Original

Sella Turcica Morphology Phenotyping in Malay Subjects with Down’s Syndrome

Haider Ali Hasan1), Hanan Ali Hameed2), Mohammad Khursheed Alam3), Asilah Yusof4), Hiroshi Murakami5) and Hatsuhiko Maeda6)

1) Oral and Maxillofacial Surgery Department, College of Dentistry, University of Babylon, Iraq
2) Prosthodontic Department, College of Dentistry, University of Babylon, Iraq
3) Orthodontic Department, College of Dentistry, Jouf University, Sakaka, Kingdom of Saudi Arabia
4) Craniofacial Morphology Unit, School of Dental Science, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia
5) Division of Implant Dentistry, Department of Gerodontics, School of Dentistry, Aichi Gakuin University, Nagoya, Japan
6) Department of Oral Pathology, School of Dentistry, Aichi Gakuin University, Nagoya, Japan

Abstract: The purpose of this study was to evaluate sella turcica morphology, calculate its size and area in subjects with Down syndrome (DS), and compare them with normal subjects. A total of 100 (50 normal and 50 DS) Malay subjects who had their computed tomography (CT) scan at the Radiology Department, Hospital Universiti Sains Malaysia (HUSM) for ordinary diagnosis. The selected age groups were divided into four groups as children (0-6 years), pre-adolescents (7-12 years), adolescents (13-20 years) and adults (21-35 years). The images were processed using Mimics V17.0 software. Conventional measurements included three different heights of the sella turcica (anterior, posterior, median), its length, diameter, area and width, measured in relation to the Frankfort reference line (FH). Morphometric methods were used to assess sella shape. Significant differences were found between control and DS groups in most parameters except for the sella height anterior and median, and sella area. No significant differences in size of the sella were found for control and DS groups in most parameters between genders. When age was evaluated, there were significant differences among some age groups and non-significant in other. The study found that sella turcica in DS presented with a three different shapes: U shape (50%), J shape (42%) and shallow (8%). The size and shape of the sella turcica is different between control and DS subjects. It was found that males had more significant differences in measured parameters compared to female. Among the age groups, the children age between 0-12 years old showed highly significant difference between DS and normal individuals, compared to adolescent and adults groups.

Key words: Morphometry, CT, Sella turcica, Linear dimensions, Down syndrome

Introduction

Evaluation of cephalometric radiographs uses several landmarks within the cranium as reference points. The centre of the sella turcica or sella point constitutes an important reference point in orthodontic analysis. In the cranial base which is located in the mid-point of the sella turcica1). In the early embryonic structure the morphological appearance of the sella turcica is set up as expressed in some studies. Kjaer et al.2) reported that a foetus with holoprosencephaly with the sella turcica malformations. Kjaer et al. 2001 stated that DS syndrome and fragile X in children displayed sella turcica shape malformation in prenatal period and continued postnatal period3).

John Langdon Down was the first person who clinically described DS in 1866. This genetic disorder happened because of a partially or complete third copy of chromosome 21 in 95% of cases4). One of the main reasons in the expansion of the condition is the age of the mother. The average birth rate for DS is 1 in 2,500, but this increases to 1 in 600 in mother’s over the age of 30 years5).

It is characterized by several morphologic and functional alterations of body structures, from cellular organelles to multiorgan systems, which are present in varying degrees in the affected individuals6). In addition, DS is characterized by several abnormalities of body organs and systems that are present in variable proportions in affected individuals7).

Individuals with DS present with distinctive phenotype manifestations which normally with; generalized physical growth delay, varying degree of mental retardation, hearing and vision problems, infertility, and thyroid disorders8). One of the reasons for the development of the latter is a malfunction in the secretion of thyroid stimulating hormone from the pituitary gland. The pituitary gland is known to be a vital structure in the human body, which is housed in the sella turcica. 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 hormones9,10).

Various imaging modalities have been used to clarify fundamental processes of craniofacial growth and development from the embryonic to adult stage11). CT imaging has a key role in the diagnosis and management of craniofacial malformations of traumatic, congenital, inflammatory and neoplastic origin12).
Previous studies of craniofacial anomalies have applied 2D imaging modalities, such as lateral cephalometric and antero-posterior radiographs, on which landmarks can be difficult to locate compared with CT scans\(^{14}\). Therefore, we must know the normal morphology of the sella turcica to determine unusual appearance of sella. Morphology may have differences among individuals. Normal parameters will help to eliminate abnormality of sella turcica. The aim of this study was to describe the shape and measure the size of the sella turcica in DS subjects, as well as to determine if a difference exists between individual with DS and normal subjects.

