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Albinism

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Introduction

Albinism, from the Latin *albus*, meaning "white," is a group of heritable conditions associated with decreased or absent melanin in ectoderm-derived tissues (most notably the skin, hair, and eyes), yielding a characteristic pallor. The most commonly thought of presentation is that of oculocutaneous albinism (OCA). OCA is a group of phenotypically similar genetic disorders derived from errors in melanin synthesis. As the name implies, the most dramatic effects are in the eyes and skin. The skin manifestations are more heterogeneous and appear along with a spectrum of severity depending upon the subtype of OCA. The ocular structures rely upon melanin for signaling as they develop, in utero; thus, misrouted optic nerve fibers yield more uniform ocular manifestations of the disorder.[1][2][3]

To date, seven types of nonsyndromic albinism (OCA1 to OCA7) have been described. These are all due to isolated genetic mutations whose constellation of signs and symptoms do not manifest so broadly that they can be classified as syndromic. A discussion on albinism, however, would be incomplete without the mention of isolated ocular albinism (OA1) and the syndromic albinisms: Hermansky-Pudlak syndrome (HPS) and Chediak-Higashi syndrome (CHS). The syndromic albinisms have the same hallmark lack of dermal and ocular pigment as OCA. They, however, involve genes that encode for proteins that have more extensive applications to cellular function. Loss-of-function mutations in these genes, therefore, yield predictable systemic consequences associated with the syndromes mentioned. Examples include inactivation of genes involved in lysosomal synthesis (and not simply melanin synthesis) that lead to bleeding diathesis in HPS and propinquity to infection in CHS. Other conditions may present like albinism with congenital nystagmus and/or generalized hypopigmentation. Most of these are included in the Differential Diagnosis section. Of special mention is a pair of syndromes that derive their albino-like features because of deletions in the same genes that are mutated in OCA type 2: Angelman (AS) and Prader-Willi (PWS) syndromes.[4][5][6]

Etiology

Albinism, in any of its forms, is the result of heritable mutations that lead to defective melanocytes, unable to properly synthesize melanin or distribute it through dermal tissues. The exact number of melanocytes in the skin are preserved, unlike conditions such as piebaldism and vitiligo, where melanocytes are absent. The specific gene mutations causing each form or albinism are mentioned below in the "History and Physical" section.

Epidemiology

Occurrence is estimated at 1:17,000 to 1:20,000 overall. Approximately one in 70 individuals carry an OCA-mutated allele, with the OCA2 mutation being the most common worldwide. OCA2 is common in sub-Saharan Africa since cultural norms permit consanguineous marriages, allowing prevalence reach 1 in 1000 and a phenomenon called pseudo-dominance where the recessive allele burden is so high in a given family, that the recessive trait is disproportionately represented. The prevalence of individual forms of albinism are included below:

- OCA1: Prevalence is 1 in 40,000 worldwide but one of the most common forms in America and China (70% of cases)
- OCA2: The most common worldwide (1:39,000). Prevalence as follows: African Americans (1:10,000), overall Americans (1:36,000), Sub-Saharan Africa (1:3,900)

- OCA3: Prevalence is 1: 8500 of African individuals primarily in southern Africa. It can also be seen in Pakistani, German, Indian, and Japanese populations.
- OCA4: Prevalence is 1:100,000 but accounts for 24% of Japanese OCA. It is also described in German, Turkish, Indian, Korean, Chinese, Danish, and Moroccan, populations.
- OCA5: Very rare, only mentioned in a case report of a Pakistani family
- OCA6: Very rare, case reports in a Chinese family and a man from eastern India
- OCA7: Very rare, consanguineous Faroese family
- Hermansky-Pudlak syndrome (HPS): Prevalence is 1:500,000 worldwide but 1:1800 in Puerto Rico
- Chediak-Higashi syndrome (CHS): Very rare (less than 500 cases published in the past 20 years)
- Angelman syndrome (AS) and Prader-Willi syndrome (PWS): Prevalence of AS (1:12,000 to 20,000) and PWS (1:15,000) are higher than the OCAs. However, only approximately 1% of AS and PWS sufferers have contiguous gene deletions that lead to OCA2-like presentation
- Ocular albinism (OA1): Prevalence is 1:50,000

