Evaluation of Serum IgA Level Among Children with Recurrent Infections in Assiut Governorate

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By

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CONTENTS

List of Abbreviations

AIDS	Acquired immune deficiency syndrome
ALC:	Absolute lymphocytic count
ANC:	Absolute neutrophil count
CD:	Cluster of differentiation
CVID:	Common variable immunodeficiency
EAA	Extrensic Allergic Alvéolites
Fc:	Fragment crystallizable
HLA:	Human leukocytic antigen
IDF:	Immune Deficiency Foundation
IDR:	Immunodeficiency disease related
Ig:	Immunoglobulin
IgA:	Immunoglobulin A
IgD:	Immunoglobulin D
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
IL:	Interleukins
ITP	Idiopathic Thrombocytopenic Purpura
IVIG:	Intravenous immunoglobulin
MALT:	Mucosal-associated lymphoid tissues
	Modulator and cyclophilin ligand interactor

O.M	Otitis media
PID:	Primary immunodeficiency
PIgA:	Polymeric IgA
PLT	Platelets
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SD:	Standard deviation
SIgAD	Selective IgA deficiency
SLE:	Systemic lupus erythematosis
TACI:	Transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TGF	Transforming growth factor
TLC:	Total leukocytic count
W.H.O:	World Health Organization
XLA:	X linked agammaglobulinaemia

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INTRODUCTION

Primary immunodeficiency diseases (PID) are disorders in which part of the body immune system is missing or does not function properly. Primary immunodeficiency diseases are caused by intrinsic or genetic defects in the immune system (***Medline and Medical Encyclopedia, 2008***).

There are wide varieties of primary immunodeficiency disorders; the World Health Organization (W.H.O) recognizes nearly 100 primary immunodeficiency diseases ***(www.ipopi.org)***.

Selective IgA deficiency is the most common primary immunodeficiency (***Quartier, 2001***). It is defined as total absence or severe deficiency of IgA. Selective IgA deficiency may be inherited as autosomal dominant or autosomal recessive trait. However, the majority of persons with selective IgA deficiency have evidence of chromosomal abnormalities (***Immune Deficiency Foundation, 2007***).The incidence of selective IgA deficiency disorder varies across racial and ethnic lines (***Immune Deficiency Foundation, 2007***).

In children suffering from recurrent infections, the frequency of IgA deficiency has been reported between 20 to 50 % by various authors (***Genel and Kutukcular, 2003***).

Children with selective IgA deficiency are lacking IgA, but usually have normal amount of other types of immunoglobulins. Most affected are asymptomatic, others may develop varieties of significant illness problem. Currently, it is not understood why some children with selective IgA deficiency have almost no illness while others are very sick. Also, it is not known precisely what percent of individuals with selective IgA deficiency will eventually develop complications (***Andrew J.Cant et al., 2003***).

The most common problem of selective IgA deficiency is increased susceptibility to infections, autoimmune disease, allergies and malignancy (***Rebecca, 1996***).

Determination of immunoglobulin concentrations in children's sera is important for the detection of immunoglobulinopathies, mainly primary immunodeficiency which, may be manifested at early age (***Dodig et al., 2002***). Early diagnosis and early implementation of the proper therapy will result in marked improvement in the quality of life for persons with primary immunodeficiency (***Khoury et al., 2000***).

AIM OF THE WORK

The aim of the present study is early diagnosis of selective IgA deficiency by measuring serum IgA levels among children presenting with recurrent infections in EL-Badary hospital, Assiut governorate. The identification of these patients would allow appropriate treatment before irreversible damage takes place.

Introduction to immunoglobulin A

General structure of immunoglobulin:

The immunoglobulin's are all made up of the same basic structure (Figure: 1) consisting of two heavy chains which are called gamma (γ) in IgG, alpha (α) in IgA, mu (μ) in IgM, delta (δ) in IgD and epsilon (ε) in IgE and two light chains-kappa (κ) or lambda (λ) which are common to all five immunoglobulin's (***Albert and Inman*, 2000).**

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 and Roitt*, 2000**).

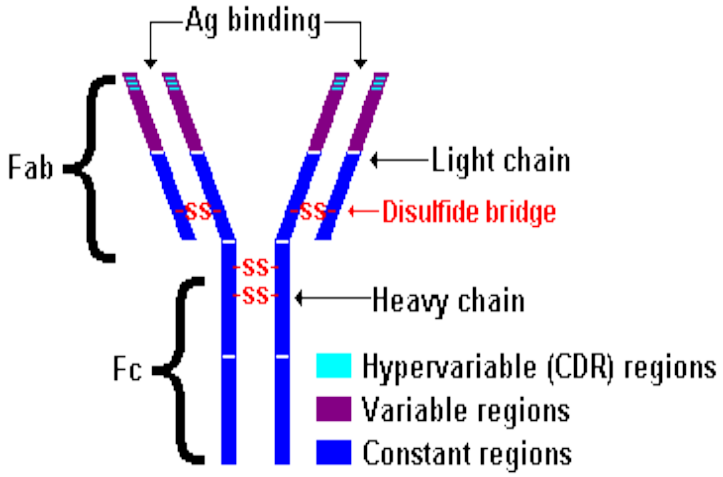

Figure (1): Basic structure of immunoglobulin molecule (***www.cehs.siu.edue***).