**Materials and Methods**

**Subjects**

This is case control study was conducted on 100 (50 normal and 50 DS) candidates who had their CT scan at the Radiology Department, HUSM. This study was approved by the Human Research Ethical Committee (HREC) of the HUSM with a study protocol code USM/JEPeM/15060174. The selected age groups were divided into four groups as children (0-6 years), pre-adolescents (7-12 years), adolescents (13-20 years) and adults (21-35 years). The DS group chosen had no history of craniofacial surgical treatment, was not institutionalized, and was living with their parents at home.

The selection criteria for normal subjects were:
1. Subjects with CT images and the presence of the sella turcica with maximum clarity were selected.
2. All subjects were clinically healthy with no syndromes, clefts, or other craniofacial abnormalities either congenital, acquired through road traffic accidents or other forms of trauma and developmental discrepancies.
3. No significant pathology of the maxillofacial region.
4. No significant facial asymmetry.
5. No significant anatomical variation in the sella turcica and sphenoidal regions.
6. Patients using hormonal medications or corticosteroids were excluded from the study.

**CT imaging**

CT images were collected and saved in the Picture Archiving and Communication System (PACS) Server, Radiology Department, HUSM. These scans were of high resolution, helical scans obtained with General Electric (GE) Light Speed Plus CT Scanner System (GE company, Medical system group, Wisconsin, USA). The CT resolution was at 1.25 mm thickness and 1.25 mm spacing.

| Landmark | Name               | Definition                                                                 |
|----------|--------------------|----------------------------------------------------------------------------|
| TS       | Tuberculum Sella   | The most anterior point of the contour of the sella turcica               |
| DS       | Dorsum Sella       | The posterior wall of the sella turcica                                   |
| SF       | Sella Floor        | The deepest point on the floor of pituitary fossa                        |
| Pclin    | Posterior Clinoid  | The most anterior point of the Pclin process                              |
| SA       | Sella Anterior     | The most anterior point of the sella                                      |
| SP       | Sella Posterior    | The most posterior point of the sella                                     |
| SM       | Sella Medium       | A point midway between Pclin and TS                                       |
| FH       | Frankfort Plane    | Is traced from Porion (Po): The most superior point on the upper rim of the external auditory meatus to Orbitale (Or): The most inferior point on the lower rim of the orbit |

**3D Reconstruction**

CT scans were saved in DICOM format, transferred to a personal computer, and reconstructed with a 3D image-segmentation program Mimics V17.0 software (Materialise N.V., Heverlee, Belgium). This software uses the existing axial view to create cross-sections in the sagittal and frontal views. The Hounsfield Unit (HU), which expresses the gray scale, was adjusted for each tissue in the CT system.

**Measurements**

Seven points were carefully selected and seven linear and area measurements were repeatedly made between identified point landmarks on each of the 3D image-segmentation using Mimics software program. Table 1 lists the landmarks used in this study and Fig. 1 shows the linear and area measurements using the above mentioned point landmarks. All linear and area measurements were repeated 3 times. The second measurements were conducted after 2 weeks, which the results were blinded to minimize the examiner’s bias. For the third time, the same blind was done which is 2 weeks after the second measurements. The averages of three readings of each measurement were considered for the statistical analysis in order to minimize the intra-examiner variation. A single operator did all the measurements.

**Statistical analyses**

All data were analyzed using SPSS software 22.0 (IBM, Armonk,
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NY, USA). The normality of the data was evaluated with the skewness and kurtosis measurements. General descriptive statistics were calculated for each parameter. An independent t-test was used to calculate the mean differences in sella turcica linear and area dimensions between normal and DS subjects, between males and females and among different age groups. Statistical significance was set at p < 0.05.

### Results

#### Size of the sella turcica

The average of three different heights of the sella turcica (anterior, posterior, median), its length, diameter and width, were measured in relation to the FH. In addition, the area of sella turcica was calculated for both normal and DS groups, which were shown in Table 2. When comparing linear and area dimensions of sella turcica between normal and DS groups, there were significant differences between normal and DS groups in most parameters except for the Sella height anterior and median (TS-SF, SM-SF), and Sella area. On the other hand, when linear and area dimensions were compared between males and females in the normal group as in Table 3, there were no significant differences in most parameters except for the Sella length (TS-PClin), while the comparison between males and females in the DS group showed no significant differences in all parameters. Furthermore, when our parameters were compared between the normal and DS groups in relation to the males as in Table 4, there were no significant differences in most parameters except for the Sella width (SA-SP), Sella diameter (TS-DS) and Sella height posterior (PClin-SF), while the comparison between normal and

