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Pigmentary disorders of the eyes and skin

Syril Keena T. Que, MD[a], Gillian Weston, BA[a], Jeanine Suchecki, MD[b], Janelle Ricketts, MBA, MD[a,*]

[a]*Department of Dermatology, University of Connecticut Health Center, 21 South Road, Farmington, CT 06032*
[b]*Department of Ophthalmology, University of Connecticut Health Center, 21 South Road, Farmington, CT 06032*

Abstract Oculocutaneous albinism, Menkes syndrome, tuberous sclerosis, neurofibromatosis type 1, dyskeratosis congenita, lentiginosis profusa syndrome, incontinentia pigmenti, and Waardenburg syndrome all are genodermatoses that have well established gene mutations affecting multiple biological pathways, including melanin synthesis, copper transport, cellular proliferation, telomerase function, apoptosis, and melanocyte biology. Onchocerciasis results from a systemic inflammatory response to a nematode infection. Hypomelanosis of Ito is caused by chromosomal mosaicism, which underlies its phenotypic heterogeneity. Incomplete migration of melanocytes to the epidermis and other organs is the underlying feature of nevus of Ota. Vogt-Koyangi-Harada and vitiligo have an autoimmune etiology; the former is associated with considerable multiorgan involvement, while the latter is predominantly skin-limited.

Oculocutaneous albinism

Background

Oculocutaneous albinism (OCA) is a condition that involves mutations in the genes mediating melanin synthesis (Table 1).[1,2] This results in the hypopigmentation of the skin, hair, and eyes; an increased risk of skin cancer; and an increased susceptibility for development of photophobia, refractive errors, and other visual anomalies. OCA1 A is the most severe form, with complete absence of melanin. Individuals with OCA1 A are born with white hair at birth, while those with the other types are born with pigmented hair and can accumulate more pigment over time.

* Corresponding author. Tel.: 860-679-4600; fax: 860-679-7534.
E-mail address: jaricketts@uchc.edu (J. Ricketts).

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Ocular manifestations

The human fovea is responsible for much of our visual function, including color vision and highly specialized central fine visual acuity.[3] In OCA, reduced visual acuity can result from foveal hypoplasia.[4] The absence of melanin also leads to optic nerve fiber misrouting, which may contribute to strabismus and reduced stereoscopic vision (depth perception).[5,6]

The development of nystagmus can occur between six to eight weeks of age and results from poor vision. It is initially slow with a large amplitude, but the amplitude often decreases within the first year of life.[7] Poor fixation related to nystagmus and the development of strabismus and high refractive errors can lead to ambylopia, defined as reduction of vision due to the lack of development of the visual pathway during childhood. Patients with OCA can also develop varying degrees of iris hypopigmentation and transillumination as well as reduced pigmentation of the retinal pigment epithelium. The amount of

Table 1 Oculocutaneous albinism gene mutations

Oculocutaneous albinism (OCA)	Responsible gene	Gene function	Gene localization	Prevalence
OCA1	Tyrosinase	Rate limiting enzyme for melanin production	11 q14-q21	1:40,000
OCA2	*P* gene	Exact function unknown, involved in transport into and out of melanosomes and regulation of melanosome pH	15 q	1:36,000 (white Europeans) 1:3900-10,000 (Africans)
OCA3	TYRP1	Involved in stabilization of tyrosinase	9 q23	Rare (white Europeans, Asians) 1:8,500 (Africans)
OCA4	SCL45 A2	May transport substances required for melanin biosynthesis	5 p	Rare (white Europeans) 1:8,500 (Japanese)

hypopigmentation varies with the type of albinism, as with the skin. All of these findings can contribute to reduced visual acuity, color vision impairment, and photophobia.[5]

Diagnostic tests for ocular manifestations include the detection of iris transillumination on slit lamp examination, assessment for macula transparency and foveal hypoplasia on retinal examination, and the detection of abnormal optic nerve fiber crossing using monocular visual evoked potential.[8] Prism and alternate cover testing often discloses strabismus.[7] Spectral domain optical coherence tomography (OCT) is the best way to evaluate the retina for the characteristic findings of ocular albinism, including the absence of or reduced foveal depression, absence of specialized foveal photoreceptors, and continuation of the inner retinal layers through the fovea.[4,9–11] Teller acuity cards[12] can be used to measure visual acuity and shows improvement in acuity upon vertical presentation compared with horizontal presentation of the cards. This is likely due to the horizontal nature of the nystagmus in oculocutaneous albinism.[7]

Treatment of the ocular manifestations in oculocutaneous albinism for the most part involves corrective lenses. Eyeglasses can correct visual acuity from 20/107 to 20/80.9[13] and also improve the patient's strabismus. In response to nystagmus, patients will often develop a compensatory head posture. Depending on the extent of this adjustment, extraocular surgery can be considered to shift this position closer to the primary gaze.[14,15]

Menkes syndrome/disease

Background

Menkes syndrome, also known as kinky hair disease, is an X-linked recessive neurodegenerative disorder caused by missense mutations in the *ATP7 A* gene (copper transport gene on chromosome Xq21.1), which causes impaired intestinal copper absorption,[16] reduced activity of copper-dependent enzymes,[17,18] progressive hypotonia, seizures, and failure to thrive.[19] Skin and hair abnormalities (including hypopigmentation of hair, twisted hairs or pili torti, and pale and lax skin) result from decreased keratin fiber strength, tyrosinase activity, and melanin synthesis.[20] Treatment includes infusions with copper salts.

Ocular manifestations

Patients with Menkes' syndrome present with various ocular findings, including poor visual acuity, myopia, strabismus, blue irides, and iris stromal hypoplasia,[21] which result from deficient cytochrome c oxidase and superoxide dismutase, copper dependent enzymes.

Menkes disease also involves visual changes secondary to retinopathy. Menkes-related retinopathy has two main causes: (1) the overall systemic copper deficiency and (2) the loss of retinal Menkes protein, which normally helps to regulate the copper levels of overlying photoreceptors.[22]

Tuberous sclerosis

Background

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome characterized by the development of multiple hamartomas in several organs. The tumor suppressor genes responsible for TSC include the TSC1 gene on chromosome 9 and the TSC2 gene on chromosome 16. These genes directly target RAS, which inactivates mammalian target of rapamycin (mTOR), the key regulator of cell proliferation and organ size.[23]

Cutaneous manifestations associated with TSC include hypomelanotic macules/ash leaf spots (present in 97.2%), facial angiofibromas (74.5%) (Figure 1), Shagreen patches (48.1%) (which are connective tissue nevi sometimes referred to as collagenomas), molluscum pendulum (22.6%), (which is a skin polyp with papillomatosis of the epidermis and dilated blood vessels), forehead fibrous plaques (18.9%), periungual fibromas (15.1%), and "confettilike" macules (2.8%) (which are multiple 1-2 mm white

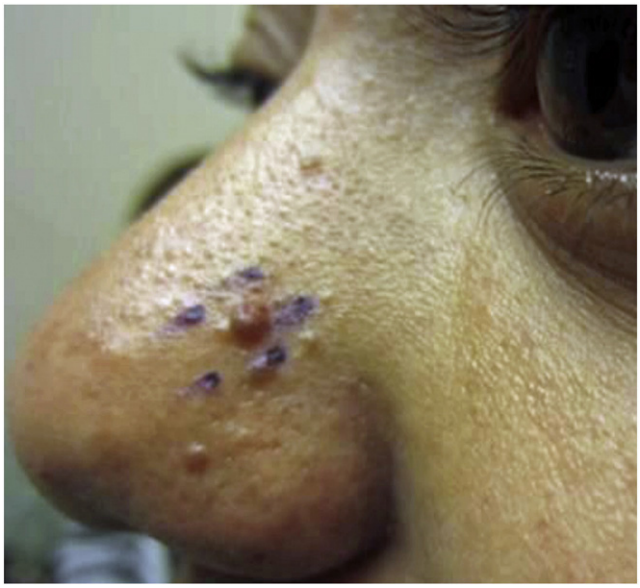

Fig. 1 Multiple facial angiofibromas in a patient with tuberous sclerosis.

spots symmetrically distributed over the extremities).[24] Systemic manifestations include seizures (which occur in 90% to 96% of TSC patients and are the leading cause of morbidity in TSC),[25] renal angiomyolipomas,[26] and cardiac rhabdomyomas.[27]

The management of TSC is, for the most part, symptomatic; however, rapamycin and its analogues hold some promise as a potential therapy. Rapamycin can normalize the dysregulated mTOR pathway in TSC. It has shown some success in inducing the regression of brain astrocytomas[28] and renal angiomyolipomas[29] associated with TSC.

