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Review

Comparison between Essential Hypertension and Pregnancy-induced Hypertension: a Genetic Perspective

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Abstract. Essential hypertension (EH) accounts for 80-90% of hypertension, and pregnancy-induced hypertension (PIH) is responsible for hypertension during pregnancy. Both considered multifactorial disorders. While both have many features in common, conditions and causes of these diseases have yet to be clarified. Since both diseases are associated with hypertension, the genetic backgrounds may contain common features. The present study reviewed similarities and differences between women with EH and PIH, with a particular focus on their genetic backgrounds.

Key words: Essential hypertension, Pregnancy-induced hypertension, Genetic backgrounds, Single nucleotide polymorphism, Case-control study

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ESSENTIAL HYPERTENSION (EH) accounts for 80-90% of hypertension, and pregnancy-induced hypertension (PIH) is responsible for hypertension during pregnancy. While both have many features in common, conditions and causes of these diseases have yet to be clarified. Initially, proteinuria and edema were thought to be the cause of PIH. However, recently it has been reported that PIH is indeed associated with the same pathophysiology as hypertension, and thus has become an important topic in the field of gynecology worldwide [1].

In recent years, genes contributing to various hereditary diseases have been identified, with some diseases found to result from specific genetic mutations. Diseases occur when changes in the DNA base sequence cause changes in the amino acid sequence, thereby altering the structure of the resulting protein. While individual differences in genetic information may not directly cause diseases, they may be involved in disease pathology. In other words, individual genetic differences or genetic polymorphisms might possibly be related to disease susceptibility. Furthermore, both environmental and genetic factors, i.e., mutations and polymorphisms, could perhaps play various roles in the onset of such diseases. For example, environmental factors such as smoking and stress could be related to the onset of myocardial infarctions, while disease susceptibility or individual genetic differences could play a role in the onset of coronary artery occlusion, which is the underlying condition for myocardial infarctions. In addition, for many of the diseases, such as EH and PIH, there are multiple genetic factors that are probably involved.

The aim of the present manuscript was to review similar and different features in women with EH and PIH, with a particular focus on their genetic backgrounds.

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I. Features of EH

1. Concept of EH

Hypertension, which is a disease that causes organ damage throughout the body, is due to high blood

pressure that is present not only during physical activity but also at rest. The term "high blood pressure" adequately describes a temporary condition caused by stress and physical activity, whereas "hypertension" is a more suitable term for the persistent disease state. Diagnosis of EH includes exclusion of secondary hypertension, such as that associated with endocrinological disease, renal disease and renovascular disease [2, 3]. There are a few monogenic diseases (inheritance hypertension) that have been defined as unusual hypertension. Although the available evidence strongly suggests that EH is a multifactorial inheritance disease [4], a causal gene for EH has not yet be clearly identified. There are many environmental factors that can affect EH, including obesity, diabetes, drinking and smoking. Accounting for these effects is one of the issues that complicates the isolation of the EH susceptibility genes.

It is very difficult to define the pathophysiology of hypertension (Table 1). Discrimination between primary hypertension and renal hypertension can help clarify this issue. In many cases of renal cortical diseases, such as glomerular nephritis, pyelonephritis, polycystic kidney disease, diabetic renal disease, lupus nephritis and toxemia of pregnancy, impaired excretion of sodium and water causes increased body fluid volume and renin secretion. If the hypertension persists, it initiates a vicious circle in which hypertension induces decreased kidney function, which in turn induces hypertension. If the blood pressure of EH patients is poorly controlled, their kidney function deteriorates during long follow-up periods. A point of discrimination between EH and renal hypertension is that protein urea is often detected in the urine before the development of renal hypertension. Additionally, renal function often improves in EH patients if their blood pressure is well controlled. Discrimination between EH and renal hypertension is difficult in many cases without long-term clinical follow-up, because patients with either disease can have very good clinical results at the end of the disease course. The question of whether impairment of kidney function precedes hypertension resembles the question, "Which came first, the chicken or the egg?" Analysis of the genome, which remains constant throughout the life of a patient, may help clarify the relative contribution of environmental changes to hypertension [5].

One question that needs to be answered is whether the laboratory animals that are commonly used for medical and biological research are useful for identifying EH susceptibility genes? There have been attempts to isolate causal genes of hypertension by using congenic strains of rats such as spontaneously hypertensive rats (SHR) and Dahl salt-sensitive and -resistant rats. In addition, there have been attempts to determine the function of genes related to hypertension by creating knockout or gene overexpressing mice. Although some loci in such hypertensive animal models have been reported to be susceptibility regions for EH, very few susceptibility genes have been successfully isolated. Another confounding factor that has to be considered is whether the results obtained using animal models can be applied to human diseases. For instance, cortisol is the main glucocorticoid in humans, whereas the main glucocorticoid in rats and mice is corticosterone, as the 17α-hydroxide enzyme is not present in murine species. Furthermore, the form of inheritance in animal models is often unclear. Thus, the use of human rather than animal samples is generally considered to be necessary for EH studies [5].

