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1. Introduction

Down syndrome (DS) is a genetic disorder caused by the presence of all or part of an extra 21st chromosome and the most likely cause is non-disjunction occurring during gametogenesis (meiosis). It was first described in 1866 by a British physician named John Langdon Down and it is also known as trisomy 21 and trisomy G. This syndrome is the most common congenital mental disability and affects individuals independent of social status or ethnic group. (Jensen et al., 1973; Coe et al., 1999; Oliveira, 2001) The incidence of Down syndrome ranges between 1 in 600 and 1 in 350 live births. (Mustacchi & Rozoni 1990, Moraes 2007c) There are around 184,000 people with DS in Brazil and over 5.8 million people in the world.

The DS involves a set of signs that characterize a delay in the pre-natal and post-natal development, mental and general alterations with stature values observed to be generally below the normal standards. Regarding mental aspects, the average of intelligence quotient (IQ) in DS individuals are around 36.5. (Coelho & Loey, 1982; Mustacchi & Rozone, 1990; Rey, 1991; Hayes & Batshaw, 1993; Moraes, 2002; Schwartzman, 2003; Barata & Branco, 2010) The general alterations involved slanting eyes, almond-shape, plica palpebronasalis (epicanthus), strabismus, myopia; flattening of the nose bridge, small, short nose with broad nasal bridge, pug nose; lop with flat or absent helix of the ears, auricles with a low implantation; wide and short neck with abundant skin; wide hands and short fingers; clinodactyly; brachydactyly; muscular hypotony and atlanto-axial instability (Ali 2006; Moraes, 2007c). They also can present dove-like chest, small genitalia, alterations of motor coordination, obesity, short stature (Cohen & Winer, 1965) thyroid diseases. Individuals with DS are more susceptible to leukemia and other types of malignant than the population at large. (Hill et al., 2003)

The systemic alterations with special dental significance in DS patients are congenital cardiopathy, pneumonia, allergy, bronchitis, tonsillitis, convulsion and blood dyscrasia. (Mariano et al., 1999; Pilcher, 1998; Ribeiro et al., 2003) The degree of systemic problems varies from individual to individual. (Jara 1993) Some people may have all the alterations, while others may have only a few of the problems. (Nadel, 2003; Mustacchi & Rozone, 1990) The facial features of DS individuals include brachycephaly (condition where the head is disproportionately wide), hypotonic facial muscles, with a flat profile, normodivergent vertical pattern, lip incompetence, an ogival and deep hard palate, (Higa & Vargas-Machuca, 2004), and Class II malocclusion (Cohen & Winer, 1965). It is possible to observe...
Prenatal Diagnosis and Screening for Down Syndrome

brachycephaly; small and underdeveloped maxilla; a fissured tongue with papillary hypertrophy and macroglossia, with an incidence of 11-60%. Labial fissures and angular cheilitis are some other common findings. (Aguiar et al., 2002)

The teeth of these patients present complete mineralization, but with a great variation in the eruption pattern, although it maintains a certain similarity in the sequence and symmetry. (Pilcher, 1998) It has been reported (Alpöz & Eronat, 1997) that these individuals usually have late eruption of the deciduous and permanent teeth, although Jara et al. did not find any differences on the sequence of eruption in DS people. Delay was also found in the mineralization chronology development of the canines and second molars. (Santos, 2004)

It is a universal finding in the literature that they have high prevalence of periodontal diseases and low prevalence of caries (Castilho & Marta, 2010). The higher prevalence of periodontal disease is probably related to the impaired host-response rather than to specific periodontal pathogens. (Reuland & Bosma, 2001; Cavalcante, 2009) The low caries prevalence seems to be due to immune protection caused by the elevated salivary S. mutans specific IgA concentrations. (Lee et al., 2004, Murakami et al., 2008)

