3.11 Chronic Kidney Disease of Unknown Aetiology (CKD*u*); A New Threat to Health

World Health Organization
COUNTRY OFFICE FOR Sri Lanka

Chronic Kidney Disease of Unknown Aetiology (CKDu); A New Threat to Health

CKDU research seminar

As an initial step towards achieving these objectives, the Epidemiology Unit of the Ministry of Healthcare and Nutrition in association with the World Health Organization organized a seminar on Unusual Occurrence of Chronic Kidney Disease in Sri Lanka on 7 th - 8th May 2008 in Colombo. The main objective of this seminar was to review all available information, with a view to providing technical assistance for developing a research proposal to address prevention issues. A panel of International experts was in attendance in addition to all the local researchers and related stakeholders.

Development of the research proposal

A draft research proposal was prepared by the team of experts following this meeting. This research proposal provides a framework for program of research activities, the main arm of which is to identify the prevalence and main determinant(s) of chronic kidney disease. This coordinated series of activities is built upon evidence generated by a body of smaller research projects, but was designed to provide a more methodical approach and thereby generate more conclusive evidence regarding the aetiology of the problem. Once the aetiology is known, preventive strategies can be developed and implemented.

Feedback on the research proposal & stakeholder meeting

This draft research proposal was shared amongst the relevant stakeholders including the researchers, academics, consultants & local authorities for necessary feedback. A three day consultative meeting was held in Polonnaruwa on 3rd, 4th & 5th August 2008.

The complete research effort entails the following different research programmes

- Case Control study
- Cohort study
- Renal biopsy study (tissue and data collection)
- Environmental study group for case control phase of the study
- Environmental study group for analysis of water for case control study
- Post mortem study group (collection of organs and data)
- Human tissue (post mortem), urine and blood analysis study
- Chronic Kidney Disease registry and Geographical Mapping study
- Study group for analysis of animal tissues
- Nutrition and Sociology Study

Partners meeting on CKDU

A partners meeting was organized by the WHO Country Office (WCO) Sri Lanka in collaboration with the Ministry of Healthcare and Nutrition on 2nd October 2008.The main objective of this meeting was to highlight the importance of the issue of CKDu and request assistance from development partners to come forward to help in this emerging public health issue which is of great concern to the country. UNICEF, UNDP, USAID, JICA, Americares and Oxfam GB were the developmental partner agencies who were present.

Estimated cost and commitments

WHO SEARO provided USD 40,000 for initial activities. The total cost for the two year period for the research would be approx USD 1,000,000. WCO has re programmed funds for CKD activities amounting to USD 100,000 with SEARO pledging a further USD 100,000 together with the Embassy of Poland contributing USD 50,000 through SEARO.

Way forward

There is a need for a comprehensive public health effort to effectively address this problem of CKDu. This should be taken as a National Priority with joint responsibility resting on Health and Developmental Partners. Ground level preparatory work has already been done which includes recruitment of field programme officer, selection of households and data collection as well as the formulation of a hospital based disease registry.

In addition, Terms of References were developed for the National Steering Committee on CKDu with addition of high level members representing the multi-sectoral agencies involved in this effort. A Management Committee, Scientific Committee & an International Steering Committee was also formed to assist in the implementation of this national research effort into CKD of unknown origin.

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Introduction

At the beginning of the 21st century, an apparently new form of chronic kidney disease of unknown aetiology (CKDu) had emerged in several areas of Sri Lanka.

The CKDu is not related to diabetes, hypertension,snake bite or any other known causes of traditional chronic kidney disease. The disease is characterized by a slow, progressive, asymptomatic development, frequently starting at a younger age group. There is a possible propensity for it to be more prevalent among men engaged in agriculture, typically around the age of 40-60 years.

History of CKDu in Sri Lanka

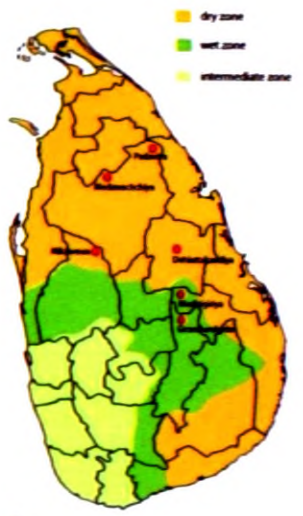
A range of studies of varying types have been carried out over the last 8 years with a view to elucidating the prevelance, nature & causes of CKDu in several parts of Sri Lanka. According to the data reported in the Annual Health Bulletin 2005, the hospital mortality rate for diseases of the genitourinary system has doubled during the period 1980 to 2005. Several studies have investigated the prevalence of this type of CKDu. However from the studies done so far over a period of 8 years, there has been no concrete evidence to support a particular environmental nephrotoxin.

