

Bachelorarbeit des Studiengangs Augenoptik und Hörakustik

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Visual Consequences Of Albinism

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Visual Consequences Of Albinism

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Abstract - 5 -

Abstract

Purpose: The purpose of this thesis is to provide a comprehensive literature

review about albinism as an inherited metabolic disorder of melanin synthesis

along with those related conditions impacting the visual system. As such, it

addresses eye care emphasizing the visual consequences of albinism along with

diagnostic and treatment options.

Methods: Background knowledge about ocular development is given as well as

information about etiological biochemical and genetic processes. The current

classification, clinical findings and their assessment and management options are

presented based on recent results of research. In conclusion, two case reports are

described as examples of visual care options.

Results: Melanin plays a big role in the retinal and chiasmal development. Melanin

biosynthesis can be disrupted by different genes in various ways which leads to the

current classification of albinism. Clinical findings include fundus hypopigmenta-

tion, nystagmus, iris transillumination, photophobia, foveal hypoplasia, excessive

chiasmal decussation, reduced visual acuity, high astigmatism (with-the-rule),

strabismus and decreased stereopsis. Treatment options to improve visual acuity,

fixation and binocularity are (tinted) prescription lenses and contact lenses, low

vision aids, surgical procedures and vision therapy. Medication and supplementa-

tion for increased pigmentation are currently being tested on mice.

Conclusions: Albinism is caused by genetic mutations resulting in ocular and

cutaneous hypopigmentation. It establishes various phenotypes that require

different therapy approaches in order to improve vision and therefore quality of life.

Keywords: albinism; vision; genes; melanin; vision therapy; low vision

Chapter 1: Introduction

1.1 Purpose of the review

The purpose of this thesis is to provide a comprehensive literature review about albinism; its etiology, epidemiology, signs and symptoms, assessment and management with emphasis upon the visual consequences. Furthermore, the review presents a useful and up-to-date tool for optometrists and ophthalmologists in order to diagnose and successfully manage patients with albinism in a clinical setting. The paper also includes recent research findings about etiology and different types as well as new approaches for the management of the resulting visual consequences. These new approaches show promise for future development and application.

The thesis first presents a comprehensive discussion on the origins of albinism followed by coverage of associated visual dysfunctions including assessment and clinical management techniques.

1.2 Historical origins

Legends and myths about albinism go way back to the first few centuries *anno domini*. They tell about very light humans that hide from the sun and hunt at night in the forest. Zivodofsky and Schrader suggest that a Talmudic account around the year 500 possibly described albinism in a tribe that lived along the River Tigris. By the end of the 18th century, African tribes with a high percentage of albinotic members gained special interest in research since the phenotype is better recognized and it occurs more often due to interfamilial marriages. Further research led to the official distinction between "partial" and "complete" albinism by the researcher Saint Hilaire in 1832. Nevertheless, in 1908, Garrod was the first who proposed that albinism may be a genetic metabolism disorder in pigment production. He also created an autosomal recessive hereditary pattern after

analyzing data that had been collected about 24 families in 1871 by Ascoles. During World War II, Edwards *et al.* and Goldzieher *et al.* estimated and established that the absence of melanin (the "dark pigment") is the underlying cause of hypopigmentation. In the 1950s, studies by Bloch and Fitzpatrick on human and animal skin slices showed the oxidation of tyrosine and dihydroxyphenylalanine (DOPA) by tyrosinase to melanin. At this time, albinism had been divided into complete albinism, incomplete albinism and ocular albinism but researchers expected more subtypes and suggested genetic analysis for further research on the disease.¹

1.3 State of the art in research

So far, a good number of albinism-causing gene and therefore enzyme defects are known which result in various types, each with their own broad variety of phenotypes. However, researchers propose the existence of other still unknown involved proteins and therefore more different subtypes.4 In terms of visual signs and symptoms, the majority of possible presentations have already been investigated although most of the studies contain only a limited number of albinotic participants. Notwithstanding, the exact etiology of some clinical findings, such as nystagmus, foveal hypoplasia and excessive chiasmal decussation, is still unknown. Nowadays, research and eye care specialists try to find better options to manage the visual consequences of hypopigmentation using medication which is being tested on mice, new electrical low vision devices and vision therapy. Yet, there are no reports about vision therapy intervention in the albinotic population. This form of therapy aims at stabilizing fixation, improving accommodation and vergences, supporting binocularity which leads to at least peripheral stereopsis. Therefore, this review also includes vision therapy as a part of the management plan as well as a case report where it had been included.

Chapter 2: Background

2.1 Structure and development of the visual pathway

This section will emphasize the development and role of the chiasm as it exhibits the most significant changes along the visual pathway in all types of albinism. The term "visual pathway" includes the optic nerve that combines nasal and temporal retinal fibers leading them to the optic chiasm in the midbrain; further to the optic tract and lateral geniculate nucleus in the thalamus and finally to the visual cortex in the occipital lobe. As seen in Figure 1, the nasal retinal fibers cross to the contralateral brain hemisphere whereas around 40% of the temporal retinal fibers stay on the same side. As a result, the information from the left half of the visual field is processed in the right hemisphere of the visual cortex. The two slightly different pictures arrive in the visual cortex to create one stereo picture.⁵ The malformation of the chiasm, including either achiasmia or excessive fiber crossing, such as in albinism, leads to non-corresponding visual fields in the visual cortex. This sets the stage for poor or no binocular vision. Studies in mice reveal the milestones in the development of the chiasm which is understood as an act of communication between retinal ganglion cells (RGC) of both eyes. First, pioneer axons from the dorso-central retina find their way to the future chiasm and form the characteristic)(shape as they all cross the midline. The ventro-temporal RGCs are the second type of axons to arrive. Nevertheless, they stay ipsilateral. The third step is the final formation of the chiasm, when the rest of the axons cross to the contralateral side, no matter where they originate within the retina.⁶

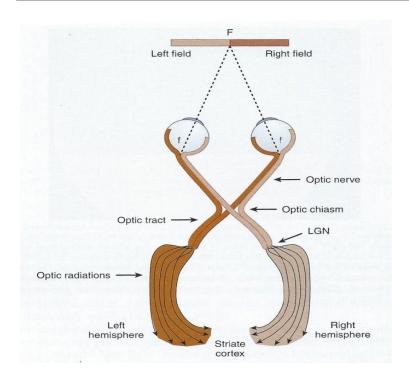


Figure 1: Normal human visual pathway. Note how the nasal retinal fibers cross at the chiasm whereas the temporal fibers stay uncrossed.⁵

There are main guidance proteins that are involved in the formation of the chiasm. First of all, Netrin, an attractant for retinal axons, is expressed at the optic nerve head in order to make the axons exit the retina at this point. After the axons reach the optic nerve head, the repulsive guidance proteins Slit1 and Slit2, at the midline on the way to the future chiasm, are responsible for the ipsilateral nerve fibers. Additionally, RGCs from the ventro-temporal retina express EphB that interacts with EphrinB as a receptor at the midline to prevent crossing. Thus, axons without EphB expression are not sensitive to EphrinB and therefore do cross the midline. That means that a lack of EphrinB leads to a lack of ipsilateral projections and, respectively, excessive crossing, as is found in albinism. The amount of EphrinB expression is basically controlled by Zic2, a zinc finger transcription factor. However, studies show that both tyrosinase and DOPA also play a role in the cell cycle of RGCs and the development of the chiasm. ^{6,7} In 2007, von dem Hagen *et al.* determined a significantly negative correlation between pigmentation and the

extent of misrouting in 18 patients with albinism.⁸ Still, further studies are needed to investigate the detailed association of melanin and the formation of the chiasm and to look for other involved guidance proteins.

2.2 Structure and development of the retina and macula

Since there are also major changes on the retina and especially in the macula and fovea in all types of albinism, it is important to describe their anatomical structure and development as well as the role of melanin. First of all, Figure 2 shows the 10 layers and their histology of a human adult retina 2mm from the fovea center with the common abbreviations. From top to bottom, the retina consists of the nerve fiber layer (NFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), inner segment and outer segment of the photoreceptors, retinal pigment epithelium ((R)PE) and the choroid (CH). Additionally, a single layer of cones (C) and multiple layers of rods (R) are indicated in the picture.

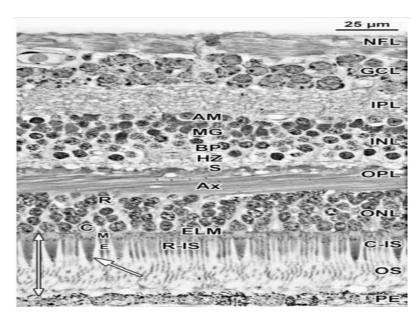


Figure 2: Healthy human retina 2mm from the fovea with 10 layers: NFL, GCL, IPL, INL, OPL, ONL, IS and OS of the photoreceptors, (R)PE and CH. Cones and rods are also indicated.⁹

Hendrickson et al. investigated the foveal development from fetal week 20 until the age of 13 and highlighted the milestones. In fetal week 20-22, the future fovea is visible as a single layer of cones in the ONL. Only three weeks later, the beginning of the formation of the foveal pit is marked by the displacement of the GCL, IPL and INL that continues until birth. Also, the photoreceptors show more distinct inner and outer segments. At 15 months postnatal, the GCL, IPL and INL are one single layer now, whereas the cones with thin and long inner and outer segments are packed two to four nuclei deep. The layers with neurons disappear by the age of 4 years. The cone pane packing continues until the age of 13 when the fovea has fully developed to an adult-like stage. 9 These results also match with the development of visual acuity in infants and children. 10 Isenberg divided macular development into different stages: First, the macula presents as an indistinct pigmented area, then the annular reflex develops. Later, the foveal pit occurs and as a last step the foveal light reflex is seen. 11 In albinism, the retinal development generally plateaus at the first step leading to a reduced amount of cells, no or almost no lengthening of the foveal cone outer segments and foveal hypoplasia. 12 The lack of dopamine plays a big role in the retinal maldevelopment as its neurotransmitter signals for development of cells and neurons in the retina are missing.¹³ Studies suggest that foveal hypoplasia and chiasmal misrouting influence each other, whereas the chiasmal maldevelopment leads to foveal hypoplasia and not vice versa. This concept is supported by two main points. First of all, patients with aniridia and foveal hypoplasia do not exhibit excessive misrouting of nerve fibers. Secondly, as mapped above, the foveal pit formation occurs later than chiasmic decussation.

Further studies are needed to prove the relationship between foveal hypoplasia and nerve fiber misrouting.¹⁴ Morever, a study in 2005 revealed a significant narrowing of optic nerves and chiasm due to a reduced number of RGCs in the underdeveloped albinotic fovea leading to a decreased volume of grey matter in the occipital lobe.¹⁵

Melanin does not only play a role in the development of the fovea and chiasm but has some major functions in the retina, especially in the RPE. It acts as an antioxidant by reducing free radicals and therefore the risk of inflammation. Oxidative stress is caused by incoming light and phagocytosis of the rods outer segments. Additionally, it decreases light toxicity by absorbing UV light together with the iris in the anterior segment of the eye. Moreover, melanin binds zinc and contributes to the transport of Vitamin A and retinal metabolism. Its drug binding properties and the slow release in non-toxic concentrations protects the retina from damage by toxic substances. ¹⁶ Figure 3 shows where melanin is found in the outer retina.

