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A Narrative Review on Nephrotic Syndrome Emphasizing its Correlation With Polymorphism of Angiotensin Converting Enzyme and Renin-Angiotensin System

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Abstract

Numerous meta-analyses have been shown that the nephrotic syndrome is one of the most important reasons of renal failure in children that is monies-taking for health organizations around the world. Because of the global and strategic importance of this issue we intend to investigate the different aspects of nephrotic syndrome to propose our suggestions with a multi-dimensional perspective. Present narrative review is based on scrutinizing the contents of relevant papers searched in PudMed search engine. The correlation of nephrotic syndrome with renin-angiotensin system (RAS) and involving enzymes, in particular angiotensin converting enzyme (ACE), has been investigated in different populations. Nephrotic syndrome in children is usually in two types of minimal change and focal and segmental glomerulosclerosis (FSGS), but more of minimal change. *ACE* gene has 2 polymorphic alleles of deletion (D) and insertion (I). *DD* genotype is associated with higher production of angiotensin-II. So it seems that persons with *DD* genotype are more at risk of renal diseases. Through identifying and screening the involving genetic diversities we can take the prophylactic actions. It seems that early starting of steroid therapy can prevent symptoms of the disease. As well, early starting of supplement administration of vitamin A and E could be a less harmful preemptive measure. Further researches on gene therapy methods is recommended.

Keywords: Nephrotic syndrome, Genetic polymorphisms, Angiotensin converting enzyme, Renin angiotensin system

Introduction

Numerous meta-analyses have been shown that the nephrotic syndrome is one of the most important reasons of renal failure in children that is monies-taking for health organizations around the world. Knowledge of involving pathways in renal injuries like renin angiotensin system (RAS) enables us to progress in treatment of both diabetic and non-diabetic nephropathies (1). Numerous factors are associated with progression of glomerulonephropathy and tubulointerstitial injuries that can lead to early development of end-stage renal diseases (2), such as the diabetes mellitus (3) and non-diabetic causes of nephrotic syndrome (4) which are now the major cause of end-stage renal failure around the world even in developed countries (3). Because of the global and strategic importance of this issue we intend to investigate the different aspects of nephrotic syndrome to propose our suggestions with a multi-dimensional perspective.

Methods

This paper is a narrative review, based on scrutinizing contents of the relevant papers searched in PudMed search engine with a historical approach. Our literature review method was Matrix.

Results and Discussion

The correlation of nephrotic syndrome with RAS and involving enzymes, in particular angiotensin converting enzyme (ACE), has been investigated in different populations in the recent decades and there are numerous meta-analyses from the findings of such populations. Numerous genes have been recognized in pediatric nephrotic syndrome so far. *ACE* gene has two polymorphic alleles of deletion (D) and insertion (I). *DD* genotype is associated with higher production of angiotensin-II. So it seems that persons with *DD* genotype are more at risk of renal diseases. Nephrotic syndrome is in 5 types that in children is usually in 2 types of minimal change and focal and segmental glomerulosclerosis (FSGS), but more of minimal change (4). In addition, it seems that resistance to steroid therapy is associated with FSGS and the procedure of the disease toward the end-stage is more rapid (5).

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History

In 1985 Cameron pointed in a paper entitled "five hundred years of the nephrotic syndrome" (6) that description of the nowadays' word "nephrotic syndrome" came into exist from the time of Hippocrates. In the conviction of Cameron, in 1484 in the book under the title of *Libre de aegritudinibus* 52 numbers of pediatric diseases were explained that the 51st of them was "swelling of total body." Cameron added another researches dealt with edema and its correlation with nephrotic syndrome until in 1830 symptoms like the hypoalbuminemia and hyperlipidemia described as a result of protein losing in urine for the first time. The phrase "nephrotic syndrome" was used for the first time by Henry Christian in 1929 (7). ACE also was discovered in 1950s (8). In 1969 histopathologic samples of nephrotic syndrome were observed under light microscope (9) and the obtained graphs were like nowadays' samples that shows that the microscopic morphology of nephrotic syndrome had been identified at least since that time as today. In the end, in 1980s administration of ACE inhibitors as a treatment was proved (8). In 1985 some papers had it that stimulation of RAS is likely observed in protein lost individuals and reduction of blood volume leads to stimulation of renin and triggering RAS (10).