Presence of high levels of fluoride, widespread use of agrochemicals such as pesticides and heavy metals (e.g. cadmium, lead, uranium) in soil and water sources could be postulated as contributing factors to the high prevalence of CKDu in certain areas.

As demonstrated in some studies, mycotoxins, use of herbal / ayurvedhic medicines, smoking and history of snake bite are some other factors to be considered. A combination of two or more of the above factors, possibly a synergistic effect, could also be responsible

Geographical distribution of CKDu

The geographical distribution of CKDu appears to be biased towards the North Central Region (NCR) of the country in which North Central, part of North Western and part of Uva provinces are included. The populations at risk are scattered in the North Central Region with high prevalence observed at Medawachchiya, Padaviya, Dehiattakandiya, Girandurukotte, Medirigiriya and recently Nikawewa



Impact of CKDu

The total number of affected individuals is unknown, however speculations suggest that in excess of 6000 people are currently undergoing treatment for this condition.

In 2005, Anuradhapura Teaching Hospital alone recorded 742 live discharges and 140 deaths due to CKDu. Mortality due to genito-urinary diseases was the leading cause of death in many districts, being the 11th leading cause of Mortality in the country. In 2005, about 350 million rupees (4.6% of the Annual Health Budget) was spent on the management of patients with Renal Diseases.

Initiation by Hon. Minister of Healthcare and Nutrition

A request was made to WHO headquarters in Geneva, in January 2008 by the Minister of Healthcare & Nutrition Hon. Nimal Siripala De Silva, to assist in elucidating the exact cause for the high prevalence of CKDu in the country. This was done as medical studies done so far have failed to establish a concrete link to any aetiological factor. In response to this request, WHO pledged to send a team to Sri Lanka to carry out a pragmatic & feasible research to elucidate a causative agent.

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Scientific Committee-CKDu
Ministry of Health

Chronic Kidney Disease of Unknown Aetiology (CKDu)

June 2011

National Research Programme

Chronic kidney disease is an emerging global health problem and Sri Lanka is no exception to this trend. The aetiology of CKD varies between countries, but diabetes and hypertension are usually the leading factors. However, for a significant proportion of CKD cases reported from certain parts of Sri Lanka, aetiology of the disease remains a mystery (CKD of Unknown Aetiology - CKDu).

To resolve this public health issue, the Ministry of Health in collaboration with the World Health Organization has initiated a multisectoral and multidisciplinary research effort built upon on existing information. This coordinated series of research activities is designed to elucidate key determinants of CKDu and ascertain feasible options for prevention.

