

## Mission Report, 6-8<sup>th</sup> June 2011

### Chronic Kidney Disease of Uncertain Aetiology (CKDu), Sri Lanka

Dr Shanthi Mendis

World Health Organization, Geneva, Switzerland

#### Background

Chronic kidney disease has emerged as an important public health problem in some parts of Sri Lanka. Diabetes and hypertension contribute to this chronic kidney disease burden. However, a significant proportion of cases of chronic kidney disease that occur in the North Central and Uva Provinces are caused by a hitherto undetermined cause (Chronic Kidney Disease of Uncertain aetiology - CKDu). In order to address this public health issue, the Ministry of Health Sri Lanka in collaboration with the World Health Organization initiated a comprehensive National Research programme on CKDu in 2008/2009. Up to now this programme has been funded by the World Health Organization and the National Science Foundation of Sri Lanka.

#### Results of the National Research Programme

Results from Phase 1 of this research programme reveal, that in the North Central and Uva Provinces, a minimum of 15% of people in the age group 15-70 years are affected by CKDu. Men over the age of 40 years, who are engaged in farming for more than 10 years, are at higher risk of developing this disease. In addition, exposure to agrochemicals also increases the risk of developing CKDu. The majority of men and women suffering from this disease excrete raised levels of arsenic and/or cadmium in the urine. This indicates consumption of arsenic and cadmium in either water or food. Studies done so far on (drinking) water samples from Anuradhapura, Polonnaruwa and Badulla show that cadmium and lead levels are within normal limits. Few water samples, (3 out of 118 tested), showed slightly high arsenic levels and are been reanalyzed. Within the next 6 months data will be available on the cadmium and arsenic content in samples of a) human tissue, b) water from tanks and tube wells c) food items and d) soil and fertilizer collected from the North Central Province and control areas.

#### Conclusions

Exposure to a combination of factors that are toxic to the kidney (rather than one single factor) seems to cause this kidney disease. Toxic factors identified up to now include, nephrotoxic agrochemicals, arsenic and cadmium. Genetic factors and other known risk factors of kidney disease appear to increase the individual susceptibility to this triple threat. Several other predisposing factors that may contribute to the development of this disease

are under investigation. The social and economic impact of CKDu on impoverished households is grave.

### **Recommendations**

Based on the above findings and the progressive nature of this serious disease for which there is no cure, the following interim measures are recommended:

1. Develop a regulatory framework to improve the quality control of imported fertilizer particularly with regard to nephrotoxic agents such as cadmium and arsenic.
2. Implement measures to reduce the exposure of farmers to the harmful health effects of agrochemicals through i) health education ii) compulsory provision of safety clothing, gloves and masks at the point of sale of agrochemicals and iii) control of the sale of agrochemicals which are known to be nephrotoxic e.g. propanil, chlopyrifos and others
3. Disseminate health education messages to people living in these areas e.g. to thoroughly wash vegetables and rice before cooking, to boil these food items in excess water and to discard the excess water once the food is cooked.
4. Increase the financial assistance provided to farmer families affected by CKDu to prevent them from getting more impoverished.
5. Provide more funds to expand and fast-track this National Research Programme of major public health importance.

It is imperative that the above steps are taken as soon as possible. Delaying action will cause further accumulation of toxic agents in the environment and result in cumulative damage to the health of the people living in these areas.

**Mission Report, 5 -7 October 2011**  
**Chronic Kidney Disease of Uncertain Aetiology (CKDu), Sri Lanka**

**Dr Shanthi Mendis**  
**Senior Adviser and Coordinator, Chronic Disease Prevention and Management**  
**World Health Organization, Geneva, Switzerland**

Further to the report of June 2011 (attached annex A), during the last four months additional progress has been made in research on chronic kidney disease of uncertain aetiology (CKDu), in North Central and Uva Provinces in Sri Lanka within the framework of the National Research Programme.

As highlighted in annex A, long-term exposure to a combination of factors that are toxic to the kidney is causing kidney damage in people residing in North Central and Uva Provinces. Nephrotoxic agrochemicals, arsenic and cadmium as well as genetic factors and other known risk factors of kidney disease appear to increase the individual susceptibility to CKDu.

