Oculocutaneous albinism

Oculocutaneous albinism type 2

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Summary

Oculocutaneous albinism represents a group of inherited skin disorders characterized by a generalized reduction of cutaneous, ocular, and pilar pigmentation from the time of birth. Oculocutaneous albinism types I and II are the most common, with several other types described. A defect in the melanin synthesis pathway, resulting in reduced formation of melanin, is responsible for oculocutaneous albinism. The etiology, clinical manifestations, diagnosis, and management are discussed.

Introduction

Oculocutaneous albinism (OCA) represents a group of inherited skin disorders characterized by a generalized diminution of cutaneous, ocular and pilar pigmentation from birth. Thus, their skin can vary from completely white to brown, but with reduced coloration as compared to unaffected parents or siblings. Up to ten different types of oculocutaneous albinism have been described with the type I (OCA1) and type II (OCA2) are the most common (1, 2).

Etiology

Albinism has been recognized for hundreds of years. In 1895, Kaposi distinguished common albinism from vitiligo, poliosis (partial albinism), and an unusual type of albinism (“semialbinism”). Oculocutaneous albinism type 2 is the most common type of albinism, occurring in one in 37,000 whites, one in 15,000 blacks, and one in 3000 Southern Africans of Bantu-speaking origin (3, 4). As a generalization, individuals with OCA2 have some hair pigment at birth or early in life, in contrast to individuals with OCA1, who do not have any hair pigmentation at birth. OCA2 can be associated with localized skin pigment (nevi, freckles, and lentigines), mainly in sun-exposed regions of the skin, but tanning is usually absent (5, 6). As observed with OCA1, there is a spectrum of pigmentation associated with OCA2. This type includes individuals with what was formally termed brown OCA (7, 8). Affected individuals of African ancestry with brown OCA have light brown skin and hair; blue to brown irides associated with nystagmus, and reduced visual acuity. Hypopigmentation associated with Prader-Willi syndrome and Angelman syndrome is also due to mutations of the P gene, with varying
levels of hypopigmentation (9, 10).

Mutations of the P gene, the homologue to the murine pink-eyed dilution gene (p), are associated with OCA2 (11). The OCA2 gene is divided into 24 exons spanning 250 to 600 kb that encodes a transmembrane protein of 838 amino acids, including 12 transmembrane regions, and is found integral to the melanosomal membrane. It is hypothesized that this protein is an ionic transport protein responsible for the regulation of melanosomal pH (12, 13).

Like the tyrosinase gene and OCA1, many missense, nonsense, frameshift, and splice site mutations have been reported. The most prevalent mutation of the P gene associated with OCA2 is a deletion of exon 7. This mutation is found in several regions in sub-Saharan Africa and accounts for 92% of the mutant alleles in Zimbabwe and 65% of the mutant alleles in Cameroon. The estimated carrier frequency of this deletion in blacks is one in 200 to one in 500. Unlike the tyrosinase gene, there are many polymorphic variations in the coding region that are not thought to affect the function of the protein, making identification of pathogenic mutations problematic, especially for mutations that result in amino acid substitutions (missense mutations) (14, 15).

Clinical features

At birth, OCA2 individuals may have pigmented hair, which can be white or light blond, golden blond, reddish blond or brown (Figure 1). The skin, although white in color, may appear creamy rather than milky (16). Pigmented birthmarks may also be present. With age, OCA2 albinos have an increase in pigmentation in the skin, hair, and eyes. The ethnic background of the individual may determine the ultimate phenotypic outcome (17, 18). With age, their hair may become yellow, light tan, or even red in color. Moreover, freckles and nevi eventually develop in sun-exposed areas. Particularly in African and African-American individuals, the irides may be blue or become light brown (19). The red reflex may decrease as pigment develops. Compared to OCA1, photophobia and nystagmus are usually less severe. Visual acuity is impaired in OCA2 as well. Over time, the pigmentation of the hair and eyes may make the diagnosis of albinism inapparent (20, 21).

OCA2 also includes individuals with what was formerly known as brown OCA. These individuals have brown hair, brown, hazel, or blue eyes, and light brown skin which tans (22). The skin color in affected children is lighter than their parents and unaffected siblings. For instance, a child of dark-skinned parents may have brown skin. These features have not been found in white or Asian races; perhaps because the phenotype may be less obvious (23). Decreased visual acuity and nystagmus are also present (24).

Complications

A person with oculocutaneous albinism is an illustrative example of the deleterious effects of ultraviolet light. Albinos require absolute protection from the sun due to their extreme sensitivity to ultraviolet light (25). Complications include the appearance of actinic keratoses, squamous cell carcinomas (SCC), and basal cell carcinomas (BCC) in sun exposed areas (26). Although uncommon in albinos, melanoma has been reported in both tyrosinase positive and tyrosinase negative forms of oculocutaneous albinism (27, 28). It is interesting to note that one albino patient was found to have melanoma and the dysplastic nevus syndrome (29,30).

