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Original Contribution

STUDY OF THE INCIDENCE AND FORMS OF DOWN SYNDROME IN STARA ZAGORA REGION

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ABSTRACT
PURPOSE: To perform a retrospective study of the prevalence of Down Syndrome (DS) in the region of Stara Zagora, Bulgaria, for a 15 year period (1993-2007). METHODS: Various sources of information concerning birth rate in the years under investigation are explored. DS was confirmed cytogenetically examining both child and parents. The data was processed using standard statistical methods. RESULTS.50967 live born children are registrated in our region for the period 1993-2007. 37 unrelated children were cytogenetically confirmed with DS. This forms a general incidence of 1:1377 live born children. Three peaks of increased incidence are observed (in 1999, 2002-2003 and 2005 years). Among the 37 cases, 16 (43%) are females and 21(57%) are males, with a females/male ratio of 1:1.3. The regular form of DS is confirmed in 33 (89%) cases, translocation form in 4 (11%) cases. Mosaic form hasn't been observed. Of all women given birth to children with regular DS, 17% are over 35 years. CONCLUSION: This research is the first step of monitoring congenital anomalies and inherited diseases in our region. It is a part of the National Program for Orphan Diseases and Genetic Disorders in Bulgaria.

Key words: live birth prevalence, inherited diseases, genetic counseling

INTRODUCTION

Down Syndrome (DS) is one of the widely spread chromosomal diseases. It was first described in 1866 by J. Langdon-Down. The etiology of the disease was determined in 1959 by Lejeune et al. with the discovery of an additional 21 chromosome in the chromosome set of the affected children. It is proved that the disease develops in the presence of an additional whole or partial 21 chromosome in all somatic cells of the organism (full form) or only in part of the cells (mosaic form of DS). The clinic of the full form combines manifestation of dysmorphism, malformations and delay in the psychosomatic development. Three cytogenetic forms of DS exist: free or regular form (consists of about 95 % of the cases), translocation form (3-4%) and mosaic form (1-2 % of the cases) (1). DS is one of the most intensively studied genetic disorders. Many epidemiologic studies have investigated the occurrence of the disease in different countries or country regions (2-8). In the Region of Stara Zagora such investigation has never been carried out, even though in the Department of Molecular biology, immunology and medical genetics of the Medical Faculty a Medical-genetic center has been functioning for a long time. It incorporates a cytogenetic laboratory for chromosome analysis, which meets the needs of all patients from South-East Bulgaria (regions of Stara Zagora, Sliven, Jambol and Burgas). In this respect we aimed to perform a retrospective study. Its goal is to determine, compare and analyze the incidence, distribution of DS, the frequency of different

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cytogenetic forms, sexual distribution and other parameters of the disease in the region of Stara Zagora for a period of 15 years (1993-2007). Results of the study would be very valuable when implementing the biochemical screening program for DS and neural tube defects in all pregnant women in our region. This activity is part of the National Program for Orphan Diseases and Genetic Disorders in Bulgaria.

MATERIALS AND METHODS

All the data concerning the new-found cases of DS in Stara Zagora region for the 15 year period were collected from the data base of the Medical Genetic Consulting Center and the Neonatal Intensive Care Unit of the Regional Hospital "Prof. St. Kirkovich" in Stara Zagora. In all cases the diagnosis of DS was confirmed by cytogenetic analysis of lymphocyte culture of both child and parents. Medico-genetic consultation was also offered to concerned relatives.

The data for the cases of DS in other regions of Bulgaria or other countries was derived from the EUROCAT Website Database: <http://www.bio-medical.co.uk/eurocatlive>. EUROCAT is the European network of population-based registries for the epidemiologic surveillance of congenital anomalies. In most of the countries members of EUROCAT, in addition to an invasive prenatal diagnosis, a mass biochemical screening for DS is performed. In these countries or regions a number of terminated pregnancies due to prenataly confirmed DS is reported. It is obvious that in these regions the incidence of DS in live-born children will be lower. In Stara Zagora region, during the period of investigation, mass screening of pregnant women for DS and neural tube defects has not been conducted. Therefore we have compared our data with such regions or countries which also lack screening programs, or termination of pregnancy is not performed due to other reasons. In Dublin (Ireland); Galway (Ireland) and Malta terminations of pregnancy for fetal anomalies is illegal, and we have used their data for comparison. There is data from Sofia region (Bulgaria) for a 4 year period (1996-1999) which is very eligible for comparison. Another nearby region is Zagreb (Croatia) whose DS related data is also used in our study. Because of the lack of reliable data presenting the number of deliveries in our region for several years (1993-1995, 1997, 1999) comparative analysis for these years was not possible. Information concerning the number of live born children is derived from several sources:

- Electronic database of the Statistical Issue – Stara Zagora http://www.chambersz.com/statistic/2006/.
- For the year 2006 - from the electronic issue "Public health statistics, Bulgaria 2006, Annual" of the National Center for Health Information http://www.nchi.government.bg/elizdania.html.
- For the year 2007 - from the National Statistical Institute Database http://www.nsi.bg/Population/PopIncrease07.htm
- For the annual number of live born boys and girls in Stara Zagora and Sofia (1996-2004) – from the website of the International health Institute and National Center for Health Information: http://www.zdrave.net/MIZZO/Statistics/Default.aspx?evntid=5604
- For the number of deliveries in Stara Zagora region – from the website of the Regional Center of Healthcare –Stara Zagora http://www.rczstarazagora.org

Microsoft Office Excel® 2003 was used for processing the data and drawing the figures.

RESULTS AND DISCUSSION

For the investigation period (1993-2007), 50 967 live born children were registered in Stara Zagora region. Among them in 37 nonrelated children DS was clinically diagnosed and cytogenetically confirmed. The live birth prevalence of DS in Stara Zagora is 0,73 ‰ (0,73 among 1000 live born) or 1:1377 live born children. The world population incidence of DS is 1:900 -1:700 live born (1), so our data for Stara Zagora region showed incidence 1,5 to 2 times lower than the world one. It was also lower when compared with the incidence for Sofia (1996-1999 years) **(Fig. 1)**, as well as in the comparative analysis with other countries and regions **(Fig. 2)**.

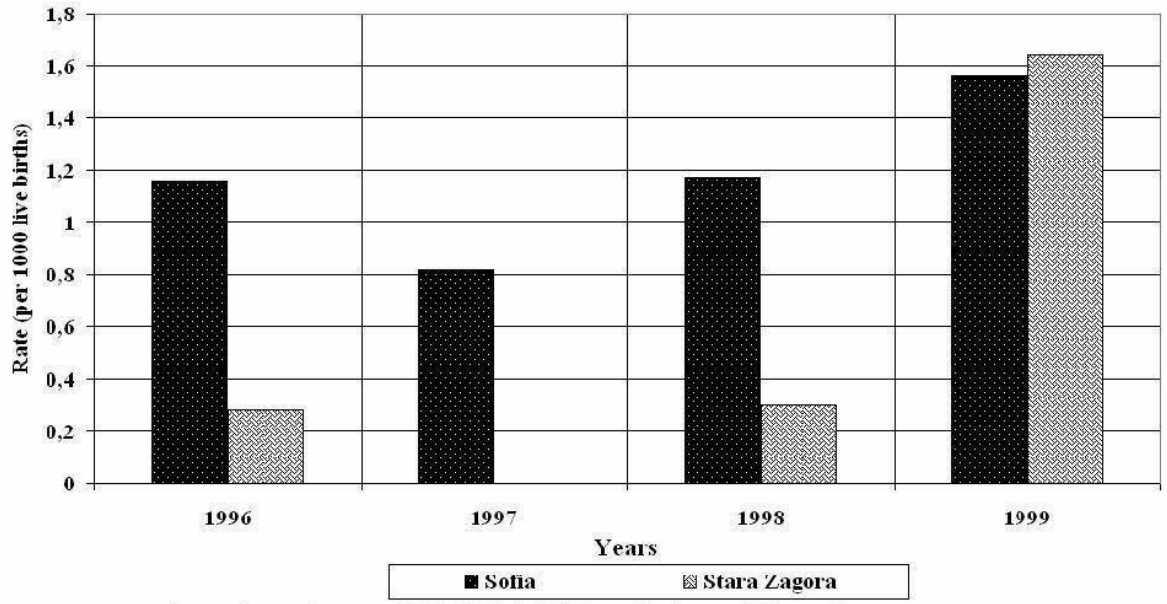

Figure 1. *Annual incidence of DS (1996-1999) in Sofia and Stara Zagora region*

A much lower incidence of DS in Stara Zagora compared to Sofia was seen for the years 1996, 1997 and 1998. In 1999 an extremely high number of cases in Stara Zagora was observed, which exceeded the incidence in Sofia and shaped the first peak in our investigation discussed later.