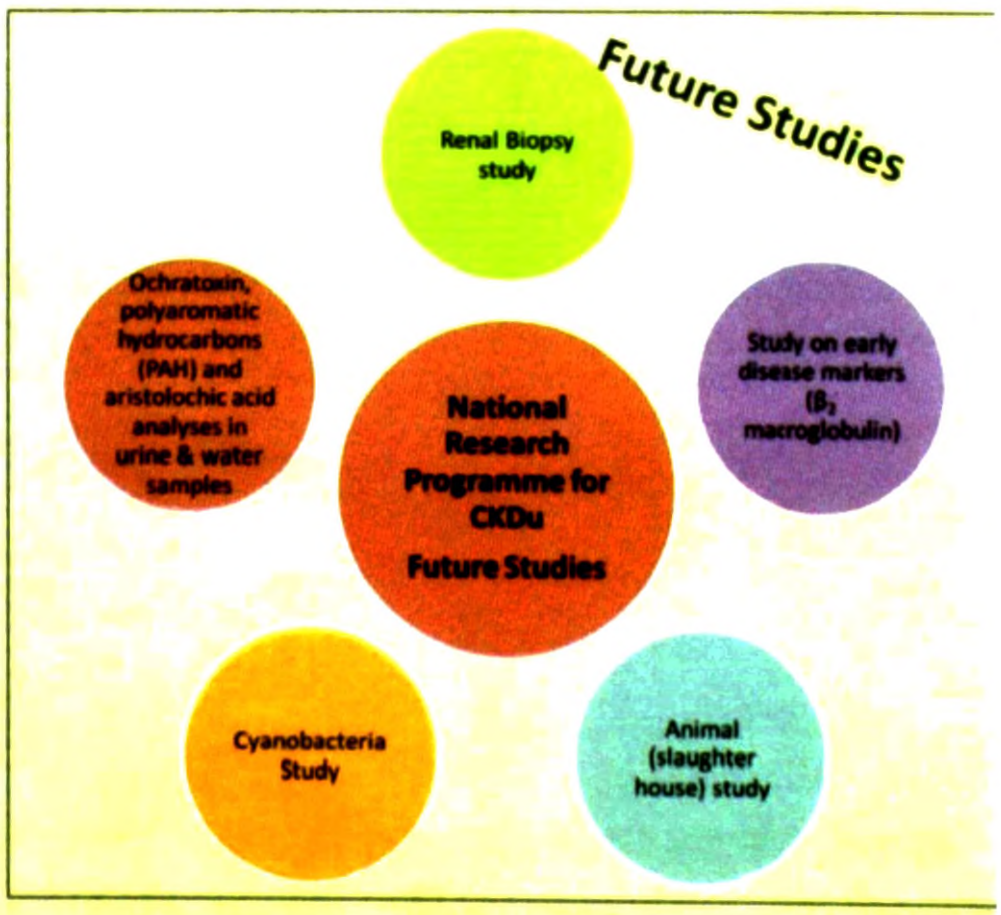
Much work has been done with participation of many stakeholders including different ministries, academia, clinicians, public health specialists, civil society and other concerned parties.

Inside this issue:

Due to limited resources it is not possible to carry out all the studies listed in the study protocol simultaneously.

As such the research activities were arranged according to priority. A series of future studies are currently being reviewed.

An update on the current and future studies is given .



Populatlon Prevalence Study

- Ethical approval obtained from Ethical Review Committee of the Sri Lanka Medical Association
- Multi stage sampling: Random selection of 6 DS areas from 3 districts (Anuradhapura, Polonnaruwa & Badulla);
  Random selection of 22 GN divisions from these 6 DS areas;
  Complete household lists prepared for selected GN divisions;
  From each GN division, random selection of 100 households;
  All members aged 15 - 70 years (both inclusive) in the selected households recruited to the study (n = 6,698)
- Interviewing of participants & GPS Mapping: Subjects were interviewed by trained field assistants & GPS mapping of their residences done, Response rate was 92% (6,132/6,698)
- Biochemical investigation: Early morning urine samples collected for ACR, Response rate was 81% (4,941/6,132)
- Anthropometric measures & further biochemical investigations done for those with urine ACR ≥ 30 mg/g: height, weight & BP measured, samples collected - urine for repeat ACR & blood for serum creatinine & HbA1C, Response rate was 92% (1,308/1,416)
- Results of analysis (prevalence of CKD & CKDu with staging) are available
- Serum samples of 1308 subjects for whom the urine ACR ≥ 30 mg/g were stored in -70°C at the Medical Research Institute for further analysis, if necessary

Case definition based on the classification recommended by the National Kidney Disease Outcomes Quality Initiative was used for this study. .

Adoption of a consistent case definition of CKDu will facilitate collaboration of study groups and, sharing and adoption research findings more readily.

Case Control Study—Metal Analysis of Urine

- A sample of **94** CKDu cases in stage III & IV and **401** CKDu cases in stage I & II (as per the case definition of CKDu) identified from the population prevalence study
- Urine samples collected from these cases for ACR (repeat) & metal analysis. The results are being analysed
- Urine metal analysis (cadmium, lead & arsenic) was done at Antwerp University, Belgium & the results are being analysed
- Urine samples from controls (n = 132, M:F = 1:1) recruited from non-CKDu households in the study areas (22 GN divisions) have been sent to University of Antwerp, Belgium for metal analysis and the results are awaited

Case Control Study—Analysis of Hair & Nail Samples for arsenic

- Hair & nail samples from 77 cases (stage I - 16, stage II - 19, stage III - 22 & Stage IV – 20) identified from the population prevalence study sent to University of Antwerp, Belgium for arsenic analysis and results are awaited
- Hair & nail samples from controls (n = 50, M:F = 1:1) recruited from non-CKDu households in the study areas (22 GN divisions) have been sent to University of Antwerp, Belgium for arsenic analysis and results are awaited.

