Assessment of T-cell Function in Patients with Maple Syrup Urine Disease

Thesis

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Abstract

Introduction: The immune system is composed of a variety of different cell types and proteins. Each component performs a special task aimed at recognizing and/or reacting against foreign material. Primary immunodeficiency result from a deficiency or defect in T, lymphocyte, B, lymphocyte, NK cells, phagocytic **Aims:** Assessment of T-cell functions in patients with maple syrup urine disease in relation to clinical presentation, disease control and duration of the disease.

Methodology: This case-control study carried out at children's Hospital, Ain –Shams University. Patients included (30) infants and children with maple syrup urine together with (30) children age and sex-matched investigated as a control group, their ages ranged between one month to 4 years, they were 17 male (56%) and 13 female (44%), during the period from 1st December 2013 to 1st July 2015.

Results: All the cases and controls were collected from the children's hospital of Ain Shams university. Parents or legal guardians were interviewed to investigate relevant medical history. The interview covered the following aspects; frequency, duration and onset of severe infections, response to antimicrobials, family history of similar condition and/or previous siblings' death. After that, clinical examination and laboratory investigations of participants to cover possible attributing variables; complete blood count with differential leucocytes.

Conclusion

A decrease in the total leucocytic count and absolute lymphocytes accompanied with a decrease in lymphocytes subsets (CD3) and T-cell activation marker (CD69 and CD69 after activation) in patients was MSUD suggesting that high levels of leucine, isoleucine, valine ratio seem to have a deleterious effect on T lymphocyte subsets and its activation process. This could be a contributing factor to the increased rate of infection seen in patients with MSUD.

Recommendations: Nationwide screening for MSUD and other IEM in all neonates for early diagnosis. All MSUD patients should undergo serial assessment of lymphocyte subsets by flow cytometry. Other studies to be done on a large sample of MSUD patients to confirm our findings and to assess the status of viral infection as CMV and HIV which lead to secondary immunodeficiency as well as genetic studies for primary combined T cell and B cell immunodeficiency.

Keywords: T-cell Function, Patients, Maple Syrup Urine Disease

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Contents

List of Abbreviations

Abbrev.	Meaning
APC	: Antigen Presenting Cell
BCAAs	: Branched Chain Amino Acids
BCKD	: Branched Chain alpha-Keto acid Dehydrogenase
BCKDC	: Branched Chain alpha-Keto acid Dehydrogenase Complex
CBC	: Complete Blood Count
CD	: Cluster of Differentiation
G6PT	: Glucose-6-Phosphate Transporter
GSD 1b	: Glycogen Storage Disease 1b
HIV	: Human Immunodeficiency Virus
IEM	: Inborn Error of Metabolism
IQR	: Inter-Quartile Range
IVIG	: Intravenous Immunoglobulin
LSDs	: Lysosomal Storage Disorders
MCD	: Multiple Caboxylase Deficiency
MHC	: Major Histo-Compitability
MSUD	: Maple Syrup Urine Disease

NK : Natural killer

PCC : Propionyl-CoA Carboxylase

TCA : Tri-Carboxylic Acid

TCii : Transcobalamin ii

TCR : T-Cell Receptor

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Introduction

The immune system is composed of a variety of different cell types and proteins. Each component performs a special task aimed at recognizing and/or reacting against foreign material. Primary immunodeficiency result from a deficiency or defect in T, lymphocyte, B, lymphocyte, NK cells, phagocytic cells or complement system. The principal clinical manifestation of immunodeficiency is increased susceptibility to infection. The pattern of organ systems affected and characteristic pathogen vary with the type of immune defects. Therefore, it is important to look for Immunodeficiency in any infant or child with recurrent infections **(Bonilla and Geha, 2006).**

Maple syrup urine disease (MSUD), also called branched-chain ketoaciduria, is an autosomal recessive metabolic disorder affecting branched-chain amino acids. It is one type of organic acidemia. The condition gets its name from the distinctive sweet odor of affected infants' urine **(Podebrad et al., 1999).**

MSUD is caused by a deficiency of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC), leading to a buildup of the branched-chain amino acids (leucine, isoleucine, and valine) and their toxic by-products (ketoacids) in the blood and urine **(Ogier de Baulny and Saudubray, 2002).**

This disease occurs in attacks which are due to accumulation of (leucine, isoleucine, and valine) in the blood causing toxic effects, such as vomiting, seizures and may end by death, approximately one newborn out of one-hundred and eighty-thousand in America has MSUD **(Pasquali et al., 2011).**

BCAAs are absolutely essential for lymphocyte responsiveness and are necessary to support other immune cell functions. Cell culture studies show that BCAA are essential for lymphocytes to synthesize protein, RNA, and DNA and to divide in response to stimulation. However, many aspects of BCAA and its effects on immune function have been understudied or not studied at all; more research is needed to understand the extent of the immune system's requirement for BCAA **(Wilmore, 1983),** However, many aspects of BCAA and their toxic by-products (ketoacids) and its effects on immune function have been understudied or not studied at all **(Calder, 2006)**.

