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Post-natal size and morphology of the sella turcica in Williams syndrome

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SUMMARY Williams syndrome (WS) is a rare congenital disorder with distinctive craniofacial features, cardiovascular abnormalities, mental retardation, and behaviour characteristics.

The purpose of this study was to investigate the size and morphology of the sella turcica on profile cephalograms in a group of individuals with WS. The material consisted of radiographic cephalograms of 62 Norwegian children, adolescents, and adults with an age range of 4.7–44.4 years. The length, depth, and diameter of the sella turcica were measured and the mean values were compared with normal reference material from the Oslo University Craniofacial Growth Archive. In total, the two-dimensional size of the sella turcica in the WS group was smaller in length, depth, and diameter compared with the control group, but only occasionally reached a significance level of 5 per cent (Student's *t*-test).

The morphology of the sella turcica was assessed and five different morphological types were identified; oblique anterior wall, extremely low sella turcica, sella turcica bridging, irregularity (notching) in the posterior part of the dorsum sellae, and pyramidal shape of the dorsum sellae. The occurrence of these morphological types was more frequent in the WS subjects compared with the reference material, except for sella turcica bridging, which was equally frequent. The females with WS had more dysmorphic sella turcicas than males.

This study has demonstrated morphological aberrations in the sella turcica in Norwegian individuals with WS, which should be further elucidated in future research and combined with neurological and endocrinological investigations.

Introduction

Williams syndrome (WS) is recognized as a congenital disorder characterized by typical facies, mental retardation, overly friendly personality, cardiovascular anomalies, and growth retardation (Morris *et al.*, 1988). WS is caused by a hemizygous microdeletion of the long arm of chromosome 7 (7q11.23) affecting multiple organ systems. During the last decades, the clinical manifestations have been well defined, but it was not until recently that the genetic deletion responsible for WS was discovered (Ewart *et al.*, 1993). The deletion includes codes for an estimated 17 genes, including elastin and four genes that are highly expressed in the brain (FZD9, STXIA, LIMK1, and CYLN2) (Schultz *et al.*, 2001). The microdeletion is detectable in approximately 97 per cent of individuals with the clinical phenotype of WS (Nickerson *et al.*, 1995; Lowery *et al.*, 1995). WS is estimated to occur in approximately 1:20 000 live births, is equally prevalent in both sexes, and in all populations throughout the world (Morris *et al.*, 1988).

Children with WS have a characteristic pattern of dysmorphic facial features, connective tissue abnormalities affecting the cardiovascular organs, developmental delay, short stature, aberrations in size, shape and number of teeth, a unique cognitive profile, learning difficulties, a distinctive personality, and sometimes a transient infantile hypercalcaemia (Beuren, 1972; Morris *et al.*, 1988; Udwin and Yule, 1991, Axelsson *et al.*, 2003a).

During recent decades, WS has received special attention in cognitive neuroscience, with the focus on the aberrant neuroanatomical and behavioural features. This approach, connecting genetics with neurobiology and behaviour sciences, explores how genes affect neural development and function. Results from high-resolution magnetic resonance imaging and autopsy studies have shown that the chromosomal deletion in WS alters the brain in complex clusters (Reiss *et al.*, 2000). Neuroanatomical studies on adults with WS have documented a decreased overall brain size, disproportionate dimensions of the brain-stem compared with other brain dimensions, and cortical changes with relative preservation of the frontal cortex, cerebellar, and superior temporal gyrus volumes (Bellugi *et al.*, 1990; Reiss *et al.*, 2000). Analyses of the cerebellum have revealed that adult individuals with WS have, in absolute terms, a normal cerebellar vermis size, but after correction for the smaller total cranial size, a

proportionately larger neocerebellum and posterior cerebellar vermis (Jerningan and Bellugi, 1990; Schmitt *et al.*, 2001).

Previous published studies have shown that the bony neurocranial morphology, including the cranial base, in WS subjects deviates from normal in dimensional measurements (Mass and Belostoky, 1993; Axelsson *et al.*, 2005). These investigations have demonstrated that both the anterior cranial fossa and the clivus are shorter in WS subjects. The cranial base angle is, however, within normal limits.

