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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