Single Nucleotide Polymorphism (C677T) in the MTHFR Gene and Essential Hypertension: A Pilot Study

Thesis

Submitted for Partial Fulfillment of Master Degree
in Clinical Pathology

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2017

Acknowledgement

*First of all, I'm grateful to **ALLAH** the most Gracious and the most Merciful for his aid and giving me the ability to accomplish this thesis.*

*My deepest gratitude and appreciation goes to **Prof. Laila Abdel Aala ElShawarby**, Professor of Clinical Pathology, Ain Shams University for giving me the privilege of working under her meticulous supervision, and for her constant support, enthusiastic guidance and encouragement.*

*My sincere thanks and appreciation are also to **Prof. Manal Zaghloul Mahran,** Professor of Clinical Pathology, Ain Shams University for her sincere contribution, great help and kind supervision to accomplish this work.*

*I'm greatly indebted to **prof. Nermeen Tayseer Aly Fouad,** Professor of Clinical Pathology, Ain Shams University for her continuous support, advice and patience. I am thankful for all the precious time and the great effort she gave me.*

*My grateful thanks to **Dr Dina Ali**, Lecturer of clinical pathology, Ain Shams University, for her efforts, cooperation and useful instructions.*

Finally, no words can express my gratitude and thankfulness to my dear father, family and friends for their continuous support and sincere love. They've always been there for me in the hardest times. May Allah bless them and keep them safe.

Contents

List of Abbreviations

A ..... …Adenine

ASH..... …American society of hypertension

BMI ..... …Body mass index

BP ..... …Blood pressure

C ..... …Cytosine

CAD ..... …Coronary artery diseases

CVD ..... …Cardiovascular diseases

DM ..... …Diabetes mellitus

DNA ..... …Deoxyribonucleic acid

dNTP..... …Deoxyribonucleotide triphosphate

dUTP..... …Deoxyuridine triphosphate

EDTA.....Ethylenediamine tetraacetic acid

EH ..... …Essential hypertension

Fig ..... …Figure

FVa..... …Activated factor V

Hcy ..... …Homocysteine

HTN ..... ….Hypertension

MGB ..... ….Minor groove bind

MTHFR ..... ….Methylenetetrahydrofolate reductase

NHANES III…The third National Health and Nutrition Examination Survey

OR…… Odds ratio

OSA..... …Obstructive sleep apnea

PCR..... …Polymerase chain reaction

RBC..... …Red blood corpuscle

RNA ..... …Ribonucleic acid

RNase..... …Ribonuclease

SD..... …Standard deviation

SNP ..... …Single nucleotide polymorphism

T ..... …. Thymine

Taq..... …. Thermophilus aquaticus

VCAM-1 ..... …. Vascular cell adhesion molecule

WHO..... …. World health organization

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INTRODUCTION

Essential hypertension (EH) is a complex disease and is the most common cardiovascular disease. The incidence of EH is increasing yearly with an apparent trend in younger patients**.** Although EH has been shown to be associated with a number of environmental and clinical risk factors as dietary intake of sodium, alcohol intake, lack of exercise, poor diet, obesity, insulin resistant diabetes, and hyperlipidemia, an individual's genetic makeup is estimated to be responsible for up to 60% of the variation in hypertension risk ***(Fowdar et al., 2012; Yin et al., 2012; and Zhang et al., 2015).***

The homocysteine (Hcy) pathway has emerged as one of the independent risk factors for EH. The third National Health and Nutrition Examination Survey (NHANES III) reported that people with the highest level of Hcy carried a 2 to 3 fold increase in hypertension prevalence than those with the lowest Hcy level.

One of the most studied genetic variants contributing to Hcy levels is the C to T single nucleotide polymorphism (SNP) at codon 677 of the methylenetetrahydrofolate reductase enzyme (MTHFR) gene. The MTHFR gene is located in chromosome 1 and plays a central role in folate metabolism and in the regulation of homocysteine concentration. The C to T substitution causes alanine to be

substituted by valine, and the TT variant codes for a thermolabile enzyme which has a 50% reduced activity compared to the CC variant ***(Fowdar et al., 2012; Cai et al., 2014; Yang et al., 2014).***

It is believed that better understanding of the risk factors for EH is of importance for understanding both EH and cardiovascular diseases (CVD) and may help to develop a new treatment or prevention strategies ***(Fenech et al., 2011)***

AIM OF THE WORK

In this study we aimed to explore the relation of MTHFR C677T single nucleotide gene polymorphism and essential hypertension in adult Egyptian patients.

