The Role of Inter Leukin-10 in Infectious Mononucleosis Like Syndrome


ABSTRACT:

BACKGROUND:
Infectious mononucleosis is caused by the ubiquitous Epstein-Barr virus. It is a common condition usually adolescents and young adults. Most cases are mild to moderate in severity with full recovery taking place over several weeks. More severe cases and unusual complications occasionally occur.

AIMS OF THE STUDY:
Determining the role of the Th1 and Th2 in infectious mononucleosis-like syndrome by measuring IL-10.

METHODS:
Enzyme immunoassay for quantitative determination of human Interleukin-10 in serum.

RESULTS:
of cytokines showed a significant increase in IL-10 in patients with EBV infection (122.3±34.97) pg/ml. In non-EBV infection the level of IL-10 was also increase (74.24±18.84) pg/ml when compared with the healthy control (2.2±0.86) pg/ml. There was high significant difference between them (p<0.001).

CONCLUSION:
High levels of IL-10 may be referred to a TH1/TH2 response in infectious mononucleosis like-syndrome in comparison with healthy control group.

KEYWORDS: Epstein Barr virus, Non-Epstein Barr virus, IL-10

INTRODUCTION:
Infectious mononucleosis-like syndrome (IMLS) is an acute infection characterized by high fever, sore throat and lymphadenopathy especially in the cervical lymph nodes. It is mainly caused by Epstein-Barr Virus (EBV), a gamma herpes virus that is believed to infect 90% of the world’s population. It’s most common presentation is a flu-like illness called Infectious mononucleosis, which usually resolves on its own, but can also be caused by the Cytomegalovirus (CMV), Herpes simplex viruses (HSV)-1 and 2, Varicella-zoster virus (VZV) and Human herpes viruses (HHV) -6, 7 and 8. These viruses are members of one family Herpesviridae, all of them share properties including a genome of double-stranded linear DNA core surrounded by an icosahedra nucleocapsides symmetry, and a viral envelop. They also share the biological properties of latency and reactivation, which cause recurrent infections in the host. Toxoplasma gondii, Hepatitis A virus (HAV), Rubella, Human immunodeficiency virus (HIV), Adeno virus, Corynebacterium diphtheriae, Betahemolytic streptococci, and other agents are associated with IMLS as well.

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cytokines are produced by less specialized cells and very often several unrelated cell types can produce the same cytokine \(^{(9)}\). The term cytokine has been designated to include soluble mediators secreted by lymphocytes (lymphokines) and those secreted by monocytes and macrophages known as monokines, while cytokines synthesized and secreted by leukocytes are named interleukins (IL) \(^{(9)}\). All are secreted in extremely low concentration (picomolar to nanomolar range), and most manifest their biological effect through specific receptors, with high binding affinities, expressed at the surface of their target cell \(^{(10)}\). Cytokines can either synergize or antagonize other cytokines. These cytokines interaction lead to a cascade of functions, However, the central role of cytokines includes cell to cell communication, inflammatory response, amplification and immune response regulation \(^{(11)}\). Cytokines participate in all phase of immune response. They affect proliferation, differentiation and migration of various cells in immune system and regulate both humoral and cellular immune response \(^{(12)}\). They serve as chemical messengers that play pivotal roles in communication both within cells of the immune system to regulate the development and behavior of immune effector cells, and between the immune system and other systems of the body forming an integrated network that is highly evolved in the regulation of immune responses \(^{(13)}\). In most tissues, constitutive productivity of cytokines is absent or minimal. However, the physiological stimulus activate cells to increase the production of cytokines, which in turn organize the tissue's response to the stimulus particular immune responses. These immune modulating activities of cytokines are a result of their influence on gene expression, protein synthesis, membrane expression and antigen shedding from the cell surface \(^{(14, 15)}\). In addition, although the immune response to a specific antigen may include the production of cytokines, it is important to remember that cytokines act in an antigen-nonspecific manner, i.e. they affect whatever cell they encounter that bear appropriate receptors and are in a physiological state that allows them to respond. The predominant pro-inflammatory type 1- biased immune response during IM was emphasize by low frequencies of IL-10 expression in both T- cells subsets. Although some patients displayed elevated serum levels, six months later, a decreased, but still elevated IFN-gamma expression within the CD8+ T -cell subset, and an increased percentage of IL-2 expressing CD4+ and CD8+ T- cells reaching

Infectious Mononucleosis like syndrome

values, shown for controls, were noted \(^{(16)}\). Type 2- associated cytokines such as IL-4, IL-13 as well as IL-6. Tumor necrotizing factor (TNF) alpha were not significantly different when compared to controls at study entry and at follow-up. Others mentioned that, accumulating data indicate that cytokines and peptides, involved in regulation of both physiological and pathological immune responses, are produced predominantly at the site of local antigen stimulation \(^{(17)}\).