Pathophysiology

Melanocytes are derived from neural crest ectoderm during embryonic development and migrate into the skin, eyes, hair, and inner ear. They represent about 5% to 10% of the cell population in the epidermal basal layer, and this number remains unaffected in albinism. Melanocytes contain specialized melanin-producing organelles (melanosomes) that usually develop by week seven embryonically. The only other tissue capable of synthesizing melanin are retinal pigment epithelium, and it is not of neural crest origin. Melanin is most known for its role in ultraviolet (UV) protection, but it also has roles in both embryologic development of the ocular structures and oculoneural pathways. The two most common forms of melanin are eumelanin and pheomelanin. Eumelanin imbues skin with black or brown coloration and plays a role in protecting the skin against ultraviolet radiation B (UVB) damage by absorbing and dissipating the rays and their carcinogenic DNA cross-linking effects. Pheomelanin is not UV protective, and people who predominantly have pheomelanin are Fitzpatrick scale 1, with red or blond hair and light-colored, ruddy skin. The synthesis of eumelanin over pheomelanin is stimulated by activation of melanocortin one receptors (coded by the *MC1R* gene) on melanocytes.[7]

The first (and rate-limiting) step in eumelanin synthesis involves the oxidation of L-tyrosine to DOPA by tyrosinase. Mutations in the tyrosinase gene, as seen in OCA1A, leads to complete loss of the ability to produce eumelanin. The loss-of-function mutations in any type of OCA, however, impair eumelanin synthesis directly or affect melanosome maturation but may leave pheomelanin levels unaffected. Most of the non-OCA1A pigmentation that accounts for the varied phenotypes is pheomelanin, which imbues the skin, hair, and iris with color. Syndromic albinism does not always affect melanin synthesis so much as it does the production or distribution of melanosomes through the basal layer into keratinocytes from melanocytes.

The two significant results of hypomelanosis can be divided into dermatological and ophthalmologic consequences. Since eumelanin is photo-protective, albinism leads to increased risk of sun-damage (solar lentigines, actinic keratoses, solar erythema) and UV-associated malignancies (especially squamous cell carcinomas). Melanin acts as an inducer and organizer of formation of the fovea, optic nerves, optic tracts, and visual cortex, in utero. In albinism, the fovea fails to develop as robustly as normal and is hypoplastic or even absent. Melanin in utero cues the migration of developing optic nerve fibers. Some crossover of nerve fibers from each eye at the optic chiasm to the contralateral occipital lobe is necessary for binocular vision. In albinism, however, some axons that originate in the retinal ganglion cells project mistakenly to the contralateral hemisphere dorsal lateral geniculate nucleus. This means an increase in optic fiber crossover. Nerve fibers misrouted from the organ or reception (the eye) to the organ of perception (the brain) further contributes to binocular vision deficits, manifesting as strabismus. The occipital lobe in albinism also shows decreased gyrification (theorized to be due to a dearth of foveal input), and localized increases in cortical thickness. The latter finding has also been found in congenitally blind subjects. In summary, complete absence or even partial melanin deficiency in utero leads to ocular structure malformation and optic tract misrouting and creates a multitude of irreversible intraocular (refractive) and extraocular (oculomotor or nonrefractive) problems. Visual acuity

usually ranges from 20/60 to 20/400.

