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Balkan endemic nephropathy in Vratza, Bulgaria, 1964–1987: An epidemiologic analysis of population-based disease registers

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Abstract. Balkan Endemic Nephropathy (BEN), first described in 1956 in Vratza region, Bulgaria, may result from prolonged, chronic exposure to environmental toxicants, but the underlying etiologic factors remain elusive. There has been no recent systematic characterization of the epidemiology of this disease. Recently, it has been suggested that the incidence of the disease is decreasing. We therefore abstracted data from registers of patients in 21 affected villages and the town of Vratza, Bulgaria maintained from 1964 through 1987. In 1964, the prevalence of BEN was 6.0 per 1000 inhabitants; among residents of the affected villages, the prevalence was 12.3 per 1000. From 1965 to 1975 the incidence rate was 0.7 per 1000 person-years, and from 1976 to 1987 the incidence rate was 0.3 per 1000 person-years (rate ratio 0.43; $p < 0.001$). Incidence was much lower in Vratza town; among residents of affected villages, the period-specific rates were 1.7 and 0.8 per 1000 per year, respectively (rate ratio 0.47; $p < 0.01$). These trends were consistent across all villages for which registers were maintained. Median survival following registration increased from 2.0 to 5.0 years over the same period ($p < 0.001$). BEN appears to be decreasing in incidence in this region.

Key words: Balkan Endemic Nephropathy, Descriptive epidemiology, Kidney disease, Survival, Time trends

Abbreviations: BEN – Balkan Endemic Nephropathy

Introduction

Balkan Endemic Nephropathy (BEN; ICD-10-N15.0) is a non-inflammatory, slowly progressing, familial, chronic, primarily tubulo-interstitial bilateral kidney disease. First described in 1956 in Vratza, Bulgaria [1], it is localized to rural areas in several regions in Bulgaria, Romania, Bosnia-Herzegovina, Croatia and Serbia. Although various investigators have postulated that the disease may result from prolonged, chronic exposure to environmental toxicants including ochratoxin and other mycotoxins [2–4], polynuclear aromatic hydrocarbons [5], heavy metals [6], selenium deficiency [7], herbs containing toxic compounds [8], viral infection [9, 10], or a genetic susceptibility [11, 12], the underlying etiologic factors remain elusive [13].

In 1956, Tanchev surveyed the Vratza region in northwestern Bulgaria and identified prevalent cases of BEN [14]. The affected villages were interspersed among villages in which, to the present day, no cases of BEN have been diagnosed. An incidence rate of 30–50 cases per year per 10,000 people in the endemic area in the 1970s has been cited [15]. However, the available reports did not provide an adequate epidemiological profile of this disease. Recently, it has been suggested that the incidence of the disease is decreasing in Serbia [16], but no similar analyses have been published for other endemic areas. Changes in the epidemiology of BEN over time, if real, would suggest directions for focussing research into the etiology of the disease. We therefore describe the distribution of BEN in the region in which it was first identified, using population-based registers for the period 1964 through 1987 that have never, to our knowledge, been previously analyzed using epidemiological approaches.

Methods

Setting

Vratza is a rural district in the northwestern region of Bulgaria. The district consists of the district capital (Vratza, 1991 population 85,174), and approximately 60 villages ranging in population from a few hundred to over 15,000 people, who are almost exclusively of Bulgarian ethnicity. The economy is based on farming. Since the 1960s the population of most villages

