CURRENT TOPIC

Oculocutaneous albinism

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Oculocutaneous albinism (OCA) is a heterogenous group of autosomal recessive disorders affecting melanin synthesis, characterised by congenital hypopigmentation of the skin, hair, and eyes. Reduced visual acuity, photophobia, iris transillumination, foveal hypoplasia, nystagmus, and an abnormal decussation of nerve fibres at the optic chiasm are common features.[1] Ocular albinism (OA) shares the ocular features of OCA including the increased nerve fibre decussation at the optic chiasm. Patients affected by OA are often fairer in complexion than their unaffected siblings and have macromelanosomes present in the skin. In general, the skin hypopigmentation seen in OA is not as marked as that seen in OCA.

Melanogenesis

The tyrosinase gene regulates ocular and cutaneous melanin synthesis. Tyrosinase catalyses the first two steps in melanin synthesis. These are the oxidation of l-tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and its subsequent conversion to dopaquinone. Later steps in the melanin pathway, resulting in the formation of insoluble eumelanin, also involve tyrosinase. Phaeomelanin, a red-yellow pigment, is produced via an alternative pathway entered into by dopaquinone. Tyrosinase contains two copper atom binding sites forming a coupled, binuclear complex.[2] Two related proteins, tyrosinase related proteins 1 and 2 (TRP-1 and TRP-2),[3 4] both contain structures similar to tyrosinase and form a tyrosinase enzyme "superfamily" involved in eumelanin production. TRP-1 regulates eumelanin production and has catalytic activity.[5 6]

The tyrosinase gene is located on chromosome 11q14–q21.[7 8] The TRP-1 and TRP-2 genes map to 9p23[9] and to 13q32,[10] respectively.

Type I OCA (OCA1)

Lesions affecting the tyrosinase gene can result in complete or partial inhibition of tyrosinase. These give rise to the various subtypes of tyrosinase negative OCA (OCA1) that have been characterised.[11] These include OCA1a (fig 1), OCA1b (yellow OCA), minimal pigment albinism (OCA1-MP) and temperature dependent albinism (OCA1-TP). Where there is no residual function within tyrosinase, as in OCA1a, full expression of the albino phenotype occurs.[11] OCA1b is an allelic variant of OCA1a,[12] where enzyme activity is reduced rather than abolished. Similarly, OCA1-MP may be caused by a mutation that reduces expression of the tyrosinase gene.[13] Individuals affected by OCA1b and OCA1-MP accumulate some pigment in the hair and irides with time. Pigment accumulation occurs to a lesser extent in OCA1-MP than in OCA1b. Many individuals with OCA1 are compound heterozygotes inheriting different allelic mutations for the tyrosinase gene from each parent. The ocular phenotypes among these individuals with OCA1 are similar.

Type II OCA (OCA2)

Tyrosinase positive OCA (OCA2) is caused by mutations at the P locus on chromosome 15q11.2–q12.[14] However, the role of the P protein in humans is unknown. The phenotypic expression of this disorder varies according to the racial background of the individual. Pigmentation increases with age, resulting in the appearance of pigmented naevi, freckles, or lentigenes. Although hair colour may darken,

Figure 1 An infant with oculocutaneous albinism type-1a. The infant has a "snowy-white" appearance with complete absence of skin and hair pigmentation. (Photograph reproduced with the permission of the child's parents.)

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the skin does not tan. OCA1 can be difficult to distinguish from OCA2 when there is partial tyrosinase enzyme activity. A positive hairbulb incubation test can help diagnose OCA2,[15] although high false negative rates make this test unreliable. Some cases of autosomal recessive ocular albinism may in fact be individuals with OCA2 who are compound heterozygotes for P gene mutations.[16]

In the Prader-Willi and Angelman syndromes the incidence of OCA2 is 1%. This high incidence may be the result of hemizygosity for inherited mutant alleles of the P gene.[16]

Type III OCA (OCA3)

Brown OCA (OCA3) arises from a defect in TRP-1.[11] The phenotype, described only in African and African-American individuals, is characterised by light brown skin and hair, moderate tanning ability, blue-grey irides, and transilluminable irides. Tyrosinase is found in normal amounts in intact cells, but it exhibits reduced tyrosine hydroxylase activity, which appears to be the consequence of absent TRP-1.[17] Rufous oculocutaneous albinism (ROCA), also ascribed to TRP-1 mutations, is characterised by bright copper red skin and hair and iris pigment dilution. Visual pathway anomalies (vide infra) are not described in ROCA.

