

THE SIGNIFICANT INCREASE IN INCIDENCE OF GRAVES' DISEASE IN EASTERN SERBIA DURING THE CIVIL WAR IN THE FORMER YUGOSLAVIA (1992 TO 1995)

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INTRODUCTION

The incidence of hyperthyroidism (autoimmune or not autoimmune), is influenced by numerous geographic, social, racial and other factors (1-5). It is expected that a population of the same region in a limited period of time should have a relatively constant incidence of hyperthyroidism. Some eventual changes in factors such as iodine prophylaxis in regions of severe iodine deficiency would certainly influence this constancy (6,7). This article reports the annual increase in the number of newly diagnosed Graves' disease patients (the most frequent form of hyperthyroidism) in the region investigated.

METHODS

The continuous registration of all newly diagnosed patients presented annually for each year from 1971 to 1996, for separate counties of Timok Region and for the whole region, was used for this evaluation. Numbers are also presented as standardized incidence (per 100,000 citizens)(8). For better understanding, some geographic and population data are presented.

Graves' disease was diagnosed using routine clinical (diffuse goiter with hypermetabolic signs) and laboratory findings (high thyroxine and triiodothyronine levels in blood) performed by standard RIA. In some cases where a hypermetabolic state was not clearly found, supplementary methods were used: FT₄, FT₃ and ultrasensitive TSH (Delfia Farmacia) or TRH test (9). In a majority of patients (in all patients without ophtalmopathy or in cases where TSH-receptor antibodies were not tested) ¹³¹I and ^{99m}Tc thyroid uptake (10) and thyroid scintiscaning were performed. Toxic adenoma was diagnosed by scintigraphy of the thyroid and visualisation of suppressed paranodular tissue by TSH stimulation (11), or since 1988 by ultrasonography. From 1986 to 1991, TSH receptor autoantibodies were tested by TRAK-Assay, Henning (12) and from 1992 to 1994 thyroid-stimulating antibodies (TSAb) were tested by cyclic adenosine monophosphate (cAMP) generation in porcine thyroid cell suspension (13,14).

RESULTS

The Timok Region is a geographic entity in eastern Serbia (Yugoslavia). The northern border of the region is the Danube River (borders Romania); the eastern border with Bulgaria is the Balkan Mountain; the southern border is the Tresibaba Mountain, which separates Timok Region from the Region of Nish; the Kucaj Mountains separate the region from central Serbia. The Timok Region consists of seven counties. In 1971, the region was united with the City

Center of Zajecar, and in 1992, it was divided into two regions (Zajecar Region and Bor Region). In Figure 1, geographic data, population and territorial organization of Timok Region are presented.



FIG. 1. Geographic data, population, and territorial organization of Timok Region.

In the period investigated, all diagnosis, therapy and clinical control of practically all thyroid patients from the Timok Region were performed in the Service for Nuclear Medicine in Medical Center in Zajecar. In the last few years, some patients were treated in Medical Center Bor, but the diagnosis and registration of the patients was still performed in Medical Center in Zajecar.

The total number of annually registered Graves' disease patients for the integral region and central Zajecar County are presented in Figure 2.

