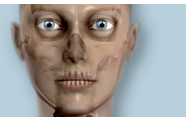
Orthodontics & Craniofacial Research



ORIGINAL ARTICLE

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Size and shape of the sella turcica in subjects with Down syndrome

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Structured Abstract

Objectives – To study size and shape of the sella turcica in individuals with Down syndrome (DS) and compare them to matched controls without the syndrome.

Setting and sample population – The Department of Pediatric Dentistry and Orthodontics. Lateral cephalograms of sixty DS individuals and sixty controls were obtained with an age range of 12–22 years.

Materials and methods – The length, depth, and diameter of the sella turcica were calculated. In addition, the shape of the sella turcica was described as either normal or with aberrations such as; oblique anterior wall, sella turcica bridging, extremely low sella turcica, irregularity in the posterior part of the dorsum sella, and pyramidal shape of the dorsum sella.

Results – An increase in the diameter and depth of sella turcica was found more frequently in DS group as compared to controls ($P < 0.05$ and $P < 0.0001$, respectively). When the shape of the sella turcica was examined, a normal sella turcica shape was found less often in DS ($P < 0.05$). The most common abnormality detected was an oblique anterior wall ($P < 0.05$). A sella turcica bridge, irregularity in the posterior wall, and a pyramidal shape of sella turcica were present simultaneously in some individuals with DS ($P < 0.01$).

Conclusion – The sella turcica in DS differs in size and morphology when compared to individuals without the syndrome. The diameter and depth of the sella turcica in DS are larger than controls, with a tendency toward more abnormalities in the shape of sella turcica.

Key words: Down syndrome; sella turcica size and shape

Introduction

Down syndrome (DS), also known as trisomy 21 and mongolism, is a congenital anomaly caused by the presence of all or part of a third copy of chromosome 21 (1–4). It is the most common

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chromosome abnormality in humans (5). Individuals with DS present with distinctive phenotype manifestations which include, but are not limited to; generalized physical growth delay, varying degree of mental retardation, hearing and vision problems, infertility, and thyroid disorders (6–12). One of the reasons for the development of the latter is a malfunction in the secretion of thyroid-stimulating hormone from the pituitary gland. It is well known that the pituitary gland, which is housed in the sella turcica, is a vital structure in the human body. It is responsible for secreting hormones which regulate the control of growth, blood pressure, body temperature, thyroid activity, urine production, and the production of sex hormones (13, 14).

Research so far has revealed that the formation of the pituitary gland during fetal life takes place ahead of the cartilaginous sella turcica (15). Thus, the development of this gland is closely coordinated with the development of the sella turcica. Previous investigators have observed that individuals affected with syndromes or disorders such as holoprosencephaly (16, 17), trisomy 18 and trisomy 21 (18–20), spina bifida (21, 22), Meckel–Gruber syndrome (23), cleft lip and palate (24), fragile X syndrome (25, 26), Cri-Du-Chat (27), Williams syndrome (28), and severe craniofacial deformities (29), all present with malformations which influence the size and/or morphology of the sella turcica formed during embryological development. Kjaer et al. in 1998 (18) conducted a histological examination of the sella turcica of fetuses with Trisomy 18 and compared them to normal controls. Their findings revealed that the sella turcica was affected to varying degrees from mild to severe especially in the posterior wall of the sella, while the anterior wall appeared either normal or with minor malformations. They concluded that the more severe the presentation of DS in embryos, the more severe the malformation of sella turcica (18).

The morphological variations of the sella turcica observed during fetal development can also be noted after development, such as in trisomy 21 (19), spina bifida (21, 22), and fragile X (25, 26). In fact, in trisomy 21, the sella turcica was found to have the same morphology postnatally as seen prenatally in the cartilage (19). In individuals with holoprosencephaly, not only the sella turcica was malformed, but also the pituitary gland within the sella was affected prenatally and postnatally in subjects with this genotype (16).

Until now, when searching for studies measuring the size of the sella turcica, disorders other than DS have been the main focus (24, 28). Studies on the postnatal structure of the sella turcica in DS have also been scarce. The only report found was an investigation conducted in 1999 by Russell and Kjaer (20), where they examined lateral cephalometric radiographs of DS individuals from 4 months to 50 years of age. They concluded that an abnormal sella turcica shape was present in 23% of the group with DS.

