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WHAT'S YOUR DIAGNOSIS?

PEER REVIEWED

What's the Cause of This Girl's White Hair, Milky Skin, and Blue Eyes?

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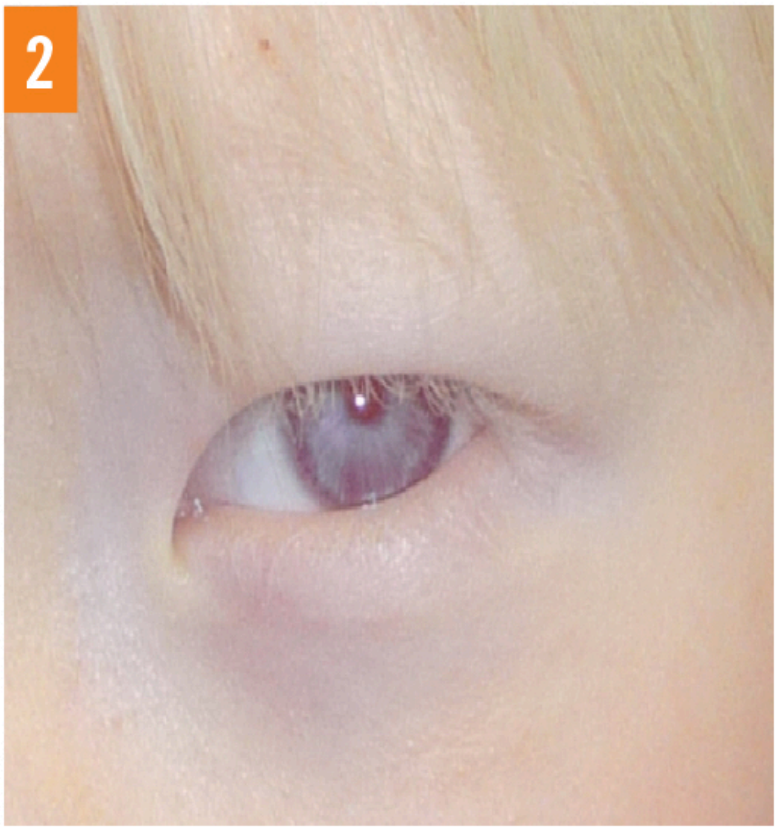
A 3-year-old Chinese girl presented with white hair (**Figure 1**), white eyelashes, white eyebrows, depigmented skin, and translucent light-blue irides (**Figure 2**), all of which had been noted at birth. The depigmentation had not improved with time.



The girl had been born to a gravida 3, para 2, 30-year-old mother at term following an uncomplicated pregnancy and vaginal delivery. The Apgar score was 7 at 1 minute and 9 at 5 minutes. Her birth weight was 2980 g and length was 49 cm. The neonatal course had been uneventful. Her developmental milestones were normal. She had prominent photophobia. The parents were first-degree cousins and were apparently in good health. Her parents, her 7-year-old brother, and her 5-year-old sister had typical Asian skin complexion, dark hair, and brown irides.

On examination, the patient's scalp hair, eyelashes, and eyebrows were white, and she had milky white skin. Ophthalmologic examination revealed reduced visual acuity, horizontal nystagmus, translucent light-blue irides, foveal hypoplasia, and retinal hypopigmentation. She had no other congenital anomalies, and the rest of the systemic physical examination findings were otherwise normal.

What’s Your Diagnosis?

A. Vitiligo

B. Waardenburg syndrome

C. Oculocutaneous albinism

D. Hypomelanosis of Ito

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Answer: Oculocutaneous Albinism

The term *albinism* is derived from the Latin word *albus*, meaning *white*, and refers to the impaired ability of an individual to produce melanin, resulting in hypopigmentation compared with others of the same racial and ethnic background.[1,2] The condition was first described scientifically by Sir Archibald Garrod in 1908.[3] Clinically, albinism is classified as either oculocutaneous albinism (OCA) or ocular albinism.[4] OCA is a group of inherited disorders of impaired melanin synthesis characterized by congenital hypopigmentation of cutaneous and ocular tissues. Seven types of OCA (numbered 1 through 7) caused by mutations in different genes involved in melanin synthesis have been described.[5,6] The clinical spectrum of OCA ranges from a generalized complete to partial loss in pigmentation of the skin, hair, and ocular tissues.[7] OCA1 is the most severe type of OCA and is characterized by milky white skin, white hair, and light blue or pink and translucent irides at birth, as illustrated in the present case.[8,9] This review focuses on OCA1.