The genetic aberrations specific to each form of OCA, syndromic albinisms, and selected albinism-associated disorders are included below:

- OCA1: Autosomal recessive. The *TYR* gene product tyrosinase normally hydroxylates L-tyrosine to L-DOPA and oxidates L-DOPA to DOPAquinone. This serves as the rate-limiting/ step in melanin synthesis. Loss of this function leads to an inability to synthesize melanin.
- OCA2: Autosomal recessive. The *OCA2* gene product is the OCA2 melanosome transmembrane protein P, with unknown function.
- OCA3: Autosomal recessive. The *TYRP1* gene product is tyrosinase-related protein 1, which is thought to stabilize and modulate the activity of tyrosinase and contribute to melanosome integrity
- OCA4: Autosomal recessive. The *SLC45A2* gene codes for a solute carrier family 45, member 2 membrane-associated transport protein (MATP) that is thought to transport substances required for melanin biosynthesis into the melanosome.
- OCA5: Autosomal recessive. Gene not yet identified.
- OCA6: Autosomal recessive. The *SLC24A5* gene (solute carrier family 24, member 5) codes for a Na/K/Ca cation exchange protein with a similar structure to that seen in OCA4. Its function is also thought to be similar.
- OCA7: Autosomal recessive. The *LRMDA* gene (leucine-rich melanocyte differentiation associated protein) codes for a protein thought to play a role in melanocyte differentiation.
- Hermansky-Pudlak syndrome (HPS): Autosomal recessive. Ten different genotypes have been identified, thus far. The genes corresponding to the subtype of HPS. *HPS1* gene (HPS1), *AP3B1* gene (HPS2), *HPS3* gene (HPS3), *HPS4* gene (HPS4), *HPS5* gene (HPS5), *HPS6* gene (HPS6), *DTNBP1* gene (HPS7), *BLOC1S3* gene (HPS8), *BLOC1S6* gene (PLDN), *AP3D1* gene (HPS10). Not all subtypes of the syndrome are identical, but similarities exist. Subjects have oculocutaneous albinism, accumulation of a wax-like fat-protein compound (ceroid lipofuscin) in tissues, especially kidneys and lungs, and bleeding diathesis due to a lack of dense platelet granules leading to abnormal aggregation. Some forms have immunodeficiency (neutropenia) and a hemophagocytic syndrome with AP gene involvement (HPS2, HPS10) due to lysosomal dysfunction. The most severe forms (HPS1, HPS4) are both BLOC-3 protein mutations and associated with pulmonary fibrosis by the thirties and granulomatous colitis.
- Chediak-Higashi syndrome (CHS): Autosomal recessive. The *LYST* gene codes for a protein that directs delivery of material into lysosomes. Mutations lead to giant cytoplasmic granules (lysosomes) with diminished chemotaxis in leukocytes and platelets. This causes the characteristic increased susceptibility to pyogenic infections, neutropenia, peripheral neuropathy, mild coagulopathy, and hypomelanosis.
- Angelman syndrome (AS) and Prader-Willi syndrome (PWS): Both due to spontaneous (not inherited) partial deletions of chromosome 15q. Albinism occurs because the OCA2 allele located on one Chromosome 15q, making subjects haploinsufficient for *OCA2* gene product, protein P. The complete mechanism by which this happens is unexplained since heterozygotes for *OCA2* gene mutations producing one nonfunctional copy of protein P still are phenotypically normal. AS is the result of deletion on maternal chromosome 15q or uniparental disomy of chromosome 15 with both copies being of paternal origin. PWS is due to the deletion of paternal chromosome 15q or through uniparental disomy of chromosome 15 with both copies being of maternal origin.
- Ocular albinism (OA1): X-linked. The *GPR143* gene product is a G-protein coupled receptor, a mutation in which yields dysfunctional melanosome biogenesis with resultant "macromelanosomes."

Histopathology

Hematoxylin and eosin staining does not reveal any defects in the skin. Melanin staining and melanocyte-special stains (dopa oxidase or HMB45) will be slight to moderately positive since pheomelanin and melanocytes are still present in the skin. Tissues pathology is rarely done outside of evaluation for dermal malignancies, as it is not

necessary to confirm the diagnosis.

History and Physical

Cutaneous findings vary widely, but the most dramatic features occur in OCA1A due to complete lack of melanin. The white hair, white eyelashes, white skin, and pink eyes are typical of what the general populations consider an albino. Some darkening over time from shampoos and water minerals may occur but spares the eyelashes and eyebrows. Every other form of albinism has some residual pigmentation that can increase with time, mostly through pheomelanin. For this reason, comparison with family members may be vital in raising the clinical suspicion of albinism, especially if ocular manifestations are mild. Relative hypopigmentation in Caucasian families is more difficult to appreciate than in families with more pigment.