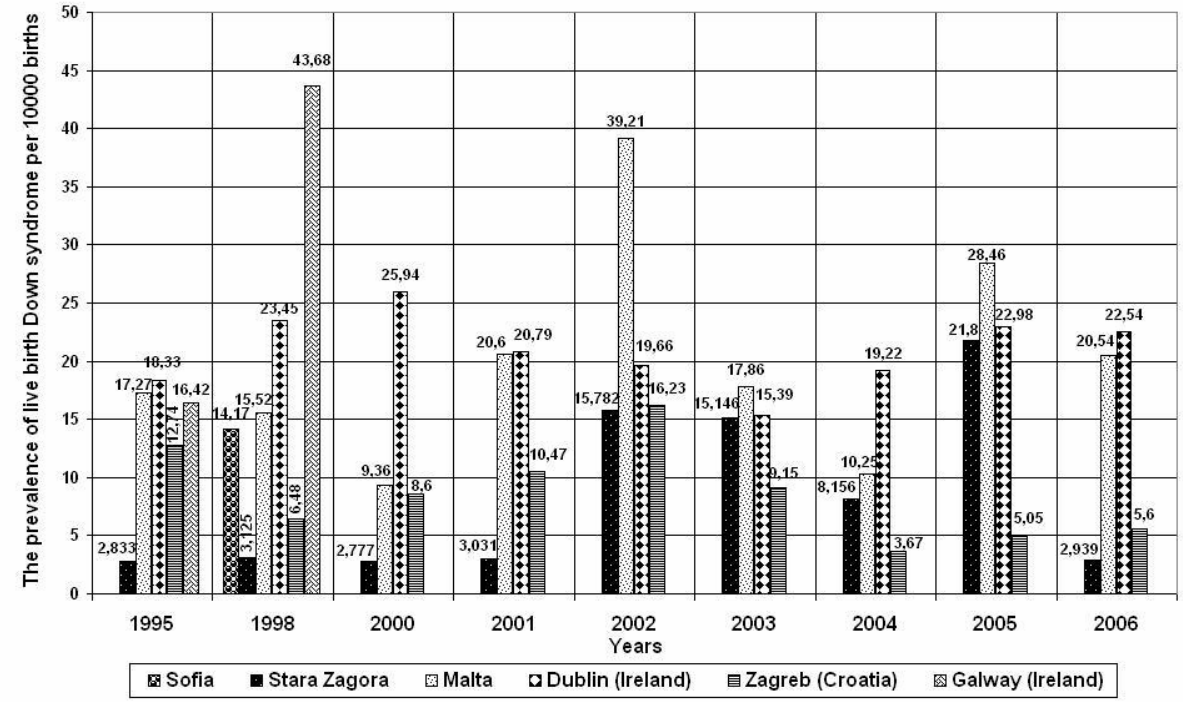

Figure 2. *Incidence of DS in different countries and regions*

For all the years indicated in Fig. 2 the incidence of DS in Stara Zagora was lower compared to Malta and Dublin, as well as Galway - for 1995 and 1998. Comparison of the data between Stara Zagora and Zagreb is difficult. Since 1998 cases of terminated pregnancies after prenatal diagnosis have also been documented in Zagreb. This might explain the lower incidence of DS in live born children. Despite the cases of terminated pregnancies after prenatal diagnosis, Zagreb had lower incidence of DS than ours only for the following years: 2003, 2004 and 2005.

