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Maternal age and Down syndrome in Southeastern Brazil

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ABSTRACT

The proportion of maternal-age-independent patients estimated among 200 Brazilian Down syndrome children (59.6%) was significantly larger than that of maternal-age-dependent cases (40.4%). The latter proportion is the smallest observed in pertinent literature and due basically to the low mean maternal age of the population analyzed. Based on the remarkable correlation (r = 0.95) between the proportion of maternal-age-dependent patients and the mean maternal age of the general population, a simple predictive equation to estimate the proportion of maternal-age-dependent Down syndrome patients based on the mean maternal age of the general population is suggested in situations where reliable data on the incidence of this syndrome according to maternal age is not available.

INTRODUCTION

The reproductive pattern of Southeastern Brazilian populations has changed considerably since the sixties, due mainly to the current use of oral contraceptives and to sociocultural changes. This drastic alteration can be seen among the Caucasoid women attended in the largest maternity hospital of the city of Campinas, SP, Brazil (Maternidade de Campinas), since the mean number of deliveries per Caucasoid mother was 2.76 in the interval between 1950 and 1965, falling to 1.97 in 1990, while the mean age of these women declined from 26.6 in the 1950-1965 period to 25.5 in 1990 (Beiguelman and Villarroel-Herrera, 1993).

Taking into account that: 1) the rate of Down syndrome increases steeply after maternal age 35 (Penrose, 1954; Renwick *et al.*, 1964; Hook and Lindsjö, 1978); 2) at any maternal age this rate is considered to be the sum of at least two components, one independent of maternal age and another age-dependent (Penrose, 1961), it seems clear that the reproductive changes recently observed may affect the epidemiology of Down syndrome, by decreasing the proportion of maternal-age-dependent patients. Since in our populations we do not have reliable statistics on the incidence of Down syndrome according to maternal age, that could enable us to apply mathematical models such as those used by Lamson and Hook (1980, 1981), we decided to study a sample of karyotyped patients and their mothers, who were compared to an appropriate control.

SUBJECTS AND METHODS

The records of patients with Down syndrome attended and diagnosed at the Departamento de Genética Médica da Universidade Estadual de Campinas (UNICAMP) from 1990 to 1994 were

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reviewed. Almost all patients were born in Campinas or in close neighboring cities (Americana, Amparo, Bragança Paulista, Cabreúva, Capivari, Cosmópolis, Indaiatuba, Itatiba, Itu, Itupeva, Jaguariúna, Jundiaí, Limeira, Louveira, Monte-Mor, Paulínia, Pedreira, Salto, Santa Bárbara D'Oeste, Santo Antônio de Posse, Valinhos and Vinhedo). The data collected included the age of the patients at the day of their ascertainment, their karyotype, the maternal age at the day of delivery and the maternal skin color (Caucasoid or Negroid).

To avoid ascertainment bias, the patients aged three years or more at the time of karyotype analysis were excluded from this study. This reduced the sample to 200 individuals (95 males), among whom 160 were Caucasoids (74 males) and 40 Negroids (21 males). The control group was composed of 1,552 normal children born at the Maternidade de Campinas to women who belong to all socioeconomic classes (1,251 Caucasoids and 301 Negroids), and who may be considered as representative of southeastern Brazilian populations.

RESULTS AND DISCUSSION

As the proportion of Negroid women among the patients' mothers did not differ significantly from that observed in the controls ($\chi^2 = 0.04$; d.f. = 1; $0.80 < P < 0.90$), both groups were analyzed without racial classification. Most of the patients (95% ± 1.54%) exhibited regular trisomy 47 (XX or XY)+21, the remainder being represented by three children with karyotype 46,XX *t*(14*q*21*q*) born to two women, 25 and 28 years old; two patients with karyotype 46,XX *t*(21*q*21*q*) born to a woman 23 years and to another 29 years old; three patients with mosaicism 46,XX/47,XX+21 born to women 22, 25 and 38 years old; and two mosaics 46,XY/47,XY+21 born to women 19 and 23 years old. Both the frequency of mosaics (2.5% ± 1.54%) and of patients exhibiting Robertsonian translocations (2.5% ± 1.54%) are included in the expected ranges mentioned in pertinent literature (Beiguelman, 1982).

