

SERUM LEVELS OF THE SOLUBLE INTERLEUKIN-2 RECEPTOR IN VITILIGO PATIENTS IN UAE

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SUMMARY:

Objective: To determine serum level of sIL-2 receptor in patients with vitiligo in a population in Al Ain, UAE.

Design: This is a prospective, descriptive, hospital based study.

Setting: Al Ain Medical District, Al Ain Hospital, UAE

Subjects: Vitiligo patients seen at Al Ain hospital in 2003.

Results: The study was based on 32 patients. The sample consisted 21 males and 11 females. 15 healthy individuals were selected as control group. Serum level of sIL-2R were significantly higher in vitiligo patient (112 ± 129.2) than in healthy control (61.1 ± 44.3 Pmol/L) $P < 0.0001$. Patient with short duration of the disease shows higher the serum level sIL-2R.

Conclusion: sIL-2R showed significant difference between vitiligo patients and control.

INTRODUCTION

Vitiligo is a relatively common skin disease characterized by development of depigmented macules and patches, milky white in color and with a tendency to expand in a centrifugal fashion. The lesions may regress and the vitiliginous areas may become repigmented. The course is often progressive with the lesions enlarging over months to years. Repigmentation of vitiliginous areas can be achieved by various treatment modalities. Some lesions, however, fail to respond and persist for many years. We estimated serum Interleukin-2 receptor (sIL-2R) in vitiligo of varying durations, in order to gain further insight into its activity and pattern of evolution.

METHODS AND MATERIALS

This study included 32 patients with vitiligo. There were 21 men and 11 women, with ages ranging from 20 - 50 years. These patients have vitiligo ranging from 6 months to 5 years. 15 healthy individuals were selected in a similar age range as controls.

Serum IL-2R levels were measured with specific enzyme linked immunosorbent assay (ELISA) kit (Beohringer Biomedica). Microtitre plates were coated with murine monoclonal antibodies against human sIL-2R. Serum samples (20 ml) were added with another murine monoclonal directed against a second epitope of the human sIL-2R. Both sIL-2R from the sample and stan-

dard were bound during incubation. The intensity of the resulting color was determined with a Titer tale unislean (Flow lab, Mclean VA, USA) at 405 nm.

The sIL-2R standard was the cellfree supernatant obtained from phytohaemagglutinin-stimulated T cells. Serum sIL-2R levels more than 2 standard deviation (SD) above the mean level in the normal control were regarded as elevated. Statistics analysis was carried out with student t-test for the companion of mean and Fisher's exact probability test for the analysis of frequency. Correlations with clinical data were assessed by Spearman's rank correlation coefficient. p values less than 0.05 were considered significant.

RESULTS

Serum levels of sIL-2R were significantly higher in patients with vitiligo than in healthy controls (112 ± 129.2 versus 61.1 ± 44.3 Pmol/L, $P < 0.0001$). Patients with short duration of the disease (<2 years) had higher the serum level sIL-2R (tables 1 and 2).

DISCUSSION

Cytokine cell surface receptors are type 1 membrane glycoproteins. Receptor expression is a carefully regulated process, which occurs only transiently upon antigenic stimulation. Receptors can be expressed on a number of cells at very low levels. Variable expression of receptors may be responsible for differing effects and functions of interleukins (1).

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Type	Number	Mean Pmol/L	SD	P value
Control	15	112	17.2	--
Patients	32	61.1	16.8	0.0001

Table 1: sIL-2R in Vitiligo and Controls.

Duration	Number	Mean	SD	P value
< 2yrs	18	176.3	21.6	0.0001
> 2yrs	14	117	17.7	

Table 2: Correlation between sIL-2R and duration of the disease.

IL2 is an important regulatory cytokine that acts as a T cell growth factor, and is a major activator of T cell and NK cell function. It stimulates formation of its receptor, the IL2R, on cell surfaces, which it binds and activates. IL2 Receptor (IL2R) belongs to the 'cytokine receptor superfamily type I' (hemopoietins with 4 α helical bundles), sharing an extracellular structural homology with receptors for IL3, IL4, IL5, IL6, IL7, IL9 and IL12. IL2R is a heterogenous receptor consisting of 3 subunits, α , β and γ . These subunits may be shared by different interleukins. Activation of cytokine receptors induces activation of Jaks (Janus Kinases) These jaks then cause phosphorylation (activation) of various signalling proteins, including stats (signal transducers and activators of transcription) The stats then bind to nuclear DNA and induce transcription of genes (2).

