Assessment of Serum IgA in Pediatric Patients with Recurrent Otitis Media

Thesis

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By

Reham Abd El Latif Ahmed Gaafar
M.B., B.Ch.
Faculty of Medicine – Ain Shams University

Under Supervision of

Prof. Dr. Shereen Medhat Reda
Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Dr. Tamer Ali Youssef
Assistant Professor of Otolaryngology
Faculty of Medicine - Ain Shams University

Dr. Reem Ahmed El-Feky
Lecturer of Pediatrics
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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وأنزل الله عليك
الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن
تَعْلَمُ وكَانَ فَضْلُ
اللَّهِ عَلَيْكَ عَظِيماً
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List of Abbreviations

Ags	: Antigens
Anti –tTG	: Anti - tissue transglutaminase
AOM	: Acute otitis media
CVID	: Common variable immunodeficiency
EAA	: Extrensic Allergic Alvéolites
ETD	: Eustechian tube dysfunction
Fc	: Fragment crystallizable
GI	: Gasterointestinal
HCT	: Hematocrit
HGB	: Hemoglobin
HIV	: Human immunodeficiency virus
HLA	: Human leukocytic antigen
Ig	: Immunoglobulin
IgA	: Immunoglobulin A
IgD	: Immunoglobulin D
IgE	: Immunoglobulin E
IgG	: Immunoglobulin G
IgM	: Immunoglobulin M
IL	: Interleukins
IVIG	: Intravenous immunoglobulin
MALT	: Mucosal-associated lymphoid tissues
MCHC	: Mean corpuscular hemaglobin concentration
MCV	: Mean corpuscular volume
MMR	: Measles, Mumps, Rubella vaccine

NSAID : Non steroidal anti-inflammatory drugs

O.M : Otitis media

PID : Primary immunodeficiency

PIgA : Polymeric IgA

PLT : Platelets

ROM : Recurrent otitis media

SD : Standard deviation

TACI : Transmembrane activator, calcium-modulator and cyclophilin ligand interactor

TLC : Total leukocytic count

URTI : Upper respiratory tact infection

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Introduction

The predominant antibody deficiency syndromes include a heterogeneous group of disorders in which the fundamental defect is inability of B cells to produce an effective antibody response to pathogen ***(Gatti & Hu, 2008).***

Patients with predominant antibody deficiency represent >50% of cases of primary immunodeficiency ***(Latiff & Kerr, 2007).***Patients with predominant antibody deficiencies usually represent with repeated bronchopneumonia, upper respiratory tract infections, gastrointestinal infections and recurrent otitis media ***(De Silva et al., 2007)***.

Serum IgA level is used as a screening tool for predominant antibody deficiencies ***(Oliveirad & Fleisher, 2010).***

Otitis media is the second most common infectious disease of childhood, after upper respiratory infection ***(Yel, 2010).***

Young children in daycare very often get frequent upper respiratory tract infections and ear infection. Usually, parents and even pediatricians don't pay attention to long standing history of recurrent otitis media despite the possibility that it may be an alarm for predominant antibody diseases ***(Sazgar et al., 2008).***

In the absence of early diagnosis and appropriate management, primary antibody deficiency can lead to serious morbidity and early mortality ***(Wood et al., 2007).***

Aim of the work

The aim of the present study is assessment of serum IgA level in pediatric patients with recurrent otitis media.

Introduction to the immune system

The immune response is divided into two arms, the innate and adaptive, based on the speed and specificity of the reaction. The former is immediate and antigen independent while the latter develops over days to weeks, is antigen targeted and characterized by the development of immune memory ***(Naik, 2003).***

The term innate immunity is sometimes used to include physical, chemical, and microbiological barriers, but more usually encompass the elements of the immune system (neutrophils, monocytes, macrophages, complement, cytokines and acute phase proteins), which provide immediate host defense ***(Parkin & Cohen, 2001).***

Adaptive immunity is the hallmark of the immune system. The cells of the adaptive immune system include B cells and T cells which are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow ***(Janeway et al., 2005).***

B-lymphocytes develop in the bone marrow and spleen through a series of stages from pluripotent precursor cells to mature B cells. This process does not require B-cell contact with antigen ***(Bonilla & Fried, 2009).***

Antibodies can occur in two physical forms, a soluble form that is secreted from the cell, and a membrane-bound form

that is attached to the surface of a B cell and is referred to the B cell receptor (BCR). The BCR facilitates the activation of these cells and their subsequent differentiation into either plasma cells, or memory B cells (***Borghesi & Milcarek, 2006)***.