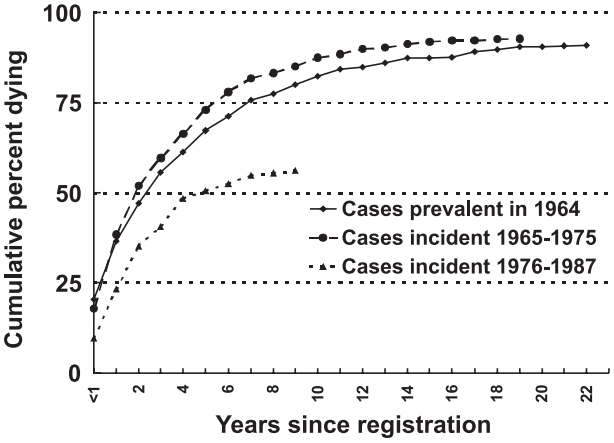

Figure 1. Cumulative density function of time to death following registration as BEN patient, Vratza District, Bulgaria, 1964–1987, by time period. Plots are based on 1191 cases (323 prevalent in 1964, of whom 29 were alive in 1987; 569 incident 1965–1975, of whom 41 were alive in 1987; and 297 incident 1976–1987, of whom 130 were alive in 1987) not subsequently deleted from the registers.

has decreased, while the population of the town of Vratza has more than doubled and that of the village of Mezdra has increased to over 15,000 inhabitants (Table 1). The population of one affected village (Karash) was systematically relocated in the early 1960s.

Sources of data

Registration of BEN patients was established in 1964, following several years of research and surveillance activity in the district of which no records remain. All previously identified surviving BEN patients were logged into hand-written registers. A separate register was maintained for each of 21 villages in which BEN cases had been identified and for patients living in the town of Vratza. Information available included the individual's full name (first, patronymic, family) and age. The registers were maintained in the District Hospital in Vratza, and were updated each year until 1987. Each year's entry for a village consisted initially of an alphabetized list of all surviving BEN patients (prevalent and newly identified) living in the village. New names were added as individuals were identified, and deaths and relocations were recorded. Some individuals were deleted from the register in later years and not subsequently followed – there is no additional information in the registers, but it is our understanding that these individuals were later thought to have a disease other than BEN. No clinical details are available, either of these deleted cases or for those retained in the register. In an independent process, BEN patients were identified in the summer of 2000 from the records of the Department of Nephrology at the District Hospital in Vratza. Most reside in the

Table 1. Population of affected villages and cases of BEN registered, 1964–1987, Vratza region, Bulgaria

	Population						Number of cases registered		
	1964	1970	1975	1980	1985	1991	Prevalent in 1964	Incident 1965–1975	Incident 1976–1987
Beli Izvor	1302	1910	1345	1250	1085	974	75	105	44
Bistretz*	1213	1322	1414	1506	1598	1653	50	69	34
Brusen	585	563	556	536	544	532	5	9	0
Darmantzi	709	661	642	593	517	415	4	7	3
Goliamo Babino	850	711	676	630	547	386	4	8	3
Goliamo Peshtene	1750	1351	1196	993	846	642	4	31	13
Gorno Peshtene	1275	1024	944	825	708	531	34	41	28
Hubavene	838	670	685	621	543	416	46	53	30
Kalen	434	429	342	254	265	201	21	15	5
Karash	417	101	61	56	37	32	11	1	1
Kravoder	1813	1813	1832	1640	1481	1052	6	22	6
Kunino	1480	155	1376	1527	1233	1184	0	7	2
Liliache	2609	1890	1997	1778	1943	1855	0	12	7
Mezdra	9885	11,852	12,701	14,117	13,949	15,323	8	36	13
Pudria	1607	1271	1308	1159	1102	915	33	51	16
Radovene	868	670	647	576	569	418	13	17	10
Roman	2179	2872	3121	3174	4434	4772	17	43	34
Tishevitza*							17	19	5
Tsakonitza	592	437	306	257	217	179	43	37	12
Vesletz	645	438	329	300	207	185	0	9	7
Vlasatitza	809	701	646	582	501	381	0	9	7
All villages with registers	31,870	30,985	30,751	32,406	29,642	30,473	391	583	266
Vratza town	35,826	51,309	61,134	65,992	78,669	85,174	14	56	32

* Population count data were not available for Bistretz in 1970, 1975, 1985, or 1991, or for Tishevitza in any year. Bistretz population estimates for these years are interpolations from available data.

town of Vratza to have easy access to services (modified food, medical care) made available to registered BEN patients. Many undergo regular dialysis. For these patients we abstracted age, sex, year of diagnosis, and village of residence at the time of diagnosis.