About Renin-Angiotensin System

This system is of the controlling systems of blood pressure, volume and electrolyte that plays important role (and even a vital role with regarding of aldosterone). In addition to above information, RAS performs a function in hematopoiesis and other physiologic processes (11). In response to blood pressure, volume and electrolyte, juxtaglomerular apparatus makes signal of releasing renin protein. Renin goes in blood stream and through affecting on liver-released angiotensinogen convert it to angiotensin-I. Angiotensin-I under effect of the ACE – which is aggregated in endothelium of vessels and in particular pulmonary circulation (12) – converts to angiotensin-II. Thus mechanic and hypoxic traumas to lung could lead to imbalance in the level of ACE (12). ACE circulates in plasma and expresses on the surface of endothelial cells (13). Angiotensin-II intern results in some phenomena such as, increasing thirsty feeling, increasing intestine uptake of salts, increasing production and secretion of aldosterone from adrenal glands, saving further water and salt by kidneys, increasing cardiac output, vasoconstrictor effect on smooth muscle layer of vessels and so forth (14).

Physiopathology of RAS and Involving Genetic Issues

ACE is a zinc dependent peptidase (15) that plays a key role in RAS (16). In addition to affecting on RAS, ACE is a nonspecific enzyme that plays a role in physiologic phenomena such as blood pressure control, hematopoiesis, reproduction, development and function of kidneys and other inflammatory and immune reactions (8,15). ACE has 2 domains (C and N); C is related to angiotensin converting and N is related to hydrolysis of other peptides (17). *ACE* gene locates on 17q23 (18) and like most of the other genes has polymorphism. This gene has 2 recognized allele; insertion (I) and deletion (D); D allele makes more danger for kidney disease (18) and *DD* has reported as the most dangerous genotype (19).

About *ACE* polymorphism, there are numerous meta-analyses. For example in one of them which was on findings of about 4000 patients in numerous researches (20), the correlation between *ACE* polymorphism and aneurysm (Figure 1) of thoracic aorta was observed and as a result of the mentioned aneurysm there is also a risk of hypertension. Males and individuals with chronic kidney disease are more at risk of the mentioned aneurysm and hypertension (21). *ACE* polymorphism also might be effective on hypertrophic cardiomyopathy (22). Another meta-analysis which was on findings of more than 11 000 patients in previous researches (19) announced that *ACE* polymorphism has correlation with restenosis (Figure 1) after the percutaneous transluminal coronary angioplasties (PTCA). In another meta-analysis (23), the risk of *ACE* polymorphism on recurrent abortion is proved, of course in estimation of its author is still controversial.

Over expression of *ACE* gene could have different effects on different cells. For instance, in monocytes and macrophages affects the immune response (24). Risk of myocardial infarction is attributed to *ACE* genotype; *DD* the most danger and *II* the least danger (15). Also as we pointed, *ACE* polymorphism plays a role in restenosis, aneurysm and atherosclerosis (25). For this reason we use ACE inhibitors for treatment of cardiovascular disease (26). According to the mentioned items and complications resulted from polymorphism and over expression of *ACE* gene, one of the preemptive measures is using ACE inhibitors. As well, we can point to the antagonists of angiotensin-II receptors and other RAS metabolites (27). Also ACE inhibitors are widely used in another disease such as Alzheimer disease (18).

About Histopathology of Glomerulus and Podocytes

Glomerulus is a capillary plexus located between afferent and efferent arterioles. These capillaries are non-diaphragmatic fenestrated. The visceral layer of bowmen capsule – which is in contact with glomerulus – differentiates to octopus like cells named podocyte in

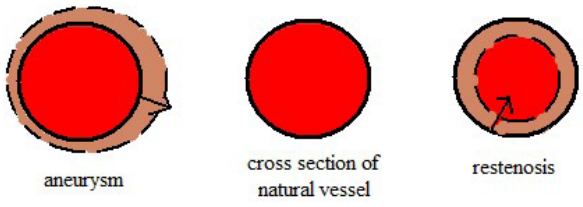

Figure 1. Difference Between Aneurysm and Restenosis. Both of them are hypertrophy of vessel wall, but aneurysm is toward the external side (with dilation) and restenosis is toward the internal side.

