

CLINICAL PROFILE OF CHILDREN WITH DOWN SYNDROME TREATED IN A GENETICS OUTPATIENT SERVICE IN THE SOUTHEAST OF BRAZIL

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SUMMARY

OBJECTIVE. Considering that studies about the frequencies of phenotypic features of Down syndrome (DS) in the Brazilian population with large ethnic variability are scarce in literature, this study analyzed clinical and demographic characteristics of DS children from the Southeastern region of Brazil.

METHODS. Sixty-two DS children with free trisomy 21 were evaluated by physical examination using reference values that considered the children's gender and age at their presentation. Data about clinical complications were collected by retrospective analysis of the children's medical records and/or information supplied by their mothers. Statistical analysis was performed using Likelihood Ratio Test, with significance level less or equal to 5%.

RESULTS. Clinical features observed in more than 90% of the individuals were flat facial profile, brachycephaly, slanted palpebral fissures, hypotonia at birth and flat nasal bridge. Congenital heart disease was present in 56.5% of the cases, verbal language acquisition disorder in 87%, and global delayed development in 77.8%.

CONCLUSION. The comparison between our data and related literature showed a great variability of the phenotype features frequencies of DS among studies. Besides environmental factors, this can reflect individual as well as population characteristics.

KEYWORDS: Down syndrome. Phenotype. Physical Examination.

INTRODUCTION

Down syndrome (DS) is a common chromosomal abnormality, usually due to an extra copy of the 21. Its incidence is approximately 1:660 live births¹, and it is the most common genetic cause of mental disability.^{2,3} DS phenotype is complex and varies among individuals, who may present a combination of dysmorphic features,⁴⁻⁶ congenital heart disease,^{7,8,9} neurological abnormalities, such as early manifestation of Alzheimer's disease,¹⁰ immunological deficiency,¹¹ and elevated risk of specific types of leukemia,¹² among other clinical complications.¹³⁻¹⁵

Diagnostic hypothesis of DS can be performed in the pre and postnatal period and confirmed by chromosome analysis (karyotype examination). Cytogenetic investigation is important to confirm clinical diagnosis and to determinate the recurrence risks of DS, helping the genetic counseling process.^{16,17}

Considering that studies about the frequencies of phenotypic features of Down syndrome (DS) in the Brazilian population, that presents a great ethnic variability, are scarce in literature, the objective of this study was to analyze clinical and demographic

characteristics of DS children with free trisomy 21 from a teaching hospital linked to a medical school in the Southeastern region of Brazil.

METHODS

This study was approved by the Research Ethics Committee of the São José do Rio Preto Medical School / SP (CEP-FAMERP), and by the National Research Ethics Commission (CONEP), Brazil. All individuals were included in this study only after the Informed Consent of their parents.

The retrospective study was carried out at a general genetics outpatient service of a teaching hospital in São José do Rio Preto, São Paulo, Brazil, which assists a region of about 100 municipalities in the Southeast of Brazil. Patients assisted in the general genetics outpatient service usually have a low socio-economic status.

A sample of 62 DS children with free trisomy 21 in follow-up were included in the study. The clinical evaluation was carried out by physical examination (anthropometric parameters and dysmorphic features), using a detailed protocol of clinical

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features of DS which is not routinely used at the service. Data regarding brachydactyly, hypertelorism, length of the hands and microcephaly were determined using reference values for non-DS individuals that consider the children's gender and age at their presentation.¹⁸

Evaluation of weight and height was carried out using specific curves for DS individuals¹⁹, and these anthropometric data were used to assess the nutritional status of the children by the body mass index for age (BMI-for-age, Kg/m²). The resulting data were plotted in specific charts of BMI for individuals DS¹⁹. Distribution of indices was expressed in Z-scores terms, also referred to as standard deviation (SD) units, and the Z-score cutoff point to classify low anthropometric levels was 2 SD units below the reference mean.

Data about clinical complications were collected by retrospective analysis of the children's medical records and/or information provided by their mothers. When an individual was not evaluated for a specific characteristic, he/she was excluded from the frequency analysis of this characteristic. Data concerning age were presented by mean and standard deviation (SD). For statistical analysis of differences between our study and the related literature, the Likelihood Ratio Test (Chi-square test) with a significance level > 5% was used.

RESULTS

Of the 62 children included in the study, 27 were female (43.5 %) and 35 male (56.5%). The average age at presentation was 3.0 years (range: 0.12 to 12.7 years). In relation to weight and height, 12.3% and 7.0% of the individuals presented low and overweight, respectively, while 16.4% presented low height and 9.1% presented increased height. Regarding the BMI, 78.2% of the DS children presented BMI below 18.5 Kg/m² and 3.6% above 25 Kg/m². Analysis of the nutritional status

(BMI-for-age) showed that 16.4% presented BMI below 2 SD and 10.9% above 2 SD.