Dental anomalies are very common, both in the primary and permanent teeth and in the patients with DS, dental anomalies occur with an incidence five times greater than in the normal population (Ingalls & Butler, 1953; Kumasaka et al., 1997). The most common dental associated with DS are variations in tooth number and morphology. (Seagriff-Curtin et al., 2006) Tooth eruption may be delayed, may occur in an unusual order and can be 2 to 3 years behind a child’s normal eruption pattern. Over-retained primary teeth are also common. (Moraes, 2004) In the primary dentition, the most commonly absent teeth are lateral incisors, while in the permanent dentition, third molars, second premolars and lateral incisors, in this sequence, are the most frequently missing teeth. (Thompson 1976) Desai, 1997, described the oral anomalies that may require medical consultation, but also emphasized that these patients are routinely managed in an office setting to treat cases of microdontia, hipoplasia, partial anodontia, taurodontism and others manifestations. According to Moraes et al., 2007c, there was a high incidence of different types of dental anomalies, such as taurodontism (50%), anodontia (50%), conic teeth (8.3%) and impacted teeth (5.9%) and in most cases, the same individual presented more than one dental anomaly.

It is noteworthy that the variations of the development parameter in relation to the skeletal and dental age were deemed normal. (Moraes et al., 1998; Moraes et al. 2007a, 2007b) The variation degree was evaluated in order to assess how different the skeletal age was difference in DS individuals when compared with non DS group. Only a few researchers have assessed the skeletal development of individuals with DS. Pozsonyi et al. (1964) and Sannomiya et al. (1998) observed a delay of skeletal development at the earlier years in relation to individuals without DS. They also observed that the process of skeletal maturation of individuals with DS was completed at around 15 years of chronological age.

The aim of this research was evaluate skeletal age of DS individuals in order to verify if they are delayed or advanced when compared with control group of non DS individuals.

2. Material and methods

This research was authorized by the Local Ethical Committee under the protocol no. 050/2005-PH/CEP.
Seventy-five hand and wrist films of DS individuals from the archive of the Discipline of Radiology at the School of Dentistry – São Paulo State University (UNESP) – São José dos Campos -SP, Brazil, were initially evaluated. The final study population comprised 40 hand and wrist radiographs of individuals with DS (19 males, 21 females). They had to fulfill the following inclusion criteria: (1) The subjects had to be between 6 and 16 years of chronological age; (2) Their radiographic films had to have high clarity and good contrast. Using the same inclusion criteria, 100 hand and wrist radiographs from individuals who did not have DS (50 males, 50 females) were selected from the same archives as a control group.

All the hand and wrist radiographs were made with a Philips Oralix X-ray machine operating at 50 kVp and 5 mA, with an exposure time of 0.2 seconds Kodak T - MAT G/RA (Eastman Kodak Corp., São José dos Campos-SP, Brazil) 18-24 cm plain films were used in association with a cassette and Kodak Lanex Regular rare earth screens (Eastman Kodak Co., Rochester, NY). The films were processed in a Macrotec MX-2 automatic processor (Macrotec, São Paulo, Brazil) with Kodak GBX processing chemicals (Eastman Kodak Co., Rochester, NY). The processing time was four minutes.

The sample was split into two groups: films from persons with DS and those without DS. The individuals of each group were divided into A and B subgroups according to their gender. Therefore, a total of four groups were created (Group 1A and Group 2A for females, Group 1B and Group 2B for males).

To prevent any bias during the assessment of skeletal age, the identification tags of the radiographs were covered with dark paper and randomly numbered for later identification. The examiner was also blinded as to the different groups. The skeletal age of all subjects was determined by an experienced oral radiologist according to the method of Greulich & Pyle (1959). This method evaluates the individual’s ossification center of the hand and wrist (FIGURE 1), which is then compared to its pair in the atlas of skeletal development of the hand and the wrist.

The authors’ suggestion was to begin the assessment of the skeletal maturation by comparing the patient’s hand and wrist film with the standard of same gender and nearest chronological age in the atlas. Then the operator compared the film with the adjacent standards, both older and younger than the one of nearest chronological age. The operator then selected the standard that was closest to the patient’s film for a more detailed comparison. The individual’s skeletal age was established by matching the majority of the ossification centers with those of a certain age in the atlas.

