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Propensity for Progressive Renal Disease in Nephroangiosclerosis: A Refractory Phenotype of Genetic Vasculopathy in Essential Hypertension

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Abstract

Background: Inadequate treatment of essential hypertension (EH), Obesity, smoking, carbohydrate intolerance, hyperlipidemia, and nephrotoxin-exposure are major confounding factors in progression of Nephroangiosclerosis (N). However, neither the prevalence nor the severity of EH is a reliable predictor of individuals at risk for subsequent nephropathy. **Patients and Methods:** A 10-years retrospective analysis of 165 adequately treated patients with EH. **Results:** We observed 2 different renal outcomes. Twenty-three (14%) patients manifested progressive renal disease with > doubling serum creatinine and proteinuria with 3 reaching end-stage kidney disease. At start, biopsy of those patients showed features of "benign" nephroangiosclerosis (N) ± secondary form of focal and segmental glomerulosclerosis (without immune deposits). On the other hand; 142 with similar demographic characteristics, duration and severity of disease did not show significant renal disease on follow up. **Conclusion:** Induction of progressive N, in patients with EH, is compatible with phenotypic susceptibilities of genetic disorders.

Keywords

Biopsy, Kidney Disease, Genetics, Hypertension, Outcome, Nephroangiosclerosis

1. Introduction

According to the United States Renal Data System; 14% of adults have chronic

kidney disease of which hypertensive nephropathy *i.e.*, nephroangiosclerosis (N) is the second most common cause of end stage renal disease (ESRD) after diabetes and accounts for 29% of ESRD patients [1]. Moreover, it had an annual mortality rate of 23.3% which is attributed to its associated cardiovascular disorders [1]. Unfortunately, such global epidemiological data of the disease and its prognosis are hampered by definite clinical diagnosis that lacked pathognomonic histology. In most retrospective studies, N was defined by exclusion though hypertension is prevalent in 80% of patients with chronic kidney disease [2]. Inadequate treatment of EH, Obesity, smoking, carbohydrate intolerance, hyperlipidemia, and nephrotoxin exposure are major confounding factors in progression of N. However, neither the prevalence nor the severity of N is a reliable predictor of individuals at risk for subsequent nephropathy. In the Hypertension Detection and Follow-up Program, a decline in the renal function was noted in some patients with EH despite optimal antihypertensive treatment [3]. In the current study; we retrospectively studied the long-term prognosis of a well-treated patients with isolated essential hypertension (EH) and its association with biopsy proven N.

2. Patients and Methods

A retrospective analysis was performed on patients with essential hypertension who had received treatment and follow up for the past 10 years starting from 1st January 2013. The study was conducted at Amiri renal center in Kuwait City. The center is a referral institution for patients with renal disease in the 2 major hospitals in Kuwait City and is a tertiary care unit for the other hospitals in Kuwait. A total of 831 kidney biopsies were done in the past 10 years. Patients were included if they were: 1) adults with age ≥ 18 and ≤ 60 years, 2) manifesting hypertension with persistent diastolic pressure ≥ 90 mm Hg, 3) compliant to low salt diet, antihypertensive medications and follow up, and 4) adequately treated with diastolic blood pressure < 80 mm Hg. ACEI or ARB were used in all patients unless; 1) intolerable respiratory side effects, refractory hyperkalemia and progressive creatinine clearance to <30 ml/minute. Diuretics were avoided unless indicated by volume overload. To ensure the essential etiology of their hypertension; patients were excluded if they had; 1) diseases likely to affect kidneys viz. diabetes mellitus, autoimmune disease, endocrinopathy, analgesic use/abuse, morbid obesity, renovascular disease, 2) treatments likely to induce hypertension viz. oral contraceptives, and 3) abnormal kidney ultrasound. Moreover, patients with heart failure, liver disease and those on anti-psychotic medications were excluded.

2.1. Study Design

Patients who satisfied the inclusion criteria were analyzed for N. Diagnosis was; 1) considered in patients who manifested decrease of creatinine clearance < 60 ml/min/1.73 m^2 with/without proteinuria and/or hematuria, and 2) confirmed by kidney biopsy. Histological evidence of N included; vascular injury attributa-

ble to ischemia, such as wrinkling of the glomerular basement membrane and global tuft collapse as well as arterial and arteriolar hyalinosis, medial hypertrophy, and intimal fibrosis. None of the patients had myointimal cell proliferation or fibrinoid necrosis indicative of malignant hypertension. Associated secondary forms of focal segmental glomerulosclerosis (FSGS) were accepted if they showed N-vasculopathy and lacked immune deposits in sclerosed segments [4].

2.2. Periodic Assessment

As per our outpatient follow up protocol, all patients had adequate assessment every 2 months. In those visits, patients were assessed clinically for hypertension, fluid overload, edema and side-effects of therapy. Laboratory investigations included complete blood count and serum estimates of sugar, renal, liver and lipid function tests and urine routine. Twenty four-hour urine collections for assessment of creatinine clearance and protein excretion were available, periodically as indicated for patients and specifically at start and end of the study. Moreover, follow up included; cardiac assessment for ischemic heart disease and echocardiography as well as renal ultrasonography to assess for superimposed renal insults.