Ocular manifestations

The most common ocular finding in TSC is a retinal hamartoma, which can be found in 40% to 50% of TSC patients.[30] The retinal hamartoma in TSC can present as a unilateral, transparent, noncalcified lesion or as bilateral calcified tumors, and is often benign with no treatment required. Rarely, the tumor requires treatment in the presence of growth, inflammation, and related ocular complications. In the past, enucleation was the treatment of choice. New potential therapeutic modalities have been described in case reports. Recently, brachytherapy was successfully used in the treatment of patients with exudates and vitritis related to an aggressive hamartoma.[31] There has also been a report of a patient with tuberous sclerosis, bilateral retinal hamartomas, and macular edema, which responded well to treatment with bevacizumab and intravitreal triamcinolone acetonide.[32]

Other ocular complications of the tuberous sclerosis complex include retinal pigment epithelial depigmented lesions,[33] refractive errors, and strabismus.[34]

Neurofibromatosis

Background

Type I neurofibromatosis (NF1) is an autosomal dominant geno-oculo-dermatosis caused by deletions or mutations in the neurofibromin gene (*NF1*) on chromosome 17 p11.2. The *NF1* gene encodes neurofibromin, which negatively regulates RAS protein,[35] leading to excess cell growth and an increased potential for malignant transformation. An individual can be diagnosed with NF1 if he or she has two or more of the following:[36]

1. Six or more café au lait spots (>0.5 cm diameter in prepubertal children, >1.5 cm after puberty) (Figure 2)
2. Axillary or inguinal freckling
3. Cutaneous neurofibromas or one plexiform neurofibroma
4. Two or more Lisch nodules
5. Optic pathway gliomas
6. Specific bony lesions (sphenoid wing dysplasia, pseudoarthrosis of the tibia)
7. A first-degree relative with NF1

The diagnosis can be difficult to make in young children, because many of the manifestations are age-dependent and many phenotypic variations exist.[37,38]

Ocular manifestations

The optic pathway includes the optic nerve, chiasm, tracts, and radiations. The optic pathway gliomas may result in mild proptosis or decreased visual acuity due to compression of the optic nerve along the pathway. Optic nerve pallor or optociliary shunt vessels may be present on examination. There is a suspected correlation between optic nerve gliomas and the risk of cerebral arteriopathy. Due to

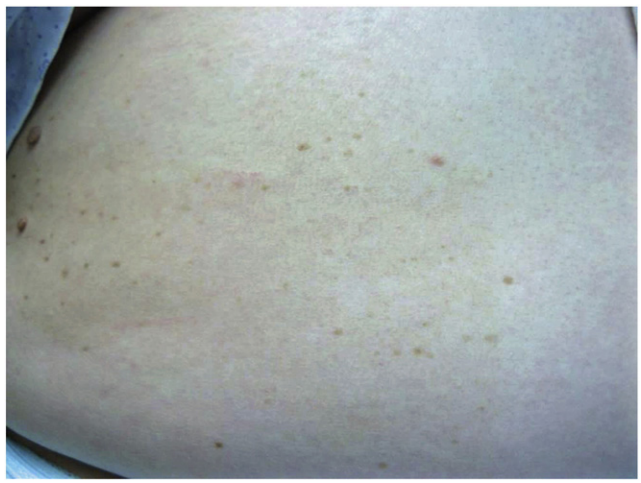

Fig. 2 Multiple café au lait macules in a patient with suspected segmental neurofibromatosis.

this correlation, it has been suggested that individuals with NF1, especially those with optic nerve gliomas, undergo vascular imaging by MRA or other brain imaging studies.[38]

The management of optic pathway gliomas remains controversial. They may remain stable or slowly enlarge in childhood or adulthood. Visual deficits in NF1 patients with optic nerve gliomas can include decreased visual acuity, loss of color vision, visual field defects, and loss of contrast sensitivity. Associated findings also include strabismus, nystagmus, proptosis, afferent pupillary defects, and optic disc pallor. Studies have shown that retinal nerve fiber layer thickness inversely correlates with optic pathway gliomas and decreased vision.[37] The location of optic nerve gliomas in the noncortical visual pathway, either in the optic nerves, chiasm, tracts, and radiations, makes biopsy or surgical resection difficult due to the risk of visual loss. Chemotherapy with carboplatin and vincristine can be used to manage rapidly enlarging optic nerve gliomas. Radiation therapy is no longer used since the risk of adversely impacting vision and the risk of developing secondary malignancies such as a malignant peripheral nerve sheath tumors.[39,40]

Lisch nodules are also present in NF1 and are one of the characteristic findings. These are benign iris hamartomas that do not impair vision. They are usually bilateral and found on the iris surface or deep within the stroma. They are present in more than 95% of carriers of the *NF1* gene mutation and can be useful as a diagnostic marker for neurofibromatosis.[38] Other findings associated with NF1 are ciliary body cysts and retinal pigmentary abnormalities.

Dyskeratosis congenita

Background

Dyskeratosis congenita is a rare, hereditary disorder involving defective telomere biology and dyskerin gene mutations and is clinically characterized by a triad of reticular cutaneous hyperpigmentation, nail dystrophy, and oral leukoplakia.[41–43] Dyskeratosis congenita is a fatal condition where patients usually develop aplastic anemia and malignant transformation of the oral leukoplakia. Bone marrow failure can also lead to opportunistic infections or hemorrhage.[43] Treatment of this condition involves short-term treatments, such as anabolic steroids (which temporarily increase blood counts), granulocyte macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and erythropoietin[44]; however, the only long-term treatment is hematopoietic stem cell transplant, which does not necessarily prolong survival.[45]

Ocular manifestations

Ophthalmic manifestations have been observed in 40% of patients with dyskeratosis congenita.[41] The most common findings are blepharitis, cicatricial entropion, trichiasis, loss of cilia, nasolacrimal duct obstruction, and optic atrophy.[41,46] Trichiasis is defined as the abnormal positioning of eyelashes that grow inward towards the eye, potentially abrading the ocular surface and causing corneal damage and subsequent decrease in vision. Most of the anterior segment findings of dyskeratosis congenita are likely related to epithelial abnormalities in the ocular skin and mucous membranes.[46] Severe ocular surface disease can occur from these epithelial abnormalities and include chronic cicatricial keratoconjunctivitis (which may lead to significant symptomatology and visual impairment).[47]

Only a small proportion of patients with dyskeratosis congenita had retinal vascular changes; however, early recognition and treatment of these changes can prevent retinal neovascularization, exudative retinopathy, and retinal detachment and, therefore, the related vision loss.[48,49] In addition to the syndromic manifestations, treatment of dyskeratosis congenitia with radiation or the use of steroids before stem cell transplantation will increase the risk of glaucoma and cataract formation. A baseline ophthalmologic exam and periodic eye exams are therefore recommended for every patient with dyskeratosis congenita.

Lentiginosis profusa/LEOPARD syndrome

Background

LEOPARD syndrome is an autosomal dominant condition and an acronym that stand for the cardinal features of this condition, including lentigines (Figure 3), ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness. While it is not part of the acronym, hypertrophic cardiomyopathy is also commonly present. The syndrome was first described by Zeisle and Becker in 1936, but the term "LEOPARD syndrome" was not coined by Gorlin until 1969.[50] Other names for this condition are lentiginosis profusa, multiple lentigines syndrome, cardiocutaneous syndrome, Moynahan syndrome, and progressive cardiomyopathic lentiginosis. Lentigines do appear in 100% of cases, usually after age 4 or 5, and thousands of lentigines can be present by puberty. Genes known to be associated with Leopard syndrome are PTPN11, RAF1, and BRAF.[51]

Ocular manifestations

Ocular associations with LEOPARD syndrome include hypertelorism, which is defined as an abnormally wide interorbital distance, and mild palpebral ptosis, a term that describes drooping of the eyelid. Lentigines can sometimes also appear in the sclera,[51] which is usually of no consequence to the vision. One paper has reported the presence of a coloboma (a missing area of tissue or gap) in