2. Definition of EH

Recent definitions of hypertension have been become more highly refined then ever before. Some standards are used as criteria in daily diagnosis and treatment, which include the guidelines from the World Health Organization/International Society of Hypertension (WHO/ISH) (1999) [6] and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) [2]. After the publication of these guidelines, revised versions such as JNC7, the ESH-ESC guideline and the WHO/ISH statement in 2003 have also been released [7]. The Japanese Society of Hypertension announced the new JSH 2009 guideline that takes into consideration the cardiovascular system and the current Japanese therapies [8]. All of these guidelines define hypertension as patients with a systolic blood pressure of 140 mmHg or more and/or diastolic blood pressure of 90 mmHg or more. As per the JNC7 guidelines, normal (optimal) blood pressures are assumed to have systolic and diastolic blood pressures that are less than 120 mmHg and 80 mmHg, respectively.

Today, annual criterion changes, along with different standards for individual countries that use guidelines besides the WHO/ISH standard are common. In humans, the blood pressure is the basic parameter for

Table 1. Comparison of pathophysiology between essential hypertension and pregnancy-induced hypertension

Classification	Subclassification	Characteristic of EH	Characteristic of PIH
Cardiovascular system	Vasopressor		
	Renin-angiotensin system	Hyporeninemia: 30% in EH, Volume expansion, Volume dependent hypertension, Occurs frequently in the elderly	Plasma renin activity↓
		Normoreninemia: 50% in EH	Angiotensin II↓
	Vasodepressor	Natriuretic peptide ↑, Adrenomedullin ↑	Natriuretic peptide ↑
		Urinary kallikrein↓	Bradykinin↑ in mild PIH, Bradykinin↓ in severe PIH,
		Calcium intake shortage	Serum ionized calcium concentration↓, intracellular calcium↓
	Injury of vascular endothelial cells	Injury of vascular endothelial cells	Vascular resistance of uterus artery↑
Coagulation and fibrinolysis system	Hypercoagulability		Antithrombin ↓, Thrombin-Antithrombin Complex↑
			Plasmin-α2-plasmin inhibitor complex↑
			Platelet number ↓
	Inhibition of fibrinolysis system		tPA↑, PAI-1↑, uPA↓, PAI-2↓
			No prevention by aspirin administration
Renal system	Depressor effect by Salinity limitation	30.0%	11.1%
Neurogenic system		Urinary free dopamine↓	Sympathetic nerve activity↑
		Blood norepinephline↑or →	Neuropeptide Y↑, Neurokinin B↑
		Sympathetic nerve activity↑in juvenile-onset hypertension	Endothelin↑
		Sympathetic nerve activity↓or →	Serotonin↑
	Overstress	Blood pressure↑	2.3 times by working
Endocrine and metabolism system	Insulin resistance	Hyperinsulinemia, Impaired glucose tolerance, Obesity	Hyperinsulinemia, Impaired glucose tolerance
	Dyslipidemia	Hypertriglyceridemia, Hypo-high-density-lipoprotein cholesterolemia	Hyperlipidemia, Unsaturated fatty acids↓, Oxidized LDL↑
	Active oxygen		Blood Mn-SOD ↓, Placenta nitrous acid radical↑
			Superoxide anion↑
	Others		Inhibin A↑, sVEGFR-1(sFlt-1)↑, free PlGF↓
Immune system	Anticardiolipin antibody		Anti cardiolipin antibody 19.4%
	Protein S		Related to Protein S Deficiency
	Protein C		Related to active Protein C resistance
	Homocystine		Related to homocysteinemia
	Cytokine		Various cytokines↑(TNFα etc.)
Infection	Virus		Related to Herpes, Cytomegalovirus, EB, HSV-2, Parvovirus B19?
	Other microorganism		Chlamydia pneumonia, Malaria?
Genetic background		The relative risk is 1.2-3.8 times greater when there is a family history of hypertension.	Pregnant women with family history of PIH (Appearance of PIH rate; 27.8% vs. 8.3% in those subjects without a family history).
			Appearance of PIH rate is 13.1% in pregnant women with previous PIH. Appearance of PIH rate is 1.7% in pregnant women with non-PIH.
		Genetic backgrounds of PIH is similar to that of EH.	PIH is complicated with 10-25% mild hypertension, 50% severe hypertension.
			Appearance of PIH rate is 25% in pregnant women with hypertension.
			Appearance of PIH rate is 42% in pregnant women with 100-110 mmHg diastolic blood pressure in hypertension.
			Hypertension will occur in 38-54% of the PIH women and in 14% of the normal pregnant women, respectively.