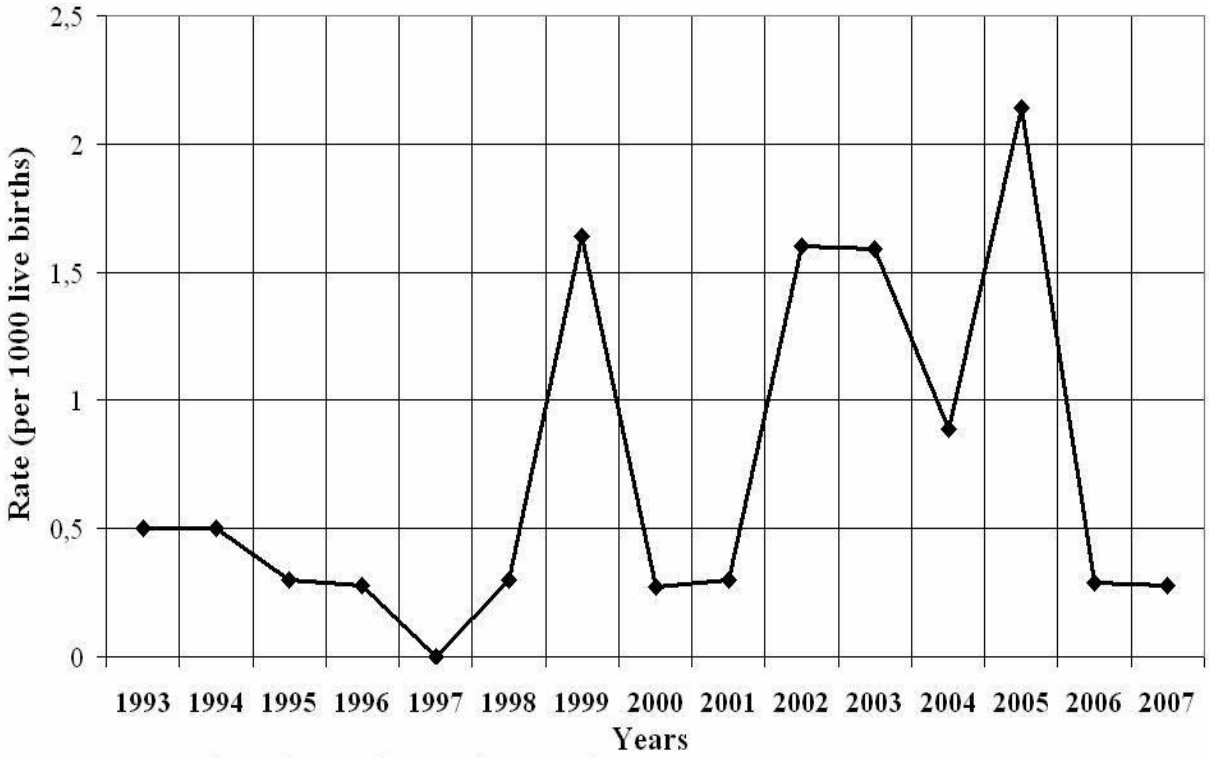

Figure 3. *Annual incidence of DS in the period 1993-2007 years.*

The incidence of DS in Stara Zagora varied between 0‰ (1997) to 2,14 ‰ (2005). Having a background of relatively stable frequency during the years, three peaks of increased incidence were observed. Two of them (1999 and 2002-2003 years) were with a twofold rise above the average. The third was in 2005 with a nearly threefold rise (2,93 times higher). Increased frequency of DS in single years of the observed period had also been documented in other countries and regions: Malta (1999, 2002 and 2005 year); Zagreb (1999 and 2002 year) and could be partially seen in Fig. 2. These observations confirm the discussed in literature periodical or cyclic change of population incidence of DS (2, 3, 4). Nowadays it is accepted that DS has multifactorial etiology (2, 3, 5), with influence of global and local environment factors. (3, 5). Numerous studies have already examined its associations with deferent environmental factors such as ionizing radiation, hepatitis, smoking, coffee drinking, contraceptive spermicides, etc. Certain chemicals, e.g., trichlor-phon can cause non-disjunction errors leading to trisomy of the chromosome 21 (6).