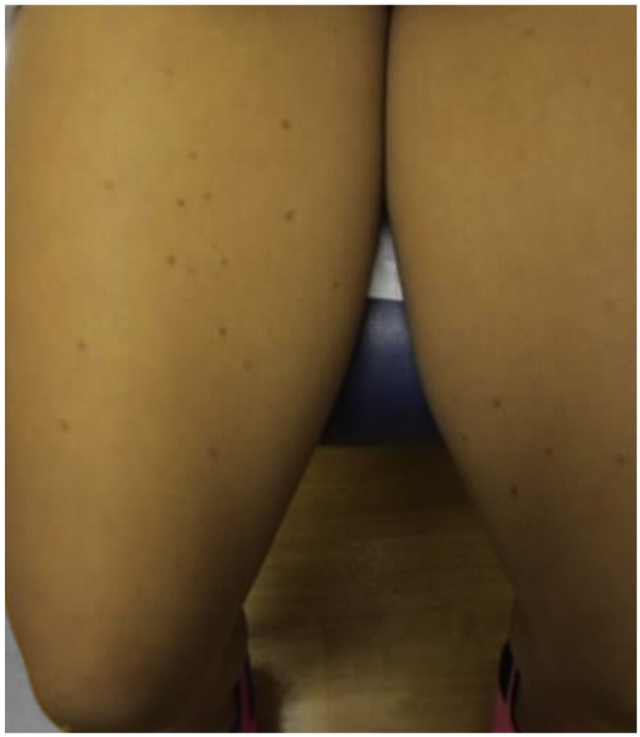

Fig. 3 Multiple lentigines in an adolescent patient. This patient was referred to specialists to rule out other possible manifestations of LEOPARD syndrome.

the iris, retina, and choroid in a child with LEOPARD syndrome,[52] but this finding is rarely seen. Colobomas are usually formed when a gap called the choroid fissure, which is present during early development, fails to close before a child is born.[53]

It was shown in one study that a significant number of patients had a high percentage of abnormalities of visual function in general and of visuo-motor integration. Ocular movements were abnormal half of the time, and stereopsis was abnormal in at least half the of patients.[54] Because these eye findings are common, baseline and follow-up ophthalmologic exams are recommended.

Onchocerciasis

Background

Onchocerciasis, also known as river blindness, is caused by the nematode *Onchocerca volvulus*. The blackfly vector *Simulium*, transmits the infective larvae to humans. The classic clinical finding in Onchocerciasis is the onchocercoma. These present as firm subcutaneous nodules usually located on the head and torso, and lower extremities. Calcification of the lesions occurs when the Onchocerca die. Skin findings in infected patients can also include leopard skin (or skin depigmentation on the lower limbs),[55] papules, lichenified plaques, and severe pruritus. HLA-DQ alleles have been found to be associated with depigmentation.[56]

Studies show that skin and eye disease occur concurrently. While only 4% of patients infected with onchocerciasis developed skin depigmentation, as many as 42% of patients with ocular onchocerciasis will also have skin depigmentation.[57] The concurrence of the two conditions may either be related to the microfilariae count or possibly related to the genetic autoimmune factors that predispose the individuals to either of these conditions.

Ocular manifestations

Onchocerciasis results in vision loss and blindness, most likely as a result of the progressive tissue damage caused by the microfiliariae. Not long ago, this had been a leading cause of blindness in rural African countries, endemic in the sub-Saharan region, but its prevalence has decreased as intervention programs have been developed[58] and implemented. The Onchocerciasis Control Program (1975-2002) and the Ivermectin Donation Program (started in 1988) were significant in the path to international control of Onchocerciasis.[59]

Localized foci also exist in Sudan and Yemen, and sporadic regions in Latin America. Ocular examination may show live microfilaria migrating through the anterior chamber and vitreous, which can be seen at the slit lamp. Severe ochocerciasis is a result of inflammation around the dead microfilaria. Initial superficial keratitis occurs, followed by sclerosing keratitis and inflammation in the anterior chamber and retina. In advanced onchocerciasis, there is often uveitis, posterior synechiae, peripheral anterior synechiae, and glaucoma.[60] Chorioretinitis, optic neuritis, and optic atrophy may also occur, leading to blindness. A recent study showed that in onchocerciasis, even without the presence of ocular onchocerciasis, there is an increased risk of glaucoma, which is currently the second leading cause of blindness in sub-Saharan Africa behind cataracts.[61]

Hypomelanosis of Ito

Background

Hypomelanosis of Ito (HI), or Incontinentia pigmenti achromicans, is a neurocutaneous syndrome characterized by blaschkoid hypopigmented patches, whorls or linear streaks; alopecia; and multisystemic abnormalities, including neurologic, ocular, dental, and musculoskeletal manifestations. Other dermatologic manifestations include café-au-lait macules, cutis marmorata, other vascular lesions, dermal melanocytosis, atopic dermatitis, pilomatrixoma, aplasia cutis, alopecia, variation in hair color, and nail abnormalities.[62–64] HI most commonly occurs sporadically and results from chromosomal mosaicism although possible familial inheritance

patterns have been reported.[65–74] HI presents usually within the first year of life with the characteristic skin lesions and the neurologic and other manifestations become readily apparent in infancy or early childhood.[62] The prevalence of HI remains around 1 in 700 new pediatric neurology referrals[62] and occurs with equal incidence in both sexes.[63] Clinical monitoring includes regular follow-up with the pediatrician and other specialists.

Ocular manifestations

The ocular manifestations, seen in about 25% of patients with HI, are varied and nonspecific. Reported ocular abnormalities have included anterior segment changes, such as subtle iris depigmentation, corneal asymmetry, and more serious diseases including corneal opacity, micro- and macro-ophthalmia, and cataracts. Posterior segment findings have also been reported and include choroidal hypopigmentation and atrophy, retinal detachment, optic nerve hypoplasia and optic atrophy. Other ophthalmic findings that have been present in patients with HI include refractive errors, strabismus, nystagmus,[75,76] scleral melanosis, hypertelorism, and eyelid anomalies.[62–64,77] In addition, a case of retinoblastoma in a 16 month old with HI was reported in 2011.[78] Due to the wide variability in ocular presentation, patients with HI should be evaluated as early as possible with a comprehensive ophthalmologic examination.

Incontinentia Pigmenti

Background

Incontinentia Pigmenti (IP) (also known as Bloch-Sulzberger syndrome, OMIM 308300) is a multisystem disease originally described by Bloch and then Sulzberger in the 1920s. The disease is characterized by four cutaneous stages. The first stage presents in the neonatal period with vesiculobullous skin lesions that follow the lines of Blaschko.[79] The second stage is marked by hyperkeratotic and verrucous lesions appearing between 2 and 6 months of age. In the third stage the lesions evolve into hyperpigmented patches, usually, by the end of infancy.[80] The fourth and final cutaneous stage is characterized by hypopigmentation, atrophy, and alopecia of the affected skin by early adulthood.[81] The dermatologic manifestations of IP can also include nail dystrophy. Potential systemic manifestations include neurologic, ophthalmologic, skeletal and dental abnormalities. IP is an X-linked dominant genetic disorder involving a mutation in the Nuclear Factor-Kappa B Essential Modulator (*NEMO*), (also known as the *IKBKG*, inhibitor of kB kinase gamma) gene. A normal copy of the NEMO gene is necessary for regulated NF-kB activation to prevent inappropriate apoptosis under TNFα signaling.[82,83]

Updates on ocular manifestations

The ophthalmologic manifestations of IP are varied and can be among the most severe and debilitating complications of the disease. It is estimated that between 16% and 66% of patients with IP have eye abnormalities,[82–85] typically in the form of proliferative retinal vasculopathy. Eye findings may also include strabismus, nystagmus, microphthalmia, cataracts, glaucoma, optic atrophy, and retinal detachment,[84] most of which are secondary to advanced retinopathy. Of these abnormalities, retinal detachment is considered a severe end stage complication of retinopathy in IP, as it can result in blindness. Retinal complications arise as a result of a vascular ischemia caused by occlusion of the retinal arterial vasculature.[79] At the junction of the avascular and vascular retina, abnormal arteriovenous malformations occur along with microvascular abnormalities and neovascularization. This inner retinal ischemic atrophy that causes proliferative vitreoretinopathy can progress to vitreous hemorrhage and retinal detachment[79] and severe loss of vision. In some cases, regression of retinopathy may occur spontaneously. Often treatment must be performed with laser or cryoablation of affected retinal areas and can slow the progression of these potential complications[82,86]; however, early detection is one of the most important aspects of effective treatment. Intravenous fluorescein angiography with a handheld retinal camera is typically performed under general anesthesia in babies with IP. Oral fluorescein may be used in place of intravenous injection.[87] Early, frequent ophthalmologic screenings of infants with IP are recommend to maximize chances of preserving vision.[88,89] Several recent studies show the considerable variation of ocular findings (Table 2).[82,84,85,90–95]

Nevus of Ota

Background

In oculodermal melanocytosis, or nevus of Ota, a hamartoma of spindle-shaped melanocytes can be found in the skin, eyes, and central nervous system. In the skin, the lesion presents as a bluish, black patch most commonly in the areas of the dermis innervated by the first and second divisions of the trigeminal nerve. Pigmentation of the sclera and other ocular tissues is readily apparent upon clinical examination. Ocular or oculodermal melanocytosis occurs in all races, but has a higher incidence in people with darker skin types and is more common in females. In Caucasians, the prevalence of ocular melanocytosis was found to be around .038% of the population.[96] The incidence in Asian populations generally may be higher, although a Chinese study cited a similar prevalence of oculodermal melanocytosis in 0.034% of the population.[97] Most cases present in infancy or childhood, but there are also reports of adult-onset nevus of Ota.