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**Table 2. Comparison of 3D sella turcica measurements between control and DS subjects.**

| Variables       | Control         | DS              | Lower Bound | Upper Bound | P value |
|-----------------|-----------------|-----------------|-------------|-------------|---------|
| TS-PClin        | 8.74(1.98)      | 7.80(2.14)      | 0.12        | 1.76        | 0.02*   |
| SA-SP           | 7.93(1.82)      | 7.01(1.81)      | 0.2         | 1.65        | <0.01***|
| TS-DS           | 9.85(2.20)      | 8.58(2.22)      | 0.39        | 2.14        | <0.001***|
| TS-SF           | 5.87(1.33)      | 5.92(1.91)      | -0.7        | 0.6         | 0.88    |
| PClin-SF        | 5.86(1.20)      | 6.75(2.22)      | -1.59       | -0.18       | <0.01***|
| SM-SF           | 5.90(1.10)      | 6.47(1.88)      | -1.18       | 0.04        | 0.06    |
| TS-SA-SF-SP-PClin| 49.88(14.53)    | 48.01(17.94)    | -4.59       | 8.36        | 0.56    |

*p value < 0.05; **p value < 0.01 and ***p value < 0.001

**Table 3. Comparison of 3D Sella measurements between DS and control groups in relation to gender differences.**

| Variables       | Males Mean(SD) | Females Mean(SD) | Lower Bound | Upper Bound | P value |
|-----------------|---------------|------------------|-------------|-------------|---------|
| TS-PClin        | 9.34(2.13)    | 7.98(1.51)       | 0.28        | 2.44        | 0.01**  |
| SA-SP           | 8.36(2.06)    | 7.39(1.30)       | -0.04       | 1.99        | 0.05*   |
| TS-DS           | 10.27(2.38)   | 9.32(1.86)       | -0.29       | 2.19        | 0.13    |
| TS-SF           | 5.75(1.47)    | 6.01(1.16)       | -1.03       | 0.51        | 0.5     |
| PClin-SF        | 5.94(1.22)    | 5.76(1.20)       | -0.5        | 0.87        | 0.59    |
| SM-SF           | 5.99(1.26)    | 5.80(0.87)       | -0.44       | 0.82        | 0.54    |
| TS-SA-SF-SP-PClin| 52.38(15.26)  | 46.69(13.19)     | -2.56       | 13.93       | 0.17    |

*p value < 0.05; **p value < 0.01 and ***p value < 0.001

**Table 4. Comparison of 3D Sella measurements between males vs males and females vs females of control and DS subjects.**

| Variables       | Control Mean(SD) | DS Mean(SD) | Lower Bound | Upper Bound | P value |
|-----------------|------------------|-------------|-------------|-------------|---------|
| TS-PClin        | 9.34(2.13)       | 8.26(2.20)  | -0.08       | 2.24        | 0.06    |
| SA-SP           | 8.36(2.06)       | 7.05(1.60)  | 0.31        | 2.3         | 0.01**  |
| TS-DS           | 10.27(2.38)      | 8.86(2.21)  | 0.17        | 2.64        | 0.02*   |
| TS-SF           | 5.75(1.47)       | 6.12(2.23)  | -1.37       | 0.64        | 0.47    |
| PClin-SF        | 5.94(1.22)       | 7.08(2.48)  | -2.18       | -0.09       | 0.03*   |
| SM-SF           | 5.99(1.26)       | 6.67(2.13)  | -1.62       | 0.25        | 0.14    |
| TS-SA-SF-SP-PClin| 52.38(15.26)     | 48.87(19.83) | -5.97       | 12.99       | 0.46    |

*p value < 0.05; **p value < 0.01 and ***p value < 0.001
DS groups in relation to females showed no significant differences in all parameters. When age was evaluated, our results in comparison between normal and DS groups regarding 0-6 years age group as in Table 5, showed highly significant differences in most dimensions except at three different heights of the sella turcica (anterior, posterior, median), regarding (13-20 years) age group most dimensions were showed no significant differences except at Sella diameter (TS-DS) and Sella height posterior (13-20 years) age group most dimensions were showed no significant differences except at Sella length (ST-PClin), Sella width (SA-SP) and Sella diameter (TS-SA-SF-PClin 46.79(15.52) 32.48(10.76) -13.41 -13.39 0.71 63.74(9.87) 65.75(7.81) -11.55 7.54 0.65 0.05*.