I- HYPERTENSION

Definition:

Hypertension is defined as a state of chronic elevation of systemic arterial pressure. The diagnosis of hypertension in adults is established whenever 2 or more subsequent systolic blood pressure (BP) measurements exceed 140 mm Hg or when 2 or more subsequent diastolic BP measurements exceed 90 mm Hg as recommended by the sixth report of " the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" ***(Carretero and Oparil, 2000; Giles et al., 2009)***. The systolic blood pressure is the basis for diagnosis in most patients. However, in geriatric patients (80 years or older), a systolic blood pressure measurement of "up to 150 mm Hg" is now acceptable, as systolic blood pressure continues to increase with increased age due to the progressive stiffness of the arteries ***(Weber et al., 2014)***. On the other hand, it was recommended that in diabetic and chronic kidney disease patients a BP level of 130/80 mm Hg should be considered ***(Weber et al., 2014).***

Epidemiology:

Hypertension constitutes a global public health problem as it affects almost one third of adults worldwide,

and is estimated to cause 9.4 million deaths every year, and about 13% of the total annual deaths ***(WHO, 2009; Lim et al., 2012; Singh et al., 2016)***. Hypertension is known to be a major contributor to the problems of heart disease, stroke, kidney failure, premature mortality and disability, and is reported as being responsible for at least 45% of deaths due to cardiac diseases and 51% of those due to stroke ***(Lawes et al., 2008)***, which made the world health organization (WHO) to report hypertension as the first cause of death worldwide. Moreover, the highest mortality rates secondary to coronary artery diseases (CAD) were encountered in Egyptians ***(Ibrahim, 2013).***

The increasing prevalence of hypertension is related to ageing, population growth, obesity and behavioral risk factors as high dietary salt intake ***(WHO, 2013; Weber et al., 2014)***. The prevalence of raised blood pressure was higher in low and middle-income countries. The highest prevalence of raised blood pressure was encountered in Africa, accounting for 46% of the population, while in America, the prevalence rate of raised blood pressure was 35% of the population, with slightly more prevalence among men than women ***(WHO, 2009)***. In United States of America hypertension was reported to affect 29% of the adults, and 65% of those older than 60 years ***(Kovell et al., 2015)***. Meanwhile in Egypt, a study done in year 2013 reported that hypertension affects about 26.3% of the adult population and more than 50% of

individuals who are older than 60 years. Thus, it was predicted that with an Egyptian population of more than 80 millions, there will be approximately 15 million persons with hypertension, of whom about 7 millions need a lifelong drug treatment and regular follow-up, which in turn constitutes a great burden on the Egyptian economy. In that context, it was reported that there was a dramatic increase in the drug cost of hypertension in 2011 in Egypt accounting for almost one billion Egyptian pounds compared with a value of about 600 millions in year 2007 ***(Ibrahim, 2013).***

Raised blood pressure is a major risk factor for coronary heart disease and cerebro-vascular disease. Progression of hypertension has been shown to be strongly associated with cardiac and vascular abnormalities that cause damage of the heart, kidneys, brain, retina, and other organs as well. Moreover, control of blood pressure markedly reduces the risk for cardiovascular (CV) events ***(Giles et al., 2009)***. Regardless of the patients' age, it was found that a 20 mm Hg increase in systolic BP or a 10 mm Hg increase in diastolic BP was associated with almost doubled risk of cardiovascular disease (CVD) death. Moreover, there is evidence that the risk for CVD increases in a log-linear manner with a BP level above 115/75 mm Hg ***(Kikuya et al., 2007; Giles et al., 2009)***. In addition, hypertension in middle age persons was reported to be associated with increased incidence of chronic kidney disease and dementia.

There are significant health and economic gains related to early detection, appropriate treatment and control of hypertension ***(WHO, 2013)***. There is increasing evidences that early markers of hypertension syndrome exists even before sustained BP elevation ***(Giles et al., 2009).*** Therefore, hypertension cannot be classified solely by discrete BP thresholds.

Stages of Hypertension:

The American Society of Hypertension (ASH) defined normotensive individuals as those who have optimal levels of BP (up to 120/80 mm Hg) and haven't any detectable markers of CVD ***(Weber et al., 2014).***

According to the level of the BP, patients with high BP can be classified into the following stages:

1- **Prehypertension:** This stage includes all patients whose systolic BP is between 120 mm Hg and 139 mm Hg, or their diastolic pressure lies between 80 and 89 mm Hg.

2- **Stage 1 hypertension:** This stage includes all patients whose systolic BP is between 140 to 159 mm Hg or diastolic BP between 90 and 99 mm Hg.

3- **Stage 2 hypertension:** Patients in this stage have systolic BP more than 160 mm Hg or diastolic blood pressure more than 100 mm Hg **(Weber et al., 2014).**