CHAPTER 5

THE CERVICAL SPINE IN INFANTS WITH CLEFT LIP AND PALATE

5.1 Introduction

Orofacial clefts, including non-syndromic cleft lip with or without cleft palate, clefts of the secondary palate and bilateral cleft lip and palate, are the most common craniofacial deformities. These conditions affect one in every 700 to 1000 live births worldwide (Murray, 1995; 2002). Shprintzen *et al*. (1985) have suggested that CLP is part of a 'malformation spectrum' because of its frequent association with other abnormalities, which may include the cervical region.

The development of the cervical spine has been described by Truex and Johnson (1978) and Farman and Escobar (1982). At about the 12th day of embryonic life, a segmental craniocaudal condensation of mesodermal tissue, the somites, develops lateral to the developing neural tube and notochord. By the 22nd day, 42-44 somites have formed. The sclerotome component of the somites migrates medially to surround the notochord. As growth continues, the cranial portion of one sclerotome unites with the caudal portion of the adjacent sclerotome to form a vertebra. Specifically, one portion of the combined sclerotome segment migrates ventrally to form the centrum (body) of a vertebra; a second migrates dorsally in close proximity to the neural tube to form the vertebral arch, and a third portion migrates ventro-laterally to establish costal centres. Endochondral ossification of the upper cervical

vertebrae commences by the eight week of fetal life and is completed by about three to six years of post-natal life (Farman and Escobar, 1982; Sandham, 1986).

Cervical spine anomalies have been reported in several studies (Minaba, 1972; Sandham, 1986; Horswell, 1991; Ugar and Semb 2001). Furthermore, Osborne *et al*. (1971) have reported an association between malformations of the cervical spine and velopharyngeal incompetency in CLP individuals.

Previous studies of cleft lip and palate have applied two-dimensional lateral cephalometric methods but these have significant limitations, such as superimposition of structures, difficulty in identifying landmarks and poor visualization of 3D structures (Moyers and Bookstein, 1979; Cohen, 1984; Maue-Dickson, 1979; Fisher *et al*., 1999; Singh *et al*., 2004). Furthermore, these studies have been undertaken in children over five years and have been limited to specific ethnic groups.

Researchers investigating CLP have recognized the potential advantages of applying 3D CT to clarify whether CLP is associated with other craniofacial malformations or is a localized anomaly (Maue-Dickson and Dickson, 1980). To author's knowledge there have been no previous CT studies of the cervical spine in unoperated CLP infants during their first year of life before any surgical intervention.

The aims of this investigation were to study anatomical variations and abnormalities of the cervical spine using 3D CT in four groups of infants with clefts: unilateral cleft lip palate (UCLP); bilateral cleft lip and palate (BCLP); isolated cleft palate (ICP); and cleft lip primary palate/alveolus (CL) and to compare the findings with an NC group. It was also aimed to compare the ICP group with the other affected groups, as previous embryological studies have indicated that CLP infants are etiologically and

developmentally distinct from ICP group (Johnston and Bronsky, 1995; Hart *et al*., 2000), and to determine whether or not differences existed between CLP males and females.

5.2 Materials and Methods

The methods of data collection and statistical analysis have already been outlined in Chapter 3.

5.2.1 Data Collection

The sources of patients selected for this study, the breakdown by age, gender and cleft (CLP) or non-cleft (NC) group, and the problems encountered in collecting this information are detailed in Section 3.5.

5.2.2 CT Protocol

Axial scans were obtained with a GE Lightspeed Plus CT Scanner System at the Department of Radiology, Hospital Universiti Sains Malaysia. The protocol used is detailed in Section 3.6.

5.2.3 Cervical Variables

In this study, the total length of the cervical spine was calculated by adding the heights of vertebral bodies (C2-C7) and the height of the intervertebral spaces (Fig. 5.1). The height of each vertebral body was measured from the anterior superior medial surface to anterior inferior medial surface and the intervertebral space was measured from the anterior inferior medial surface of the vertebra above to the

anterior superior medial surface of the vertebra below (Fig. 5.2). The height of each vertebral body and intervertebral space was calculated and compared between CLP and NC individuals. Any cervical spine anomalies present in CLP and NC infants were also noted, including tilting of C1 (in relation to C2), synostosis and short posterior arch of cervical vertebrae.

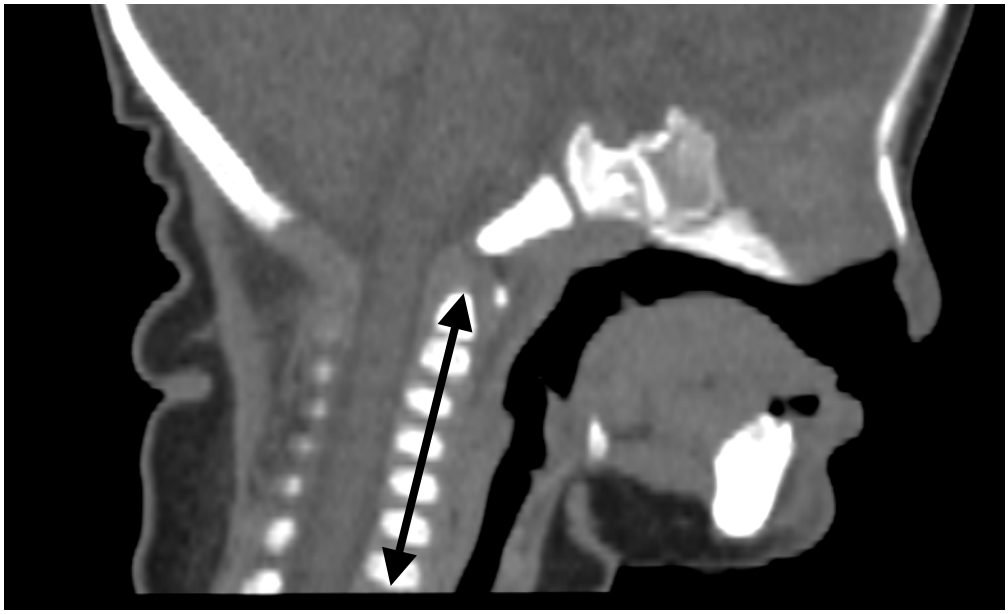


Figure 5.1 The overall length of the cervical spine was calculated by adding the heights of vertebral bodies (C2-C7) and intervertebral spaces (sagittal view).

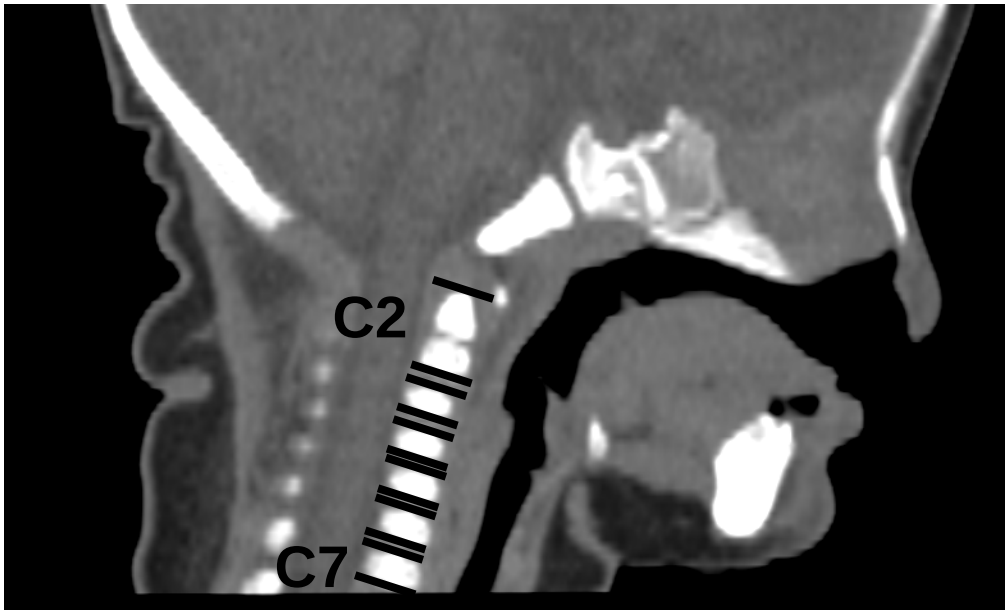


Figure 5.2 Measurement of the individual vertebral bodies and intervertebral spaces from C2 to C7 (sagittal view).

5.2.4 Statistical Analysis

The statistical model used to analyse the hyoid bone data has already been described in Section 3.11.

5.2.5 Errors of the Method

The methods for determining errors in the landmark determination and anthropometric variables derived from these landmarks by the use of repeated determinations are outlined in Section 3.12. Systematic errors in landmark location were tested using Hotelling's T^2 statistic. For anthropometric variables Student's paired t-tests were used to detect systematic errors (i.e. to ascertain whether the mean difference between repeated measures deviated significantly from zero) and Dahlberg's (1940) method of double determination was used to quantify the magnitude of random errors.

5.3 Results

The relocation errors for individual landmarks ranged from 0.2mm for anterior superior midline of C3 to 0.7mm for anterior inferior midline of C7.

Paired t-tests between repeat determinations of anthropometric variables indicated that there were two systematic errors at $p<0.05$ level. The statistically significant systematic errors associated with the measurement of the height of C5 and the intervertebral space of C5/C6 most probably resulted from the anatomical variation in the shape of C5. However, the mean differences were only 0.1mm and 0.2mm, and the cervical variables quantified using the Dahlberg statistic were 0.3mm for height of

C5 and 0.4mm for the intervertebral space between C5 and C6. This indicated that the errors were small, acceptable for this study and unlikely to bias the results.

Table 5.1 shows the descriptive statistics, including unadjusted means, standard deviations (SD) and coefficients of variation of hyoid bone variables.

Table 5.2 shows adjusted means and standard errors derived from the linear modeling analysis for the four cleft groups and NC group. None of the study variables significant differences between males and females in either the CLP and NC groups and so data are presented for both sexes combined. Using Generalized Linear Modeling analysis (PROC SAS, 2001), the vertebral body heights of C3, C4, C7 in CLP infants were found to be significantly smaller than in the NC ($p<0.05$) (Figs. 5.3 to 5.5). In contrast, the intervertebral spaces between C4/C5 and C5/C6 in CLP infants were significantly greater compared with the NC group ($p<0.05$) (Fig. 5.6). The intervertebral space of C5/C6 in the ICP group was significantly smaller when compared with the other cleft groups ($p<0.05$). The intervertebral space of C4/C5 in the ICP group was also smaller but of borderline significance ($p=0.053$). Even though the CLP group displayed smaller individual vertebral heights, the overall length of their cervical spine was found to be in the normal range. The cervical angle was significantly reduced in CLP compared to NC group ($p<0.05$) (Fig. 5.7). The GLM analysis indicated that the UCLP and BCLP infants comprised a homogenous group in terms of their cervical dimensions. The CL group had some similarities with the NC group, while the ICP group appeared to differ in cervical dimension from the UCLP and BCLP groups.

Table 5.1 Unadjusted means ($\bar{x}$), standard deviations (SD) and coefficients of variation (CV) of the vertebral bodies and intervertebral spaces (in mm and degrees).