EH: essential hypertension, PIH: pregnancy-induced hypertension

the definition, but it is considered to be a continuous variable, as it can change on an hourly basis. Thus, it is sometimes difficult to make a confirmed diagnosis of EH. It is these types of situations that are thought to be at least part of the difficulties that exist when attempting to clarify the pathophysiology of EH, as was described in the previous chapter.

3. EH susceptibility genes

Until recently, it has been difficult when trying to use human samples for genetic research. However, with the marked advancements in molecular biology that have occurred during the recent decades, some of these technical problems have been overcome. With the polymerase chain reaction (PCR) method [9] that was developed in the latter half of the 1980s, it is now possible to perform familial linkage analysis that can be used to identify many of the causal genes of monogenic diseases with clear Mendelian inheritance patterns. These previous successes once inspired optimism that the susceptibility genes of EH would be able to be isolated by using methods such as linkage analysis. However, recent findings have indicated that for many multifactorial disorders, linkage analysis is not a reliable method when it comes to identifying susceptibility genes. Consequently, greater attention has been paid to alternative methods such as case-control studies, which include association studies. One of the most important reports in this research field was a study published by a French research group in 1992 that showed an association between the angiotensinogen (*AGT*) gene and EH [10]. This study applied the sib-pair analysis to a linkage analysis that compared EH patients and a DNA sample from the patient's brother. Results indicated there was a polymorphism in the 235th amino acid of *AGT*, which corresponded to methionine (M235) or threonine (T235). The T235 type was significantly higher in EH than in NT. The M235T polymorphism was found to be 100% linked with the G-6A variant in the promoter region of the *AGT* gene. Because the promoter activity of -6A is significantly higher than that seen for -6G, it is expected that T235 (-6A) might very well be associated with AGT activation that subsequently leads to EH. These sentences are unclear. While the second sentence makes sense, the first one does not. Do you perhaps mean, "Although there has been much discussion about the positive association of the *AGT* gene with EH, subsequent experiments have yet to positively prove this suspected association. Even so, this article still has an impact on the field although more than 15 years have passed since its initial publication. In addition, there have been no other reports that have provided any other evidence on a significant susceptibility gene that surpasses what is currently known for the *AGT* gene.

With the advent of whole genome scanning, linkage analysis of families with specific phenotypes, and continued perseverance of the candidate gene approach, it is hoped that progress will eventually be made in elucidating the susceptibility gene for EH.

4. EH susceptibility genes in women

In essence, with the exception of research in the fields of obstetrics and gynecology, which has studied pregnancy, delivery and female gonad function, the basis for the field of medicine comes from research that was done solely on male subjects. Recently, differences from not only those strictly based on the distinct sex organs but also differences that are associated with the socially grounded 'gender' between women and men have become much more important. This has led to 'gender-specific medicine' becoming widely recognized. Some promising attempts to establish guidelines have been presented, such as at Monash University in Australia, where gender mainstreaming has become part of the medical education program. Other such programs include the Office of Research on Women's Health at the NIH Institute (Bethesda, MD, USA), which has scheduled web-based training courses on gender/sex medicine for 2006 and at the Charité, which also will commence teaching a European graduate course in gender-specific medicine this coming year [11].

There are many known differences between men and women with regard to cardiovascular diseases. Atherosclerotic diseases such as ischemic heart disease occur more frequently in women than in men. The incidence of atherosclerotic diseases is low in premenopausal women, but rises in postmenopausal women [12]. Estrogen increases vasodilatation and inhibits the response of blood vessels to injury and the development of atherosclerosis [13]. However, in more than a few reports it has been stated that there is no clear theoretical explanation as to why there are differences detected between men and women. Therefore, it might be very important to perform re-

search on the genetic background in women with hypertension and examine if there is any relationship to estrogen synthesis and metabolism.

