Ocular Pigment Disturbances Associated with Vitiligo

Thesis
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by

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List of Abbreviations

Abbreviation	Meaning
>	More than
<	Less than
%	Percent
APS-1	Autoimmune poly-endocrine syndrome type 1
BIO	Binocular indirect ophthalmoscope
BMPs	Bone morphogenic proteins.
C3	Complement 3
c DNA	Complementary DNA
CMV	Cytomegalovirus.
COMT	Catechol o -methyl transferase gene
CTLA4	Cytotoxic T lymphocyte antigen-4
DHA	Dihydroxydimethylacetone
DHI	Dihydroxyindol
DHICA	Dihydroxyindole-2-carboxylic acid
DOPA	Dihydroxyphenylalanine.
e.g	For example
EGM	Extracellular granular material
EM	Electron microscope
ET3	Endothelin-3.
Fig	Figure
FU	Flurouracil
H2O2	Hydrogen peroxide.
HBV	Hepatitis B virus.
HCV	Hepatitis C virus.
HEV	Hepatitis E virus.
HGF	Hepatocyte growth factor.
HIV	Human immunodeficiency virus.
HLA	Human leukocytic antigen
IFN- γ	Interferon gamma.
Ig	Immunoglobulin.
IL 2	Interleukin 2.

IL 4	Interleukin 4.
IL-2 sR	Interleukin 2 soluble receptor
KCs	Keratinocytes
KUVA	Khellin and UVA
LC	Langerhan's Cells
MAO	Monoamine oxidase
MBEH	Monobenzyl ether of hydroquinone.
MCs	Melanocytes.
MOP	Methoxypsoralen.
MSH	Melanocyte stimulating hormone.
MW	Molecular weight
NALP 1	NLR family, pyrin domain containing 1
NALP 2	NLR family, pyrin domain containing 2
NB-UVB	Narrow band ultraviolet B.
NE	Norepinephrine
NK	Natural killer.
NPY	Neuropeptide Y.
PUVA	Psoralen plus ultra-violet A.
RER	Rough endoplasmic reticulum
RPE	Retinal pigment epithelium
ROS	Reactive oxygen species.
SCC	Squamous cell carcinoma.
SCF	Stem cell factor
SF	Steel factor
SV	Segmental vitiligo.
TNF- α	Tumor necrosis factor alpha.
TYRP 2	Tyrosinase related protein 2.
TYRP 1	Tyrosinase related protein 1.
UV	Ultraviolet
UVB	Ultraviolet B.
UVR	Ultraviolet radiation.
VKH	Vogt Koynaga Haradai syndrome.

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INTRODUCTION

Vitiligo is an acquired, idiopathic disorder characterized by circumscribed depigmented macules and patches. Functional melanocytes disappear from involved skin by several mechanisms ***(Ortonne, 2008)***.

The characteristic lesion in vitiligo is a sharply demarcated milky white patch which is surrounded by normal skin. Vitiligo may be divided into localized (focal, unilateral), generalized (vulgaris, acrofacial or mixed), universal (complete or nearly complete depigmentation) the most common morphological pattern is vitiligo vulgaris ***(Shah, 2008).***

Vitiligo affects approximately 0.5-2% of general population worldwide and it may appear in any age but the average age of onset is approximately 20 years ***(Ortonne, 2008).***

Vitiligo is a part of a systemic autoimmune process as it is associated with ocular and auditory abnormalities as well as other autoimmune disorders ***(Gopal et al., 2007).***

Depigmentation of the lids and poliosis of the brows and eyelashes are commonly seen in vitiligo. The association of vitiligo with inflammation of uveal tract has long been recognized ***(Perry and Font, 1977).***

Vitiligo may be associated with hypopigmented spots on the iris, depigmentation of the anterior champer, retinal pigment epithelium hypopigmentation, uveitis or chorioretinal degeneration ***(Biswas et al., 2003).***

There is an association between vitiligo and retinal pigment epithelium hypopigmentation and / or degeneration. In most cases mild asymptomatic hypopigmentation of the retinal pigment epithelium is seen associated with generalized systemic pigmentary disturbances, but in rare occasions there may be sufficient degeneration to produce a retinitis pigmentosa like syndrome ***(Albert et al., 1983).***

Aim of the Work

Aim of study is to detect the prevalence of pigment disturbances in the eye of vitiligo patients in comparison with normal subjects.