Table 2 Studies documenting ocular features in patients with Incontinentia Pigmenti

Author/year	# patients	Type study	Ocular anomalies
Kim BJ 2006	40 Korean patients with IP	Retrospective	66% (16/24) of total had ocular anomalies 56.3% (9/16) retinopathy 31.3% (5/16) strabismus 1/16 myopia 1/16 microphthalmia 1/16 aphakia
Ardelean D 2006	40 male patients with IP	A series of patients presented by authors plus a review of literature	32% of total had ocular anomalies 69% retinal abnormality (vascular anomalies, retinal detachment, pigmentary abnormalities) 31% had strabismus, optic nerve atrophy, retrobulbar glioma, glaucoma, corneal opacity, myopia
Landy SJ 1993	At least 111 patients in a clinical study by authors + analysis of published cases	Clinical study	33% squints 40% abnormal retinal vessels and RPE 10% with retinal abnormalities develop intraocular scarring and vision loss >90% patients have normal vision
Macey-Dare L 1999	7 IP patients with dental manifestations	Case reports	4/7 had ocular abnormalities 4/7 had myopia and strabismus
Hadj-Rabia S 2003	40 patients with IP	Retrospective study	7/34 (20%) had ocular anomalies 4/34 (12%) had strabismus 2/34 (6%) microphthalmia 1/34 retinal pigment anomaly 1/34 coloboma 1/34 occlusion of central retinal artery
Phan TA 2005	53 females with IP	Retrospective case series	19/51 (37%) had ocular anomalies Strabismus most common
Holmstrom G 2000	30 Swedish patients	Prospective study of patients previously diagnosed with IP	9/30 (30%) had severe visual impairment 7 patients had myopia (2 with severe myopia) 7 had widespread anterior segment changes 18/30 (60%) had posterior segment pathology 13/30 (43%) had strabismus 7 patients had monocular amaurosis 2 patients had grade 2 retinal changes 13/30 (43%) with vision threatening abnormalities (visual impairment, severe myopia, or grade 2 retinal changes)
Minic S 2013.	831 patients, multiple ethnicities	Meta-analysis IP patients 1993-2012	37% of total had ocular diagnoses 53% had retinal abnormalities 47% has nonretinal abnormalities 3.38% vitreous anomalies 2.61% lens anomalies 2.3% microphthalmia 6.91% amaurotic eyes 69.89% of ocular anomalies had potential to affect vision
Pacheco TR 2006	9 boys with IP Normal karyotypes	Case reports	8/9 patients had normal eye examination No report of ocular anomaly in the one patient for which a normal eye exam was not reported
O'Doherty M 2011	19 Irish patients with IP	Case series	5/11 (47%) had vision threatening ocular findings 2/11 retinal detachment 2/11 squint 2/11 corticovisual impairment 1/11 amblyopia 1/11 cataract 1/11 abnormal vasculature

Ocular manifestations

Oculodermal melanocytosis is usually a benign condition but patients have a 10% chance of developing glaucoma[98] and possibly an increased risk of associated melanoma,[99] which has been documented to occur in the skin[100,101]; the uveal tract (which includes the iris, ciliary body, and choroid)[102–107]; the central nervous system[108,109]; and the orbit.[110] The clinical presentation of cutaneous melanoma developing within Nevus of Ota can be subtle. Case reports displayed that the melanomas do not show typical clinical features of cutaneous melanoma and may mimic features of a benign subcutaneous cyst or nodule.[100] Treatment with lasers can result in reasonable clearance of pigmented skin lesions[111]; however, it does not eliminate the risks of glaucoma or melanoma in either the skin or ocular tissues.

Ocular manifestations occur in two thirds of patients with cutaneous lesions. In the eye, melanocytosis has been shown to be present in the episclera and choroid in 100% of patients; 10% have conjunctival involvement; and 18% have retinal involvement, depending on the study.[112,113] When examining patients, ultrasound biomicroscopy can be used in conjunction with a slit lamp examination to evaluate the iris and ciliary body. The choroid is evaluated by fundus examination and B-Scan ultrasound. Recently, using ultrasound biomicroscopy, the mean ciliary body thickness was found to be statistically significantly greater in the affected than in contralateral, unaffected, eyes. The affected eyes also consistently showed hyperreflectivity.[114] Ciliary body melanomas, by contrast, would show evidence of a mass and lower reflectivity.[114] This technique for assessing the ciliary body may now provide additional important information when evaluating nevus of Ota.

Malignant melanoma in association with Nevus of Ota, although rare, is often difficult to treat and can result in a local spread to orbital tissues, nerves, and bone. Early treatment can allow for preservation of orbital tissues and vision[110,115]; therefore, patients with nevus of Ota may benefit from regular skin and ophthalmologic examinations to facilitate earlier diagnosis and treatment.

Since as many as 10% of patients with nevus of Ota will develop glaucoma,[98] it is important to monitor for any changes in intraocular pressure and pigmentation.[116] Treatment of cutaneous lesions can be performed with Q-switched Alexandrite and Q-Switched (QS) Nd-YAG lasers.[111] Ocular lesions are not amenable to laser treatment. It should be noted that Q-switched lasers are among the most damaging to the eye and proper eye protection for both the physician and the patient is important.

Lastly, a recent retrospective review showed that surgical reduction of conjunctival and scleral pigmentation for cosmetic improvement of pigmentation within the eye itself can be performed as well.[117]

Vogt-Koyanagi-Harada

Background

Patients with Vogt-Koyanagi-Harada (VKH) Syndrome, of which vitiligo is a characteristic feature, are at risk of serious visual loss if treatment is delayed.

VKH, named after the three physicians who initially described the condition, is considered a multisystemic, autoimmune inflammatory disorder[118,119] that affects the skin, eyes, ears, and meninges. VKH likely results from the complex interplay of genetic and environmental factors.[120–128] There are several criteria required for diagnosis.[129]

Ocular manifestations

Ocular manifestations of VKH include a bilateral chronic diffuse granulomatous uveitis. Uveitis is the most common ocular complication of VKH and, if untreated, can result in blindness. Among patients referred to uveitis clinics around the world, VKH is identified in as many as 1% to 4% of patients.[130–133] In Japan, as many as 8% of uveitis cases result from VKH.[133] Inflammation targets melanocytes located in the uveal tract. A recent study of VKH in Indian children showed evidence of vision loss, which was attributed most commonly to the development of cataracts and the presence of active inflammation, but complications due to chronic uveitis, such as subretinal fibrosis, retinal pigment epithelium changes, and cystoid macular edema contributed to vision loss in a subset of patients as well.[134] Ocular anterior segment findings may include mild to severe bilateral inflammation with seclusion of the pupil and posterior synechiae. Keratic precipitates, which can be small or large, are granulomatous. Perilimbal vitiligo may be present. Bilateral panuveitis, optic disc hyperemia, vitreous opacities, edematous exudative choroiditis with nodular yellow lesions and serous retinal detachment can develop. Late in the disease neovascularization of the optic nerve and retina can occur, leading to vitreous hemorrhage. When evaluating patients with VKH, fluorescein angiography can be performed to show characteristic retinal findings. Choroidal thickening can be seen on B-scan ultrasound. Another potential test to differentiate VKH is ocular coherence tomography.[135] Ocular manifestations also include development of cataracts (40%), glaucoma (38% that require intervention), retinal fibrosis, and neovascularization, all of which can increase a patient's risk of developing blindness. Although more studies regarding the factors affecting visual outcomes are needed, early, aggressive treatment in the acute phase and prompt treatment of any recurrent inflammation may help to delay disease progression.[134] Treatment includes systemic, local and periocular corticosteroids, steroid sparing agents, or both.

