Familial Aggregation of Urinary System Tumors in a Region with Endemic Nephropathy

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ABSTRACT

In hyperendemic villages in the Vratza district of Bulgaria, 193 patients with urinary system tumors (UST) were diagnosed during 1965 to 1976. A tendency towards familial aggregation was revealed when the patients were compared with two groups of controls, namely, patients with tumors other than UST and healthy persons. Each control group consisted of 193 persons matched by sex, age, and place of birth. This tendency was observed in all relatives who lived together as well as in those related by blood. The probability of having relatives with UST was 2.5 times higher than could be expected as chance occurrence among UST patients than among the controls. The UST cases also had significantly more relatives with endemic nephropathy than did the controls. The familial clustering of both UST and nephropathy in the endemic region is considered another clue to their common etiology.

INTRODUCTION

In the village with endemic nephropathy in the Vratza district of Bulgaria, UST1 are the most common cancers. The mean age-adjusted incidence rates for 1965 to 1974 are 89/105 in males and 104/105 in females (2). Thus these cancers rank among the most frequent neoplasms recorded for any world population (22).

Nephropathy endemic to the Balkan and Danubian regions manifests itself as a chronic and progressive kidney disorder. It was first described almost 25 years ago in certain areas of Bulgaria, Yugoslavia, and Rumania. Its etiology remains unknown (18). Endemic nephropathy and UST display close geographic clustering and most often affect people, chiefly women, between 40 and 60 years of age (2). Endemic nephropathy has also been called “familial nephropathy” because many families with multiple cases of the disease are encountered (3, 5, 6, 8, 23).

Recently, we described multiple cases of UST in families from the endemic region (16). The problem has been further investigated and now a study of the familial distribution of all UST cases diagnosed in hyperendemic villages of the Vratza district between 1965 and 1976 is presented.

MATERIALS AND METHODS

All cases came from 9 hyperendemic villages of the Vratza district, Bulgaria. Their total population, as the sum of the population recorded for each year of the period 1965 to 1976, was 110,080. The familial distribution of UST patients was analyzed in a case-control study carried out on 3 population groups of equal size.

Group A consisted of all well-documented cases of UST diagnosed during the years 1965 to 1976 in specialized clinics; 57% were diagnosed in Sofia, 43% were in other large cities. Diagnosis was by the following methods: histological (116 cases); cytological (4 cases); gross examination and cystoscopy (58 cases); radiological and clinical (15 cases). When more than 1 method was reported, preference was given in the described order. As recommended (22), papillomas and carcinomas of the urinary tract were grouped together.

Group B included cases of well-documented malignant tumors other than UST. They were also diagnosed in specialized clinics in large cities during the same period of time.

Group C consisted of healthy persons taken as a systematic sample from the electoral list of the villages. These people were considered healthy because they were not registered for any chronic disease.

The people of Group A made up the group of UST cases, while those in Groups B and C were the controls. In every village each person of Group A was matched with a person from Groups B and C by sex, place of birth, and age ±3 years.

The occurrence of endemic nephropathy in families of UST patients and controls was also examined. For this purpose all so-called “positive” cases of endemic nephropathy from the same villages, i.e., those diagnosed in specialized clinics by the diagnostic criteria for the disease adopted in the 3 Balkan countries (see Ref. 18), were taken from the follow-up documentation by the kidney clinic of Vratza District Hospital and analyzed.

Persons from Groups A, B, and C or members of their families were interviewed about all their relatives in the same group as well as about their relatives among the endemic nephropathy patients mentioned above. Thus, the relatives in each group and their relatives among endemic nephropathy patients were encountered. When people were questioned about their relatives by blood, first, second, and third degree relatives were taken into account. Relatives by blood and relatives by marriage who shared common households were considered as relatives living together.

To check the size of the families from which cases and controls originated, we gathered information on the years of birth, death, or migration of parents, siblings, offspring, and spouses. Only such relatives were included because the information about them was more reliable and because they made up a large part of the family members living together. The number of these relatives as well as the number of years they spent in the villages under study were...
calculated. The sum of the years spent by all specified family members in each of the 3 groups gave the number of person-years in the respective group.