All cases were diagnosed in postnatal period. The average of maternal age at birth of the affected child was 32.0 ± 8.6 years (range: 13.1 - 46.9 years). The majority of mothers (58.1%) was under 35 years old at birth of the affected child.

Frequencies of clinical features were presented in Table 1. The clinical characteristics presented in more than 90% of individuals were flat facial profile, brachycephaly, slanted palpebral fissures, hypotonia at birth and flat nasal bridge. Verbal language acquisition disorder, and overall delayed development were referred by mothers in 87% and 77.8% of cases, respectively.

Clinical complications presented in DS individuals are shown in Figure 1. Congenital heart diseases were represented by interatrial communication (57.1%), patent ductus arteriosus (34.3%), interventricular communication (22.9%), defect of the atrioventricular septum (17.1%), tetralogy of Fallot (5.7%), and valve insufficiency (14.3%). In one case, the problem was not specified. Forty-three percent of children presented more than one type of congenital heart disease.

We performed a comparison among frequencies observed in our study and other studies previously published, and this analysis disclosed significant statistical differences for the majority of characteristics (Table 2).

DISCUSSION

Three types of chromosomal alterations may result in DS: free trisomy, translocation, and mosaicism.¹⁸ Advanced maternal age is an important risk factor in free trisomy cases due to imperfections in chromosomal segregation.¹⁰⁻²² In this study, most mothers had maternal age under 35 years at birth of their DS child. Occurrence of DS independent of maternal age presents an evidence for other risk factors for this syndrome. More recently,

Figure 1. Clinical complications presented by DS patients. Distribution according to the number of patients evaluated: (1) 59; (2) 51; (3) 53; (4) 62; (5) 61.

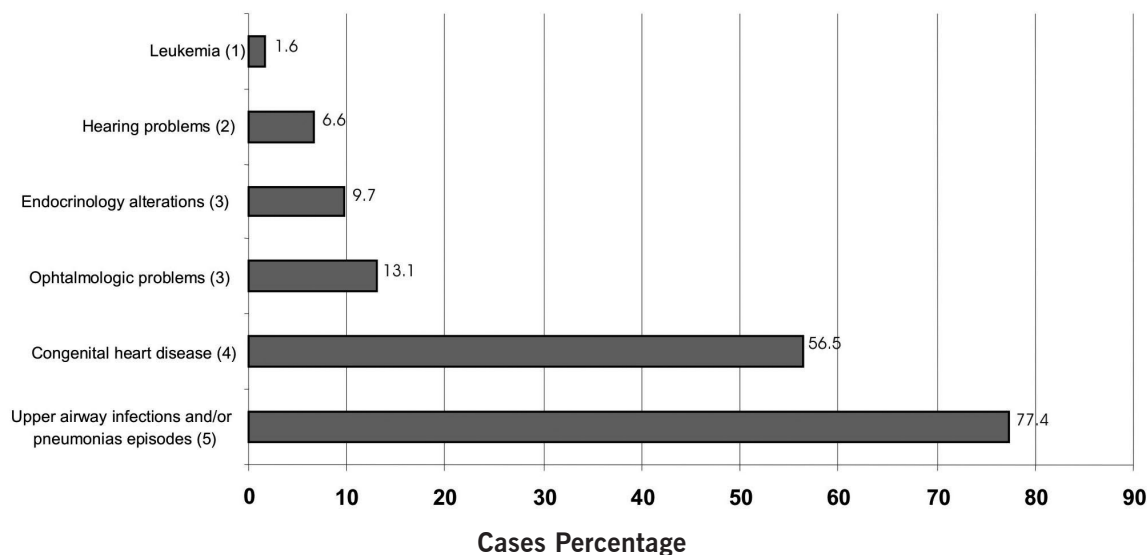


Table 1. Clinical characteristics observed in DS patients.

