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RESEARCH ARTICLE

SERUM INTERLEUKIN 13 (IL-13) LEVELS IN IRAQI CHILDREN WITH NEPHROTIC SYNDROME.

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Abstract

The aim of this study is to compare the levels of IL-13 in children with nephrotic syndrome and healthy control children. Fifty children with NS were divided into four groups: 14 steroid sensitive infrequent relapse (SSIFR), 12 steroid sensitive frequent relapse (SSFR), 9 steroid resistance (SR) and 15 newly diagnosis (ND) compared to twenty-five unrelated healthy children. The serum IL-13 levels for NS patients and healthy control children were measured by R&D quantitative ELISA kit. The results of mean IL-13 level in healthy children serum (205.18 ± 2.61 pg/ml) was significantly lower than children with NS (335.50 ± 40.68 pg/ml). we showed serum IL-13 was increased significantly ($P=0.0271$) in children with NS in compared with healthy control children, this raised in IL-13 levels could have a role in nephrotic syndrome pathogenesis.

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Introduction:-

Nephrotic syndrome is an immune mediated renal disease. It is related with dysfunction of T cell and secondary disorder of B cell that leads to changes in scales of immunoglobulins (Roy *et al.*, 2009; Bahbahet *al.*, 2015). This systemic disturbance of function of T cell results in the production of humoral factors or lymphokines that responsible for the rise of permeability of glomerular basement membrane (Sahali *et al.*, 2002; Bagga *et al.*, 2005). Nephrotic syndrome is described by huge proteinuria, edema and hypoalbuminemia, the additional features are hyperlipidemia also generally present (Bahbahet *al.*, 2015). Hypercoagulable status, the dysregulation of fluid, imbalance in electrolyte and capability to infections can caused by large urinary wastage of serum proteins (Kim *et al.*, 2016). Estimates on the annual incidence of nephrotic syndrome range from two to seven per 100,000 children, and prevalence from twelve to sixteen per 100,000 (Eddy and Symons, 2003).

The pathogenesis of minimal change nephrotic syndrome is not completely clear, but it is probably due to the imbalance between T helper 1 and T helper 2 cells. It appears that activation of T helper 2 lymphocytes has an important role in pathogenesis of minimal change disease (MCD). Cytokines of T helper 2 cells that have some possible roles in the induction of proteinuria include IL-4, IL-10, and especially IL-13. Interleukin 13 may alter glomerular permeability and induce proteinuria in patients with MCD (Mamizadeh *et al.*, 2017). IL-13 is a cytokine that is secreted by various T-cell subsets and dendritic cells. IL-13 composed of 132 amino acids and its molecular weight is 12 kd. IL-13 shares many biologic activities with IL-4, IL-4 receptor (IL-4R) and IL-13 receptor (IL-13R) complexes share the IL-4R α chain needed for signal transduction (McCormick and Heller, 2015). High production of IL-13 are by activated CD4⁺ TH2 cells. While, TH1 and CD8⁺ T cells also produce large levels of IL-

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13 (Vries, 1998). The expression of IL-13 can lead to injury of podocyte and IL-13 overexpression caused the downregulation of podocin, nephrin and dystroglycan and these proteins are critical molecules in preserving integrity of slit diaphragm (SD), and upregulation of the concurrent of IL-4R α , IL-13R α 2 and CD80 in IL-13-transfected rats (Kim *et al.*, 2016).

Another studies have identified that increased IL-13 expression can lead to podocyte injury and induce a minimal-change-like nephropathy (Yap *et al.*, 1999; Cheung *et al.*, 2004 and weiet *et al.*, 2005). Lai *et al.* (2007) reported that overexpression of IL-13 caused downregulation of nephrin, podocin, and dystroglycan—all of which are important molecules in maintaining SD integrity—and a concurrent upregulation of B7-1 as well as MCNS in a rat experiment model.

