Volume 3, Issue 3, March 2025 ISSN (E): 2938-3765

MOLECULAR GENETIC FACTORS OF ARTERIAL HYPERTENSION IN CHILDREN

Dilfuza Ibragimova Narzikulovna
Assistant of the Department of "Clinical Sciences" of the University of Zarmed.

Ashurova Noila Shuxratovna
Assistant of the Department of "Clinical Sciences" of the University of Zarmed.
E-mail: nellie.neonilla@gmail.com

Abstract
Information is presented on the types of inheritance of hypertension in children, a description of monogenic forms of pathology is given, modern results of studies on the adhesion of hypertension, including in children with different chromosomal loci, are presented. An extensive comparative analysis of the results of studies on the association of the M235T polymorphism of the AGT gene with essential arterial hypertension of childhood and with hypersensitive arterial hypertension was carried out. It is shown that these results can be influenced by additional factors (ethnic, geographical, etc.), which makes it necessary to achieve a maximally homogeneous sample for the study with clear selection criteria when conducting such a genetic analysis.

Keywords: Childhood essential hypertension, monogenic forms, linkage analysis, association analysis, polymorphisms, genes.

INTRODUCTION

One of the most problematic forms of cardiovascular pathology in modern medicine is arterial hypertension, or essential arterial hypertension. Essential arterial hypertension is understood as a polyetiological cardiovascular disease characterized by a persistent and prolonged increase in blood pressure associated with a primary violation of various mechanisms of its physiological regulation. Thus, essential arterial hypertension is contrasted with symptomatic (or secondary) hypertension, which it is included in the symptom complex of other diseases and in which an increase in blood pressure it occurs as a secondary (or side) pathophysiological reaction, which is part (or stage) of the pathogenesis of a specific nosological form. As is known, essential arterial hyperthyroidism is a multifactorial disease, because in the regulation of blood pressure (in particular, arterial) as the most important physiological parameter, many factors are involved - investigative and environmental factors. Currently It has been established that there are the following variants of inheritance of hypertension - Mendelian inheritance, which is characteristic of monogenic forms of arterial hypertension. In this case, we should talk about monogenic diseases in which arterial hypertension is the leading symptom. For some of these diseases, key genes have already been described, mutations in which leads to pathology - polygenic inheritance. This is how inherently essential arterial hypertension is inherited.

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

To begin with, let's consider through which physiological mechanisms in the human body the regulation of systemic blood pressure is carried out. There are the following basic physiological systems for controlling arterial pressure.

1. The sympathetic-adrenal system primarily controls systolic arterial pressure. Through this system, the mechanism of short-term regulation of blood pressure is realized. The main components of the system are the mediator's adrenaline and nor-adrenaline, as well as vascular adrenergic receptors of various types.
2. The renin-angiotensin-aldosterone system is responsible for controlling both systolic and diastolic blood pressure. Through it, the mechanism of medium-term regulation of blood pressure is carried out. The main components are angiotensinogen, Angiotensin converting enzyme, renin, aldosterone and aldosterone receptors.
3. The tubular reabsorption system of the epithelium of the distal tubules of the kidneys is primarily responsible for controlling the volume of circulating blood and diastolic arterial pressure. It is under control the final acceptor of the renin-angiotensin-aldosterone system is aldosterone. Through this system implements the mechanism of long-term regulation of blood pressure. The main components are aldosterone receptors of the epithelium of the distal kidney, structural and kinase proteins of the ion channels of the distal renal epithelium.
4. The vascular membrane calcium receptor system controls both systolic and diastolic blood pressure. It provides short- term regulation of blood pressure. The main components are Ca2+ ions, vascular calcium receptors.

Among the various monogenic variants of arterial hypertension, the most studied nosological forms associated with the genes of WNK kinases. It turned out that mutations in the WNK1 and WNK4 genes are the cause of pseudo hyperaldosteronism type 2. It is an autosomal dominant disease characterized by arterial hypertension, hypokalemia and metabolic acidosis with normal glomerular filtration rate. Both genes are expressed in kidneys. WINK1 is endoplasmic, while WNK4 is associated with impenetrable dense connective tissue proteins. WNK proteins are members of a new family of serine—threonine kinase proteins, which have a cysteine residue instead of lysine in the catalytic region. They are involved in several conductive signal transduction pathways and belong to the system of tubular reabsorption of the epithelium of the distal tubules of the kidneys described above, which regulates arterial pressure. WNK proteins have been found in a number of multicellular animals, but interestingly, they are absent in unicellular organisms.