The radiographic images were displayed in a darkened room over a light box and viewed with a dark mask to block excess light. Data were tabulated and submitted for statistical analysis. Simple linear regression analysis was used to compare the relationship between the skeletal age and the chronological age of each group of individuals. The difference between the chronological age (CA) and the skeletal age (SA) of each individual was calculated to establish whether the skeletal age was delayed or advanced in relation to the chronological age. The mean values of these differences for Group 1A were compared with those of Group 1B by means of Student’s t-test. The same comparison was made with Groups 2A and 2B. Student’s t-test was used to compare the mean values for the differences of the chronological age and the skeletal age of Group 1A and Group 2A, etc. These comparisons were made to evaluate whether the skeletal maturation would be the same among individuals of same population (Group 1A _ Group 1B and Group 2A _ Group 2B) and among individuals of same gender but from different populations.
Fig. 1. (A) Anatomy of hand and wrist of bones used to evaluate Greulich & Pyle method (1959). (B) Sequence of ephyfises and diaphesis maturation.

3. Results

The sample of 40 individuals with DS included 21 females (52.5%), mean age of 11.12 ± 3.05 years, and 19 males (47.5%), mean age of 12.43 ± 3.13 years. The control group comprised 100 individuals who did not have DS, 50 females (50%), mean age of 11.26 ± 2.38 years, and
50 males (50%), mean age of 11.02 ± 2.40 years. The mean and the standard deviation of chronological age (CA), skeletal age (SA), and the difference between the CA and the SA in months are shown in Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>Chronological age</th>
<th>Skeletal age</th>
<th>Difference CA-SA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>1A Females with DS</td>
<td>133.05</td>
<td>36.67</td>
<td>144.19</td>
</tr>
<tr>
<td>2A Females</td>
<td>135.16</td>
<td>28.63</td>
<td>131.16</td>
</tr>
<tr>
<td>1B Males with DS</td>
<td>149.16</td>
<td>37.60</td>
<td>164.68</td>
</tr>
<tr>
<td>2B Males</td>
<td>132.28</td>
<td>28.91</td>
<td>126.36</td>
</tr>
</tbody>
</table>

CA= Chronological age, SA= Skeletal age, SD= Standard-deviation, DS= Down syndrome

The skeletal age (SA) of Groups 2A and 2B, individuals without DS was, on average, 4.0 and 5.9 months delayed in relation to the chronological age (CA) (Table 1). However, the SA of Groups 1A and 1B, individuals with DS was, on average, 11.1 and 15.5 months advanced in relation to the CA.

Student’s t-test results for comparisons of mean values for the differences of the SA and the CA between Groups 1 and 2 are shown in Table 2.

<table>
<thead>
<tr>
<th>CA-SA (non-DS individuals x DS individuals)</th>
<th>t critical</th>
<th>Stat t</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2.06</td>
<td>3.23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>2.07</td>
<td>3.72</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

CA= Chronological age, SA= Skeletal age, SD= Standard-deviation, DS= Down syndrome, *<=0.05

Table 2. The p-values for comparisons of the mean values of the differences between the CA and SA for Groups 1A and 2A and groups 1B and 2B.

When the mean values of the CA and SA differences for Groups 1A and 2A were compared, significant statistical differences were found (p < 0.05). The same was detected for the comparison of Groups 1B and 2B (p < 0.05) (Table 2). Therefore, the subjects with DS had their SA advanced in relation to their CA, when compared to the subjects who did not have DS.
The $t$-test results were used to compare the SA and the CA differences between males and females. When the mean values of the differences of CA and SA for Groups 2A and 2B were compared, no significant statistical differences were detected ($p > 0.54$). The skeletal maturation of non-DS male and female individuals was also similar. In other words, they had, on average, a delayed SA in relation to their CA. No significant statistical differences between the mean values of the differences between SA and CA were found when Groups 1A and 1B were compared ($p = 0.40$). Hence, the SA of individuals with DS, males and females, on average, was advanced in relation to the CA (Table 1).