Syndromes associated with OCA

There may be an association between oculocutaneous albinism and several multisystemic diseases. The Chédiak-Higashi syndrome is another multisystemic disorder characterized by partial oculocutaneous albinism, hematologic and neurologic abnormalities, and frequent pyogenic infections. Cutaneous findings include blond to dark brown hair, with a metallic tint that is accentuated in light. Hypopigmentation in this disorder is due to abnormal melanocytes, not defective tyrosinase. Giant melanosomes present within the melanocytes cause a dilution of pigmentation, producing hypopigmentation of the skin, hair, and ocular fundi (31).

The Hermansky-Pudlak syndrome (HPS) is a type of oculocutaneous albinism associated with ceroid-like pigment accumulation within the reticuloendothelial system and a platelet storage pool deficiency resulting in a bleeding diathesis (32, 33). Albinism in HPS is characterized as tyrosinase-positive, and is usually found in persons of Puerto Rican descent (34). Cutaneous manifestations include varying degrees of hypopigmentation since pigmentation may increase with age, as well as hair that may develop a light brown to red color. Problems with bleeding are usually less severe compared to those with clotting defects. Bleeding in people with HPS often manifests as episodes of epistaxis, gingival bleeding, or bleeding secondary to surgical procedures such as tooth extractions. The lungs and the gastrointestinal system are affected by the accumulation of ceroid material, leading to pulmonary fibrosis and granulomatous colitis. The gene responsible for HPS is located on chromosome 10q23, and could play an important role in organelle-membrane function related to calcium ATPase activity or calcium channel integrity (35).

The Prader-Willi (PWS) and Angelman (AS) syndromes have a 1 percent incidence of OCA2 associated with these conditions. PWS is a developmental disorder characterized by neonatal hypotonia, hyperphagia and obesity, small hands and feet, hypogonadism, and

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mental retardation. Although the majority of PWS patients do not have OCA2, approximately fifty percent are hypopigmented. Angelman syndrome is a developmental condition characterized by neonatal hypotonia, developmental delay, microcephaly, severe mental retardation, ataxic movements, and inappropriate laughter. Hypopigmentation is also generally noted in many of these individuals, but the percentage of people demonstrating this characteristic is unknown (36). Both syndromes are due to a microdeletion on chromosome 15q11-13, the same region involved in OCA2. This high incidence may be attributed to microdeletions that cause hemizygosity for inherited mutant alleles of the P gene (37).

Diagnosis

Several methods are available for prenatal and postnatal diagnosis of oculocutaneous albinism. Prenatal diagnosis may be made by the acquisition of fetal cells by amniocentesis, followed by the analysis of fetal genomic tyrosinase by allele-specific hybridization and PCR amplification of the mutated gene. Prenatal diagnosis of OCA can also be made at twenty weeks’ gestation by electron microscopic examination of fetal skin biopsies (38). However, fetal cell analysis by amniocentesis may be superior to fetal skin biopsies, because it is a less invasive procedure that can be performed as early as fourteen weeks’ gestation (39).

Postnatal diagnosis is largely based on clinical and ocular examination. Incubating hair bulbs to determine tyrosinase activity formerly supported the diagnosis (40). However, recent progress in linear PCR and automated fluorescent DNA sequencing allow for rapid determination of specific tyrosinase mutations. One study was able to determine the entire nucleotide sequence of a protein-coding region of the tyrosinase gene from only 25 uL of blood from a given patient. Future advances in technology will permit the everyday use of various types of DNA testing in the physician’s office (41).

Histopathology

Histologic examination shows marked orthokeratosis. The epidermis is of normal thickness. The dermo-epidermal junction is flattened in some parts, while in others the rete pegs are retained or even elongated. The number of melanocytes is normal. Rows of consecutive pigmented cells are present in the basal layer. They varied in number from 20 to 50 and alternated with rows of unpigmented cells (Figure 2). The pigment is usually more prominent in the basal cells of the rete pegs than in those of the flattened epidermis. The basement membranes of both the epidermis and the vessels are thickened. The capillaries are dilated. The collagen in the dermis showed fragmentation and solar elastosis, with fine elastotic fibers in the upper and mid-dermis and thick fibers in the deeper dermis (41). In OCA-2 melanosomes contain melanin, representing stage III and IV macromelanosomes (42).

Therapy

No treatment exists for albinism at the present time. Rather, management must emphasize the importance of photoprotection to minimize the risk of cutaneous cancers. Affected individuals should be advised to diligently use UVA and UVB topical sunscreens. Clothing such as long sleeved shirts, long pants, and large-bri-
mmed hats that would cover or shade commonly sun-exposed areas are tremendously important. Patients with photophobia may benefit from the use of sunglasses. It must also be stressed that albinos be examined yearly by their physician for the development of precancerous and cancerous skin lesions. Ensuring that albinos be allowed to receive the full benefits of a strong education should also be an important focus of management. The albino may be faced with several physical and psychological obstacles, due to ocular defects and lack of awareness and resources in some societies. Glasses may improve vision by correcting for refractive error and magnifiers may be beneficial as well (43). Efforts should also be made to provide large print textbooks and seating in the front of the classroom. Furthermore, support groups and self-help groups may be provided for albinos in some areas. Most importantly, worldwide awareness and tolerance of albinism are absolutely necessary for the integration of albinos into society (44).

REFERENCES


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