Data abstraction and analysis

For each individual identified in a register, we recorded the year of first registration, age at registration, and year of death. Sex was inferred from the individual's name; in Bulgaria this is unambiguous.

We considered cases entered into the register in 1964 as prevalent, as no information is available concerning the year of first diagnosis. We considered cases registered in subsequent years to be incident in that year. Population count data (without age and gender distribution) were available for 21 of the 22 villages with registers, and for the town of Vratza, for the years 1963–1967, 1970, 1975, 1976, 1980, 1985, and 1991. Population counts for years in which census data were not available were computed by linear interpolation. Prevalence in 1964, and incidence rates for each year from 1965 to 1987 were computed for each affected village, for all the affected villages of the district taken together, and for the town of Vratza. We also combined the years 1965–1975, and 1976–1987, to provide larger number of cases in each of two periods of approximately one decade, to compare trends in annual incidence rates and survival over time. For these periods we computed the average incidence rate by summing the new cases that occurred in the period, and then dividing by the total person-years at risk, calculated as the sum over the years 1964–1987 of the population counts for each year. Survival post-registration was calculated as the difference between the recorded date of death and the year of registration, in complete years. Survival was considered censored at 1987. Probability of survival post-registration was computed as the proportion alive among those not known to have previously died or relocated.

For cases prevalent in the hospital records in 2000, we computed survival as the time (in complete years) between the year of diagnosis and 2000.

Results

Registers

A total of 1375 unique individuals were listed in the registers. Table 1 provides the population counts for selected years, and cases registered in 1964, 1965–1975, and 1976–1987, for each village and for the town of Vratza. Of these, 405 (29.5%) were prevalent in 1964, 656 (47.7%) were first registered between 1965 and 1975, and 312 (22.7%) were registered between 1976 and 1987. Of the 1375 registered cases, 184 (13.4%) were subsequently considered as questionable diagnoses and deleted. The proportion of subsequently deleted cases decreased over time (19.8% of cases prevalent in 1964, 13.3 of cases incident in 1965–1975, and 4.8% of cases incident in 1976–1987).

The distribution of the cases by age and sex is provided in Table 2. The ratio of women to men was 1.5:1 among cases prevalent in 1964 and incident between 1965 and 1975, and it was closer to 1:1 among cases registered between 1976 and 1987. Age was unknown for three cases registered between 1965 and 1975, and for 32 cases registered between 1976 and 1987; among cases with known age, approximately 60% of cases were between 50 and 70 years of age, with little difference between men and women. Cases incident in 1976–1987 were older at registration than cases incident in the earlier period ($p < 0.001$). In 1965–1975, 62% were 50 years and older; in 1976–1987, 79% were over 50 years old. Deleted cases did

Table 2. Registered cases of Balkan endemic nephropathy in Vratza district, Bulgaria in 1964, 1965–1975, 1976–1987, and 2000, by sex and age

	Population-based registers in 22 communities						Vratza district hospital	
	Prevalent in 1964		Incident 1965–1975		Incident 1976–1987		Prevalent in 2000	
Age at first registration (years)	Male N = 148 (%)	Female N = 257 (%)	Male N = 277 (%)	Female N = 379 (%)	Male N = 150 (%)	Female N = 162 (%)	Male N = 33 (%)	Female N = 81 (%)
<30	1.4	1.6	0.4	2.1	0.0	0.0	0.0	1.2
30–39	9.5	10.1	6.9	7.7	2.2	0.7	6.1	23.5
40–49	20.3	21.0	24.9	26.9	17.7	20.1	24.3	22.2
50–59	35.1	31.5	30.3	26.9	35.3	34.7	45.5	28.4
60–69	25.7	28.0	27.4	25.9	29.4	32.6	18.2	14.8
70+	8.1	7.8	10.1	9.8	15.4	11.8	6.1	9.9

Age was unknown for three women registered 1965–1975 and 18 women registered 1976–1987, and for 14 men registered 1976–1987. Percentages in table were calculated after excluding individuals with unknown ages.

not differ from retained cases with respect to sex and age.