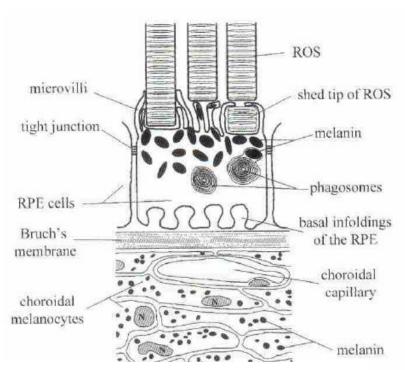


Figure 3: Melanin in the retina is found in the RPE as well as in the choroid.¹⁶

Besides the contribution to eye health, studies show a significant positive correlation of macular pigment optical density (MPOD) with best corrected visual acuity (BCVA) under photopic conditions. Additionally, MPOD improves contrast sensitivity under mesopic and photopic conditions as it absorbs UV light and thus reduces rod activation. Further studies are needed in terms of glare

sensitivity and photostress recovery time since results from various experiments conflict.¹⁹ The main reason for the different findings is most likely the light source used. While short wavelengths cause more photophobia than long wavelengths, it is not surprising that studies using mainly blue light find a higher correlation between MPOD and glare sensitivity than studies using longer wavelength light sources.

2.3 Eye movements and infantile nystagmus

Eye movements are necessary for foveation of visual stimuli, fixation during head movements or moving targets and awareness of body orientation. The eye movement system includes the extraocular muscles (EOM), ocular motor nerves and nuclei in the cerebral cortex, cerebellum and vestibular structures. Defects in saccades, smooth pursuits including nystagmus arise from the supranuclear subsystem which describes, rather, processing/sensory issues instead of oculomotor dysfunction.²⁰ Physiological eye movements consist of drifts, microtremors, microsaccades, saccades, smooth pursuits, optokinetic nystagmus (OKN) and vestibulo-ocular reflex (VOR). Physiological microsaccades and saccadic intrusions inhibit adaption and therefore blur by maintaining small image motions. Blur and oscillopsia occur in case of too much image motion (>4deg/sec), such as in nystagmus which is also found in albinism. In summary, perception is dependent on the quality of the retinal image, neurological processing (with a feedback control system) and fixation control. The latter is responsible for gaze holding, corrective eve movements on target and suppression of saccades off target while it also relies on varying exogenous factors, e.g. attention, tiredness or stress. Abnormal fixation results from inappropriate visual input during early sensitive periods contributing to a retinal image movement and visual degradation.²¹ Saccades, smooth pursuits and nystagmus can be recorded using electronystagmography, infrared limbal tracking, video oculography or the scleral search coil technique.²²

A common form of disturbed fixation is nystagmus; with its various types and recorded waveforms. There are two big groups concerning waveforms: pendular and jerk nystagmus. Both types are found in albinism and have various subtypes; this section will only emphasize the most common ones. Pendular nystagmus is described as a periodic eye movement resulting in a sinusoidal waveform. The motion has the same velocity in every direction and foveation is possible during the two peaks of the amplitude, in between the change of direction, respectively. Pendular nystagmus can either be symmetric, asymmetric or with small refoveating saccades at the end. See Figure 4.

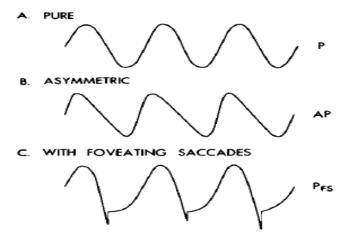


Figure 4: Types of pendular nystagmus: Pure, asymmetric and with foveating saccades. An upward line means a movement to the left, downward to the right. The Y axis figures as a measurement for amplitude.

The X axis displays a timeline and therefore the velocity of nystagmus. 23

Jerk nystagmus consists of a slow drift (slow phase) away from the target stopped by a saccade back (fast phase) as a corrective eye movement. The direction of the fast phase is also the definition in case of unidirectional nystagmus, e.g. right jerk nystagmus. Bidirectional is rarer where the direction changes every cycle. The subtypes of unidirectional jerk nystagmus are pure jerk, nystagmus with extended foveation and therefore better vision, pseudo-cycloid (accelerated drift to one direction, small saccade back followed by a slow eye movement to refoveate) and

pseudo-jerk (often misidiagnosed as jerk nystagmus in opposite direction). Figure 5 displays these different waveforms schematically.²³

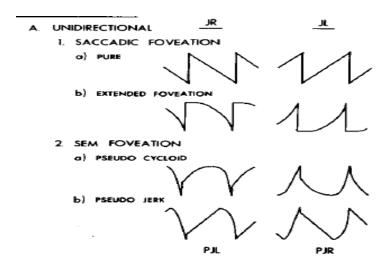


Figure 5: Different types of both left and right jerk nystagmus where the fast phase determines the direction of the nystagmus.²³

Various forms of congenital nystagmus do not always present equally; such as (a)periodic alternating nystagmus or fusion maldevelopment nystagmus syndrome. The latter is only visible if one eye is occluded or fixating and described as a jerk nystagmus with the direction of the jerk towards the viewing/fixating eye. (A)periodic alternating nystagmus has long periods (up to 10 minutes) of jerk nystagmus followed by short periods (up to 20 seconds) with pendular or no nystagmus at all.²⁴ Moreover, there is a null point in nystagmus which is a gaze with lowest nystagmus intensity, longest foveation period and improved VA. This might lead to an anomalous head posture in case of a null point in an eccentric gaze. Generally, patients with congenital nystagmus do not experience the movement of their whole visual field due to adaption and reduced sensitivity of retinal image drift. However, nystagmus leads to impaired fixation, smooth pursuits and therefore stereo and motion perception.²¹

Chapter 3: Epidemiology and Etiology

3.1 Prevalence

The different types of albinism have a different prevalence rate worldwide, depending on the population and region. Generally, the overall prevalence in the United States of all types of albinism is 1:18,000.25 Oculocutaneous albinism type 1 (OCA1) is the second common type with a frequency of 1:40,000 worldwide whereas it is the most common type in Germany with 50% of all cases. Nevertheless, precise numbers for oculocutaneous albinism type 1A and type 1B (OCA1A and OCA1B) are unknown as not every affected person is tested in order to determine the subtype. 26,27 Oculocutaneous albinism type 2 (OCA2) is the most prevalent subtype worldwide with an overall prevalence of 1:38,000 (in Caucasian populations around 1:36,000) except in Africa where it occurs with a 1:1,500 -1:3,900 rate. 28,29 Oculocutaneous albinism type 3 (OCA3) is only found in African populations where it is also the most common autosomal recessive disorder in southern Africa with a prevalence of 1:8,500.30 Oculocutaneous albinism type 4 (OCA4) is generally very rare among all subtypes of albinism with a worldwide prevalence of 1:100,000. In Japan, however, 24% of all known OCA cases are defined as OCA4. 31,32 The prevalence of ocular albinism type 1 (OA1) is also guite low with an occurrence of 1:60,000 in Denmark and 1:50,000 in the United States, but still the most common type among all OA types.³³

3.2 Biochemical aspects and genetics of melanin synthesis

Albinism is a disorder of melanin synthesis that leads to hypopigmentation of the eyes, hair and skin (oculocutaneous albinism, see 3.3.1) or only the eyes (ocular albinism, see 3.3.2). A lack of melanin presents a higher risk of malignant tumors due to its absent ultraviolet (UV) light protection properties. The following discussion describes the general process of melanin synthesis as well as its various break points due to different genetic changes in albinism.

At the beginning of melanin synthesis, melanoblasts from the neural crest migrate to the hair follicles, eyes (including iris, choroid and retina), inner ear, medulla oblongata and the epidermis of the skin. The melanoblasts in the skin develop to melanocytes that produce melanin which is stored in melanosomes. The produced melanin is passed to keratinocytes. The degree and color of pigmentation is given by the activity, not the quantity of melanocytes and the ratio of the two different types of melanin: eumelanin (black) and pheomelanin (yellow-red). Figure 6 shows the biochemical process of the production of eumelanin and pheomelanin. Tyrosine reacts to DOPA and DOPAquinon using the enzyme tyrosinase as catalyst. This step is the same in both production of pheomelanin and eumelanin. Pheomelanin forms after DOPAquinon and the amino acid cysteine combine to CysteinylDOPA. In contrast, there are many more proteins involved in the production of eumelanin, such as the tyrosinase-related protein 1 and 2 (TRP-1 and TRP-2), the P-protein, the membrane-associated transporter protein (MATP) and the ocular albinism protein 1 (OA1-protein). These are the main proteins that are affected due to genetic mutation in the various types of albinism and that therefore also cause different phenotypes.

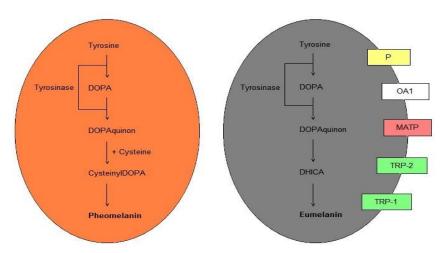


Figure 6: Pheomelanin and eumelanin production with involved proteins whose malfunction leads to different types of albinism. Adapted from: ²⁷

Moreover, Table 1 shows an overview of most commonly affected genes and proteins in the most common and best researched types of albinism.

Tyrosinase-negative OCA1A with a mutation on chromosome 11 in the tyrosinase gene leads to a complete loss of the catalyst function during the reaction from tyrosine to DOPAquinon and therefore to a complete lack of melanin for the whole life. Tyrosinase-positive OCA1B describes a certain rest function of the tyrosinase gene with increasing melanin production after birth. OCA2 presents with a mutation of the P-gene/OCA2 gene on chromosome 15. The P-gene and the P-protein as its product is responsible for a nearly neutral pH value in the melanosomes in order to assure a proper tyrosinase function. In case of OCA3 (also "rufous OCA"), the TRP-1 gene on chromosome 9 is changed which leads to a malfunction in the synthesis of eumelanin but not pheomelanin. The consequences of OCA4 with a mutation in the MATP gene on chromosome 5 resemble to OCA2 since the MATP has the same function in terms of the pH value as the P-protein.²⁷ OA1 presents with a mutated OA1 gene on the X chromosome that leads to an impaired G-protein receptor and therefore impaired signal conduction, growth and transport of melanosomes in pigment cells.³⁴⁻³⁶

Nevertheless, studies suggest that there are more mutations that have not been identified yet. There are cases, especially in OCA1B, with distinct phenotypes of albinism but without any know mutations of the known genes.²⁹ A recent review in 2014 by Montoliu *et al.* even proves the existence of three more types of oculocutaneous albinism: OCA5, OCA6 and OCA7 with new mutations but similar phenotypes.⁴ Moreover, even a hemizygote mutation of the OCA2 gene in the spectrum of Prader-Willi syndrome and Angelman syndrome is able to cause hypopigmented skin despite their second normal allele.³⁷ All these results confirm the suggestion that further research is needed in order to reveal more genetic mutations and subtypes of albinism but also associated disorders.