Vitiligo

Background

In vitiligo, autoimmune destruction of melanocytes in the skin results in cutaneous depigmentation. Risk factors include a family history of vitiligo, medical history of autoimmunity, trauma, and the presence of several identified gene loci.[136] Vitiligo occurs in people of all ethnicities and disease onset usually occurs in childhood or adolescence. Other associated conditions include autoimmune thyroid disorders, diabetes, and alopecia areata.

Ocular manifestations

There are very few studies documenting the ocular findings in patients with vitiligo. It was shown that patients with vitiligo have retinal pigment epithelial (RPE) atrophy or hypopigmentation ,[137] pigment hypertrophy, choroidal nevi,[138] peripapillary atrophy around the optic nerve,[139] and choroidal hypopigmentation.[140,141]

Finally, uveitis may also occur with greater frequency in patients with vitiligo,[142,143] but this is not shown in all studies.[139,144–148] Because eye disease has been documented in patients with vitiligo, patients should receive routine ophthalmologic exams.

Waardenburg syndrome

Background

Waardenburg syndrome is a genetic syndrome consisting primarily of anomalies of the skin, hair, eyes, and ears and affects 1 in 40,000 according to population studies. The musculoskeletal system and gastrointestinal tract can also be affected in certain subtypes. As established at the Waardenburg consortium, diagnosis requires fulfillment of either two major criteria or one major and two minor criteria.[149] Major criteria include the characteristic white forelock (hair depigmentation), pigmentary anomalies of the iris, congenital sensorineural deafness, dystopia canthorum, or an affected first degree relative. Minor criteria are depigmented macules or patches, synophrys, broad nasal root, nose hypoplasia, or early graying of the hair by age 35. There are four major types of Waardenburg syndrome, generally involving the *PAX3* (Paired box 3), *MITF* (microophthalmia-associated transcription factor), *SOX10* (Sry box 10), *EDN3* (endothelin 3), and *EDNRB* (endothelin receptor type B) genes.[150,151]

Ocular manifestations

Recently, in patients with Waardenburg syndrome, the presence of both choroidal and iris hypopigmentation was confirmed. Fortunately, visual acuity was generally not affected.[152] Reduced visual acuity, when present, can result from foveal hypoplasia, amblyopia, and/or vitreous hemorrhaging.[153]

Other scattered case reports of possible ocular associations include bilateral congenital cataracts,[154] diabetic retinopathy,[155] retinoblastoma,[156] congenital eyelid ptosis,[157] branch retinal vein occlusion,[158] and strabismus.[159] Japanese patients with WS type II were also found to have hypopigmentation of both the iris and retina.[160]

Although reduced visual acuity is not typically an issue in Waardenburg syndrome, there are cases of loss of vision. Due to this and the reported variations in ophthalmologic findings, comprehensive eye examinations should be performed routinely.

References

1. Cheng T, Orlow SJ, Manga P. Loss of OCA2 disrupts the unfolded protein response and increases resistance to endoplasmic reticulum stress in melanocytes. *Pigment Cell Melanoma Res.* 2013;26:826-834.
2. Manga P, Orlow SJ. The pink-eyed dilution gene and the molecular pathogenesis of tyrosinase-positive albinism (OCA2). *J Dermatol.* 1999;26:738-747.
3. Hendrickson A. Organization of the adult primate fovea. In: Penfold PL, Provis JM, eds. Macular Degeneration. Heidelberg: Springer-Verlag; 2005. p. 1-20.
4. Harvey PS, King RA, Summers CG. Spectrum of foveal development in albinism detected with optical coherence tomography. *J AAPOS.* 2006;10:237-242.
5. Grønskov K, Ek J, Brondum-Nielsen K. Oculocutaneous albinism. *Orphanet J Rare Dis.* 2007;2:1-8.
6. Schmitz B, Krick C, Käsmann-Kellner B. Morphology of the optic chiasm in albinism. *Ophthalmologe.* 2007;104:662-665.
7. Summers CG. Albinism: Classification, clinical characteristics, and recent findings. *Optom Vis Sci.* 2009;86:659-662.
8. Bouzas EA, Caruso RC, Drews-Bankiewicz MA, Kaiser-Kupfer MI. Evoked potential analysis of visual pathways in human albinism. *Ophthalmology.* 1994;101:309-314.
9. Seo JH, Yu YS, Kim JH, et al. Correlation of visual acuity with foveal hypoplasia grading by optical coherence tomography in albinism. *Ophthalmology.* 2007;114:1547-1551.
10. Izquierdo NJ, Emanuelli A, Izquierdo JC, et al. Foveal thickness and macular volume in patients with oculocutaneous albinism. *Retina.* 2007;27:1227-1230.
11. Mohammad S, Gottlob I. The functional significance of foveal abnormalities in albinism measured using spectral-domain optical coherence tomography. *Ophthalomology.* 2011;118:1645-1652.
12. Preston KL, McDonald M, Sebris SL, Dobson V, Teller DY. Validation of the acuity card procedure for assessment of infants with ocular disorders. *Ophthalomology.* 1987;94:644-653.
13. Anderson J, Lavoie J, Merrill K, King RA, Summers CG. Efficacy of spectacles in persons with albinism. *J AAPOS.* 2004;8:515-520.
14. Kestenbaum A. New operation for nystagmus. *Bull Soc Ophtalmol Fr.* 1953;6:599-602.
15. Anderson JR. Causes and treatment of congenital eccentric nystagmus. *Br J Ophthalmol.* 1953;37:267-281.
16. Danks DM, Cartwright E, Stevens BJ, Townley RR. Menkes' kinky hair disease further definition of the defect in copper transport. *Science.* 1973;179:1140-1142.
17. Royce PM, Camakaris J, Danks DM. Reduced lysyl oxidase activity in skin fibroblasts from patients with Menkes' syndrome. *Biochem J.* 1980;192:579-586.

