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Review Article

Hypertensive nephropathy – A yet unsolved problem

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ARTICLE INFO

Article history:
Received 26 February 2014
Received in revised form
15 May 2014
Accepted 27 August 2014
Available online 26 September 2014

Keywords:
Arterial hypertension
Hypertensive nephropathy
MYH9
APOL1 genes

ABSTRACT

Introduction: Despite increasingly more effective treatment methods of arterial hypertension (AH), there is a constant increase in the diagnosis of hypertensive nephropathy (HN). Diagnostic criteria of HN are not precisely defined.

Aim: The aim of this paper is to present literature reports and systematize current knowledge on HN.

Discussion: Although HN is defined as histological lesions in renal arteries, arterioles and interstitium that occur due to long-term primary AH, rarely diagnosis of HN is made on the basis of renal biopsy. Nephrologists agree that high blood pressure values exacerbate all forms of chronic kidney disease (CKD), accelerating its progression to end stage renal disease. However, there is no evidence that mild and moderate AH may initiate kidney damage. Recent years' discoveries of MYH9 and APOL1 gene polymorphism association with HN seem to confirm these doubts and prove that, at least in the African American population, HN may be a genetically determined disease.

Conclusions: The concept of primary AH being the cause of HN requires reconsideration. There is evidence suggesting that lesions considered as secondary to AH may indeed be a genetically determined disorder.

1. Introduction

Historical sources of interest in association between arterial hypertension (AH) and kidney diseases reach into the second half of the 19th century. It brought two breakthroughs: the ability to measure blood pressure using a sphingomanometer and histological evaluation of tissue with the use of microscope.[1] Renal tissue and vascular wall changes observed in autopsy of subjects who died of AH and kidney disease were explained in two ways. One theory treated renal lesions as an organ damage secondary to AH, while the second recognized

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http://dx.doi.org/10.1016/j.poamed.2014.08.002
1230-8013/

kidney changes as the cause of AH.[1] Clear answer on whether the primary cause is due to renal vascular changes or AH was not provided until German physician and pathologist Theodor Fahr described and propagated hypothesis that chronic renal vascular changes result from long-term AH. He called it Nephrosklerose.[2] Since then, the idea was widely accepted and nephroangiosclerosis, or hypertensive nephropathy (HN), was eventually considered a consequence of AH.[3] Epidemiological data demonstrate that in 30% of patients on dialysis in the U.S. and 13% in Europe AH is the cause of renal failure. Despite such a high prevalence of this condition, diagnostic criteria of HN are not precisely defined.[4] In the study of Perneger et al.[5] nephrologists were presented with almost identical clinical cases of patients with non-diabetic renal disease, minor proteinuria and AH and asked for preliminary diagnosis. Twice more often presumptive diagnosis of HN was made in African Americans (AA). In European Americans, particularly Caucasians (EA), physicians were more likely to suspect chronic glomerulonephritis. Results of this study clearly demonstrate, how despite high prevalence of AH and its renal complications, diagnosis of HN remains highly imprecise, being rather a diagnosis of exclusion of other evident causes of chronic kidney disease (CKD), than a precise choice of a physician. This is particularly caused by lack of clear diagnostic criteria of HN, which results in certain arbitrariness in individual clinical interpretation of a physician. Previous years' findings regarding possible genetic determinants of HN presented by the authors should affect current view on the prevalence of HN.

2. Aim

The aim of this work is to summarize current knowledge on HN, review the available literature and, in particular, draw attention to the controversy over diagnosis of HN.

3. Discussion

3.1. *Hypertension and kidneys – pathophysiologic basis*

Primary site of hypertensive renal damage is assumed to be located in arterial vessels. In case of AH, due to the increased impact of blood on vessel wall, tissue renin–angiotensin–aldosterone system (RAA) is activated, production of pro-inflammatory cytokines is increased and in consequence renal vessels, glomeruli and renal interstitium are damaged.[6] There is however another hypothesis, according to which primary lesions occur within renal tubules and interstitium, and then biologically active substances (cytokines, free radicals) released from inflamed interstitial tissue damage other renal structures.[7] It was observed that interstitial changes occur prior to renal artery lesions.[8] Tylicki and Rutkowski[7] in their study observed that in patients with untreated primary AH urinary excretion of tubular damage markers is increased, with no evidence of vascular or glomerular damage. Due to similar results of their study, Johnson et al.[9] suggested that interstitial renal damage is a manifestation of hypertensive renal damage, but not a primary cause of AH.

Table 1 – Histopathology of HN.