Recently, we reported that one variant in the follicle-stimulating hormone receptor (*FSHR*) gene was specifically associated with hypertension in Japanese women [14]. Inactivating mutations in the *FSHR* gene have been reported to cause hereditary hypergonadotropic ovarian failure. It has also been found recently that the *FSHR* knockout mouse exhibits hypertension. The aim of the present study was to investigate the association between polymorphisms in the human *FSHR* gene and essential hypertension (EH) by using single nucleotide polymorphisms (SNPs). We selected 5 SNPs in the gene (rs1394205, rs2055571, rs11692782, rs1007541, rs2268361) and performed two genetic case-control studies in different populations. A confirmative case-control study was performed using 1035 EH patients and 1058 age-matched controls. Transcriptional activities were measured with a luciferase assay system. The first case-control study found that the A allele of rs1394205 was significantly higher in EH females ($p = 0.010$). Additionally, in the confirmative case-control study, there was a significant difference for this SNP between female NT subjects (44.5%) and EH patients (50.7%) ($p = 0.043$). Multiple logistic regression analysis in female subjects also revealed a significant association of subjects with the A allele of rs1394205 with EH ($p = 0.033$), with the odds ratio calculated as 1.68 (95% CI: 1.04-2.73). Transcriptional activity of the A allele was 56 ± 8% (means ± SD) of that observed for the G-type allele ($p = 0.001$). Serum estradiol levels were significantly lower in patients with the A/A genotype than in patients without the A/A genotype ($p = 0.004$). The SNP in the 5'-untranslated region of the *FSHR* gene affects levels of transcriptional activity and is a susceptibility mutation of EH in females. Since there have been many studies reporting that low estrogen levels are associated with hypertension in postmenopausal women [15, 16], our results may also provide evidence on the etiology of at least one of the causes of hypertension in postmenopausal women. However, our report in which we showed that the candidate gene could reasonably be associated with the pathophysiology of postmenopausal women was a rare case, as many other case-control studies have not been able to clarify the pathophysiology of the gender-specific hypertension.

II. Features of PIH

1. Concept of PIH

PIH is a syndrome that is usually defined as the onset of hypertension and/or proteinuria after 20 weeks of gestation in previously normotensive non-proteinuric pregnant women [17]. If left untreated, PIH can progress to a convulsive state known as eclampsia [18]. PIH is a leading cause of maternal and fetal morbidity and mortality [19, 20].

However, it should be noted that these symptoms are not due to a coexisting illness related to a mere pregnancy. Since an accurate cause of PIH is still uncertain, many consider the mechanism of this disease to be highly theoretical with various etiologies having been postulated for the course of the disease.

In many countries there has been a lot of controversy with regard to labeling the condition as 'pregnant induced hypertension'. In the early 20th century 'toxemia of pregnancy' was used. In addition, since it was thought to be a sign of eclampsia, 'preeclampsia' has also been widely used throughout the world. After the 1970's, 'pregnant-induced hypertension (PIH)' became part of the mainstream literature due to the belief put forth by the American College of Obstetrics & Gynecologists that hypertension was the main pathophysiology behind PIH. Afterwards, a definition, classification, and criterion were submitted by the World Health Organization (WHO, 1987) [21], the National High Blood Pressure Education Program (NHBPEP, 1990, 2000) [22, 23], the Canadian Hypertension Society (CHS, 1997) [24], the International Society for the Study of Hypertension in Pregnancy (ISSHP, 1988, 2001) [25, 26], and the Australasian Society for the Study of Hypertension in Pregnancy (ASSHP, 1993, 2000) [27, 28]. Hypertension, edema and urinary protein are the three main symptoms that have been documented for PIH. Hypertension has been recognized as being the main symptom since organ damage associated with vascular endothelial damage and blood vessel spasms is believed to be the main pathophysiology of PIH (Table 1).

2. Classification of PIH

The definition of hypertension in pregnancy was originally proposed by the American College of Obstetricians and Gynecologists' in conjunction with

the National Institutes of Health working group in 1990 [29], and in 2000 [30]. The criteria were further refined by the National High Blood Pressure Education Program (NHBPEP) Working Group 1 and separated into the following groups: (1) pre-eclampsia-eclampsia; (2) chronic hypertension; (3) pre-eclampsia superimposed on chronic hypertension; and (4) gestational hypertension [31].

