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Cytogenetic findings and maternal age in patients with Down syndrome in a pediatric referral hospital from Peru

Yesica Llimpe Mitma de Barrón
Facultad de Medicina. Universidad Nacional Mayor de San Marcos. Lima-Perú.

Maribel Susana Ccoyllo Álvarez
Facultad de Medicina. Universidad Nacional Mayor de San Marcos. Lima-Perú, Laboratorio Precisa, Clínica San Borja, Lima-Perú.

Milana Trubnykova
Servicio de Genética y Errores Innatos del Metabolismo. Instituto Nacional de Salud del Niño. Lima-Perú, Facultad de Ciencias en Salud. Universidad Peruana de Ciencias Aplicadas. Lima-Perú.

Rocío Margarita González Moreno
Servicio de Genética y Errores Innatos del Metabolismo. Instituto Nacional de Salud del Niño. Lima-Perú

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CYTOGENETIC FINDINGS AND MATERNAL AGE IN PATIENTS WITH DOWN SYNDROME IN A PEDIATRIC REFERRAL HOSPITAL FROM PERU

HALLAZGOS CITOGENÉTICOS Y EDAD MATERNA EN PACIENTES CON SÍNDROME DOWN EN UN HOSPITAL DE REFERENCIA PEDIÁTRICO EN EL PERÚ

Yesica Llimpe Mitma de Barrón [1,a,d], Maribel Susana Ccoyllo Álvarez [1,b,4], Milana Trubnykova [2,c,3], Rocío Margarita González Moreno [2,a]

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ABSTRACT

Introduction: Down syndrome is a congenital disorder caused by a total or partial trisomy of chromosome 21 and is considered the most common genetic cause of congenital malformations and intellectual disability. The objective of this study was to describe the cytogenetic alterations of patients with Down syndrome and their relationship with maternal age. **Methods:** Cross-sectional, descriptive-analytical study. 436 patients with Down syndrome admitted to the Instituto Nacional de Salud del Niño during the 2017-2019 period were included. The variables analyzed were: cytogenetic diagnosis and maternal age. **Results:** It was found that 99,3% (n=433) of patients presented some type of cytogenetic alteration and three patients presented a normal karyotype. The age of the patients at the time of sampling was between 0,03 and 17 years, the male/female ratio was 1.2:1. The most frequent cytogenetic alteration was free trisomy 21 (94,7%), followed by Robertsonian translocation (n=16) and mosaicism (n=6). In the case of maternal age, a median of 37 years was found (range: 13-47).**Conclusions:** Free trisomy 21 is the most common cytogenetic condition in Down syndrome; however, the Robertsonian translocation and mosaicisms were more frequent in patients whose mothers were les than 35 years old, suggesting that there are other risk factors than advanced maternal age in this group.

Keywords: Down syndrome; Cytogenetic analysis; Maternal age; Pediatrics. (Source: MESH-NLM)

RESUMEN

Introducción: El síndrome Down es un trastorno congénito originado por una trisomía total o parcial del cromosoma 21 y es considerada la causa genética más común de malformaciones congénitas y discapacidad intelectual. El objetivo de este estudio fue describir las alteraciones citogenéticas de pacientes con Síndrome Down y su relación con la edad materna. **Métodos:** Estudio transversal, descriptivo-analítico. Se incluyó 436 pacientes con Síndrome Down admitidos en el Instituto Nacional de Salud del Niño durante el período 2017-2019. Se analizaron las variables: alteración citogenética y edad materna. **Resultados:** Se encontró que el 99,3% (n=433) de pacientes presentaron algún tipo de alteración citogenética y tres pacientes presentaron cariotipo normal. La edad de los pacientes al momento de la toma de muestra estuvo comprendida entre los 0,03 y 17 años, la relación masculino/femenino fue de 1.2:1. La alteración citogenética más frecuente fue la trisomía 21 libre (94,7%), seguida por la translocación Robertsoniana (n=16) y el mosaicismo (n=6). En el caso de la edad materna se encontró una mediana de 37 años (rango: 13-47). **Conclusiones:** La trisomía 21 libre es la alteración citogenética más común en Síndrome Down; sin embargo, la translocación Robertsoniana y los mosaicismos fueron más frecuentes en edad materna menor de 35 años, sugiriendo que existe otros factores de riesgo diferentes a la edad materna avanzada en este grupo etario.