Variables	**Groups**														
Cervical Spine	**NC (n=12)**			**UCLP (n=10)**			**BCLP (n=4)**			**CL (n=7)**			**ICP (n=8)**		
	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**
Height C2	13.3	1.22	9.1	12.8	1.75	13.7	12.8	1.79	14.0	13.1	1.86	14.2	13.7	1.89	13.8
IV space C2/3	3.3	0.99	30.3	3.3	0.51	15.6	3.1	0.98	32.3	3.2	0.85	26.3	2.9	0.62	21.2
Height C3	4.5	0.57	12.6	3.6	0.57	15.6	3.1	0.52	17.0	4.2	0.51	12.1	4.1	0.59	14.5
IV space C3/4	2.6	0.78	29.7	3.1	0.52	17.0	2.9	0.62	21.5	2.7	0.38	14.2	2.7	0.56	21.3
Height C4	4.5	0.51	11.2	3.8	0.52	13.8	3.7	0.88	24.1	4.3	0.52	12.1	4.0	0.77	19.0
IV space C4/5	2.4	0.67	27.5	3.2	0.38	12.1	3.0	0.91	30.4	2.6	0.39	14.9	2.6	0.55	20.9
Height C5	4.6	0.44	9.6	3.9	0.38	9.9	3.9	0.94	24.2	4.4	0.56	12.8	4.5	0.62	13.7
IV space C5/6	2.5	0.59	23.3	3.2	0.53	16.9	3.2	0.75	23.8	2.8	0.52	18.5	2.5	0.63	24.9
Height C6	4.8	0.67	14.0	4.2	0.73	17.4	4.1	0.92	22.7	4.6	0.69	15.1	4.6	0.52	11.3
IV space C6/7	3.0	0.61	20.3	3.1	0.29	9.3	3.0	0.28	9.4	3.1	0.69	22.4	2.8	0.41	14.5
Height C7	5.3	0.77	14.6	4.5	0.53	11.8	3.4	-	-	5.0	0.96	19.4	4.5	0.31	6.9
Length C2-C6 inf	38.4	4.11	10.7	38.9	3.10	8.0	36.2	6.86	19.0	39.3	4.63	11.8	39.8	3.34	8.4
Length C2-C7 sup	40.4	5.01	12.4	41.6	3.21	7.7	38.6	7.28	18.9	41.9	5.03	12.0	42.1	3.57	8.5
Length C2-C7 inf	42.5	4.72	11.1	44.6	4.50	10.1	36.8	-	-	45.8	6.75	14.7	44.9	2.30	5.1
Cranio-cervical angle	119.3	5.14	4.3	112.9	6.89	6.1	113.3	4.55	4.0	114.9	6.97	6.1	111.3	7.24	6.5

Table 5.2 Adjusted means and standard errors of the cervical spine variables (in mm and degrees).

Variables	Groups									
Cervical Spine	**NC (n=12)**		**UCLP (n=10)**		**BCLP (n=4)**		**CL (n=7)**		**ICP (n=8)**	
	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**
Height C2	13.0	0.40	13.0	0.43	13.1	0.68	13.1	0.50	13.5	0.48
IVS C2/C3	3.1	0.23	3.3	0.25	3.1	0.39	3.2	0.29	2.9	0.27
Height C3*	4.4	0.16	3.7	0.17	3.1	0.27	4.2	0.20	4.0	0.19
IVS C3/C4	2.5	0.18	3.0	0.19	2.9	0.30	2.7	0.22	2.7	0.21
Height C4*	4.5	0.19	3.8	0.19	3.8	0.30	4.3	0.22	4.0	0.21
IVS C4/C5*	2.3	0.16	3.3	0.16	3.1	0.25	2.6	0.19	2.6	0.18
Height C5	4.6	0.16	3.9	0.16	4.0	0.25	4.5	0.19	4.5	0.18
IVS C5/C6*	2.5	0.18	3.2	0.19	3.2	0.30	2.9	0.24	2.5+	0.21
Height C6	4.7	0.20	4.3	0.21	4.2	0.48	4.6	0.26	4.6	0.23
IVS C6/C7	2.9	0.18	3.2	0.17	3.1	0.35	3.1	0.19	2.8	0.17
Height C7*	5.3	0.26	4.6	0.26	3.8	0.54	4.8	0.25	4.5	0.20
Length C2-C6 inf	37.4	0.93	39.6	0.98	37.8	2.18	39.5	1.21	39.3	1.06
Length C2-C7-sup	39.4	1.18	42.4	1.11	40.6	2.34	42.2	1.28	41.5	1.13
Length C2-C7-inf	41.4	1.50	45.0	1.50	38.6	3.05	44.5	1.44	45.0	1.14
Cranio-cervical angle (deg)*	119.0	1.86	111.8	2.00	111.9	3.12	114.6	2.30	112.2	2.35

*Significant difference at $p<0.05$ between all cleft groups and non-cleft

IVS = Intervertebral spaces

+ Significant difference at $p<0.05$ between ICP and other cleft affected groups

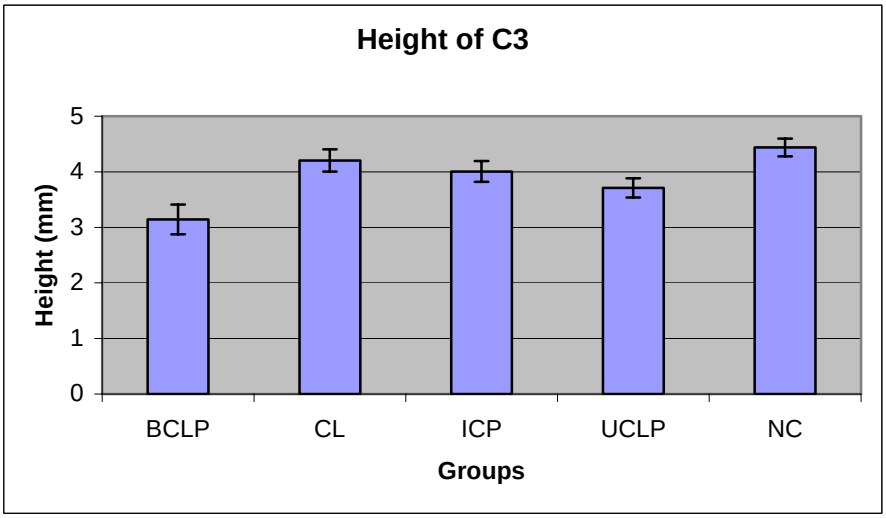


Figure 5.3 The height of vertebral body of C3 was significantly smaller in CLP compared to NC ($p<0.05$).

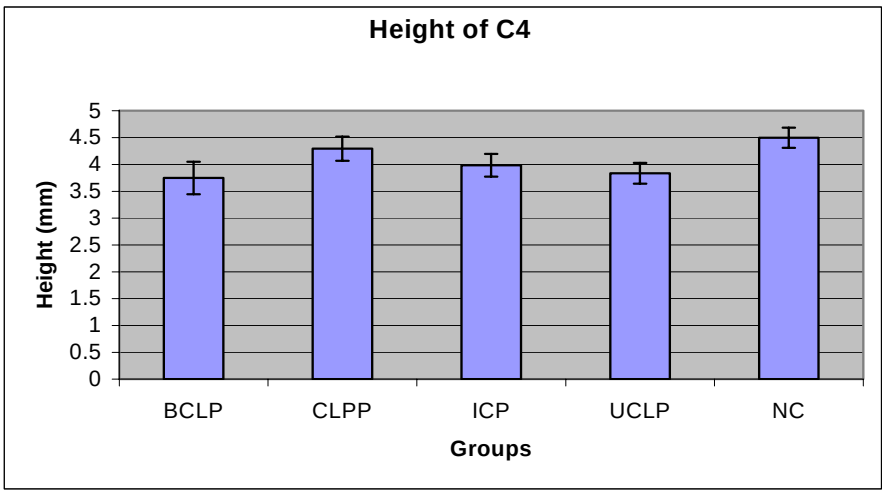


Figure 5.4 The height of vertebral body of C4 was significantly smaller in CLP compared to NC.

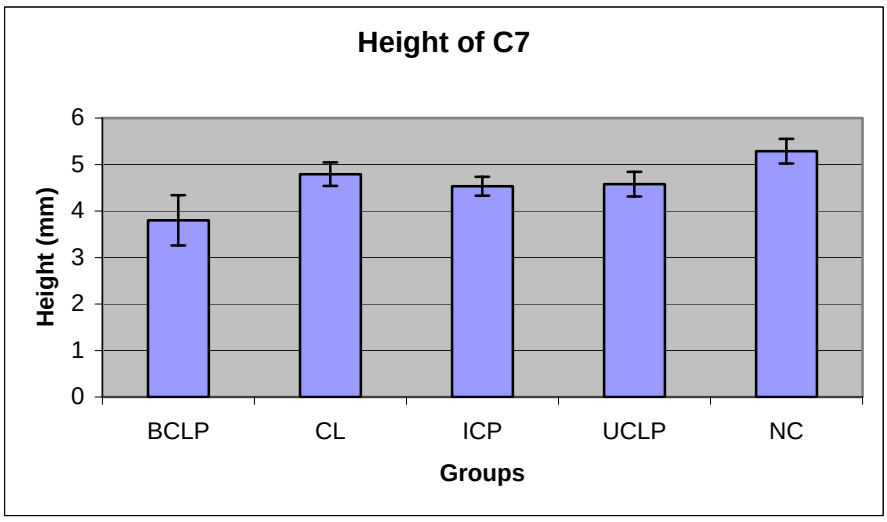


Figure 5.5 The height of vertebral body of C7 was significantly smaller in CLP compared to NC.

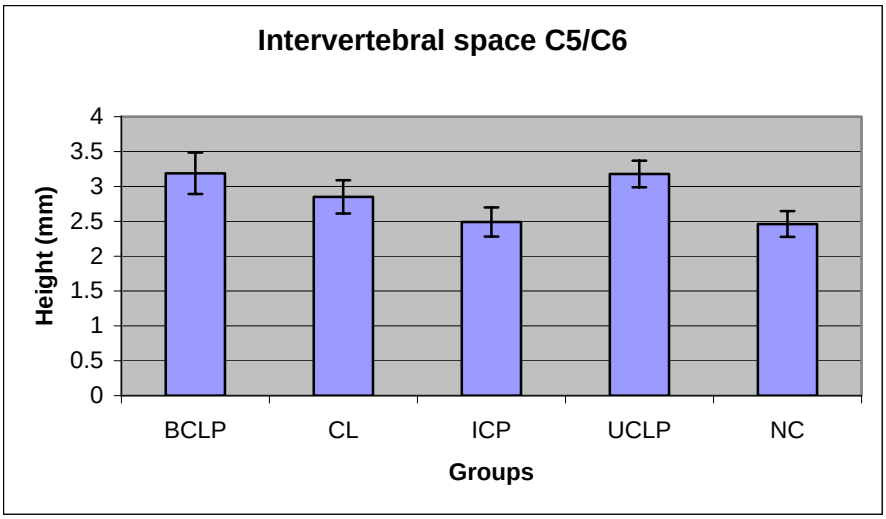


Figure 5.6 The intervertebral spaces between C5/C6 in CLP infants were significantly greater compared to the NC group. However, the intervertebral space of C5/C6 in the ICP group was significantly smaller than in the other cleft groups.