In the variable regions of both the heavy and light chains, there are hypervariable or complementarily-determining regions and framework regions with less variability (***Albert and Inman***, **2000**). Hinge region is the region at which the arms of the antibody molecule form 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, 2008***).

IgA structure:

IgA is mainly present (> 80%) in the form of monomeric IgA (mIgA) composed of two α and two κ or λ chains. Human α chains are glycoproteins consisting of one variable and three constant domains. The remaining part of serum IgA is in a polymeric, mainly dimeric form, with monomers connected by disulphide bonds and linked to an additional polypeptide called J chain (***Mestecky et al.,* 1999** "a").

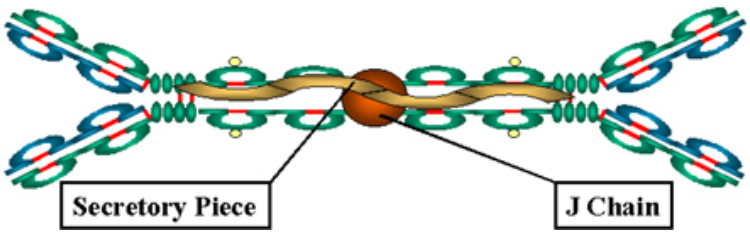

Figure (2): Dimeric structure of IgA (***Mayer, 2008***)

IgA is the immunoglobulin present in the respiratory and gastrointestinal mucosa (***Lindsey, 2005***)**.** There are two subclasses, IgA1 and IgA2. IgA1 is the predominant subclass (90%) in serum, whereas IgA1 and IgA2 are found at similar concentrations in many secretions (***Woof et al.,*** **2004**)**.**

IgA production:

IgA-bearing B cells first appear about three months after birth, IgA-producing cells have not been observed before the 32nd week of pregnancy. Serum IgA is usually undetectable at birth, and adult serum concentrations are not attained until around the time of puberty. In adults, the majority of human plasma cells produce IgA. More IgA is produced than all other immunoglobulin isotypes combined (***Woof and Kerr,*** **2006).**

Plasma IgA:

Plasma IgA is produced by B lymphocytes in the bone marrow and in some peripheral lymphoid organs (***Lattif and Kerr, 2007***)**.** In the plasma, IgA constitutes about 20% of the total Ig pool and it exists mainly as monomeric IgA1, (with a minor percentage of polymeric IgA (pIgA). Plasma IgA has a half-life of 3-6 days. The function of plasma IgA antibodies remains unclear although it is recognized that aggregated IgA can efficiently trigger inflammatory cells (***Woof et al., 2005***)**.**

Secretory IgA:

The IgA produced by lymphocytes in organized germinal centers of mucosal-associated lymphoid tissues (MALT) such as Peyer's patches; called secretory IgA, this type is found in secretions such as; saliva, tears, colostrum, gastrointestinal fluids, nasal, bronchial secretions and urine (***Lattif and Kerr, 2007***)**.** IgA is the second dominant isotype in the blood circulation following IgG. It can be found in both monomeric and polymeric forms. Circulating IgA is in monomeric form, whereas secretory IgA, in the mucosal secretions of respiratory, intestinal, and genitourinary systems, is dimeric. In humans, there are two subclasses of IgA: IgA1 and IgA2, constant heavy chains of which are encoded by two separate α1 and α2 genes on chromosome 14 ***(Woof and Kerr, 2006).***The main structural difference between them is that IgA2 has a shorter hinge region which may render this isotype more resistant to bacterial proteases in the lumen of gastrointestinal or respiratory systems (**Corthésy *B, 2007).*** The function of serum IgA in the systemic immune response has not been clearly understood. However, it may have a role in activation of phagocytic system by means of the FcRα receptors ***(Woof and Kerr, 2006).***

IgA, which is mostly in dimeric form, is the dominant immunoglobulin in luminal secretions comprising more than two thirds of total IgA production in the body. Being more resistant to proteolytic activity of the bacteria, IgA2 is the main IgA subclass found in secretions ***(Macpherson et al., 2008).***

In the gastrointestinal system, organized Payer's patches or isolated lymphoid follicles as well as nonorganized lamina propria can be sites for local IgA production by T cell-dependent as well as T cell-independent mechanisms ***(Cerutti, Rescigno, 2008 and Suzuki, Fagarasan, 2008).***

Bacteria endogenous to the intestinal tract, oral cavity, and respiratory and genital tracts are coated with secretory IgA. As a result, the epithelial adherence and penetration of bacteria are limited, and the bacteria are confined to the mucosal surfaces ***(Macpherson et al., 2005).***

Recently, it has been proposed that there is a link between the specific antibody-dependent protection and the innate glycan-mediated mucosal immunity by means of *N*- and *O*-glycans of secretory IgA. It is likely that glycan-mediated interactions in concert with Fab-mediated poly reactivity enforce protective functions of secretory IgA ***(Mestecky and Russell, 2009)***.