Table 1 and Figure 1 show the percentage distribution of Down syndrome and normal children, according to maternal age. As expected, the mean maternal age of these patients was significantly higher than that of the mothers of the normal children as demonstrated by comparing non-parametrically the distributions in Table I ($\chi^2 = 216.72$; d.f. = 9; $P < 0.001$).

Since the graphical distribution of the patients exhibited two peaks which are suggestive of a double, binomial-like curve, it was tempting to estimate the percentages of maternal-age-independent and maternal-age-dependent Down syndrome individuals as a function of this distribution. This was performed arithmetically, starting from the first peak, at the maternal age interval 24-27 years (12.5%), taking for reference the corresponding frequency of the normal children (17.5%). As from the maternal age interval 24-27 years to the 27-30 years interval the frequency of children in the normal group decreased 17.5%-14.2% = 3.3%, it was estimated that among the Down syndrome children the maternal-age-independent component would have decreased 2.4%, varying, therefore, from 12.5% to 10.1%. The same procedure applied to the

Table I - Distribution in percent of Down syndrome and normal children according to maternal age.

Maternal age (years)	Down syndrome (N = 200)	Control (N = 1,552)
< 15	-	0.6
15-18	4.5	6.2
18-21	8.0	17.8
21-24	9.5	22.6
24-27	12.5	17.5
27-30	11.0	14.2
30-33	10.0	9.0
33-36	10.5	6.2
36-39	13.5	3.5
39-42	11.0	2.0
42-45	5.5	0.4
45-48	3.5	-
48-51	-	-
51-54	0.5	-
Mean	31.34	24.77
S.D.	8.18	5.71

$\chi^2 = 216.72$; d.f. = 9; $P < 0.001$

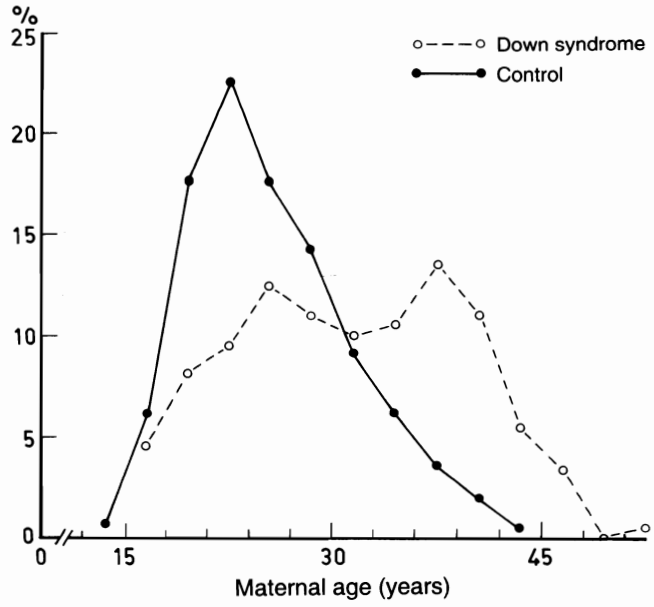

Figure 1 - Graphical representation of the maternal age distributions.

Table II - Maternal-age-independent and maternal-age-dependent Down syndrome patients, estimated in percent as a function of a double, binomial-like distribution.