Table 1: Mutation overview of the most common types of ocular and oculocutaneous albinism. Adapted from: ²⁷

Main groups	Mutated genes and exact location
OCA1A/1B	Tyrosinase gene on chromosome 11q14-21
OCA2	P-gene/OCA2 gene on chromosome 15q11-q13
OCA3	TRP-1 gene on chromosome 9p23
OCA4	MATP gene on chromosome 5p13.3
OA1	OA1 gene on chromosome Xp22.3

3.3 Genetic testing and counseling

Beside research purposes, genetic testing is usually performed on a clinical basis in order to gain information about mutant genes and proteins as impaired gene products. After the isolated DNA from a blood sample is amplified and sequenced, it is compared to the wild-type sequence in terms of changes. A diagnosis is made if two mutations are present in the known genes.²⁷ DNA sequencing reveals the exact order of nucleotides in the genes. Almost 50% of mutations are missense mutations which are a result of an exchange of one nucleotide by another leading to a wrong amino acid and therefore protein product.³⁸ So far, only TYR and OCA2 screening is available on a clinical basis, TYRP1 and MATP screening is only performed in research. Prenatal (DNA extraction from chorion villus sampling or cultured amniocytes, fetal skin biopsy) and preimplantation genetic diagnosis is possible but only rarely offered and/or requested since both OCA and OA do not affect general health or intelligence.³⁹ In patients with obvious albinotic phenotype but without detectable mutation, a sporadic or novel mutation is possible. Studies report difficulties in determining the underlying mutations especially in OCA1B and OCA2. Therefore, a precise laboratory work-up is often limited.^{29,39}

However, in case of successfully detected mutations, genetic counseling is necessary. Its aim is the interpretation of results and the education about further inheritance for offspring and siblings. Since all forms of OCA are inherited autosomal recessively, healthy parents of an affected child are obligate carriers. There is a 25% chance of either another affected child and a 50% chance of having an asymptomatic carrier child. A so-called "pseudo-dominant pattern" occurs if a person with albinism and an asymptomatic carrier have children since the likelihood increases up to 50% for the offspring to be affected with all healthy siblings being carriers. The X-linked recessive forms of OA mostly affect males because the mutated gene that they inherit from their carrier mother manifests the phenotype. Females are only affected if they have two mutated copies from their affected father and carrier/affected mother. The risk for a female carrier's offspring is 50% for sons to be affected and for daughters to be an asymptomatic carrier. There is no transmission from father to son as he always transmits his unaffected Y chromosome. The typical mosaic phenotype for female carriers (see section 4.2) in X-linked recessive OA results from Lyonization which means that every cell is controlled by either the affected or unaffected X chromosome. Therefore, half of the cells (e.g. in the skin or RPE) are healthy whereas the other half of the cells use the mutated X chromosome.³⁸

Chapter 4: Description of the phenotypes and syndromes in albinism

Albinism can be divided into two big groups: Oculocutaneous albinism affects the eyes, skin and hair whereas ocular albinism affects the eyes only. Furthermore, there are multi-organ syndromes including the clinical features of albinism.

4.1 Oculocutaneous albinism

Oculocutaneous albinism is a group of autosomal recessive inherited disorders of melanin synthesis leading to hypopigmentation of the skin, hair and eyes. Affected patients present with a normal mental development and lifespan.³⁹

OCA1A

OCA1 can be divided into the subtypes 1A and 1B which are both related to a complete or reduced tyrosinase activity whereas the term "tyrosinase-negative albinism" for the description of the subtype should no longer be used. OCA1A presents with a complete lack of tyrosinase function at birth and throughout life. Patients are most commonly compound heterzygotes carrying two different tyrosinase mutant alleles from both parents. It is the most obvious type of albinism and results in white hair, eye brows, eye lashes and white skin without the ability to tan. Patients also suffer from a high risk of basal or squamous cell carcinoma, pachydermia and premalignant lesions due to the complete absence of pigment and unprotected exposure to sunlight. The ocular signs include photophobia and pink irises with full transillumination because of the absence of melanin in the iris stroma and posterior iris epithelium. Nystagmus is first seen between 3 and 12 weeks after birth; it most commonly presents as horizontal nystagmus and might decrease over time. Patients often use a compensatory head tilt in order to achieve better vision by using the null point, the point with the smallest amplitude of

nystagmus. Studies show a range of reduced visual acuities from 20/100 to 20/400. As a result of greatly decreased RPE pigmentation, choroidal blood vessels show through all the layers of the retina which also exhibits areas of hyperreflectivity due to increased light scattering. Albinotic patients also present with strabismus, most commonly esotropia and reduced or no depth perception which is associated with the excessive crossing and misrouting of optic nerve fibers at the chiasm. ^{26,17} Furthermore, a study by Käsmann-Kellner *et al.* reveals a tilted optic disc syndrome including a tilted, smaller and dysplastic optic nerve head in addition to a smaller nervus and tractus optici in a majority of patients. The degree of manifestation hereby correlates with visual acuity. ⁴⁰ Since the lack of melanin disrupts the foveal development the fovea appears fully hypoplastic without an avascular zone and annular reflex. ¹²

OCA1B

OCA1B presents with the same clinical features as OCA1A at birth although the tyrosinase enzyme has a partial rest function. Therefore, especially pheomelanin production increases until young adulthood in most of the patients. Nevertheless, the phenotype does not always correlate with the genotype in terms of the expected pigmentation after genetic analysis. ⁴¹ Patients have white, blond or almost yellow or orange hair since the pheomelanin production increases over time. Furthermore, the ocular signs also tend to be less severe than in OCA1A with visual acuities from 20/100 to 20/200 which may improve through adolescence. The severity of nystagmus, foveal hypoplasia, strabismus, optic nerve misrouting and iris transillumination varies among patients. ²⁶

Temperature-sensitive OCA1B

A subtype of OCA1B is the temperature-sensitive mutant type with similar ocular signs but more distinct physical attributes. It was first described in 1991 by King et

al. in an individual with albinism who presented with white hair in warmer parts of her body such as the scalp and axilla but darker hair in cooler areas, e.g. the extremities. The study group tracked it down to a mutant tyrosinase enzyme that is only active below a temperature of 35-37°C. 42,43 A case report by Wang et al. explains the biochemical defect and its consequences in more detail: "The mutation ... results in a temperature-sensitive trafficking defect preventing the translocation of the mutant tyrosinase into melanosomes. Thus, at 37°C, ... tyrosinase is retained in the endoplasmic reticulum and degraded by proteasomes and no pigment is produced. At lower temperatures (31°C) the enzyme can be successfully translocated into the melanosomes and can produce pigment." Figure 7 shows the pigmented hair on the arms but the white axillary hair of an individual with temperature sensitive OCA1B.



Figure 7: Temperature sensitive OCA1B results in white hair in warmer body parts (here: axilla) and dark hair in colder areas of the body (here: arms).⁴³

OCA2

In contrast to OCA1, OCA2 with normal tyrosinase activity, but a defect P-protein, shows a small degree of melanin production in newborns' eyes, skin and hair. Therefore, the same clinical features for albinism are present but less severe than in OCA1. Generally, there is a broad variety of phenotypes that are also strongly related to the ethnic background and origin (also see "Brown OCA"). The hair color

ranges from light blond to brown and a variable amount of iris and RPE pigment is detectable. Visual acuities in OCA2 patients are between 20/25 and 20/200 but are usually found in the range from 20/60 to 20/100.^{17,28} A study by King and associates in 2003 revealed eight cases with mutations in the OCA2 gene and the melanocortin-1 receptor gene (MC1R). The MC1R gene influences the balance between pheomelanin and eumelanin. A mutation is therefore responsible for red hair in the normal pigmented population. The combination of the OCA2 and MC1R gene mutation leads to a modified albinotic phenotype with bright red hair in the OCA2 patients.⁴⁵

Brown OCA2

Brown OCA2 belongs to the OCA2 spectrum whereas it is often found in Africa, especially in Nigeria and Ghana. It is associated with light brown to brown hair and skin, grey irises, a slight foveal reflex and visual acuities between 20/60 and 20/150. Patients with Brown OCA present with more pigment than typically found in albinism but less than expected in terms of their ethnic background. Thus, it often remains undiagnosed or misdiagnosed due to the atypical phenotype. 17,28,39

OCA3

OCA3 or "rufous/red OCA" with a mutated TYRP1 gene is mostly found in African countries, such as brown OCA2. Affected individuals show signs of xanthism including reddish or ginger-colored hair and red-bronze skin color considering that only the eumelanin but not pheomelanin production is interrupted. Anomalies of the visual system are only mild since the amount of pigment is sufficient for a nearly normal ocular development. Thus, visual acuity is slightly reduced and the iris color ranges from blue to brown. 76% of patients present with nystagmus; misrouting can be absent as well as strabismus.

OCA4

OCA4 with a mutated MATP gene is generally very rare except in Japan. In general, OCA4 presents with the same clinical features as OCA2 and can only be distinguished by molecular genetic analysis. The phenotype ranges from a mild to a more severe degree of hypopigmentation. Figure 8 shows the differences in phenotype in two Japanese girls with blond or white hair and grey-blue or blue irises. Hair and skin pigmentation varies from minimal to near normal and might increase over life. Ocular features are often more dominant than the physical attributes but include nystagmus, strabismus, nerve fiber misrouting and visual acuities between 20/400 and 20/30. Iris transillumination may be present at birth but might disappear if the iris color darkens during childhood. A study with affected German individuals shows a higher percentage of optic nerve head dysplasia in OCA4 than in other OCA forms.



Figure 8: Differences in the OCA4 phenotype from white to dark blond hair.³²

OCA 5, OCA6, OCA7

As already mentioned in section 3.2, new rare types of OCA have been found recently. OCA type 5-7 occur with the typical clinical symptoms of OCA, whereas OCA5 presents with golden to brown hair, OCA6 with light hair that possibly darkens over time from white to blond to brown and OCA7 with light blond to light brown hair color. All three new types show the common signs and symptoms of the visual system.⁴ Due to the few reported cases, a statement about the typical severity and range of ocular signs is not reliable at this point.

Overview

Table 2 gives a short overview about distinguishable clinical features and the different forms of OCA in order to make a first and rough differential diagnosis.

Table 2: Brief overview about the prevalence, location of appearance and clinical features of different forms of OCA. Adapted from: ³⁰

Type of OCA	Location and prevalence	Skin and hair color	Severity of common ocular signs
OCA1A	common, worldwide	white hair and skin at birth and throughout life	severe full iris transillumination, VA 20/100 – 20/400
OCA1B	common, worldwide	white hair and skin at birth but increased pigment production over time leading to light blond or yellow hair	moderate to severe, varies among patients depend on amount of pigment full or partial iris transillumination VA 20/100 – 20/200

Temperature- sensitive OCA1B	rare, worldwide	white hair in warmer but dark hair in cooler parts of the body	same as OCA1B
OCA2	most common, worldwide	slightly pigmented at birth, hair color from light blond to brown including red, also dependent on ethnical background	mild to moderate mostly partial iris transillumination VA 20/25 – 20/200, mostly 20/60 – 20/100
Brown OCA2	very common, Africa (Nigeria and Ghana)	light brown to brown skin and hair color	mild to moderate mild or absent nystagmus, VA 20/60 – 20/150
OCA3	very common, southern Africa	mahogany or red skin, ginger to reddish hair color	mild to nearly normal mild or absent nystagmus and only slightly decreased VA
OCA4	common in Japan, rare worldwide	same as OCA2	same as OCA2 higher percentage of optic nerve head dysplasia
OCA5-7	very rare OCA5: Pakistan OCA6: China OCA7: Denmark	OCA5: golden to brown hair OCA6: same as OCA2 OCA7: same as OCA2	Further research needed in order to collect reliable data

4.2 Ocular albinism

Ocular albinism is a group of disorders describing a disturbed structure of melanosomes. It affects only the visual system as the name indicates. Nevertheless, asymptomatic changes in skin and hair bulbs occur, too.

