Case report

Gray hair in children on triptorelin treatment

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Introduction

In humans, different hair colors are affected by two types of pigments, eumelanins and pheomelanins. Different colors of hair in different people are due to a mixture of these two different pigments.[1]

The key enzyme in melanin formation is tyrosinase. The more tyrosinase activity the more eumelanin is formed and the person has darker hair. Many factors may change eumelanin production by interacting with tyrosinase activity. Melanin is formed in the melanosome of the melanocyte. Melanocytes are found in the skin, hair follicles, and pigmented tissues of the eye. Genetic mutations affecting proteins/enzymes along this pathway inevitably result in reduced melanin production.[2]

Graying of hair or canities is usually a manifestation of aging and results from reduction in melanocyte function. There is gradual reduction in pigment in gray hairs; this loss of color is associated with deceased and eventual cessation of tyrosinase activity. In white hairs, melanocytes are infrequent or absent or possibly dormant. The age of onset of graying primarily depends on genetic background, but acquired factors may also play a role.[1,2] Melanogenic activity in the hair follicle is closely related to hair cycle. Tyrosinase activity becomes apparent in anagen 3, transferring the pigment to cortical epithelium in anagen 4 stage of development.[1]

Functional melanocytes respond to α-melanocyte-stimulating hormone or adrenocorticotropic hormone (ACTH) through MC1R receptor to stimulate melanin production. This receptor expresses the tyrosinase gene, melanocyte proliferation, and increased dendricity. Mutations in MC1R gene are associated with a switch from eumelanin (dark) to pheomelanin (red). Melanocytes are functional only during the anagen phase of hair cycle. It is possible that the full complement of melanocytes is the result of not only reactivation of dormant melanocyte but also of new cells resulting from melanocyte replication. Whiteness of hair seen in the absence of melanin is an optical effect resulting from reflection and refraction of incidence light. In general, nonpigmented hair with a broad medulla appears paler than nonmedullated hair. Perceived color is affected by the physical characteristics of the hair shaft.[1]

Some topical agents such as dithranol and resorcin may have transient effect on the color of the hair. Systemic drugs alter the hair color by changing the melanin pathway. Hydroquinone interferes with tyrosinase activity causing gray hair. A variety of phenols and cathecols can produce depigmentation in animals.[3,4] Phenol such as hydroquinone and cathecol derivatives such as epinephrine induce gray hair in rats.[2]

Gonadotropin-releasing hormone (GnRH) agonists are produced by substituting a D-amino acid in the sixth amino acid position of the natural hormone. This substitution confers a higher resistance to enzymatic degradation and higher affinity for the luteinizing hormone releasing hormone (LHRH) receptor therefore transforming them to a super-agonist. Triptorelin (decapeptyl) is made by substituting D-tryptophan in glycin at sixth position.[5] It inhibits the synthesis of luteinizing hormone (LH) by blocking the production of β-subunit of LH but not the α-subunit. This effect is a postreceptor one in contrast to other GnRH antagonists that block the receptor and decrease the production of both α- and β-subunits.[6]

It has been shown that bioactivity of LHRH is due to its pulsatile secretion, and administration of continuous doses of the hormone has an opposite effect by inhibiting follicle-stimulating hormone (FSH) and LH. Therefore, injection of

Table 1 The characteristics of 16 patients on triptorelin therapy

Patient	Age, years (months)[a]	Age, years (months)[b]	Menarche	Pubic hair growth[c]	Breast growth[c]	Initiation of graying
1	6 (9)	6 (7)	–	I	III	–
2	7	7 (5)	–	II	III	Second half of second year
3	7	6 (10)	–	II	III	–
4	7 (1)	7	–	I	III	–
5	9	9	–	III	–	Second half of second year
6	7 (2)	7 (5)	–	III	III	–
7	9	9	–	III	–	–
8	7	7 (9)	–	II	III	Second year
9	9	8	+	IV	IV	Second year
10	8	8	–	I	III	–
11	7 (9)	7 (8)	–	III	III	–
12	7 (8)	7 (8)	–	II	III	–
13	6 (8)	6 (6)	–	II	III	–
14	7 (10)	7 (9)	–	III	II	–
15	9	9	+	IV	IV	–
16	9 (9)	9 (9)	+	IV	IV	After 2 years

Side effects: (i) One case of myocarditis (patient 10), and (ii) gray hair – begins 2 years after the treatment and continued for a further 2 years during follow-up.
[a]At the onset of treatment.
[b]At referral.
[c]Sex maturity rating (SMR).

slow released GnRH agonist triptorelin has a prolonged and inhibitory effect on LH and FSH secretion after a transient initial agonist effect (flare-up).[8]

Patients and Methods

Between 2003 and 2006, 16 children with a mean age of 7.8 ± 0.94 years including 14 females and two males with final diagnosis of constitutional precocious puberty were enrolled in the study. Complete work-up to rule out other causes of precocious puberty including sonography of pelvis, testes and adrenal, bone age, and computed tomography scan and magnetic resonance imaging of brain were done in all cases. The diagnosis of precocious puberty was based on the appearance of secondary sexual characteristics at equal or less than 8 and 9 years of age in girls and boys, respectively, or the occurrence of menarche in girls before the age of 10 years.[6] Long-acting GnRH agonist triptorelin in a dose of 0.3 mg/kg intramuscularly every 28 days was prescribed for all the patients. One case of myocarditis (diagnosed by a pediatric cardiologist) and one case who had discontinued her medication were excluded from the study. No case of adrenal hyperplasia, McCune-Albright or familial male precocious puberty was found among them. Central adrenal hyperplasia was excluded by normal androgen response to ACTH test and normal adrenal sonography. The study was described for the patients and their parents, and written informed consents were taken.