Ocular findings are the more debilitating clinical feature due to its effect on vision; they can be divided into refractive and nonrefractive errors.

- Photophobia (light sensitivity or the perception of light as brighter than it is) or photodysphoria (discomfort in bright light or extreme photophobia)
- Refractive errors (astigmatism 73%, myopia 24%, hyperopia 3% frequency by one study)
- Foveal hypoplasia on dilated eye exam (lack of foveal reflex)
- Involuntary pulsatile horizontal nystagmus: Usually beginning 1.5 to two months after birth when visual acuity starts to sharpen; almost all children develop it by 4 months of age; gradually diminishes in amplitude with age. Postural head changes (such as side gazing) and convergence (like when looking at things very close to the face) damps the nystagmus, and these compensatory maneuvers improve vision and may be some of the earliest indicators of visual deficits. Nystagmus is exacerbated with fatigue, physiological (illness, pain) or psychic stress (anger, anxiety), and monocular vision (covering one eye).
- Strabismus: Misaligned eyes or disconjugate gaze due to misrouted optic nerve fibers at the chiasm, for example, exotropia, esotropia, vertical misalignment
- Reduced stereopsis (fine depth perception) and binocular vision due to strabismus
- Reduced iris pigmentation (variable from pink, to light blue, green, gray, or light brown)
- Iris transillumination (“pink irides” with spoke wheel appearance) in ambient light or on slit lamp examination as light reflects off the retina and back through the iris
- Yellow or orange retina due to hypomelanosis of retinal epithelium, it loses its normal red appearance and has prominent choroidal vessels
- Selective visual evoked potential (VEP) confirm that retinostriate nerve fibers have excessively crossed as they have been misrouted to the occiput at the optic chiasm. Regular VEP will not demonstrate this; only the selective VEP, however, this is usually not necessary since strabismus implies misrouted optic nerve. Normal optic nerve routing, as demonstrated on a selective VEP, rule out OCA.

The most common phenotypes of each of the forms of albinism, including visual deficit ranges, are included below:

- OCA1
    - Type A has a complete absence of melanin. Subjects have white skin and white hair. Irides are light colored, pink or red (in ambient light) with (+) nystagmus, (+) foveal hypoplasia, (+) iris transillumination, and (+) photophobia. Visual acuity 20/100 to 20/400
    - Type B (aka, “yellow OCA”) has some residual TYR function. Subjects are initially identical to type A, but by age 3 will show some melanization of skin (cream to tan with light nevi and freckles) and hair (from yellow to light brown). Irides are blue, green, hazel, or light brown. Visual acuity ranges from 20/100 to 20/200.
- OCA2