There was considerable variation in prevalence and incidence across the villages (Table 3). Overall prevalence in the affected villages was 6.0 per 1000 in 1964, and incidence rates fluctuated between 0.4 and 1.2 per 1000 from 1965 to 1987, with a clear decreasing trend over time. In the period 1965–1975, the average incidence rate was 0.7 per 1000 per year, and in the period 1976–1987 it had decreased to 0.3 per 1000 per year (rate ratio 0.43; $p < 0.001$). Incidence was much lower in Vratza town; among village residents, the period-specific rates were 1.7 and 0.8 per 1000 per year, respectively (rate ratio 0.47; $p < 0.01$).

Dates of death were noted for 83.2% of the 1191 cases retained in the registers. The distribution of times to death following registration is displayed in Figure 1. Among cases prevalent in 1964 median time to death was 3.0 years, among cases incident in 1965–1975 it was 2.0 years, and among cases incident in 1976–1987 it was 5.0 years (log–rank test, 2 d.f., $p < 0.001$). Survival patterns did not differ notably between men and women.

Prevalent hospital cases

The age–sex distribution of the 114 patients receiving care at the District Hospital are provided in Table 2. There were 2.5 times as many women as men. As a group, they were younger than the patients included in the registers. The median period since diagnosis was 15 years. Among 59 prevalent hospital cases diagnosed prior to 1987 and living in a village with a BEN register at the time of diagnosis, only eight could be matched to individuals listed in the respective register.

Discussion

Our data suggest that the incidence of BEN declined by 50% between 1965–1975 and 1976–1987 in Vratza District, Bulgaria. If true, our findings suggest that the epidemic of this disease, which is thought to have appeared in the late 1940s and was first described as a separate clinical entity in this region in 1956 [1], may have peaked sometime in the late 1960s and incidence has decreased since then.

Our data are consistent with those of Cukuranovic et al. [16], who studied a region of Yugoslavia during the period 1987–1997. There have been few other rigorous epidemiologic studies of BEN; most authors appear to cite incidence and prevalence data from the 1970s. Much of the focus in recent years has been the attempt to relate patterns of disease to selected environmental factors, usually at an ecological or geographical level.

Our study is limited by constraints of the data available to us. BEN is an elusive condition, with imprecise diagnostic criteria. Several other conditions, including hypertension and diabetes mellitus, also predispose to renal failure, so careful workup of suspected cases is required to establish the diagnosis. The registers contain no clinical data, therefore no retrospective confirmation of diagnoses is possible, either for cases deleted from the registers or those retained. However, all registers were maintained in one district hospital which provided services to the whole region. It is therefore likely that diagnostic criteria remained consistent for this surveillance period, although diagnostic drift is certainly possible and could account for changes in survival patterns.

It is possible that the reduced incidence that we observed resulted from reduced intensity of case finding during the more recent period. We lack any data to address this concern directly, although we were struck by the higher proportion of individuals in the latter part of the registry for whom age was not known, suggesting less intensive monitoring. We are concerned that we were unable to match in the registers a majority of the patients receiving care at the District Hospital in 2000 who should have been registered based on a reported year of diagnosis prior to 1987. This suggests that these individuals were not ascertained via village-based surveillance, and that the various ascertainment methods may not have been cross-referenced. It is also possible that the cases prevalent in 2000 represent a different form of the disease, given their very long survival and the marked preponderance of women in the prevalent series. Arguing against a deterioration of the surveillance system is our observation that the annual update was maintained consistently for cases who were identified in the villages, with no evidence of increased losses to follow-up. Thus follow-up of registered cases continued with the same rigor (although there may have been a reduced focus on identification of new cases). The age of incident cases increased between 1965–1975 and 1976–1987, suggesting that cases were being identified at a later age, consistent with less aggressive case finding and screening. However, median time to death following registration was longer among cases identified in the later period, arguing that these later cases do not appear to be weighted towards a later stage of the disease, as might be expected if active surveillance were scaled back.