Chapter 1

THE MELANOCYTES BIOLOGY

Pigmentation of the skin, also referred to as complexion coloration, results from a complex process of melanin synthesis within melanocytes of the interfollicular epidermis, and the subsequent transfer, translocation and degradation of this melanin to and by the recipient keratinocytes respectively**.** Therefore, skin pigmentation is a combination of type and amount of melanin synthesized by the melanocyte factory and the handling of the melanin product by the keratinocyte consumer ***(Boissy, 2003).***

Melanin pigmentation of the human skin is conveniently divided into two components: constitutive skin colour and facultative skin colour. Constitutive pigmentation is the amount of cutaneous melanin pigmentation generated according to cellular genetic programs without any direct effect by radiations of solar origin. It is the level of pigmentation acquired in those parts of the body habitually shielded from the light ***(Abdel-Malek and Kadekaro, 2006).***

On the other hand, facultative skin color results from exposure to UV light and other environmental factors, leading to changes in the composition of melanin in the skin and increases the amount and size of melanin produced by melanocytes. Thus, facultative skin is darker than constitutive skin ***(Yamaguchi et al., 2007).***

1.1Embryonic development

Melanocytes are derived from melanoblasts that migrate from the neural crest and the outer layer of the optic cup during the first 2 months of fetal development ***(Kovacs, 1998).***

Progenitor melanoblasts migrate dorsolateraly between the mesodermal and ectodermal layers to reach their final destinations in the hair follicles and the skin as well as inner ear cochlea, choroids, ciliary body and iris. Melanocytes can be found in fetal epidermis as early as the fiftieth day of gestation ***(Christiansen et al., 2000).***

Melanoblast migration and differentiation into melanocytes is influenced by a number of signaling molecules produced by neighboring cells. These include endothelin-3 (ET3), bone morphogenic proteins (BMPs), steel factor (SF), stem cell factor (SCF), c-kit ligand and hepatocyte growth factor (HGF). By

interacting with their specific cell surface receptors, these molecules induce intracellular and intranuclear signaling to influence gene transcription and protein synthesis ***(Kleber et al., 2005).***

1.2 Function of Melanocytes

The major differentiated function of melanocytes is to synthesize melanin in specialized organelles (melanosomes) within the melanocyte and to transfer melanosomes to neighboring keratinocytes to provide protection from ultraviolet radiation (UVR) ***(Park et al., 2008).***

1.3 Melanosome Biogenesis

The melanosome is a unique membrane bound organelle in which melanin biosynthesis takes place. Because melanosomes contain enzymes and other proteins that present in lysosomes, they are thought to represent a modified version of the later ***(Park et al., 2008).***

Depending on the type of melanin synthesized, melanosomes can be divided into eumelanosomes and pheomelanosomes. Eumelanosomes are large (0.9 x 0.3mm), elliptical in shape and contain a highly structured fibrillar glycoprotein matrix required for eumelanin synthesis.

Pheomelanosomes are smaller (0.7mm in diameter), spherical in shape and their glycoprotein matrix appears disorganized and loose ***(Slominski et al., 2004).*** Both eumelanosomes and pheomelanosomes may be present within a single melanocyte ***(Oyehaug et al., 2002).***

1.4 Melanogenesis

Melanin is indole derivatives of DOPA and they are formed in melanosomes through a series of oxidative steps. Melanosomal pH affects the activity of the melanogenic enzymes and influences melanin polymerization ***(Sarangarajan and Apte, 2006).***

Two types of melanins are synthesized within melanosomes: eumelanin and pheomelanin. Eumelanin is dark, brown-black and insoluble, whereas pheomelanin is light, red-yellow, sulfur-containing and soluble ***(Ito and Wakamatsu, 2003).***

The synthesis of both types of melanin involves the rate limiting catalytic step in which the amino acid tyrosine is oxidized by the enzyme tyrosinase to L-DOPA, a reaction known as the Raper-Mason pathway. Inhibition of this reaction blocks melanin synthesis**.** In these reactions, L-DOPA acts as a co-factor and also as a substrate for tyrosinase ***(Hearing & Jimenez, 1987).***

L-DOPA (L-3,4-dihydroxyphenylalanine) is oxidized into DOPA quinone, DOPA quinone is further converted to DOPA chrome and DOPA chrome can be converted to 5, 6-dihydroxyindol (DHI) or to 5,6-dihydroxyindole-2-carboxylic acid (DHICA). The latter reaction is catalyzed by the enzyme DOPA chrome tautomerase or TYRP2. The level of brown versus black eumelanin appears to correlate with the DHI/DHICA ratio, with a higher ratio leading to the formation of black eumelanin and a lower ratio leading to brown eumelanin. DOPA quinone can also combine with glutathione or cysteine to form cysteinyl DOPA, which then becomes the yellow/red, soluble, low molecular weight pheomelanin ***(Fig.1)(Park et al., 2008).***

The synthesis of constitutive pigmentation by the melanocyte is controlled, primarily by the tyrosinase gene family of proteins tyrosinase, TYRP1 and TYRP2 which regulate the type of melanin synthesized ***(Abdel-Malek and Kadekaro, 2006).***