In cephalometric analyses of craniofacial and neurocranial morphology, the sella point (the midpoint of the sella turcica) constitutes an important reference point. A number of studies have illustrated changes in sella turcica shape during growth (Björk, 1955; Melsen, 1974; Björk and Skieller, 1983, Axelsson *et al.*, 2005). Melsen (1974), in a comprehensive study of growth patterns of the different parts of the cranial base, found that bone apposition on the anterior part of the interior surface of the sella turcica ceased at an early age, whereas resorption continued for a long time on the distal part of the sella floor and on the posterior wall. The reference point 'sella' would, therefore, during growth and development, be displaced backwards and downwards. There are, however, no reports that give an account of sella turcica size and morphology in individuals with WS.

Attention has recently been drawn to the pattern of sella turcica malformations in various genetic disorders and syndromes, such as Cri du Chat (Kjær and Niebuhr, 1999), fragile X (Hjalgrim *et al.*, 2000; Kjær *et al.*, 2001a), holoprosencephaly (Kjær and Fischer-Hansen, 1995; Kjær *et al.*, 2002), Meckel (Kjær *et al.*, 1999a), Seckel (Kjær *et al.*, 2001b), solitary median maxillary central incisor (SMMCI) (Kjær *et al.*, 2001c), spina bifida (lumbosacral myelomeningocele) (Kjær *et al.*, 1998a, 1999b), trisomy 18 (Kjær *et al.*, 1998b), and trisomy 21 (Kjær *et al.*, 1998c; Russell and Kjær, 1999).

From an embryological point of view, a close interrelationship exists between the development of brain tissue and the bones surrounding the brain—the neurocranium. Consequently, congenital malformations of brain development may be detected by analyses of the bones in the neurocranium. Abnormal morphology of the cranial base and the sella turcica should therefore be included in post-natal evaluation of craniofacial malformations (Kjær *et al.*, 1999c). This scientific discipline linking osseous and neurological analyses has been termed neuro-osteology (Kjær, 1998).

The purpose of the present study was to analyse the size and morphology of the sella turcica on lateral radiographic cephalograms of a group of individuals with WS and to compare the findings with a normal Norwegian sample (Axelsson *et al.*, 2004).

Subjects and methods

This study was performed at the Dental Faculty, University of Oslo, as well as at the TAKO-Centre, a national interdisciplinary resource centre for oral health in rare medical conditions (conditions with a frequency of less than 1:10 000 inhabitants). Health workers from different disciplines refer patients to the centre for diagnostic purposes, oral treatment planning, and treatment of complicated cases. Most of the patients in this WS group were recruited from the TAKO-Centre, but also from the members of the Norwegian Williams Syndrome Association.

Size of the sella turcica

Study population. Lateral skull radiographs from 62 individuals with a clinical and/or cytogenetic diagnosis of WS were analysed. The sample consisted of all available lateral cephalograms of WS individuals radiographed at the Dental Faculty, University of Oslo. The material comprised 25 males and 37 females ranging in age from 4.7 to 44.4 years. They were divided into six age groups; individuals less than 8 years, 8–10 years, 11–13 years, 14–16 years, 17–19 years, and more than 20 years of age.

From the total sample of 108 radiographs, two were excluded due to poor quality. In cases where more than one radiograph from the same individual existed within a particular age group, the additional radiographs, eight in total, were excluded. Thus, the same individual could appear with a radiograph in more than one age group, but not more than once within the same age group. The final sample thus comprised 98 radiographs (39 males and 59 females) (Table 1).

Control group. For comparison, lateral cephalometric radiographs from the Oslo University Craniofacial Growth Archives were used. This longitudinal reference material has previously been described in detail (Axelsson *et al.*, 2003b, 2004).

Cephalometric analyses. The calculated variables, length, depth, and diameter of the sella turcica are illustrated in Figure 1. The definitions of the variables are in accordance with Silverman (1957) and Kisling (1966). All reference lines used were situated in the midsagittal plane.