Hermansky-Pudlak and Chediak-Higashi syndromes

Both of these syndromes are multisystemic disorders associated with albinism and are an important part of the differential diagnosis. Abnormal synthesis of the pigmented melanosome as well as abnormal organellogenesis underscores these disorders. Hermansky-Pudlak syndrome (chromosome 10q23.1–q23.3) has a variable pigment phenotype, but affected individuals do not tan. The triad of albinism, abnormal platelet aggregation, and abnormal tissue ceroid accumulation characterises the disorder.[17] Chediak-Higashi syndrome (chromosome 1q43) is characterised by albinism, increased susceptibility to infection as a result of dysfunctional leucocyte degranulation, and large eosinophilic, peroxidase positive inclusion bodies in peripheral blood.[17] Patients with both of these disorders have ocular features that fit the diagnostic criteria for albinism.

Ocular features

The ocular features of albinism are similar among the subgroups but may vary in degree. Recent research has focused on developmental retinal abnormalities that include underdevelopment of the central retina, reduction in rod photoreceptor and ganglion cell numbers, and a relatively small uncrossed retinofugal pathway.

Melanin is transiently present in the retinal part of the developing optic stalk in many mammals. However, the possibility that it influences the decussation pattern of developing retinofugal fibres has been discounted.[18] The influence of the optic chiasm on retinofugal fibre decussation patterns has also been studied. Midline chiasmal cells influence the differential growth of crossed and uncrossed retinal ganglion cells.[19] Cues present within chiasmal cells are involved in the pathway choice of retinofugal fibres. However, no difference has been observed in the ability of chiasmal cells to influence the growth of ipsilateral retinal ganglion cell axons of albino compared with pigmented mice.[20]

The site of influence of the albino mutation on the fate of retinal ganglion cell axons is likely to be the retina. There are decreased numbers of ipsilaterally projecting retinal ganglion cells in albino retinas. In animals with a sharp vertical naso-temporal divide in retinal ganglion cell projections, there is a shift in the line of retinal decussation 20° temporal to its normal midline position in albino retinas.[21] It has been suggested that lack of melanin, or a related agent, alters the normal spatio-temporal sequence of retinal ganglion cell production. The influence of retinal pigment epithelium over retinal development was reviewed by Jeffery.[22] He suggested that normal development of the neural retina occurs via a series of overlapping waves operating over a roughly "centre to peripheral" gradient. In albinos, the normal spatio-temporal sequences of cell generation within the ganglion cell layer are delayed. The time scale of this delay (in the order of two days) could result in decreased generation of ipsilaterally projecting ganglion cells.

Similarly, a disturbance in the spatio-temporal sequence of retinal development might disrupt the normal gradient of maturation of the retina. Consequently, this might result in underdevelopment of the central retina and thinning of the inner and outer nuclear layers within this region.[22] Melanin is normally absent in the retinal pigment epithelium during these early developmental stages, although tyrosinase is present. DOPA or its breakdown product seems the likely active agent capable of influencing retinal development. Lack of DOPA in the albino retina might result in excessive mitosis. Excessive cell death is a sequela of this and results in a thinner retina with a reduced number of rod photoreceptors. Cone photoreceptor numbers are unaffected, but because they are generated at about the same time as the affected retinal ganglion cells, and at an earlier stage than rods, this suggests that the albino mutation is operating in a cell specific manner rather than in a particular time frame.[22] The influence of DOPA, and lack of it, on spatio-temporal events in retinal development awaits further investigation.

Misrouting of retinofugal fibres, detected by visual evoked potential (VEP) studies,[23] confirms the diagnosis of albinism. In albinism the VEP detected at the occiput is of the opposite polarity when comparing each eye (crossed asymmetry). Crossed asymmetry is a universal finding in all forms of albinism (except ROCA). Various test paradigms are used according to age.[24] VEPs can distinguish albinoid individuals and other equivocal cases from true albinos.