Vessel lesions:
Medial hypertrophy of arterioles, internal elastic lamina duplication, thickening of vessel wall associated with hyaline deposits and eosinophilic infiltration
Glomerular lesions:
1. Generalized sclerotization: collapsed capillary network undulating basal membrane cell loss mesangial matrix expansion
2. Focal segmental glomerular sclerosis: collapse and capillary fibrosis basement membrane thickening capsular fibrosis mesangial matrix expansion
Interstitial and glomerular lesions:
Connective tissue expansion and lymphocyte and macrophage infiltrations atrophy of renal tubules with the presence of eosinophilic casts in its lumen

3.2. *Renal histopathological changes in hypertensive nephropathy*

Typical histopathological changes involve medium and small renal arteries, most frequently arcuate and interlobular arteries and afferent and efferent glomerular arterioles. Characteristic lesions also involve renal interstitium, tubules and glomeruli.[1,10] Characteristics of changes are presented in Table 1.

3.3. *Clinical indications for diagnosis of hypertensive nephropathy*

In clinical practice HN is diagnosed based only on clinical presentation. Most frequently Schlessinger criteria, presented in Table 2, are used.[11] Clinical symptoms of HN are very diverse: from asymptomatic proteinuria and hematuria to full-blown nephrotic syndrome.[12]

3.4. *Main objections to the diagnosis of HN*

3.4.1. *Low specificity of clinical criteria for HN*

HN is used to define kidney disease that occurs in the course of AH. In practice, this condition is frequently diagnosed in patients with CKD of unknown etiology when long-term AH with organ damage is predominant in clinical picture.[13] It should be noted that AH is the leading symptom of CKD, particularly in the advanced stages (stages 4–5 CKD). The assumption that the absence of other causes of renal failure proves the sole role of AH in generating impaired glomerular

Table 2 – Diagnostic criteria of HN.

Schlessinger criteria:
(1) Family history of hypertension
(2) Long-term primary AH
(3) Moderate proteinuria or renal impairment
(4) Left ventricular hypertrophy or hypertensive retinopathy
(5) Absence of nephrotoxin exposure or other renal disease
(6) Renal size reduction in imaging studies
AASK criteria for HN:
(1) Urine protein to urine creatinine ratio < 2.0
(2) Absence of other renal disease

filtration seems to be too much simplification.[14] Studies show a positive correlation between the severity of kidney disease and values of blood pressure, but severe AH secondary to advanced stages of CKD is quite common and typical.[15] In their study, Zarif et al.[6] demonstrated that only four of 100 patients from the study group of 607 subjects with HN previously registered in Health Care Financing Administration (HCFA) registry as a cause of end-stage renal damage (ESRD), met all Schlessinger criteria and only 28 of 91 AA met criteria (Table 2) previously used in African American Study of Kidney Disease (AASK) for diagnosis of HN. It was found that restrictive use of the above criteria reduced frequency of diagnosis of HN from 37% to 3.7%–13.0%. Low specificity of HN diagnosis based on clinical criteria is also evidently proven by two studies of Zucchelli. In the first, only 48% of patients (the study included 56 Caucasians) with HN primarily diagnosed on the basis of clinical criteria had characteristic changes in renal biopsy that confirmed the diagnosis.[16] In the second, after renal biopsy in 136 patients with previous clinical diagnosis of AH without biopsy, diagnosis was confirmed only in 44.1% of subjects.[4] Even Schlessinger observing in his study 43 patients with ESRD caused by HN demonstrated that in none of the patients lesions typical for mild HN were found in renal biopsy. In addition, less than 5% of patients had documented normal renal function at the time of diagnosis of AH.[17] This may confirm previously underlined fact that diagnosis of HN as a cause of ESRD is overused in situations when other etiology of renal failure is not evident. The consequences of diagnosis of HN based only on clinical criteria with no confirmation in renal biopsy may be falsified epidemiology causes of ESRD. This may unfavorably affect treatment and evaluation process of patients with kidney diseases.[18] The above-mentioned controversies over HN and cited studies present HN as an unclear condition in clinical practice.[19]