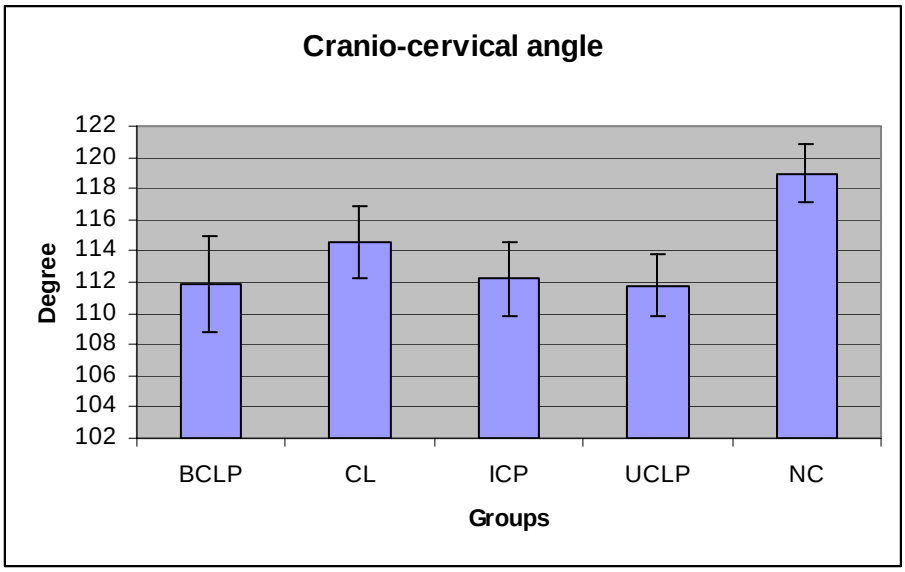


Figure 5.7 The cervical angle was significantly reduced in CLP compared to the NC group.

Using chi-square test, there was a borderline association between the occurrence of CLP and the presence cervical spine anomalies (X^2=3.49, df=1, p=0.06) (Tables 5.3a and 5.3b). The presence of ossification of the anterior arch of C1 in both CLP and NC groups before the age of six months is indicated in Table 5.4, showing 35% of

infants with CLP and 42% of the NC group.

Table 5.3a Cleft lip and palate and cervical spine anomalies.

Groups	N	Tilting of posterior arch of C1	Synostosis	Short posterior arch	C1	Abnormalities (total patients)
UCLP	10	0	1	1	0	1
BCLP	4	1	0	1	0	2
ICP	8	1	0	0	1	2
CL	7	0	1	0	1	2
Total CLP	**29**	**2**	**2**	**2**	**2**	**7/29 (24%)**
NC	**12**	**-**	**-**	**-**	**-**	**0/12 (0%)**

Table 5.3b Chi-square analysis of occurrence of CLP and cervical spine anomalies.

	CLP	NC	Total
Anomaly	7	0	**7**
Normal	22	12	**34**
Total	**29**	**12**	**41**

Borderline association (X^2=3.49, df=1, p=0.06)

Table 5.4 Ossification of anterior arch of C1 in CLP and NC infants.

Groups	Number	Ossification present before the age of 6 months
UCLP	10	2 (20%)
BCLP	4	3 (75%)
ICP	8	3 (50%)
CL	7	2 (42%)
Total CLP	**29**	**10 (35%)**
NC	**12**	**5 (42%)**

Anomalies noted were fusion of the posterior upper arch (in 2 cases) and short posterior arch of C1 (in 2 cases) (Fig. 5.8), tilting of atlas (C1) (in 2 cases) (Fig. 5.9a & b) and anterior arch anomalies of C1 (in 2 cases) (Figs. 5.10a & b) which included two anterior arches instead of one and an asymmetric anterior arch to the right. None of the NC group showed any of these cervical anomalies.

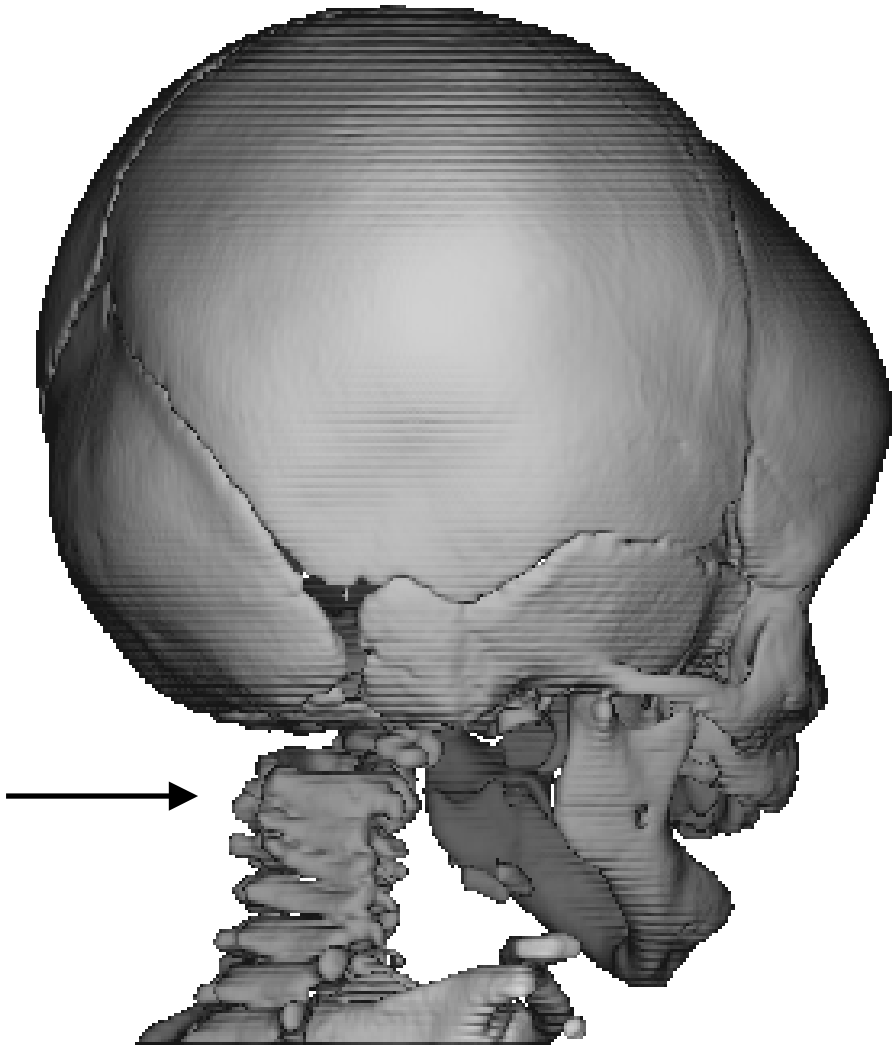


Figure 5.8 Synostosis of the posterior arch at C2, C3 and C4 in a patient with UCLP. This patient also shows a short posterior arch of C1 (posterior view).

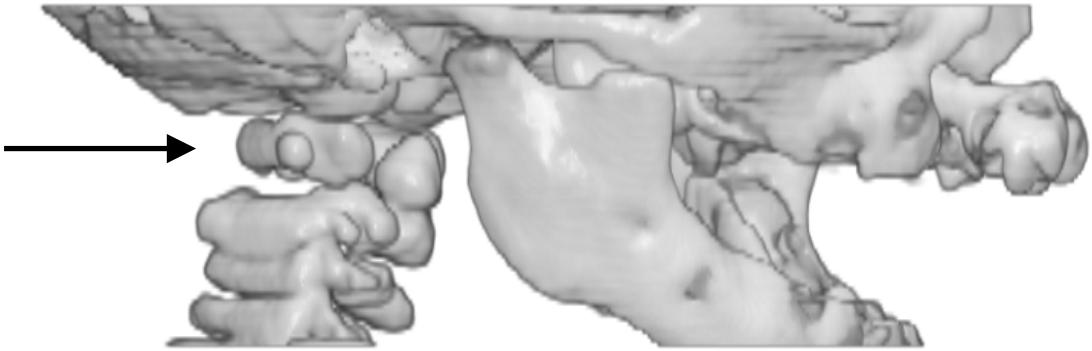


Figure 5.9a Right view of a patient with BCLP showing tilting of the posterior arch of C1.

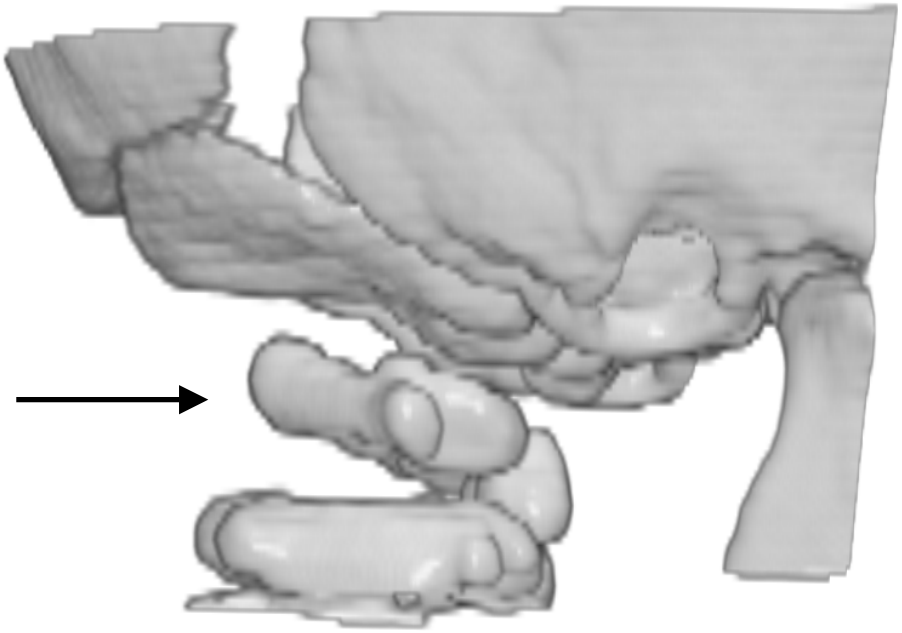


Figure 5.9b Right view of a patient with ICP showing tilting of the posterior arch of C1.