Before making further use of the information collected, we double-checked with the families and local councils, and discrepancies were resolved. The statistical analyses were made with the $\chi^2$ test, and the relative risk was calculated according to the procedures described by Mantel and Haenszel (15).

RESULTS

Groups A, B, and C consisted of 193 persons each. Cases were successfully matched to controls; each group included 104 males and 89 females. The mean age ± S.D. and the age intervals (years) were as follows: Group A, 64.8 ± 10.7 (40 to 88); Group B, 66.5 ± 11.9 (38 to 90); Group C, 64.5 ± 10.5 (41 to 87). In Group A 32 persons with more than 1 tumorous site of the urinary system were encountered. The following percentages of UST subsites were observed: kidney pelvis, 34.7; kidney (part unspecified), 13.1; ureter, 16.7; urinary bladder, 35.5. Group B included various locations of malignant tumors. In males, leading cancers were (%): skin, 24; lung, 18; stomach, 16; liver, 7. In females, leading cancers were (%): skin, 33; stomach, 11; mammary gland, 10; cervix uteri, 10. In all villages 714 well-documented endemic nephropathy cases were analyzed.

The number of relatives in each of the 3 groups is shown in Table 1. Highest values are seen in Group A; i.e., in this group more people were relatives and the frequency of UST differed significantly from values for Groups B and C.

The familial distribution of the persons in each of the 3 groups studied is presented in Table 2. Here again it is seen that UST cases tend to aggregate; the number of families with multiple UST cases is significantly higher than the corresponding numbers for the 2 control groups.

The family size of the 3 groups was fairly comparable.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Kind of relatives</th>
<th>With 1 member studied</th>
<th>With 2 members</th>
<th>With 3 members</th>
<th>With 4 and 5 members</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>By blood</td>
<td>123</td>
<td>29</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Living together</td>
<td>124</td>
<td>31</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>B</td>
<td>By blood</td>
<td>155</td>
<td>17</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Living together</td>
<td>154</td>
<td>17</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>By blood</td>
<td>165</td>
<td>14</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Living together</td>
<td>152</td>
<td>20</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

The numbers of first-degree relatives and spouses in these groups were 819, 812, and 870, respectively. The corresponding person-years were 42,944, 43,366, and 46,662.

Data on the occurrence of endemic nephropathy cases in families of Groups A, B, and C (Table 3) show that significantly more endemic nephropathy patients are related by blood to UST patients than to control families.

DISCUSSION

The data on familial occurrence of cancers are still inconclusive, and no generalization can be made on their basis. Most reports describe families with multiple cases; few analyses on large population groups have been undertaken. A familial aggregation is more pronounced in certain cancers and in cancer-predisposing syndromes; namely, retinoblastoma, intestinal polyposis, xeroderma pigmentosum, and multiple neurofibromatosis, which are clearly determined by a hereditary mechanism (4, 10). A certain familial aggregation is also observed in other cancers like Hodgkin's disease (12, 19) in which a horizontal transmission of the disease was postulated (20, 21). In studies on Hodgkin's disease (19) and breast carcinoma (1, 7, 11), a similar value of about 3-fold-increased familial risk is reported. The results call for appropriate caution, but tend to aggregate; the number of families with more than 1 UST case differ significantly from those for the corresponding number of families in Groups B and C ($p < 0.01$ to $0.001$); differences between Groups B and C are not significant ($p > 0.05$).

### Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Relatives by blood in the group</th>
<th>RELATIVES LIVING TOGETHER IN THE GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First-degree relatives</td>
</tr>
<tr>
<td>Total</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>A</td>
<td>70</td>
<td>36.3</td>
</tr>
<tr>
<td>B</td>
<td>38</td>
<td>19.7</td>
</tr>
<tr>
<td>C</td>
<td>28</td>
<td>14.5</td>
</tr>
</tbody>
</table>

a familial aggregation is more pronounced in certain cancers and in cancer-predisposing syndromes; namely, retinoblastoma, intestinal polyposis, xeroderma pigmentosum, and multiple neurofibromatosis, which are clearly determined by a hereditary mechanism (4, 10). A certain familial aggregation is also observed in other cancers like Hodgkin's disease (12, 19) in which a horizontal transmission of the disease was postulated (20, 21). In studies on Hodgkin's disease (19) and breast carcinoma (1, 7, 11), a similar value of about 3-fold-increased familial risk is reported. The results call for appropriate caution, but tend to aggregate; the number of families with more than 1 UST case differ significantly from those for the corresponding number of families in Groups B and C ($p < 0.01$ to $0.001$); differences between Groups B and C are not significant ($p > 0.05$).
Familial Aggregation of UST

