Detection of Selective IgA Deficiency Among Infants and Children With Recurrent Infection In Assiute Governorate

Thesis Submitted For Partial Fulfillment
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
ورَسُولُهُ والْمُؤْمِنُونَ

صدق الله العظيم

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Belal Abuzied Abd alhamed

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List of Abbreviations

AD	Autosomal dominant inheritance
ADA	Adenosine deaminase
ADAD	Adenosine deaminase deficiency
AID	Activation-induced cytidine deaminase
ALC	Absolute lymphocytic count
ALPS	Autoimmune lymphoproliferative syndrome
ANC	Absolute neutrophil count
AOM	Acute otitis media
AR	Autosomal recessive inheritance
A-T	Ataxia-telangiectasia
Autoimm	Autoimmunity
BMT	Bone marrow transplantation
BPG	Benzathine pencillin G
BTK	Bruton tyrosine kinase
CBC	Complete blood count
CD	Celiac disease
CGD	Chronic granulomatous disease
CHH	Cartilage hair hypoplasia
CID	Combined immunodefiency
CINCA	Chronic infantile neurologic cutaneous and articular syndrome
COPD	Chronic obstructive pulmonary disease
CVID	Common variable immunodeficiency
D	Days
dATP	Deoxyadenosine triphosphate
DC	Dendritic cell
DD	Duration of infections per day
dGTP	Deoxyguanosine triphosphate
EAA	Extrinsic allergic alveolitis
EIAS	Enzyme immune assay
ELIAS	Enzyme linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
F	Female

List of Abbreviations (Cont.)

FD	Frequency of infections per year
G-CSF	Granulocyte colony stimulaing factor
H.S	Highly significant
HB	Hemoglobin
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
Ht	Height per Cm
ICOS	Inducible costimulator
Ig(k)	Immunoglobulin of k light-chain type
IVIG	Intravenous immunoglobulin
L	Less severe (moderate)
M	Male
MASP-2	MBP-associated serine protease2
MBL	Mannose binding lectin
MBP	Mannose binding protein
MHC	Major histocompatibility complex
Mo	Month
N.S	Non significant
NHEJ	Non-homologous end joining
NK	Natural killer cells
NOMID	Neonatal onset multisystem inflammatory disease
OM	Age of onset of recurrent infections per months
PAN	Poly arteritis nodosa
PAPA	Pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome
PCP	Pneumocystis carinii pneumonia
PHAI	Passive haemagglutination inhibition assay
PID	primary immunodeficiency
PLT	Platelet count
PNP	Purine nucleoside phosphorylase
R	Pearson correlation
RAG	Recombinase activation gene
RID	Radial Immunodiffusion method

List of Abbreviations (Cont.)

RP	Repeated infections without a symptom free interval
S	Significant
SADNI	Specific antibody deficiency with normal immunoglobulins
SC	Subcutaneous
SCID	Severe combined immunodeficiencies
SD	Standard deviation
Sig	Significancy
SIgAD	Selective IgA deficiency
SLE	Systemic lupus erythematosus
SPRCA	Solid phase red cell adherence assay
STAT1	Signal transducer and activator of transcription 1
SV	Severe
TAP	Transporter associated protein
TCD	T –cell disease
THI	Transient hypogammaglobulinemia of infancy
TLC	Total leucocytic count
TRC	T-residual cell
UNG	Uracil-DNA glycosylase
Vs	Versus
WAS	Wiskott-Aldrich syndrome
WHN	Winged helix nuden
Wt	Weight per Kg
XHIGM	X-linked hyper-IgM syndrome
XL	X-linked inheritance
XLP	X-linked lymphoproliferative syndrome
Y	Year
ZAP	Zeta associated protein

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Introduction

Primary immunodeficiency disorder (PID) refers to a heterogeneous group of disorders that result from defects in immune system development and/or function. PIDs are broadly classified as disorders of adaptive immunity or of innate immunity.Most primary immunodeficiencies are genetic disorders (***McCusker, 2011).*** The majority are diagnosed in children under the age of one year, although milder forms may not be recognized until adulthood ***(Megan S. Lim, 2004).***

Although the clinical manifestations of PIDs are highly variable, most disorders involve at least an increased susceptibility to infection.There are wide varieties of primary immunodeficiency disorders **(*McCusker, 2011).*** The World Health Organization (W.H.O.) recognizes nearly 100 primary immunodeficiency, selective IgA is the most common disorder of primary immunodeficiency diseases ***(Quartier, 2001).***

Selective IgA Deficiency is the most common of the primary Immunodeficiencies. It is defined as the total absence or severe deficiency of IgA in the blood serum .The incidence of Selective IgA deficiency disorder varies across racial and ethnic lines .Most individuals with sIgAD are asymptomatic and identified coincidentally. However, some patients may present with recurrent infections, allergic disorders and autoimmune manifestations. Several autoimmune diseases ***(Bonilla, 2005).***