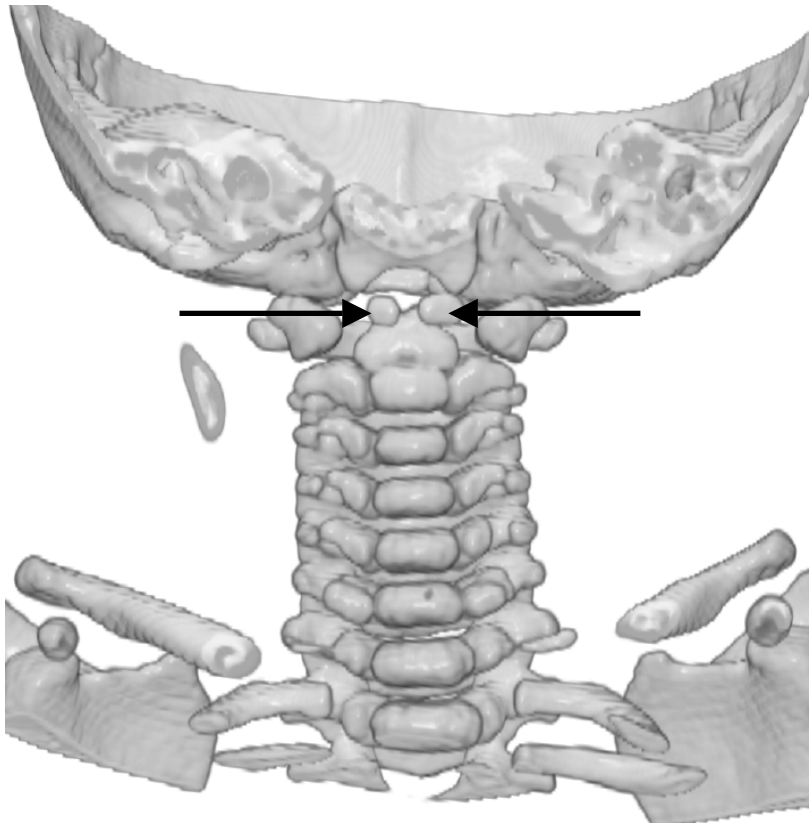
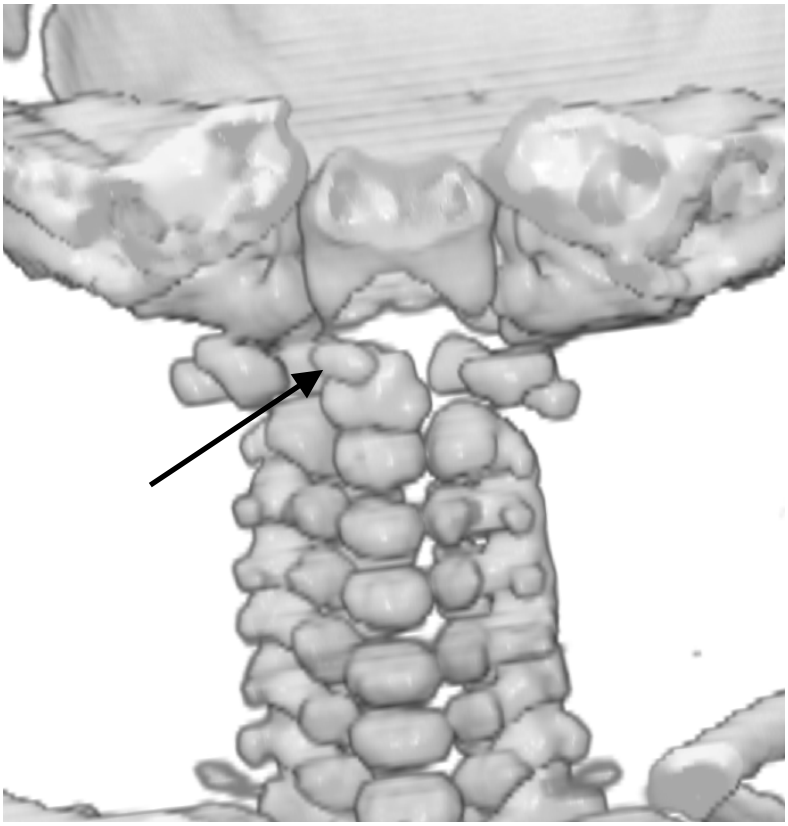


Figure 5.10 Posterior views of patients with: UCLP showing separation of the anterior tubercle of C1 (above) and ICP showing asymmetry of the anterior tubercle of C1 to the right (below).



5.4 Discussion

For the identification of cervical anomalies, previous studies suggest a lower age limit of 6 years because malformations of the upper cervical vertebrae could not be assessed using conventional radiography until complete development and synostosis (Sandham, 1986). Indeed, Sandham (1986) and Ugar and Semb (2001) excluded those patients below the age of 6 years with CLP because they claimed that failure of upper cervical vertebral components to develop or fuse can only be determined after the usual time for complete development and fusion has passed. In contrast to these suggestions, using 3D CT technology it was possible to observe anomalies of the cervical spine at an earlier stage of childhood.

In this study of the cervical spine of unoperated CLP infants in the 0-12 month age range, shortening of individual cervical vertebral bodies was found compared with an NC group. The inter-vertebral spaces were larger in the CLP groups, except for the ICP group which was smaller when compared to other affected groups. These changes may relate to an altered ossification pattern or skeletal development of the cervical spine in the cleft cases.

The finding of short vertebral bodies in the cervical spines of infants with clefts may be consistent with a delay in growth in infancy. Previous studies have shown a delayed growth in children with clefts of the lip and palate (Bowers *et al*., 1987; Seth and McWilliams, 1988; Harris and Hullings, 1990; Lilius and Nordstrom, 1992; Neiman and Savage, 1997; Grippaudo and Kennedy, 1999; Spyropoulos and Burdi, 2001).

These findings differ from these of Smahel and Skvarilova (1993) who reported

shortening of the overall length of the cervical spine in UCLP and BCLP groups. However, the shortening of the spine was less affected in ICP. In contrast to this study the ICP intervertebral spaces were smaller when compared to other combined cleft groups. Smahel and Skvarilova (1993) further suggested that the shortening of the spine in ICP was indicative of the participation of the spine in their development while, in other cleft groups, a simultaneous exposure to a teratogenic agent or any other developmental error during early stages of embryogenesis could explain the concomitant occurrence of clefting and spine anomalies. This finding is consistent with other embryological studies that ICP is morphologically different from other affected groups. However, the subjects in their study were adults who had been treated surgically and lateral head radiographs were used for the comparison.

The reduced cervical angle in CLP may be associated with postural changes to facilitate airway maintenance. Anderson (1997) in his study on craniosynostosis patients reported that cervical spine fusion, particularly those affecting the higher levels, may also have important consequences for head posture with resulting influences on craniofacial growth and dental occlusion. Other researchers have also proposed that cervical spine anomalies may alter head posture (Solow *et al*., 1984; Solow and Siersbaek-Nielsen, 1986; Hellsing *et al.*, 1987; Solow and Siersbaek-Nielsen, 1992; Nevard, 1994). These previous studies have also demonstrated associations between head posture and craniofacial morphology. However, all of these findings were obtained from non-cleft populations and so they should be assessed with caution when extrapolating to cleft individuals.

Previous studies indicate that anomalies of the cervical spine may influence the lifting of the head of the fetus and could be associated with the failure of the palatine shelves

to fuse, precipitating orofacial clefts (Ross and Lindsay, 1965; Smahel and Skvarilova, 1993: Ugar and Semb, 2001). Moore and Dalley (1999) propose that the joints between the vertebral bodies are designed for weight bearing, so decreased weight bearing could be a factor leading to larger intervertebral spaces. It might be associated with limitation in lifting of the head observed in utero (Ross and Lindsay, 1965). In babies born without clefts, the normal lifting of the head would probably put some weight on the spines that could account for the differences in the height of their intervertebral spaces compared to the cleft patients.

Many authors have noted the relationship between facial malformations and spinal anomalies (Sherk *et al*., 1982; Moore *et al*., 1995; Anderson, 1997; Anderson *et al*., 1997a; Anderson *et al*., 1997b) that is thought to result from the close spatial relationship between sclerotomic derivatives of the cervical somites and the branchial arches (Sherk *et al*., 1982). This study's findings suggest that upper cervical spine anomalies may be more common in Malaysian children with CLP (24%) than in American children (22%) (Horswell, 1991), Scottish children (13%) (Sandham, 1986), and Norwegian children (18%) (Ugar and Semb, 2001). However, it must be stressed that the study groups referred to include different proportions of cleft types so comparisons of incidence should be undertaken with some caution. Furthermore, the present study was based upon 3D CT scans of subjects while earlier studies were based upon 2D cephalometric radiographs.

The enhanced clarity offered by CT images may well display anomalies more clearly and thereby facilitate the diagnosis of CLP associated defects. Previous studies have reported similar frequencies of fusion in NC groups or in the general population, ranging from 0.5 – 5% (Gray *et al*., 1964; Brown *et al*., 1964; Farman and Escobar,

1982). In contrast, the author did not find any fusion anomalies, probably due to small sample size of the NC group. However, ethnicity cannot be ruled out as an explanation.

It has been reported that congenital fusion of the cervical spine is due to the failure of normal segmentation of cervical somites in utero (Hensinger, 1990). In addition, another study reported that deficiencies of the disc-like material between the cartilaginous hemicentra might favour bony fusion (Muller *et al*., 1986). Congenital fusion of the cervical spine has been associated with clinical sequelae in another condition known as Klippel-Feil syndrome where cleft palate is also a frequently associated finding with short neck and low posterior hairline (Cohney, 1963; Helmi and Pruzansky, 1980).

Variation in the inclination of the posterior arch of the atlas, referred to as tilting, was observed in two cases (one case each in BCLP, ICP). It is possible that tilting relates to head posture so further studies are required to determine whether this feature is linked specifically to CLP.

The findings of Wang *et al*. (2001) contrast those of this study. They reported that the anterior arch of NC children ossified by three months in 33% of subjects and in 81 % of the children by the age of 1 year. Wang's longitudinal study of normal children included a larger sample size and those findings remain significant.

Osborne *et al*. (1971) suggested a smaller than normal anterior arch of the atlas could have a direct effect on the anterior-posterior dimension of the pharynx. The anterior arch of C1 is suggested to play a significant role in the establishment of adequate velo-pharyngeal function and speech in children with CLP (Osborne *et al*., 1971;

Sandham 1986). These findings suggest that the ossification of anterior arch of C1 may be compromised in patients with CLP and this may later contribute to problems in speech.

The importance of the anterior arch of C1 and upper cervical vertebrae was highlighted by Berkowitz (1996) in achieving adequate velopharyngeal closure and speech because the musculofascial layer covering the upper cervical vertebrae that forms the posterior pharyngeal wall is only 2 to 5 mm thick. Epidemiologic studies have shown that patients with craniofacial birth defects, many of whom suffer velopharyngeal incompetence, have a higher prevalence of upper cervical spine anomalies than the general population (Osborne *et al*., 1971). The cervical spine anomalies noted in this study could further contribute to the disproportion between the normal anatomic components of the local speech mechanism, a finding consistent with a previous study by Cohney (1963).

The anomalies of C1 found in this current study suggest a predictive role for C1 in the management of children with CLP particularly in relation to speech. The emerging importance of the development of C1 as an early indicator of craniofacial growth in NC subjects has also been highlighted by previous studies (Huggare, 1989; Solow and Siersbaek-Nielsen, 1992).

In summary, smaller bodies and greater intervertebral spaces in CLP, may indicate that cervical skeletal development is abnormal and/or that cervical maturation is delayed in infants with CLP. This perturbation may influence head posture or lifting of the head and could be associated with the failure of the palatal shelves to fuse, resulting in cleft lip and palate formation. There is also evidence of a high frequency of cervical anomalies in CLP infants that may also be associated with delayed

ossification and lead to subsequent problems with speech. The mechanism underlying the apparently altered development of the cervical spine in CLP infants is yet to explained. However, it has been pointed out that the presomitic and somitic development of the upper cervical spine is transitional and unstable, and is presumably susceptible to environmental disturbances (Bland, 1987).

5.5 Conclusions

This is the first CT study of the cervical spine in patients with cleft lip and palate. The smaller bodies and greater intervertebral spaces may indicate that skeletal development is delayed in cleft lip and palate groups. Furthermore, the observed cervical spine anomalies and the delay in the ossification of the anterior arch of C1 may contribute to problems with speech. The results of this study support the suggestion that the cervical spine plays a significant role in the development of cleft lip and palate.