#### **Analysis of water**

As was outlined in annex A, arsenic and cadmium were analyzed in 118 water samples. 99 of these samples were taken from drinking water sources of people with features of CKDu. In 3 of these samples, arsenic levels were raised above WHO standard levels. Repeat analysis of new samples from the same sources did not show raised arsenic values. 118 Samples that were analyzed were obtained from 22 GN divisions in Anuradhapura, Polonnaruwa and Badulla Districts. 12 water samples taken from drinking water sources from Hambantota were also analyzed and were normal. These findings indicate that drinking water is unlikely to be the source of the Arsenic and Cadmium exposure that is causing CKDu. However it must be noted that as there is no central supply of water, and people are using water from a variety of different sources (Lakes, shallow wells, deep wells, springs outside the study area, tube wells, rain water and canals). Thus the findings of these analyses cannot be generalized to assume that arsenic and cadmium levels in water from all these sources are normal.

#### **Agrochemicals**

Analysis of 32 samples of agrochemicals showed that 10% were contaminated with arsenic and 20% were contaminated with lead.

#### **Socioeconomic impact**

The study to investigate the socioeconomic impact of CKDu was commenced. Preliminary findings from 200 patients interviewed indicate that in the advanced stages of the disease patients are too ill to continue in gainful employment.

Due to frequent shortage of medicines and laboratory tests in the public sector they are compelled to purchase private health services out-of-pocket. The government allowance currently provided to CKDu patients is inadequate.

### **Randomized controlled trial**

The randomized controlled trial has been commenced to test the efficacy of an angiotensin converting enzyme inhibitor for slowing down/reversing the progression of CKDu. About 200 people who fulfill the diagnostic criteria of CKDu have been recruited to the study, up to now.

### **Recommendations**

Cumulative nature of heavy metal exposure and progressive natural history of CKDu for which there is no known cure, demand urgent action to improve safe use and quality control of agrochemicals and quality control of fertilizer.

As advised by the Honourable Minister of Health, a multisectoral strategic plan need to be developed jointly with relevant ministries with short, medium and long-term measures by the end of 2011 and implemented as early as possible in 2012 to minimize the growing public health risks to the population.

1. Currently, the registrar of pesticides issues licenses to import pesticides if importers submit documents from any analytical laboratory certifying the efficacy of ingredients. A regulatory framework is needed to ensure that pesticides imported to the country are tested for toxic impurities (e.g. arsenic) in accredited laboratories selected by the Government.

Nephrotoxic agrochemicals such as propanil and chlopyrifos are heavily utilized by farmers. As they are already exposed to other renal toxins in the environment, more stringent measures need to be implemented to reduce harmful health effects of agrochemicals through i) health education ii) compulsory provision of safety clothing, gloves and masks at the point of sale of agrochemicals. Trained technical assistants can perform these tasks at pesticide outlets. In addition, the legal support and capacity of the national entities for quality control of pesticides and fertilizer need to be strengthened.

2. Strategies need to be included in the plan to address the absence of quality control and regulations related to toxic impurities in fertilizer (e.g. cadmium, arsenic and others). They need to be developed and implemented by relevant officials of the Ministry of Agriculture particularly in the context of fertilizer subsidies. In the long-term alternative approaches to substitute or complement chemical fertilizer use need to be investigated.
3. Increase the financial assistance provided to farmer families affected by CKDu to prevent them from getting more impoverished due to their health care needs. In this regard if Rs. 1000 is given only to CKDu patients in Grade 3 and Grade 4, the cost per month for a population of 100,000 adults above the age of 30 years, would be

two million rupees a month approximately. If the results of the ongoing RCT study demonstrate that progression of the disease can be slowed or prevented with drug treatment it would be essential to improve access to the relevant medicines for those in Grade 1 and Grade 2 so that larger numbers will not progress into Grade 3 and Grade 4.

4. The available scientific data of the national research project need to be published in the peer reviewed literature, at the latest by early next year so that the scientific basis of the strategic plan is documented and the impact of its implementation could be monitored and evaluated in the interest of accountability.