Palabras clave: Síndrome de Down; Análisis citogenético; Edad materna; Pediatría. (Fuente: DeCS- BIREME)

[1] Facultad de Medicina. Universidad Nacional Mayor de San Marcos. Lima-Peru
[2] Servicio de Genética y Errores Innatos del Metabolismo. Instituto Nacional de Salud del Niño. Lima-Peru.
[3] Facultad de Ciencias en Salud. Universidad Peruana de Ciencias Aplicadas. Lima-Peru.
[4] Laboratorio Precisa, Clínica San Borja, Lima-Peru.
[a] Biologist.
[b] Medical Technologist
[c] Surgeon - geneticist.
[d] PHD.

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INTRODUCTION

Down syndrome is caused by a total or partial trisomy of chromosome 21 [1,2]. It is considered the most common genetic cause of congenital malformations and intellectual disability, also comprising a complex set of pathologies in practically all organs and systems[1]. The incidence of Down Syndrome worldwide is 1 per 1,000 to 1,100 live births [3], which may vary according to the distribution of maternal age and the possibility of prenatal diagnosis [4]. In the Latin American Collaborative Study of Congenital Malformations, a prevalence of 1.88 per 1000 births was reported in the period 1998-2005 for 9 South American countries[5].

The diagnosis of Down syndrome is clinical and is confirmed with cytogenetic analysis [1], the latter is performed from the culture of peripheral blood lymphocytes in a liquid medium, which allows their proliferation and subsequent interruption in the metaphase stage in which the chromosomes achieve their maximum condensation. There are three most common cytogenetic findings in this syndrome, and they include free trisomy 21 (total trisomy), Robertsonian translocations involving chromosome 21, and mosaicisms; likewise, other cytogenetic variants related to the clinical picture of Down syndrome have been identified [6]. Free trisomy 21 is an autosomal aneuploidy characterized by an extra chromosome 21, showing 47 chromosomes in the karyotype. The Robertsonian translocation is the product of the fusion of chromosome 21 with an acrocentric chromosome. Mosaicism characterizes individuals with two or more distinct cell lines, one with trisomy 21. In studies carried out in Mexico, Algeria, Australia, Egypt and other countries in different periods of time, free trisomy 21 has been reported in frequencies that vary from 60% to 96% [12,7-10]. and, to a lesser extent, percentage, Robertsonian translocation and mosaicisms [11-14].

In Peru, no epidemiological studies determine the incidence or prevalence of Down syndrome [15]. However, in 2016 the National Council for the Integration of Persons with Disabilities published that it had registered 8,800 people with Down Syndrome between the ages of 0 and over 60 [16]. However, few reports have been found regarding cytogenetic alterations in patients with Down syndrome and its relationship with maternal age. The objective of this study was to describe the cytogenetic findings in patients with Down syndrome and their relationship with maternal age, as it would contribute to strategies to reduce its incidence and warn parents if there is a need for genetic counseling.

Population and methods

Cross-sectional, descriptive-analytical study. The study population consisted of 991 patients diagnosed with Down Syndrome admitted to the Instituto Nacional de Salud del Niño (INSN) in Lima (Peru), during the period 2017-2019. The cytogenetic finding and maternal age data were collected from the INSN Genetics and Inborn Errors of Metabolism Service records. To this aim, a data collection format was used whose content was uploaded to an electronic database.

Variables

Cytogenetic alteration and maternal age.