The sella turcica was measured by tracing the contour of the pituitary fossa from the tip of the dorsum sellae to the turberculum sella and then following a straight line from the turberculum sella back to the origin. This straight line corresponded to the position of the diaphragma sellae. The length of the sella turcica was measured as the distance from the turberculum sella to the tip of the dorsum sellae, and the depth of the sella turcica was measured perpendicular to this line to the

Table 1 The number of lateral cephalograms used for measurement of the sella turcica in the Williams syndrome group.

	Age groups	*n*	Mean age	SD	Minimum	Maximum
Male	<8 years	6	6.8	1.4	4.7	7.9
	8–10 years	6	9.8	1.0	8.3	10.7
	11–13 years	10	12.6	0.7	11.4	13.7
	14–16 years	7	15.4	1.0	14.1	16.4
	17–19 years	6	18.4	0.7	17.5	19.1
	>20 years	4	22.9	2.2	21.2	26.0
Female	<8 years	11	7.1	0.7	5.9	8.0
	8–10 years	10	9.8	0.8	8.5	10.9
	11–13 years	15	12.3	0.9	11.0	14.0
	14–16 years	5	15.4	1.1	14.2	16.8
	17–19 years	6	18.9	0.9	17.4	19.8
	>20 years	12	26.6	7.7	20.9	44.4

SD, standard deviation.

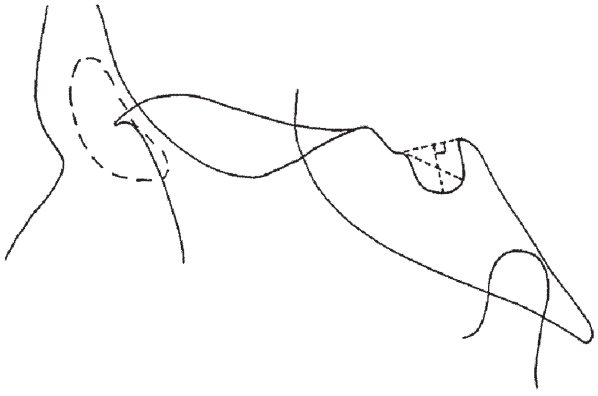

Figure 1 The reference lines used in the analysis of the sella turcica.

floor of the pituitary fossa. The antero-posterior greatest diameter of the sella turcica was measured from the turberculum sella to a point on the posterior inner wall of the pituitary fossa furthest from the turberculum sella.

The reference points were digitized and processed using the Dentofacial Planner® computer program (Dentofacial Software Inc., Toronto, Ontario, Canada). The measurements were calculated to the nearest 0.1 mm. The results were corrected for the radiographic magnification of 5.6 per cent.

Assessing the errors of the methods. Twenty of the total sample of 98 radiographs from the WS group chosen at random were traced and digitized by the same investigator (SA) on two separate occasions at least 2 weeks apart.

The measurement errors were estimated according to Dahlberg (1940). The coefficient of reliability and the variance of the duplicate measurements were also calculated, as recommended by Houston (1983). The errors of duplicate measurements in both groups were generally small. The range was 0.0–0.5 mm. The results from the error analyses are given in Table 2.

Statistical analyses. Data from all measurements were transferred to a statistical program (SPSS® Base 10.0, SPSS Inc., Chicago, Illinois, USA). The statistical differences between the arithmetic means of the measurements in the WS and control groups were compared using the Student's *t*-test for independent data, with a significance level of $P < 0.05$.

Morphology of the sella turcica

One lateral skull radiograph from each of the 62 individuals with WS described above was used in the assessment of sella turcica morphology. In cases of multiple radiographs from one individual, the most recent was used for the assessment. One radiograph was excluded due to poor quality. Thus, the final sample comprised 61 radiographs from 24 males and 37 females.

The contour of the sella turcica was traced on thin acetate paper under optimal illumination. For comparison, the normal sella turcica morphology reported by Björk and Skieller (1983) was used (Figure 2).

Table 2 The error of the method assessed from duplicate tracings of 20 radiographs of Williams syndrome subjects.