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CHAPTER 6

THE NASOPHARYNX IN INFANTS WITH CLEFT LIP AND PALATE

6.1 Introduction

The pharynx is a fibromuscular tube situated behind the nose, mouth and larynx. It extends downwards from the base of the skull to the level of C6 vertebra, where it becomes continuous with the oesophagus (Moore, 1999). Anteriorly, it communicates with the nose through the posterior nasal apertures (choanae). Inferiorly, it communicates with the oropharynx at the oropharyngeal isthmus. The roof and the posterior wall forms a continuous slope, opposite the posterior part of the body of the sphenoid, basi-occiput, and anterior arch of atlas. In the mucous membrane on the posterior wall there is a collection of lymphoid nodules that are referred to as adenoids when enlarged in children (Moore, 1999).

The opening of the auditory tube lies above the soft palate in the lateral wall of the pharynx. The opening is guarded above, behind and in front by a prominent rounded ridge, the torus or tubal elevation, formed by the trumpet-shaped medial end of the tubal cartilage. At the lower margin of the opening is a very slight bulge, due to the underlying levator palati muscles. The auditory tube (pharyngotympanic tube, eustachian tube) is a trumpet-funnel shaped tube connecting the middle ear cavity with the nasopharynx. In adults, it is about 3 cm long and is directed downward, forward and medially but in children it is shorter and straighter. The posterior one-

third of the auditory tube lies in bone and anterior two-thirds is cartilaginous. The posterior one-third, which is about 1 cm long, lies in the petrous temporal bone and it opens into the anterior wall of the middle ear cavity. The medial end is narrow and is called the isthmus. It lies postero-medial to the spine of the sphenoid and attaches to the cartilaginous part.

The muscles associated with opening and closing the auditory tube are the tensor palati and levator palati (Dickson, 1972). Tensor palati, which lies antero-laterally to the auditory tube, arises from the base of the skull and the lateral side of the tube. Its fibers descend and converge to form a delicate tendon that winds around the hamulus and extends forward to form the muscle of the soft palate. Posterior-medial to the auditory tube is the levator palati, which arises from the base of the skull and inferior surface of the auditory tube. It enters the pharynx and extends forward to merge with the muscles of the soft palate. When these muscles relax, the lumen of the auditory tube is closed but during contraction the lumen is opened, such as during swallowing, yawning and sneezing.

The primitive pharynx forms in the late embryonic period as a dilatation of the cranial end of the foregut, lying between the developing heart anteriorly and developing chondrocranium postero-superiorly. The lateral aspects project as a series of pouches, referred to as pharyngeal pouches between the branchial arches (Sperber, 2001).

Cleft lip and palate is responsible for a number of physiological disorders. Babies born with cleft lip and palate can have difficulty in swallowing and breathing due to the communication between the nasopharynx, the nasal fossae and the oral cavity (Tisza and Gumpertz, 1962). There is a high frequency of middle ear infection in children with clefts and this has been related to auditory tube dysfunction (Paradise,

1975; Cole and Cole, 1974; Fara and Dvorak 1970; Seif and Dellon, 1978; Doyle *et al*., 1980; Rood and Doyle, 1982; Aniansson *et al*., 2002). Speech is also, therefore, often impaired.

The morphology of the nasopharynx is of importance when evaluating the function of the velopharyngeal components (Wada *et al*., 1997). However, this has received little attention because of the limitation of the methods available to make measurements. Previous studies of cleft lip and palate have applied two-dimensional lateral cephalometric methods but these have significant limitations, such as superimposition of structures, difficulty in identifying landmarks and poor visualization of 3D structures (Moyers and Bookstein, 1979; Cohen, 1984; Maue-Dickson, 1979; Richtsmeier and Cheverud, 1986; Fisher *et al*., 1999; Singh *et al*., 2004). Furthermore, the subjects of these studies have been older children and adults, limited to specific ethnic groups. Researchers investigating CLP have recognized the potential advantages of applying 3D CT to clarify whether CLP is associated with other craniofacial malformations or is a localized anomaly (Maue-Dickson and Dickson, 1980). However, the author is not aware of any previous CT studies of the nasopharynx in CLP infants during their first year of life before any surgical intervention.

The main aim of this study was to use CT imaging and computer technology to compare skeletal components of the nasopharynx and to quantify anatomical variation between a unaffected group (NC) and four groups of infants with clefts: unilateral cleft lip palate (UCLP); bilateral cleft lip and palate (BCLP); isolated cleft palate (ICP); and cleft lip primary palate/alveolus (CL). The other aims were to compare the ICP group with the other affected groups, as previous embryological studies have

indicated that CLP infants are etiologically and developmentally distinct from ICP group (Johnston and Bronsky, 1995; Hart *et al*., 2000), and to compare males and females.

6.2 Materials and Methods

The methods of data collection and statistical analysis have already been outlined in Chapter 3.

6.2.1 Data Collection

The sources of patients selected for this study, the breakdown by age, gender and cleft (CLP) or non-cleft (NC) group, and the problems encountered in collecting this information are detailed in Section 3.5.

6.2.2 CT Protocol

Axial scans were obtained with a GE Lightspeed Plus CT Scanner System at the Department of Radiology, Hospital Universiti Sains Malaysia. The protocol used is detailed in Section 3.6.

6.2.3 Nasopharyngeal Variables

Linear and angular variables were computed from selected landmarks to quantify nasopharyngeal width, height and depth, as well as enabling nasopharyngeal angles, vomerine angles and sphenopalatine angles to be determined. Definitions were as follows:

6.2.3.1 Nasopharyngeal width

i. Inter-hamular notch distance was the distance measured between the deepest points of the left and right hamular notches that were located posteriorly between posterior tuberosities and the pterygoid processes of sphenoid (Fig. 6.1).

ii. Inter-hamular distance was the distance measured from the tip of the left and right hamular processes of the medial pterygoid plates of the sphenoid (Fig. 6.1).

iii. Inter-lateral pterygoid plate distance was measured between the most lateral points on the left and right lateral pterygoid plates located at their posterior/inferior points (Fig. 6.1).

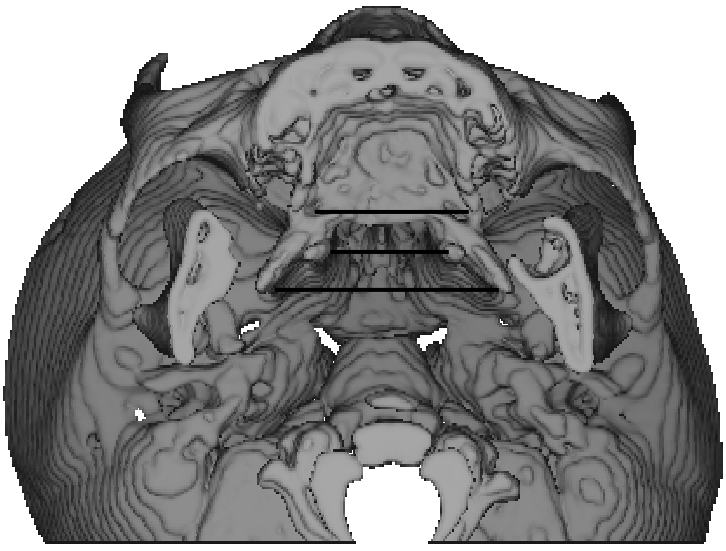

Figure 6.1 3D CT reconstruction of axial view showing the measurement of the width from the hamular notch, hamular process and posterior inferior point of the lateral pterygoid plate.

iv. The width of the hamulus to the lateral pterygoid plate was measured from the left and right hamulus on the medial pterygoid plate to the most lateral points on the left and right lateral pterygoid plates located at their posterior-inferior points (Fig. 6.2).

Areas of the posterior part of the maxilla and zygoma were measured to determine if there was any change in the width of the bony nasopharynx and whether this affected the maxilla and zygoma. This was because of the relationship of these structures with the nasopharynx.

v. Inter-maxillary tuberosity distance was the distance measured from the most posterior-inferior point in the midline of the maxillary tuberosity on left and right sides (Fig. 6.2).

vi. The width of the zygoma was measured between landmarks that were located at the lowest point on the external suture between zygomatic and maxillary bones to determine if this area was also affected (Fig. 6.2).

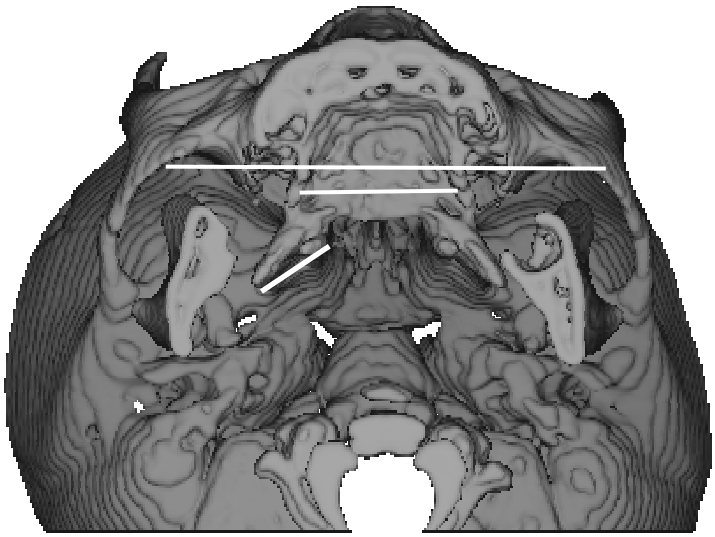

Figure 6.2 3D CT reconstruction of axial view showing the measurement of the width from the hamulus to posterior inferior point of the lateral pterygoid plate, maxillary tuberosity and zygoma.

6.2.3.2 Nasopharyngeal height

This was measured from the landmarks on the posterior part of the vomer called hormion to the hamulus on the left and right sides (6.3).

6.2.3.3 Nasopharyngeal depth

The depth of the nasopharynx was measured from:

i. The most anterior part of the foramen magnum (basion) to the posterior part of the vomer (hormion) (Fig. 6.3).

ii. From basion to the hamulus on left and right sides (Fig. 6.3).

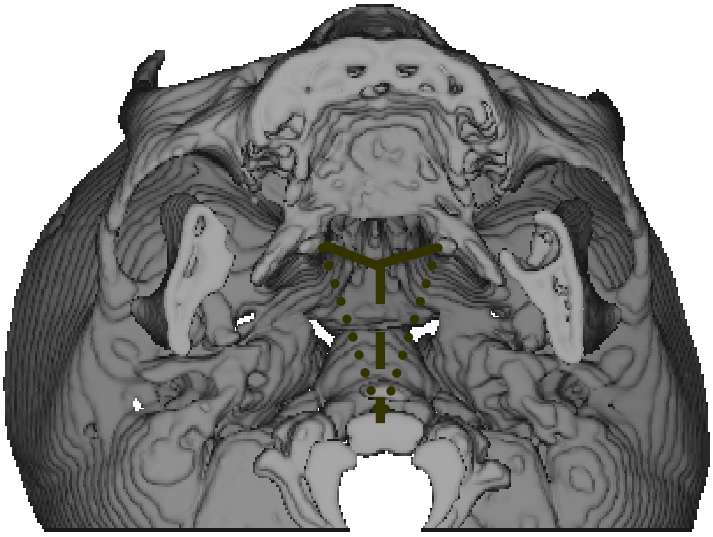

Figure 6.3 3D CT reconstruction of axial view showing the measurement of the height from the vomer to left and right hamulus (——) and the depth measured from basion to left and right hamulus (**……**) and basion to posterior part of vomer (**▬ ▬ ▬**).