The longer life expectancy for cases diagnosed in the periods 1976–1987, and the long median survival among cases prevalent in 2000 might also be due to the better treatment of BEN [17]. A district dialysis unit was opened in 1972 [14]. It might represent a staging effect, as a result of earlier detection. It may also reflect changes in diagnosis, with a higher proportion of severe nephropathies being classified as diseases other than BEN (e.g., end-stage renal disease consequent to diabetes mellitus) in more recent years. It is important to note that any prevalent series will always be biased towards those with longer survival,

Table 3. Prevalence in 1964, and incidence rates (both per 1000 population) 1965–1987, for cases of BEN, Vratza district, Bulgaria, by village of residence

	Prevalent cases in 1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1965–1975	1975–1987
Beli Izvor	57.6	2.2	4.4	9.9	7.0	2.7	6.8	1.7	5.9	7.0	7.5	6.7	3.7	5.3	6.2	3.1	4.0	5.8	0.8	3.5	0.9	0.9	0.9	0.0	5.5	2.4
Bistretz	41.2	1.6	1.6	7.9	4.7	9.2	5.3	4.5	4.4	5.1	2.1	5.7	1.4	2.1	4.1	1.3	2.0	0.7	4.5	1.3	3.8	0.6	0.6	0.0	4.7	2.3
Brusen	8.5	1.8	3.6	1.8	0.0	3.6	1.8	1.8	0.0	0.0	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0
Darmantzi	5.6	0.0	1.5	0.0	3.0	1.5	3.0	0.0	0.0	1.5	0.0	0.0	0.0	1.6	0.0	0.0	0.0	0.0	0.0	0.0	1.9	1.9	0.0	0.0	1.0	0.4
Goliamo Babino	4.7	1.3	2.5	0.0	0.0	0.0	5.6	0.0	1.4	0.0	0.0	0.0	3.0	0.0	0.0	1.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.4
Goliamo Peshtene	2.3	1.2	3.8	5.3	2.7	0.7	0.7	1.5	2.3	0.0	0.8	2.5	0.0	1.8	0.9	2.9	2.0	1.0	1.1	2.2	0.0	1.2	0.0	0.0	2.0	0.9
Gorno Peshtene	26.7	2.4	5.1	7.9	1.8	0.9	2.0	2.0	3.0	3.1	6.3	4.2	2.2	3.3	3.4	4.7	3.6	3.7	1.3	2.6	4.1	2.8	1.5	1.5	3.5	2.5
Hubavene	54.9	10.0	3.9	28.5	4.2	2.9	7.5	3.0	0.0	2.9	8.8	1.5	7.5	4.6	6.2	3.2	8.1	5.0	1.7	3.5	7.2	1.8	0.0	0.0	6.8	3.9
Kalen	48.4	0.0	2.0	12.7	2.2	6.8	2.3	2.4	0.0	0.0	5.6	0.0	3.0	3.2	0.0	0.0	3.9	3.9	0.0	0.0	3.8	0.0	0.0	0.0	3.2	1.1
Karash	26.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.8	0.0	0.0	0.0	0.0	0.0	0.0	17.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	1.0
Kravoder	3.3	0.5	1.0	2.5	2.6	0.0	0.0	2.2	1.1	0.0	0.5	1.1	1.1	0.0	1.2	0.6	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0	1.1	0.3
Kunino	0.0	0.0	0.0	0.0	0.0	0.0	3.2	0.0	0.7	0.0	0.7	0.0	0.0	0.0	0.7	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.1
Liliache	0.0	0.8	0.4	0.0	0.0	0.0	1.6	0.0	0.5	0.0	2.0	0.5	0.0	0.0	0.0	0.5	0.6	0.6	0.0	0.5	0.5	0.0	1.0	0.0	0.5	0.3
Mezdra	0.8	0.1	0.4	0.4	0.6	0.4	0.3	0.3	0.2	0.2	0.2	0.1	0.2	0.1	0.1	0.0	0.2	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.3	0.1
Pudria	20.5	0.6	0.7	8.3	13.0	0.8	1.6	2.3	3.9	1.5	0.8	3.8	1.6	1.6	1.6	0.8	1.7	1.8	0.9	0.0	0.9	1.9	1.0	0.0	3.4	1.1
Radovene	15.0	1.2	2.5	9.1	1.4	0.0	3.0	0.0	1.5	1.5	3.1	0.0	1.6	1.6	3.3	0.0	0.0	3.5	1.7	0.0	1.8	0.0	3.6	0.0	2.2	1.3
Roman	7.8	2.1	0.7	5.2	2.8	0.0	0.7	0.3	0.3	1.3	0.7	0.6	1.6	1.6	0.0	1.3	1.3	0.6	1.4	0.5	1.2	0.5	0.0	0.0	1.3	1.0
Tsakonitza	72.6	7.6	3.9	20.3	12.7	4.4	4.6	4.9	5.2	8.4	9.0	3.3	0.0	7.0	3.6	0.0	3.9	8.0	8.3	0.0	4.4	9.2	4.7	0.0	7.9	2.7
Vesletz	0.0	2.1	4.2	0.0	0.0	0.0	6.8	0.0	0.0	5.4	2.9	0.0	6.2	3.1	0.0	0.0	0.0	0.0	0.0	4.1	8.9	0.0	4.9	0.0	1.9	1.6
Vlasatitza	0.0	1.4	2.7	0.0	0.0	0.0	4.3	0.0	0.0	3.0	1.5	0.0	3.2	1.6	0.0	0.0	0.0	0.0	0.0	1.9	3.9	0.0	2.1	0.0	1.2	0.9
All villages with registers	12.3	1.2	1.5	4.2	2.4	1.1	1.8	1.0	1.4	1.3	1.5	1.2	1.0	1.0	1.0	0.8	1.0	0.8	0.7	0.6	0.9	0.5	0.3	0.0	1.7	0.8
Vratza	0.4	0.3	0.2	0.1	0.0	0.0	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.1	0.1
All registers	6.0	0.7	0.7	1.9	1.0	0.4	0.7	0.4	0.6	0.5	0.6	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.2	0.3	0.1	0.1	0.0	0.7	0.3