Variables	Dahlberg's calculation	Houston's coefficient of reliability (%)	Variance of the difference between duplicate measurements
Length	0.16	98.78	0.02
Depth	0.15	97.21	0.02
Diameter	0.13	99.37	0.01

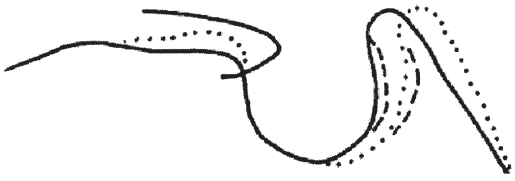

Figure 2 The contour of normal sella turcica morphology analysed from profile radiographs (anterior to the left), from childhood (solid line) to adulthood (dotted line). The upper contour of the anterior wall of the sella turcica appears to be perpendicular and unchanged during the normal course of development. The increasing size of the sella turcica under normal conditions is a result of resorption and apposition processes on the dorsum sellae. Redrawn with permission from Björk and Skieller (1983).

In order to assess morphological aberrations in the sella turcica in a normal population, the results from assessment of the Oslo University Craniofacial Growth Archive were used (Axelsson *et al.*, 2004).

Results

Size of the sella turcica

Data from the cephalometric measurements of the sella turcica for males and females divided into six age groups, with arithmetic means, standard deviations, maximum and minimum values, number of individuals, and the level of statistical significance between the study groups and the control groups are presented in Tables 3 and 4, respectively.

For all measurements, the means of the measurements for the WS groups were smaller than those for the control groups, with a few exceptions. The length of the sella turcica showed a variable result for the WS male groups with mostly smaller values than the male control groups, but the WS female groups showed mostly larger values compared with the female control groups but without reaching significant levels of difference (Figure 3a). The depth of the sella turcica was smaller for both WS males and females compared with their control groups, but the differences were not sufficiently large to be significant in all age groups (Figure 3b). The diameter of the sella turcica in the WS female groups was almost similar to that of the female control groups, while the WS males showed significantly smaller values at nearly all ages (Figure 3c).

Morphology of the sella turcica

Assessment of the morphological aberration of the sella turcica in the WS subjects showed five distinct types; oblique anterior wall, extremely low sella turcica, sella

Table 3 Sella turcica dimensions (in mm) in males with Williams syndrome (WS) versus Oslo University Craniofacial Growth Archive (control).

	WS males					Male control group					Significance
	Mean	SD	Minimum	Maximum	*n*	Mean	SD	Minimum	Maximum	*n*	
<8 years											
Length	8.7	1.7	6.0	10.0	6	8.8	1.5	5.3	13.2	35	ns
Depth	5.6	0.9	4.8	6.7	6	6.3	0.8	4.5	8.1	35	ns
Diameter	8.6	0.6	7.9	9.3	6	10.0	1.3	8.2	14.1	35	*
8–10 years											
Length	6.7	1.3	4.7	8.3	6	8.7	1.3	6.1	12.2	35	**
Depth	6.0	0.5	5.2	6.7	6	6.7	0.9	4.5	8.6	35	ns
Diameter	8.4	1.7	6.3	10.5	6	10.1	1.1	8.1	12.8	35	**
11–13 years											
Length	8.0	1.5	5.7	10.7	10	8.6	1.2	5.9	10.9	35	ns
Depth	5.9	0.7	4.8	6.7	10	6.7	1.1	4.6	9.7	35	*
Diameter	9.6	1.4	7.3	11.7	10	10.6	1.2	7.7	12.8	35	*
14–16 years											
Length	6.9	1.5	4.7	8.7	7	8.7	1.2	5.4	11.4	35	**
Depth	6.3	0.6	5.5	7.3	7	7.1	1.2	4.6	9.7	35	ns
Diameter	9.8	1.6	6.6	11.7	7	11.0	1.0	8.6	13.3	35	*
17–19 years											
Length	8.2	1.1	6.7	9.9	6	9.0	1.3	6.2	12.1	35	ns
Depth	6.9	1.2	5.2	8.3	6	7.4	1.2	4.9	9.6	35	ns
Diameter	10.9	1.0	9.7	12.6	6	11.5	1.1	9.0	13.5	35	ns
>20 years											
Length	10.0	1.4	8.8	12.0	4	8.9	0.9	7.4	10.7	19	ns
Depth	7.2	1.3	5.7	8.7	4	7.3	1.1	5.3	9.6	19	ns
Diameter	11.6	1.0	10.6	12.8	4	11.3	1.1	8.4	13.2	19	ns