Environmental Study

Phase I

- Drinking water samples of 99 CKDu cases in stage III & IV (identified in the population prevalence study) and sent to Antwarp University for metal analysis (cadmium, lead & arsenic). Results are being analysed.

- Environmental samples (sediments of reservoirs, irrigation water, drinking well water, agro-well water, pipe borne water, tube well water, soils of agricultural & non-agricultural lands, locally grown pulses, onsite pasture, rice, maize, tamarind, beetle, tobacco, weeds, vegetables consumed in the region, lotus, kohila, field products, freshwater fish) from CKDu high prevalent areas sent Antwarp University for metal analysis (awaiting results) . In addition, 10 rice samples from CKDu patients' residences also sent to Belgium (awaiting results)

- From Hambantota (control area), environmental samples (sediments of reservoirs, irrigation water, drinking well water, agro-well water, pipe borne water, tube well water, soils of agricultural & non-agricultural lands, locally grown pulses, onsite pasture, rice, beetle, tobacco, weeds, manioc, mushroom, leafy vegetables, lotus, kohila, field products, freshwater & sea fish) from CKDu high prevalent areas sent to Belgium for metal analysis (awaiting results)

- Completed GPS mapping of tube wells in 22 GN divisions selected for population prevalence study

Phase II

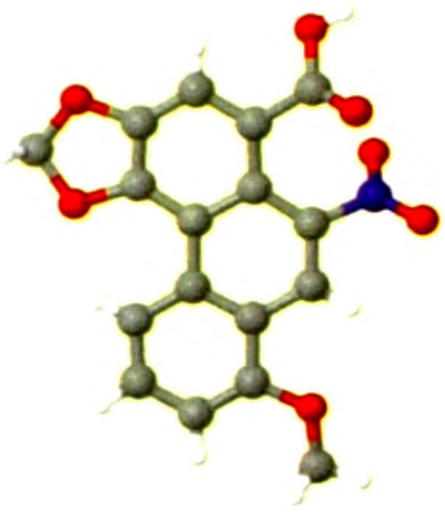
- Soil (from paddy field, vegetable plots & chena cultivation) & fertilizer/ pesticides samples collected from 22 GN divisions (a total of 88 soil & 22 fertilizer/ pesticides samples). Samples dispatched to Belgium for metal analysis

- Soil & fertilizer samples (n = 50) from control area (Hambantota) collected. Samples dispatched to Belgium for metal analysis

- A comprehensive list of pesticides used in study and control areas has been prepared.

Study on Nephrotoxic Herbal Remedies

A group of investigators from the Bandaranayake Memorial Ayurvedhic Research Institute are involved in this study. From this study it is expected that a list of aristolochic acid containing herbal remedies & their prescription pattern in Sri Lanka especially in CKDu high prevalent areas, will be obtained.



Aristolochic Acid Nephropathy (AAN) is a rapidly progressive renal interstitial fibrosis. Clinically, the initial presentation is silent and the renal failure is discovered by routine blood testing. There are reports of AAN cases due to use of herbal remedies.

In Sri Lanka, where use of herbal preparations is common, there is a risk of AAN due to ingestion of aristolochic acid containing remedies.

Postmortem Study

Analysis at International Reference Laboratory (University of Antwerp, Belgium)

Phase I (Pilot study)

- Material Transfer Agreement (MTA) signed with University of Antwerp, Belgium and the ethical approval was obtained from the SLMA Ethical Review Committee
- Postmortem specimens of 06 CKDu patients & 03 dead due to accidents from North Central Province, and 01 CKD patient (known aetiology) & 02 dead due to accidents from Western Province were sent to Belgium for metal analysis. The results are available.