EPIDEMIOLOGY

The overall prevalence of OCA ranges from 1 per 17,000 to 20,000 in the general population.[2,7,10-12] The estimated prevalence of OCA1 is 1 per 40,000 in the general population.[2,13] OCA1 is the most frequent type of OCA, accounting for approximately 42% of all cases, and is the most common type found in the Chinese (70%) and white (50%) populations.[7,10,14,15] The sex incidence is equal.[14]

ETIOPATHOGENESIS

Melanin is synthesized in melanocytes from the amino acid tyrosine. This process takes place in melanosomes.[16] There are 2 types of dermal melanin—pheomelanin, colored reddish yellow, and more commonly, eumelanin, colored black or brown. Eumelanin is responsible for tanning and serves a protective function against UV radiation.[1] On the other hand, free radicals are

produced when pheomelanin is exposed to UV radiation.[1] The free radicals may contribute to the development of skin cancer.[1]

In the biosynthesis of melanin, the hydroxylation of tyrosine to dihydroxyphenylalanine (DOPA) and subsequently dehydrogenation of DOPA to dopaquinone is catalyzed by tyrosinase, a copper-containing enzyme.[1,10,13,16] Dopaquinone is then converted to leucodopachrome and subsequently to dopachrome through auto-oxidation.[1] Dopachrome is then converted to 5,6-dihydroxyindole, the oxidation of which leads to indole-5,6-quinone and eumelanin.[1]

On the other hand, in the presence of glutathione or cysteine, dopaquinone is converted to cysteinyldopa. Oxidative polymerization of cysteinyldopa via 1,4-benzothiazinylalanine intermediates leads to the formation of pheomelanin.

OCA1 is an autosomal recessive disorder caused by mutations in the tyrosinase gene, *TYR*, which has been mapped to 11q14.3.[6,14] OCA1A is caused by null (frameshift, missense, and nonsense) mutations of *TYR*, resulting in lifelong absence of melanin formation.[5,8,9] OCA1B is caused by leaky mutations of *TYR*, resulting in reduced tyrosinase activity and the ability to develop some melanin pigment with time.[6,8,13]

Inability or reduced ability to synthesize melanin results in absent or reduced skin, hair, and ocular pigmentation. Melanin is also important for neural connections between the retina and the brain. Absent or reduced melanin leads to misrouting of optic nerve fibers, resulting in an excessive crossing of optic nerve fibers in the optic chiasma.[11,13,17] The chiasmatic misrouting of optic nerve fibers, in turn, results in reduced stereoscopic vision and strabismus.[1,11,13]

HISTOPATHOLOGY

Histopathologic examination of the skin or hair is usually not necessary but if performed will show a generalized absence of melanin pigment.[9]

CLINICAL MANIFESTATIONS

Patients with OCA1 have no pigmentation in their skin, hair, or eyes.[10,13,18] Affected patients are born with white scalp hair, eyelashes, and eyebrows; milky white skin; and translucent or pale light-blue irides.[10,13,18] The absence of pigmentation in the skin, hair, and eyes is permanent in patients with OCA1A.[6] Our patient's case is a classic example of OCA1A. In contrast, patients with OCA1B may develop some brown pigmentation in their skin and hair, and the translucent light-blue irides may change to green or brown over time.[6,13,17] Other features include nontanning of the skin, photophobia, decreased visual acuity, high refractive errors, astigmatism, reduced depth perception, color vision impairment, iris transillumination, poor eye contact, nystagmus (mostly pendular), strabismus (mostly esotropic), foveal hypoplasia, absence of yellow macula lutea pigment, and fundus hypopigmentation.[8,10,11,13,17,18]

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Developmental milestones are usually normal. Intelligence is not affected. Most children with OCA1 have normal neurologic development.[19]

DIAGNOSIS AND DIAGNOSTIC STUDIES

The diagnosis is mainly clinical, based on the history and physical examination findings. A hair-bulb tyrosinase assay may be performed to confirm the diagnosis.[9] In this assay, scalp hair bulbs are gently plucked from the patient and incubated with DOPA in a test tube for up to 4 hours.[9] In patients with OCA1, the hair bulbs remain white due to a lack of tyrosinase activity. On the other hand, hair bulbs from all other subtypes of OCA demonstrate some degree of pigment production.