SD, standard deviation.
ns, not significant; *significant at $P < 0.05$; **significant at $P < 0.01$.

Table 4 Sella turcica dimensions (in mm) in females with Williams syndrome (WS) versus Oslo University Craniofacial Growth Archive (control).

	WS females					Female control group					Significance
	Mean	SD	Minimum	Maximum	*n*	Mean	SD	Minimum	Maximum	*n*	
<8 years											
Length	8.6	2.3	6.3	13.3	11	8.5	1.3	5.7	11.0	37	ns
Depth	5.6	0.6	4.9	7.0	11	6.4	0.8	5.1	8.2	37	**
Diameter	8.8	1.4	7.0	12.5	11	9.8	1.3	7.8	12.6	37	*
8–10 years											
Length	8.7	1.7	5.7	12.1	10	8.2	1.4	5.1	10.7	37	ns
Depth	5.5	0.7	3.7	6.3	10	6.6	0.7	5.0	8.1	37	***
Diameter	9.6	1.5	7.0	12.3	10	10.2	1.3	6.9	12.4	37	ns
11–13 years											
Length	8.3	1.1	6.3	10.8	15	7.9	1.6	4.1	11.6	37	ns
Depth	6.1	1.0	4.6	8.7	15	6.7	1.1	2.9	8.9	37	ns
Diameter	10.1	0.9	8.3	12.3	15	10.5	1.2	7.3	12.8	37	ns
14–16 years											
Length	8.1	1.9	5.7	7.9	5	7.9	1.4	5.1	11.4	37	ns
Depth	6.9	1.0	5.7	10.1	5	7.2	1.0	5.3	9.2	37	ns
Diameter	10.8	1.9	9.1	13.1	5	11.1	1.1	8.6	12.9	37	ns
17–19 years											
Length	8.7	1.3	5.6	10.1	6	8.1	1.3	5.0	10.0	37	ns
Depth	5.9	1.3	4.3	7.8	6	7.1	1.1	4.5	8.9	37	*
Diameter	11.7	1.4	9.4	13.2	6	11.4	1.0	9.3	14.0	37	ns
>20 years											
Length	8.8	1.8	5.9	12.7	12	8.4	1.6	5.0	11.2	15	ns
Depth	6.6	1.2	4.6	9.2	12	7.2	1.2	4.8	9.3	15	ns
Diameter	11.3	2.1	7.6	5.5	12	11.7	1.1	10.1	13.2	15	ns

SD, standard deviation.
ns, not significant; *significant at $P < 0.05$; **significant at $P < 0.01$; ***significant at $P < 0.001$.

turcica bridging, irregularity (notching) in the posterior part of the dorsum sellae, and pyramidal shape of the dorsum sellae. The different types of sella turcica dysmorphology, including the normal sella turcica, are illustrated as tracings of the sella turcica and with enlargements from the profile radiographs in Figure 4a–f.

In WS subjects, a normal morphology of the sella turcica was found in only 36 per cent of the total population and consequently 64 per cent had one or more dysmorphological trait in the sella turcica. The WS females showed more sella turcicas with dysmorphological traits than WS males (68 versus 58 per cent).

The most frequent morphological traits in the WS male group were irregularity of the posterior part of the dorsum sellae in 42 per cent and a sella turcica bridge in 13 per cent. In the WS female group, the most frequent morphological traits were irregularity of the posterior part of the dorsum sellae in 43 per cent and an oblique anterior wall in 35 per cent (Tables 5 and 6).