Figure 2 presents a chart with values of the differences between the CA and the SA for each subject in Group 1, and for each subject in Group 2. From the analysis of the results, we verified that there was a tendency of young individuals with DS (around 7 years of age) to have their SA delayed in relation to their CA. However, the SA of these individuals overtook their CA during adolescent maturation. At the age of 15, most individuals had their SA advanced in relation to their CA. Figures 3A, 3B, 3C, 3D show the examples of male and female at 7 years and at 15 years old, with different cases of delayed and advanced SA.

Fig. 2. Charts representing the difference between CA and SA of each subject in each group. A: Group 1A; B: Group 1B; C: Group 2A; D: Group 2B.

The linear regression analysis showed that the duration of skeletal maturation was shorter in individuals with DS when compared to those who did not have DS, as shown by the tendency lines (Figure 2A, C) and by the angular coefficients of the linear regression equations (Table 3). During the early stages of skeletal maturation, the subjects with DS tended to have their SA delayed in relation to their CA. However, during the latter stages of skeletal maturation, these individuals tended to have an advanced SA in relation to their CA (Figure 2B, D). Still, a good correlation between SA and CA was observed in individuals with DS ($R^2 > 0.85$) (Table 3).

Figure 5 presents tendency charts (A,C) of the SA in relation to the CA, line charts of the SA, and the CA of each individual without DS (B,D), divided by gender.
Male - Delayed skeletal age (SA) at 6 years old. Chronological age (CA) 75 = months; Skeletal age (SA) = 54 months

Female - Delayed skeletal age (AS) at 7 years old. Chronological age (CA) 87 = months; skeletal age (SA) = 60 months.
Male – Advanced skeletal age (SA) at 15 years old. Chronological age (CA) 188 months and skeletal age (SA) 228 months.

Female – Advanced skeletal age (SA) at 15 years old. Chronological age (CA) 191 months and skeletal age (SA) 204 months.

Fig. 3. Examples of skeletal age (SA) evaluated by Greulich & Pyle method, around 7 years and at 15 years, for both, male and female.
Figure 4 presents the tendency charts (A,C) of the SA in relation to the CA, line charts of the SA, and the CA of each subject without DS (B,D), divided by gender. The SA tended to be similar to the CA in females who did not have DS, as shown in Figure 3 (A,B) and by angular coefficient of the linear regression analysis (Table 3). We also observed a good correlation between the SA and the CA in these individuals (R² = 0.927). Nevertheless, in males without DS there was a tendency for their SA to be delayed in relation to their CA, as shown in Figure 3 (C,D) and by the angular coefficient of the linear regression analysis (Table 3). A good correlation between the SA and the CA was found in males (R² = 0.824), although this correlation was lower than the correlation between the SA and the CA for females.

Figure 4 presents tendency charts (A,C) of the SA in relation to the CA, line charts of SA, and the CA of each subject with DS (B,D), divided by gender.

4. Discussion

It is known that DS is a result of a genetic anomaly that causes a number of local and systemic changes whose manifestations are expressed in various degrees. However, to what extent the condition alters the timing of growth and the duration of growth is a subject that needs further study.
In our study, we observed that the skeletal age (SA) of females without DS (Group 2A) and males without DS (Group 2B) was on average 4.0 and 4.92 months delayed in relation to the chronological age (CA) (Table 1). On the other hand, the SA of Groups 1A and 1B was on average 11.14 and 15.53 months advanced in relation to their CA (Table 1).

When the mean values of the differences of CA and SA of Groups 1A and 2A were compared, statistically significant differences were found ($p < 0.05$) (Table 2).

The same was detected for the comparison of Groups 1B and 2B ($p < 0.05$) (Table 2).

Therefore, subjects with DS had their SA advanced in relation to their CA (Table 1) when compared to the control subjects.