18. Maehara M, Ogasawara N, Mizutani N, Watanabe K, Suzuki S. Cytochrome c oxidase deficiency in Menkes kinky hair disease. *Brain Dev.* 1983;5:533-540.
19. Kim YH, Lee R, Yoo HW, et al. Identification of a novel mutation in the *ATP7 A* gene in a Korean patient with Menkes disease. *J Korean Med Sci.* 2011;26:951-953.
20. Finner AM. Nutrition and hair: Deficiencies and supplements. *Dermatol Clin.* 2013;31:167-172.
21. Gasch AT, Caruso RC, Kaler SG, Kasier-Kupfer M. Menkes' syndrome: Ophthalmic findings. *Ophthalmology.* 2002;109:1477-1483.
22. Krajacic P, Qian Y, Hahn P, et al. Retinal localization and copper-dependent relocalization of the Wilson and Menkes disease proteins. *Invest Ophthalmol Vis Sci.* 2006;47:3129-3134.
23. Tee AR, Manning BD, Roux PP, Cantley LC, Blenis J. Tuberous sclerosis complex gene products, tuberin and hamartin, control mTOR signaling by acting as a GTPase-activating protein complex toward Rheb. *Curr Biol.* 2003;13:1259-1268.
24. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: Advances in diagnosis, genetics, and management. *J Am Acad Dermatol.* 2007;57:189-202.
25. Curatolo P, Verdecchia M, Bombardieri R. Tuberous sclerosis complex: A review of neurological aspects. *Eur J Paediatr Neurol.* 2002;6:15-23.
26. O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP. An epidemiological study of renal pathology in tuberous sclerosis complex. *BJU Int.* 2004;94:853-857.
27. Webb DW, Thoma RD, Osborne JP. Cardiac rhabdomyomas and their association with tuberous sclerosis. *Arch Dis Child.* 1993;68:367-370.
28. Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. *Ann Neurol.* 2006;59: 490-498.
29. Wienecke R, Fackler I, Lisenmaier U, et al. Antitumoral activity of rapamycin in renal angiomyolipoma associated with tuberous sclerosis complex. *Am J Kidney Dis.* 2006;48:e27-e29.
30. Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: A population based study. *Br J Ophthalmol.* 2001;85:420-423.
31. Drummond SR. Retinal astrocytoma managed by brachytherapy. *Ophthalmology.* 2009;116:597.
32. Lonngi M, Gold AS, Murray TG. Combined bevacizumab and triamcinolone acetonide injections for macular edema in a patient with astrocytic hamartomas and tuberous sclerosis. *Ophthalmic Surg Lasers Imaging.* 2013;44:85-90.
33. Shields CL, Reichstein DA, Bianciotto C, Shields JA. Retinal pigment epithelial depigmented lesions associated with tuberous sclerosis complex. *Arch Ophthalmol.* 2012;130:387-390.
34. Akinci A, Oner O, Guven A, Degerliyurt A, Munir K. Refractive errors and strabismus in children with tuberous sclerosis: A controlled study. *J Pediatr Ophthalmol Strabismus.* 2009;46:345-348.
35. Jett K, Friedman MJ. Clinical and genetic aspects of neurofibromatosis 1. *Genet Med.* 2010;12:1-11.
36. Neurofibromatotis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch Neurol.* 1988;45: 575-578.
37. Avery RA, Fisher MJ, Liu GT. Optic pathway gliomas. *J Neuroophthalmol.* 2011;31:269-278.
38. Schnur RE. Type I, neurofibromatosis: A geno-oculo-dermatologic update. *Curr Opin Ophthalmol.* 2012;23:364-372.
39. Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: Controversies and recommendations. *Ann Neurol.* 2007;61:189-198.
40. Segal L, Darvish-Zargar M, Dilenge ME, Ortenberg J, Polomeno RC. Optic pathway gliomas in patients with neurofibromatosis type 1: Follow-up of 44 patients. *J AAPOS.* 2010;14:155-158.
41. Drachtman RA, Alter BP. Dyskeratosis congenita: Clinical and genetic heterogeneity. Report of a new case and review of the literature. *Am J Pediatr Hematol Oncol.* 1992;14:297-304.
42. Ogden GR, Connor E, Chisholm DM. Dyskeratosis congenita: Report of a case and review of literature. *Oral Surg Oral Med Oral Pathol.* 1988;5:58-91.
43. Bessler M, Wilson DB, Mason PJ. Dyskeratosis congenita and telomerase. *Curr Opin Pediatr.* 2004;16:23-28.
44. Erduran E, Hacisalihoglu S, Ozoran Y. Treatment of dyskeratosis congenita with granulocyte-macrophage colony-stimulating factor and erythropoietin. *J Pediatr Hematol Oncol.* 2003;25:333-335.
45. Gadalla SM, Sales-Bonfim C, Carreras J, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with dyskeratosis congenita. *Biol Blood Marrow Transplant.* 2013;19:1238-1243.
46. Tsilou ET, Giri N, Weinstein S, et al. Ocular and orbital manifestations of the inherited bone marrow failure syndromes: Fanconi anemia and dyskeratosis congenita. *Ophthalmology.* 2010;117:615-622.
47. Merchant A, Zhao TZ, Foster CS. Chronic keratoconjunctivitis associated with congenital dyskeratosis and erythrokeratoderma variablis. Two rare genodermatoses. *Ophthalmology.* 1998;105(7): 1286-1291.
48. Teixeira LF, Shields CL, Marr B, Horgan N, Shields JA. Bilateral retinal vasculopathy in a patient with dyskeratosis congenita. *Arch Ophthalmol.* 2008;126:134-135.
49. Vaz-Pereira S, Pacheco PA, Gandhi S, et al. Bilateral retinal vasculopathy associated with autosomal dominant dyskeratosis congenita. *Eur J Ophthalmol.* 2013;23:772-775.
50. Gorlin RJ, Anderson RC, Blaw M. Multiple lentigines syndrome. *Am J Dis Child.* 1969;117:652-662.
51. Martínez-Quintana E, Rodríguez-González F. LEOPARD syndrome: clinical features and gene mutations. *Mol Syndromol.* 2012;3:145-157.
52. Rudolph G, Haritoglou C, Kalpadakis P, Boergen KP, Meitinger T. LEOPARD syndrome with iris-retina-choroid coloboma. Discordant findings in monozygotic twins. *Ophthalmologe.* 2001;98:1101-1103.
53. Hero I, Farjah M, Scholtz CL. The prenatal development of the optic fissure in colobomatous microphthalmia. *Invest Ophthalmol Vis Sci.* 1991;32:2622-2635.
54. Alfieri P, Cesarini L, Zampino G, et al. Visual function in Noonan and LEOPARD syndrome. *Neuropediatrics.* 2008;39:335-340.
55. Coffeng LE, Fobi G, Ozoh G, et al. Concurrence of dermatological and ophthalmological morbidity in onchocerciasis. *Trans R Soc Trop Med Hyg.* 2012;106:243-251.
56. Murdoch ME, Payton A, Abiose A, et al. HLA-DQ alleles associate with cutaneous features of onchocerciasis. The Kaduna-London-Manchester Collaboration for Research on Onchocerciasis. *Human Immunol.* 1997;55:46-52.
57. Browne SG. Onchocercal depigmentation. *Trans R Soc Trop Med Hyg.* 1960;54:325-334.
58. Budenz DL. Blindness and visual impairment in an urban West African population: The Tema Eye Survey. *Ophthalmology.* 2012;119:1744-1753.
59. Richards Jr FO, Boatin BA. Control of onchocerciasis. *Adv Parasitol.* 2006;61:349-394.
60. Newland HS, White AT, Greene BM, Murphy RP, Taylor HR. Ocular manifestations of onchocerciasis in a rain forest area of West Africa. *Br J Ophthalmol.* 1991;75:163-169.
61. Egbert PR, Jacobson DW, Fiadoyor S, Dadzie P, Ellingson KD. Onchocerciasis: A potential risk factor for glaucoma. *Br J Ophthalmol.* 2005;89:796-798.
62. Pascual-Castroviejo I, Roche C, Martinez-Bermejo A, et al. Hypomelanosis of Ito: A study of 76 infantile cases. *Brain Dev.* 1998;20: 36-43.
63. Ruiz-Maldonado R, Toussaint S, Tamayo L, Laterza A, del Castillo V. Hypomelanosis of Ito: Diagnostic criteria and report of 41 cases. *Pediatr Dermatol.* 1992;9:1-10.
64. Pascual-Castroviejo I, López-Rodriguez L, de la Cruz Medina M, Salamanca-Maesso C, Roche Herrero C. Hypomelanosis of Ito. neurological complications in 34 cases. *Can J Neurol Sci.* 1988;15: 124-129.

