7.3.7 URINARY β 2 MICROGLOBULIN VARIATION BETWEEN CHRONIC KIDNEY DISEASE PATIENTS OF UNKNOWN ETIOLOGY AND NON AFFECTED CONTROLS

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Introduction: Chronic kidney disease of unknown aetiology (CKDu) prevails in the North Central Province (NCP), parts of North Western and Uva provinces of Sri Lanka. Owing to the indistinct symptoms in early stages the disease remains undiagnosed to the end stage, at times, even requiring renal replacement therapy. Consequently early diagnosis becomes vital.

Objective: This study was initiated to investigate the variation in urinary β_2-microglobulin (β_2M) levels of CKDu patients (Test) and to use it as a marker for early diagnosis.

Materials and Method: CKDu patients, males and females, were selected at random from Medawachchiya Divisional Secretariat formed the test group (n=30). Age and sex matched normal individuals from the same division (Control M, n=30) and from a different area, Ja – Ela (Control J, n=30) were used as controls. Spot urine samples from all subjects were analyzed in duplicate using an ELISA test kit.

Results: The mean urinary β_2M level in CKDu patients (1.24 ± 0.71 μg/mL) was significantly higher ($P<0.05$) than that of control groups M (0.16 ± 0.05 μg/mL) and J (0.17 ± 0.05 μg/mL). Mean urinary β_2M of males of the test group was significantly higher ($p< 0.05$) than that of the males of control groups. Similar results were seen among the females.

Conclusion: Normal subjects from the same environment as CKDu patients did not show high urinary β_2M levels. Among the CKDu patients, no significant difference was seen between the males and females in their urinary β_2M levels.

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FLUORIDE
TOXINS
TRACE ELEMENTS
RADIONUCLIDES

8.1 CYANOBACTERIAL TOXINS : A HIDDEN HEALTH HAZARD

THE CYANOBACTERIAL TOXINS: A HIDDEN HEALTH HAZARD

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Abstract

Introduction: In early nineties investigators in Sri Lanka have noticed an alarmingly high incidence of a new form of chronic kidney disease of unknown aetiology (CKDu) in North Central Region of the island. This kidney disease was not related to any of the known causes such as diabetes mellitus, hypertension & infection. However, histopathology of affected kidneys showed tubulo interstitial nephritis which is suggestive of a toxic aetiology. Researchers who investigated the disease proposed number of risk factors including high level of fluoride in ground water, leaching of heavy metals such as cadmium from agrochemicals into water sources, exposure to inorganic pesticides and usage of aluminium containers for cooking. However, the lack of sufficient epidemiological studies made the identification of the aetiological agent difficult. The present study was carried out to with the aim of identifying potential aetiological agent/s which could be associated with the disease.

Discussion: We studied the epidemiology of the disease using 11630 CKD-U patients which consisted of all the reported cases in the in NCR . Information of these patients was used for GIS mapping (ARC 9.2 soft ware) to get the geographical distribution. The male:female ratio was 2.4 :1 with mean age of 54.7 yrs. Most of the patients were farmers and their source of drinking water was either shallow wells or water reservoirs. Some of the patients used boiled water for drinking. Clustering of patients in some families was noted.

The epidemiological data indicated five high prevalent areas in the region namely Medawachchiya (identified 20 yrs ago), Padaviya (identified 18 yrs ago), Girandurukotte (identified 12 yrs ago), Medirigiriya (identified 8 yrs ago) and Nikawewa (identified 5yrs ago). The data infers while older foci are persisting, there is an emergence of new foci with the time. All the high prevalent areas are clustered around reservoirs of the irrigation system. Low prevalence of the disease was noted in communities who consume water from natural springs for drinking. The analysis of the water from the natural springs revealed absence of algae & cyanobacteria and contains very low levels of fluoride, Nitrogen, Potassium and Phosphate etc. Analysis of pedigrees of those families with history of CKD-U showed no definite pattern of Mendelian inheritance. The family clustering could have been due to the exposure of the members to the same toxin or the aetiological agent. The kidneys of the cattle living in the high prevalent areas were examined histopathologically to identify the presence of the disease. It is noted that 40% of the cattle had been affected with interstitial nephritis. This finding is suggestive of that there could be an environmental toxin in common for both cattle and human.

Hospital based statistics showed that CKD-U appeared in early nineties for the first time and then the incidence of the disease amplified gradually reaching highest in 2002. The incidence of the disease has been stable but at a lower level thereafter. Alcoholic liver disease and malignancies reported to the General Hospital Anuradhapura during the same time frame also showed the similar distribution.

The epidemiological data most likely indicates that the aetiological agent could present in stagnant water. As the disease is commonly seen in among the people who consume water from the shallow wells the aetiological agent could be a water soluble one. The presence of disease in people who consumed boiled water indicates that aetiological agent could be heat stable. Similarity in the variations of incidence over time in CKD-U, alcoholic liver disease and malignancies in the North Central Region indicates the possibility of common aetiological agent for all three diseases. Literature reveals that cyanobacterial toxin present in stagnant water is one of the probable aetiological agents which is heat stable and water soluble with well identified hepatotoxic and carcinogenic properties. The environmental conditions in the North Central Region is highly favorable for cyanobacterial blooming and toxin production. However, the nephrotoxic effect of this toxin has not yet been identified.

Mouse bioassay was performed to find out potential effect of the stagnated water in the irrigation system. A group of mice were fed with concentrated water obtained from reservoir in the high prevalent area with a control group. Substantial number of mice died 6 weeks after feeding concentrated water. A lymphoma, nephritis with mesangial proliferation and interstitial infiltration with hepatic amyloidosis were detected in dead mice at the post mortem. Analysis of the water samples from same reservoir showed presence of blooms of cyanobacteria capable of producing hepatotoxic and carcinogenic effects. At present we are focusing our experiments to identify potential nephrotoxic effects of toxin extracted directly from these the bloomed cyanobacteria. There were 15 different toxin producible cyanobacterial types identified in these reservoirs and canals.

Conclusion: According to our ongoing research studies, it is substantiate that toxins produced by the cyanobacteria may have a role in the pathogenesis of CKD-U in Sri Lanka. Further we can suggest that the cyanobacterial toxin could be the causative agent for the nephropathy in Balkan countries because there are very close similarities between Balkan Nephropathy and CKD-U in Sri Lanka. Environmental factors such as global warming and admixing of Nitrogen, Phosphate and Potassium of chemical fertilizers with run off water provide a favorable ecological background for the blooming and toxin production of cyanobacteria. The presence of large number of the water reservoirs within a given area in the North Central Region of Sri Lanka due to unique cascade irrigation systems could have been another reason for the disease. The management of patients with renal disease is expensive and need long term care. This is an unbearable burden to the economy of the country. As such short term and long term preventive strategies like introduction of new water sources, measures to control the usage of

chemical fertilizers and control of global warming are mandatory to alleviate the disease in addition to early detection.