Reported VEP crossed asymmetry in cases of Prader-Willi syndrome has been disputed.[25] It has been argued that these patients may have had albinism.[26] Asymmetric VEPs have also been reported in conditions other than albinism such as congenital idiopathic nystagmus,[27] dissociated vertical deviation,[28] and congenital stationary night blindness type II.[29] This would reduce the value of the VEP as a diagnostic tool, but other VEP studies have not confirmed the presence of crossed asymmetry in these conditions.[30 31] In addition, no histological verification of visual pathway misrouting has ever been provided. Moreover, VEP asymmetry reported in dissociated vertical deviation and congenital idiopathic nystagmus might just be revealing a variation in hemispheric lateralisation rather than specific crossed asymmetry. The contrasting language, different recording techniques, different response criteria, and different stimuli used in various studies could also lead to confusion regarding the specificity of VEP asymmetry.[32]

Foveal hypoplasia (fig 2), like visual pathway misrouting, is said to be a consistent diagnostic feature of albinism.[24] Other disorders that may feature foveal hypoplasia include aniridia, achromatopsia, and isolated foveal hypoplasia.[33] The underlying cause of albinism may arise from the same events that result in the visual pathway anomaly. Histopathological studies of foveal hypoplasia in albinism demonstrate an absent foveal pit on light microscopy.[34] Although abnormal vessels have been noted coursing over the central macula these may not affect vision.[35] In general, visual acuity follows the degree of pigmentation. More than 60% of patients with OCA2 have a visual acuity better than 6/60, whereas less than 40% of patients with OCA1 have a best visual acuity better than 6/60.[36] Visual acuity ranges from 6/18 to 6/48 in brown OCA,[37] but acuities of 6/9 or better are seen in ROCA, despite the presence of nystagmus. Because 14% of all albinos have refractive errors greater than 10 dioptres,[36] correction of this might result in a modest improvement in vision.

Nystagmus is a consistent finding in all forms of albinism although, occasionally, individuals exist with albinism but without nystagmus.[24] It usually appears in the first 2 or 3 months of life and often lessens with age. Nystagmus has been well characterised in albinos and factors that might be responsible for it include anomalous visual pathways and foveal hypoplasia.[38] It is usually in the horizontal plane but mixed patterns also exist (torsional or vertical). A rare form of nystagmus, periodic alternating nystagmus, is a conjugate horizontal jerk nystagmus that periodically reverses its direction. It might have a higher prevalence among albinos.[39] Here, the "null zone", the position of reduced amplitude of nystagmus, may shift periodically and unpredictably.

Near vision is generally better in albinism, as a result of dampening of nystagmus on convergence. In general, visual acuity improves with increasing percentage of time during the nystagmus cycle, where the eye movement velocity is < 10°/second. However, a threshold is reached in albinism where acuity fails to improve further because of factors such as foveal hypoplasia and increased light scatter.[40]

Key messages

- Oculocutaneous albinism comprises a heterogenous group of disorders of melanin metabolism resulting in a variable cutaneous phenotype that ranges from mild to severe depigmentation. Similarly, the ocular features generally vary in severity with degree of depigmentation. Visual evoked potential crossed asymmetry signifies an abnormal decussation of nerve fibres at the optic chiasm that is the hallmark of the disorder
- Molecular analysis of gene sequences may be an accurate tool for diagnosis and reveals that compound heterozygosity is common in all forms of oculocutaneous albinism
- Developmental events in the albino retina might be affected by abnormal melanin metabolism and could underlie the increased decussation at the optic chiasm, as well as the underdevelopment of the central retina
- Abnormal melanin metabolism might be responsible for other neurodevelopmental defects that underlie delayed visual maturation and nystagmus commonly seen in albinism

Surgical attempts to reduce nystagmus, such as the Kestenbaum-Anderson procedure and its variants, have been warned against in albinism because of the higher prevalence of periodic alternating nystagmus, with its accompanying shifting null zone. A more successful approach involves large retroequatorial recessions of the horizontal recti muscles that stabilise the eye position and increase foveation times.[41]