Pre-eclampsia-eclampsia is diagnosed on the basis of hypertension and proteinuria while chronic hypertension is diagnosed as hypertension that is present prior to the 20th week of pregnancy or is hypertension that is only diagnosed during pregnancy, and which persists 6 weeks after delivery, as either primary (essential) or secondary (i.e., pre-existing renal disease) hypertension. Pre-eclampsia superimposed on chronic hypertension is regarded as a sudden increase in blood pressure, a new onset or acutely worsening proteinuria, thrombocytopenia, or elevated liver enzymes after 20 weeks of gestation in women with pre-existing hypertension. Gestational hypertension is regarded as hypertension that is first diagnosed after 20 weeks of gestation and which is not accompanied by proteinuria. This form can be transient (resolving by 12 weeks postpartum) or chronic (does not resolve by 12 weeks postpartum). Specific definitions of the symptoms and factors that are present in subjects with a positive diagnosis are as follows: Hypertension refers to a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg that occur after 20 weeks in a subject who was normotensive prior to 20 week's gestation. In order for a positive definition of hypertension to be made, the pressure readings need to be confirmed by two separate measurements. Proteinuria is defined as the presence of 300 mg/L protein in a random specimen, urinary protein excretion > 300 mg/day, or preservation of podocyte foot processes in the presence of substantial proteinuria. Decreased plasma volume is a contraction of the volume by 30–40% as compared with normal pregnancy, while edema is interstitial fluid retention. To be considered multifactorial, the factor had to be observed in > 50% of normal gravidas. Decreased renal blood flow was classified as a renal perfusion level that was less than that seen in normal pregnant women. Other factors that are used to make a diagnosis include, increased plasma uric acid that is secondary to a reduced uric acid renal clearance, increased aminotransferases and lactate dehydrogenase that is associated with hepatocellular necrosis with leakage of liver enzymes into maternal blood, cerebral edema caused by hypertension and vascular autoregulatory dysfunction, thrombocytopenia (platelet count < 150,000 cells per cubic millimeter), and abnormalities of the coagulation system as reflected by changes in the coagulation cascade and fibrinolytic system [32].

There are three definitions that are commonly cited, and which include guidelines from the NHBPEP [29, 33, 34]. In general these definitions are advocated for epidemiological purposes, i.e., they are used to describe the incidence and prevalence of hypertension in pregnancy in populations rather than applying them as a guide for clinical management or for characterizing patients with pre-eclampsia for research purposes.

Davey and MacGillivray's definition of pregnancy hypertension provides details and information on several different forms of hypertension that could arise in pregnancy [33]. With regard to gestational proteinuric hypertension and pre-eclampsia, their definition stipulates that normotension must be present before 20 weeks' gestation, with hypertension and proteinuria then developing after 20 weeks. The diagnosis of hypertension is made by a single diastolic blood pressure of 110 mm Hg or greater (phase IV) or consecutive readings of 90 mm Hg or greater on more than one occasion at least 4 h apart. Proteinuria is defined as a 24 h excretion of 300 mg or more of protein, which is determined by two clean-catch urine specimens obtained at least 4 h apart. Results are considered to be positive if there is 2+ proteinuria for dipstick determinations, 1+ proteinuria with a specific gravity less than 1030, and a protein/creatinine index of 300 or more.

Redman and Jefferies [34] attempted to determine blood pressure characteristics that would maximize the chance of identifying women with other features of pre-eclampsia, such as a high proportion of primigravidae and the development of proteinuria. Therefore, their definition was based on a diastolic blood pressure that was below 90 mm Hg prior to 20 weeks followed by a subsequent rise of at least 25 mm Hg, with a maximum reading of at least 90 mm Hg. In many ways, of all of the definitions, this is the most practical definition because it allows a diagnosis to be made in the absence of proteinuria and does not rely on edema. However, there are limitations associated with this approach in that blood pressure data from the first half of pregnancy needs to be known and in addition, currently it is not possible to be able to diagnose pre-eclampsia that is present at the same time as pre-existing hypertension.

Table 2. Susceptibility genes reported as positive associations with pregnancy-induced hypertension