Therefore, due to the limited research on the sella turcica in DS and the growing number of individuals in Saudi Arabia with this genotype, the current investigation was undertaken to calculate the size, and examine the morphology of the sella turcica, and to compare the findings with controls without the syndrome.

Materials and methods

Subjects

Seventy-five Saudi individuals affected with DS in both genders (40 Females, 35 Males) with an age range from 12–22 years (mean age 15.8 years), were included in this study. After obtaining approval from the ethics committee at the College of Dentistry Research Center (CDRC) at King Saud University (in accordance with the Helsinki Declaration of 1975), different hospitals, DS care centers and schools were contacted and visited with an official form explaining the study. A list of individuals affected with DS in the age range of interest was obtained. Families were contacted, and the study was explained to them. Those who agreed to participate in the study were included. The DS group chosen had no history of craniofacial surgical treatment, was not institutionalized, and was living with their parents at home.

Dental examinations were performed for all DS individuals at the College of Dentistry, King Saud University. For the majority of the sample that was their first visit to a dentist and therefore oral hygiene instructions and toothbrushes and dentifrices were given to them and their parents. In addition, urgent dental care and referrals were provided free of cost for all DS individuals. At this stage, the cooperation of the DS group was assessed subjectively. Those with poor cooperation and inability to follow instructions were excluded (n = 15). Therefore, the final number of individuals with DS included in this study was sixty. After signing a consent form by their parents, lateral cephalometric radiographs were obtained (Planmeca PM 2002 CC Proline Cephalostat; Instrumentarium Corp. Imaging Division, Tusula, Finland). The parameters for the machine were standardized and routinely calibrated at a regular and fixed schedule, with a tube voltage of 57–85 Kv and tube current of 2–16 mA with a minimum total filtration of 2.5 mm Al, using the cranex intensifying screen (HI plus regular speed) and Kodak X-OMAT RP pan Df 75, and under strict radiation protection measures.

All radiographs were processed according to the manufacturer's instructions. The procedure for obtaining the cephalometric radiographs was carried out by a well-trained technician and under close supervision. All participants were positioned in the cephalostat with the sagittal plane at right angle to the path of the X-ray, the Frankfort plane parallel to the floor, teeth in centric occlusion, and lips in relaxed position. Sixty cephalometric radiographs of subjects without DS matching the DS group in age and gender were obtained from the archives of the College of Dentistry at King Saud University.

The selection criteria for the control group were non-syndromic; Class I skeletal relation, average facial height; Angle Class I molar and canine relationship, average over jet and overbite, no dental protrusion, no extractions or congenital missing teeth; no history of orthodontic treatment; no known medical problems such as growth abnormalities. This information was taken from the orthodontic file for each chosen radiograph.

Methods

The cephalometric radiographs were scanned using the Epson Perfection 4990 Photo Scanner (Seiko Epson Corporation, Suwa Nagano, Japan), then digitized, and traced by one examiner using the orthodontic imaging and management solutions software Dolphin 11.0 (Premium Imaging and Management Solutions Software, Chatsworth, CA, USA). The degree of resolution was 300 dpi and 8 bit gray scale. The linear measurements were adjusted and calibrated for actual size in millimeters based on measurements of the known distance (100 mm) between two fixed points on the Dolphin ruler. This allowed the software to adjust for magnification. An example of a cephalometric radiograph of an individual with DS is shown in Fig. 1. The linear dimensions of the sella turcica were measured and compared in both groups using the methods of Silverman (30) and Kisling (31). The Sella turcica structure in each radiograph was traced digitally