Approximately one-third (31 per cent) of the individuals in the WS group had more than one type of morphological aberration of the sella turcica. The WS females also had more sella turcicas with multiple morphological aberrations.

In the reference material, one female showed a double contour of the sella turcica floor (Axelsson *et al.*, 2004), but this type could not be found in the WS group. Altogether, significantly more sella turcicas with dysmorphological traits were found in the WS group than in the reference group. All dysmorphological traits were more common in WS subjects, except for sella turcica bridging and a double contour of the floor.

Discussion

This investigation was part of a series of studies on children, adolescents, and adults with WS concerning dental, craniofacial, and neurocranial characteristics. In this study, the size and morphology of the sella turcica were investigated. An investigation of this type does not appear to have been performed previously.

The size of the sella turcica in the WS subjects in the present study was found to be slightly smaller compared with a normal age- and gender-related sample. Size measurements of the sella turcica have to-date almost solely been used as a diagnostic tool concerning expanding tumours or tumour-like processes in the pituitary gland (Weisberg *et al.*, 1976; Friedland and Meazzini, 1996; Alkofide, 2001).

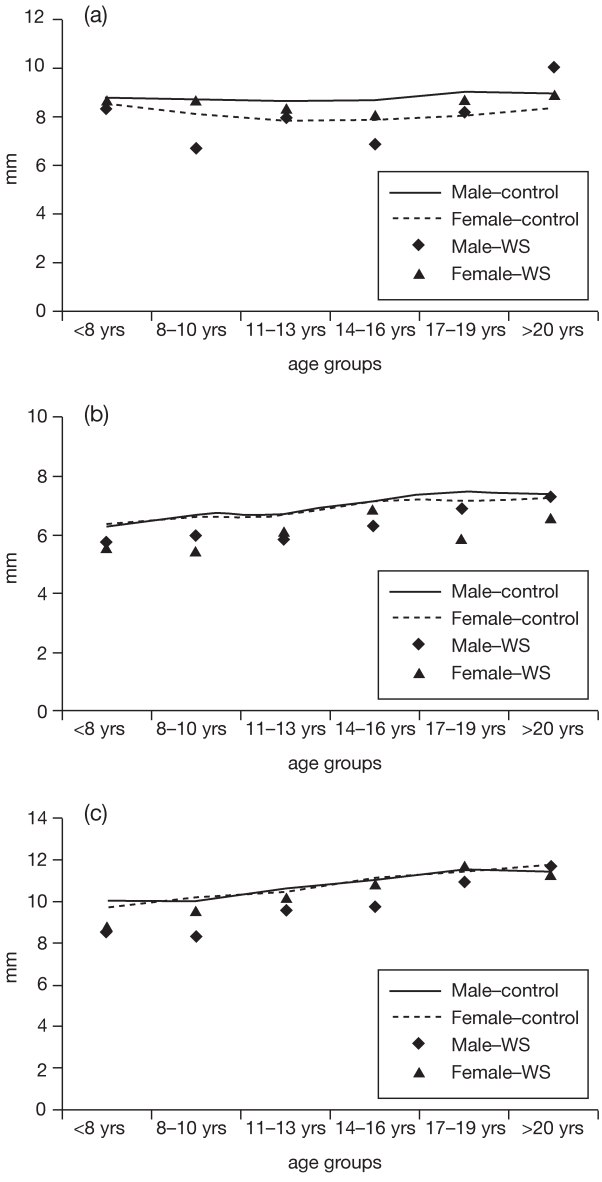

Figure 3 Graphical illustrations of (a) the length, (b) the depth, and (c) the diameter of the sella turcica for the Williams syndrome (WS) groups versus Oslo University Craniofacial Growth Archive.

The occurrence of sella turcicas with dysmorphological traits was also more frequent in the WS group than in the reference group. The most frequent trait in both WS males and females was irregularities or notching of the posterior part of the dorsum sellae. The occurrence of a sella turcica bridge was similar in both the study and reference groups, indicating that this dysmorphological trait is not more common in WS than in the normal population.