Table 3
Occurrence of endemic nephropathy cases in families with UST cases (Group A), people with tumors other than UST (Group B), and healthy persons (Group C) from 9 endemic villages of the Vratza district, Bulgaria

Groups A, B, and C comprise 193 persons each. Relatives living together include all relatives by blood and by marriage living in a common household. The tabulations for relatives by blood and relatives living together are not mutually exclusive; i.e., 1 person can be counted in both groups. Percentages are computed on the number of endemic nephropathy cases in the families of Groups A, B, or C and the total number of 714 endemic nephropathy cases recorded in all villages under study. The values for Group A differ significantly from those for Groups B and C (p < 0.001) with the exception of relative by marriage (p > 0.05); differences between Groups B and C are not significant (p > 0.05).

Endemic nephropathy cases relating by blood to the persons in the group

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>199</td>
<td>27.9</td>
<td>73</td>
<td>10.2</td>
<td>72</td>
<td>10.1</td>
</tr>
<tr>
<td>B</td>
<td>91</td>
<td>12.7</td>
<td>36</td>
<td>5.5</td>
<td>37</td>
<td>5.2</td>
</tr>
<tr>
<td>C</td>
<td>87</td>
<td>12.2</td>
<td>39</td>
<td>6.3</td>
<td>26</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Endemic nephropathy cases living together with the persons in the group

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>193</td>
<td>27.0</td>
<td>118</td>
<td>16.5</td>
<td>75</td>
<td>10.5</td>
</tr>
<tr>
<td>B</td>
<td>110</td>
<td>15.4</td>
<td>63</td>
<td>8.8</td>
<td>47</td>
<td>6.6</td>
</tr>
<tr>
<td>C</td>
<td>118</td>
<td>16.5</td>
<td>56</td>
<td>7.8</td>
<td>62</td>
<td>8.7</td>
</tr>
</tbody>
</table>

although a fair number of well-documented cases were analyzed and were successfully matched to 2 comparably sized control groups. In general the work faces the usual methodological problems of a case-control study. Nevertheless, the methodology available for detection of family aggregation in chronic diseases, including cancer, is based chiefly on description of patients with the disease in the family background and on the case-control approach (13). Mathematical models and methods such as those used for detection of space-time clustering in diseases with low endemicity (9, 14, 17) are less suitable for similar analyses. In this case the high incidence of UST and the rather frequent familial relationships in the villages could easily result in biases due to chance occurrences that falsely suggest familial agglomeration of diseased persons. For measurement of this chance occurrence of relatives, a comparison of their number in each of the case and control groups was made and evaluated statistically. Another bias may be caused by the likelihood that ascertainment and report of a second case of UST or endemic nephropathy in the families with such patients might be greater than in control families. The impact of such bias seems small because the whole endemic area is under strict medical control and because hematuria is the leading symptom in the patients with UST. This alarming symptom urges people to seek medical care regardless of the medical history of the family to which they belong.

All presented data gave support to the conclusion that UST cases tended to concentrate in some families. The probability of having relatives with the same disease was 2.5 times higher than could be expected as chance occurrence among UST cases than among the controls. The same tendency was also suggested by the aggregation of endemic nephropathy cases in the families with UST cases. Following the discovery of a close geographic clustering of both endemic nephropathy and UST and their frequent combination in some individuals, it is now seen that these diseases exhibit a close familial aggregation. This can be another clue to their common etiology.

The data showed that UST cases were concentrated not only among relatives by blood but also among those sharing common households, irrespective of whether they were relatives by blood or by marriage. This may be an indication that genetic factors play a minor role in the disease. Further studies are therefore needed to elucidate the relative role of environmental and genetic factors in the etiology of UST and nephropathy in the endemic regions.

REFERENCES

16. Petkova-Bocharova, T., Chernozemsky, I. N., Nikolov, I. G., and Stoy-


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