In 1995 an article on the topic was published. It showed a highly significant association between prevalence of DS and radiation from fallout produced by atmospheric testing of atomic weapons. (7). Ginsburg B. discusses the frequency of DS in several regions of Russia, Belorussia and Germany. He stated the necessity of widespread investigation and monitoring of the adverse (teratogenic and mutagenic) factors in the environment. This should be done in conjunction with the forms and incidence of the congenital malformations (3). Such parallel investigations are very important for our region because there has been an increase of hazard environmental factors (both anthropogenic and natural) in Stara Zagora in recent years.

The variation of the incidence of DS may be due to the limited size of the study and other factors.

From all 37 cases of DS 16 (43%) were females and 21 (57%) were males, with a proportion females to males ratio of 1 : 1.3. This observation completely corresponded with the results of other investigators - 1: 1,52 (8), 1:1,28 (2), 1:1,30 (9), 1:1,15 (10). The male sex predominance was evident.

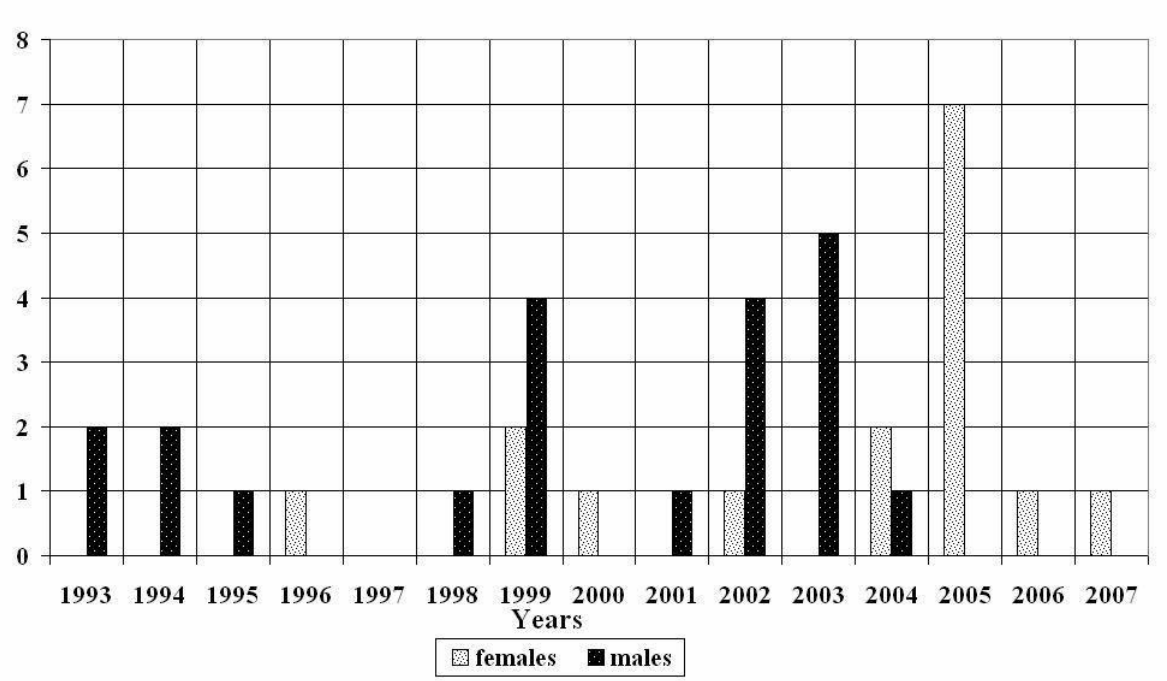

Figure 4. *Sexual distribution of the newborn children with DS in different years.*

An interesting finding of our study is that predominance of male sex was up to 2002, with a sharp rise in the number of affected females with DS later. This finding may be due to the relatively small number of cases in the different years. In order to define it, a longer period of time and bigger sample size is needed in connection to the findings of other authors.