Patients and methods:-

Fifty blood samples of patients suffering from nephrotic syndrome during the period from September 2017 to January 2018 from the Al-Emamain Al-Kadhemain Medical City and Welfare Teaching Hospital in Medical City of Baghdad and twenty-five blood samples have been collected from unrelated healthy children. The age of NS patients was from 2 to 14 years with mean 7.78 ± 3.52 years and from 5 to 14 years with mean 8.64 ± 3.08 years for healthy control. Out of 50 cases, 35 cases (70%) were males and 15 cases (30%) were females and the male to female ratio was 2.3:1. Pathological types based on response to steroid nephrotic syndrome among patients revealed that 14 cases (28%) steroid sensitive infrequent relapse (SSIFR), 12 cases (24%) steroid sensitive frequent relapse (SSFR), 9 cases (18%) steroid resistance (SR) and 15 cases (30%) newly diagnosis (ND). The biochemical test was done to determine the levels of blood urea, serum creatinine, serum albumin and serum cholesterol in patients and healthy control. Serum IL-13 levels were detected for NS patients and healthy control by using R&D ELISA kit.

The Statistical Analysis System- SAS (2012) program was used to study the effect of different factors in study parameters. Chi-square test was used to significantly compare between percentages and Least significant difference –LSD test (ANOVA) or T-Test was used to significantly compare between means. correlation coefficient was estimated between variables in this study.

Results:-

Fifty children with NS compared to twenty-five healthy children as a control group were recorded in this study. Pathological types based on response to steroid nephrotic syndrome among patients revealed that 14 cases (28%) steroid sensitive infrequent relapse (SSIFR), 12 cases (24%) steroid sensitive frequent relapse (SSFR), 9 cases (18%) steroid resistance (SR) and 15 cases (30%) Newly diagnosis.

The mean level of serum albumin, serum creatinine and blood urea was significantly decreased in patients in compared with healthy control, while the mean level of urine albumin and serum cholesterol was significantly increased in patients in compared with healthy control. The results of mean IL-13 level in healthy serum (205.18 ± 2.61 pg/ml) was significantly lower than children with nephrotic syndrome (335.50 ± 40.68 pg/ml) Table 1.

Comparison between the IL-13 concentration among types of NS and healthy control demonstrated that insignificant difference between ND (406.21 ± 131.79 pg/ml), SR (290.40 ± 25.27 pg/ml), SSFR (306.82 ± 18.55 pg/ml) and SSIR (313.31 ± 33.75 pg/ml) Figure 1.

There is a significant correlation between IL-13 serum concentration and serum albumin levels in nephrotic syndrome patients and no significant correlation with other biochemical parameters Table 2.

Table 1:-Compare between patients and control in IL-13 levels

Group	IL-13 (pg/ml) Mean \pm SE
Patients	335.50 ± 40.68
Control	205.18 ± 2.61
T-Test	115.14 *
P-value	0.0271
* (P<0.05).	

