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EPIDEMIOLOGICAL EVIDENCE ON BALKAN NEPHROPATHY AS A VIRAL DISEASE

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ABSTRACT

Balkan nephropathy is a chronic kidney disease of a completely unknown etiology. Most epidemiologists believe that the disease has been caused by viruses, though all attempts to prove such a relationship have been fruitless. A common feature of most of the clues offered for elucidating the role of the viruses, is that they interfere with the epidemiological evidence on BN. Therefore, a hypothesis is put forward that the disease has been caused by slow viruses transmitted by rodents which contaminate food and articles in the house. Such an explanation fits most of the existing epidemiological data.

INTRODUCTION

Balkan nephropathy (BN) is a peculiar kidney disease which has been described up to now only in the three countries of the Balkans: Bulgaria, Romania and Yugoslavia. Its main epidemiological features are: all foci are situated in the vicinity of the Danube or its tributaries, often in flooded areas; the disease has no tendency of spreading out of the known endemic foci; there is a very marked tendency of clustering of cases within families; immigrants may develop the disease if having spent a sufficient period of time in an endemic area (usually over 20 years); except for children which do not develop an overt disease, and the oldest age groups, the incidence of BN is proportional to age; both sexes have similar risk of dying from BN; the incidence of tumors of the kidney pelvis and ureters may be over 100 times higher in endemic than in neighbouring non-endemic villages; a high percentage of apparently healthy persons from endemic foci have an increase of urinary beta-2-microglobulin (1,2,3,4).

Many clinical, morphological, epidemiological and other characteristics of BN have been elucidated, but its etiology remains an unresolved problem. Hereditary factors, trace-elements (in excessive or deficient amounts), other chemical substances, live agents, mycotoxins and many other presumed causes have been proposed as answers by different groups of investigators. Provided any generalization can be made, most authors abandoned the idea of the exclusive or crucial role of gene-

tical determinants while, on the other hand, more and more researchers believe that viruses might be etiologically related to BN.

BN AND VIRUSES

In 1966 Kraus reported results of his investigations suggesting that the West Nile virus had been etiologically related to BN (5). The author speculated that the virus was transmitted by migratory birds. However, the role of the West Nile virus could not be confirmed by any subsequent study (6,7). Up to now, antibody levels to several viruses have been tested (8,9,10). Furthermore, a couple of authors saw virus-like particles with electron microscopy (11,12,13).

However, as concluded recently by Draganescu et al. (14), it has not been yet possible to establish a relationship between these findings and BN. In spite of the fact, most epidemiologists keep believing that the disease is caused by viruses.

Two particular investigations related to viruses as possible causes of BN called wider attention.

In the kidney tissue of affected persons Apostolov et al. (11) saw virus-like particles identified by them as coronaviruses, and speculated that the disease had been transmitted by pigs. This paper was challenged on several grounds related mainly to the reliability of the results (4), but the most vulnerable postulation is that BN is associated with pig husbandry, so that Moslems (who traditionally do not raise pigs and do not eat pork meat) have been spared of the disease. In fact, Moslems may contract the disease as well as Christians.

More recently, a group of Yugoslav epidemiologists investigated an endemic village and postulated that BN is caused by an arthropod-borne virus transmitted from natural foci of infection (15). A rather sound explanation was given why one needs to spend several years in an endemic area in order to be affected: a natural focus is not active all the time and there is only a remote, practically negligible, possibility of an occasional traveller to enter a focus just in time of its activity so to be bitten by an infected vector.

Apart of the absence of any virological evidence at all, the most serious objection to this, from an epidemiological point of view, very detailed analysis is that it has been based on data from a very restricted area. This experience could not be generalized. There is hardly any other endemic focus where women have been exposed to vectors in heavily forested areas as much as men, and the sex ratio of the risk of developing the disease has been generally agreed upon to be at least the same (1,2).

A POSTULATED ETIOLOGICAL MODEL

There is no model of a viral disease which would completely fit the epidemiological evidence on BN. However, the Bolivian hemorrhagic fever (16) to some extent resembles BN. It is an arenaviral disease spread by rodents.

The similarities involve topography of the terrain (flat plains with rivers and streams), clustering of cases within certain households, absence of the evidence on human-to-human transmission and coincidental occurrence of the two diseases (or, at least, their recognition as a public health problem) after the beginning of malaria control programmes by DDT.

It is hardly possible to assess retrospectively, after several decades, the impact which residual DDT spraying in the Balkans had on the reduction of the number of cats, the most susceptible animal species, as a natural barrier for rodents to enter the households. However, it may be indicative that large-scale malaria control by DDT started in the area in 1947 and BN was described independently and almost simultaneously about a decade later in all three affected countries (1).

The analogy with Bolivian hemorrhagic fever may well explain why both sexes and all age groups up to the age of 60 have a similar risk of exposure, at least as judged by hyperbeta-2-microglobulinuria, as an indicator of renal tubular damage (17).

If rodents contaminated overnight food, dishes etc., all family members would have fairly equal chance of being infected (though clinical manifestations depending on a long period of latency). An insufficient resistance of a virus in the environment may than be a reason why occasional visitors to the affected households do not contract the disease: later in the morning there are no live viruses on contaminated surfaces.

Thus, many epidemiological features of BN may be satisfactorily explained: the medical geography, a mozaic pattern of BN, and stability of foci - by the topographical distribution of a reservoir, the absence of inter-human transmission - by no excretion of viruses by man, a rise of the incidence of BN in the mid-fifties - as a consequence of an ecological disbalance caused by DDT poisoning of cats, the familial pattern of the disease and the similar mortality of both sexes - by a common exposure in the house, the lack of propagation of BN to the visitors of affected households - by a susceptibility of viruses, liable to be transmitted only early in the morning, shortly after being excreted by rodents, etc.

There are, however, conspicuous differences between the Bolivian hemorrhagic fever and BN. The former begins suddenly, with fever and bleeding, while the latter is a chronic condition of a very insidious onset. But, could BN be a slow virus infection, as already suggested (11,14). If so, one could easily understand the absence of the disease among children, the occurrence of clinically overt disease only several years after having been settled down in a focus, and the obscured seasonal pattern of the incidence of BN. Moreover, slow virus infection might help us to understand one of the most peculiar features of BN - its relation to the upper urothelial tumors (18,19).

CONCLUSIONS

There is no evidence that a virus has anything to do with BN. The role of rodents in contaminating food and articles has not been documented either. However, there is no strong laboratory support for any of the numerous hypotheses on the etiology of BN and, if a viral infection is suspected, the exposed hypothesis fits the epidemiological data more closely than all other alternatives.

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