6.2.3.4 Nasopharyngeal angles

i. Hamulus angle (Fig. 6.4)

As the hamulus is one of the important anatomical structures associated with

the function of the auditory tube, the angulation of the hamulus was measured using landmarks on the tip of the hamulus , the posterior-inferior point on the maxillary tuberosity and the most inferior-posterior point on the lateral pterygoid plate. The left and right sides were compared to see if there was any asymmetry in these bony landmarks.

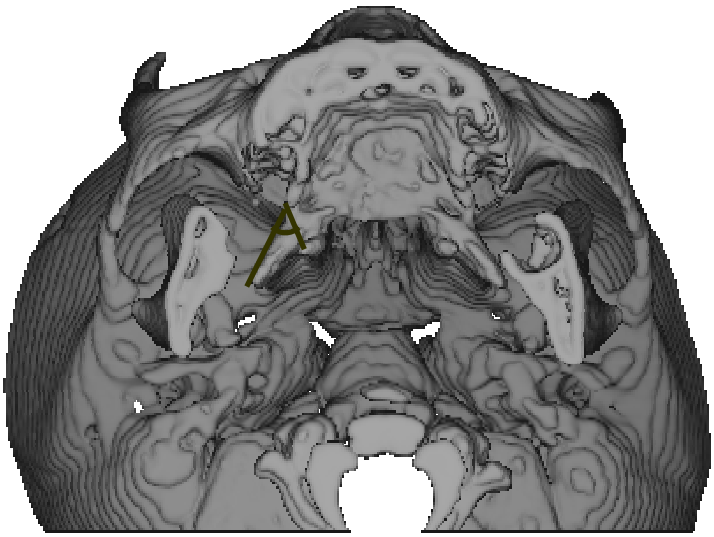

Figure 6.4 3D CT reconstruction of axial view showing the measurement of the hamulus angle from the hamulus to the maxillary tuberosity and to the lateral pterygoid plate.

ii. Sphenopalatine angle (Fig. 6.5)

This is the angle between the anterior nasal spine, sella and nasion (the junction between the frontal bone and nasal bone)

iii. Vomerine angle (Fig. 6.6)

The vomerine angle or the angle of the midface was obtained by joining the line extending from the anterior nasal spine-posterior part of the vomer and nasion-sella.

These angles (sphenopalatine and vomerine) were measured to determine whether there was any vertical compression of the structures in the region.

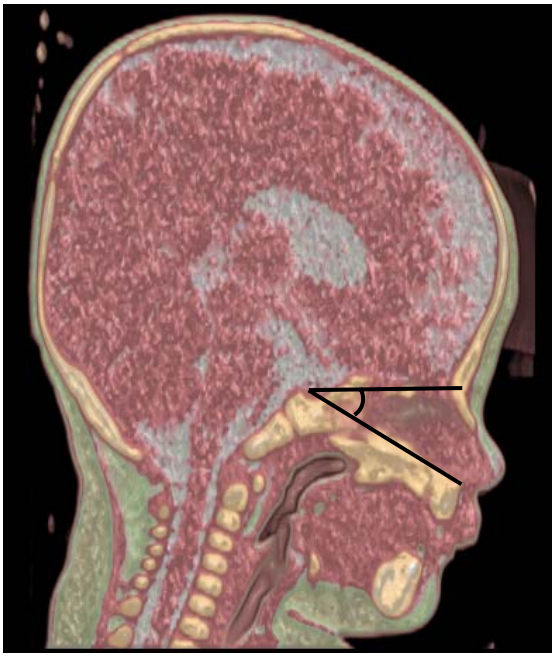

Figure 6.5 3D CT reconstruction of sagittal view showing the sphenopalatine angle was measured as the angle between nasion, sella and anterior nasal spine.

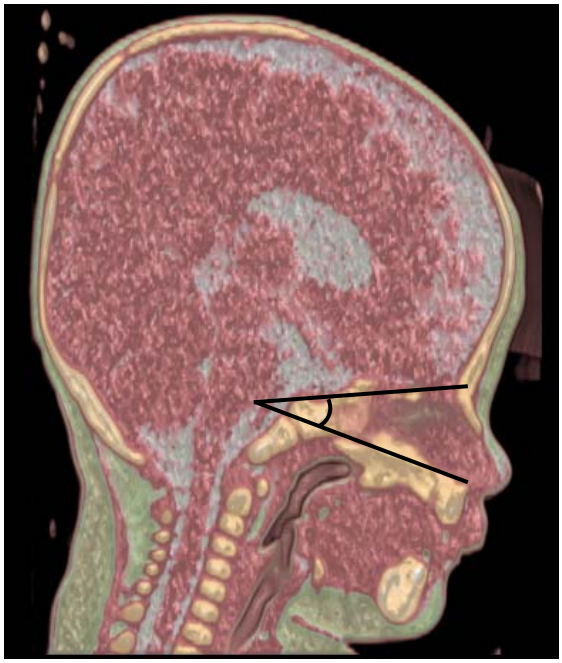

Figure 6.6 3D CT reconstruction of sagittal view showing the vomerine angle measured between nasion-sella and anterior nasal spine-vomer.

6.2.4 Statistical Analysis

The statistical model used to analyse the nasopharynx data has already been described in Section 3.11.

6.2.5 Errors of the Method

The methods for determining errors in the landmark determination and anthropometric variables derived from these landmarks by the use of repeated determinations are outlined in Section 3.12. Systematic errors in landmark location were tested using Hotelling's T^2 statistic. For anthropometric variables Student's paired t-tests were used to detect systematic errors (i.e. to ascertain whether the mean difference between repeated measures deviated significantly from zero) and Dahlberg's (1940) method of double determination was used to quantify the magnitude of random errors.

6.3 Results

The relocation errors for individual landmarks were not significant. This ranged from 0.3mm for the right hamular notch to 0.8mm for the landmark right zygo-maxillare inferius. These findings indicated that errors in the method were small and unlikely to bias the results.

Paired t-tests between repeat determinations of anthropometric variables indicated that there were two systematic errors at $p<0.05$ level. The statistically significant systematic errors were associated with the height of the vomer to left and right hamulus and the width of the right hamulus to posterior inferior point of the lateral pterygoid plate, and most probably they resulted from anatomical variation in its

shape. However, the mean differences were only 0.2mm, and the nasopharyngeal variables quantified using the Dahlberg statistic were 0.4mm for both heights and 0.5mm for the width. This indicated that the errors were small, acceptable for this study and unlikely to bias the results.

Table 6.1 shows the descriptive statistics, including the unadjusted means, standard deviations and coefficients of variation of nasopharyngeal variables. Table 6.2 shows adjusted means and their standard errors using the PROC GLM SAS 2001 statistical package.

Table 6.1 Unadjusted means ($\bar{x}$), standard deviations (SD) and coefficients of variation (CV) of the nasopharyngeal variables (in mm and degrees).

Variable	**Groups**														
Nasopharynx	**NC (n=12)**			**UCLP (n=10)**			**BCLP (n=4)**			**CL (n=7)**			**ICP (n=8)**		
	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**
Inter-hamular notch	26.7	3.07	11.2	33.0	2.65	7.9	33.6	3.72	11.1	29.5	2.92	9.9	29.7	6.32	21.3
Inter-hamulus	23.4	3.22	13.8	29.9	2.27	7.6	29.3	2.54	8.7	25.7	2.57	10.0	26.3	4.59	17.5
Inter-lateral pterygoid	37.6	4.13	11.0	42.9	3.79	8.8	41.2	3.91	9.5	39.1	3.33	8.5	39.9	6.19	15.5
Hamulus – lat pterygoid pl lt	8.7	2.27	26.1	7.1	1.48	20.8	6.4	2.19	34.1	7.4	1.04	14.0	7.1	1.67	23.6
Hamulus – lat pterygoid pl rt	8.3	1.76	21.2	7.4	1.56	21.0	7.3	1.59	21.8	7.9	1.95	24.6	7.6	1.33	17.6
Intermaxillary tuberosity dist.	27.5	3.32	12.1	34.5	3.31	9.6	34.2	3.07	9.0	29.8	2.80	9.4	30.6	5.21	17.0
Interzygomatic	64.3	6.70	9.8	69.6	3.78	5.4	68.0	7.55	11.1	67.4	6.40	8.9	66.7	7.16	9.5
Hormion – hamulus lt	19.2	2.33	12.1	20.3	1.42	7.0	20.9	2.07	9.9	20.0	2.16	10.8	19.1	3.75	20.1
Hormion – hamulus rt	18.6	2.93	15.8	19.9	1.49	7.5	20.1	1.86	9.3	19.3	2.30	11.9	18.3	3.47	19.4
Hormion – basion	23.6	2.05	8.7	23.9	1.60	6.7	23.5	3.13	13.3	22.8	1.44	6.3	26.4	3.70	14.5
Basion - hamulus lt	27.7	3.11	11.2	28.4	2.31	8.2	27.4	3.12	11.4	28.0	3.42	12.2	27.4	2.70	9.0
Basion - hamulus rt	27.4	3.32	12.1	28.3	2.34	8.3	27.7	3.13	11.3	27.6	2.65	9.6	27.3	2.94	9.3
Hamulus angle lt	40.5	5.50	13.6	36.1	6.49	18.0	37.4	3.20	8.6	39.2	4.27	10.9	42.6	7.51	17.6
Hamulus angle rt	40.2	5.51	13.7	39.0	6.25	16.0	42.3	6.50	15.4	36.1	6.08	16.8	44.8	5.04	11.3
Sphenopalatine angle	33.0	5.79	17.6	31.0	2.03	7.0	28.0	2.55	9.1	31.1	1.99	6.4	31.5	2.19	7.0
Vomerine angle	21.3	5.11	24.0	19.5	2.74	15.8	17.3	4.13	23.8	17.1	2.37	13.9	20.4	2.94	14.2

The coefficient of variation (CV) is used to describe the variation in a population. The sphenopalatine angle CV is smaller in the CLP group than the NC group. This increase in variation in the NC group could be due to growth and a larger age range in the small sample.

Table 6.2 Adjusted means and standard errors of the nasopharyngeal variables (in mm and degrees).