Classification	Subclassification	Gene name	Official symbol	Variants	Race	Reference number
Cardiovascular system	Vasopressor	Angiotensinogen (AGT)	*AGT*	M235T polymorphism	American-White	[51]
		Angiotensinogen (AGT)	*AGT*	M235T polymorphism	Japanese	[52]
		Angiotensinogen (AGT)	*AGT*	L10F polymorphism	American-White	[53]
		Angiotensin type 1 receptor (AT1)	*AGTR1*	A1166C polymorphism	American-White	[54]
	Vasodepressor	Endothelial nitric oxide synthase (eNOS)	*NOS3*	splicing of intron 13	British	[55]
		Endothelial nitric oxide synthase (eNOS)	*NOS3*	Glu298Asp polymorphism	Japanese	[56]
		Estrogen receptor beta	*ESR2*	rs928554 (A→G) polymorphism	Japanese	[57]
Endocrine and metabolism system	Lipid metabolism	Apolipoprotein E (APOE)	*APOE*	epsilon 2 allele	Hungarian	[58]
		Lipoprotein lipase (LPL)	*LPL*	N291S polymorphism, D9N/-93T→ G polymorphism	American-White	[59]
	Homocystine	5,10-methylenetetrahydrofolate reductase (MTHFR)	*MTHFR*	C677T polymorphism	Japanese	[60]
Coagulation and fibrinolysis system	Coagulation factors	Coagulation factor V	*F5*	Leiden mutation	American	[61]
		Coagulation factor V	*F5*	Leiden mutation	Italian	[62]
		Coagulation factor V	*F5*		Japanese	[63]
		Coagulation factor XI	*F11*	Haplotype	Japanese	[64]
	Inhibition of fibrinolysis system	Plasminogen activator inhibitor 1 (PAI-1)	*SERPINE1*	4G/5G polymorphism	Japanese	[65]
Immune system	Cytokine	Tumor necrosis factor-alpha (TNF-α)	*TNF*	20 bp insertion/deletion	British	[66]
	Detoxification	Glutathione S-transferase (GSTP1)	*GSTP1*	1b-1b genotype	Dutch	[67]

3. PIH susceptibility genes

PIH is thought to be a multifactorial disorder that develops due to an interaction of hereditary and environmental factors as well as the EH that is present. A variety of candidate genes that might be responsible for PIH have been analyzed (Table 2). Possible susceptibility genes that have been reported include: *AGT*, angiotensin type 1 receptor (*AGTR1*), endothelial nitric oxide synthase (*NOS3*), estrogen receptor β (*ESR2*), apolipoprotein E (*APOE*), lipoprotein lipase (*LPL*), 5,10-methylenetetrahydrofolate reductase (*MTHFR*), coagulation factor V (*F5*), coagulation factor XI (*F11*), plasminogen activator inhibitor (PAI1; *SERPINE1*), tumor necrosis factor-alpha (TNF-α; *TNF*), and glutathione S-transferase (*GSTP1*). More recently, it has been theorized that an abnormal placenta formation is involved in increases in thrombus diseases, and thus, may cause PIH. Therefore, thrombus factors such as the Leiden mutation of coagulation factor V (*F5*) and the 20210A mutation of prothrombin (*F2*) are thought to be potential PIH candidate genes. However, while there are quite a few candidate genes, many of these have been found to have no relationship to PIH.

III. Similarities and differences between EH and PIH

A literature search revealed that there have been very few reports and books on the similarities and differences between essential hypertension and pregnancy hypertension. This is because, although essential hypertension is treated by internists, pregnancy hypertension is treated by obstetricians and gynecologists. In addition, as the onset factors for both diseases have not been clarified, the significance of comparing the two diseases itself can be questioned. Although there have been a vast amount of studies on both diseases, I have attempted to clarify the similarities and differ-

ences between essential hypertension and pregnancy hypertension. Table 1 compares the two diseases, and to the best of my knowledge, such a table has not been published.

The obvious common feature between the two diseases is hypertension. Related symptoms include systemic vascular resistance, increased left ventricular work, and increased cardiac output. Because mild hypertension is largely asymptomatic, both diseases in their early stages are difficult to detect, and subjective symptoms are lacking until disease becomes severe. In pregnancy hypertension, total cholesterol, neutral lipid and body mass index (BMI) are high following delivery, and these clinical manifestations are similar to lifestyle diseases, including essential hypertension [35]. It has been reported that women with pregnancy hypertension are likely to develop metabolic syndrome [36]. It has also been stated that insulin resistance and hyperinsulinemia are related to pregnancy hypertension and essential hypertension [37]. While it is certain that blood coagulation is increased in pregnancy hypertension, increased coagulation is not considered to be a major symptom for essential hypertension, but blood coagulation is reportedly elevated in most studies on essential hypertension. Cerebral hemorrhage and infarction are complications associated with essential hypertension, but hemorrhage and infarction appear to be contradictory conditions. In cerebral hemorrhage, persistent hypertension causes fibroid necrosis of intracerebral perforator arteries and microaneurysm formation, and pressure differences inside and outside of vessels damage vessels. Cerebral infarction involves local vascular damage, blood congestion and increased blood coagulation. In other words, the relationship between hypertension, cerebral hemorrhage and infarction is complex. Furthermore, studies have suggested immune system involvement in pregnancy hypertension [38-41], but not in essential hypertension.

With regard to differences, while pregnancy hypertension quickly disappears after the end of pregnancy, essential hypertension is chronic. Essential hypertension is rare in women of child-bearing age, but often affects women older than 40 years of age. Clear differences exist in therapy. The basic treatment for pregnancy hypertension is to allow pregnant women to deliver, and if hypertension develops early in pregnancy, palliative therapy is largely performed while taking into account the maturity and prognosis of the fetus, as well as patient health.