Ethical aspects

This study was approved by the Executive Office for Research Support and Specialized Teaching and by the Institutional Research Ethics Committee of the INSN. The informed consent of the patients' parents was not required.

Statistical analysis

The Microsoft Office–Excel version 2207 program and the statistical package Jasp version 0.16.1 were used to carry out the descriptive and analytical statistics. The Shapiro-Wilk test was performed to assess whether the maternal age data presented a normal distribution. The chi-square test was to determine if there is a relationship between maternal age and the type of cytogenetic alteration, with a significance level of $p < 0.05$. The data for the categorical variable are presented in absolute numbers and percentages, while the quantitative variable is presented as median, first and third quartile range and intervals since it did not present a normal distribution.

RESULTS

During the study period, 991 patients with a clinical diagnosis of Down Syndrome were registered, of which

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436 underwent chromosome study with the GTG technique (G bands, trypsin digestion, and Giemsa staining) and the cytogenetic findings were described according to the nomenclature according to The International System for Human Cytogenomic Nomenclature 2016. It was found that 99.3% of cases presented some type of cytogenetic alteration, and only three patients presented a normal karyotype. The age of the patients at the time of sampling was between 0.03 and 17 years, the male/female ratio was 1.2:1. Free trisomy 21 was the most frequent cytogenetic alteration (94.7%, n=410), followed by Robertsonian translocation (n=16) and finally mosaicism (n=6). Two patients with free trisomy 21 also presented another cytogenetic alteration in the same clone, which are described as: ?dup(10)(q21q22) and t(1;8)(q21;p22). A case was found with a non-classical cytogenetic alteration in Down syndrome represented by reciprocal translocation. t(5;21). Robertsonian translocations were mostly rob(14;21)(50%, n=8), but were also found: rob(21;21)(37.5%) and rob(15;21)(12.5%)(table 1), being 11 female patients and five male patients. In the cases of mosaicisms, between 15 and 82 metaphases were analyzed, observing that the normal cell line was the most predominant (83.3%), likewise, there was equal distribution by sex.

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Table 1. Karyotype in patients with Down syndrome due to translocation.

Karyotype	n
Robertsonian translocation	
46,XX,rob(14;21)(q10;q10)+21	4
46,XY,rob(14;21)(q10;q10)+21	4
46,XX,rob(15;21)(q10;q10),+21	2
46,XX,rob(21;21)(q10;q10),+21	4
46,XY,rob(21;21)(q10;q10),+21	2
Reciprocal translocation	
47,XY,+21,t(5;21)(q13;q22)	1
Total	17

The maternal age of the population did not present a normal distribution, so the median was calculated, obtaining a value of 37 years (range: 13 to 47) (figure 1a). A greater number of patients with Down syndrome was found in the age group of 36 to 40 years (30.7%, n=134). Considering the most common cytogenetic alterations, it was found that between 36 and 46 there were more cases of free trisomy (n=132), 31 to 35 years for Robertsonian translocation (n=6) and 21 to 25 for mosaicism (n=3).

The data on maternal age were organized into three groups in order to analyze the relationship between the variables maternal age and cytogenetic alteration. Thus we have: under 30 years in group 1, from 30 to under 40 years in group 2 and, from 40 years and over in group 3. On the other hand, the cytogenetic alterations were grouped into: free trisomy 21, Robertsonian translocation and mosaicism (Table 2). Figure 1b shows the interquartile ranges, where the values corresponding to the medians of each group can also be seen: 25, 28.5, and 37, respectively. Although free trisomy 21 was the most frequent finding in the three age groups, a greater number of cases of Robertsonian translocation (n=8) and mosaicism were observed in group 1 (n=4).

Finally, it was found that there is a relationship between maternal age and the most common cytogenetic alterations in Down Syndrome (p=0.002).