It is interesting that the occurrence and severity of the different morphological aberration types are more frequent in females with WS than in males. This gender difference was also shown by Kjær *et al.* (2001b) regarding sella turcica dysmorphology in Seckel syndrome. However, it has been reported that the morphology of the sella turcica is different in various genotypes (Kjær *et al.*, 1996, 1998b, c). In a study by Axelsson *et al.* (2005) on neurocranial size and morphology in WS subjects, the deviations were more severe in the female group than in the male group compared with a normal reference sample.

Sella turcica morphology has been investigated in a group of children with lumbosacral myelomeningocele using profile skull radiographs. In all cases, the anterior wall of the sella turcica differed from normal morphology (Kjær *et al.*, 1998a). In a study of sella turcica morphology in a group of Down syndrome foetuses it was shown that in this condition there are four types of deviation in the sella turcica (Kjær *et al.*, 1998c). Most of these pre-natal sella turcicas had a normal structure, whereas others exhibited notching in the anterior wall or in the sella floor, and in a few cases there was complete clefting of the sella floor. Russell and Kjær (1999) analysed the post-natal shape of the sella turcica in a group of Down syndrome patients using profile skull radiographs and found two major morphological types of deviation; in the anterior wall and in the floor. Kjær *et al.* (2001c) assessed the morphology of the sella turcica in 10 patients with a SMMCI and found that five had malformations, including a sella turcica bridge, very deep sella turcica, and small, narrow sella turcica.

Table 5 Morphological types of aberration in the sella turcica in males with Williams syndrome (WS) versus the male control group.

	WS males (n = 24)		Control males (n = 35)		95% confidence interval for WS males
	n	%	n	%	
Normal sella turcica	10	42	25	71	22–61
Oblique anterior wall	2	8	8	23	0–19
Low sella turcica	2	8	2	6	0–19
Sella turcica bridge	3	13	0	0	0–26
Irregularities of the posterior part of the dorsum sella	10	42	0	0	22–61
Pyramidal shape of the dorsum sella	2	8	0	0	0–19
More than one type	4	17	0	0	2–32

Table 6 Morphological types of aberration in the sella turcica in females with Williams syndrome (WS) versus the female control group.

	WS females (n = 37)		Control females (n = 37)		95% confidence interval for WS females
	n	%	n	%	
Normal sella turcica	12	32	24	65	17–48
Oblique anterior wall	13	35	1	3	20–51
Low sella turcica	5	14	6	16	2–25
Sella turcica bridge	4	11	1	3	1–21
Irregularities of the posterior part of the dorsum sella	16	43	4	11	27–59
Pyramidal shape of the dorsum sella	6	16	2	5	4–28
More than one type	15	41	1	3	25–56

