Increasing total prevalence rate of cases with Down syndrome in Hungary

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Abstract. Recently the population-based large data set of the Hungarian Congenital Abnormality Registry showed an increase in the recorded total (birth + fetal) prevalence rate of informative offspring with Down syndrome. This finding was checked and confirmed in the completed data set due to the field study including all cytogenetic labs and prenatal diagnostic centres. The previous birth prevalence of 1.17 per 100 in the 1970s increased to 1.50 per 1000 between 1989 and 1999 with a maximum 1.77 in 1992. The completeness of the Registry was only 65.9% between 1970 and 1999, i.e. 30 years. One-third of cases had not been karyotyped, however, this figure is now about 10%. The major explanation of this increase is the significantly higher proportion of prenatally diagnosed fetuses with Down syndrome and an increasing number of women over 35. In addition better ascertainment may also contribute to this increase, but new etiological factors cannot also be excluded.

Key words: Advanced maternal age, Ascertainment, Down syndrome, Increasing prevalence, Prenatal diagnosis

Introduction

Down syndrome (DS) due to trisomy 21 may be the result of germinal aneuploidy or a chromosomal mutation [1]. The additional chromosome 21 arises most commonly as a result of non-disjunction in maternal meiosis I [2]. The familial full trisomy 21 is so rare that these cases are considered as an exception to a rule. Robertsonian translocations account for approximately 3% of all cases [3], and about two-third of these cases had parents with normal karyotype, i.e. Down syndrome is a consequence of a new chromosomal mutation. About 2% of Down syndrome are caused by mosaicism due to an error of mitosis after conception [3]. Thus, about 98% of DS are the result of a de novo event [1].

The recent sequencing of chromosome 21 allows the identification of every gene on the chromosome and at least 31 genes are involved in the pathogenesis of DS [4, 5]. Nevertheless, little is known about the etiology of DS [6]. The strongest risk factor is older maternal age [7–8]. Numerous studies have already examined associations with different environmental factors such as ionizing radiation [9], hepatitis [3], smoking [10], coffee drinking [11], contraceptive spermicides [3], etc. Certain chemicals, e.g., trichlorphon [12] can cause non-disjunction errors leading to trisomy 21.

Recently the population-based large data set of the Hungarian Congenital Abnormality Registry (HCAR) showed an increase in the reported rate of cases with DS [13]. The main objective of this study was to determine whether there was a real increase in the total prevalence of DS or it was the consequence of a more complete ascertainment. Thus we have decided to check the completeness of the data set of the HCAR and to supplement it with unreported cases with DS.

Material and methods

A registry of malformed cases was established in Hungary, in 1962 but HCAR has been launched officially in the Department of Human Genetics and Teratology, National Institute of Public Health in 1970 [14]. Notification of congenital abnormalities is mandatory for physicians and most are reported by obstetricians (in Hungary practically all deliveries occur in inpatient obstetric clinics), and by pediatricians (who are working in the neonatal units of inpatient obstetric clinics and various inpatient and outpatient pediatric clinics), in addition by experts of 13 prenatal diagnostic centres since 1984. An autopsy was obligatory for all infant deaths and usual in stillborn fetuses during the study period. Pathologists were asked to send a copy of autopsy report to the HCAR in stillbirths and infant deaths. In addition to the name and address the notified data included the date of pregnancy outcome: livebirth, stillbirth and
elective termination of pregnancy, sex of newborn infants and fetuses, singleton-multiple birth, birth weight-gestational age, maternal age, region of parents's residence. The recorded total (birth + fetal) prevalence of malformed cases, diagnosed from the second trimester of pregnancy through the age of 1 year was calculated for 1000 informative offspring (liveborn infants, stillborn fetuses and electively terminated malformed fetuses). However, the number of electively terminated fetuses was not known during the whole study period therefore the denominator includes only total (live and still) births. Isolated and multiple congenital abnormalities have been differentiated, thus the unit of the HCAR is the affected subject and a case with two or more congenital abnormalities is considered as a multimalformed person [15].