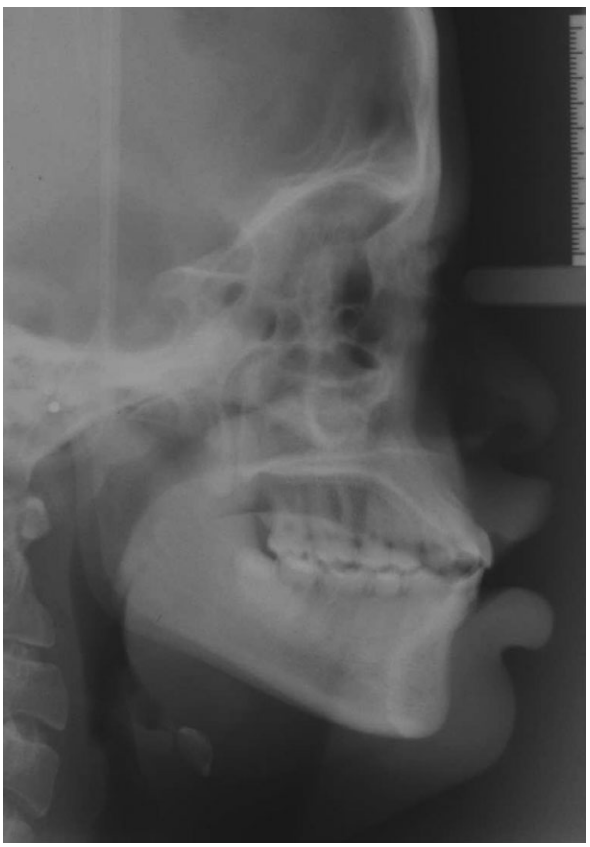

Fig. 1. Lateral cephalometric radiograph of an individual with DS.

using the Dolphin 11.0 software. The length, depth, and antero-posterior diameter of the sella turcica were measured after correction for magnification. A customized analysis was done to obtain the required measurements. After digital tracing, a layout of the tracing was performed, and a tool to measure the distance between two points was used. The length of the opening of the sella turcica was measured as the distance from the tuberculum sella to the tip of the dorsum sella. The depth was measured as the distance from a perpendicular line drawn from the length of the opening of sella to the deepest point on the floor. A line was drawn from the tuberculum sella to the furthest point on the posterior inner wall of the fossa. This line was considered as the antero-posterior diameter of the sella turcica (Fig. 2).

To determine the shape of the sella turcica in the DS and control groups, the sella turcica structure in each radiograph was digitally traced using the same orthodontic imaging software mentioned above (Dolphin 11.0). The method described by Axelsson et al. was utilized to determine the morphology of sella turcica (32). A normal shape and five morphological variations from normal were noted; oblique anterior wall, sella turcica bridging, extremely low sella turcica, irregularity (notching) in the posterior part of the dorsum sella, and pyramidal shape of the dorsum sella.

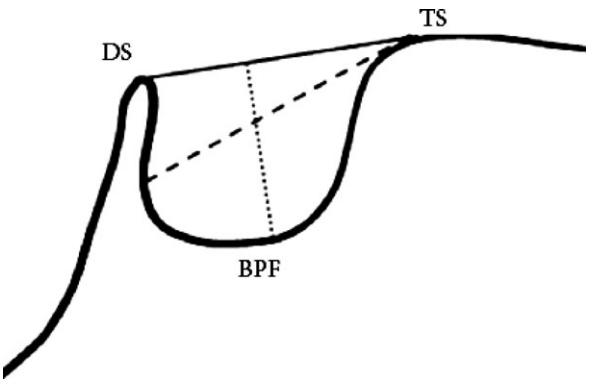

Fig. 2. Normal sella turcica morphology and reference lines used for measuring sella size: TS, tuberculum sella; DS, dorsum sella; BPF, base of the pituitary fossa; black line, length of the opening of sella turcica; dashed line, diameter of sella; dotted line, depth of sella (Silverman (30) and Kisling (31).

Reliability and error analysis

The random error was evaluated by calculating the intra-examiner error. A subsample of 30 cephalograms (15 DS and 15 controls) was randomly chosen from the total sample. These were traced on two different sessions by one examiner to replicate the measurements within a 2-week interval. The Cronbach's alpha (33) and Cohen's kappa (34) values were calculated to assess the reliability of measurements.

Statistical analysis

The data were entered in Microsoft software Excel and analyzed using SPSS Pc+ version 18.0 (Statistical Software, Michigan, Chicago, IL, USA). Student's t-test for two independent samples was used to compare the mean values of the quantitative variables when the distribution of the data was symmetric. Chi-square was used to observe the association between the distributions of two categorical variables, while the Fisher's exact test was used when the cell frequencies of the sample were small. A *P*-value of ≤ 0.05 and 95% confidence intervals were used to assess statistical significance and precision of the estimates.