Phase II

- Permission for extension of study obtained from SLMA Ethical Review Committee
- Postmortem specimens of 20 CKDu patients & 11 dead due to accident from NCP & Uva Provinces sent to Antwerp University, Belgium for metal analysis (awaiting results)
- Postmortem specimens included kidney, liver and bone tissues

Analysis at University of Peradeniya

- Postmortem specimens of 06 CKDu patients & 03 controls will be analyzed for aluminium, lead, cadmium, arsenic and fluoride
- Postmortem specimens include kidney and bone tissues & the study to be started shortly

Hospital-based Chronic Kidney Disease Registry

- Database has information on basic socio-demographics, lifestyle factors, environmental factors, health status, anthropometry & laboratory investigations for 1997 patients registered in selected hospitals (TH Anuradhapura, DGH Polonnaruwa, BH Medirigiriya & BH Medawachchiya)
- It will serve as a resource to the academic & clinical medicine communities
- Need to be expanded further to include newly diagnosed CKD patients and other hospitals in the region
- Computerization & linking of data to a central database to be done

Randomised Clinical Trial

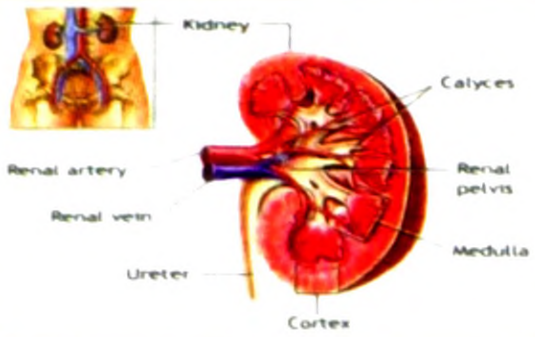
- A double blind clinical trial to examine the renal effects of an Angiotensin Converting Enzyme Inhibitor (enalapril) in CKDu patients (Hypothesis: Enalapril would significantly reduce progression of renal disease in CKDu patients)
- Purpose of the study is to examine the renal effects of enalapril versus placebo in CKDu patients by comparing & evaluating the effect of enalapril to a placebo on: estimated GFR, albuminuria & change in stage of CKDu
- Ethical approval obtained from Ethical Review committee / Medical Research Institute. Sub-Committee on Clinical Trial, Drug Regulatory Authority has issued "no objection" letter for the trial

Socioeconomic & Productivity Impact Study

- Objective is to estimate the socio-economic impacts of CKDu & recommend mitigation measures (Estimation of costs of CKDu to the affected households & communities and the health system; Description of modes of coping adapted to mitigate adverse socio-economic impacts; Estimation of economic impact of CKDu on the GDP; and Evaluation of different mechanisms of social support & recommend the best options for implementation
- Study to be started shortly (Sociological aspects have been studied to some extent)

Chronic Kidney Disease of Unknown Aetiology (CKDu)

Future Studies



Renal Biopsy Study

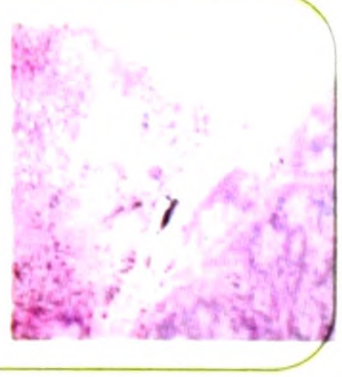
- Immunofluorescence & electron microscopy, and metal mapping of renal tissues will be done (Biopsies will be obtained from CKDu patients followed at TH Anuradhapura)

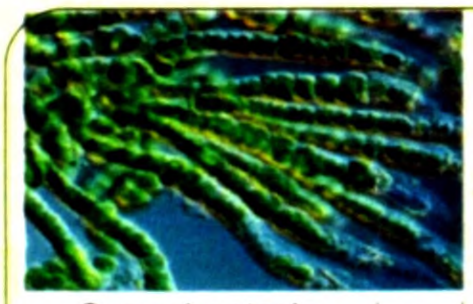
Study on Early Disease Markers

- Proposal to be finalized

Animal (Slaughter House) Study

- Histopathology study (metal analysis) of slaughterhouse samples will be done at a local University
- Metal analysis of randomly selected slaughterhouse samples will be done at University of Antwerp, Belgium