  - Classic OCA2: Skin is creamy white (not stark white like in OCA1) or tan skin, frequently with nevi and freckles. Hair, eyebrows, and eyelashes are yellow, blond, or light brown. Irides are blue, hazel, brown or gray. Visual acuity ranges from 20/25 to 20/200, usually 20/60 to 20/100.
  - Brown OCA2: Subjects appear normal with brown skin, hair, and eyes, but are relatively hypopigmented compared to family members
  - Red OCA2: This variant occurs with a concomitant *MC1R* gene mutation. Subjects have light-colored eyes and vision problems; however, they typically have red hair.
- OCA3: This condition, however, mostly affects dark-skinned individuals where it may be brown or "rufous" OCA. The latter is characterized by reddish brown (copper) skin, red or reddish yellow (ginger) hair, hazel or light brown irides, and sometimes undetectable visual impairment.
- OCA4: Similar to classic OCA2 because of pheomelanin predominance. Skin is cream colored to tan to normal. Hair is never stark white; it may be silvery white to light blond to yellow to very light brown. Skin and hair color are usually correlated. Irides are blue, hazel to light brown. Visual acuity ranges from 20/30 to 20/400; usually 20/100 to 20/200.
- OCA5: Subjects have white skin and golden hair. (+) nystagmus, (+) foveal hypoplasia, (+) photophobia, (+) impaired visual acuity
- OCA6: Similar to OCA4 because of similar gene product function. Subjects have white skin and light hair that darkens with age. Irides are brown with (+) mild nystagmus, (+) foveal hypoplasia, (+) mild photophobia. Visual acuity is 20/100.
- OCA7: Skin coloration is lighter only when compared to relatives. Hair is light blond to dark brown. (+) Nystagmus, (+) foveal hypoplasia, (+) iris transillumination. Visual acuity ranges from 20/30 to 20/400.
- Hermansky-Pudlak syndrome (HPS): Subjects have white to olive skin. Hair is white to brown. Irides are hypopigmented with (+) nystagmus, (+) foveal hypoplasia, and (+) iris transillumination. Visual acuity ranges from 20/50 to 20/400. Subjects also have mild to moderate bleeding due to platelet dysfunction and some lung or kidney abnormalities due to ceroid deposition. Two subtypes have immunodeficiency (with recurrent infections) and hemophagocytic syndrome. Other types develop pulmonary fibrosis by the thirties and granulomatous colitis.
- Chediak-Higashi syndrome (CHS): Subjects have partial OCA (hypopigmented skin, gray or silver-sheen hair, nystagmus, foveal hypoplasia, photophobia). All subjects exhibit increased susceptibility to pyogenic infections, neutropenia, peripheral neuropathy, mild coagulopathy.
- Angelman syndrome (AS) and Prader-Willi syndrome (PWS): Subjects have hypopigmented skin and hair relative to other family members. Ocular features (nystagmus, foveal hypoplasia) are usually absent or mild but, when present, are associated with the OCA2 pathogenic variant on the non-deleted chromosome.
  - AS: characteristic facies, short stature, mental retardation, spastic gait, stiff arm movements, an inappropriate outburst of laughter
  - PWS: poor muscle tone, short stature, small hands and feet, mental retardation, hyperphagia resulting in obesity and type 2 diabetes
- Ocular albinism (OA1): Hypopigmentation is limited to the eye, with perhaps slightly paler skin and eyes only when compared to other family members. (+) nystagmus, (+) foveal hypoplasia, (+) photophobia. Visual acuity ranges from 20/100 to 20/200. Females rarely have some nystagmus and low vision. Because 90% of female carriers have X-inactivation, they possess pigmentary mosaicism in the retina, which helps to make the diagnosis in the affected male children and distinguish OA1 from OCA2 in lighter skinned families.

Evaluation

Early diagnosis is most important to manage ocular symptoms and maximize visual potential, which has further ramifications on general safety and wellbeing, education, self-esteem, and cognitive development. Family and

providers are not always alerted by hypopigmentation of skin, hair, and eyelashes, except in the context of family members who are constitutionally darker pigmented and the contrast is more striking. Iris hypopigmentation may be overlooked initially as it is not uncommon in infants for iridic melanin deposits to take six to nine months to reach adult coloration. Ocular manifestations usually grip the attention of caregivers or physicians within the first 3 to 6 months of life. Pediatricians often suspect OCA at the 2 or 4-month well-baby check. While patchy congenital hypopigmentation may lead clinicians to investigate piebaldism or Waardenburg syndrome, generalized hypopigmentation with nystagmus and normal hearing is sufficient to pursue an evaluation for albinism, be it OCA or one of the syndromic forms.

Special attention needs to be given to associated symptoms (recurrent infections in CHD, bleeding in HPS, and mental retardation in Cross syndrome, Angelman syndrome, or Prader-Willi) so that a diagnosis of syndromic albinism is not missed.

Ophthalmology can help confirm the diagnosis with testing. Characteristic ocular changes (infantile nystagmus, photophobia, reduced iris pigment with transillumination, reduced retinal pigment, visualization of choroidal blood vessels on a fundoscopic exam, foveal hypoplasia, decreased visual acuity, strabismus, misrouting of optic nerves on selective VEP exam) combined with cutaneous hypopigmentation.