Visual evoked potential tests may be used to demonstrate the characteristic chiasmatic misrouting of optic nerve fibers in patients with OCA.[1,13] Patients with OCA show an asymmetry of visual evoked potential between the 2 eyes secondary to chiasmatic misrouting of the optic nerve fibers.

Molecular genetic testing using polymerase chain reaction and DNA sequencing analysis may be necessary to establish the gene defect of different types of OCA due to high level of genetic heterogeneity, lack of genotype-phenotype correction, and overlap of phenotypes between the OCA types.[7,13]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of OCA1 includes other types of OCA. Milky white skin, white hair, and translucent light-blue irides at birth are virtually diagnostic of OCA1. Other types of OCA exhibit some pigmentation of the skin, hair, and ocular tissues. OCA1 should also be differentiated from syndromic OCA such as Chédiak-Higashi syndrome, Hermansky-Pudlak syndrome, and Griscelli syndrome; these syndromes have extracutaneous and extraocular features.[7,10,20] Other disorders associated with skin and hair hypopigmentation include Waardenburg syndrome, piebaldism, Prader-Willi syndrome, Angelman syndrome, Cross-McKusick-Breen syndrome, Vici syndrome, Forsius-Eriksson syndrome (Åland Island eye disease), and Tietz albinism-deafness syndrome.[6,20]

In ocular albinism, the hypopigmentation is limited to the ocular tissues without cutaneous involvement. Other differential diagnoses include hypomelanosis of Ito, vitiligo, pityriasis alba, tinea versicolor, nevus depigmentosus, tuberous sclerosis, nevus anemicus, achromic nevus, idiopathic guttate hypomelanosis, progressive macular hypomelanosis, lichen sclerosis, and postinflammatory, chemical-induced, or drug-induced hypopigmentation.[21] The distinctive features of each condition allow a relatively straightforward diagnosis to be made.

COMPLICATIONS AND PROGNOSIS

Clinical Findings and Prognosis

Persons with albinism are more commonly victims of prejudice, social rejection, bullying, and even brutal assaults, especially in developing countries.[2] The abnormal skin color, social stigma, and impaired vision may result in lower self-esteem, emotional distress, and a negative impact on quality of life.[2,11,12] Persons with OCA1 are at higher risk for sunburn, solar lentigo, freckles, elastosis, actinic keratosis, Bowen disease, and early-onset UV-induced skin cancer, notably squamous cell carcinoma, followed by basal cell carcinoma, and melanoma.[2,4,9,12,22-24] Patients with OCA1A are at lower risk of skin cancer than those with other types of OCA, because patients with OCA1A do not synthesize pheomelanin, which promotes production of reactive oxygen species. The damaging effect of reactive oxygen species on DNA is well known.[22,23]

While morbidity is significant, longevity is usually not affected except among those with skin cancer.[17]

MANAGEMENT

Currently, there is no cure or treatment for hypopigmentation in the skin, hair, or eyes in patients with OCA1. The importance of avoidance of sun exposure, regular use of broad-spectrum sunscreens, and wearing of protective wide-brimmed hats and clothing when outdoors cannot be overemphasized.[12,24] Photosensitizing agents and tanning bed use should be avoided. Periodic skin examination at 6- to 12-month intervals is recommended for early detection of skin cancer.[6] Ophthalmologic examination in the first 2 years of life at 3- to 6-month intervals and less frequently thereafter is recommended for early detection and management of refractive errors.[6] Young children may need eyeglasses, and older children may require bifocals.[11] Sunglasses may be worn when going outdoors to reduce photophobia.[11] Affected persons and their families may benefit from genetic counseling. Good public awareness about OCA is key to reducing discrimination, social stigmatization, bullying, and emotional distress.[25]

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