Study of the relation between serum levels of long acting penicillin and the inflammatory markers: C-Reactive Protein and Interleukin-6 in patients with chronic rheumatic heart disease

Thesis

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Dedication

To the soul of my Mother

May ALLAH gather me with here in his paradise.

To my Father

Who lights my life.

To my great brothers and sister

Wael, Moustafa and Noha

My best support in this life.

To my beloved wife, Somaya

The rose of my life

To my sweet daughter, Maryam

The best gift from ALLAH

Abstract

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Background

Rheumatic heart disease refers to the functional and structural changes of the heart muscle and valves affected by rheumatic fever

Rheumatic fever has a marked tendency to recur leading to high risk of chronic heart lesions or worsening lesions in patients with previous rheumatic heart disease.

C-reactive protein (CRP) and inflammatory cytokines, as TNFa, IL-8 and IL-6, may play a pathogenic role in rheumatic fever and there levels indicate the activity of the disease.

Efficacy of long acting penicillin for secondary prevention of rheumatic fever has not been widely studied.

Objectives

Our study is a prospective cross-sectional controlled study that aims to study the relation between serum levels of long acting penicillin and the inflammatory markers, CRP and IL-6, in patients with chronic rheumatic heart disease.

Methods

Eighty patients from rheumatic heart disease patients coming to Ain Shams university hospitals' outpatient clinic for rheumatic fever prophylaxis by regular long acting penicillin administration were subjected to the study. Patients were divided into to 2 groups: Group A ; 70 patients with rheumatic heart disease already on prophylactic long acting penicillin, and Group B; 10 patients with rheumatic heart disease who have not started prophylactic long acting penicillin yet in addition to Group C; control group of 10 healthy individuals not known to have rheumatic heart disease.

Venous blood samples were drawn under aseptic conditions, centrifuged and 2 ml serum were collected and were stored at minus 20ºC for ELISA at El-Demerdash hospital immunology laboratory. All the serum samples were analyzed for long acting penicillin, CRP and IL-6 at Ain-Shams University Clinical Pathology Department using ELISA techniques using ELISA kit for Benzathine Benzylpenicillin, High Sensitivity C-Reactive Protein ELISA Test Kit and Human Interleukin-6 ELISA Kit.

Conclusion

Study results emphasize the importance of long acting penicillin in secondary prevention of chronic rheumatic heart disease.

Results showed a strong negative relation between long acting penicillin and the rheumatic inflammatory mediators; CRP and IL-6. Also the study results emphasized that chronic rheumatic heart disease is an inflammatory process mediated with some mediators as CRP and IL-6.

More large studies need to be done to prove the rule of long acting penicillin in secondary prevention of chronic rheumatic heart disease and to study the nature of the CRHD as an inflammatory process that may need more control with anti-inflammatory therapies.

Key words: CRP, IL-6 LAP, RF, RHD, CRHD

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LIST OF ABBREVIATIONS

Abbreviation	Title
AF	Atrial fibrillation
CRHD	Chronic rheumatic heart disease
CRP	C-reactive protien
ESR	Erythrocyte sedimentation rate
HS-CRP	High sensitivity C-reactive protein
IFN	Interferon
IL	Interleukin
LAP	Long acting penicillin
MR	Mitral regurgitation
MS	Mitral stenosis
MV	Mitral valve
MVA	Mitral valve area
MVR	Mitral valve replacement
P-value	Calculated Probability
r (statistics)	Pearson correlation coefficient
RF	Rheumatic Fever

LIST OF ABBREVIATIONS (CONTINUE)

RHD	Rheumatic Heart Disease
SD	Standard Deviation
TNF	Tumor Necrosis Factor

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Introduction

Rheumatic fever is the most important cause of acquired heart disease in children and young adults worldwide. It is an inflammatory reaction that occurs approximately 10 to 21 days after throat infection with virulent strains of Group A beta-haemolytic streptococci. It affects large joints (arthritis), the heart (carditis) and less frequently the brain (chorea), skin (erythema marginatum) and subcutaneous tissues. Rheumatic heart disease refers to the functional and structural changes of the heart muscle and valves affected by rheumatic fever **(Manyemba J. *et al.* 2002)**.

