

Upper Urothelial Tumours and the Balkan Nephropathy

Inference from the Study of a Family Pedigree

ZORAN RADOVANOVIC,* DRAGISA VELIMIROVIC† and TODOR NAUMOVIC†

**Institute of Epidemiology, Faculty of Medicine, Belgrade, Yugoslavia and †Institute of the Balkan Nephropathy, Lazarevac, Yugoslavia*

Abstract—*In an area heavily affected by both Balkan nephropathy (BN) and upper urothelial tumours (UUT), an outbreak of UUT (followed later by BN) affected at least four of five siblings. Their cousins developed BN in a high proportion but no one of them had any sign of UUT. It has been suggested that host factors determine the outcome of exposure to the same agent(s) responsible for both diseases.*

INTRODUCTION

BALKAN NEPHROPATHY (BN) is a peculiar kidney disease of an unknown etiology which is known to occur in the three countries of the Balkans: Bulgaria, Romania and Yugoslavia [1]. An association with the upper urothelial tumours (UUT) of the papillary transitional cell type is one of its most intriguing characteristics [2]. Observing the situation in the Yugoslav Republic of Serbia, the region most affected by BN, we estimated that the relative risk of developing UUT in BN endemic villages was 18.4, as compared to the urban non-endemic areas [3]. However, the approach used had two serious limitations: place of residence at the time of surgery rather than the life-long exposure was taken into account (in order to provide the denominator for incidence rates), and BN endemic areas have not been exactly delineated. Allowing for these shortcomings, the real risk ratio might be considerably (even several times) higher.

A few years ago, we reported on five (out of five) siblings from a BN endemic village who developed hematuria, and four of whom had histologically proven papillary transitional cell UUT [4]. The aim of the present study was to obtain data on the relatives of the probands.

METHODS

Progeny of the probands' grandparents were identified and households of all individuals visited. For all of them data on medical history, water

supply, exposure in the field, nutrition and personal habits were obtained. Available medical documentation for all of them was searched for in the local health center. Other medical institutions were visited for individuals who used to be treated outside the area. The local registrar helped the causes of death for deceased persons to be verified.

RESULTS

Four siblings who underwent surgery due to UUT had hematuria as the first sign of a disease of urinary organs. All of them developed BN only after the surgery took place. The fifth sibling experienced hematuria in 1982, at which time he showed no indication of an impaired kidney function. His state of health since then has been uncertain, because he refused any further medical procedure. However, even if he has been affected by BN up to now, in all five siblings hematuria preceded any sign of BN.

This situation sharply contrasts with the experience of their uncles' children, a high proportion of whom developed BN, but none of them having a history either of hematuria or UUT (Fig. 1).

A scrutinized investigation failed to reveal any difference between the subjects. They shared the same land inherited from their grandparents, forests as well as flooded areas. No difference in water supply and food intake, including the use of local herbs, preservation of food or consumption of alcoholic beverages could be detected. Neither smoking nor the use of analgesics helped a coherent explanation to be found.

There was no evidence that any family member developed any cancer other than UUT. The father and grandfather of the probands died in their early 80s, both as victims of accidents.

Accepted 7 February 1990.

Correspondence and requests for reprints to: Professor Zoran Radovanovic, Department of Community Medicine, Faculty of Medicine, P.O. Box 24923, 13110 Safat, Kuwait.

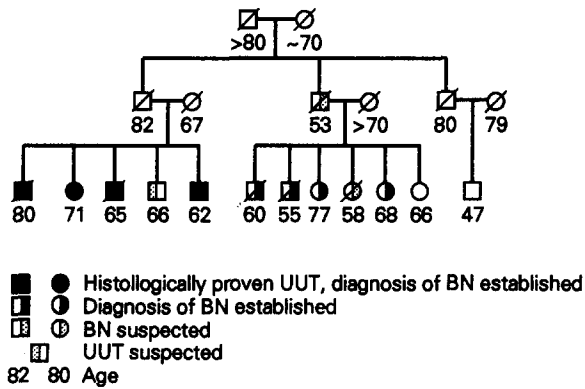


Fig. 1. Pedigree of the family.

DISCUSSION

As we already pointed out [3], the observed clustering of UUT should not be understood as a family cancer syndrome, as described by Li and Fraumeni [5].

The epidemiologic studies point to an environmental etiology of BN [6]. Whatever the cause(s), nobody ever suggested that it (they) might be differ-

ent for BN and UUT occurring in excess in BN endemic areas. The same agent(s) seem(s) to have both nephrotoxic and blastogenic properties. Theoretically, one might expect that all sufficiently exposed individuals—if living long enough—would eventually develop both BN and UUT. However, field studies demonstrate remarkable differences regarding not only the frequency but the ratio of the two diseases as well, both between and within the hamlets/extended families of endemic areas.

The two branches of a single family are a striking example of this point: one branch seems to have been more prone to develop UUT than BN, while the other one has escaped UUT completely, at least up to now.

Failing to observe any difference related to the exposure, we postulate that the genetic set-up of an individual, superimposed upon the environmental factors, influences the outcome, i.e. that host's characteristics determine if a person exposed to common environmental risks will develop BN, UUT or both diseases, and in which sequence. Data provided strongly support this assumption.

REFERENCES

1. Report of the WHO Planning Conference. The 'Endemic Nephropathy' of South-Eastern Europe. *Bull Wld Hlth Org* 1965, **32**, 431–448.
2. Hall PW, Dammin GJ. Balkan nephropathy. *Nephron* 1978, **22**, 281–300.
3. Radovanovic Z, Krajcinovic S, Petkovic S, Hall PW. Papillary transitional cell tumours, Balkan nephropathy, and beta-2-microglobulin. *Lancet* 1981, **2**, 689.
4. Radovanovic Z, Naumovic T, Velimirovic D. Clustering of the upper urothelial tumours in a family. *Oncology* 1984, **41**, 396–398.
5. Li FP, Fraumeni JF Jr. Prospective study of a family cancer syndrome. *J Am Med Ass* 1982, **247**, 2692–2694.
6. Radovanovic Z. Aetiology of Balkan nephropathy: a reappraisal after 30 years. *Eur J Epidemiol* 1989, **5**, 372–377.