Molecular Study of Endothelin-1 and Endothelin Beta Receptor Genes in Vitiligo Patients

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

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ABSTRACT

Background:

Vitiligo is a hypopigmentation disease in which disorder in melanocytes causes the appearance of white patches in the skin. Endothelin-1 (ET-1) stimulates a variety of physiologic responses in melanocytes including increase in dendricity, mitogenesis, chemotaxis, pigment production in addition to activation of tyrosinase enzyme. Endothelin-1 increases the intracellular calcium concentration through endothelin beta receptor (ET-BR) in skin melanocytes.

Aim of work:

The aims of work were to detect gene expression of ET-1 and ET-BR in lesional & perilesional epidermis in a sample of vitiligo patients, to find a relation between gene expression of these markers and development of vitiligo, also to detect possible hidden susceptibility in perilesional skin of vitiligo patients through comparison with gene expression in skin of normal individuals & finally to use these genes expression data for the purpose of adding new strategies to the management of vitiligo.

Patients and methods:

Fifteen patients with vitiligo, from the outpatient clinic of Kasr AlAiny Hospital and National Research Center were involved in this study in which they were diagnosed clinically. A written consent was assigned by each patient before participation in the study. Every patient was subjected to the following: full history taking into consideration family history of vitiligo, exposure to stress, full general and dermatological examination (including VASI “vitiligo)

Conclusion:

The ET axis may have a positive role in vitiligo. However one may suggest that this role is most probably through the down regulation of the expression of the ET-BR rather than a defect in the level of ET-1.

Key words: vitiligo, endothelin-1, endothelin beta receptor

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ARABIC SUMMARY

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LIST OF ABBREVIATIONS

bFGF	Basic fibroblast growth factor
Ca^{2+}	Calcium
cAMP	Cyclic adenosine monophosphate
cDNA	Complementary deoxyribonucleic acid
CT	Cycle threshold
ECE	Endothelin converting enzyme
EGF	Epidermal growth factor
ET-1 , 2, 3	Endothelin-1, 2, 3
ET-AR	Endothelin-alpha receptor
ET-BR	Endothelin-beta receptor
HGF	Heptocyte growth factor
HLA	Human leukocyte antigen
IL	Interleukin
IP3	Inositol triphosphates
MAPK	Mitogen activated protein kinase
MHC	Major histocompatibility complex
MITF	Microphthalmia associated transcription factor
mRNA	Messenger Ribonucleic acid
NBUVB	Narrow band ultraviolet type B
P value	Probability value
PKC	Protein kinase C
PLC	Phospholipase C
PUVA	Psoralen ultraviolet type A
ROC	Receiver operating characteristic
RT-PCR	Reverse transcriptase – polymerase chain reaction
SCF	Stem cell factor
SD	Standard division
SYBR	Synergy brands
TGF α	Transforming growth factor alpha
TNF α	Tumor necrosis factor alpha
UVB	Ultraviolet type B
UVR	Ultraviolet rays
VASI	Vitiligo area scoring index
VIDA	Vitlilgo disease activity score

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LIST OF ERRATA

Page	Line	Mistake	Correction
13	3	Kilodalton	Kilodaltons
13	4	common antigens	common tissue antigens
16	25	levels of antioxidants	levels of ROS
30	11	this clinical effect	that clinical effect
31	16	important in proliferation & melanogenesis	important role in proliferation and melanogenesis
33	3	mean 37.61±11.822 years	mean 37.67±10.97 years
33	6	mean 38.5±12.215 years	mean 36.13±9.34 years
41	3	standard division	standard deviation

CHAPTER 1: VITILIGO

INTRODUCTION

The word "vitiligo" may have evolved from the Latin word vitilium, meaning a defect ***(Carter, 1992)***, or vitelius signifying a calf's white patches ***(Fitzpatrick, 1964)***.

In ancient Arabic texts, white skin was expressed using the term "baras" and others like "bohak" ***(Koranne and Sachdeva, 1988)***. The word "baras" is mentioned in the Quran. The Quran states that in accord with the will of Allah, Jesus was able to cure those affected by "baras"{Surat AlMa'aeda:110} ***(El Mofty, 1968)***.