### Table 5. Comparison of 3D Sella turcica measurements between two age groups (0-6, 7-12 years)

| Variables | Control | DS | Lower Bound | Upper Bound | P value |
|-----------|---------|----|-------------|-------------|---------|
| TS-PClin  | 9.67(2.26) | 6.70(2.05) | 1.54 | 4.39 | <0.001*** |
| SA-SP     | 8.10(2.20) | 5.70(1.46) | 1.17 | 3.63 | <0.001*** |
| TS-DS     | 9.88(2.45) | 6.74(1.95) | 1.68 | 4.6 | <0.001*** |
| TS-FS     | 5.16(1.50) | 4.55(1.53) | -0.38 | 1.61 | 0.21 |
| PClin-SF  | 5.16(1.20) | 5.15(2.13) | -1.13 | 1.14 | 0.99 |
| SM-SF     | 5.11(1.06) | 4.90(1.61) | -0.68 | 1.12 | 0.62 |

### Table 6. Comparison of 3D Sella turcica measurements between two age groups (13-20, 21-35 years)

| Variables | Control | DS | Lower Bound | Upper Bound | P value |
|-----------|---------|----|-------------|-------------|---------|
| TS-PClin  | 13-20 years | 13-20 years | 21-35 years | 21-35 years | 13-20 years | 21-35 years | 13-20 years | 21-35 years | p value |
| TS-SA-SF- | TS-SA-SF- | TS-SA-SF- | TS-SA-SF- | TS-SA-SF- | TS-SA-SF- | TS-SA-SF- | TS-SA-SF- | TS-SA-SF- | TS-SA-SF- | PClin |
| SM-SF     | 5.11(1.06) | 4.90(1.61) | -0.68 | 1.12 | 0.62 |

Ds groups in relation to females showed no significant differences in all parameters. When age was evaluated, our results in comparison between normal and DS groups regarding 0-6 years age group as in Table 5, showed highly significant differences in most dimensions except at three different heights of the sella turcica (anterior, posterior, median), regarding (7-12 years) age group. Most dimensions showed significant differences except at Sella length (ST-PClin), Sella width (SA-SP) and Sella diameter (TS-SA-SF-PClin 46.79(15.52) 32.48(10.76) -13.41 -13.39 0.71 63.74(9.87) 65.75(7.81) -11.55 7.54 0.65 0.05*.

### Shape of the sella turcica

In respect of its shape, the sella turcica in DS group was radiologically shown as three different shapes: in a U shape (50%), when the dorsum and tubercle of the sella turcica are maintained at the same height; in a J shape (42%), when the sella turcica tubercle is in a lower position in relation to the dorsum; and shallow shape (8%), when the sella turcica depth is minimum as in Fig. 2.

### Discussion

In this study, DS in particular was investigated because in Malaysia there is a relatively high incidence of DS with a reported incidence of 1 in every 690 live births. This could be due to a tendency towards more advanced maternal age which increased the prevalence of DS. Moreover, the life expectancy of DS subjects has increased significantly in the last few years. Advanced medical care and developed new facilities, DS subjects are living longer and are being more socially compatible than before. With this decreased mortality rate and increased in incidence, there is a trend in a growing population of DS individuals in Malaysia.

Until now, the majority of studies which have been conducted on DS have examined areas other than the sella turcica except the only report found was an investigation conducted by Korayem et al., where they examined the size and the shape of the Sella turcica in individuals with DS from 12-22 years of age by using lateral cephalometric radiographs. They found the size of sella turcica to be smaller in normal group. On the other hand, current study showed the sizes of four out of seven parameters were bigger in control compared to DS group.

To our knowledge, the current investigation is the only one describing in detail the dimensions of sella turcica in DS included three different heights of the sella turcica (anterior, posterior, median), its length, diameter, area and width, measured in relation to the Frankfort reference line (FH) and compared to controls by using the research tool 3D CT. This is due to the ability of observing and performing measurements from several viewing angles with interactive and rapid repositioning of the 3D images. Furthermore, 3D digitization method was proved to be very accurate and sensitive to obtain the data, and it can be used in both clinical practice and research fields.

This study also investigated the comparisons between gender and difference among age groups which provides better understanding which could not be found in previous studies. Between genders, it was
found that males had more significant differences in measured parameters compared to female. Among the age groups, the first group (age 0-6 years old) and second group (7-12 years old) showed highly significant difference between DS and normal individuals. As they grew older, the differences had reduced.

The results reveal significant differences in the size of the sella turcica in DS, where a larger diameter, length, width and posterior sell height were more frequently found than in the normal subjects. Craniofacial features in DS were examined and the pituitary fossa was measured by Suri et al., but the authors did not explain how the exact location of the diameter was determined. Furthermore, the depth and the length of the sella turcica were not calculated\textsuperscript{24,25).}

Studies examining the shape of the sella turcica are scanty. Only one could be found when searching for those studies. Russell et al.\textsuperscript{26) investigated the shape of sella turcica in lateral cephalograms of 78 DS individuals, aged 4 months to 50 years old. They used different type of shape classification. 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. A comparison of their results with the present study showed the same results as the normal shape was the most common one (50\%).

The size and shape of the sella turcica is different between control and DS subjects. It was found that males had more significant differences in measured parameters compared to female. Among the age groups, the children age between 0-12 years old showed highly significant difference between DS and normal individuals, compared to adolescent and adults groups.

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Conflict of Interest
The authors have declared that no COI exist.

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