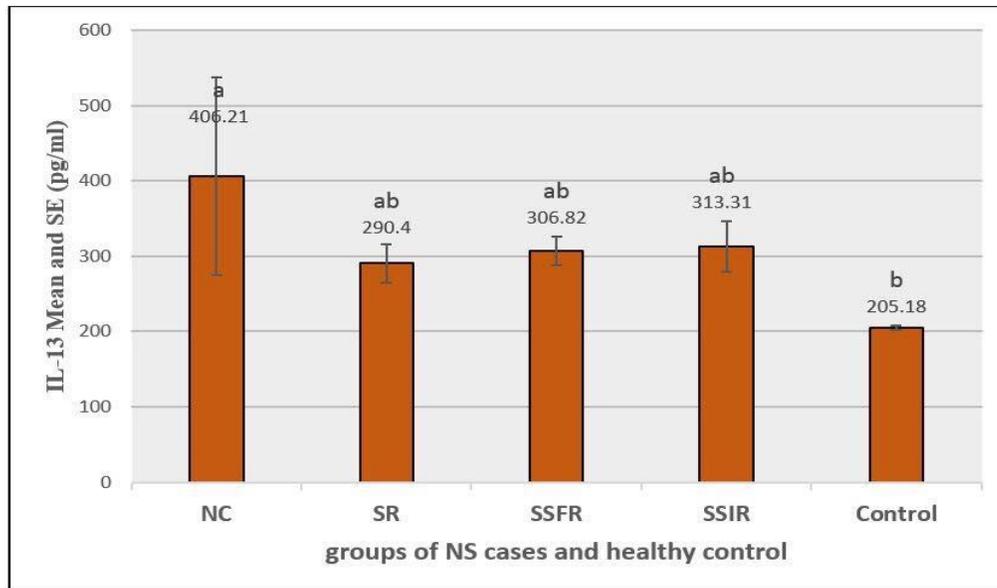


Figure 1:-Serum IL-13 levels among groups of NS and control

ND: Newly diagnosis, SR: steroid resistance, SSFR: Steroid sensitive frequent relapse, SSIR: Steroid sensitive infrequent relapse. Different letters mean significant differences between means at $P < 0.05$

Table 2:-Correlation between IL-13 and diagnostic features in patients

Laboratory parameters for diagnosis NS	IL-13
Urea	-0.06 NS
Creatinine	-0.17 NS
Serum albumin	-0.22 *
Cholesterol	0.08 NS
Urine albumin	0.11 NS
Pus cell in urine HPF	-0.07 NS
RBC in urine HPF	-0.06 NS
* ($P < 0.05$), NS: Non-Significant.	

Discussion:-

The increased of IL-13 in NS patients was in agreement with Mishra *et al.* (2014) who suggested that raised serum IL-13 in active phase and normalization in remission, Greater concentration of urinary IL-13 in untreated nephrotic syndrome patients in comparison to healthy controls and the percentage of CD3+ IL-13-producing cells was significantly greater in relapsing nephrotic and reduced during remission. increased IL-13 mRNA expression in CD4+ and CD8+ in nephrotic relapse than remission. Cytokines receptors of IL-4 and IL-13 are expressed by podocytes in different glomerular diseases, increasing the potential that IL-13 might participate to the proteinuria pathophysiology (Zhang *et al.* 2011). Mamizadeh *et al.* (2017) also reported that Level of serum IL-13 does not significantly drop after steroid therapy. higher concentration of serum IL-13 in children with acute minimal change disease (MCD) in comparison with a healthy control group. the raised expression of IL-13 by T-helper 2 cells in patients with acute nephrotic syndrome. Steroid can repress the IL-13 production by CD4+ cells rather than by CD8+ T-lymphocyte.

IL-13 correlated with the induction of podocyte structural alteration that are capable of changing the filtration selectivity and causing nephrotic syndrome (Medrano *et al.* 2012). overexpression of IL-13 give rise to the downregulation of podocin, nephrin, and dystroglycan. These proteins are decisive molecules in maintaining the integrity of slit diaphragm, and the synchronous upregulation of CD80, IL-13R α 2 and IL-4R α in IL-13 transfected rats (Kim *et al.* 2016). Park *et al.* (2015) demonstrated a redistribution and decrease in Zonula Occludens-1 (ZO-1) proteins from podocytes of human treated with IL-13. The ZO-1 molecules exposure to IL-13 caused ZO-1 to get about and accumulate inside toward the cytoplasmic actin filaments, suggesting that the watched redistribution and

decrease in ZO-1 proteins could be involved in the nephrotic syndrome pathogenesis. IL-13 may change ZO-1 proteins expression, leading in proteinuria, and also supply an explanation for the sensible connection of T-helper 2 cytokines, minimal change nephrotic syndrome, and atopy.

IL-13 prompts CD80 expression in podocytes, and CD80 is the key mediator for prompting proteinuria. It is assumed that NS has two steps: the first step is raised serum IL-13 concentration and then CD80 in podocytes cytoplasm and the second step is inadequate CD80 silencing by deficient release of soluble CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) (Mamizadeh *et al.* 2017).

Nephrotic syndrome can begin with a raise in production of IL-13 but its remission may concern with CD80/CTLA-4 ratio not on the serum IL-13 concentration. Additionally, the action of IL-13 on podocytes may be local depending on the concentration of IL-13 in the zone and its receptors expression (Mamizadeh *et al.* 2017).

Conclusion: we concluded that serum IL-13 levels were increased in NS patients in compared with healthy control, and the highly significant concentration of IL-13 was reported in newly diagnosis patients. we need more studies to determine the precise role of IL-13 in the NS pathogenesis.

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