![Fig. 5. Group 2A (A, B) and Group 2B (C, D). A and B: Tendency chart representing the skeletal age versus the chronological age. C and D: Line chart of the skeletal age and the chronological age of each subject.](image)

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation</td>
<td>$R^2$</td>
</tr>
<tr>
<td>Group 1</td>
<td>IO=$1,45xIC-52,4^*$</td>
</tr>
<tr>
<td>Group 2</td>
<td>IO=$0,92xIC+4,21^*$</td>
</tr>
</tbody>
</table>

*$Y=ax+b$, where $y=SA$; $x=CA$; $a =$ angular coefficient; $b =$ linear coefficient

Table 3. Results of the linear regression tests for the comparisons between CA and SA in each group.
When the mean values of the differences of CA and SA of Groups 2A and 2B were compared, no significant differences were detected ($p > 0.05$). Therefore, the skeletal maturation of the control subjects (male and female) was similar, which means their SA was delayed in relation to their CA (Table 1).

No statistically significant differences between the mean values of the differences between the SA and the CA were found when Groups 1A and 1B were compared ($p > 0.05$). Therefore, the SA of male and female subjects with DS was advanced in relation to their CA (Table 1).

From the analysis of the results, we verified that there was a tendency for individuals with DS, at about 7 years of age, to have their SA delayed in relation to their CA. However, the SA of these individuals overtook their CA during adolescent maturation. At the age of 15 years, most of these individuals had their SA advanced in relation to their CA (Figure 2). An evaluation of the linear regression analysis showed that the duration of skeletal maturation was shorter for individuals with DS when compared to the controls group (Figure 4A,C), and also from the angular coefficients of the linear regression equations (Table 3). A good correlation between the SA and the CA was observed for subjects with DS ($R^2 > 0.80$) (Table 1). Similar results have been reported by Pozsonyi et al. (1964) and statistically Sannomiya et al. (1998).

In female individuals without DS, their SA tended to go along with their CA, as seen (Figure 5A, B) in the angular coefficient of the linear regression analysis (Table 3). We also observed a good correlation between the SA and the CA of the control subjects ($R^2 > 0.927$). For male subjects, there was a tendency for their SA to be delayed in relation to their CA, as can be seen in the angular coefficient of the linear regression analysis (Table 3). They also had a good correlation between their SA and their CA ($R^2 > 0.824$), although this correlation was lower than the correlation between the SA and the CA of the female subjects. Thus, contrary to what we expected, in this study the skeletal development of individuals with DS had a shorter period of skeletal maturation when compared to individuals who did not have DS.

Although the SA was delayed in relation to the CA in young individuals with DS, there was a more pronounced period of growth, which caused the skeletal maturation of individuals with DS to be completed earlier. These results have also been reported by Pozsonyi et al. (1964) and Sannomiya et al. (1998).

The results of our study are important if patients with DS need orthodontic treatment because the correct time for treatment of skeletal malocclusions depends on the skeletal maturation stage of the individual. Also, the outcome of some treatment modalities, such as palatal expansion for the correction of posterior cross-bites, can be affected by the stage of skeletal development of an individual.

5. Conclusion

Based on the results of this study, we concluded that the skeletal age (SA) of the individuals with DS was delayed in relation to the chronological age (CA) by the age of 7 years (SA < CA) when compared to those who did not have DS. However, at the age of 15 years, their skeletal age was advanced in relation to their chronological age (SA > CA). Therefore, we suggest that individuals with DS had a shorter period of skeletal adolescent development with early maturation when compared to the individuals without DS which end of skeletal maturation is usually around 18 years of age.
6. References


Moraes, MEL; Moraes, LC; Dotto, GN; Dotto, PP; Santos, LRA. (2007b) Dental anomalies in patients with Down syndrome. *Braz Dent J.* Vol. 18, No. 4, pp. 346-350.


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This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book focuses on exciting areas of research on prenatal diagnosis - Down syndrome screening after assisted reproduction techniques, noninvasive techniques, genetic counselling and ethical issues. Whilst aimed primarily at research worker on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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