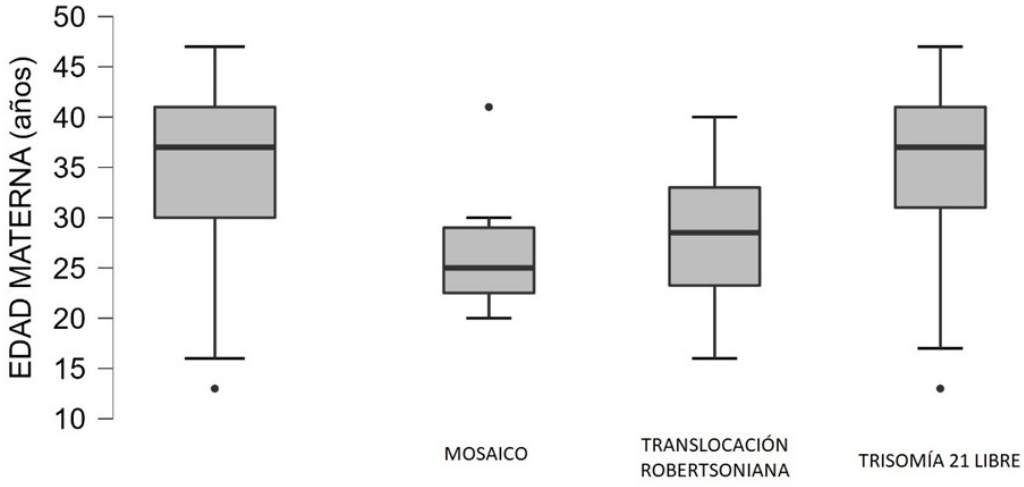

Figure 1. Distribution according to age group and cytogenetic alteration.

1a: N=991
1b: Most common cytogenetic alterations

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Table 2. Distribution of cytogenetic alterations according to maternal age group.

Maternal age (years)	n	Free trisomy 21	Robertsonian translocation	Mosaic
<30	97	85	8	4
30≤x<40	182	174	7	1
≥40	153	151	1	1
Total	432	410	16	6
X2=16.784	gl=4	p=0.002		

gf: grades of freedom

DISCUSSION

Ethe cytogenetic study is a diagnostic tool for congenital disorders such as Down Syndrome. In the INSN, one of the most complex hospitals, which cares for children and adolescents from all over Peru, it was found that free trisomy 21 was the most frequent cytogenetic alteration in patients with Down syndrome (94.7%). A previous investigation carried out by Mansilla (2014) in another health institution in Peru found a similar value (98.6%) [17]. In other regions, studies conducted in Egypt and India found free trisomy 21 in 96.1% and 93.75%, respectively [7,11], lower percentages were found in Bosnia and Herzegovina with 86.6% [18]. and 87.3% in Mexico[8].

This variation could be attributed to the population studied, maternal age, or the number of metaphases analyzed, although free trisomy 21 is always predominant in all reports. It has been described that the additional chromosome 21 is of maternal origin in about 95%, mainly in meiosis I [19]. This study observed Robertsonian translocation in 3.7%; similarly, in Mexico, Kosovo, Cuba, Bosnia and Herzegovina, and India, percentages ranging from 4.3 to 15.2% were reported , this finding being the second in frequency, with the exception of Mexico [8]. Belmokhtar et al.(2016) compared the cytogenetic findings in patients with Down syndrome in various countries, finding that, in some, Robertsonian translocation is less frequent than mosaicism[9]. Since Robertsonian translocations are

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more common de novo[8] and of maternal origin[21], the differences between these frequencies probably respond to genetic variability[22] or factors that affect the mother, specific to each region. Nevertheless, since the Robertsonian translocations that cause Down syndrome can be de novo or inherited, it is necessary to perform a karyotype on the parents to detect a possible carrier and assess the risk of recurrence[6], which is important in genetic counseling. In this study, the information on the karyotypes of the parents was not available, so its origin could not be known.