Age, height, weight, growth rate, bone age, Tunner stages of puberty, and estimated adult height were determined on the first visit, and written informed consents were obtained from the patients' parents.[7] The patients were visited periodically at least four times in a year. All of them were followed up for an average of 2.5 years. In each visit, weight, height, secondary sexual characteristics including breast growth, pubic hair, occurrence of menarche, and any untoward effects of the drug were sought carefully by a physician. On the first visit and 6 months, 1, 1.5, 2 and 2.5 years later, height, weight, and secondary sexual characteristics were recorded.

Results

Sixteen patients including two boys and 14 girls with a mean age of 7.8 ± 0.94 years and final diagnosis of constitutional precocious puberty completed the study (Table 1).

Five out of 16 patients complained of gray hair, all of them about 2 years after the initiation of the treatment with triptorelin. In two of them, the graying was severe involving about 60% of the entire hair (Fig. 1). The graying of hair began at a mean 1.5 years from the beginning of treatment with triptorelin and continued in all of the patients after 2 years of close follow-up.

Discussion

Hair graying, an age-dependent process of unknown etiology, is characterized by a reduction in the number and activity of hair follicle melanocytes. Stem cell factors and its

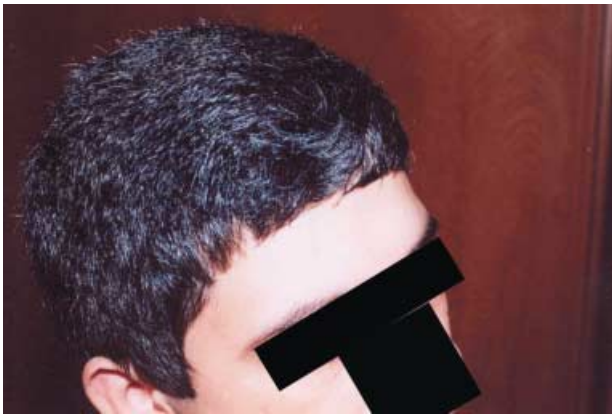

Figure 1 A 9.5-year-old boy with gray hair 1.5 years after triptorelin therapy in a dose of 0.3 mg/kg intramuscularly every 28 days

receptor c-kit are necessary for melanocyte survival during development. Mutation in this gene may result in depigmentation of the follicles. Melanin-producing melanocytes express c-kit while nonfunctioning melanocytes do not. During the hair cycle, administration of an anti-c-kit antibody decreases hair pigmentation leading to partial (gray hair) or full (white hair) depigmentation of the hairs in a reversible manner.[9]

Topical administration of monobenzylether of hydroquinone or intraperitoneal injection of phenol induces gray hair in eumelanic mice. Anti-inflammatory drug amicinoide elicited whitening of hairs in mice.[10]

Oxygen free radicals play a role in the aging process, and the protective effect of various antioxidants against skin aging has largely been studied. Superoxide dismutase plays an important role in preventing skin aging and graying of hair by inhibiting free radical-mediated skin changes. It prevents damage to the melanocytes DNA by dismutating superoxide.[10]

Robert *et al.* have noted hair depigmentation in 18 out of 28 patients with recurrent metastatic cancers treated with SU11428 (Sugen), a new tyrosinase kinase inhibitor. Depigmentation appeared after 5–6 weeks of treatment and was apparent in all body hair in a reversible manner.[11] On the contrary, Etienene *et al.* reported an opposite side-effect for tyrosinase kinase inhibitor, repigmentation of gray hairs in nine out of 133 patients on imatinib. This effect may be due to blocking of c-kit which inhibits the tyrosinase pigmentation gene promoter in the melanocyte.[12,13]

It has been shown that cysteaminylphenol is a tyrosinase substrate and a potent depigmenting agent of dark skin and black hair. Jimbow *et al.* have found that acetoxyphenyl thioethyl acetamide although was not a tyrosinase substrate, it could react with tyrosinase *in vivo* and produce marked depigmentation of dark skin after daily topical application.[14]

Triptorelin and its analogs stimulate the release of FSH and LH from the pituitary gland. It is a synthetic form of hypothalamic GnRH that stimulates the synthesis and release of FSH and, in particular, LH from the pituitary gland. Endogenous GnRH secretion is pulsatile and controlled by several factors including sex hormones. Gastrointestinal upset, sexual dysfunction, breast swelling, mood changes, dry skin, alteration in liver function, menopausal symptoms, and tumor flare are among its side-effects. No evidence on graying of hair has been yet reported.

Hair color changes result not only from alterations of melanin production but also from changes in the hair structure itself, altering its optical properties.[2]

Two separate mechanisms can be suggested to explain the ability of triptorelin to produce gray hair. The first is the effect of the drug on the enzymatic conversion of tyrosine to melanin and the other is cytological changes in melanocytes in contact with this agent. Most depigmention-inducing chemicals block the hydroxylation of tyrosine to dopa. Microscopic examination of melanocytes revealed no structural changes in gray hair of these patients, so we propose that triptorelin may have some effect on the melanin pathway to produce gray hair after prolonged prescription.

Dermatologists, pediatricians, and endocrinologists should be aware of this newly reported side-effect of triptorelin.

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