2.3. Statistical Analysis

SPSS statistical package version 26 was used for data entry and processing. The p-value ≤ 0.05 was used as the cut-off level for significance. Since age, prior duration of EH and duration of follow up were normally distributed; they were expressed as Mean ± SD. Comparison of the latter demographical data, between both groups, was done using student t test.

3. Results

In the past 10-years; a total of 168 patients fulfilled the criteria of essential hypertension and hence were included in the study. However, 3 patients were excluded, on follow up, for non-compliance with medications. At entry and during follow up period of 93 ± 13 months; 23 patients (14%) had renal impairment and their kidney biopsy confirmed N. Those patients were categorized as (N group) while the rest as EH group. The demographical data of the patients in both groups and their follow up are summarized in **Table 1**. The 2 groups, N and EH), were not different with regards age (40 & 39 years), gender (F/M: 48/94 & 8/15), prior duration of hypertension detection (Both were 4 months) and duration of follow up (94 & 93 months). However, those with N had higher initial serum creatinine, proteinuria and lower creatinine clearance.

Outcome

As seen in **Table 1**; by the end of study, all patients in the N-group had progressive renal disease with > doubling of serum creatinine and proteinuria as well as significant decline in creatinine clearance ($p < 0.00001$). Moreover, 3 patients

Table 1. Demographical data and changes in renal function between the 2 study groups.

	Study groups	
	Essential hypertension	Nephroangiosclerosis
	(n = 142)	(n = 23)
Characteristics:		
Age (years):	40 ± 4	39 ± 4
Gender (F/M):	48/94	8/15
Duration of hypertension (months):	4 ± 2	4 ± 1
Duration of follow up (months):	94 ± 12	93 ± 13
Changes in renal function:		
Initial:		
Serum creatinine (umol/L):	74 ± 12	153 ± 9
Proteinuria (mg/day):	126 ± 18	932 ± 195
Creatinine clearance (ml/minute)	108 ± 6	38 ± 4
Final:		
Serum creatinine (umol/L):	75 ± 11	437 ± 138
Proteinuria (mg/day):	129 ± 19	1941 ± 343
Creatinine clearance (ml/minute)	107 ± 6	13 ± 4
Doubling of:		
Serum creatinine:	None	All
Proteinuria:	None	All
ESRD:	0	3

Significance difference (p = 0.00001) between: 1) Initial and final serum creatinine, proteinuria and creatinine clearance between 2 groups. 2) Initial and final serum creatinine, proteinuria and creatinine clearance in N group.

had reached ESRD by the end of the study. On the other hand; all patients in the EH group; maintained normal serum creatinine, proteinuria and creatinine clearance during the same period.

4. Discussion

Our study describes 2 subsets of patients with EH; of whom one had variable progression of renal disease and their kidney biopsy confirmed N as the etiology and ruled out others. On the other hand; the remaining EH patients did not have significant disease over 10 years of follow up. Such phenomenon indicates genetic predisposition to variable degree of N in subsets of patients with EH despite aggressive control of hypertension. Previous research suggested a heterogenicity of EH and its multiple phenotypic presentations of genetic predisposition [5]. The latter may explain the variable propensity for progressive renal disease in its refractory phenotypic subtypes leading to N [6]. Multiple animal studies

documented the strong genetic component exerted in hypertension-induced vascular injury in; 1) spontaneously hypertensive rats (SHR), unless uninephrectomized, rarely develop renal damage, while Dahl salt-sensitive rats exhibit proteinuria before blood pressure increase and before high salt-diet feed, 2) elegant transplantation experiments involving SHR and Brown Norway rats disclosing to propensity to kidney damage in subtypes, and 3) mapping a gene for N in the rats [7] [8]. In humans; there are rare forms of hypertension due to single genetic mendelian mutations. These involve mutations in the epithelial sodium channel (ENaC) in the distal renal tubule (Liddle syndrome), mineralocorticoid receptor, chimeric CYP11B2 (familial hyperaldosteronism type I), and others. The inheritance of the mutation almost always results in the development of EH. However, the majority of cases of EH are broad phenotypes which result from perturbations of many mechanistic pathways that require multiple hits to manifest. The latter was evident in; 1) the genome-wide association studies (GWAS) with over 30,000 subjects have identified 30 or more variants with relatively modest contribution of the risk of hypertension, such as in the adrenergic receptor (ADRB1) and angiotensinogen genes, 2) genome profiling based on identifying ApoL 1 gene variants on chromosome 22 that is associated with N, and 3) identification of MYH9 (myosin, heavy chain 9, nonmuscle) gene polymorphisms that are associated with a spectrum of kidney diseases in African Americans with EH and nephropathy attributed to hypertension, focal segmental glomerulosclerosis, or HIV-associated nephropathy [9] [10] [11]. Recently, research disclosed early podocyte injury prior to hypertensive vasculopathy with podocyturia and reduced gene expression of podocyte-related proteins [12]. Finally; such previous animal and human data suggested a genetic role for N which was confirmed clinically and histologically in our study. However, despite the adequate design of our long-term study; its retrospective nature and its small population were limitations. Our pioneer work, hopefully, may stir the water and expands our knowledge of EH and N.

5. Conclusion

EH should be managed as a broad phenotypic susceptibility of genetic disorder with variable induction of progressive N.

Statement of Ethics

The case was reported according to World Medical Association Declaration of Helsinki; There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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