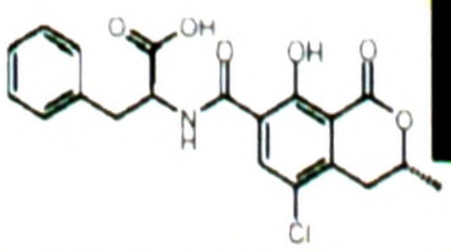


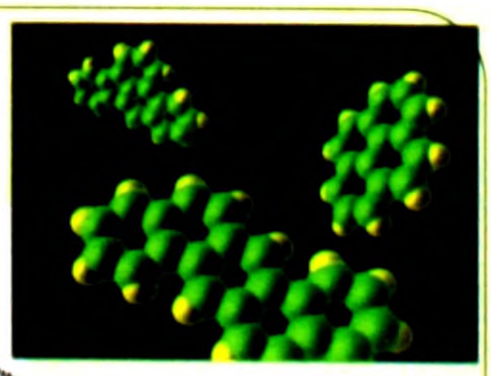
Cyanobacteria Study

- As per the decisions taken at the Scientific Committee meeting held in January 2011, awaiting for a joint proposal from the study group

Ochratoxin, Polyaromatic Hydrocarbons (PAH) and aristolochic acid analysis

- Awaiting for more details on lab procedures and cost price from reference laboratories





In Summary

CKD of unknown origin is an important public health problem for Sri Lanka

- Disease burden is high in terms of premature mortality & morbidity, quality of life and cost
- It is perceived as a threat by the public
- It is distributed unfairly i.e. regional clustering of cases & the prevalence is comparatively high among lower socioeconomic class
- There is evidence that upstream preventive strategies i.e. strategies that target socioeconomic & environmental factors could substantially reduce the burden of this condition
  Such preventive strategies are not yet in place

Prevention

Prevention is the most cost-effective, affordable & feasible approach. However, prevention is **not** an option at present as the cause is unknown. If the cause is known only, preventive strategies can be developed & implemented

Failure to find solutions may cost millions of rupees worth of human lives. In 2005, about 350 million rupees (4.6%) of the annual health budget was spent on management of patients with renal disease
Urgent need for a comprehensive globally conceivable study with a multisectoral & multidisciplinary approach to launch a national public health response for prevention of CKDu

Involvement of WHO

- In 2007, a request was made to WHO by then Hon. Minister of Health to provide technical assistance
- National Research Programme for CKDU initiated in 2008
- Role of WHO
  - Technical, management & logistical assistance
  - Ensuring quality & ethical standards of research
  - Fund mobilization & fund management
  - Secretarial support

Other benefits

- Capacity building in research, field work and lab analysis
- Intersectoral collaboration with local government authorities
- Community involvement & mobilization
- Establishment of a convening platform for researchers to address the public health problem

Lessons from global experiences

Balkan Endemic Nephropathy—Still more questions than answers...

Balkan Endemic Nephropathy (BEN), is a form of interstitial nephritis . It was first identified in the 1920s among several small, discrete communities along the Danube River and its major tributaries, in the modern countries of Croatia, Bosnia and Herzegovina and Bulgaria. Striking feature of the disease is its very localized occurrence. There are approximately ten small areas where it occurs, all of them more or less rural, but nothing seems to connect those areas, other than the occurrence of this illness. Geographic distribution of BEN has not changed significantly since the first descriptions; Non-endemic villages in between sometimes located only a few km from endemic villages

The estimated prevalence of BEN in endemic areas ranges between 0.5 to 4.4 percent. It has been suggested that the prevalence would be as high as 20 percent if aggressive screening were to be performed in at-risk populations; a striking observation is that nearly all affected patients were *farmers*. family aggregation without an obvious pattern of genetic inheritance; at least 10-20 years residence in endemic villages; age 30 - 50 being most heavily affected; sex ratio F: M = 1.5: 1; similar incidence in different ethnic and religious groups. The clinical presentation is characteristic with a long sub clinical period with a rapid onset of end stage renal disease.

The etiology for BEN, is still a matter of contradiction and controversy, despite research efforts since 1950s Many factors have been postulated as aetiological agents: bacteria and viruses, heavy metals, radioactive compounds, trace element imbalances in the soil, chromosomal aberrations, mycotoxins (ochratoxin A), plant toxins (aristolochic acid), & industrial pollution

In recent years, field and laboratory investigations have supported an environmental aetiology - involvement of toxic organic compounds (e.g. pliocene lignite, a type of coal) present in groundwater Whatever the aetiological agent suggested up to now "are all possibilites rather than a certainty "

A typical view of a BEN endemic village in Romania

A patient with BEN

A map showing the geographical distribution of the Balkan nephropathy