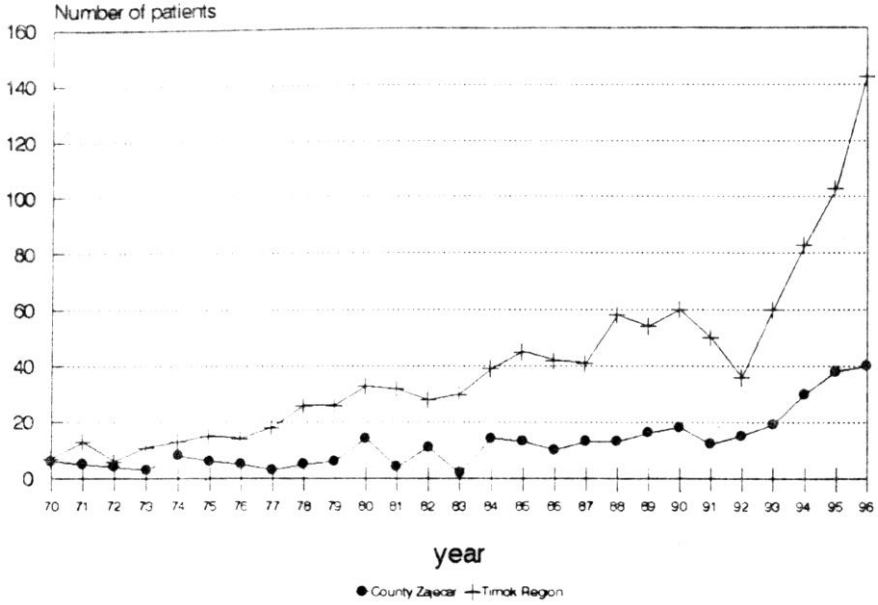


FIG. 2. Number of annually registered patients with Graves' disease for Timok Region and County Zajecar.

The standardized incidence (number of newly diagnosed patients per 100.000 people) for the Timok Region and Zajecar County is presented in Figure 3.

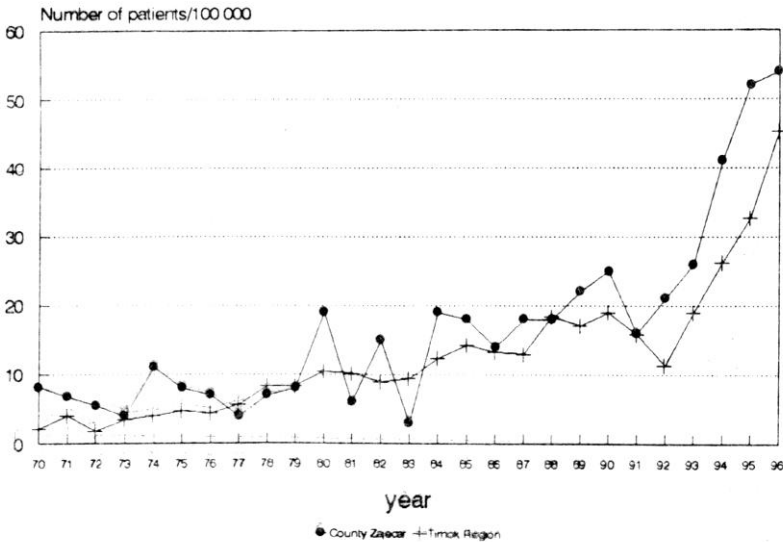


FIG. 3. Standardized incidence (number of newly diagnosed patients per 100,000 people) of Graves' disease for Timok Region and County Zajecar.

The possible influence of the quality of the registration technique on incidence of Graves' disease is presented by comparative incidence of toxic adenoma (Plummer's disease) in Figure 4.

