vitiligo, any significant or chronic scalp disease, and use of hair dye in the past 6 months were excluded from the study. In addition, pregnant or lactating women, and patients with a history of serious systemic disease within 3 months of the onset of graying of hair were also excluded. The retrieved records provided details of the onset, duration and pattern of involvement, history, and examination findings (scalp, cutis, and general physical). Since all these patients had been screened for anemia, thyroid disorder, diabetes, and Vitamin B12 levels at the time of presentation, these laboratory parameters (hemoglobin, serum ferritin, serum Vitamin B12 levels, serum levels of thyroid stimulating hormone (TSH), fasting plasma glucose, and antiparietal cell antibodies were also available for analysis.

Statistical analysis To determine the association between premature graying and serum levels of Vitamin B12, serum TSH, and serum ferritin, one sample t -test was used after checking for normalcy of data using Shapiro–Wilk test of normality. $P \leq 0.05$ was considered for statistical significance.

Results

Demographic profile The study included 71 cases with PHG, with a mean age at onset of graying of 10.2 ± 3.6 years (range: 5–19 years). The earliest age of onset was 5 years. The majority of cases (n = 34, 47.9%) reported onset of graying before 10 years of age; followed by the 10–

14 years range (*n* = 25, 5.2%), and remaining at or after the age of 15 years (*n* = 12; 16.9%) [Figure 1]. The gender distribution was almost equal, with 37 males (52.2%) and 34 females (47.8%). On an average, females tended to report an earlier onset of graying, although this result was not statistically significant.

Clinical profile Duration and origin of graying

The mean duration of graying at the time of presentation was 47.8 ± 32.4 months (range: 3 months–14 years). There was no statistically significant difference in the duration of graying between males and females. In terms of the part of the scalp from which onset of graying was reported, a large majority of patients noticed it to arise from the temporal regions (*n* = 25; 35.2%), followed by the frontal region in 13 (18.3%) cases, the vertex in 10 (14.1%), occipital in 8 (11.3%), and diffuse or undefined in the remaining 15 (21.1%) cases. History of premature graying of other hairy sites was encountered as follows: eyebrows (1 woman) and beard (3 men); with sparing of other sites including the eyelashes, moustache, sideburns, axillae, or groins in all the cases.

Family history

A positive family history of PHG (at least one of the biological parents or siblings) was obtained in 64 (90.1%) of the cases. Although an attempt was made to dwell on history of PHG in senior generations, the exact details could not be gathered effectively due to poor recall of the index cases with respect to history of PHG in grandparents and second degree maternal and paternal aunts/uncles/cousins excepting an odd case. Of the 64 cases, 14 cases (21.9%) reported PHG in both the parents and the remaining, i.e. 50 cases (78.1%) reported it in one of the parents (22 in maternal and 28 in paternal; no statistically significant difference). Thus, there was no obvious sexual predilection of inheritance. Further, 17 of these 64 patients (26.6%) reported infliction of at least one of their siblings with PHG.

Correlation with hematology and biochemical parameters

Compared to the normal population, the mean serum Vitamin B12 level was statistically significantly lower in the study group when compared to normal population Vitamin B12 levels[9] (t (69) = −2.785; P = 0.007). The mean serum TSH levels were statistically significantly higher in the study group when compared to normal population[10] (t (69) = 8.169; $P \leq 0.005$). The hemoglobin levels of the patients, as per their age and gender, were found to be lower than expected,[11] but the difference was statistically insignificant. The mean serum ferritin level was 35.41 ng/ml for females (t (69) = 0.613; P = 0.544), and 55.86 ng/ml for males (t (69) = −0.569; P = 0.573); results being statistically insignificantly different from the normal population.[12] Nine out of the 71 patients (12.7%) had a positive antiparietal cell IgG antibody, with most of them being females, and only one male patient. These nine patients had low serum Vitamin B12 levels. No patient was detected with fasting hyperglycemia. Of note, none of the patients with Vitamin B12 deficiency or raised serum TSH had any specific symptoms of the biochemical abnormality, except for complaints of a general feeling of weakness during heavy physical activity.