Characteristics^a	(%)	n evaluated
Flat facial profile	98.4	62
Brachycephaly	98.2	57
Slanted palpebral fissures; Flat nasal bridge	93.5	62
Hypotonia at birth	93.4	61
Downward-oriented corners of the mouth	85.5	62
Flat occipital; Short neck; Micrognathia; Simian crease	83.9	62
Brachydactyly	80.6	60
Epicanthal folds	79.0	62
Wide neck; Broad hands	78.7	61
Hypertelorism	72.6	62
Cutis marmorata	70.0	60
Small or absence ear-lobes	69.4	62
Short hands	68.9	61
Wide feet	66.1	62
Sandal gap sign	64.5	62
Microcephaly	60.7	61
Ogival palate	59.7	62
Hypotonia at evaluation date	59.0	61
Slightly open mouth	47.8	62
Clinodactyly	46.7	62
Tooth alterations	44.7	47 ^b
Plantar crease between first and second toes	41.9	62
Brachydactyly with clinodactyly	41.0	61
Ear dysplasia	40.3	62
High palate	37.1	62
Protruding tongue	33.9	62
Small ears	32.3	62
Umbilical hernia	25.5	61
Nystagmus	24.2	62
Fissured tongue	19.4	62
Strabismus	16.4	61
Low placement of ears	16.1	62
Ear malformation	14.6	61
Nail hypoplasia	11.5	61
Criporquidia	11.1	35
Abnormal rotation of the ears; Fifth finger mid-phalanx hypoplasia	9.7	62
Syndactyly	4.8	62
Cheilitis	1.6	62

^a Characteristics grouped in the same frequency are not necessarily present in the same individual.

^b Characteristics evaluated in individuals above 1 year old.

Table 2. Comparison of clinical characteristics between our study and related literature*

Characteristics	Present study (%)	Kava et al. 2004 5 (%)	Ahmed et al. 2005 6 (%)	Granzotti et al. 1995 7 (%)	Ribeiro et al. 2003 11 (%)	P-value
Sandal gap sign	64.5	46.2	46.4			0.024
Epicanthal folds	79.0	56.9	63			0.006
Strabismus	16.4	2.7	6.4			<0.0005
Protruding tongue	33.9	29.9				0.7453
Simian crease	83.9	33.2	64.7			<0.0005
Flat facial profile	98.4	50.9				<0.0005
Hypertelorism	72.6	33.9	62.4			< 0.0001
Hypotonia	59.0	76.3	55.9			<0.0005
Clinodactyly	46.7	36.1	24.7			<0.0005
Brachydactyly	80.6	11.1	23.7			<0.0005
Brachydactyly with clinodactyly	41.0	8.9				<0.0005
Slanted palpebral fissures	93.5	83.9	83			0.18
Flat nasal bridge	93.5		61			<0.0005
Short neck	83.9		36.7			<0.0005
Microcephaly	60.7		61			0.9911
Brachycephaly	98.2		40			<0.0005
Congenital heart disease	56.5	18.3	34.9	51	62.2	< 0.0001
Short stature	42.3		21			<0.0005

* The comparison between the frequencies observed in this study and other studies was possible with those that present the number of individuals evaluated.

several studies have related the maternal risk for DS with genetic polymorphisms involved in the folate metabolism.^{17,23-28} DS is responsible for manifestation of a combination of clinical features that makes clinical diagnosis possible. However, some characteristics in frequency and severity are variable among the individuals.^{5, 6,11,29} The knowledge of clinical manifestations of DS by physicians and other health professionals is important to make an early postnatal diagnosis possible, since prenatal diagnosis is not frequently performed, as in our sample, where all cases were diagnosed in the postnatal period, with diagnostic hypothesis confirmed by cytogenetic analysis. Late DS diagnosis can result in delayed early intervention and appropriate therapy for some risk conditions, such as congenital heart diseases. These must be detected and treated, otherwise they contribute to morbidity and mortality of these children, in addition, resulting on an impact in the physical and psychological development.^{5,30}

Frequencies of DS clinical features vary within the different studies, and some of them described only specific characteristics. Bibliographic reviews on DS have shown a large variability of these frequencies.^{1,4-8,10-12,16-18,31} Comparison of frequencies observed in our study and other studies disclosed significant statistical differences for most characteristics (Table 2). It is possible that the differences may reflect the cytogenetic profile of the individuals included in the study, since in our study only individuals with free trisomy 21 were included while other studies used for comparison evaluated individuals with free trisomy, translocation and mosaicism, even though free trisomy is present in the majority (>90%) of DS cases,^{5,6,18,32} alongside individuals with diagnostic hypothesis of DS without cytogenetic diagnosis. According to Devlin and Morrison's study¹, the accuracy of DS clinical diagnosis varies according to the cytogenetic alteration

involved (90% for free trisomy, 100% for translocation and 37.5% for mosaicism), apparently reflecting a clinical variability according to cytogenetic abnormality.