Incidence rates could not be calculated for Tishevitza due to absence of population estimates.

and hence true median survival is probably still lower than that observed for the prevalent cases, but we cannot establish the true distribution of survival times with certainty. In the absence of unambiguous diagnostic criteria it is unlikely that the reason for the changes in survival following diagnosis will be easily resolved. In this context, we note the report by Bukvic et al. [18], who found that mean survival in their patients exceeds 10 years, far greater than the 2–3 years reported in earlier descriptions of the disease [14].

Overall, the population in the villages (excluding Vratza) was stable (Table 1). However, it is important to note that the population of the eight villages that had a prevalence of 25 cases (or greater) per 1000 inhabitants in 1964 (Table 2) lost about 36% of their population over the study period (from n = 7678 to 4901), while that of Mezdra increased proportionally. This might indicate that a redistribution of the population of BEN-villages occurred (including current and potential future cases); this likely reduced the prevalence and incidence of the disease in the BEN-affected villages. In this regard, the systematic transfer of the population of Karash is noteworthy. The implications of these population transfers to previously BEN-free areas depends on the true underlying etiology. If the cause is related to a localized environmental exposure and indeed out-migration reduces risk, then we would expect incidence in the areas to which these people moved to remain low. If, however, the etiology is viral or genetic, then we might expect to have seen the emergence of BEN in areas previously free of the disease. While we are unaware of new cases of BEN occurring in other regions of Bulgaria, surveillance of the out-migrating population is required to address this question thoroughly.

We conclude that the incidence of BEN declined in the late 1970s and 1980s in the endemic region of Bulgaria, while survival of identified cases increased over the same period. Studies designed to identify etiologic factors need to take declining incidence into consideration in order to identify candidate factors and develop studies with adequate power to test hypotheses. There is also a need for additional epidemiological studies, including clinical examination of apparently healthy individuals using objective diagnostic criteria, to increase our confidence that the decrease in incidence is indeed occurring throughout the BEN endemic region.

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