GENETIC FACTORS IN THE PATHOGENESIS OF CHRONIC KIDNEY DISEASE OF UNKNOWN AETIOLOGY IN SRI LANKA

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Introduction

The likelihood of developing chronic kidney disease in an individual results from complex interactions between multiple genetic and environmental factors. Familial clustering of nephropathy has repeatedly been observed in many population groups studied for multiple etiologies of kidney disease (Goldfarb-Rumyantzev *et al.*, 2006). However, studies reporting chromosomal regions influencing CKD are very limited. The detection of kidney disease genes holds great promise for detecting novel pathways that initiate renal fibrosis leading to progressive loss of renal function. These pathways are likely to offer new therapies that may slow or halt development of chronic kidney failure.

Given the overwhelming burden of kidney disease worldwide, it is imperative that we develop a clear understanding of the pathogenesis of nephropathy so that individuals at risk can be identified and treated at earlier, potentially reversible, stages of their illness.

In recent years investigators in Sri Lanka have noticed alarmingly high number of patients with CKD in certain parts of the country with a common although yet unknown aetiology, leading to marked tubulointestitial fibrosis of the kidneys that finally causes kidney failure. The studies done so far show that the possible etiological factors (Fluoride, heavy metals, insecticides/ pesticides etc) tend to be localized to the specific geographical areas where CKD is prevalent along with evidence of strong family history. The environmental factors identified in these studies are likely to affect both sexes equally. However, the reason for male predominance was not explained in these studies. Thus the aetiology of the chronic renal failure in Sri Lanka still remains a mystery.

Objectives

The objectives of the study are (1) to determine how common the family clustering of CKD of unknown aetiology (CKD-U) in different locations (Medawachchiya and Girandurukotte) and (2) to draw pedigrees of the patients with the family history and study the likely inheritance.

Materials and Method

One hundred and forty three biopsy proven CKD patients with unknown aetiology attending the nephrology clinics from affected areas were

selected for the study. Pedigrees of patients with the family history were drawn to a minimum of three generations and demographic information was collected.

Results

The demographic data shows that there is no significant difference between Medawachchiya and Girandurukotte groups with respect to male to female ratio (4:1 vs 4:1.5), age (44±10 vs 47±8 years), occupations (90% vs 91%, farming), history of moderate to severe alcoholism (38% vs 35%). The history of malaria (78% vs 24%) and family clustering (38% vs 30%) were different in these two populations.

The pedigree analysis showed no evidence of single gene disease with Mendelian patterns. Some pedigrees showed possibility of autosomal recessive type of inheritance in very few pedigrees with a possibility of sex linked recessive pattern. No evidence of autosomal dominant, sex-linked dominant, Y linked inheritance or mitochondrial inheritance patterns were seen.

Discussion

The possibility of multifactorial disease is more likely, as the inheritance patterns, do not follow Mendelian Inheritance. In addition to the environmental factors some biological factors too play an important role eg., age, sex etc. The pedigree analysis shows no evidence of very clear autosomal dominant disease. However the possibility of autosomal recessive inheritance cannot be excluded.

It is important that nephrologists and primary care physicians recognize that individuals who have relatives with advanced nephropathy are themselves at high risk for subsequent kidney disease, proteinuria, and atherosclerotic cardiovascular complications. Until genes for kidney failure are identified, it is reasonable to use "family history" as a surrogate marker for risk of future nephropathy.

References

Goldfarb-Rumyantzev, A.S., Cheung, A.K., Habib, A.N., Wang, B.J., Lin, S.J., Baird, B.C., Naiman, N. and Cannon-Albright, L. (2006). A population based assessment of the familial component of the chronic kidney disease mortality. American Journal of Nephrology, 26(2): 142-8.