**Interleukin-10 (IL-10):** Interleukin-10 is an MW18000 protein, produced by Th2 cells, activated fetal thymocytes, macrophages, keratinocytes and normal B cells. Cells lines found to have the capacity to produce IL-10 in humans include : Th0, Th1 and Th2 like CD4+T-cells clones(Del prete and De Carli,1993 \(^{(18)}\)). Interleukin-10 can exert either immunosuppressive or immunostimulating effects on a variety of cell types. IL-10 could inhibit production of number of cytokines, especially IFN-gamma, by Th1 cells responding to antigen in the presence of antigen-presenting cells, IL-10 is a potent modular of monocyte/macrophage function. As a down regular of the cell-mediated immune response, IL-10 can suppress the production of prostaglandin E2 and numerous pro-inflammatory cytokines, including TNF-alpha, IL-1, IL-6,IL-8 etc by monocytes following activation. It also enhance the release of soluble TNF receptor and inhibits the expression of surface ICAM-1 and B7. Finally, IL-10 has been reported to suppress the synthesis of superoxide anion plus reactive oxygen intermediates (ROI), and either inhibits or facilitate NO synthesis, depending on the time of exposure to activated macrophages. Interleukin-10 can serve as both macrophage activator and deactivator and exhibit potent anti-inflammatory activities. In vivo, the induction of IL-10 synthesis during certain parasitic infections has been suggested to be an important strategy by which parasites evade IFN-gamma dependent, cell mediated immune destruction. Based on both the in vivo and in vitro functions of IL-10, it has been suggested that an IL-10 antagonist can be applied to boost anti-viral immunity against such viruses as EBV and the IL-10 may be used as anti-inflammatory reagent (Mosmann,1994 \(^{(19)}\)).

**Materials and Methods:**

**Subjects:** Patient's study group: Patien's groups included in this study could be devided as follows.A total of 100 patients were subjected to this study .These patients with presumably clinical picture (fever, lymphadenopathy, pharyngitis and atypical Lymphocytosis) of infectious
mononucleosis. They were referred to central public health laboratory (CPHL). Sixty five of them (the range of age 4-40 years) were send to CPHL from different Hospitals. Blood samples from patients with suspected of infectious mononucleosis-like illness were chosen for sampling and were investigated there in Hematology, Virology, Serology and immunology departments. In addition to the groups, 30 control blood samples (the range of age 4-39 years) were collected from normal persons attending the CPHL for the purpose of obtaining Health Certification.

Methods:

Enzyme immunoassay for Quantitative Determination of human Interleukin-10 in serum.

A- Principle:
The immunoenzymatic assay of interleukin-10 (IL-10) is sandwich type assay with two immunological steps. The first step leads to capture IL-10 by monoclonal anti IL-10, antibody bound to the wells of microtiter plate. In the second step, a second monoclonal anti-IL-10 antibody, which is biotinylated is added together with streptavidin-peroxidase conjugate. The biotinylated antibody is bound to the solid phase antibody-antigen complex and in turn, binds the conjugate. After incubation period, the wells are washed and the binding of the streptavidin-peroxidase via biotin is followed by the addition of chromogenic substrate of the peroxidase.

B-Immunoassay procedure:
Procedure, according to the information supplied by Immunotech A Beckman Coulter Company.

C- Calculation of the results:
The standard curve was drawn by plotting on the horizontal axis the IL-10 concentrations of the standards and on the vertical axis the corresponding average absorbance.

To locate the concentration of IL-10 in the samples, the average absorbance for each sample on the vertical axis was located and the corresponding IL-10 concentration was located on the horizontal axis.

RESULTS:
 Serum IL-10 level:
Serum level of IL-10 in the control were (2.2±0.86) pg/ml significantly lower than that in patients with I.M. (122.3±34.97) pg/ml. In the Non EBV infection the levels were (74.24±18.84) pg/ml which were significantly lower than patients with EBV groups (<0.001). There was high significant difference between non EBV group and control group (p<0.001). See figures (2,3 and 4).
Figure 2: Serum levels of IL-10, measured by ELISA in EBV, Non EBV and control groups.

Figure 3: Serum levels of IL-10, measured by ELISA in patients of EBV and Non EBV groups.


DISCUSSION:

Results of IL-10 confirmed the results showed by Margaret and David, (2001\(^{20}\)) who stated that I.M patients have increased expression of IL-10 mRNA as an important strategy for down-regulating T-cells response. Epstein Barr virus infection is known to induce endogenous secretion of IL-10 as a mechanism of parasitism because IL-10 seems to be responsible for inhibition synthesis of IFN-gamma the main macrophage –stimulating cytokine involved in the defense against EBV which facilitated the intracellular survival of virus by down-regulating the oxidative and inflammatory response (Battacharry \textit{et al.}, 2001\(^{21}\)). In fact in human severity of EBV has been closely associated with increased levels of IL-10 and the use of anti-IL-10 antibody to block the IL-10 activity or IL-10 receptor blocked can be effective approach for the treatment of I.M (Murray \textit{et al.}, 2002\(^{22}\)).

CONCLUSION:

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