Maternal age (years)	Age-independent	Age-dependent	Probability of age-independency
15-18	4.5	-	~ 1
18-21	8.0	-	~ 1
21-24	9.5	-	~ 1
24-27	12.5	-	~ 1
27-30	10.1	0.9	0.92
30-33	6.4	3.6	0.64
33-36	4.4	6.1	0.42
36-39	2.5	11.0	0.19
39-42	1.4	9.6	0.13
42-45	0.3	5.2	0.05
45-48	-	3.5	~ 0
48-51	-	-	~ 0
51-54	-	0.5	~ 0

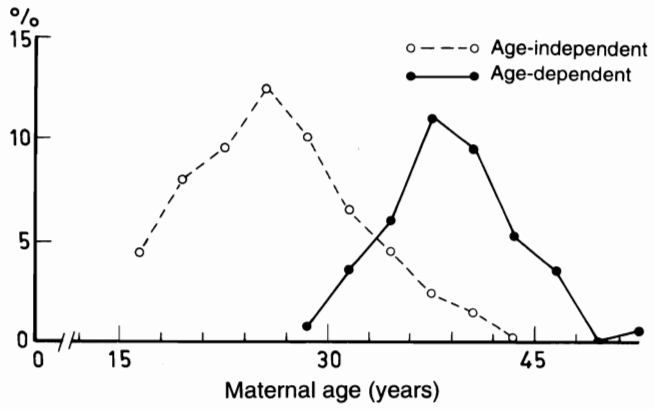

Figure 2 - Estimated percentages of maternal-age-independent and maternal-age-dependent Down syndrome patients.

subsequent intervals allowed the preparation of Table 2 in which the probability of maternal-age-independency of Down syndrome was estimated for each maternal age group. Figure 2 is the graphical representation of this table.

According to Table II, the maternal-age-independent component of the distribution of Down syndrome patients explains 59.6% of all cases, a proportion that is significantly larger than the 40.4% estimated for the maternal-age-dependent component ($\chi^2 = 7.37$; d.f. = 1; $P < 0.01$). This also means that in our data the maternal-age-dependent component is not only significantly smaller than the proportion estimated by Penrose (1961), and usually accepted (75%), but also smaller than the proportions calculated by Lamson and Hook (1980) for Massachusetts (63.7%), New York (59.6%), Australia (54.7%), British Columbia (54.2%), and Sweden (49.3%).

This difference is basically due to the younger composition of the population we analyzed. In fact, taking into account the mean maternal ages in the general population calculated from the data of Hook and Chambers (1977) for New York (26.10), Hook and Fabia (1978) for Massachusetts (27.01), Hook and Lindsjö (1978) for Sweden (25.88), Sutherland *et al.* (1979) for Australia (25.98), and ours (24.77), the correlation coefficient between the maternal-age-dependent component of the distribution of Down syndrome patients and the mean maternal age of the general population is as high as 0.95.

Since the distribution of these paired data fitted well to both the linear regression $y = -2.2708 + 0.1081x$ and the quadratic regression $y = -9.4433 + 0.6632x - 0.0107x^2$, where x is the mean maternal age of the general population, being in both cases $r = 0.95$, either one or the other regression may be used for estimating the maternal-age-dependent component of the distribution of Down syndrome patients (y), although the linear model is more parsimonious. If this model is correct, it can be inferred that the proportion of maternal age-dependent cases in the population increases around 10% per year of increase of the average maternal age of the population.

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RESUMO

A proporção de pacientes independentes da idade materna estimada em 200 crianças brasileiras com síndrome de Down (59,6%) foi significativamente superior à daqueles dependentes da idade das mães (40,4%). Essa última proporção é a menor observada na literatura pertinente e devida, basicamente, à baixa idade média materna da população geral. Em decorrência da alta correlação ($r = 0,95$) entre a proporção de pacientes dependentes da idade materna e a média da idade das mães da população geral, sugere-se uma equação preditiva simples para estimar a proporção de casos de síndrome de Down dependentes da idade materna com base na idade materna média da população geral, quando não existem dados confiáveis sobre a incidência dessa síndrome segundo a idade materna.

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