The IL2R γ is a common receptor subunit shared by many interleukins, and lack of this receptor leads to a profound deficiency of immunity, manifesting as SCID (Severe Combined Immunodeficiency) (3).

Extracellular domains of cytokine receptors are released from the cell surface, bind to soluble cytokines in circulation, and can be detected in serum and urine. Serum sIL2R levels are indicative of in vivo immune T cell activation, and they are proportionate to cell-surface receptor levels. IL-2R α shed from the cell surface reflects the degree of T cell activation.

IL2R levels are raised in a number of conditions such as autoimmune diseases, infections, end stage renal disease, veno-occlusive disease, certain drugs and allograft rejection (bone marrow, cardiac, liver, renal). Autoimmune diseases include systemic lupus erythematosus, scleroderma, Sjögren's syndrome, vasculitis, Wegener's granulomatosis, Behçet's syndrome,

Crohn's disease, giant cell arteritis, juvenile rheumatoid arthritis, Kawasaki disease, multiple sclerosis, polymyalgia rheumatica and sarcoidosis.

Since the release of sIL-2R is correlated with the amount of IL-2R expressed on the surface of activated T cell lymphocytes (4), many studies have been shown that serum sIL-2R levels are raised in patients with chronic plaque psoriasis (5, 6) atopic dermatitis (7), systemic sclerosis (8), cutaneous T cell lymphoma (9) and vitiligo (10).

Immunological alterations have been implicated in the etiopathogenesis of vitiligo. Both cellular and humoral immunity cooperate in the destruction of melanocytes. In vitro, the presence of lymphocytes as well as autoantibodies significantly decreased the number of living melanocytes in a dose-dependent manner illustrating the role of cellular immunity by antibody-dependent cellular cytotoxic reaction (11). A simultaneous increase of leucocyte migration inhibition factor (LMIF) released by activated T cells, and circulating IgG and immune complexes was observed in vitiligo, suggesting a T-cell mediated B-cell activation (12).

Immunohistochemical studies of the perilesional area in generalized vitiligo mainly detects CD4 and CD8 positive T cells in the infiltrate (often with an increased CD8/CD4 ratio) which express activation molecules such as interleukin 2 receptor, HLA-DR, and major histocompatibility complex II, and interferon γ , which enhances T-cell trafficking to the skin by increasing ICAM-1 expression (13). T helper/inducer cells, CD4/CD8 ratio and activated (HLA-DR+) T cells are decreased in vitiligo patients, suggesting a role for changes in cellular immunity (14).

The beneficial effects of UV radiation were another proof for the role of immunological processes. UV radiation induced soluble factors (e.g. cytokines, neuropeptides) with anti-inflammatory and immunosuppressive effects and also modulated the expression and function of cell-surface associated molecules, including adhesion molecules, cytokine receptor and growth factor receptors (15). It also induced apoptosis of skin-infiltrating T cells (16).

An activation of the T cell mediated immune system was confirmed in vitiligo by detecting significantly increased levels of soluble interleukin-2 receptors (sIL-2R) especially in generalized, focal and non-dermatomal types of vitiligo. A significant correlation of increased sIL-2R with disease activity and less than a 1 yr period from the initiation of the disease was observed. Tissue fluids from the margin of hypopigmented macules, especially in active disease, contain higher levels of sIL-2R than uninvolved skin of the same patient (17).

Honda et al. (10) investigated sIL-2R levels in 38 vitiligo patients and 12 normal controls. They found elevated sIL-2R levels in patients with non-dermatomal-y distributed vitiligo in active stage. Yeo's study (18) showed that sIL-2R levels were significantly higher in vitiligo patients (671 ± 368.59 U/ml) compared with controls (370 ± 71.8 U/ml), as expected, but not significantly correlated with the disease activity as assessed by clinical information.

The results of our study were in concurrence with expected findings. Serum levels of sIL-2R were significantly higher in patients with vitiligo than in healthy controls (112 ± 129.2 versus 61.1 ± 44.3 Pml/L, $P < 0.0001$) and patients with shorter duration of the disease (<2 years) had higher serum levels.

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