Cases with DS have been classified as a specified multiple congenital abnormality entity. In the first level of registration, a clinical diagnosis was accepted because in general DS is recognizable on the basis of clinical symptoms [5]. A chromosomal diagnosis is recommended in these suspected cases because karyotyping offers a clear-cut confirmation of clinical diagnosis and the type of DS with more accurate recurrence risk estimation for the next pregnancy. Thus, the second level of registration includes the karyotyped cases of DS.

Three extra efforts have been made to supplement the data set of the HCAR in this study.

1. The Hungarian Case-Control Surveillance of Congenital Abnormalities [16] was created in 1980. Cases with isolated and multiple congenital abnormalities (including DS) who were reported in the first 3 months after birth or pregnancy termination were included into this Surveillance.

A postpaid questionnaire and explanatory letter were mailed immediately after the selection of cases to their parents. The questionnaire provides an opportunity (i) to ask mothers to check the accuracy of data previously reported by medical doctors to the HCAR as these are mentioned on each questionnaire, (ii) to complete or revise the previous diagnosis on the basis of recent medical examinations, (iii) to complement our data set concerning paternal age, parental occupation and employment status, birth and pregnancy order, marital status, outcomes of previous pregnancies, family history, (iv) to obtain written informed consent for further registration of personal data and for invitation in possible studies, (v) to obtain the name and address of cases’ pediatrician. The data of recorded cases with DS were checked and supplemented from this source.

2. All cytogenetic laboratories were visited in Hungary, their records were reviewed and the available data set of the HCAR was checked and corrected if necessary, in addition the so-called new cases were added to the data set of the study.

We supposed that all cases with DS had cytogenetic examination, except early lethal cases. In general, unfortunately, the maternal age was not recorded in the records of cytogenetic laboratories and we had no right to contact the parents of these cases.

3. All prenatal diagnostic centres were visited, their records were reviewed and the available data set of the HCAR was checked and revised, in addition new cases were also included to the data set of the study. However, we had no right to contact the parents of these cases.

The demographic data of the Hungarian pregnant population at large (e.g., maternal age distribution) were obtained by the series of Demographic Yearbooks [17].

For the statistical analysis in general the chi-square and z test was used.

Results

Table 1 shows our basic data according to the years of the study period. The recorded number of cases with DS in the HCAR was 3312 between 1970 and 1999. Our extra efforts have resulted in 1714 new cases, therefore the revised number of cases with DS was 5026. Thus, the completeness of the HCAR was 65.9% during the study period. The point is that the recorded rate of DS, i.e., 0.77 per 1000 increased to 1.21 per 1000 due to the study.

The annual revised rate of DS reflects three time periods (Figure 1). The first period covers the first 3 years (1970–1972), particularly 1970, with the rate of DS less than 1.0 per 1000. Obviously these years had an underascertainment on the contrary of the high number of new cases in the revised data set. The second period may represent the previous Hungarian birth prevalence of DS between 1.0 and 1.3 per 1000. These years cover the period between 1973 and 1988 (except for 1984) and between 1996 and 1998 with the usual random fluctuation around 1.1 per 1000. The third period contains years between 1989 and 1995, in addition in 1999 with a higher mean rate of DS which was 1.57 per 1000. The rate of cases with DS was particularly high in 1992 when 1.77 per 1000 was found. The higher figure of 1.50 per 1000 between 1989 and 1999 cannot be explained by chance because it indicates a significant increase ($z = -2.18; p = 0.03$).

Of 5026 cases, 2720 were male and 2306 female, thus the proportion of males was 54.1%. There was no secular change in the distribution of sex during the study period.

Of 5026 informative offspring, 57 (1.1%) were twins. Six twin pairs (i.e. 12 twins) were concordant for DS, while 45 discordant.