65. Rubin MR. Incontinentia Pigmenti achromians, multiple cases within a family. *Arch Dermatol.* 1972;105:424-425.
66. Lungarotti MS, Martello C, Calabro A, Baldari F, Mariotti G. Hypomelanosis of Ito associated with chromosomal translocation involving Xp11. *Am J Med Genet.* 1991;40:447-448.
67. Steichen-Gersdorf E, Trawöger R, Duba HC, et al. Hypomelanosis of Ito in a girl with plexus papilloma and translocation (X;17). *Hum Genet.* 1993;90:611-613.
68. Koiffmann CP, de Souza DH, Diament A, et al. Incontinentia Pigmenti achromians (hypomelanosis of ITO, MIM 146150): Further evidence of localization at Xp11. *Am J Med Genet.* 1993;46:529-533.
69. Bitoun P, Philippe C, Cherif M, Mulcahy MT, Gilgenkrantz S. Incontinentia Pigmenti (type 1) and X;5 translocation. *Ann Genet.* 1992;35:51-54.
70. Pinheiro A, Mathew MC, Thomas M, et al. The clinical profile of children in India with pigmentary anomalies along the lines of Blaschko and central nervous system manifestations. *Pediatr Dermatol.* 2007;24:11-17.
71. Ritter CL, Steele MW, Wenger SL, Cohen BA. Chromosome mosaicism in hypomelanosis of Ito. *Am J Med Genet.* 1990;35:14-17.
72. Chitayat D, Friedman JM, Johnston MM. Hypomelanosis of Ito—a nonspecific marker of somatic mosaicism: Report of case with trisomy 18 mosaicism. *Am J Med Genet.* 1990;35:422-424.
73. Donnai D, Read AP. Hypomelanosis of Ito. *Lancet.* 1992;339:819-820.
74. Pellegrino JE, Schnur RE, Kline R, Zackai EH, Spinner NB. Mosaic loss of 15 q11 q13 in a patient with hypomelanosis of Ito: Is there a role for the P gene? *Hum Genet.* 1995;96:485-489.
75. Weaver Jr RG, Martin T, Zanolli MD. The ocular changes of Incontinentia Pigmenti achromians (hypomelanosis of Ito). *J Pediatr Ophthalmol Strabismus.* 1991;28:160-163.
76. Amon M, Menapace R, Kirnbauer R. Ocular symptomatology in familial hypmelanosis Ito. Incontinentia Pigmenti achromians. *Ophthalmologica.* 1990;200:1-6.
77. Ruggieri M, Pavone L. Topical review: Hypomelanosis of Ito: Clinical syndrome or just phenotype? *J Child Neurol.* 2000;15:635-644.
78. El-Sawy T, Abramson D. Retinoblastoma presenting in a child with hypomelanosis of Ito. *Open Ophthalmol J.* 2011;5:55-58.
79. Goldberg M. The skin is not the predominant problem in Incontinentia Pigmenti. *Arch Dermatol.* 2004;140(6):748-750.
80. Bodak N, Hadj-Rabia S, Hamel-Teillac D, de Prost Y, Bodemer C. Late recurrence of inflammatory first-stage lesions in Incontinentia Pigmenti. *Arch Dermatol.* 2003;139:201-204.
81. Minić S, Trpinac D, Obradović M, Incontinentia Pigmenti diagnostic criteria update. *Clin Genet.* 2014;85:536-542. doi: http://dx.doi.org/10.1111/cge.12223. Published online June 26, 2013.
82. O'Doherty M, McCreery K, Green AJ. Incontinentia Pigmenti-ophthalmological observation of a series of cases and review of the literature. *Br J Ophthalmol.* 2011;95:11-16.
83. Al-Zuhaibi S, Ganesh A, Al-Waili A. A female child with skin lesions seizures: Case report of Incontinentia Pigmenti. *Sultan Qaboos Univ Med J.* 2009;9:157-161.
84. Minić S, Trpinac D, Obradović M, Systematic review of central nervous system anomalies in incontinentia pigmenti. Orphanet J Rare Dis. 2013. doi: http://dx.doi.org/10.1186/1750-1172-8-25. Published online August 25, 2013.
85. Kim BJ, Shin HS, Won CH, et al. Incontinentia Pigmenti: Clinical observation of 40 Korean cases. *J Korean Med Sci.* 2006;21:474-477.
86. Rahi J, Hungerford J. Early diagnosis of the retinopathy of Incontinentia Pigmenti: Successful treatment by cryotherapy. *Br J Ophthalmol.* 1990;74:377-379.
87. Patel CK, Fung THM, Muqit MMK. Non-contact ultra-widefield retinal imaging and fundus fluorescein angiography of an infact with Incontinentia Pigmenti without sedation in an ophthalmic office setting. *J AAPOS.* 2013;17:309-311.
88. Berlin AL, Paller AS, Chan LS. Incontinentia Pigmenti: A review and update on the molecular basis of pathophysiology. *J Am Acad Dermatol.* 2002;47(2):169-187.
89. Meuwissen MEC, Mancini GMS. Neurological findings in Incontinentia Pigmenti; a review. *Eur J Med Genet.* 2012;55:323-331.
90. Hadj-Rabia S, Froidevaux D, Bodak N, et al. Clinical study of 40 cases of Incontinentia Pigmenti. *Arch Dermatol.* 2003;139:1163-1170.
91. Ardelean D, Pope E. Incontinentia Pigmenti in boys: A series and review of the literature. *Pediatr Dermatol.* 2003;23(6):523-527.
92. Phan TA, Wargon O, Turner AM. Incontinentia Pigmenti case series: Clinical spectrum of Incontinentia Pigmenti in 53 female patients and their relatives. *Clin Exp Dermatol.* 2005;30:474-480.
93. Pacheco TR, Levy M, Collyer JC, et al. Incontinentia Pigmenti in male patients. *J Am Acad Dermatol.* 2006;55:251-255.
94. Landy SJ, Donnai D. Incontinentia Pigmenti (Bloch-Sulzberger syndrome). *J Med Genet.* 1993;30:53-59.
95. Macey-Dare LV, Goodman JR. Incontinentia Pigmenti: Seven cases with dental manifestations. *Int J Paediatr Dent.* 1999;9:293-297.
96. Gonder JR, Ezell PC, Shields JA, Augsburger JJ. Ocular melanocytosis: A study to determine the prevalence rate of ocular melanocytosis. *Ophthalmology.* 1982;89:950-952.
97. Leung AK, Kao CP, Cho HY, et al. Scleral melanocytosis and oculodermal melanocytosis (nevus of Ota) in Chinese children. *J Pediatr.* 2000;137:581-584.
98. Teekhasaenee C, Ritch R, Rutnin U, Leelawongs N. Glaucoma in oculodermal melanocytosis. *Ophthalmology.* 1990;97:562-570.
99. Dutton JJ, Anderson RL, Schelper RL, Purcell JJ, Tse DT. Orbital malignant melanoma and oculodermal melanocytosis: Report of two cases and review of the literature. *Ophthalmology.* 1984;91:497-507.
100. Patel BC, Egan CA, Lucius RW, et al. Cutaneous malignant melanoma and oculodermal melanocytosis (nevus of Ota): Report of a case and review of the literature. *J Am Acad Dermatol.* 1998;38:862-865.
101. Lindsey SF, Sanchez MI, Elgart GW, et al. Malignant melanoma from a nevus of Ota in a pediatric patient with fatal outcome. *J Am Acad Dermatol.* 2013;69:e195-197. doi: http://dx.doi.org/10.1016/j.jaad.2013.05.009. Published, online October 2013.
102. Chen YC, Chang CH, Hsu SL, Hsu MW, Lee CL. Malignant melanoma of the choroid in the eye with oculodermal melanocytosis of a Chinese woman. *Kaohsiung J Med Sci.* 2010;26:673-678.
103. Sharan S, Grigg JR, Billson FA. Bilateral naevus of Ota with choroidal melanoma and diffuse retinal pigmentation in a dark skinned person. *Br J Ophthalmol.* 2005;89:1529-1545.
104. Singh M, Kaur B, Annuar NM. Malignant melanoma of the choroid in a naevus of Ota. *Br J Ophthalmol.* 1988;72:131-133.
105. Carreño E, Saornil MA, Garcia-Alvarez C, et al. Prevalence of ocular and oculodermal melanocytosis in Spanish population with uveal melanoma. *Eye (Lond).* 2012;26:159-162.
106. Qian Y, Zakov ZN, Schoenfield L, Singh AD. Iris melanoma arising in iris nevus in oculo (dermal) melanocytosis. *Surv Ophthalmol.* 2008;53:411-415.
107. Hudson HL, Valluri S, Rao NA. Choroidal melanomas in Hispanic patients. *Am J Ophthalmol.* 1994;118:57-62.
108. Rivers JK. Dural melanoma associated with OCD and blue nevi. *J Cutan Med Surg.* 2001;5:381-385.
109. Wang J, Guo ZZ, Zhang SG, et al. Microsurgical treatment of meningeal malignant melanoma accompanied by nevus of Ota: Two case reports and a literature review. *Melanoma Res.* 2013;23:502-504.
110. John H, Britto JA. Nonchoroidal intraorbital malignant melanoma arising from naevus of Ota. *J Plastic Reconstruc and Aesthet Surg.* 2010;63:e387-389. doi: http://dx.doi.org/10.1016/j.bjps.2009.09.014. Published online on October 21, 2009.
111. Chan HH, Leung RS, Ying SY, et al. A retrospective analysis of complications in the treatment of nevus of Ota with the Q-switched alexandrite and Q-switch Nd:YAG lasers. *Dermatol Surg.* 2000;26:1000-1006.
112. Kim TI, Yoon J, Choi J, Tchah H. Flipped scleral flap surgery for reduction of ocular pigmentation in oculodermal melanosis. *Cornea.* 2005;24:482-485.
113. Teekhasaenee C, Ritch R, Rutnin U, Leelawongs N. Ocular findings in oculodermal melanocytosis. *Arch Ophthalmol.* 1990;108:1114-1120.