Several other factors may contribute to phenotype variability in DS, such as allelic heterogeneity for chromosome 21 genes present in three copies, the individual's genetic constitution and environmental factors²⁹. Brazil is one of the countries with the largest ethnic heterogeneity in the world. This is a result of miscegenation in the immigrant population for centuries, mainly Portuguese, African and Amerindians. This process of miscegenation has provided the gene propagation and contributed to the characteristics of the Brazilian population. Moreover, since Brazil is a country with a large territory, there is a great geographic heterogeneity.³³

In relation to weight, a higher frequency of low weight (12.3%) as compared to overweight (7.0%) was observed in the present study. Regarding the BMI, a high frequency of DS children presented BMI below 18.5 Kg/m² (78.2%), while only 3.6% presented BMI above 25 Kg/m². Although obesity is frequent in DS,¹⁶ the higher frequency of low weight and BMI observed in our study may be explained by the fact that 50% of the evaluated children presented an age below 2 years old. DS neonates are often born below the usual weight and gain weight as age increases. Analysis of the nutritional status showed that 16.4% of the children presented undernutrition (BMI-for-age below -2 SD), probably due to the low socioeconomic status of the patients assisted by the general genetics outpatient service of the Hospital de Base de Sao José do Rio Preto. Regarding height, according to literature,³⁴ low height is common in DS, and was present in 16.4% of our DS individuals.

The incidence of congenital heart diseases in DS is about 60%.^{9,35} In this study, 56.5% of the children presented congenital heart diseases, similar frequency in Brazilian studies, which ranges from 51 to 62.2%.^{7,11}

The frequencies of types of congenital heart diseases were similar between our study and Ribeiro et al.¹¹ with a greater frequency of interatrial communication in both studies (62% and 46.4%, respectively). In Granzotti et al.'s study,⁷ frequencies of types of congenital heart diseases differ from those observed in our study.

Upper airway infections and/or pneumonia episodes presented a frequency of 77.4%, while in literature this was 50-60% and 40%, respectively.¹¹ DS individuals presented high risk for endocrinology alterations, hearing problems and development of leukemia.^{12,15,16,31} In our study, the mothers reported endocrine alterations and hearing problems in 9.7 and 6.6%, respectively. One case had a diagnosis of acute myeloid leukemia.

Some DS characteristics can be less evident in the individual over the years^{15,36}, and environmental factors, such as early stimulation, may also contribute to this change. An example is the difference in frequency of muscular hypotonia at birth (93.4%) and at evaluation date (59%), observed in this study. Kava et al.⁵ observed similar frequencies of muscular hypotonia between neonates and non-neonates; however, distinct individuals comprised both groups.

The children included in this study were screened in the Outpatient Service of Genetics of a medical school hospital that offers early stimulation services, such as Phonoaudiology, Physiotherapy, and Occupational Therapy. Other characteristic, the protruding tongue, observed in 33.9% of the evaluated children, can be modified by earlier stimulation, mainly by Phonoaudiology. Kava et al.⁵ described similar frequency (29.9%) in a sample of DS individuals in India. The performance of a multidisciplinary group of health professionals that assist the needs of DS persons and their families, the Ding-Down workgroup, in the medical school - FAMERP, can provide an effective care to DS individuals and family compliance to the programs of earlier stimulation, therefore improving the quality of life of these persons.

CONCLUSION

The comparison between our data and related literature showed a great variability of the phenotype features frequencies of DS among studies. In addition to environmental factors, this can also reflect individual and population characteristics.

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Conflict of interest: none

RESUMO

PERFIL CLÍNICO DE CRIANÇAS COM SÍNDROME DE DOWN ATENDIDAS EM UM AMBULATÓRIO DE GENÉTICA NA REGIÃO SUDESTE DO BRASIL

OBJETIVO. Considerando que estudos relacionados às frequências das características fenotípicas da síndrome de Down (SD) na população brasileira, que apresenta grande variabilidade étnica, são escassos na literatura, este estudo analisou características clínicas e demográficas de crianças com SD da região Sudeste do Brasil.

MÉTODOS. Sessenta e duas crianças com SD com trissomia livre do 21 foram avaliadas por meio de exame físico utilizando-se valores de referência que consideram o gênero e idade da criança na data da avaliação. Dados sobre complicações clínicas foram coletados por análise retrospectiva dos prontuários médicos e/ou informação das mães. A análise estatística foi realizada utilizando-se o teste da razão de máxima verossimilhança com nível de significância menor ou igual a 5%.

RESULTADOS. As características clínicas observadas em mais de 90% dos pacientes foram perfil facial achatado, braquicefalia, fenda palpebral oblíqua, hipotonia muscular ao nascimento e ponte nasal baixa. Doenças cardíacas congênitas estiveram presentes em 56,5% dos casos, distúrbio de aquisição de linguagem em 87% e atraso do desenvolvimento global em 77,8%.

CONCLUSÃO. A comparação entre nossos dados e a literatura prévia mostrou grande variabilidade das características fenotípicas da SD entre os estudos. Isso pode refletir características individuais e populacionais, além de fatores ambientais. [Rev Assoc Med Bras 2009; 55(5): 547-52]

UNITERMOS: Síndrome de Down. Fenótipo. Exame físico.

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