In recent decades, women with pregnancy hypertension were instructed to restrict their dietary intake and strictly monitor salt intake, depending on severity, and many patients blamed themselves for developing pregnancy hypertension. However, it has been clarified that dietary and salt-intake restrictions need to be reexamined. While obese women are more likely to develop pregnancy hypertension, the amount of body weight increase during pregnancy is not closely correlated to severe pregnancy hypertension, and no significant differences are seen among body weight increases from 5 to 15 kg. It is interesting that the incidence of severe pregnancy hypertension is the highest in women who gained less than 5 kg, about three times more likely than in women who gained normal amounts of weight and about 1.5 times more likely than in women who gained more than 5 kg. In other words, excessive dietary restrictions actually increase the risk of pregnancy hypertension, and normal weight gain during pregnancy is important [42, 43].

The same applies to salt intake. It has been shown that excessive restrictions in salt intake lower blood volume, increase blood pressure, and lower placental blood flow, thus negatively affecting pregnancy and delivery [44]. In Japanese patients with severe pregnancy hypertension, the amount of salt intake was reduced below 5 g/day, but blood pressure decreased in only 11.1% of patients, and no significant hypotensive effects were seen [45]. On the other hand, in essential hypertension, salt intake is first restricted to lower blood pressure. Oral administration of calcium has been shown to lower blood pressure in patients with pregnancy hypertension, and metaanalysis has proven its efficacy [46].

Japan is one of the few countries where numerous types of hypotensive drug are used. In the treatment of essential hypertension, diuretics, calcium antagonists, ACE inhibitors, angiotensin II receptor antagonists and β blockers are used depending on symptoms, but in the treatment of pregnancy hypertension, α-methyldopa and hydralazine are often used to ensure the safety of the fetus. When absolutely necessary, drugs that are contraindicated in pregnant women, such as calcium antagonists, are administered with patient consent. ACE inhibitors and angiotensin II receptor antagonists are contraindicated because these may cause fetal death or neonatal renal failure [47]. Today, essential hypertension can be controlled using various hypotensive agents in almost all patients, and this has lowered

the prevalence of many complications, such as, cerebral infarction and myocardial infarction. However, one study found that hypotensive therapy for pregnancy hypertension does not necessarily lower the prevalence of premature birth, intrauterine fetal development delay and perinatal mortality [48].

Several studies have linked essential hypertension and pregnancy hypertension. When women with a past history of pregnancy hypertension were followed for several years, the prevalence of hypertension was 2-3 times higher when compared to women with normal blood pressure during pregnancy. Thus, even after blood pressure normalizes after delivery, women with a past history of pregnancy hypertension are more likely to develop hypertension during midlife. It has also been clarified that the BMI of women with a past history of pregnancy hypertension in whom blood pressure did not increase in later years was lower than that for older hypertensive women, and as a result, it is important for women with a past history of pregnancy hypertension to stay thin. This point has been clarified by studies from multiple groups. Furthermore, it has been shown that intrauterine fetal development delays are linked to future hypertension [49].

Qiu *et al.* interviewed postpartum women in order to determine first-degree family history of hypertension [50]. When compared to women without a family history of hypertension, the risk for pregnancy hypertension was significantly higher for women with mothers having hypertension (odds ratio: 1.9), women with fathers having hypertension (odds ratio: 1.8), women with both parents having hypertension (odds ratio: 2.6), and women with one parent and a sibling having hypertension (odds ratio: 4.7). Therefore, family history of hypertension is a predictor for pregnancy hypertension.

In this manner, essential hypertension and pregnancy hypertension appear to share some genetic background factors.

IV. Candidate genes of EH and PIH

The candidate genes reported to be associated with PIH are classified into four groups and include the blood pressure regulation system, metabolic system, coagulation and the fibrinolysis system, and immunity system groups (Table 2)[51-67]. This classification is dependent upon the molecules and the factors presumed to be responsible for the pathophysiology of the PIH. In this classification for PIH it is different from EH. The genes related to the coagulation and the fibrinolysis system are considered for PIH not for EH.