Regarding mosaics, these were observed in 1.4% and normal karyotypes were only 3 (0.7%). In other studies, no normal karyotypes were found, as in a previous report in Peru[23], or percentages such as 4%[12] and 7.4% [24] were found in India and 4.8%[13] and 12.2%[8] in Mexico. The normal karyotypes in Down syndrome could actually be mosaics in which there were not a sufficient number of metaphases analyzed to determine them, or they are a consequence of the duplication of a "critical region" on chromosome 21 [13]. This would be, in part, an explanation for the variable clinical manifestations in this syndrome, to which are added the effect of other genes not located in this region and which, as a whole, interact with each other and with the environment, giving it a high complexity to its underlying pathophysiology . Modi et al. (2003) showed the direct relationship between the percentage of trisomic cells and the degree of phenotypic manifestations in mosaic Down syndrome [25].

Thus, it is essential to consider the number of metaphases that should be included in the cytogenetic analysis when mosaicism is suspected, since it depends on the proportion of trisomic cells[26] and this, in turn, on the selected tissue[27]. Even for certain clinical characteristics of Down syndrome, there would be a different affectation than mosaicism on tissues of the same embryonic origin[28]. Therefore, to improve the ability to detect mosaicisms, the analysis of hundreds of interphase nuclei is established through the fluorescence in situ hybridization technique (FISH)[29] due to its greater sensitivity. Maternal age has been determined to be the most important risk factor for Down syndrome [30]. This study had information on maternal age in the entire population, which did not present a normal distribution, verified with the Shapiro-Wilk test, determining a median of 37 years. The three age groups formed presented medians of: 25; 28.5 and 37, respectively. Most of the mothers of patients with Down syndrome presented in age group 2 (42.1%, n=182), followed by group 3, which reflects that the majority were elderly mothers (over 35 years, 59.6%); however, 3.9% (n=17) were adolescent mothers (under 20 years of age), a characteristic that has also been suggested as a risk factor [30]. To analyze whether maternal age varies according to the type of cytogenetic alteration in Down Syndrome, our findings are represented in Figure 3, where it can be seen that there is a different distribution of Down Syndrome cases by translocation, in the age group 1:50. % (n=8), group 2: 43.8% (n=7) and group 3: 6.3% (n=1). Mosaics were more frequent in group 1 (66.7%, n=4). Free trisomy 21 was common in all three age groups, but translocation Down syndrome was more frequent in the offspring of mothers under 30 years of age.

Several biological processes are likely to be affected by advanced maternal age, such as the accumulation of toxic effects and the degradation of the meiotic machinery during oocyte arrest, leading to a suboptimal resumption of meiosis. Chromosomal disjunction errors explain free trisomy 21 in Down syndrome, but there would be other risk factors beyond maternal age, such as environmental exposure and ethnicity[22] , that could also account for Down syndrome due to translocation or mosaicism which, as has been reviewed in other works, is mostly present in patients with this syndrome whose mothers are under 30 years old [7,12,13,18,31]. The limitations of this study include the difficulty of performing the cytogenetic analysis, both in the entire study population and in the parents of patients with Robertsonian translocations, in addition to the reduced number of metaphases examined in cases of mosaicisms (between 15 and 82).

CONCLUSIONS

It was found that free trisomy 21 was the most frequent cytogenetic alteration in patients with Down syndrome, representing 95%, followed by Robertsonian translocation, represented mostly by translocation rob(21;21).

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Free trisomy was more common in children of elderly mothers, but Robertsonian translocation and mosaicism in children under 35, suggesting that there are risk factors other than advanced maternal age involved in this age group

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Correspondence: *Yesica Llimpe Mitma de Barrón.*
Address: *Av. Miguel Grau 755, Lima 15001.*
Telephone number: *+51 6197000 Anexo: 4630 / 940 144 524*
E-mail: *yllimpem@unmsm.edu.pe*

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