OA1

Ocular albinism type 1 (OA1, also Nettleship-Falls type or X-linked OA) is X-linked recessively inherited. Thus, most of the affected individuals are male and females act as carriers unless both of their X chromosomes are mutated. Skin and hair color appears normal whereas minor hypopigmentation is possible. Still, subtle changes in skin, hair bulbs and RPE are present since the OA1 protein impacts the transport and growth of melanosomes. Biopsies show 10-12x bigger macromelanosomes or giant melanin granules in the tissue as indicated by the arrows in Figure 9. These macromelanosomes are an important diagnostic tool to differentiate between OA and OCA in individuals with overall reduced pigmentation such as Northern Europeans but also to filter out carrier females in the family history. A reduced amount of normal sized melanosomes occurs, too.

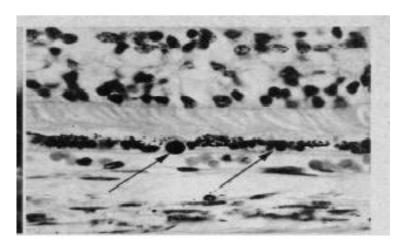


Figure 9: The RPE in X-linked OA shows enlarged melanin granules (see arrows).⁴⁷

In terms of ocular signs, affected males present with similar abnormalities of the visual system as OCA patients, however, they are often less severe and dependent on the ethnical background. The signs include photophobia, reduced visual acuities between 20/30 and 20/200, nystagmus, foveal hypoplasia without annual reflex and noticeable blood vessels of the choroid. Iris transillumination exists even though there can be pigment accumulation at the pupillary border. Electroretinography (ERG) might show a supranormal scotopic response and electrooculography (EOG) an increased Arden ratio. 47,48 Furthermore, patients with OA develop strabismus with greatly decreased or no stereovision due to the excessive crossing of optic nerve fibers at the chiasm.³⁵ A small study by Charles and associates in 1993 shows that vasculature enters through the nasal half in hypoplastic and dyplastic optic nerve heads. Additionally, 30% of the examined subjects present with posterior embryotoxon in the anterior chamber. 48 Female carriers are usually asymptomatic but still show mild ocular signs and the macromelanosomes. 80 -90% have small transillumination defects and mosaic-like or clumped areas of hyper- and hypopigmentation on the retina; only one of the two X chromosomes can produce pigment. 17,47 Figure 10 shows this phenomenon. Only a small number of carriers suffer from foveal hypoplasia, reduced visual acuity and maybe infantile nvstagmus.³³ A rare form of OA is the combination with late-onset sensorineural deafness that Winship et al. found in an African kindred in 1984. The mutation is X-

linked recessive on the same locus as OA1 (Xp22) which is why it is here listed under OA1. 49,50

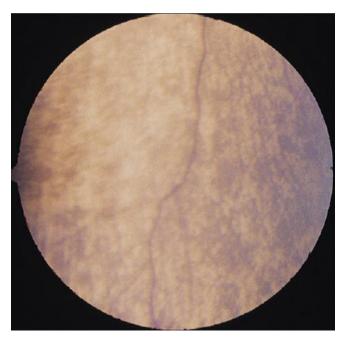


Figure 10: Retina from a female carrier. The areas of hypo- and hyperpigmentation form a mosaic like pattern. 43

<u>OA2</u>

Ocular albinism type 2 (OA2, also Áland Island Eye Disease, Forsius-Eriksson syndrome) is also X-linked recessively transmitted. It was first described in 1964 on the Áland Island by Forsius and Eriksson. A study in a Welsh family shows the following ocular signs of affected men which are typical for ocular albinism: reduced visual acuities, along with a usual nystagmus, foveal hypoplasia and fundus hypopigmentation. Notwithstanding, there is no occurrence of abnormal routing of optic nerve fibers or iris transillumination. Nevertheless, they also present with additional signs such as a protan color deficiency, axial and progressive myopia with astigmatism and defective dark adaptation. Female carriers might suffer from latent nystagmus, a shift to myopia and slightly reduced visual acuities

if they are symptomatic at all.⁵² Since the appearance of the disease is very similar to incomplete congenital stationary night blindness, researchers suggest the same entity. A genetic study in 2007 investigated that mutations of both diseases overlap on the CACNA1F gene leading to a broad spectrum of also overlapping phenotypes.⁵³

<u>OA3</u>

Ocular albinism type 3 (OA3 or AROA for autosomal recessive ocular albinism) affects females and males equally such as all types of OCA. It presents the typical ocular signs including reduced visual acuities, iris transillumination, congenital nystagmus, photophobia, strabismus, hypopigmented fundus and hypoplastic fovea. Skin and hair color usually appear normal to slightly hypopigmented compared to family members. Nevertheless, there are no macromelanosomes found in affected individuals. Compound heterozygote carriers are completely asymptomatic.⁵⁴ In 2008, Hutton *et al.* indicated in a comprehensive genetic study with 36 Caucasians, that most of the OA3 phenotypes result from compound heterozygote mutations of the tyrosinase, OCA2 and TYRP gene which are related to OCA1, OCA2 and OCA3. Therefore, OA3 is said to be a mild presentation of the OCA types.⁵⁵ Previous studies report the case of a few families where OA3 appears together with Waardenburg syndrome type 2, including congenital deafness.⁵⁶

4.3 Associated syndromes

<u>Hermansky-Pudlak Syndrome</u>

Hermansky-Pudlak Syndrome (HPS) was first described in 1959 and is a rare autosomal recessive multisystem disorder with unknown overall prevalence except in Puerto Rico where it occurs in 1 out of 1,800 births. It consists of 9 subtypes

whereas the HPS1 gene mutation on chromosome 10 is the most common and most severe of all. All forms are characterized by hypopigmentation of skin, hair and eyes due to OCA1B and a platelet defect leading to impaired coagulation ability and easy bruising. Visual acuity is often less than 20/200 whereas HPS3, HPS5 and HPS6 usually show milder signs and symptoms. Figure 11 shows the difference in clinical presentation within the HPS1 subtype in terms of pigmentation. Moreover, affected individuals might develop interstitial lung disease, pulmonary fibrosis and granulomatous colitis depending on the subtype. The disease has a limited prognosis, especially for HPS1 patients showing progressive pulmonary fibrosis without a lung transplant as supportive treatment.⁵⁷



Figure 11: Different degrees of hair and skin pigmentation in HPS1.⁵⁷

Chédiak-Higashi Syndrome

Chédiak-Higashi Syndrome is a very rare autosomal recessive and lethal disease with less than 500 reported cases in the last 20 years. It is induced by the mutation of the CHS1/LYST gene leading to enlarged melanosomes that cannot be equally transported to keratinocytes and epithelium. Therefore, patients present with particularly grey-silvery to white hair and the common ocular signs found in

albinism. Additionally, it is characterized by enlarged vesicles and a defective plasma membrane causing immunodeficiency with recurrent bacterial infections and progressive neurodegeneration with ataxia and sensory deficits. Bruising and mucosal bleeding occurs due to a mild thrombocyte defect. CHS is also described by so-called "accelerated phases" where major organs are penetrated by lymphohistocytes followed by organ failure and often death. Treatment is only supportive with prophylactic antibiotics against bacterial infections and bone narrow transplantation in order to reduce the coagulation and immunologic but not the neurological consequences.⁵⁸

Griscelli syndrome

Griscelli syndrome, a very rare autosomal recessive disease, was first described in 1978 whereas less than 40 cases were reported in the following two decades. It is caused by a mutation of a gene that is responsible for membrane transport and organelle trafficking. The consequences include silvery/metallic hair with accumulation of melanosomes in melanocytes and pigment in hair shafts with more pigmentation of the skin than CHS or HPS. The amount of pigment in the eye is usually normal. Neurological disorders consist of seizures, intracranial hypertension and hemiparesis among other findings. Furthermore, deficits of the immune system lead to frequent pyogenic infections accompanied by fever. Such as in CHS, possibly lethal accelerated phases are present. Treatment is rather supportive with systemic steroids; only bone marrow transplantation, in early stages, show success as a curative treatment. Pevertheless, experts are still unsure whether Griscelli syndrome can be listed as syndromic albinism as it does not involve ocular hypopigmentation.

Chapter 5: Assessment of the visual system and differential diagnoses

5.1 Assessment of the albinotic visual system

General fundus appearance

Ophthalmoscopy reveals an extraordinary blond fundus in OCA and OA with visible choroidal vasculature shining through the hypopigmented retina. This leads to a vascularized foveal zone which is also called macular transparency, associated with photophobia and visual impairment. Moreover, the normal annular reflex in young individuals is completely or almost completely missing. ^{12,17,47} Figure 12 and Table 3 present a grading system for macular transparency together with matching fundus photos.

Table 3: Grading system for macular transparency. 17

Grade	Description
Grade 1	Choroidal vessels fully visible in macula
Grade 2	Choroidal vessels indistinct visible with translucent RPE
Grade 3	Choroidal vessels not visible with opaque RPE



Figure 12: Example fundus photos for different gradings of macular transparency and visibility of choroidal vasculature. 67

As the peripheral retina can easier absorb photons because of the altered integry of RPE and photoreceptors, EOG and peripheral ERG results may be altered in albinism. In terms of EOG, studies display relatively homogenous results with a hypernormal Arden ratio >250% which is the ratio of the highest amplitude during photopic measurement (light peak) and lowest amplitude during scotopic measurement (dark trough). 47,60 Furthermore, the central retina (5-10°) shows a reduced ERG amplitude due to macular underdevelopment. 61 Nevertheless, peripheral ERG studies display conflicting answers. Russell-Eggitt et al. and O'Donnell et al. show supranormal responses with larger amplitudes of the a-wave (negative deflection from photoreceptors) and shorter latencies for a- and b-wave (positive deflection from Müller and/or bipolar cells) of the peripheral retina in albinism. 47,62 However, Nusinowitz and colleagues could not find any significant difference between the healthy control group and OA affected patients who show the same ocular features as individuals with OCA. 60 Only in OA2 are there negative rod responses due to the additional congential stationary nightblindness. 63 In summary, opthalmoscopy and grading of the macular transparency is more valuable and easier to perform for diagnostic means in a clinical setting.

Foveal hypoplasia

Foveal hypoplasia is detected objectively by optical coherence tomography (OCT). The OCT uses the time difference between the probe and reference beam due to different reflectivity of the retinal layers. With the help of an interferometer that measures the altered coherence, the retinal structures are displayed as a greyscale or false-color image. 64 There are two types of OCT: time-domain and spectral-domain. The latter is 50 times faster and provides better quality as it reduces artifacts due to eye movements which is particularly helpful in patients with nystagmus and children with a shorter attention span. In albinotic persons, OCT shows the absence of the typical foveal pit due to missing centripetal displacement of the NFL, GCL, IPL, INL and OPL. This leads to an increased macular thickness and hyper-reflectivity. However, the existence of a rudimentary foveal pit does not exclude the diagnosis of albinism. Additionally, the choroidal vessels contrast with the unusually hyper-reflective sclera since the inexistent melanin in the RPE and choroid causes an increased signal for the interferometer. 65 The OCT imaging is consistent with the histopathologic findings. 66 In 2007, Seo and associates revealed the significant correlation of visual acuity and degree of foveal hypoplasia. Moreover, they specify the underdeveloped fovea as the main cause for visual impairment in albinism but also as the most reliable factor for the prognosis of visual acuity in children.⁶⁷ Nevertheless, there is also a broad variety in the foveal architecture leading to the need of a uniform grading system shown and explained in Table 4 and Figure 13 which are adapted to the use spectral-domain OCT.