It is essential that the above steps are taken as soon as possible. Delaying action will cause further accumulation of toxic agents in the environment and result in cumulative damage to the health of the people living in these areas and with time also affects younger age groups. In the long-term there will also be severe social and economic consequences that will negatively impact the ongoing developmental and poverty alleviation efforts of this region.

**Annexure A: Mission Report, 6-8<sup>th</sup> June 2011**

**Progress report 13 Feb 2012**

**Chronic Kidney Disease of Uncertain Aetiology (CKDu) Sri Lanka**

**Dr Shanthi Mendis**

**Senior Advisor and Coordinator, Chronic Disease Prevention and Management**

**World Health Organization, Geneva, Switzerland**

Further to the previous reports (June & October 2011) during the last three months additional progress has been made in research on chronic kidney disease of uncertain aetiology, in North Central and Uva Provinces in Sri Lanka within the framework of the National Research Programme.

Overall, the results up to now indicate that long-term exposure to several risk factors toxic to the kidney in causing damage in people residing in the North Central and Uva provinces.

In the urine analysis of 496 cases of CKDu 56% had a urine cadmium excretion over 1 ug/g creatinine. Data from recent studies show that changes of early kidney damage occurs at cadmium excretion levels of even 0.6-1 ug/g creatinine. About 63% of CKDu patients had urine arsenic levels above 21 ug/g creatinine. Urine arsenic levels above 21 ug/g creatinine have been shown to cause changes in kidney tissue that lead to chronic kidney disease. Approximately 88% of CKDu patients had urine arsenic >21 ug/g and/or urine cadmium >0.6 ug/g

Arsenic was also analyzed in hair and nails of people living in NCP including CKDu patients. In about 90% arsenic levels in hair were higher than those observed in developed countries (0.02 ug/g). In about 94% arsenic levels in nails were higher than those observed in developed countries (>0.03 ug/g)

Our analysis did not find high levels of cadmium exposure as reported in previous studies. The mean exposure for adults is at borderline of Recommended Total Weekly intake (TWI) of 2.5 ug/kg body weight. Subgroups such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the TWI. The data for arsenic are not available yet.

Among the patients with CKDu recruited for the clinical trial with a confirmed diagnosis of CKDu about 15% had a family history of CKDu in a sibling or parent. Although current knowledge has not evolved for direct public health application, there are several genes that confer tolerance to heavy metals which are responsible for both common and specific defence mechanisms which protect cells from arsenic and cadmium toxicity. Tolerance and detoxification mechanisms often involve extrusion of the toxic ions from the cell,

sequestration within internal organelles, chelation by metal-binding proteins, and reduction of uptake.

Water from 98 water sources used by patients with CKDu was analysed for hardness. 99% are hard to very hard. Hardness of water is known to affect heavy metal toxicity through antagonistic mechanisms and this may play a role in renal toxicity caused by cadmium and arsenic in the North Central Province.

The laboratory in Antwerp has experienced difficulties in digestion of soil and fertilizer samples to determine content of heavy metals accurately and reliably and results of these analyses are still not available.

### **Recommendations**

1. Implement the recommendations in previous reports (June 2011 and October 2011)
2. Strengthening the institutional arrangements for the implementation, inter sectoral coordination, monitoring and evaluation of control of pesticides and fertilizer. Pollution of environment with agrochemicals cannot be controlled by a single agency. Control activities should include necessary amendments to existing legislation, regulation and processes and control measures should be monitored using sensitive indicators.
3. Increasing the public awareness of the adverse health effects of agrochemicals. The general public should be made aware of the actions taken to control agrochemicals and the importance of applying safety and control measures. Health education programmes should focus on high risk populations including farmers, vendors and also expanded to involve school children and the public at large.
4. Strengthen water purification schemes in the North Central Region: Some studies have shown a weak inverse relationship between water hardness and cardiovascular disease up to a level of 170 mg calcium carbonate per litre of water. The World Health Organization has reviewed the evidence and concluded the data were inadequate to allow for a recommendation for a level of hardness. Recommendations have been made for the maximum and minimum levels of calcium and magnesium in drinking water, and total hardness.
5. As there are 66 ayurvedhic prescriptions that contain Aristolochia. Aristolochia increase awareness of Ayurvedhic Practitioners and the public of renal toxicity of Aristolochia species.