There are an immense number of candidate genes that have been analyzed for EH as compared to PIH. Most of the candidate genes that have been chosen are based on the assumed pathophysiology of EH. Thus, all candidate genes that are listed in Table 2 have already analyzed for EH, including the coagulation and the fibrinolysis system. Some of the other candidate genes that have been reported to have positive associations for EH include the renin (*REN*) gene [68], angiotensin converting enzyme (*ACE*) gene [69], G protein β-3 (*GNB3*) subunit gene [70] and genes associated with the natriuretic peptide system [54]. Candidate genes that have been determined by using animal hypertension models include the SA gene of spontaneous hypertensive rat (SHR)[72], the 11β-hydroxylase genes of the Dahl salt-sensitive rat [73], and the adducin gene of the Milan hypertensive rat [74]. Candidate genes determined by using positional cloning technology for hypertension include the β2 adrenoceptor gene [75] and the lipoprotein lipase gene [76]. However, even when using recently discovered technological methods such as case-control studies, animal models and positional cloning, the EH causal genes have yet to be isolated.

Since the susceptibility genes for both EH and PIH have not been clearly defined, in an attempt to identity these genes we performed a unique case-control study for PIH that subdivided the genes based on a family history of hypertension. Estrogen's action in the target tissues occurs via the activation of one or both of the two estrogen receptors, ERα (ESR1) and ERβ (ESR2), which are members of the nuclear receptor superfamily. *ESR1* and *ESR2* are also both expressed in vascular endothelial and smooth muscle cells, in addition to the myocardial cells. Estrogen receptors have been studied intensely within the field of female reproductive physiology. Recently, theories on the function of estrogen receptors for both genders have been proposed, with a special emphasis on cardiovascular diseases. Accumulating evidence derived from clinical, epidemiological, and experimental studies suggest that an estrogen deficiency plays a major role in the pathogenesis of cardiovascular diseases such as hypertension in postmenopausal women. Estrogen receptors are necessary and sufficient for estrogen-mediated pro-

tection against vascular injury. Furthermore, in 2002 it was reported that the ESR2-deficient knockout mouse exhibited hypertension that resulted from a change in blood vessel contraction [77]. Therefore, we analyzed the association between the *ESR2* gene and PIH by using single nucleotide polymorphisms (SNPs)[57]. No significant differences in the overall distributions for all of the SNPs were observed between the PIH and the non-PIH groups. However, after dividing the groups into subjects with and without a family history of hypertension, the allelic distribution of one of the SNPs (rs928554) was revealed to have a positive association. PIH subjects with a family history of hypertension had a significantly lower allelic percentage (28.7%) as compared to that seen for non-PIH controls without a family history of hypertension (41.5%) ($p = 0.042$). Multiple logistic linear regression analysis adjusted for age showed a significant difference in distributions of the genotypes between the non-PE and PE groups for the total study population (odds ratio = 1.08; 95% CI, 1.17 – 1.37). Thus, a possible mutation that is linked to a SNP may prescribe a genetic predisposition for patients with a family history of hypertension in PIH.

Because the coagulation and the fibrinolysis system are thought to be involved in PIH, which differs from EH, the coagulation factors might well be candidate genes. Thus, we performed an association analysis for the coagulation factor XI (*F11*) gene and PIH [64]. We chose 3 SNPs in the human F11 gene as genetic markers and observed that the frequency of the rs925453 genotypes were significantly different between the 2 groups. The frequencies of C/C, C/T, and the T/T genotype of rs925453 were 75.3%, 24.0%, and 0.6% in the non-PIH group, and 70.1%, 22.1%, 7.8% in the PIH group ($p = 0.012$), respectively. Furthermore, the frequency of the T-G-G haplotype was significantly higher in the PIH group than in the non-PIH group ($p = 0.0002$).

Therefore, methods that divide candidate genes into subgroups that are based on a family history of hypertension and a haplotype-based case-control study might provide some benefits such as elevating the sensitivity for isolating susceptibility genes of PIH. Since the genetic background of PIH may be similar to that of EH, these methods may potentially help to focus the research strategy for further experiments.

V. Problems that still need to be investigated

This review described the similarities and differences between EH and PIH in women, with a particular focus on their genetic backgrounds.

Both EH and PIH are thought to have similar genetic backgrounds. However, since no genetic factor have been clarified for these diseases, further research is required in order to perform familial linkage studies and transmission disequilibrium tests that will help to isolate certain genetic factors. Unfortunately, at the current time there have been few review manuscripts that have examined the problem from this particular viewpoint. The authors of this review also noticed that the research that has been performed for each of these diseases has been advanced by different investigators in different fields, e.g., EH was investigated by researchers in internal medicine, while PIH was investigated by researchers in obstetrics and gynecology. Therefore, a strategy needs to be developed that will utilize the knowledge and methodology of all of the various study areas that are involved in the clarifying of the pathophysiology of EH and PIH, such as the genetic and molecular biology fields.

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