Visual pathway anomaly might also be responsible for the increased incidence of strabismus seen in albinism. It is aggravated by decreased visual acuity and increased light scattering. Although fine grade stereoscopic vision is absent, gross random dot stereopsis has been demonstrated in some albinos.[42] The anatomical substrate for this is uncertain, but gross stereopsis might be supported by either

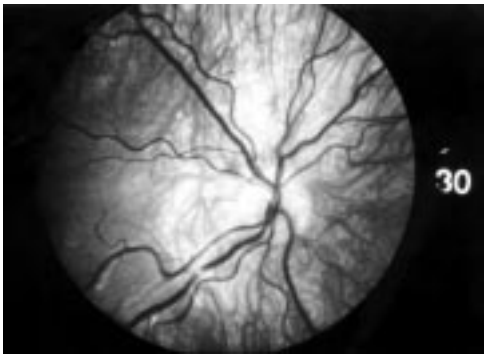

Figure 2 Fundus photograph of an albino retina demonstrating pallor of the retinal pigment epithelium with prominence of the choroidal vasculature, fovea hypoplasia, and retinal vessels coursing over the central macula.

projections from the temporal retinal periphery, whose fibres remain correctly routed, or via intercortical and intracortical communications via the corpus callosum.[42] Whether this serves any useful function is debatable. "Size constancy" is an attribute of stereopsis that enables an individual, under binocular viewing conditions, to perceive an object to be of constant size despite varying distances between object and subject. By assessing whether stereopsis can support "size constancy" in albinos, three groups of albinos have been classified: (1) those with no stereopsis, (2) those with measurable stereopsis in whom it serves no function, and (3) those with stereopsis in whom it is functional.[43]

Infants with albinism commonly display visual inattention for the first few months after birth, often followed by an improvement at about 3–8 months of age. This form of delayed visual maturation has been classified as type III.[44] This distinguishes it from type Ia delayed visual maturation where no ocular or neurological abnormality exists, type Ib where a perinatal intercurrent illness occurs, and type II where widespread neurological abnormalities are present. The subtypes of delayed visual maturation behave differently in terms of the onset and rate of visual recovery. Type III delayed visual maturation behaves intermediately between types I and II. In type III delayed visual maturation the final visual acuity is dictated by the severity of the underlying ocular disease.[44] Lambert *et al* found no significant difference between flash and pattern VEPs in infants with type I delayed visual maturation and age matched normal controls. This suggested that delayed visual maturation was not attributable to abnormalities in the visual cortex.[45] Fielder and Evans speculated that visual improvement coincided with the emergence of the geniculostriate pathway as the main pathway for visual function. A subcortical (collicular–pulvinar–parietal) pathway may serve as the main visual system in the first 2–3 months of life. Thus, delayed visual maturation could result from a subcortical pathway lesion, with improvement in visual function corresponding to arising function within the geniculostriate pathway.[46] Investigations of subcortical connections of the superior colliculus of pigmented and albino rats demonstrate that the albino mutation may have widespread effects extending to the subcortical visual pathway.[47] Subcortical delay might secondarily delay development of cortically mediated responses.[48] The well defined onset and homogeneous rate of visual improvement in type I delayed visual maturation supports this "dual visual system" theory. The slower improvement in vision among albinos with type III delayed visual maturation might be the result of the influence of visual pathway abnormalities on the interaction of this dual visual system.

Nevertheless, the presence of a dual visual system remains controversial. Normal electroretinograms, normal or mildly prolonged VEP latencies, and normal pupil responses tend to discount a delay of macula maturation or delayed visual pathway myelination as causes for delayed visual maturation. Delay in establishment of synapses in the visual cortex seems unlikely because pattern VEP results in patients with delayed visual maturation are age appropriate, reflecting appropriate cortical function. Delay in the development of visual association areas that mediate visual attention has also been proposed as a possible cause.[45]

OCA remains a much stigmatised condition, particularly in countries with a high incidence. However, with appropriate ophthalmic care, including refractive correction and the provision of tinted spectacles and low vision aids, individuals may attain reasonable visual function. Albinos perform equally well compared with control subjects in intelligence tests. This might mean that with improved parental and teacher understanding, and early recognition of any specific educational problems, these children might achieve the same performance levels as their unaffected counterparts, often within mainstream schooling.[49]

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