The genes of proteins of the WNK family are a clear confirmation of the hypothesis of a connection between the genetic etiology of monogenic and polygenic forms of hypertension. If the monogenic form is characterized by the presence of mutations leading to pronounced dysfunction of a certain gene product encoded by this gene, then certain dimorphic haplotypes contribute to the summative pathogenesis of the formation of polygenic essential arterial hypertension. Currently, to analyze the genetic etiology of any multifactorial disease, in particular, essential arterial hypertension, another approach is mainly used - the analysis of the association of a gene selected according to certain criteria with this nosological form.

We present a number of genes with which a positive association of essential arterial hypertension has been obtained at the moment: ACE (angiotensin converting enzyme gene), AGT (angiotensinogen gene), AGTR1 (type 1 angiotensin receptor gene), NOS3 (NO synthase 3 gene),

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

ADRB2 (β2-adrenergic receptor gene), ADRB1 (β1-adrenergic receptor gene), ADRA2A (a2A-adrenergic receptor gene), GNB3 (protein 3 gene), REN(renin gene), APOE (apolipoprotein E gene). The central role in this regulation is played by the renin-angiotensin-aldosterone system, which is quite complex and causes various effects in the body. For classical essential arterial hypertension of childhood, the main role in the pathogenesis of increased blood pressure is played by excessive activation of the sympathetic-adrenal system followed by activation of the renin angiotensin-aldosterone system (an important component of which is angiotensinogen) in response to the accumulation of pathological immune complexes in the cortical substance of the kidneys, which it leads to a significant increase in the volume of circulating blood.

1 Research Group	The number of works showing the association with the disease	The number of works for which no association with the disease has been identified
1. Classical essential arterial hypertension of childhood (actually essential arterial hypertension of childhood	48 (76%)	15 (24%)
2. Salt sensitive (Na-volume-dependent) essential arterial hypertension	3 (20%)	12 (80%)
3. Isolated systolic essential hypertension	1 (20%)	4 (80%)
4. Essential arterial hypertension with severe myocardial hypertrophy	2 (67%)	1 (33%)

Below, in a comparative aspect, we try to analyze the reproducibility of the association results in two groups of studies performed in children with essential arterial hypertension and its clinical and biochemical variant, salt-sensitive (or Na-volume-dependent) essential arterial hypertension, and show that in studies on less heterogeneous populations have a higher reproducibility of the result. There are a number of papers devoted to the study of the association of M235T polymorphism with salt-sensitive essential arterial hypertension, including in children and adolescents. Clinically, it is characterized by edema, a predominant increase in diastolic blood pressure and so—called salt sensitivity - during stress tests with sodium chloride, there is a sharp increase in diasystolic blood pressure.

Essential arterial hypertension in childhood is characterized by the development of an isolated hypertension syndrome with a predominant increase in systolic blood pressure at about 12-16 years of age. The etiology of this condition has not yet been established, but from a clinical point of view, this nosological form is close to the sympathetic-adrenal variant of essential arterial hypertension in adults.

Thus, with essential arterial hypertension, children from what age, in contrast to such a sensitive variant, it is possible to talk about the presence of an association of M235T polymorphism of the AGT gene. It should be noted- note that the clinical manifestations of essential arterial hypertension of childhood and salt sensitive essential arterial hypertension varies. It is quite

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

possible that essential arterial hypertension is a heterogeneous group of diseases, in each of which, from an etiological and pathogenetic point of view, a specific blood pressure control pathway is predominantly involved, and the remaining regulatory mechanisms either play an auxiliary role or do not develop at all. We analyzed the results of a study of the association of the M235T AGT variant with essential arterial hypertension, conducted on samples differing by national, geographical and gender characteristics. We found no significant differences in the results of the work performed on isolated male samples compared with isolated female ones. Also, we have not established a significant difference in reproducibility of the result for works performed with the participation of adult patients of different age categories.