114. Velazquez-Martin JP, Krema H, Fulda E, et al. Ultrasound biomicroscopy of the ciliary body in ocular/oculodermal melanocytosis. *Am J Ophthalmol.* 2013;155:681-687.
115. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue nevi. *Nature.* 2009;457:599-602.
116. Magaresevic L, Abazi Z. Unilateral open-angle glaucoma associated with the ipsilateral nevus of Ota. Case reports Ophthalmol Med. 2013 doi: http://dx.doi.org/10.1155/2013/924937. Published, online April 9, 2013.
117. Kim JY, Hong JT, Lee SH, et al. Surgical Reduction of ocular pigmentation in patients with oculodermal melanocytosis. *Cornea.* 2012;31:520-524.
118. Chi W, Yang P, Li B, et al. IL-23 promotes CD4+ T cells to produce IL-17 in Vogt-Koyanagi-Harada disease. *J Allergy Clin Immunol.* 2007;119:1218-1224.
119. Rathinam SR, Namperumalsamy P, Nozik RA, Cunningham Jr ET. Vogt-Koyanagi-Harada syndrome after cutaneous injury. *Ophthalmology.* 1999;106:635-638.
120. Ishikawa A, Shiono T, Uchida S. Vogt-Koyanagi-Harada disease in identical twins. *Retina.* 1994;14:435-437.
121. Rutzen AR, Ortega-Larrocea G, Schwab IR, Rao NA. Simultaneous onset of Vogt-Koyanagi-Harada syndrome in monozygotic twins. *Am J Ophthalmol.* 1995;119:239-240.
122. Shindo Y, Ohno S, Nakamura S, Onoé K, Inoko H. A significant association of HLA-DPB1*0501 with Vogt-Koyanagi-Harada's disease results from a linkage disequilibrium with the primarily associated allele, DRB1*0405. *Tissue Antigens.* 1996;47:344-345.
123. Zhao M, Jiang Y, Abrahams IW. Association of HLA antigens with Vogt-Koyanagi-Harada syndrome in a Han Chinese population. *Arch Ophthalmol.* 1991;109:368-370.
124. Weisz JM, Holland GN, Roer LN, et al. Association between Vogt-Koyanagi-Harada syndrome and HLA-DR1 and -DR4 in Hispanic patients living in southern California. *Ophthalmology.* 1995;102: 1012-1015.
125. Hu K, Yang P, Jiang Z, et al. STAT4 polymorphism in a Chinese Han population with Vogt-Koyanagi-Harada syndrome and Behcet's disease. *Hum Immunol.* 2010;71:723-726.
126. Jiang Z, Yang P, Hou S, Li F, Zhou H. Polymorphisms of IL23 R and Vogt-Koyanagi-Harada syndrome in a Chinese Han population. *Hum Immunol.* 2010;71:414-417.
127. Shu Q, Yang P, Hou S, et al. Interleukin-17 gene polymorphism is associated with Vogt-Koyanagi-Harada syndrome but not with Behcet's disease in a Chinese Han population. *Hum Immunol.* 2010;71:988-991.
128. Hu K, Hou S, Li F, et al. JAK1, but not JAK2 and STAT3, confers susceptibility to Vogt-Koyanagi-Harada (VKH) syndrome in a Han Chinese population. *Invest Ophthalmol Vis Sci.* 2013;54:3360-3365.
129. Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: Report of an international comittee on nomenclature. *Am J Ophthalmol.* 2001;131:647-652.
130. Mondkar SV, Biswas J, Ganesh SK. Analysis of 87 cases with Vogt-Koyanagi-Harada disease. *Jpn J Ophthalmol.* 2000;44:296-301.
131. Rathinam SR, Namperumalsamy P. Global variation and pattern changes in epidemiology of uveitis. *Indian J Ophthalmol.* 2007;55:173-183.
132. Singh R, Gupta V, Gupta A. Pattern of uveitis in a referral eye clinic in North India. *Indian J Ophthalmol.* 2004;52:121-125.
133. Damico FM, Kiss S, Young LH. Vogt-Koyanagi-Harada disease. *Semin Ophthalmol.* 2005;20:183-190.
134. Martin TD, Rathinam SR, Cunningham ET. Prevalence, clinical characteristics, and causes of vision loss in children with Vogt-Koyanagi-Harada disease in South India. *Retina.* 2010;30:1113-1121.
135. Ishihara K, Hangai M, Kita M, Yoshimura N. Acute VKH disease in enhanced sptectral domain optical coherence tomography. *Ophthalmology.* 2009;116:1799-1807.
136. Jin Y, Birlea SA, Fain PR, et al. Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. *Nat Genet.* 2012;44:676-680.
137. Albert DM, Wagoner MD, Pruett RC, Nordlund JJ, Lerner AB. Vitiligo and disorders of the retinal pigment epithelium. *Br J Ophthalmol.* 1983;67:153-156.
138. Cowan CL, Halder RM, Grimes PE, Chakrabarti SG, Kenney Jr JA. Ocular disturbances in vitiligo. *J Am Acad Dermatol.* 1986;15:17-24.
139. Baskan EB, Baykara M, Ercan I, Tunali S, Yucel A. Vitiligo and ocular findings: A study on possible associations. *J Eur Acad Dermatol Venereol.* 2006;20:829-833.
140. Vingerling JR, Owens S, van der Meijden WI, Hoyng CB, Bird AC. Cutaneous vitiligo associated with choroidal hypopigmentation. *Eye.* 2004;18:939-940.
141. Ciardella AP, Horsely MB, Brown DM. Hypopigmentary fundus changes seen with cutaneous vitiligo. *Arch Ophthalmol.* 2007;125:576.
142. Biswas G, Barbhuiya JN, Biswas MC, Islam MN, Dutta S. Clinical pattern of ocular manifestations in vitiligo. *J Indian Med Assoc.* 2003;101:478-480.
143. Wagoner MD, Albert DM, Lerber AB, et al. New observations on vitiligo and ocular disease. *Am J Ophthalmol.* 1983;96:16-26.
144. Shankar DS, Shashikala K, Madala R. Clinical patterns of vitiligo and its associated comorbidities: A prospective controlled cross-sectional study in South India. *Indian Dermatol Online J.* 2012;3:114-118.
145. Narita T, Oiso N, Fukai K, et al. Generalized vitiligo and associated autoimmune diseases in Japanese patients and their families. *Allergol Int.* 2011;60:505-508.
146. Handa S, Dogra S. Epidemiology of childhood vitiligo: A study of 625 patients from north India. *Pediatr Dermatol.* 2003;20:207-210.
147. Agarwal S, Gupta S, Ojha A, Sinha R. Childhood vitiligo: Clinicoepidemiologic profile of 268 children from the Kumaun Region of Uttarakhand. *Indian Pediatr Dermatol.* 2013;30:348-353.
148. Ayotunde A, Olakunle G. Ophthalmic assessment in black patients with vitiligo. *J Natl Med Assoc.* 2005;97:286-287.
149. Farrer LA, Grundfast KM, Amos J, et al. Waardenburg syndrome (WS) type I is caused by defects at multiple loci, one of which is near ALPP on chromosome 2: First report of the WS consortium. *Am J Hum Genet.* 1992;50:902-913.
150. Pingault V, Ente D, Dastot-Le Moal F, et al. Review and update of mutations causing Waardenburg syndrome. *Hum Mutat.* 2010;31:391-406.
151. Bansal Y, Jain P, Goyal G, Singh M, Mishra C. Waardenburg syndrome—A case report. *Cont Lens Anterior Eye.* 2013;36:49-51.
152. Shields CL, Nickerson SJ, Al-Dahmash S, Shields JA. Waardenburg Syndrome: Iris and choroidal hypopigmentation findings on anterior and posterior segment imaging. *JAMA Ophthalmol.* 2013;131:1167-1173.
153. Ang CS. Recurrent vitreous haemorrhage in a patient with Waardenburg syndrome. *Asian J Ophthalmol.* 2002;4:13-14.
154. Vichare N, Bhargava N. Waardenburg syndrome: A rare case with bilateral congenital cataract: An unusual entity. *Med J Armed Forces India.* 2013;69:172-174.
155. Kashima T, Akiyama H, Kishi S. Asymmetric severity of diabetic retinopathy in Waardenburg syndrome. *Clin Ophthalmol.* 2011;5: 1717-1720.
156. Moshfeghi DM, Wilson MW, Haik BG, et al. Retinoblastoma metastatic to the ovary in a patient with Waardenburg syndrome. *Am J Ophthalmol.* 2002;133:716-718.
157. Chen H, Jiang L, Xie Z, et al. Novel mutations of PAX3, MITF, and SOX10 genes in Chinese patients with type I or type II Waardenburg syndrome. *Biochem Biophys Res Commun.* 2010;397:70-74.
158. Kadoi C, Hayasaka S, Yamamoto S. Branch retinal vein occlusion in a patient with Waardenburg syndrome. *Ophthalmologica.* 1996;210: 354-357.
159. Delleman JW, Hageman MJ. Ophthalmological findings in patients with Waardenburg syndrome. *J Ped Ophthalmol and Strabismus.* 1978;15:341-345.
160. Ohno N, Kiyosawa M, Mori H. Clinical findings in Japanese patients with Waardenburg syndrome type 2. *Jpn J Ophthalmol.* 2003;47: 77-84.