Generalized congenital hypopigmentation with normal ocular motion or normal ophthalmic examination is not OCA, and an assessment for nutritional or metabolic disorders should ensue. These include phenylketonuria, homocystinuria, histidinemia, Menkes syndrome (copper deficiency), and kwashiorkor. If the patient has impaired hearing, Tietz syndrome should be considered.

Molecular genetic testing can confirm the diagnosis but is not routinely done. It is expensive and best done using multigene or comprehensive genome sequencing. Clinical diagnosis, especially incorporating a complete ophthalmologic exam, is sufficient. An exception is to distinguish OCA1A and OCA1B in infancy, as they can be phenotypically identical during the first year of life. If patients develop some pigmentation after the first year of life, genetic testing may be useful to distinguish OCA1B from clinically similar OCA2.

Carriers are asymptomatic heterozygotes of autosomal recessive genes. Carrier testing makes sense in child-bearing age family members of albino patients but requires the pathogenic variant in the family to be already identified, thus necessitating gene sequencing of the albino, themselves.

Prenatal diagnosis or preimplantation genetic diagnosis can similarly be made if the pathogenic variant is already identified.

No specific serological tests or imaging needs to be performed in the diagnosis or routine management of albinism.

Treatment / Management

Management of Dermal Manifestations

There is no substitute for lifelong sun protection in albinism, and the importance cannot be overestimated. Subjects should be educated on avoidance of prolonged UV light exposure (sun, tanning beds) and avoidance of medications that increase photosensitivity. Any outdoor activities, no matter how brief, should be preceded by the application of sunscreen (SPF 30+) with liberal and frequent reapplication (every 2 hours) when in the sun. No good studies support the use of high SPF, but some resources recommend SPF 50 or higher. Additional protection can be enlisted with the use of protective clothing and eyewear (hats, UPF-labeled clothing, long-sleeves, long pants, collared shirts, socks, UV protective sunglasses). Photophobia can be managed with dark lensed glasses, but because of the resultant vision reduction, some patients opt for brimmed hats. Self-examination and self-education on melanoma ABCDE criteria, prompt referral to dermatology for any suspicious or changing lesions, such as (1) new lesions in sun-exposed areas, (2) painful, itching, bleeding, nonhealing, changing lesions, or (3) asymmetrical, irregularly bordered, variably colored, diameter greater than 6 mm, evolving lesions. Lifelong, periodic skin examinations (once to twice per year) with dermatology for early detection and treatment of skin cancers. Referrals to pediatric dermatology should be early to illuminate the benefit and decode the terminology of sun-protective options. Surveillance should start at adolescence, as skin cancer may appear as early as the teenage years. Special attention from providers to changes in pink and red lesion, since most melanoma in OCA is amelanotic melanoma.[8]

Management of Eye Abnormalities

Nystagmus naturally decreases over time. Additionally, individuals enact learn to adjust head posture to time the gaze position the yields the lowest nystagmic amplitude. This position is called the nystagmus null point. Eye muscle surgery can improve ocular alignment, improve head posture, and improve vision only in severe cases, but surgery may need to be repeated several times. Unless strabismus is severe, it is usually not necessary unless it is pursued for cosmetic reasons. Ophthalmic evaluation for optical correction 2 to 4 times per year (age 1 and 2), 1 to 3 times per year (age 3 to 6), annually (age 5 to 18), then every 2 to 3 years (adults). Refractive errors require treatment with corrective lenses, preferably by 4 to 6 months of age with frequent changes in prescriptions in the first years of life. Even with refractive correction, vision may never fully normalize because of irreversible foveal hypoplasia. Lenses that darken in sunlight help with photophobia but decrease vision. Lenses should have UV protection. Bifocals and low-vision aids may also be considered in older children and adults. Teaching aids and special classroom considerations (high contrast reading material, large print texts and worksheets, close-to-board seating, magnification settings on computers, among others) can help overcome the educational delays associated with visual deficits.