SIgAD varies in it's causes. SIgAD may be autosomal dominant with incomplete penetrance, SIgA deficiency is commonly associated with certain HLA haplotypes, and rare alleles or deletions of genes in the major histocompatibility complex (MHC) class III region are common. SIgA deficiency also occurs in siblings of children with common variable

immunodeficiency (CVID) and evolves into CVID in some patients ***(Bonilla, 2005).***

Determination of immunoglobulin concentrations in immunoglobulinopathies, mainly primary immunodeficiency, which may be manifested at an early age ***(Dodig et al., 2002)***. Early proper dignosis 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 infants and children presenting with recurrent infections. The identification of these patient would allow appropriate treatment before irreversible damage takes place.

Primary Immunodeficiency Diseases

Definition :

Primary immunodeficiency diseases are heritable disorders of immune system function. Many are associated with single gene defects ***(Puck, 1994)***, whereas others may be polygenic or may represent interactions of genetically determined characteristics with environmental or infectious stresses ***(Bonilla and Geha, 2003).***

Classification :

The International Union of Immunological Societies Expert Committee has used a more updated scheme to classify the primary immunodeficiencies (Table 1). This takes into account the frequent interactions of the B-cell and T-cell systems and the multiple variants of several syndromes. The inheritance patterns are also shown ***(Notarangelo et al., 2004)***.

Table (1): The International union of immunological societies classification of primary immunodeficiencies.

Disease	Inheritance	Disease	Inheritance
T- and B-cell immunodeficiencies		2. Autosomal recessive agammaglobulinemia	AR
1. T-B+ SCID* :			
a. γ c deficiency	XL	3. Ig heavy-chain gene deletions	AR
b. Jak3 deficiency*	AR	4. k Chain deficiency	AR
c. IL7Rα deficiency	AR	5. AID deficiency*	AR
d. CD45 deficiency	AR	6. UNG deficiency*	AR
e. CD3δ deficiency	AR	7. ICOS deficiency	AR
2. T-B- SCID:		8. Common variable Immunodeficiency_	Variable
a. RAG ½ deficiency	AR	9. Selective Ig deficiency:	
b. Artemis deficiency	AR	a. IgG subclass deficiency	Unknown
c. ADA deficiency	AR	b. IgA deficiency	Variable
d. Reticular dysgenesis	AR	10. Specific antibody deficiency	Unknown
3. Omenn syndrome	AR	11. Transient hypogamma -	Unknown

Disease	Inheritance	Disease	Inheritance
		globulinemia of infancy	
4. DNA ligase IV	AR	Other well-defined immuno-deficiency syndromes	
5. X-linked hyper-IgM syndrome	XL	1. Wiskott-Aldrich syndrome	XL
6. CD40 deficiency	AR	2. DNA repair defects	
7. PNP deficiency	AR	a. Ataxia-telangiectasia	AR
8. MHC class II deficiency	AR	b. Ataxia-like syndrome	AR
9. CD3γ and CD3ε deficiency	AR	c. Nijmegen breakage syndrome	AR
10. CD8 deficiency	AR	d. Artemis deficiency	AR
11. ZAP-70 deficiency	AR	e. DNA ligase IV	AR
12. TAP-1 deficiency	AR	f. Bloom Syndrome	AR
13. TAP-2 deficiency	AR	3. Thymic defects	
14. WHN deficiency	AR	a. DiGeorge anomaly	De novo Defect or AD
Predominantly antibody deficiencies		b. Winged helix nude deficiency	AR
1. X-linked agammaglobulinemia	XL		
Diseases of immune dysregulation		Rac 2 deficiency	AD
1. Immunodeficiency with albinism:		β-actin deficiency	AD
a. Chediak Higashi syndrome	AR	Papillon-Lefe`vre Syndrome	AR
b. Griscelli syndrome type2	AR	Specific granule deficiency	AR
2. Familial hemophagocytic lymphohistiocytosis:		Shwachman-Diamond Syndrome	AR
a. Perforin deficiency	AR	CGD: X-linked CGD Autosomal CGD's	XLAR
b. Munc deficiency	AR	Neutrophil G-6PD deficiency	XL
3. XLP	XL	Myeloperoxidase deficiency	AR
4. Syndromes with autoimmunity a. ALPS		IL-12 and IL-23 receptor deficiency	AR
i. CD95 (Fas) defects, type 1a	AR	IL-12p40 deficiency	AR
ii. CD95L (Fas ligand)	AR	IFN-γ receptor deficiencies	AR, AD*