Variables	**Groups**									
Nasopharynx	**NC (n=12)**		**UCLP (n=10)**		**BCLP (n=4)**		**CL (n=7)**		**ICP (n=8)**	
	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**
Inter hamular notch*	25.6	0.77	33.5	0.83	34.3	1.30	29.6	0.96	29.3^{+}	0.91
Inter hamulus*	22.3	0.59	30.2	0.63	29.8	0.99	25.7	0.73	25.9^{+}	0.70
Inter-lateral pterygoid*	36.0	0.86	43.1	0.92	41.7	1.43	39.9	1.06	39.5	1.00
Hamulus - lateral Ptry.plate lt*	8.3	0.50	7.2	0.53	6.5	0.84	7.4	0.62	7.0	0.59
Hamulus - lateral Ptery.plate rt	8.0	0.49	7.4	0.52	7.3	0.81	7.9	0.60	7.6	0.57
Inter-maxillary tuberosity distance*	26.4	0.77	35.0	0.83	34.9	1.30	29.9	0.96	30.2^{+}	0.91
Inter-zygomatic distance*	62.3	1.23	70.0	1.32	68.5	2.07	67.4	1.53	66.2	1.44
Hormion - hamulus lt*	18.2	0.47	20.1	0.50	21.5	0.78	20.1	0.58	18.7^{+}	0.55
Hormion - hamulus rt*	17.8	0.47	20.2	0.50	20.6	0.79	19.3	0.59	18.0^{+}	0.55
Hormion - basion	23.0	0.64	24.0	0.69	23.7	1.07	22.9	0.80	26.2^{+}	0.75
Basion - hamulus-lt	26.8	0.65	28.6	0.69	27.7	1.08	28.0	0.80	27.2	0.76
Basion - hamulus rt	26.5	0.63	28.4	0.66	27.9	1.04	27.6	0.77	27.1	0.73
Hamulus angle lt	40.2	1.84	36.0	1.97	37.2	3.08	39.2	2.28	42.7	2.16
Hamulus angle rt	40.8	1.77	38.2	1.90	42.1	2.97	36.1	2.20	45.0^{+}	2.08
Sphenopalatine angle	32.7	1.16	31.0	1.24	27.9	1.94	31.1	1.44	31.5	1.46
Vomerine angle	21.2	1.19	19.4	1.28	17.2	2.00	17.0	1.48	21.4	1.51

* Significant difference at $p<0.05$ between all cleft groups and non-cleft

+ Significant difference at $p<0.05$ between ICP and combined cleft groups

The widths at the hamular notches (Fig. 6.7), hamuli (Fig. 6.8) and lateral pterygoid plates of the nasopharynx were significantly greater in the CLP groups compared with the NC group ($p<0.05$).

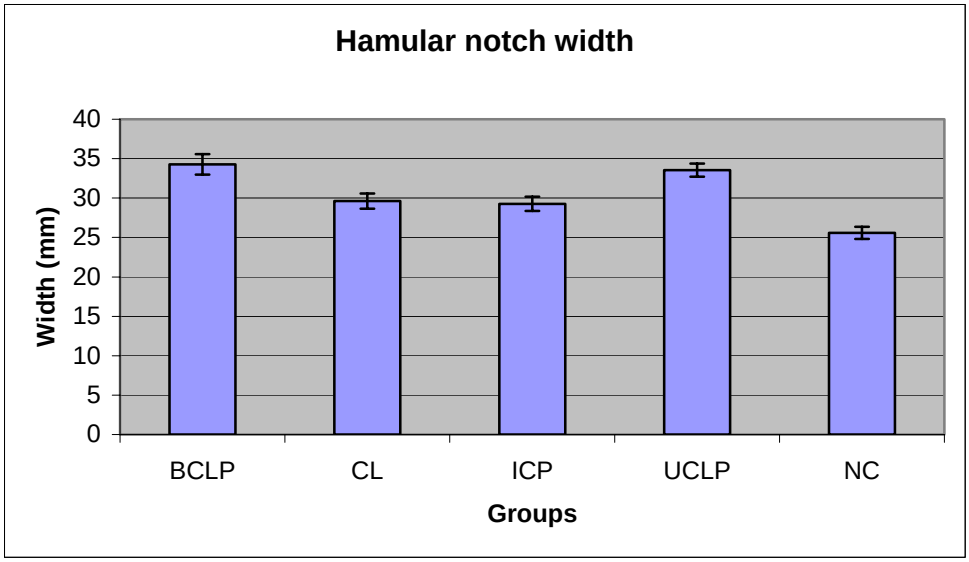

Figure 6.7 Adjusted mean values and standard errors for the hamular notch width in CLP and NC groups. The CLP groups were significantly wider than the NC group and the ICP group was significantly smaller when compared to other CLP groups.

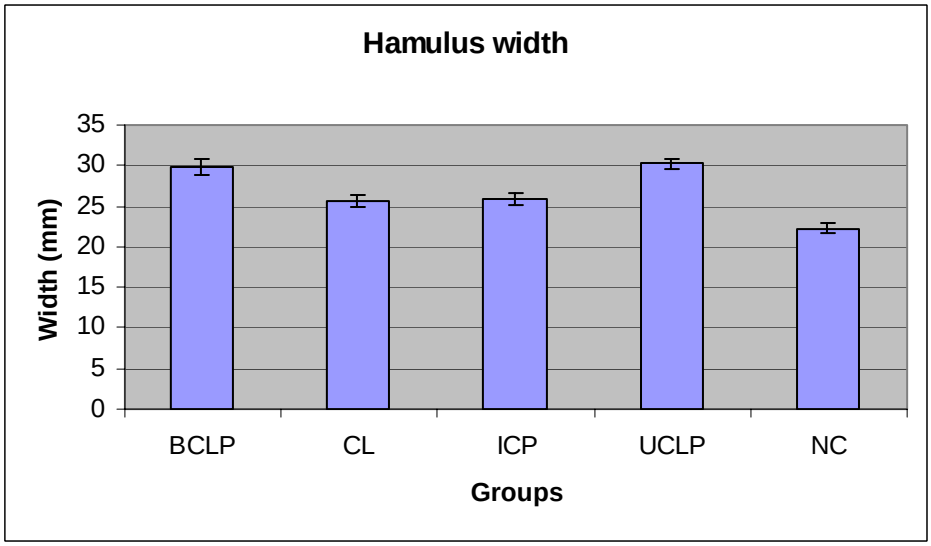

Figure 6.8 Adjusted mean values and standard errors for the hamulus width in CLP and NC groups. The CLP groups were significantly wider than the NC group and the ICP group was significantly smaller when compared to other CLP groups.

The width of the lateral pterygoid plate in the ICP group was not significantly different when compared to other CLP groups, however, the males (M) were significantly larger than the females (F) (Fig. 6.9). The width from the hamulus to lateral pterygoid plate was significantly smaller on the left side in the CLP groups compared with the NC group ($p<0.05$) but the right side was not significant. The widths of the hamular notch and the hamulus of ICP were significantly smaller when compared to the other cleft groups ($p<0.05$).

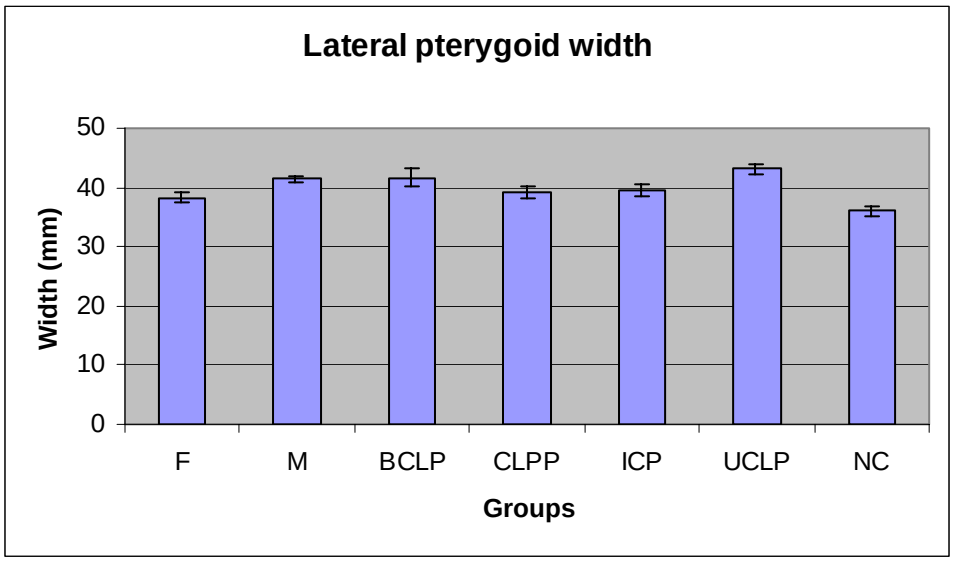

Figure 6.9 Adjusted mean values and standard errors for the lateral pterygoid plate width in CLP and NC groups. The CLP groups were significantly wider than the NC group and the ICP group was not significantly different when compared to other CLP groups. The males (M) were significantly larger than females (F).

There was a significant increase in the distance between the maxillary tuberosities in CLP groups compared to NC ($p<0.05$). However, when the ICP group was compared with other affected groups the distance was significantly smaller ($p<0.05$) (Fig. 6.10). The width of the zygoma was significantly greater in the CLP group compared with the NC group ($p<0.05$) (Fig. 6.11) and the ICP group was not significantly different to the other cleft groups. The width of the zygoma was significantly larger in males than in females ($p<0.05$) (Fig. 6.11).

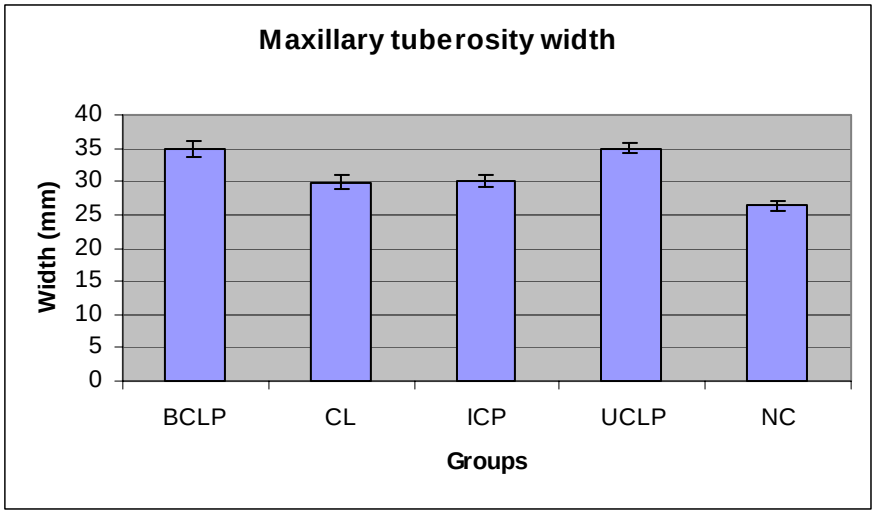

Figure 6.10 There was a significant increase in the distance between the maxillary tuberosities in CLP groups compared to NC ($p<0.05$). The ICP group distance was significantly smaller when compared with other affected groups.

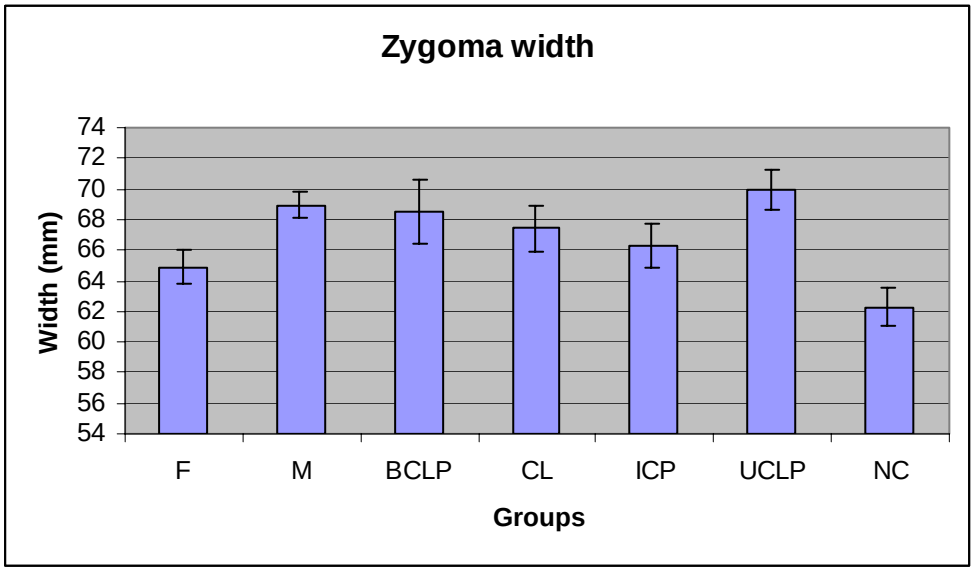

Figure 6.11 The width of the zygoma was significantly greater in the CLP group compared with the NC group ($p<0.05$). The ICP group was not significantly different compared to the other cleft groups. The width was significantly larger in males (M) than females (F).