EPIDEMIOLOGY

Vitiligo is an acquired hypopigmentation disorder characterized by chronic white asymptomatic macules and/or patches, which are usually symmetrical, due to loss of functioning epidermal with or without hair follicle melanocytes ***(Picardo and Taïeb , 2010)***.

Vitiligo occurs worldwide 0.1-8% in population. Congenital vitiligo is very rare, while the peak age of onset in all series was between 10 and 30 years. In 50% of cases, the age of onset fell within the first two decades of life ***(Alikhan et al., 2011).***

Adults and children of both sexes are equally affected, although larger numbers of females consult the doctor probably due to the greater psycho–social perceived impact of the disease ***(Boissy and Manga, 2004).***

Abdel-Hafez and Colleagues in 2003 performed a survey in Upper Egypt and found the prevalence of vitiligo to be 1.2%.

About 20% of vitiligo patients have at least one first degree relative (parents, children, siblings) with vitiligo. The relative risk of vitiligo for first degree relatives is elevated by 7 to 10 folds; second degree relatives also have significantly elevated relative risks. These observations support a genetic involvement in the etiology of vitiligo ***(Nath et al., 1994; Sun et al., 2006).***

Segmental vitiligo, that affects 10-20% of the patients, has an earlier onset and more rapid evolution as compared with generalized vitiligo. Moreover, segmental vitiligo is rarely associated with immune-related disorders, but it seems usually to cease with the extension of the disease to the involved dermatome within one year ***(Njoo et al., 1999).***

PRECIPITATING FACTORS

Many patients could not relate the onset of vitiligo to any apparent cause and report accidental discovery of a white patch somewhere in the body. However, others could attribute the onset of their disease to a specific life event, crisis, or illness **(*Picardi et al., 2003).***

Some medications may be related to vitiligo development for example; "infliximab" has been described in inducing vitiligo ***(Ramirez-Hernandez et al., 2005).*** Also other drugs for instance as "chloroquine", "quinine" and "hydroquinone monobenzylether ester" have been proved in the development of vitiligo **(*Curzytek et al., 2007)***. An industrial chemicals exposure like "catechols" may induce vitiligo ***(Ortonne and Passeron, 2012)***. A phenolic derivative, such as "4-tertiary butylphenol" increases the incidence of vitiligo through competitive inhibition of tyrosinase enzyme ***(Yang and Boissy., 1999).***

Vitiligo may follow a physical injury such as trauma; this phenomenon is called isomorphic Koebner phenomenon ***(Ortonne and Passeron, 2012)***. It is significantly noticed in patients with progressive vitiligo and with non-segmental vitiligo ***(Gauthier, 1995*)**.

CLINICAL FEATURES

The asymptomatic amelanotic milky white macule (or patch) surrounded by normal skin is the commonest form of vitiligo **(*Taieb and Picardo, 2007*).** These macules (or patches) have discrete margins and they are round, oval, or linear in shape. The borders are usually convex as if the depigmenting processes were invading the normally pigmented skin. Lesions enlarge centrifugally over time but the rate may be slow or rapid. In very lightly pigmented people, the lesions are not very apparent but they are easily distinguishable with Wood's lamp examination or after tanning of uninvolved skin ***(Ortonne and Passeron, 2012).***

Leukotrichia (whitening of hair) is common in vitiligo. It may affect any terminal hair of the body. Premature graying of the scalp hair can occur with or without an underlying vitiligo macule. Paradoxically, vitiligo macules were found on the scalp from which normally pigmented hair arise. This supports the suggestion that melanocyte population of the skin differs from that in the hair. The latter may act as a reservoir for the former supplying it with melanocytes during repigmentation. The presence of leukotrichia in vitiligo macule is associated with a poorer prognosis for repigmentation ***(Cui et al., 1991).*** Poliosis circumscripta (localized leukotrichia) can be observed; while mucosae are rarely involved ***(Moretti, 2003).***