Table 4: Grading system for foveal hypoplasia. Adapted from: 67

Characteristic	Grade 1	Grade 2	Grade 3	Grade 4
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Foveal hyperreflectivity	Severe	Moderate	Mild	Normal
Choroid transillumination ratio = depth of choroid / depth of sensory retina	>3	2-3	<2	Normal
Foveal depression	Absent	Absent	Absent	Present

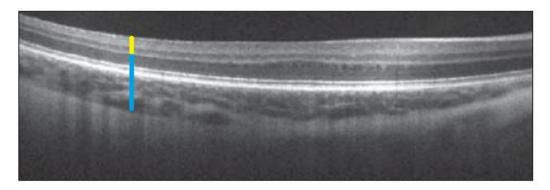


Figure 13: Albinotic fovea without pit but persisting nerve fiber layer instead. The blue and yellow line indicate the choroid transillumination ratio. Blue = depth of chorid, yellow = depth of sensory retina.

Multifocal ERG topography is consistent with OCT and histopathologic findings, showing overall reduced amplitudes of waveforms at the macula region compared to healthy individuals. Nevertheless, care should be used in interpretation of the results should be careful because of unstable fixation associated with nystagmus during measurements.⁶⁰

Visual acuity

Best corrected visual acuity (BCVA) depends on the subtype of albinism and severity of the phenotype as already presented in Chapter 4. Generally, VA is limited by factors such as photosensitivity, nystagmus, lack of macular melanin content and foveal hypoplasia. Under normal conditions, VA does not reduce in albinism over time. Studies suggest that the development of visual acuity in children with albinism levels off earlier than usually. Up to 6-12 months, limited data with albinotic children show normal VA compared to healthy infants. Between the age of 1 and 3 years, the overall grating acuity obtained by Teller cards is 1.5-3.0 octaves lower than the average. Recognition acuity at ages 4-6 is also significantly worse than in normals. However, grating acuity often overestimates recognition acuity by symbols matching or Snellen optotypes at ages 4-6.¹⁷ Visually evoked potentials (VEP) testing can be used for a rough VA testing in pre-verbal young patients along with preferential looking charts. ⁶⁸ Although there might be some changes over time or due to nystagmus amplitude, head position, prescription and dispensing skills, these early results can still figure as a rough estimate of the future VA for parents.⁶⁹ Furthermore, near acuity in school children and adults is significantly worse where almost 75% of all patients with albinism have a near acuity of 20/40 or worse. Near acuity also depends on the dampening of nystagmus occurring with convergence during near work. 70 Amblyopia is relatively uncommon and mostly due to strabismus or high refractive errors. Notwithstanding, it is difficult to determine small interocular differences in BCVA < 20/100, especially in children.71

Refractive status

A careful refraction is important for persons with albinism since providing prescription lenses improves both distance and near VA. Current studies show an overall shift towards hyperopia and especially high hyperopia >5D in OCA1A patients. However, there is no significant correlation between subtype and refractive error. A

consistent finding is also high astigmatism around 2D where 90-100% of the cases include astigmatism "with the rule". Researchers suggest a link to horizontal nystagmus since the majority of albinotic patients are hyperopic and exhibit a more emmetrop refractive status in the horizontal meridian. Moreover, the shift towards higher hyperopia in the group with poor VA supports the theory of arrested emmetropization in children with albinism. The theory names appropriate visual input, normal VA respectively, as one main factor for emmetropization; these are atypical in albinotic infants. Consequently, their development towards emmetropia plateaus and most of them stay hyperopic as the predominate refractive status in early years. 72,73

<u>Iris transillumination</u>

Due to missing pigment in the iris, incoming light is reflected by the retina and makes albinotic irises appear pink/reddish. Iris transillumination defects are best detected with the slit lamp using a small beam through the middle of the pupil. If some pigment is detectable it is most likely found at the border of the pupil. ⁴⁷ A uniform grading is useful to describe the severity as seen in Table 5. ¹⁷ Figure 14 shows specific examples of the different grades which also figures as a factor for reduced VA and photophobia. ⁶⁷

Table 5: Grading system for iris transillumination. 17

Grade	Description
Grade 1	Minimal punctuate transillumination Marked amount of pigment
Grade 2	Diffuse, irregular punctuate transillumination Moderate amount of pigment

Grade 3	Almost complete transillumination Minimal amount of pigment
Grade 4	Full transillumination with visualization of the edge of the lens No iris pigment

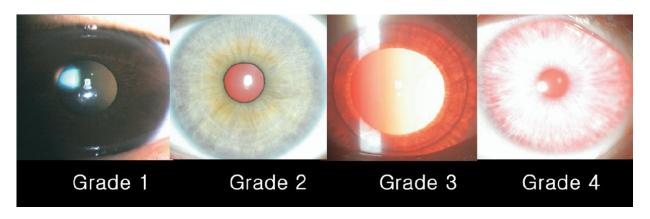


Figure 14: Examples for the different grades of iris transillumination. 67

Excessive chiasmal decussation

As already mentioned in Section 2.1, the majority of temporal retinal fibers cross to the contralateral side instead of staying ipsilateral at the albinotic chiasm. VEP testing helps to assess the existence and degree of the so-called misrouting by measuring the evoked responses of monocular stimulation at both sides of the occipital lobe. VEPs are often used as a diagnostic tool if the typical phenotype of albinism is not present and clinical features such as nystagmus are missing. The amplitudes of the evoked potential are the main parameters for interpretation of the results whereas latency is less common in clinical application. Both strongly correlate with the degree of foveal hypoplasia ⁶³ This finding and the existence of chiasmal misrouting and foveal hypoplasia without albinism again support the theory of the influence of the chiasm on foveal development.¹⁴

Figure 15 explains the expected flash VEP results in albinotic and healthy patients measuring the amplitude of the potentials. Normally, monocular stimulation of the left eye leads to approximately similar polarity in the left and right occipital lobe since half of the fibers stay ipsilateral and the other half cross the midline at the chiasm. In albinism, in contrast, the response at the contralateral side is much higher (negative) than at the ipsilateral side (positive) due to excessive crossing at the chiasm. The crossed asymmetry of amplitudes can be best seen at around 80-100ms.⁶²

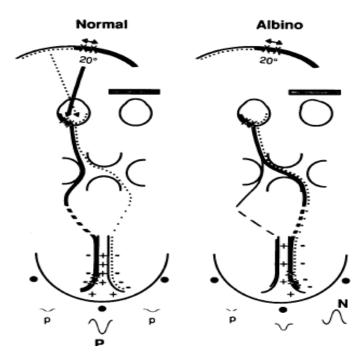


Figure 15: Due to the excessive crossing of temporal retinal fibers, the contralateral VEP signal of the stimulated eye is greatly increased compared to the ipsilateral signal. 62

Figure 16 shows the typical waveform of asymmetrical, contralateral VEP responses in albinism. O1 and O3 are channels on the left occipital lobe, O2 and O4 on the right side, respectively. The black traces display the left eye response, the grey traces display the responses from the right eye. First of all, comparing the responses of OD and OS at the same channel and same latency, an inverse

polarity is seen due to the almost complete contralateral projections. Secondly, peaks of OD responses on the left electrodes correspond with troughs on the right electrodes and vice versa. An additional technique for the interpretation of the waveforms is the interhemispheric difference potential where the signals of each eye at the right electrodes are subtracted from the left ones (O1-O2, O3-O4) as seen in Figure 17. The typical polarity reversal occurs again whereas the sensitivity for detection of asymmetry increases compared to the other technique.⁷⁴

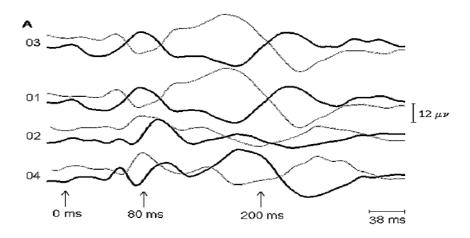


Figure 17: Typical non-quantitative asymmetrical VEP waveforms in albinism. O1 and O3 are channels on the left occipital lobe, O2 and O4 on the right side. The black trace displays the left eye response, the grey trace the response from the right eye.⁷⁴

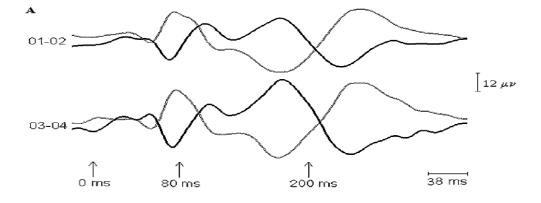


Figure 16: Quantitative interpretation of VEP waveforms by calculating the interhemispheric difference between left and right eye. Albinotic tendencies are better seen.⁷⁴

Furthermore, a chiasm coefficient can be calculated based on the similarity of the incoming potentials. Possible values are between +1 and -1 where positive values indicate normal routing and negative values the reversal of polarity and misrouting as in albinism.⁷⁵ Less common diagnostic tools for chiasm evaluation are (functional) magnetic resonance imaging (MRI and fMRI, respectively). Studies show the

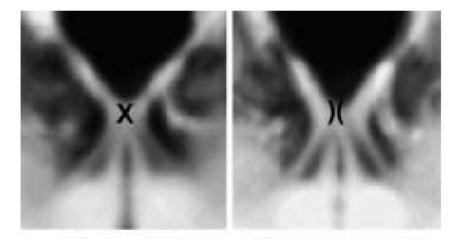


Figure 18: MRI pictures show the X-shaped chiasm in albinism on the left side, a normal)(-shaped chiasm on the right side.⁴⁰

same results as VEP examinations where the left eye stimulates the right cortex and vice versa. Also, the chiasm looks more like the letter X instead of)(due to complete crossing of optic nerve fibers as seen in Figure 18.⁴⁰ Moreover, another study reveals a horizontally smaller chiasm due to the reduced amount of RGCs. This chain reaction also leads to a reduction of grey matter volume in the occipital lobe.¹⁵

Optic nerve head dysplasia

A dysplastic or hypoplastic optic nerve head (ONH) can be found in some albinotic individuals using ophthalmoscopy. MRI and funduscopy show a smaller and hypopigmented ONH together with a reduced diameter of the nervus optici and tractus optici. Also, vessels commonly enter through the nasal side of the ONH

leading to the presence of a tilted optic disc syndrome as seen in Figure 19 on the right side. 40 48 Those findings are also associated with the excessive decussation at the chiasm, reduced cortical volume of grey matter and reduced BCVA. A new grading system by Käsmann-Kellner (see Table 6) and associates was developed in 2003 in order to maintain a uniform and easy description of the ONH dysplasia.