3.5. *Does mild and moderate hypertension damage kidneys?*

In accordance with 2013 ESH/ESC guidelines three grades of AH are recognized. Grades 1 and 2 of this classification are also defined as mild and moderate hypertension.[20] Properly functioning kidney dynamically responds to changes in blood pressure by intra-renal hemodynamic and sodium excretion changes, which effectively leads to normalization of blood pressure. Loss of this specific renal capacity results in AH. The fact that certain renal function impairment may be observed in normotensive descendants of subjects with AH suggests the key role of kidneys in pathogenesis of this condition. It is known, that AH causes ESRD in its malignant form; however, the question of whether mild and moderate AH can lead to kidney damage remains open.[21] There is a general consensus that AH exacerbates all forms of CKD accelerating its progression to ESRD; however, evidence that suggests a causal relationship of mild AH and CKD remains quite weak.[15] In the study of Perer, in which 500 untreated patients with AH were observed, 42% of subjects developed proteinuria, 10% died of malignant hypertension, 18% developed renal failure, which suggests harmful effect of AH on kidneys, but only in some of the patients.[22] As the study did not involve renal biopsy, it cannot be definitely excluded that patients presenting with progression of AH and organ damage (e.g. proteinuria) did not suffer from primary renal disease. Recent studies show that compared to kidney damage resulting from primary glomerulopathy or diabetes, progression of hypertensive kidney damage, particularly in Caucasians, is slow. Renal function in the majority of patients remains stable over a long period of time, if blood pressure control is satisfactory. On the other hand, there are a group of patients who have a tendency to progress to ESRD even despite the effective antihypertensive treatment. Factors distinguishing this group of patients remain undefined. Most frequently reported include: origin (AA), level of renal damage at the time of diagnosis, the amount of systolic blood pressure and level of proteinuria. Controversial is also the effect of antihypertensive treatment on the progression of CKD. Several studies showed that in accurately treated AH the proportion of patients who develop ESRD is small and equals 2%.[3] Results of meta-analysis of 10 studies conducted by CY Hsu were different.[23] No reduction of ESRD risk was demonstrated in antihypertensive therapy patients. Similarly, in another study Madhavan et al.[24] proved that antihypertensive treatment does not significantly affect renal function in subjects with mild AH and suggested that the cause of renal failure may be primary renal disease and not the existing AH. Effective treatment of AH with pre-existing renal damage may reduce the rate of progression of CKD, but such effects of antihypertensive treatment were proven only in diabetic renal disease.[21] Thus, it is not completely certain whether mild and moderate AH, especially actively treated, leads to ESRD. Number of authors suggest that renal lesions characteristic of HN may precede onset of AH and that HN is a spontaneous pathological process affecting the preglomerular renal vessels, which leads to abnormal autoregulation of glomerular blood flow, and in consequence inadequate vasoconstriction or vasodilatation.[19] Lack of correlation between the appropriate hypertensive control and rate of progression of CKD in numerous cases also suggests the pre-existence of primary renal disease as a cause of AH. On the other hand however, according to the study of Dasgupt, which analyzed cases of 60 patients with lesions typical for mild HN confirmed in biopsy, ESRD developed in 50% of patients within 10 years of observation. Negative effect of these lesions on survival was also observed. Authors emphasize however, that these patients had advanced severity of the disease manifested as significant clinical symptoms (proteinuria above 1 g/day was in majority of cases indication for biopsy).[11] AASK trial demonstrated that HN with smaller proteinuria had a better prognosis.[25] Given such different opinions of researchers and study results, Raine postulated that the answer to the question of whether mild AH leads to ESRD will only be possible after prospective study, which will enroll hypertensive patients with no renal damage, in whom renal biopsy will be performed as soon as there is any evidence of renal impairment.

3.6. *Presence of benign nephrosclerotic changes in subjects with no arterial hypertension*

Concerns related to the diagnosis of HN are exacerbated by the fact that histological changes characteristic of HN are observed in kidney diseases, in which increase in blood pressure values is not observed, at least in the initial stage of the disease. These

Table 3 – Diseases with no AH with presence of histopathological changes typical for HN.

Chronic interstitial nephritis FSGS
IgA nephropathy
Bartter syndrome (tubulopathy, in which hypovolemia is caused by impaired sodium absorption in the loop of Henle and associated activation of RAA system),
Congenital chloridorrhea

changes are also found in normotensive patients (Table 3). Studies also prove that changes typical for HN occur in AA prior to the development of AH. Moreover, in AASK trial no correlation between severity of renal histological changes and blood pressure values was found; it was therefore concluded that it cannot be the cause of these changes.[26]

3.7. *The importance of genetic factors in the development of nephroangiosclerosis*