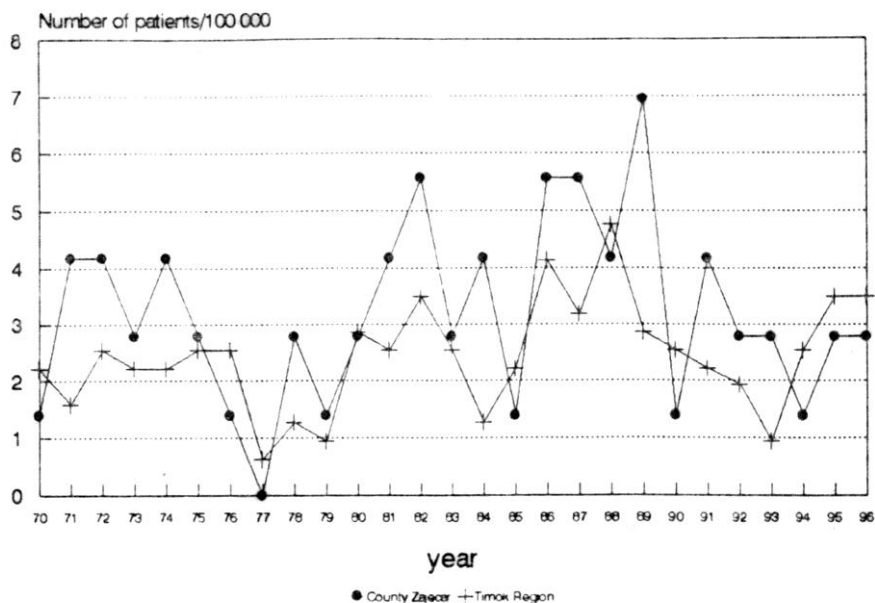


FIG. 4. Standardized incidence of toxic adenoma (Plummer's disease) for Timok Region and County Zajecar.

DISCUSSION

The incidence of Graves' disease in the first decade of investigated period (1971 to 1980) was relatively low (8 per 100,000 people per year for Zajecar County and 5,56 per 100,000 people per year for Timok Region). In the second decade, the incidence doubled (15,8 and 11,7 respectively), with a decline in 1992 and increase of the number in 1995 and especially in 1996 (55 per 100,000 for Zajecar County and 45,3 for Timok Region). The low number of newly registered Graves' disease patients from 1971 to 1980 was due mostly to organizational limitations. The Nuclear Medicine Service in Zajecar, where all registrations are performed, was established in 1970, but the integrity of diagnostic and therapy procedures was not established until the middle of that decade. In the second half of next decade (1986 to 1990), all medical institutions in the region were united in one single institution and registration of patients improved. However, the number of registered patients from Zajecar County not influenced by organizational changes had the same tendency to increase. The decrease in number of registered patients in 1992 is understandable. The United Nations sanctions against Yugoslavia limited materials for diagnosis and disabled the majority of civil transport, so patients did not have opportunity for medical service.

The extreme increase in incidence of Graves' disease during 1995 and 1996 is difficult to explain. This increase is genuine and not a consequence of, for example, improved registration. The incidence of Plummer's disease did not increase for the same period. This was not due to increase in some other forms of hyperthyroidism such as silent thyroiditis. Practically all newly

diagnosed patients with hyperthyroidism were tested for TSH-receptor antibodies or by radioactive uptake tests (10).

The complexity of factors that influenced the population in the period between 1990 and 1996, and maybe even earlier, should be studied very systematically. The political and economic situation characterizing this period was difficult: desintegration of the former Yugoslavia; war in Bosnia and Herzegovina with significant impact on the population in Serbia where a majority of the people were influenced by the war. Economic destruction with catastrophic inflation should be emphasized. It was a period of prolonged stress for the entire population, a controversial trigger factor for Graves' disease in numerous reports (1,15-17).

The iodine intake is also significant factor for consideration. During the period investigated, many table salts of different origins were used for human and animal consumption, often lacking any information about the content of iodine. In Timok Region, iodine deficiency was never distinct, and iodine prophylaxis was continuously performed by iodination of table salts (10 mg KI per kg of NaCl) since 1953 (18,19); and from 1993 iodination was increased to 20 mg KI/kg NaCl (20). Unfortunately, »official« table salt was not always available in the period 1992 to 1995, and often was more expensive than imported salts of unknown origin or iodine content (usually higher than 30 mg KI/kg). Correction of mild iodine deficiency in this region should not have such influence on the significant increase in incidence of Graves' disease (21). The lack of increase in incidence of Plummer's disease, reduces the significance of iodine intake in the increase of Graves' disease influence (6).

The Chernobyl accident is also a factor that requires further analyses, considering the reports on the effect of low radiation doses incidence of thyroid diseases (22). Reports on the effects of much higher absorbed doses on population did not report an increase in Graves' disease incidence (23).

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