Plasma cells and memory B cells represent the end stages of B cell differentiation and maturation. They are responsible for the continuous production of specific antibodies and long-lasting immunological memory, respectively ***(Burg et al., 2009).***

The binding of antigen to the BCR induces BCR clustering and signaling cascades that lead to the activation of a variety of genes associated with B-cell activation ***(Tolar et al., 2008)***.

After leaving the bone marrow, IgM positive B cells activated by antigen in blood enter a germinal center in lymphoid tissues. Here, the interaction of B and T cells contributs to the generation of IgG, IgA, and IgE positive plasma cells and memory B cells by initiation of class switch recombination (CSR) (figure 1) (***Maródi & Notarangelo, 2007).***

Somatic hypermutation of the variable region of Ig heavy and Ig light chains increases the affinity of the BCR for antigen ***(Driessen & Burg, 2011)*.**

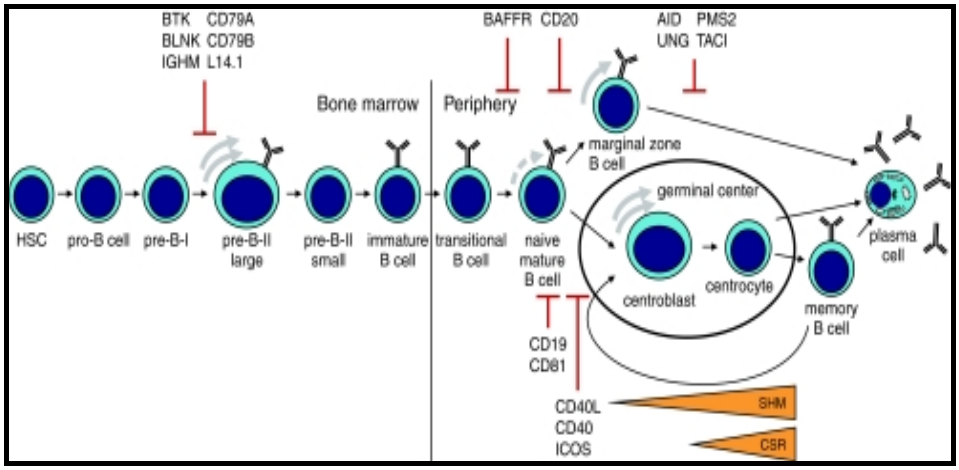

Figure (1): B cell development & differentiation ***(Driessen & Burg, 2011).***

Immunoglobulin:

Immunoglobulin is a large Y-shaped protein produced by B-cells that is used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. The antibody recognizes a unique part of the foreign target, called an antigen ***(Janeway et al., 2005).***

All immunoglobulins have a four-chain structure as their basic unit. They are composed of two identical heavy and two identical light chains-kappas (κ) or lambdas (λ) which are common to all five immunoglobulins. The heavy and light chains are bound together by disulfide bonds and by non-covalent interactions ***(Bonilla et al., 2012).***

Immunoglobulins can be divided into five different classes, based on differences in the amino acid sequences in the constant region of the heavy chains; gamma (γ) in IgG, alpha (α) in IgA, mu (μ) in IgM, delta (δ) in IgD and epsilon (ε) in IgE ***(Mayer,2011).***

The heavy and light chains each have highly variable regions; which give the immunoglobulin specificity, and constant regions; in which there is virtual complete correspondence in amino acid sequence in all antibodies of a given isotype (eg. IgA, IgG, etc.) or isotype subclass (eg. IgG1, IgG2, etc.) ***(Dalves & Roitt, 2000).*** Hinge region is the region at which the arm of the antibody molecule forms a Y. It is called the hinge region because there is some flexibility in the molecule at this point. They can be broken into a constant Fc fragment and two highly variable Fab fragments ***(Mayer, 2011).***

Immunoglobulin gene arrangement:

The immunoglobulin heavy chain and light-chain genes occur on chromosomes 14, 2 and 22, respectively, in humans. In the embryonic germ line state the heavy-chain gene occur as separate segments for variable (V), diversity (D), joining (J) and constant (C) regions ***(Albert & Inman, 2000).*** During early differentiation of B cells, there is rearrangement of heavy-chain genes so that one of the V heavy-chain segments combines with one of the D segments already combined with one of the J segments. They thus form a transcriptional active gene for the heavy chain (***Hoffbrand et al.*****, 2001**).

Immunoglobulin classes:

(1) Immunoglobulin G (IgG):

IgG is composed of four peptide chains (two heavy chains γ and two light chains) ***(Mayer, 2011).*** It provides the majority of antibody-based immunity against invading pathogens ***(Pier***