Discussion

Graying of hair is a physiological phenomenon, and it used to be a popular aphorism that by the age of 50 years, 50% of the population will have at least 50% gray hair.[1] However, the validity of this 50/50/50 rule of thumb is doubtful, evidenced from the results of a survey conducted on 4192 healthy male and female volunteers, in which calculating the percentage of people showing at least 50% gray hair coverage at age 50 years lead to a global range of 6%–23%, according to ethnic/geographical origin and natural hair color, well below that expressed by the "50" rule of thumb.[13]

Despite a strong genetic control and inheritance pattern of onset of hair graying, little is known about the mechanism(s) by which functional melanocytes are lost from anagen graying hair follicles. Graying of hair is believed to have a multifactorial etiology including a genetic component, environmental factors, endocrine abnormalities, and nutritional status, among others. The role of accumulation of reactive oxygen species in human gray/white scalp hair follicles leading to oxidative damage to hair follicle melanocytes is gaining support from recent evidence.[14]

Few studies have addressed the epidemiology of PHG in India and evaluated the role of specific risk factors. In the current study, the mean age of the beginning of PHG resulting in seeking medical attention was in late childhood and early adolescence, i.e., 10.2 ± 3.6 years, a little earlier than the reported age of onset by Bhat *et al*. and Daulatabad *et al*.[4,8] The impact of psychosocial stress stemming from PHG at a young age may become daunting for such children and adolescents. Similar to other Indian studies, we found no gender predilection for PHG.

The wide range of the duration of graying reported before seeking medical help (3 months–14 years) may be a result of the relatively benign nature of the problem or the use of henna for hair coloring at home. Indeed, a majority of the patients reported having started using henna themselves to camouflage the gray hair.

The majority of the cases noticed the first strands of gray hair in the temporal areas followed by the frontal region. A significant number of patients reported diffuse onset with no particular area mentioned as the site of onset. Even physiological graying also tends to start from the temporal region and sideburns in men and scalp margins in women. While Daulatabad *et al*. reported a reverse pattern, i.e., frontal involvement more than temporal and hypothesized that premature canities may represent an entity distinct from chronological graying,[8] the findings of our study remotely hint that PHG may indeed be an "early" variant of chronological aging itself. Indeed, in the study by Kocaman *et al*., the degree of PHG was reported to be an independent risk marker for coronary artery disease; a predictor of biological age rather than chronological age.[15] However, racial variation may be an important contributor to the different pattern reported in different studies. In a study from Korea, the parietal and occipital areas were observed to be involved first in cases with early onset of graying (onset before 40 years of age) whereas the frontal area was involved in those with late onset of graying (after 40 years).[16]

A positive family history of PHG (at least one of the biological parents or siblings) was obtained in 64 (90.1%) of the cases, of which 14 cases (21.9%) reported PHG in both the parents, and the remaining, i.e., 50 cases (78.1%) reported it in one of the parents. Further, 17 of these 64 patients (26.6%) reported infliction of at least one of their siblings with PHG. Earlier reports

have indicated a possible autosomal dominant inheritance for premature canities, though it has not been proven.[17] Although the results of our study lend further credence to the significant role of family history and genetic component of the pathogenesis of PHG, the exact mode of inheritance can only be ascertained by elaborate pedigree charting on a larger sample size. Environmental factors including increasing environmental pollution, faulty dietary habits and imbalanced diet, and stressful lifestyle may have contributed to relatively early age of the onset of premature canities, especially in genetically predisposed people.[8]

Cells of the hair follicle are rapidly dividing and proliferating, making them dependent on synthesis of DNA that in turn required sufficient supply of micronutrients especially iron, and Vitamin B12.[18,19,20] Thus, deficiency of iron and/or Vitamin B12 may have a role to play in the pathogenesis of PHG. In the current study, we found no correlation of PHG with patients' hemoglobin (for age and gender) or serum ferritin levels, a marker of body's iron stores. However, a statistically significant relation was established with deficiency of Vitamin B12; with 9 cases also demonstrating IgG antibodies to anti-parietal cells, the cells responsible for absorption of Vitamin B12; suggestive of pernicious anemia. The lack of association of serum iron has been reported in the case–control study of Fatemi Naieni *et al*. comprising of 66 cases and controls each.[21] A case of reversible generalized hyperpigmentation of the skin and nails with reversible premature gray hair due to pernicious anemia-associated Vitamin B12 deficiency has also been reported.[22] The only contradictory results have been reported by Bhat *et al*., who found a correlation of PHG with low serum ferritin levels but not with levels of Vitamin B12.[4] However, the number of patients enrolled in this study was smaller. Further, the studies by Bhat *et al*. and Fatemi Naieni *et al*. were case–control studies, whereas in the current study, we compared the patients' values against the established standard cutoffs for Indian population.[9,10,11,12]