Results

Reliability of measurements

The values obtained from the Cronbach's alpha ranged from 0.80 to 0.95, which indicates a highly statistically significant reliability of measurements. For the categorical variables of sella turcica shape, the results of the kappa statistics showed a significant agreement between the two set of values (> 0.80).

Comparison of sella turcica dimensions in DS and controls

There was a highly statistically significant difference in sella turcica diameter ($P < 0.05$) and depth ($P < 0.0001$) between DS subjects and controls. The measurements of the DS group were significantly larger than the controls. No

statistically significant difference in the length of the opening of sella turcica was noted between DS and controls (Table 1).

Comparison of sella turcica morphology in DS and controls

When the shape of sella was examined, a statistically significant difference between the DS group and the controls was found. A normal sella turcica shape was found less frequently in the DS group ($P < 0.05$) (Table 2).

An oblique anterior wall, in addition to the simultaneous presence of more than one abnormality in the shape of the sella turcica in the same individual (sella turcica bridge, irregularity in posterior wall, and pyramidal shape), was found more frequently in the DS group than the controls ($P < 0.05$ and $P < 0.01$, respectively) (Table 2). On the other hand, no significant difference was found between both groups with regard to the presence of sella turcica bridging or an extremely low sella turcica position.

Discussion

Down syndrome is the most common of all malformation syndromes affecting 1 in 600 to 1 in 2000 live births in different populations (4, 35–37). In this study, individuals with DS were chosen in particular because there is a relatively high incidence in Saudi Arabia with 1 in every 554 live births (38). Two groups of Saudi subjects matched in age and gender were selected. For the sake of collecting the sample, various centers for DS in Riyadh, Saudi Arabia had been contacted with official forms explaining the study. A list of patients of both genders in the target age group was taken. From the list obtained, some patients refused to participate; moreover, among the families that agreed to participate, some individuals with DS were eventually excluded because of the difficulty they faced following the technicians instructions and staying still at the machine while taking the radiographs.

Until now, the majority of studies which have been conducted on DS have examined areas

Table 1. **Comparison of mean values of sella turcica measurements (in mms) between the DS group and controls**

Sella Turcica measurements	DS $n = 60$	Controls $n = 60$	*t*-value	*P*-value	95% confidence interval of mean
Length of sella mm (SD)	10.2 (2.0)	10.1 (1.7)	0.33	>0.05	(−0.56, 0.79)
Depth of sella mm (SD)	8.9 (1.1)	7.8 (1.4)	5.02	<0.0001****	(0.71, 1.63)
Diameter of sella mm (SD)	13.0 (1.6)	12.3 (1.5)	2.5	<0.05*	(0.15, 1.30)

Student's *t*-test.
*$P = 0.05$; ****$P = 0.0001$.

Table 2. **Comparison of distribution of variables of sella turcica (ST) shape between DS and controls**

Groups	Normal ST (%)	Oblique ant wall (%)	Extreme low ST (%)	ST bridge (%)	Irregularity in posterior part of dorsum sellae (%)	Pyramid shape (%)	>1 abnormality (%)
DS ($n = 60$)	27 (45)	20 (33.3)	2 (3.3)	7 (11.7)	12 (20)	3 (3)	11 (18.3)
Controls ($n = 60$)	38 (63.3)	12 (20)	6 (6.7)	1 (1.7)	7 (11.7)	0	1 (1.7)
Chi-square	4.06	2.73	–	–	1.56	–	8.1
P-value	<0.05*	<0.05*	>0.05	>0.05	>0.05	>0.05	<0.01**

Chi-square test & Fisher's exact test.
*$P = 0.05$; **$P = 0.01$.

other than the sella turcica (39–42). To our knowledge, the current investigation is the only one describing in detail the dimensions of sella turcica in DS in which the depth, diameter, and length of the opening of the sella turcica were measured and compared to controls. The results reveal significant differences in the size of the sella turcica in DS, where a larger diameter and depth were more frequently found than in their counterparts without the syndrome. Suri et al. also examined craniofacial features in DS and measured the diameter of the pituitary fossa (the greatest sagittal dimension present), but the authors did not elucidate how the exact location of the diameter was determined. In addition, neither the depth nor the length of the opening of sella turcica was calculated (43, 44).