Rheumatic fever has a marked tendency to recur following new group A streptococcal upper respiratory tract infection. Recurrence has a high risk of chronic heart lesions or worsening lesions in patients with previous rheumatic heart disease. The severity of rheumatic heart disease and the prognosis depend on the extent of the carditis and the frequency of recurrent attacks. There is much evidence from randomised controlled trials concerning the primary prevention of rheumatic fever or the treatment of pharyngitis caused by Group A beta-haemolytic streptococci (GAS) but less data is available concerning secondary prevention of the disease **(Manyemba J. *et al.* 2002)**

C-reactive protein (CRP) is increased in patients with acute rheumatic fever, High levels of hs-CRP in patients with chronic rheumatic valve disease indicate the persistence of inflammation in the chronic phase**(Golbasi Z. *et al.* 2002)**.

Inflammatory cytokines, as TNFa, IL-8 and IL-6, may play a pathogenic role in rheumatic fever **(Yegin O. *et al.* 1997)**.

Single monthly injection of 1,200,000 unit of benzathine penicillin confer a high degree of continious protection against Group A streptococci and afford reliable means of protecting the patient against recurrences of rheumatic fever**(Stollerman G. H. *et al.* 1955)**.

Efficacy of long acting penicillin for secondary prevention of rheumatic fever has not been widely studied, consequently the relation between serum levels of long acting penicillin and inflammatory markers CRP and IL-6 is largely unknown.

Aim of the Study:

To detect the relation between serum levels of long acting penicillin and the inflammatory markers C-Reactive Protein and Interleukin-6 in patients with chronic rheumatic heart disease.

REVIEW OF LITERATURE

Immunological Background:

Interleukins as Inflammatory Mediators:

Immunocytes constantly exchange signals among themselves. Some of these signals are possible due to direct contact between cells. Others are effected through chemical messengers called cytokines which circulate in the blood.**(Morris K. *et al.* 1993)**

Interleukins are cytokines that have very important role in the function of the immune system. The term interleukin is formed from (inter-) "as a means of communication", and (-leukin) "deriving from the fact that many of these proteins are produced by leukocytes and act on leukocytes". It has since been found that interleukins are produced by a wide variety of body cells. The majority of interleukins are synthesized by helper CD4+ T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. They promote the development and differentiation of T, B, and hematopoietic cells.**(Ben Menachem-Zidon O. *et al.* 2011)**

Interleukin-6:

IL-6 is a soluble mediator with a pleiotropic effect on inflammation, immune response, and hematopoiesis. At first, distinct functions of IL-6 were studied and given distinct names based on their biological activity.

For example:

1- The name B-cell stimulatory factor 2 (BSF-2) was based on the ability to induce differentiation of activated B cells into antibody (Ab)-producing cells. **(Kishimoto T. 1985)**

2- The name hepatocyte-stimulating factor (HSF) on the effect of acute phase protein synthesis on hepatocytes, the name hybridoma growth factor (HGF) on the enhancement of growth of fusion cells between plasma cells and myeloma cells.

3- The name interferon (IFN)-β2 owing to its IFN antiviral activity. When the BSF-2 cDNAwas successfully cloned in 1986 **(Hirano T. *et al.* 1986)**

However, it was found that the molecules with different names studied by various groups were infact identical, resulting in the single name IL-6. **(Kishimoto T. 1989)**.

Human IL-6 is made up of 212 amino acids, including a 28-amino-acid signal peptide, and its gene has been mapped to chromosome 7p21.**(Tanaka T. *et al.* 2014)**

Furthermore, IL-6 promotes specific differentiation of naïve CD4 Tcells, thus performing an important function in the