Although thyroid disorder including thyroiditis, hypo- and hyper-thyroidism have conventionally been suggested to be associated with PHG, and screening for thyroid function has been recommended,[7] till date, robust data to support this recommendation has been lacking. The study by Daulatabad *et al*. found no association of any thyroid abnormality in their 52 self-reporting patients with premature canities.[8] The current study is the first that has found a statistical association of PHG with hypothyroidism. The limitations of our study include, lack of a control group for comparison, lack of use of an objective scale for the evaluation of the severity of premature graying, lack of few other laboratory tests such as serum iron profile, free T3 and free T4 levels, and antithyroid peroxidase antibody levels that would have added to the significance of the tests considered in this study. In addition, the study population may not be truly representative of the general population as this was a clinic-based study and records of only those cases were analyzed who sought medical care. Last but not the least, the random age cutoff of 25 years and quantitative cutoff of at least 5 gray hairs noticed before this age, had to be taken to define the inclusion criteria for our study, owing to the lack of any well-defined consensual cutoffs based on scientifically plausibility and the paucity of studies on this relatively uncharted subject.

Conclusion

The present study reveals that PHG is a significant trichological disorder in India. The onset is typically in late childhood or early adolescence, with the temporal and frontal areas being the most commonly involved sites. A strong history of PHG suggests a strong role of genetic predis-

position. Other significant associations that were observed in the study include Vitamin B12 deficiency and hypothyroidism. The role of iron deficiency and autoimmunity need further exploration. An interesting and valid query remains unanswered; if PHG seemingly stems from a single or combination of "systemic problem(s)" then why only few hairs of the total scalp containing 100,000 hairs are affected. We hypothesize that the melanogenic potential and susceptibility to environment/nutrition-induced demelanization for individual hair follicular units may be determined during the embryonic development with a tightly regulated genetic control. Thus, hairs with an embryologically-determined low melanogenic potential and/or higher susceptibility to extrinsic factor-induced demelanization may become gray earlier while others remain dark for many years despite graying of a significant proportion of hairs over time. Whether this postulate represents the survival of the fittest or the withering of the weakest remains conjectural.

Financial support and sponsorship Nil.

Conflicts of interest There are no conflicts of interest.

What is new?

- We report for the first time the statistical association of Vitamin B12 deficiency and premature graying of hair
- Thyroid dysfunction, in particular hypothyroidism has a strong association with premature graying of hair
- Screening for serum Vitamin B12 levels and thyroid functions should be undertaken in all patients presenting with premature graying of hair.

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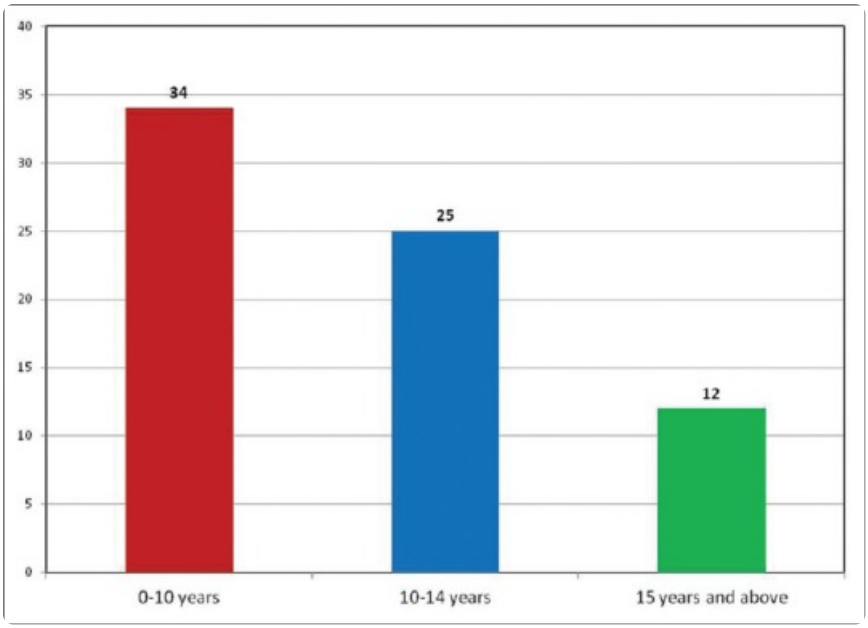
Figures and Tables

Figure 1



Age distribution of patients with premature graying of hair