Management of the Inheritable Nature of the Condition

Genetics consultation before childbearing years is beneficial to parents of albino children considering future offspring, the patient with albinism and their siblings. Albinism is an obligate homozygote condition with a 100% chance of passing on their defective gene. Coordinated genetic testing of the nonaffected partner is possible if the pathogenic variant is known. This will confirm the offspring have the potential to inherit the condition, if the partner is a carrier of the same pathogenic variant, or just be obligate carriers if the partner has only wild-type genes. A couple who has already had an albino child has a 25% chance of having another child with albinism, a 50% chance of producing carrier offspring, and 25% of producing non-carrier offspring. This is assuming that one of the parents is not albino, in which case the chance of producing a second albino offspring is 50% after a confirmed albino offspring. The fact than non-albino siblings have a 67% chance of being carriers is important to convey before they consider childbearing. Of note, if two parents carry genes for different types of albinism (for example, a patient with OCA2 and a carrier for OCA1), no children will be born with albinism, but the children are at risk for being heterozygous for both mutant alleles.

Direct Therapeutic Modalities

Nitisinone triggers tyrosine accumulation in blood and mouse models have suggested that it could improve pigmentation in OCA1B subjects, but a clinical trial is currently underway. Aminoglycosides are a potential and unconfirmed therapy. Despite anecdotal reports, L-DOPA did not result in any improvement in visual acuity in a study of 45 patients. Adeno-associated viruses (AAV) vectors is a potential gene therapy introducing a functional copy of the tyrosinase gene in OCA1 and OA1 patients.

Differential Diagnosis

Based upon similar ocular findings (early onset nystagmus):

- OCA syndromes
- Ocular albinism
- Optic nerve atrophy and hypoplasia: The condition of broad etiology resulting in decreased visual acuity, nystagmus, and optic nerve atrophy, optic disc pallor
- Inherited retinal dystrophy: A family of disorders of variable heritance patterns (autosomal dominant, X-linked, recessive) and broad phenotypes that included congenital nystagmus and decreased visual acuity
- FRMD7-related infantile nystagmus syndrome (also known as congenital motor nystagmus, congenital infantile nystagmus): An X-linked disorder with nystagmus and reduced visual acuity with normal VEPs
- Aniridia: The absence of the iris, which demonstrates foveal hypoplasia, nystagmus, amblyopia, and cataracts
- Aland Island eye disease (Forsius-Eriksson syndrome): An X-linked disorder with fundal hypopigmentation, foveal hypoplasia, myopia, nystagmus, astigmatism, night blindness

- Cross-McKusick-Breen syndrome: An autosomal recessive disorder with hypopigmentation of skin, silvery gray hair, microphthalmia, corneal opacification, nystagmus, with or without mental retardation, athetosis, ataxia, joint contractures, and spastic tetraplegia
- Achromatopsia: An autosomal recessive disorder causing dysfunctional cone cells in the retina, resulting in partial or complete loss of color vision with associated photophobia, nystagmus, low visual acuity, and hyperopia.

Based on hair and cutaneous finding (hypopigmentation):

- OCA syndromes
- Hermansky-Pudlak syndrome
- Chediak-Higashi syndrome
- Angelman syndrome and Prader-Willi syndrome
- Vici syndrome: An autosomal recessive disorder with absent corpus callosum; subjects present with hair and skin hypopigmentation, findings similar to OA1, microcephaly, immunodeficiency, cardiac abnormalities, failure to thrive, cataracts, cleft lip and palate, and neurologic abnormalities
- Waardenburg syndrome type II: Autosomal dominant MITF gene mutation presenting with patchy skin hypopigmentation, white forelock or prematurely gray hair, iris heterochromia, sensorineural hearing loss
- Tietz albinism-deafness syndrome: Autosomal dominant *MITF* gene mutation presenting with white eyebrows and eyelashes, iris hypopigmentation, normal visual acuity, and sensorineural hearing loss
- Griscelli syndrome: Autosomal recessive defects in myosin, myosin receptors, and binding; melanocytes fail to transfer melanosomes to dendrites and peripheral keratinocytes leading to diluted skin/hair color; present with hypopigmentation, melanin aggregation in silvery-gray hair, immunodeficiency, decreased visual acuity with roving eye movements, pancytopenia, hemophagocytic syndrome, and cerebral demyelination