Table 6: Grading system for ONH dysplasia in albinism. 40

Grade	Description
Grade 0	normal ONH
Grade 1	light ONH
Grade 2	small ONH
Grade 3	small and light ONH
Grade 4	dysplastic ONH

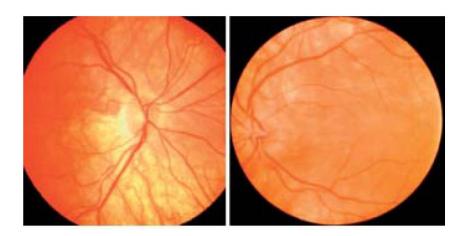


Figure 19: Left photo shows a Grade 1, light ONH. The right fundus photograph presents a Grade 4, small ONH.

Note the tilted optic disc syndrome with Grade 4.40

Eye movements and nystagmus

The prevalence of nystagmus in this population is on average 90% whereas it is higher in OCA1 than OCA2.73 Its exact etiology in albinism is still unknown. Researchers suggest that it results from an impaired communication between the sensory and oculo-motor system during the sensitive developmental period in early age due to foveal and ONH hypo/dysplasia and therefore insufficient visual input.²⁰ Furthermore, misrouting might be an additional cause but not the major contributor since not all patients with nystagmus suffer from it.24 Nystagmus in albinism is congenital and mainly horizontal and conjugate although it might have vertical or torsional elements. Moreover, (pseudo-cycloid) jerk nystagmus with an accelerating slow phase is more common than pendular nystagmus. An eccentric null point leads to the typical "chin up/down" head posture. Its intensity (amplitude X frequency) builds up with fixation, stress or tiredness and diminishes with sleep, inattention, age and convergence. 62,76 The intensity also influences the crowding ratio and VA due to the reduced foveation period. However, in albinism, it is difficult to observe the foveation period because of the altered foveal structure. 22,71,77 In 1985, Collewijn et al. divided albinotic individuals into three groups in terms of nystagmus and their resulting oculo-motor behavior. Class 1 shows the most severe signs with almost no ability to perform voluntary saccades and smooth pursuits. Even horizontal OKN is absent, vertical OKN is somewhat present. Patients in Class 2, with moderate signs, have more precise saccades and pursuits mainly with saccades. Horizontal OKN is only induced by large gratings otherwise nystagmus continues with its own pattern. Vertical responses are better. Class 3 individuals present with mild to absent nystagmus and therefore normal oculomotor behavior concerning saccades, pursuits and OKN. 78 Also, VOR duration is shorter in albinism.⁷⁹ According to Timms, patients with albinism but without nystagmus show more frequent and larger saccadic intrusions during fixation and pursuits of a target. Still, further research is needed to investigate whether there is a correspondence between these saccadic intrusions and common nystagmus in albinism.80

Strabismus

Strabismus is frequent in albinism with a reported prevalence of 27-53% and most likely due to the anomalous decussation of axons at the chiasm. The missing binocular input results in a defective control system for ocular alignment. The most common form is esotropia, vertical misalignments are less common. Generally, strabismic amblyopia is very rare in albinism since the tropia occurs equally in both eyes and therefore also the reduction of BCVA. Thus, strabismic albinotic patients use either monocular but more often alternating fixation. The quantification of strabismus becomes more difficult in patients with nystagmus. According to Wolf and associates, there is a lower overall prevalence of strabismus in albinotic individuals also showing nystagmus than in those without nystagmus. Nevertheless, they tend to have higher tropias than the group without nystagmus. Furthermore, various studies reveal the presence of a positive angle kappa in 95-99% which is also associated with the optic nerve fiber misrouting.81,82 The angle kappa is "... formed between the papillary axis and the visual axis. The papillary axis is the line from the center of the entrance pupil that intersects perpendicularly the cornea and the visual axis is the line that connects the fixation point and the fovea in the retina through the eye's nodal points."83 Figure 20 shows the situation schematically. Thus, esotropias seem to be more exo or less eso, respectively. The consideration of a positive angle kappa becomes important if an exact measurement of strabismus is needed, such as in case of strabismus surgery (more in section 6.2).17

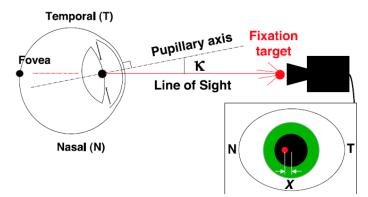


Figure 20: Relationship of angle kappa with the displacement of the corneal reflex.⁸³

Binocularity and stereopsis

The frequent occurrence of nystagmus, strabismus and misrouting results in greatly reduced or completely missing stereopsis in most individuals with albinism. It is recommended to assess stereovision with Random-Dot-Stereograms to exclude the use of monocular clues. Notwithstanding, binocular depth perception is still possible in albinism - assuming the absence of strabismus - despite the underlying chiasmal misrouting because of the remaining ipsilateral projections from the temporal retina. It is also suggested that parts of the misrouting are compensated as a consequence of neuroplasticity in the albinotic corpus callosum.⁸⁴ A study by Lee and colleagues revealed that even fine stereovision <100arcsec is possible in albinism. However, it is associated with a small degree or absence of nystagmus and therefore better VA >20/100. They also found a correlation between stereopsis and iris transillumination, annular reflex and macular melanin content. Those findings theoretically exclude the ability of stereo skills for all OCA1 patients. One known methodical weakness of the study is the use of Titmus chart for the assessment of stereovision where monocular clues at ring 1-4 can simulate false positives. After all, people with albinism still have limited stereopsis compared to healthy individuals within the same range of BCVA.85 These findings are overall consistent with a study by Wolf et al. in 2005. They also revealed that the testing for depth perception is not part of the standard testing battery as ophthalmologists and optometrists often assume the absence of stereovision in albinism.71 The development of binocularity and stereopsis in milder cases of albinism could be a starting point for vision therapy (VT) in order to improve these skills while taking advantage of neuroplasticity even in adult patients. A more detailed discussion about this topic is found in section 6.2.

5.2 Differential diagnoses

Beside the various forms of OCA and OA, there are other possible differential diagnoses to be made if signs of albinism show up in infancy. The most common diseases mimicking OCA or OA together, but with different results in assessment methods, are listed below. In case that the clinical phenotype is not distinguishable, molecular testing is recommended.

Hermansky-Pudlak Syndrome

Hermansky-Pudlak Syndrome differs from OCA with a history of bleeding and easy bruising due to the platelet storage pool deficiency. ^{26,31,57}

Chediak-Higashi Syndrome

Chediak-Higashi Syndrome shows an immunodeficiency with a history of recurrent severe infections beside hypopigmentation of skin and hair. Additionally, children suffer from easy bruising because of an anomalous platelet aggregation. ^{26,58}

Griscelli syndrome

The differential diagnosis between OCA and Griscelli syndrome is mainly made by the much rarer prevalence of the latter. Moreover, patients with Griscelli syndrome present with silvery hair and typically normally pigmented eyes.⁴

Idiopathic infantile nystagmus

OA or mild OCA can be easily mistaken for idiopathic infantile nystagmus (IIN). However, there are a few subtle differences between these disorders that present with nystagmus shortly after birth. First of all, IIN shows more pendular waveforms in contrast to a higher percentage of jerk type nystagmus in albinism. Also, strabismus is less common in IIN resulting in a better stereopsis rate. BCVA is significantly worse in albinism patients, too. 86 Furthermore, VEP reveals normal

decussation at the chiasm which also might be related to a lower prevalence of positive angle kappa in IIN.^{81,87} A less valuable diagnostic tool is ERG that does not display accentuated peripheral retinal responses in IIN compared to OA and OCA.⁶²

Blue cone monochromacy / rod monochromacy / congenital cone dysfunction

Blue cone monochromacy and rod monochromacy differ from OA or mild OCA in terms of color vision defects and negative ERGs. Misrouting is absent.²⁶ The same is true for congenital cone dysfunction.⁶²

Prader-Willi syndrome

Prader-Willi syndrome presents with hypopigmentation and atypical VEP similar to OCA. ²⁰ Notwithstanding, muscle weakness, hypotonia and intellectual delay can be found, additionally.⁸⁸

Phenylketonuria

If Phenylketonuria is not diagnosed early enough in infants, it leads to hypopigmentation of skin and hair. This appears to be the only sign that could mimic OCA whereas ocular architecture appears normal. However, screenings for Phenylketonuria are normally performed after birth so that it should be easy to differentiate it from OCA.²⁰

Idiopathic chiasmal misrouting and foveal hypoplasia

As already mentioned, idiopathic chiasmal misrouting and foveal hypoplasia can occur together since both findings influence each other during development. However, they are not associated to OA because of normal ocular pigmentation.¹⁴

Chapter 6: Management of the patient with albinism

6.1 Management of physical attributes

Patients with OCA suffer from sunburns and an increased risk of skin cancer due to the missing melanin in the skin with its protective and UV light absorbing properties. Therefore, it is important and often more comfortable for patients to wear sunglasses and sunscreen with a high sun protection factor if sun exposure cannot be avoided. Long-sleeved clothes that cover the skin are an additional safety measure. Nevertheless, UV light is able to go through light and wet shirts causing dermatological problems. Regular appointments at the dermatologist are recommended in order to perform skin screenings for pathological changes such as carcinoma. The management of clinical features, regarding the skin, is relatively easy to realize in well developed and northern countries. However, this can present a problem in countries with higher sun exposure and less availability of sun protection. Additionally, the prevalence of OCA in certain less developed African countries is many times higher which exacerbates the issue. 26,39 In contrast, de Vijlder and colleagues suggest that patients with OCA1A have an overall reduced risk of skin cancer as they are unable to produce pheomelanin at all. Pheomelanin leads to reactive oxygen species causing damage to DNA and resulting in a higher chance of cancer. They also indicate that further research is needed on this topic.89

6.2 Management of visual consequences

Prescription lenses

As already has been mentioned, high refractive errors are common in albinism and should be corrected according to Anderson and associates. Their study shows a significant improvement in VA – although it still remains subnormal – and ocular alignment with spectacle correction. However, the spectacle correction did not

seem to change anomalous head posture (AHP). The study also emphasizes the very high compliance in young patients with spectacle correction which is another reason for the obvious use in correction of ametropia. The use of cyclopegic refraction in children is commonly recommended in order to reveal latent hyperopia that can set the stage for accommodative esotropia. In case of photophobia, tinted glasses or special filters might ease the discomfort of light. However, darkened lenses can also lead to a reduction in vision. There are no specific guidelines whether filters or what specific lens tints are helpful. The affected individual has to choose the best subjective solution after trying various types of hues and densities.

Contact lenses

Contact lenses (CL) for albinotic individuals can be beneficial in various ways. First of all, they improve distance and near acuities by correcting refractive errors. According to a recent study in 2014 by Jayaramachandran et al., rigid gas permeable CL cause statistically significant sharper vision than soft CL. Nevertheless, the difference was less than one logMAR line which is not clinically significant for the vast majority of patients. Also, they found no difference in nystagmus compared to spectacle wearing.91 The second valuable function of CL is the reduction of photosensitivity by using iris-print CL. Iris-print CL lower the amount of transmitted light through the light pigmented iris in OCA and OA. Less transmission of light leads to less reflectance by the fundus and glare and therefore improvement of VA and overall comfort. However, it is important to consider the disadvantages of the iris-print CL. On the one hand, corneal edema, followed by increased photosensitivity, can occur in case of inappropriate fitting or material. On the other hand, a fixed pupil in mid-stage (around 4mm) cuts down contrast sensitivity and visual field span under mesopic and scotopic conditions. Consequently, eye care providers and patients have to compare the potential benefits against adverse effects of opaque CL.92

Low vision aids and devices

Albinism contributes to 13% of pediatric low vision (LV) cases in the USA which emphasizes the need for comprehensive LV examinations and provision of appropriate LV aids. First of all, a long and careful examination is required in order to include proper counseling. Use of trial frames and lenses is highly recommended as they allow natural head and eye movement, head posture, working distance and an adjustable vertex distance. This would not be possible by using a phoropter. If the best corrected distance VA with standard glasses is not good enough for work, school or everyday life, LV aids are helpful tools to manage these tasks. Figure 21 shows a general guideline for the LV examination and an overview about LV aids displayed as a flowchart.