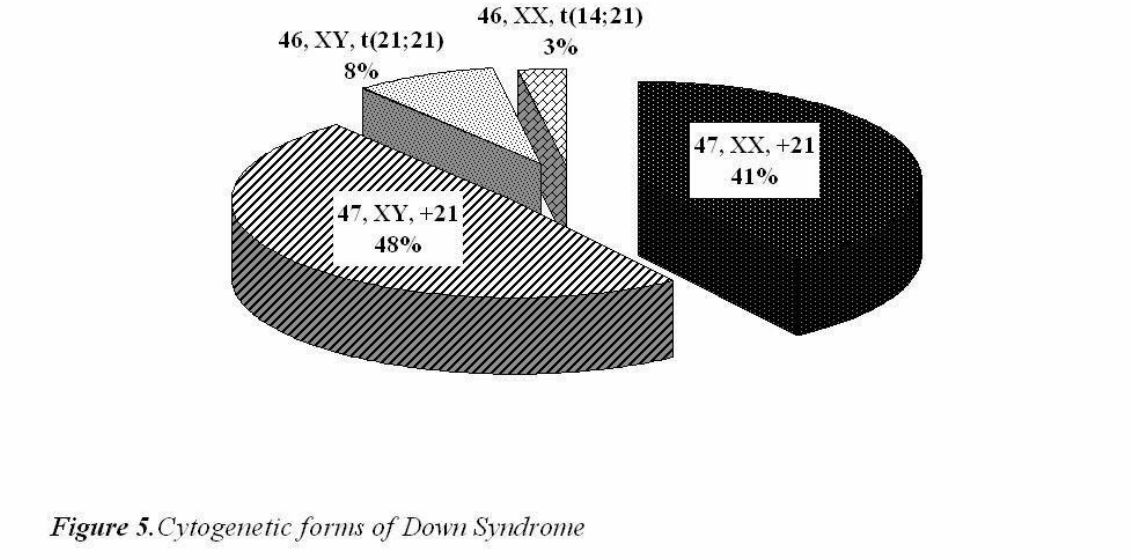

Figure 5. *Cytogenetic forms of Down Syndrome*

The regular form of DS was confirmed in 33 (89%) cases, translocation form in 4 (11%) cases, three of them t (21; 21) and in one t (14; 21). We did not observe mosaic form for the 15 year period.

Well known and extensively discussed is the connection between the risk of delivering a child with regular DS and mother's age. In our study the women over 35 years constituted 17% of all women delivered children with regular DS.

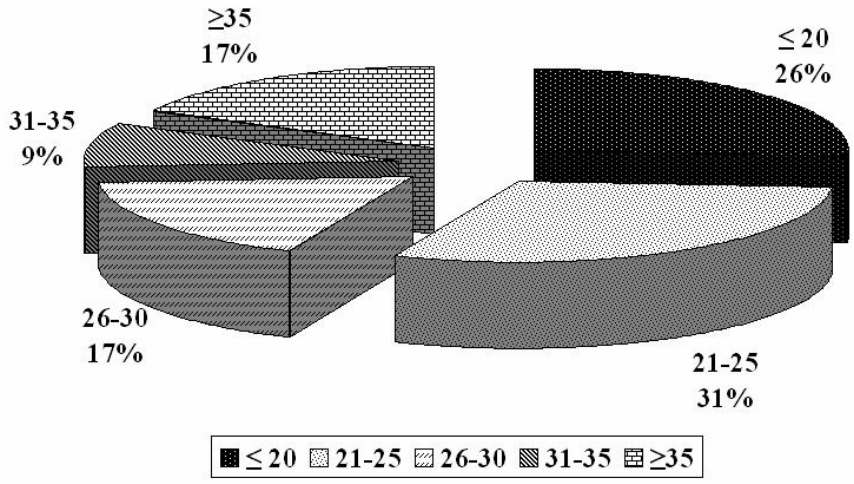

Figure 6. *Age structure of women, given birth to children with regular Down Syndrome*

The data concerning different cytogenetic forms of DS and the age structure of the mothers is very helpful when organizing the biochemical screening program for DS and neural tube defects. It would help medical-genetic consulting and prenatal diagnosis to define more precisely the risk of a chromosome aberration in the offspring.

CONCLUSION

This study gives the contemporary information about the incidence of DS among the live-born children in our region. It also describes the ratio of different cytogenetic forms as well as the age structure of mothers delivered children with DS. This research is the first step to monitoring of congenital anomalies and inherited diseases in our region. It has to be connected with the monitoring of teratogenic and mutagenic factors in the environment. Last but not least, this study would enable health authorities to be more precise in the organization and planning recourses for medical-genetic counseling and invasive prenatal diagnosis.

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