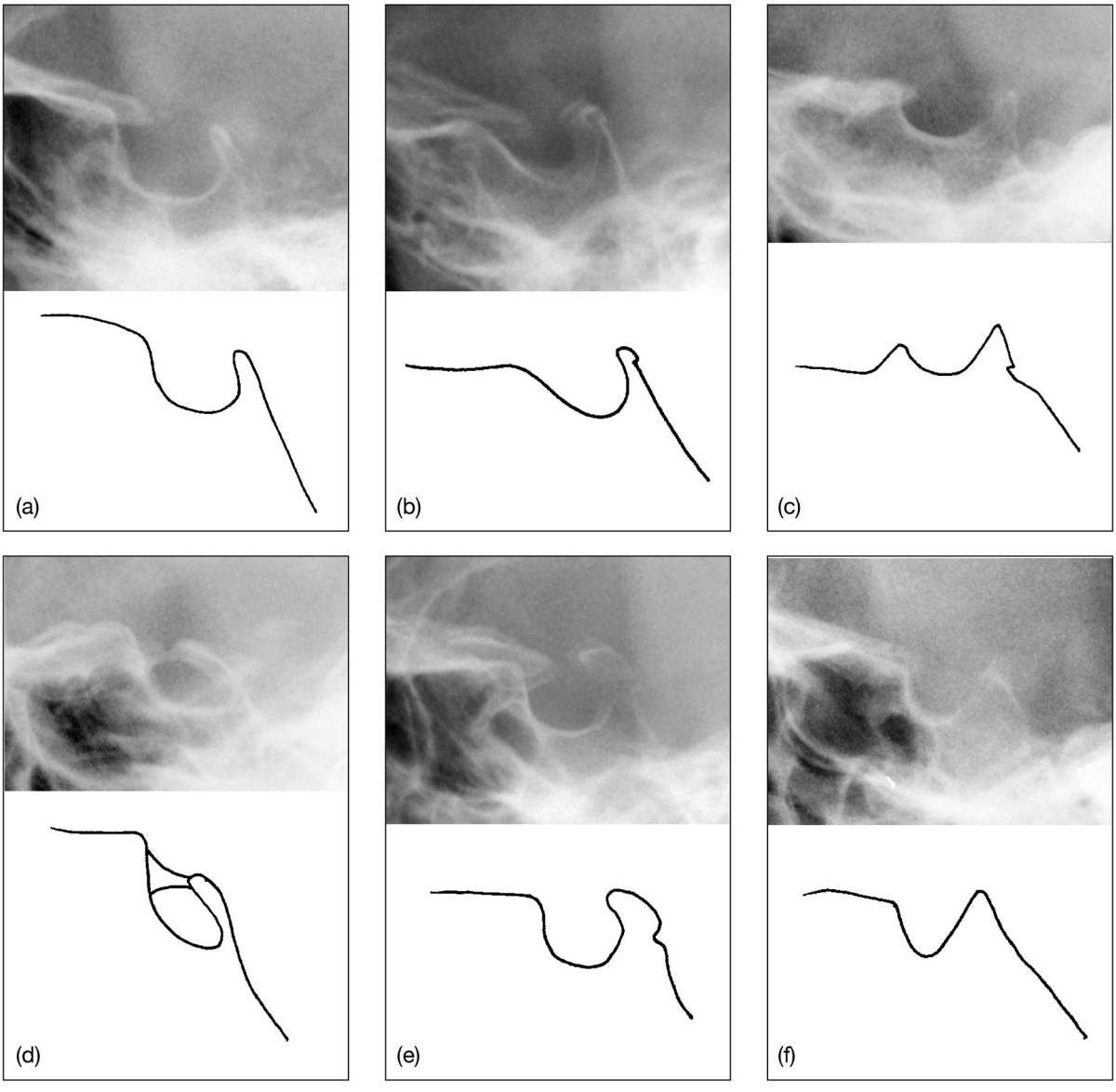

Figure 4 Tracings and details from lateral cephalograms of the different morphological types of sella turcica: (a) normal sella turcica, (b) oblique anterior wall, (c) extremely low sella turcica, (d) sella turcica bridge, (e) irregularity (notching) in the posterior part of the sella turcica, (f) pyramidal shape of the dorsum sellae.

Post-natal growth retardation is a consistent finding in WS subjects, but detailed endocrine studies have so far been scarce. A few single case reports concerning individuals with growth hormone deficiency have been published (Spadoni *et al.*, 1983; Kuijpers *et al.*, 1999). Partsch *et al.* (1994) found that insulin-like growth factor I (IGF-I) was within the reference range in both sexes, and IGF-II levels were normal in 80 per cent in a large number of individuals with WS.

The results of this study demonstrate morphological aberrations in the sella turcica in individuals with WS, which should be elucidated in future research and combined with neurological and endocrinological investigations. This study has also shown that the underlying gene defect in WS may influence the morphology of the sella turcica. The difference between sella turcica size and morphology in males and females with WS may also indicate a difference in hormonal factors between males and females. Sex-linked aspects of craniofacial syndromes may thus contribute to a better understanding of bone tissue development.

Conclusions

1. The sella turcica in subjects with WS showed a great variation in size.
2. The mean dimensions in length, depth, and diameter of the sella turcica in individuals with WS were smaller in both males and females compared with the control groups.
3. Specific morphological aberration types of the sella turcica occur more frequently and with greater severity in WS subjects.

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