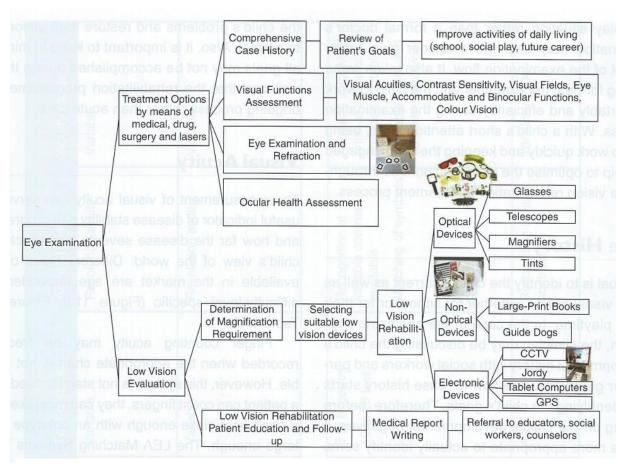


Figure 21: "The general course of a low-vision examination that forms the foundation of a low-vision rehabilitation model."⁹³

Various case reports describe telescopes or telescopic lenses (Galilean or Keplerian) on spectacles as a useful distance device for school children and adults. Here, it is important to choose the smallest possible magnification factor so that the field of view is minimally impacted. Reports also emphasize the benefits of variable-focus telescopes in order to use them for near work. There are some cautions in case of single-focus devices; the patient first has to be comfortable with the distance telescopic lenses before he/she can be trained with near telemicroscopes. 94-96 In the early grades, visually impaired children in a normal classroom setting should first try to perform visual tasks without near LV support taking advantage of sitting up front and using large print and high contrast material. Later, if they reach their visual limit, reading glasses, bifocals, high aspheric lenses, hand-held magnifiers or telemicroscopes are appropriate, dependent on the required magnification. 94 Besides the normal LV near chart, a research group at the University of Minnesota developed the "MNREAD chart" and tested it successfully for the assessment of near acuity. This chart contains continuous text and provides information about near acuity, maximum reading speed (which is not limited by print size) and critical print size (where the maximum reading speed slows down). These measurements are useful indicators for the required print size and therefore magnification in order to maintain effortless reading in educational and vocational settings. Furthermore, the MNREAD test helps to assess whether a certain enlargement is appropriate since too much magnification slows down the reading speed.⁷⁰ Another group of devices include visual stabilization devices for nystagmus patients. They can be particularly helpful in settings with electronic screens. An eye tracker combined with a motion processor extract the pathologic eye movements so that they can be nullified. This information is sent to an imageshifting optic which is adapted to a computer screen. These devices are still in a development stage, however.²¹

In summary, the clinician's experience, patience and approach is a very important part in the LV management of patients with albinism. It is a first step towards patient motivation and cooperation which is required for the successful adaption and use of LV devices.⁹⁴

Vision therapy and biofeedback

Vision therapy (VT) is a relatively new approach to the visual consequences of albinism including treatment procedures for fixation, accommodation and vergence, binocularity and eventually stereopsis. A main goal here is to improve reading skills and to develop depth perception, necessary in many daily living requirements. The therapy procedures are similar to those used in non-albinotic children, however, larger targets are used when necessary. VT for albinotic infants younger than 2 years of age consists of visual stimulation with high contrast toys. These toys should be placed in different directions of gaze to lower the risk of strabismus. Parents should also encourage their child to reach for objects. Visual perceptual training with puzzles, books and games is particularly helpful in children older than 2 years. For older children and even adults, Table 7 gives an overview about various VT procedures and the visual skills they train as primary or secondary aim. For the description or other possible training methods see "Applied Concepts of Vision Therapy" by Leonard Press. 97

Table 7: Overview about VT procedures that can be used to improve visual skills in albinism. "P" indicates the primary aim of the exercise, whereas "S" indicates the secondary aim.

VT procedures	Motility	Accommodative endurance and facility	Vergence ranges	Fusion	Stereopsis
Eye ball	Р				
stretches					
Monocular					
Accommodative		Р	S		
rock					
Binocular					
Accommodative		Р	S	Р	
Rock with red-		·		•	
green filters					
Barrel Card _a		S	Р	Р	
Bernell Card				Р	S
(BC909) _b				•	
Brock String _c			S	Р	
Tranaglyphs _d			Р	S	
Bernell			Р	Р	S
Stereoscopee				·	

a: https://www.bernell.com/product/BC1011

c: https://www.bernell.com/product/BC109/1080

e: https://www.bernell.com/product/BCVPT/305

b: https://www.bernell.com/product/BC900

d: https://www.bernell.com/product/3250/866

Training for nystagmus and strabismus can be enhanced with biofeedback prior to or during the actual therapy plan. The most common procedure is auditory biofeedback where eye movements during fixation are recorded and then translated into a sound. The more stable (in case of nystagmus) and the more ortho (in case of strabismus) the eye position the more silent the sound. Case reports of albinotic individuals that underwent biofeedback show reduction of nystagmus and strabismus deviation after eight to ten weekly sessions. One individual with nystagmus even had a 40% increase in VA; a real bonus for her in everyday life. The other test person with strabismus and nystagmus did not show a change in VA after biofeedback therapy. Nevertheless, biofeedback is a fairly inexpensive and easy procedure that does not affect the patient's body in a mechanical or chemical way in contrast to medication or surgeries. 98,99

Surgical procedures

Indications for EOM surgery are functional and/or cosmetic in patients with strabismus and nystagmus. Typical procedures include recessions of the horizontal muscles, sometimes enhanced by Botulinum toxin (known as "Botox"). One purpose of nystagmus surgery is a reduction in intensity mainly by lowering slow phase velocity. This leads to longer foveation periods in a wider range of gaze angles. The other goal is to diminish the anomalous head posture (AHP) in case of a null point outside of primary position, therefore decreasing neck posture issues due to secondary torticollis (an asymmetrical head/neck tilt). The outcome of surgery in nystagmus patients with albinism is good with a significant improvement in foveation time but also null point position respectively range and AHP. 100 Figure 22 displays the pre and post-operative nystagmus waveform which exhibits the same frequency than before but a longer foveation time.20 Nevertheless, the success rate in terms of vision is controversial. Indeed, other studies show a reduction of nystagmus intensity and AHP but a significant increase in VA in only 46-58%. The main reason given for the lower percentage with improved vision, is foveal hypoplasia. 22,101,102

Strabismus surgery with bilateral rectus recession has a promising outcome. According to a study by Villegas and colleagues, all albinotic patients are orthophoric after surgery despite an intentional undercorrection of 0.5mm per side. Some individuals even show peripheral binocularity. Notwithstanding, pre-operative measurements of strabismus angles remain a challenge because of angle kappa and nystagmus. Therefore, it is important to define whether strabismus surgery is performed because of cosmetic or functional reasons. Due to the present positive angle kappa, there seems to be a higher – but real – esotropic deviation if the prism alternate cover test is used for measurements compared to the Krimsky method. Thus, the Krimsky method should be used in case of cosmetic reasons whereas the alternate prism cover is better if improved VA and fusion are the post-surgical aims. To

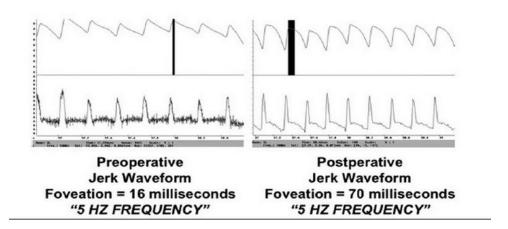


Figure 22: Comparison between pre- and postoperative nystagmus.

The foveation time increased from 16ms to 70ms whereas the frequency did not change.²⁰

Medication and supplementation

There are ongoing studies providing suggestions for treatment of both impaired melanin production as cause and nystagmus as one of the symptoms of albinism. As GABAergic agents (GABA = gamma-aminobutyric acid), inhibitory neurotransmitter, Gabapentin and Memantine diminish nystagmus intensity. The side effects, however, are dizziness, tiredness, headaches, nausea and weakness.²¹ Another approach by Lopez et al. is L-DOPA supplementation in order to stimulate pigment production in the RPE in OA1. Unfortunately, a functioning OA1 gene is necessary for this type of treatment which is not the case in OA1. 104 A promising alternative for OCA1B was researched in a study by Onojafe and colleagues. They used Nitinisone in albino mice, a FDA-approved agent for tyrosinemia type 1. A 2-4 times higher dose increases plasma tyrosine levels in OCA1B mice which consequently built up hair and skin pigmentation after one month of treatment. Additionally, Nitisone supplementation also works prenatally if given to the pregnant mother. It is not certain whether this drug would work in human albinos and whether it would really alter retina and visual pathway development prenatally or improve vision postnatally. Still, an elevation of melanin content in the eye would decrease photosensitivity and therefore indirectly enhance vision performance even in adults. Increased pigment in the skin would also provide better UV protection. 105 In summary, these topics deserve further research.

6.3 Living with albinism

Albinism does not affect lifespan, intelligence or fertility compared to other systemic disorders. 106 Vision is one of the most important senses for humans, thus, albinotic visual impairment lowers the affected person's quality of life (QOL) in e.g. social, vocational or everyday-life aspects. Kutzbach and colleagues evaluated vision-specific QOL of albinotic adults in order to compare it to other vision-related diseases. According to them, QOL is similar to moderate/severe diabetic retinopathy. It is also better than in late stage macular degeneration or Graves'

opthalmopathy but worse than in cataract, glaucoma or early macular degeneration. Notwithstanding, individuals with albinism are able to live independently and feel well accepted in society. 107 Kutzbach et al also evaluated the neuro- and motor development including school performance in children with albinism. Their findings reveal that the majority of children have normal balance, fine and gross motor skills despite their visual impairment. Nevertheless, there are some difficulties in motor coordination, such as eye-hand coordination resulting, most likely, from nystagmus and strabismus. 108 Furthermore, the research group showed a higher prevalence of attention deficit hyperactivity disorder (ADHD) in albinism whereas the association to albinism is unknown and more research is required. Still, most of the evaluated children perform at grade level in math and even reading. However, studies emphasize the importance of support in the form of special education "vision impaired" teachers, individualized education programs and more time for visually based tasks. 108,110

One of the most important elements for affected children is parental support. They can only understand and accept their situation if their parents do. Therefore, it is important that parents reach out for further information and interdisciplinary counseling, such as in health care, support groups, books or the internet. This also avoids the risk of underestimating their kid's ability concerning school, sports or everyday life tasks. Moreover, informed parents know how to answer somewhat provoking questions from strangers, e.g. about stereotypes with red eyes, white hair and skin. Thus, they have to act as examples for their children as to their behavior in difficult situations. In summary, parents play a big role in building their child's self-esteem and their capabilities. This knowledge is the most valuable and important part for a successful life with albinism and all the consequences. 111,112

Chapter 7: Case reports

7.1 Case report #1: 22 year old female

A 22 year old female presented for routine examination. Her systemic history is negative without medication intake and allergies. There is no history of tobacco, alcohol and drug abuse. Her last ocular examination was in 2010 when she also had been diagnosed with a mild form of oculocutaneous albinism. Molecular genetic testing had not been performed but skin and hair pigmentation were consistent with the diagnosis. She has been wearing glasses since the age of 4 when patching of the right eye had been necessary for 1 year due to left esotropia. She reported long-standing decreased distance visual acuity and poor stereovision as well as near point symptoms, such as blur and eye strain in the evening.