First reports that HN may be a genetically determined renal disease, symptom of which is AH, appeared from studies using experimental animals.[3,27–29] In the 1990s, Luke[30] suggested the existence of genes determining renal susceptibility to the development of changes associated with AH and reaction of glomeruli and renal tubules to ischemia caused by contraction of afferent arteriole. Several years ago, Kopp et al. and Kao et al. found a significant correlation between the risk of ESRD and MYH9 gene variants in non-diabetic AA, suggesting that this mutation may cause primary renal disease and the resulting AH.[31,32] Two years after discovery of the role of MYH9 gene polymorphism, Genovese, Freedman et al. proved that the two of the Apolipoprotein L1 (APOL1) G1 and G2 gene variants are more strongly associated with the occurrence of non-diabetic renal disease in AA than MYH9 gene polymorphism. Its prevalence in AA is probably associated with the ability of APOL1 protein to provide resistance to *Trypanosoma gambiense*, and thus protect against Chagas disease.[33–35] Studies on APOL1 gene polymorphism and results of AASK trial have undermined the existing view that mild and moderate AH has a significant influence on the development of ESRD in AA. APOL1 polymorphism was found to be responsible for the entire spectrum of renal disease. In addition to hypertensive renal damage, relationship with focal segmental glomerulosclerosis (FSGS) and HIV-associated nephropathy was found.[33] It suggests that increased risk of ESRD in these patients results from the presence of the mutant gene and AH causes progression of renal impairment only in genetically predisposed subjects or is a cause of renal disease. In view of this results, a number of researchers postulate that HN should no longer be considered secondary to AH. At least in AA population it seems to be a genetically determined disease,[19] similar to FSGS. In accordance with the conducted studies, in 43% of AA with progression of CKD there is a relationship with MYH9 gene polymorphism and treatment of AH in these subjects does not inhibit progression of the disease. Representation of histopathological changes in renal biopsy varies between AA and Caucasians and these differences are not associated with values of blood pressure or amount of proteinuria.[36] Moreover, antihypertensive treatment seems to be more effective in the population of Caucasians as compared to AA. In view of this data, Weisstuch and Dworkin[37] defined HN as a rare cause of ESRD in Caucasians and Meyrier in his article emphasized that HN in AA is not the same condition as in Caucasians.[1] There are no studies to determine correlation between MYH9 gene polymorphism with HN in Caucasians. However, Pattaro et al.[38] found a relationship between these genes and creatinine levels in Europeans with no renal disease. Similarly, O'Seaghdha et al.[39] in their study reported relationship between MYH9 gene polymorphism with increased risk of non-diabetic renal disease in European subjects, who were participants of Framingham Heart Study and Atherosclerotic Risk in Communities Study. In the study of Tavira et al.[40] MYH9 gene polymorphism was an independent risk factor for reduced eGFR in a group of 595 Spanish Caucasians. Representation of APOL1 gene variants is very low in Caucasian population and no correlation between polymorphism of this gene and kidney diseases in this population was proven. No relationship between kidney diseases and APOL1 in Japanese and Chinese population has been also found so far.[35] McKnight in her studies in white British has found no relationship between MYH9–APOL1 variants.[41] Does the demonstrated lack of correlation between MYH9–APOL1 variants in populations other than AA exclude the genetic background of HN in these groups? Perhaps in other populations different gene polymorphisms may be responsible for predisposition to certain renal diseases similar to those in AA. In 2013 there were reports on the importance of glutathione S-transferases (GSTs) gene mutation. In AASK trial participants with mutant inactive GSTM1 allele (one of GSTs variants) progression of CKD to ESRD wasso fast. Since GSTs are associated with cellular response to reactive oxygen species (ROS), a significant influence of oxidative stress on the development of HN is suggested. Prevalence of GSTs polymorphism and the presence of the mutant GSTM1 allele are dependent on race and, interestingly, inactive allele occurs in 50% of Caucasian population and Asians, and in AA population its prevalence is 27%.[42,43]

4. Conclusions

In view of the above-mentioned facts, previous common belief that primary AH may be the cause of HN, requires reconsideration. As it was demonstrated in this work, there is evidence suggesting that renal lesions treated as secondary to AH may indeed be a genetically determined disease.[1,42,43] Studies on MYH9 and APOL1 gene polymorphism prove that changes previously defined as HN are indeed primary renal disease in AA.[31–34] Should the concept of HN continue to exist for populations other than AA? This fact certainly requires further studies. It is possible that also here we are dealing with a group of patients with undiagnosed primary renal disease. The above mentioned study results clearly indicate that HN ceases to be sufficient to accurately determine AH as an initial kidney disease that translates into typical renal histopathological changes, particularly in the absence of other specified etiology of CKD.

Conflict of interest

None declared.

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