Aim of the Work

Assessment of T-cell functions in patients with maple syrup urine disease in relation to clinical presentation, disease control and duration of the disease.

CHAPTER (1)

Immunity and T-cell Function

The immune system is a system of biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, known as pathogens, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue. In many species, the immune system can be classified into subsystems, such as the innate immune system versus the adaptive immune system, or humoral immunity versus cell-mediated immunity **(Beck et al., 1996).**

Innate immune system:

Microorganisms or toxins that successfully enter encounter the cells and mechanisms of the innate immune system. The innate response is usually triggered when microbes are identified by pattern recognition receptors, which recognize components that are conserved among broad groups of microorganisms, or when damaged, injured or stressed cells send out alarm signals, many of which (but not all) are recognized by the same receptors as those that recognize pathogens **(Matzinger, 2002).**

Innate immune defenses are non-specific, meaning these systems respond to pathogens in a generic way. This system does not confer long-lasting immunity against a pathogen. The innate immune system is the dominant system of host defense in most organisms **(Litman et al., 2005).**

Adaptive immune system:

The adaptive immune system evolved in early vertebrates and allows for a stronger immune response as well as immunological memory, where each pathogen is "remembered" by a signature antigen **(Pancer and Cooper, 2006).**

The adaptive immune response is antigen-specific and requires the recognition of specific "non-self" antigens during a process called antigen presentation. Antigen specificity allows for the generation of responses that are tailored to specific pathogens or pathogen-infected cells. The ability to mount these tailored responses is maintained in the body by "memory cells". If a pathogen infect the body more than once, these specific memory cells are used to quickly eliminate it.

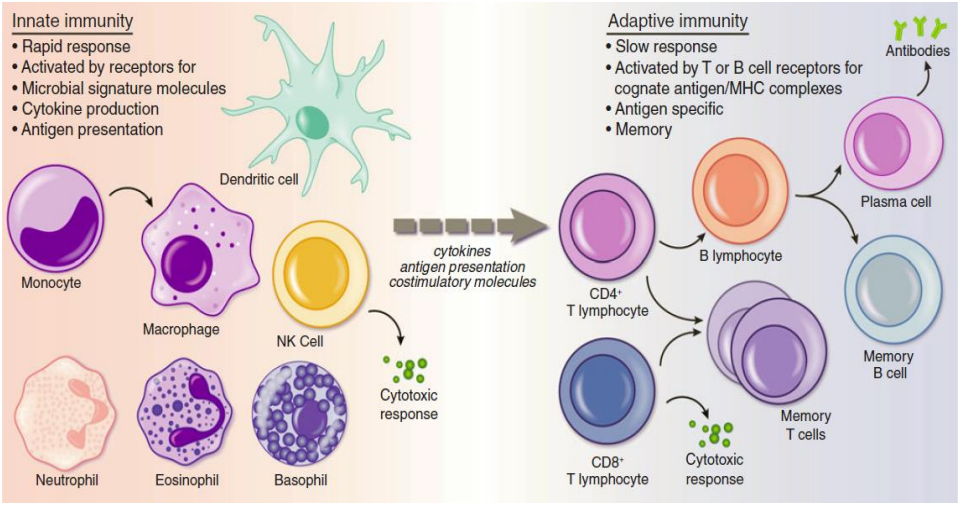

Figure (1): Innate immunity versus adaptive immunity **(Beutler and Goodnow, 2011)**.

Lymphocytes:

The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow **(Charles A and Janeway Jr, 2005).**

B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response, Both B cells and T cells carry receptor molecules that recognize specific targets. T cells recognize a "non-self" target, such as a pathogen, only after antigens (small fragments of the pathogen) have been processed and presented in combination with a "self" receptor called a

major histocompatibility complex (MHC) molecule. There are two major subtypes of T cells: the killer T cell and the helper T cell. In addition there are suppressor T cells which have a role in modulating immune response. Killer T cells only recognize antigens coupled to Class I MHC molecules, while helper T cells only recognize antigens coupled to Class II MHC molecules. These two mechanisms of antigen presentation reflect the different roles of the two types of T cell. A third, minor subtype is the γδ T cells that recognize intact antigens that are not bound to MHC receptors **(Holtmeier and Kabelitz, 2005).**

In contrast, the B cell antigen-specific receptor is an antibody molecule on the B cell surface, and recognizes whole pathogens without any need for antigen processing **(Charles and Janeway, 2005).**

Killer T cells:

Killer T cells are a sub-group of T cells that kill cells that are infected with viruses (and other pathogens), or are otherwise damaged or dysfunctional. As with B cells, each type of T cell recognizes a different antigen. Killer T cells are activated when their T cell receptor (TCR) binds to this specific antigen in a complex with the MHC Class I receptor of another cell. Recognition of this MHC: antigen complex is aided by a co-receptor on the T-cell, called