Prognosis

Life expectancy within the non-syndromic OCA population is comparable to the general population. There is an increased mortality risk due to skin cancer. This risk changes based on the amount of relative sun exposure in a geographic area and certain socioeconomic issues. These socioeconomic issues include limited access to sunscreen, limited education on sun-protective measures, cultural differences in dress, limited access to healthcare professionals for surveillance leading to late presentation and late treatment, inability to comply with or complete treatment courses. In these same lower socioeconomic regions, there is often a palpable stigma associated with albinism, and the afflicted may be victims of persecution, prejudice, and violence. Some albinos have even been murdered as their organs are highly valued on the black market. Albinos have normal intelligence compared with the general population. There is some delayed visual maturation, and this can lead to educational delay if not addressed early enough. Furthermore, poor self-image and social alienation can lead to feelings of isolation and depression. Albinos do have an increased rate of attention deficit disorder.

Complications

Visual deficits can lead to the following:

- Limited work opportunities where a minimum visual acuity is required
- Difficulty in reading due to uncorrected visual deficits that may lead to educational delays
- Inability to obtain driver’s license due to visual impairment

Infection risk in Chediak-Higashi syndrome

Bleeding Diathesis in Hermansky-Pudlak syndrome

Solar damage: Pachydermia (coarse, rough, thick skin), actinic keratoses, solar lentigines (in non-OCA1A albinos),

solar erythema

Malignancy: Basal and squamous cell carcinomas (BCC, SCC). SCC is by far the most common malignancy reported among albinos (representing more than 75% of cases of malignancy), developing as early as the teens. One study found that more than 70% of them were diagnosed on the head and neck areas. Another study found the head, face, and hands equally affected at approximately 20% each. Albinism increases the relative risk of SCC as much as 1000 times, at least in the African population. Cumulative sun exposure is the major risk factor, with the incidence of cancers increasing with patient age. BCC account for about 24% of malignancies, with the remaining 1% being melanoma. Melanomas are rare in albinos with only a few case reports in the literature, despite melanocytes still being present in the skin in the same relative number. Surprisingly, melanomas often occur in non-exposed areas, which speaks against UV-radiation being the culprit. Practitioners need to have a high level of suspicion since these lesions are both rare and tend to be amelanotic in albinos.

Consultations

Early consultation to ophthalmology and dermatology, as mentioned above. Family referral to geneticist may be beneficial.

Pearls and Other Issues

- Melanocytes number and distribution is preserved in the skin in patients with OCA, making melanoma a possible, albeit rare, a complication of albinism.
- Albinism has a broad range of presentations, and sometimes, hypomelanosis can only be considered in relation to the average pigmentation of other family members. When this is the case, ocular findings may be more likely to lead caregivers and providers to seek out a diagnosis.
- Vision deficits are the major source of debility in non-syndromic albinism subjects. These should be addressed early to maximize outcomes and limit the social and educational impact.
- Squamous cell carcinomas are the most common malignancy in albinism, which can increase the relative risk as much as 1000 times.
- Albinos with systemic signs such as easy bruising or frequent infections should be assessed for a syndromic form of albinism.

Enhancing Healthcare Team Outcomes

Albinism is a relatively common genetic disorder which affects many organ systems. Thus, the disorder is best managed by an interprofessional team. Vision deficits are the major source of debility in non-syndromic albinism subjects. These should be addressed early to maximize outcomes and limit the social and educational impact. Squamous cell carcinomas are the most common malignancy in albinism, which can increase the relative risk as much as 1000 times. Albinism is not curable. The focus should be on early assessment and correction of visual deficits and lifelong, risk-factor modification, early detection, and treatment of the skin malignancies. Early consultation to ophthalmology and dermatology, as mentioned above. Family referral to geneticist may be beneficial.

Continuing Education / Review Questions

- Access free multiple choice questions on this topic.
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