order to limit the permeability of glomerulus with its foot processes (pedicel). The basal lamina of capillary and basal lamina of podocytes are integrated each other and make basal glomerular membrane. The spaces between the pedicels and relating diaphragms are called filtration slit. The most important protein of this diaphragm is nephron. All of the above items make a barrier that impedes losing macromolecules such as proteins and cells such as red blood cells. This barrier is called filtration barrier that the layers from blood side to urine side are respectively fenestrated endothelium, basal glomerular membrane and diaphragm of filtration slit. Hence, impaired in diaphragm and nephron results in the protein losing which is called nephrotic syndrome (Figure 2) (7,28,29).

Physiopathology of Kidney and Nephrotic Syndrome

Nephrotic syndrome is of the most common place pediatric disease that in 90% cases is primary and in 10% is secondary to systemic, metabolic and infectious reasons (30). Numerous involving genes have been recognized so far in pediatric nephrotic syndrome. Its prevalence in Europe and America is 16 per 10000 children (31). This syndrome in 10%-20% of patients reaches to end-stage (32). Recurrence of this syndrome is wide spread after kidney transplantation and of the reasons of graft rejection (33). It proves the genetic base of this syndrome. This recurrence usually occurs two weeks after kidney transplantation (32). Patients with nephrotic syndrome because of coagulation disorders and fibrinolysis are at risk of venous thrombo-emboli (34). It seems that passing of heavy proteins through nephrons triggers proceeding of the coagulation cascade, and the coagulating cytokines from damaged cells are released to renal vein (34).

Because of anti-inflammatory effect of steroids, steroid therapy is used for nephrotic syndrome in children (30). Individuals with this syndrome fall into two categories of sensitive and resistant to steroid therapy (35). About 90% of them are sensitive and 10% are resistant to steroid therapy, and the resistant ones are at risk of reaching to end-stage that unfortunately end-stage occurs in 30%-40% of them by the age of 10 (31).

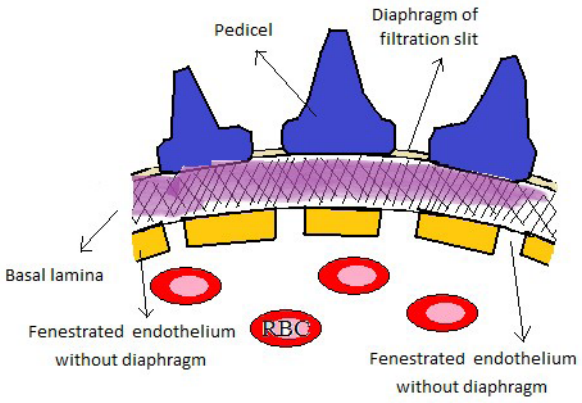

Figure 2. Barriers of Filtration From Blood Side to Urine Formation Side.

3.6. Reasons of Nephrotic Syndrome

Nephrotic syndrome is in 5 types of minimal change, FSGS, diabetic nephropathy, membranous disease and immune-based like amyloidosis. The point is that FSGS is not a disease but it is a tissue damage in kidney with impaired function of podocytes (36). Mutation in alpha-actinin-4 (*ACTN4*) gene – locating on 19q13 and responsive for encoding the cross proteins with actinin filaments – counts as a reason of FSGS; also the genes nephrosis-1 congenital finnish type (*NPHS1*) and nephrosis-2 idiopathic steroid-resistant (*NPHS2*) are respectively responsive for encoding of nephrin and podocin that podocin gene is involved with resistance to steroid therapy (7,37). It seems that mutations in the genes involving with podocytes play important roles in nephrotic syndrome (35). For example, it seems that genetic factors involving with alpha-glucocorticoid receptors, glycoprotein P and cytochrome P450 are relevant to steroid resistance (30). Two-thirds of steroid resistant individuals has mutation on below seven genes (Table 1) (29,31,37) which are responsible for encoding the involving filtration macro-proteins.