When evaluating other syndromes such as Williams syndrome (28) or disorders such as cleft lip and palate (24), a difference in sella turcica size was also evident between affected groups and controls, but contrary to DS, the sella turcica was found to be smaller in controls.

Similarly, when searching for studies examining the shape of the sella turcica, only one could be found. Russell and Kjaer in 1999 (20) investigated the shape of sella turcica in lateral cephalograms of 78 DS individuals, aged 4 months to 50 years old. They compared their findings to a normal sella turcica shape and growth pattern from childhood to adulthood. A comparison was also made with an earlier study in which they examined the sella of human fetuses with DS. The shape was categorized as Type I (almost normal appearance), Type II (deviations in the anterior wall), or Type III (deviations in the floor of sella turcica). Type I was found in the majority of their DS group. When evaluating postnatal and prenatal radiographs, Type I was also found to be the most common morphological appearance of sella. A comparison of their results with the current study is difficult because the method used for description of sella morphology was different than the one used in the present investigation. Nevertheless, the occurrence of an abnormal sella turcica was found in 23% (18/78) DS individuals that they had examined, in contrast to the current investigation where 55% (33/60) individuals with DS presented with an abnormal normal shape of sella turcica ($P < 0.05$). An oblique anterior wall of sella turcica, in addition to the presence of more than one abnormality in a single radiograph (sella turcica bridge, irregularity in posterior wall, and pyramidal shape), was both characteristics found in the current study.

Similar results with regard to the increase in frequency of an oblique anterior wall of sella turcica were also reported by Kjaer et al., (16) but in individuals with holoprosencephaly. They also reported that a sella turcica bridge and a diminished sella volume were more commonly found (16).

During embryological development, the formation of the sella turcica and the pituitary gland begins at about the 7th week of gestation, with the pituitary gland developing before the sella. Any disturbance in this area during fetal growth remains throughout life (15, 45, 46). This can be observed when studying the sella turcica prenatally of individuals with lumbosacral myelomeningocele (47) trisomy 21 (19) or fragile X (25), in which the same abnormalities can be detected postnatally, while in holoprosencephaly, not only the sella turcica was found to be affected, but also the pituitary gland (16).

It is unclear if the presence of an abnormal sella turcica in DS has any relation to the function of the pituitary gland. Prior clinical studies reveal hypothyroidism in many individuals with DS with a raised level of thyroid microsomal auto-antibodies (proteins that attack the body's own tissue) and thyroid-stimulating hormone (6–8, 12). In addition, an increase in serum androgen levels was found with an excess of associated male sex chromosomal abnormality in males (48, 49). When compared with the general population, serum estrogen, prolactin, and gonadotropin concentrations in females were also elevated (48–50).

Whether the larger size of sella turcica and the morphological aberrations found in the DS group of the current study are due to differences in the craniofacial bony structure when compared to controls, or due to developmental prob-

lems of the pituitary gland, are questions that need further exploration. The results of the current study support the notion that the dimensions and morphology of the sella turcica in individuals with DS are different than in controls. A larger sample size of both DS and normal controls, the use of certain scans such as MRI's, in addition to the incorporation of necessary endocrinological testing during investigations, are required to address the above mentioned questions.

Conclusions

The size and shape of the sella turcica differ in individuals with DS when compared to controls. A larger diameter and depth of the sella turcica were more commonly found in the DS group. When the shape was examined, an abnormal morphological appearance with an oblique anterior wall was more frequently found in DS. In addition, a sella turcica bridge, irregularity in the posterior wall, and a pyramidal shape of sella turcica appeared simultaneously in some individuals with DS.

Clinical relevance

The sella turcica is an important structure, which is observed frequently by the orthodontist when viewing lateral cephalograms. Previous investigators have studied the size and shape of sella turcica in syndromic and non-syndromic subjects or in subjects with disorders. However, studies on Down syndrome have been scarce. Therefore, the examination of the shape and size of the sella turcica in individuals with DS was made in an attempt to familiarize the clinician with the variations that are present in the sella turcica in DS that can be detected on routine lateral cephalometric radiographs.

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