There is only one work that demonstrated a statistically significant difference in the outcome of studying the association in patients of different ages. The authors examined two relatively homogeneous groups of patients with essential arterial hypertension from a clinical and biochemical point of view. One consisted of individuals whose essential arterial hypertension was detected before the age of 60, the other after the age of 60 (the so-called late essential arterial hypertension). The authors showed that in a subsample of people younger than 60 years old, there is an association of the T 235T AGT genotype with a fairly high OR (3.5; CI 1.1—5.2) For the sample of patients with late essential arterial hypertension, such an association was not obtained. It is also necessary to take into account the influence of ethnic and geographical features of the studied samples on the results of the association of M235T AGT polymorphism with classical essential arterial hypertension. After analyzing the publications selected according to these criteria, we concluded that there are no statistically significant differences in the reproducibility of the result in the works conducted on ethnically homogeneous samples. For example, we provide information on the number of positive results obtained from samples of patients belonging to different continental mega populations, which demonstrated approximately similar data. Thus, the positive association of classical essential arterial hypertension and M235T ACE polymorphism is indicated by the results of 19 out of 25 the results of 24 out of 29 works performed on a sample of patients of European origin, and the results of 24 out of 29 works performed on a sample of patients of Asian origin. Moreover, the average OR obtained, for example, for a sample of patients with hypersensitive essential hypertension, calculated for patients of Asian and European origin (1.2 and 1.33, respectively), is also approximately the same. This fact may indicate that it is the clinical and biochemical homogeneity of the sample when analyzing the association of a particular variant with a specific multifactorial disease that has a decisive influence on the result of the study, while other factors play a supporting role.

Conclusion

Thus, in this paper we have summarized the main hereditary factors of predisposition to essential arterial hypertension. The goal at the first stage is to identify the clinical and biochemical forms of essential arterial hypertension as clearly as possible, on the basis of which it is necessary to form samples and compare numerical markers of association (for example, relative risk) of an undivided sample of patients with control, and certain subgroups of patients with a control sample. . It is this approach that will help us to more clearly characterize the genetic etiological and pathogenetic mechanisms of essential arterial hypertension, including childhood.

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

References

1. Heart and vascular diseases: A guide for doctors in 4 volumes. Edited by E.I. Chazov. Moscow: Medicine 1992; 3: 50-90.
2. Komarov F.I. (ed.). Diagnosis and treatment of internal diseases: A guide for doctors in 3 volumes. Moscow: Medicine 1996; 2: 40-78.
3. Lifton R. P., Gharav, A. G., Geller D. S. Molecular mechanisms of human hypertension. Cell 2001; 104: 545—556.
4. Garcia E.A., Newhouse S., Caulfield M.J. et al. Genes and
5. Hypertension. Current Pharmaceutical Design 2003; 9: 1679—1689.
6. Kivinen K., Peterson H., Hiltunen L. et al. Evaluation of STOX1 as a preeclampsia candidate gene in a population- wide sample. Eur J Hum Genet 2007; 7: 494—497.
7. Wilson F. H., Hariri A., Farhi A. A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. Science 2004; 306: 1190—1194.
8. Friedrich C., Luft F. Mendelian Forms of Human Hyper- tension and Mechanisms of Disease. Clin Med Res 2003; 1: 4: 291—300.
9. Hansson J. H., Nelson-Williams C., Suzuki H. et al. Hyper- tension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. Nature Genet 1995; 11: 76—82.
10. Kastelan D., Giljevic Z., Perkovic Z. et al. Low-renin hy- pertension and inherited mineralocorticoid diseases. Lijec Vjesn 1999; 121: 7—8: 245—249.
11. Torpy D.J., Stratakis C.A., Chrousos G.P. Hyper- and hy- poaldosteronism. Vitam Horm 1999; 57: 177—216.
12. Luft F.C. Molecular genetics of salt-sensitivity and hyper tension. Drug Metab Dispos 2001; 29: 4: 2: 500—504.
13. Nussberger J. Investigating mineralocorticoid hypertension. J Hypertens Suppl 2003; 21: 2: 25—30.

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5