At far and near, her unaided VA was OD, OS and OU each 20/40, aided VA was 20/30, respectively. Motility was normal except excyclotorsion rotary nystagmus that occurred when switching gazes between adduction and abduction. Color vision and pupil responses were normal. Cover Test showed alternating esotropia with 20 prism diopters at distance and 18 prism diopters at near. The objective and subjective refractive status was as follows (Table 8):

Table 8: Subjective and objective refraction results.

Refraction	OD	os
Objective	sph +1.25 cyl -1.00 X 180	sph +1.25 cyl -1.00 X 180
Subjective	sph +1.50 cyl -1.25 X 174	sph +1.25 cyl -1.00 X 175

Phoria at distance was 5 eso and 4 left hyper. At near it was 3 exo and 1.5 left hypo.* Blur for negative relative accommodation established at +2.25D, recovery was at +2.00D, it was -2.00D and -1.50D for positive relative accommodation,

respectively. Fused cross cylinder testing revealed +1.25D for both OD and OS. The phoria through above is 2 exo.* Only gross local stereopsis (Titmus fly with 3600 arcsec) was established.

The patient's anterior segment was normal except the grade 2 diffuse punctate iris transillumination of her originally blue iris in 360° OU as seen in Figure 23. The fundus had a very blond appearance with mild tortuosity of the vessels. The optic disc was light and intact but slightly tilted with a cup-to-disc ratio of 0.1 (grade 1). The fovea was grade 1 hypoplastic with only slight temporal macular annular reflex and granular pigment (grade 3 macular transparency). Fundus photos of OD and OS are seen in Figure 24. Figure 25 displays the macula OCT without foveal pit and a choroidal transillumination ratio >3. Scotopic ERG amplitudes were slightly supranormal in the periphery.

These findings are consistent with a mild form of OCA as it was already diagnosed. Due to her main complaints of near point symptoms and greatly reduced stereopsis in everyday life requirements, the treatment plan consisted of weekly vision therapy sessions in clinic with daily home-training (as described on page 63 and 64).

^{*} These findings are most likely not reliable since the patient reported suppression.

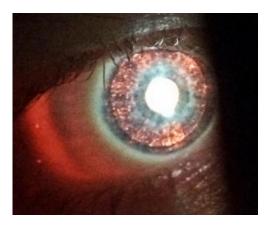


Figure 24: Grade 2, circular iris transillumination under slit lamp examination.



Figure 25: Fundus photos from right and left eye. Note the absent fovea, the granular macular pigment and the slightly tilted, light ONH with vessel tortuosity.

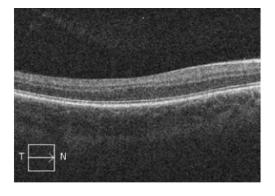




Figure 23: OCT scans from right and left eye without foveal pit. A little change in the photoreceptor layer is notable where the pit should be.

VT intervention was done to increase accommodative facility, vergence ranges, simultaneous perception and stereopsis. Table 9 illustrates the home-training procedures that were prescribed for her. Furthermore, Table 10 presents the preand post-VT results of the evaluated visual functions after 5 weeks of therapy.

Table 9: Home-therapy for daily procedures.

Week 1	Eyeball Stretches, Monocular Accommodative Rock (+2.00D, -3-00D), BC909 (with 5 B.O. prism)
Week 2	Eyeball Stretches, Monocular Accommodative Rock (+2.00D, -6.00D), BC909, Barrel Card, Brock String
Week 3	Eyeball Stretches, Binocular Accommodative Rock (red- green filter and suppression bar with +-1.75D flippers), Brock String, Tranaglyphs (1-3 B.I.), Bernell Stereoscope (B.I. cards), BC909 with head movements
Week 4	Eyeball Stretches, Binocular Accommodative rock (+-2.00D), Tranaglyphs (3-6 B.I.), Bernell Stereoscope (B.I. cards), BC909 with 5 B.I. prism, Brock String
Week 5	Eyeball Stretches, Binocular Accommodative rock (+-2.00D), Tranaglyphs (4-8 B.I.), Bernell Stereoscope (B.I. cards and tromboning), BC909 with 7 B.I. prism, Double Brock String, free space activity with 7 B.I. prism

Table 10: Pre- and post-treatment results of the evaluated visual functions after 5 weeks.

Visual function	Pre-treatment	Post-treatment
VA OU	20/30	20/25 ⁻²
Crowding VA OU	20/40	20/40
Positive relative accommodation (blur/recovery)	-2.00/-1.50	-2.50/-2.50
Negative relative accommodation (blur/recovery)	+2.25/+2.00	+3.00/+2.75
Monocular accommoda- tive facility (+-2.00D)	OD: 11 cycles/min OS: 10 cycles/min	OD: 16 cycles/min OS: 14 cycles/min
Binocular accommoda- tive facility (+-2.00D)	unable to reliably assess due to suppression	12 cycles/minute
Single letter contrast sensitivity	OD 20%, OS 20%	OD 8%, OS 10%
Vergence facility (8 prism diopters)	unable to reliably asses due to suppression	11 cycles/ minute
Convergence range Distance Near (blur/break/recovery)	unable to reliably assess due to suppression	10/20/18 20/24/18

Divergence range Distance Near (blur/break/recovery)	unable to reliably assess due to suppression	X/6/6 X/14/12
Adult Developmental Eye Movement Test (z- scores)	vert. 0.57, horiz. 0.29, ratio -0.08	vert. 0.83, horiz. 0.36, ratio -0.25
Stereopsis	3600 arcsec	120 arcsec
Convergence Insufficiency Symptom Survey (CISS)	18 out of 60 points	7 out of 60 points

Distance lateral phoria was 9.5 exo, vertical 1 left hyper after VT. Near phorias were both ortho.*

Subjectively, the patient reported the complete disappearance of the mentioned near point symptoms (blur, fatigue) which is consistent with the CISS points. Objectively, the relief of near point symptoms might be most likely associated with better accommodative facility and endurance (see Table 9) as well as the more stable visual system due to increased vergence ranges and binocularity after VT. The most notable achievement was the rise of stereopsis from 3600 arcsec up to 120 arcsec. Still, only local stereovision was established due to strabismus. However, she could not detect any change of depth perception or VA in everyday life requirements.

In summary, the objective and subjective findings of this case report show promise for the future management of albinotic patients, especially for near work. Since there were no VEP results about chiasmal crossing defects, further research is required in order to detect the association between the possibility of enhancement of stereopsis and the degree of decussation.

7.2 Case report #2: 5 year old female

The patient presented in 10/2014 in the Pacific University clinic. She had already been diagnosed with OCA in the past. Her ocular and systemic health history was negative. There was no information about family history available due to adoption. She had no known drug allergies. However, she took Claritin and Flonase for hay fever symptoms. The patient reached all her developmental milestones in appropriate time. She knows about her condition but tries to hide her visual impairment. She was wearing soft, tinted, centered CL that significantly reduced her photophobia. A clear 3mm zone for the pupil was left. The CL parameters, dry over-refraction and aided distance VA assessed with LEA symbols are as shown in Table 11.

Table 11: CL parameters, dry over-refraction and aided distance VA.

CL OD	sph -3.75	base curve 8.4mm	ø 13.8mm
CL OS	sph -2.75	base curve 8.4mm	ø13.8mm
Over refraction OD	sph -1.00 cyl -2.00 X 180	VA 20/300	preferred eye for distance
Over refraction OS	sph +0.00 cyl -1.50 X 180	VA 20/300	preferred eye for near

^{*} These findings are most likely not reliable since the patient reported suppression.

Currently, the patient's right eye was undercorrected but she was using it as her preferred eye at near which creates a monovision situation. This strategy did not interfere with stereopsis (assessed with Lang Test) development since it was completely absent. The mother also reported reduced squinting and nystagmus with the CL that are worn 10 hours per day. Motility was normal, as well as confrontation visual fields. Nystagmus was measured by objective oberservation. Cover test revealed no phoria and tropia. In kindergarten, the patient started training with low vision aids and iPads. The mother reported that the new school will also have electronic textbooks. Due to reasons of time and moving away, a dilated fundus exam was not possible at this visit and clinic. A follow-up on the CL fitting and comprehensive pediatric examination was recommended in 6 months.

Chapter 8: Conclusion

In summary, research about albinism has progressed considerably in the last few decades but there are still unknown facts about certain aspects, especially about the exact etiology and the general management of visual consequences. However, research in the following areas show promise:

- High-tech low vision devices such as electronic tablets and visual stabilization devices for nystagmus
- Electronic tablets with games for the enhancement of visual skills and/or treatment of vergence range disorders, strabismus, amblyopia, binocularity and stereopsis
- Medication and supplementation for increased pigment production in children, adults and unborn affected individuals
- Vision therapy in order to enhance overall visual skills leading to a more stable visual system, such as accommodative facility/endurance and vergence ranges, leading to better near work skills. Also, as shown in section 7.1, vision therapy could be a helpful tool to increase binocularity and stereopsis. Further research with utilizing an appropriate sample size is required to show the benefits of these procedures.

To sum up, once albinism as a metabolic disease is diagnosed in early years, affected individuals can access a broad management spectrum; this is to be expanded in the future.

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List of abbreviations

Abbreviation	Meaning
ADHD	attention deficit hyperactivity disorder
AHP	anomalous head posture
BCVA	best corrected visual acuity
С	cones
CH	choroid
CHS	Chédiak-Higashi syndrome
CL	contact lenses
DOPA	dihydroxyphenylalanine
ERG	electroretinography
EOG	electrooculography
EOM	extraocular muscles
(f)MRI	(functional) magnetic resonance imaging
GABA	gamma-aminobutyric acid
GCL	ganglion cell layer
HPS	Hermansky-Pudlak syndrome
INL	inner nuclear layer
IPL	inner plexiform layer
IS	inner segment
LV	low vision
MATP	membrane associated transporter protein
MC1R	melanocortin-1 receptor
MPOD	macular pigment optical density
NFL	nerve fiber layer
OA	ocular albinism
OA1-protein	ocular albinism 1 protein

vestibule-ocular reflex

vision therapy

OCA oculocutaneous albinism OCT optical coherence tomography OD right eye OKN optokinetic nystagmus ONH optic nerve head ONL outer nuclear layer OPL outer plexiform layer left eye OS QOL quality of life R rods **RGC** retinal ganglion cells (R)PE (retinal) pigment epithelium TRP-1/TRP-2 tyrosinase-related protein 1 and 2 UV ultraviolet visually evoked potentials **VEP**

VOR

VT

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