Variety of immune factors such as interleukins are involving with nephrotic syndrome (33). Circulating permeability factors also might be effective. These factors are secreted in blood mainly by T-cells (32,38,39). Hence immunosuppressive therapy had been responsive (33).

Circulatory, immune and inflammatory factors are mainly effective through changing in glomerular permeability; but among them there is a controversy about vascular endothelial growth factor (VEGF). In the study of Schachter (33) VEGF has located in the above group like the other harmful factors. But it seems that in verse, with helping endothelial repairing it could improve glomerular barrier. Among the factors, VEGF is potentially regulatory for permeability that in vitro is produced by immune cells and in vivo by podocytes (39). In the word of the review article of Brenchley (40), systemic injection of VEGF could not induce proteinuria and also among the 15 recognized polymorphisms of VEGF no significant correlation was observed between nephrotic syndrome and three most widespread allelic types of *VEGF* gene (Of course the nephrotic syndromes other than diabetic nephropathies).

Table 1. Genes Which Are Responsible for Encoding Involving Filtration Macroproteins That Might Be Mutated In Nephrotic Syndrome

NPHS1	nephrosis-1, congenital, finnish type
NPHS2	nephrosis-2, idiopathic, steroid-resistant
CD2AP	CD2 associated protein
PLCE1	Phospholipase C, epsilon 1
ACTN4	alpha-actinin-4
TRPC6	Transient receptor potential action channel, subfamily C, member 6
INF2	Inverted formin, FH2 and WH2 domain containing

How to Diagnose and Treat

In our literature review generally 2 invasive and non-invasive methods are represented. Invasive methods include biopsy (41) and non-invasive methods include assessment of circulatory immune biomarkers (42), amount of protein in 24 hours urine (proteinuria more than 3.5 g/24 h) and of course infectious assessment (10,41). In addition to protein losing, edema is of the clinical expressions and hypoalbuminemia and hyperlipidemia are of the circulatory markers of nephrotic syndrome. If this proteinuria reaches to 20-30 g/d, it is called nephrosis (37). Evaluation of blood creatinine level is not a marker for diagnosis of nephrotic syndrome, but is a good marker for evaluation of the progression of the disease. It should be regarded in future researches to screen diabetic patients; why diabetes leads to increasing of the level of serum creatinine (43) that this creatinine upcoming could be a reason of mistake with the creatinine upcoming secondary to up-grading of idiopathic nephrotic syndrome.

Generally the therapeutic protocol is based on below items (44):

- Reduction of glomerular permeability factors;
- Inhibition of the above factors' receptors on podocytes;
- Protecting glomerular endothelium with inhibition of glycoprotein digestion through improving the level of VEGF and anti-oxidants;
- Protecting kidney with lipid control and using anti-inflammatory and anti-fibrinotic drugs. This protection is based on RAS inhibition, anti TNFs, anti TGFs and reducer factors of fibrates and lipids.

In addition to the items above, there are some co-treatment suggestions to improvement of histologic complications such as the nephrotoxicity modeled by gentamicin in animal studies, and the other nephropathies has been proved in previous researches that some of them needs to be investigated in human samples:

- Vitamin E with the amount of 400-800 unit/day can have saving effect on kidney as supplement (45).
- Erythropoietin therapy; because erythropoietin may attenuate renal fibrosis via macrophage adjustment and endothelial cell protection (46).
- Co-enzyme Q10 because of its antioxidant effects (43,47).
- Herbal medicines like olive leaf extract because of its antioxidant and anti-inflammatory effects and reduction of creatinine (48,49).

Conclusion

Through identifying and screening the involving genetic diversities in patients with family history – from the most recognized gene *ACE* to genes encoding involving proteins in glomerular barrier formation – we can take the prophylactic actions. It seems that the early starting of steroid therapy can prevents the symptoms of disease. As well, early starting of supplement administration of vitamin E and A (50) could be a less harmful preemptive measure rather than other pharmaceutical prophylaxes. Further researches on gene therapy methods is recommended.

Ethical Issues

Not applicable.

Conflict of Interests

The authors declare that there are no conflicts of interest.

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