The height of the nasopharynx from the posterior part of the vomer (hormion) to hamulus left and right was significantly greater in the CLP groups compared to the NC ($P<0.05$). The ICP group was significantly smaller on both sides when compared

to other cleft groups ($p<0.05$), however, the width from the vomer to hamulus right was significantly larger in males than in females (Figs. 6.12 and 6.13).

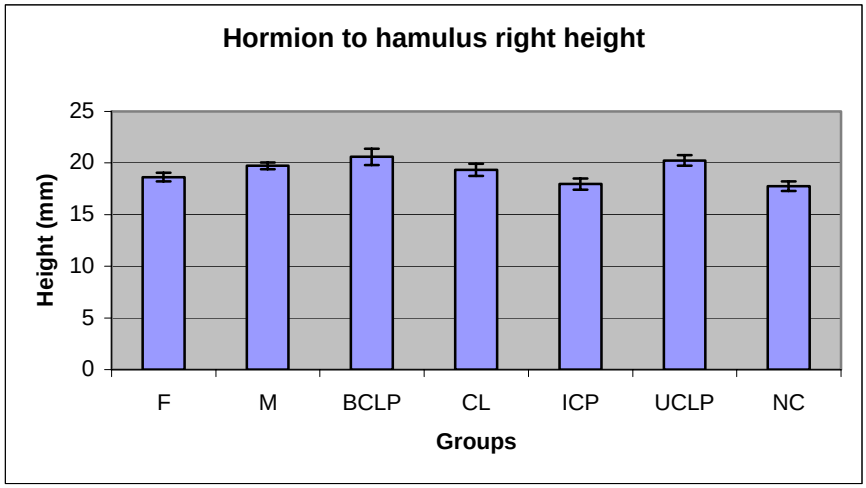

Figure 6.12 Adjusted mean values and standard errors for the hormion to hamulus right height in CLP and NC groups. Values for the CLP groups were significantly greater than for the NC groups and the ICP group was significantly smaller when compared to other CLP groups. Males (M) were significantly larger than females (F).

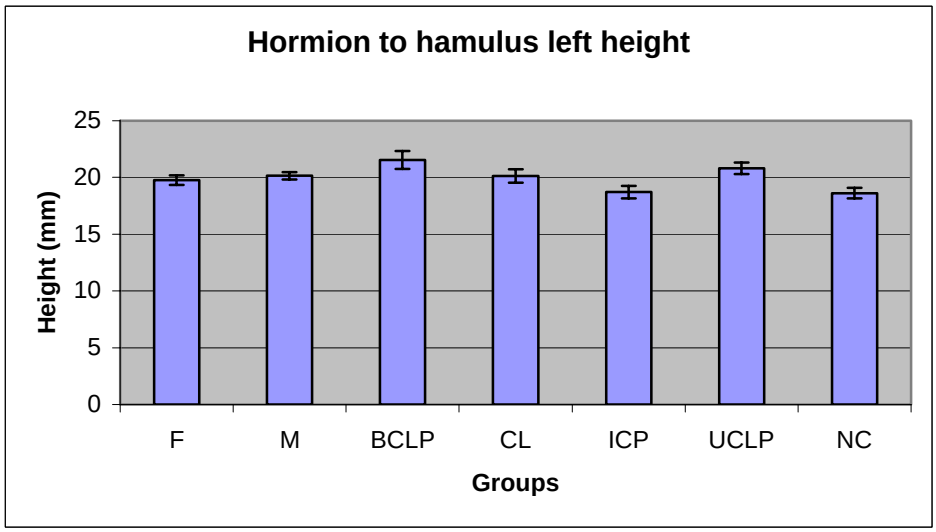

Figure 6.13 Adjusted mean values and standard errors for the hormion to hamulus left height in CLP and NC groups. Values for the CLP groups were significantly greater than for the NC group and the ICP group was significant smaller when compared to other CLP groups. Males (M) were not significantly different from females (F).

No significant differences was found when the depth from vomer to basion was compared between CLP and NC groups, however, the depth from vomer to basion was significantly larger in the ICP group when compared to other affected groups ($p<0.05$). The nasopharyngeal depth from basion to the both sides of the hamulus was not significantly different in CLP when compared to the NC groups. The nasopharyngeal depths from basion to left and right hamuli in the ICP group were also not significantly different when compared to other affected groups.

The angle of the hamulus on the both sides was not significantly different in the CLP and NC groups. The hamulus angle in the ICP group on the right was significantly greater when compared to other affected groups ($p<0.05$) and the p value associated with the hamulus angle in the ICP group on the left when compared to other affected groups was $p = 0.056$.

The sphenopalatine angle was smaller ($p=0.09$) and the vomerine angle was also smaller ($p=0.07$) in the CLP group when compared to the NC group but not statistically significant. The sphenopalatine and vomerine angles in the ICP group were not significant when compared to other affected groups.

6.4 Discussion

The results of this 3D study demonstrate significant increases in the width of the nasopharynx in unoperated CLP infants compared with NC infants. This finding is consistent with Subtelny (1955) who found that the nasopharynx was abnormally wide and the width between the maxillary tuberosities was increased in unoperated CLP subjects.

The present results suggest that the increase in nasopharyngeal space in CLP may be related to a potential compression of the nasopharyngeal structures. This is in agreement with findings of Maue-Dickson and Dickson (1980), who described an increased distance between right and left pterygoid plates in subjects with clefts. Furthermore, they reported an increased pharyngeal width and an increased area of the Eustachian tube cartilage. Dickson and Maue-Dickson (1983) analyzed age-matched fetuses with and without cleft palate, and reported that there was compression of those structures between the lateral walls of the pharynx and the side-walls of the cranium, including the eustachian tube.

The significant increase in width of the maxillary tuberosity is associated with the significantly larger nasopharyngeal width in the CLP cases. This is not surprising, since the pterygoid plates are locked to the maxillary tuberosities through the medium of the pyramidal process of the palatine bones (Subtelny, 1955).

The widths of the hamular notch, hamulus and maxillary tuberosity of ICP are significantly smaller, in addition to being significantly smaller in height, when compared to other affected groups. The significant different in the variation of the width and height of ICP group from the other affected groups is in agreement with other embryological studies suggesting that clefts of the lip and palate are etiologically and developmentally distinct from cleft palate alone (Johnston and Bronsky, 1995; Hart *et al*., 2000).

Data on patients with abnormalities of the pterygoid plates have led researchers to suggest that compression of structures lying between the lateral pharyngeal walls and the side-walls of the cranium, may result in a negative impact on auditory tube patency (Maue-Dickson and Dickson, 1980). These researchers have further

suggested that many ear problems that are observed in infants with cleft lip and palate may be related not only to cleft palate and associated functional conditions in the pharynx, but also to anatomical features of in the sphenoid and temporal bones. In this study, the width of the zygoma at the zygomaxillary suture was significantly greater in CLP infants when compared to NC infants. This finding is consistent with Hermann *et al*. (1999) who used 2D cephalometrics and different landmarks. This suggests that increased nasopharyngeal space could also be associated with increases in external cranial base width at the level of the zygoma.

The significant increase in the height of the nasopharynx noted in this study is not consistent with findings of Hermann *et al*. (1999), who found that the height of the bony nasopharynx was decreased in UCLP compared to unilateral incomplete cleft lip. The authors suggested that the decrease in the height was due to reduced posterior height of the maxilla. However, as regards to maxillary height, this 3D study was able to investigate in considerable detail the bony landmarks of the area with the enhanced imaging permitting description of subtle changes that could not be observed with earlier technology.

Osborne *et al*. (1971) showed that patients with congenital palatopharyngeal incompetence had greater antero-posterior diameters of the nasopharynx. In this study, the significantly larger pharyngeal depth in ICP compared to other combined cleft groups is consistent with the clinical importance of insufficient velopharyngeal closure especially in this particular group compared to others**.**

Difference were found between males and females in the width of the zygoma and lateral pterygoid plates, as well as the height of the vomer to right hamulus. In both cases the average for males was significantly larger than for females.

The angulation of the hamulus was not significantly different in CLP compared to NC. However, the hamulus angle in the ICP group on the right was significantly greater when compared with other affected groups ($p<0.05$). The hamulus angle on the left in ICP group was larger but of borderline significance only ($p=0.056$). This suggests that there was a variation in the angulation of the hamulus in the ICP group compared to the other affected groups.

These findings are not consistent with those of Subtelny (1955), but comparisons must be undertaken with caution because of methodological issues. Subtelny utilized laminagraphy, a body sectioning radiographic technique, to evaluate the lateral dimensions of the osseous naso-pharyngeal and related areas. Analysis of the angular inclination of the pterygoid plates using this method revealed asymmetry of right and left inclinations, with greater asymmetry being evident in cleft cases. He also found the angulation of the medial pterygoid plates was greater in all cleft types. The precise methodology employed including landmark determination is unclear from his report.

The width from the hamulus to the lateral pterygoid plate was significantly smaller on the left side in the CLP groups compared with the NC group and the difference in angulation of the hamulus may reflect alterations of the medial pterygoid plates and hamulus. These findings may lead to alteration in the origin of the associated tensor vela palatini muscle, the orientation of its tendon, and the function or pull of the muscle, leading to an alteration in the biomechanics of tubal dilator mechanism. The hypothesis that deviation of the anatomical structures may cause eustachian tube dysfunction is supported by a case report by Aizenbud *et al*. (2000). A 12-year old boy with UCLP underwent maxillary expansion prior to bone grafting. The patient

had secretory otitis media causing temporary hearing loss. The possible causes of these problems may have been related to enlargement of an oro-nasal fistula and this communication could have led to a higher risk of infection of the nasopharynx. In addition, the expansion procedure may have caused stretching of the tensor and levator veli palatini muscles, affecting eustachian tube function. These sequelae of the expansion were resolved when the appliance was removed. A similar mechanism might also explain the high prevalence of middle ear infection in CLP. It has been estimated by some investigators that virtually all patients with a cleft palate have middle ear disease (Paradise, 1975).

The smaller vomerine and sphenopalatine angles found in this study also suggest a potential vertical midface compression in CLP. The vomerine angle was defined as the intersection of the line joining the anterior nasal spine to the vomer, and the nasion to the sella. The sphenopalatine angle was measured between the anterior nasal spine, sella and nasion (the junction between the frontal bone and nasal bone). In an earlier study that reported a similar result (Brown *et al*., 1989; Carrie *et al*., 2000) the sphenopalatine angle (SPA) was assessed using lateral cephalometric techniques. The angle was defined as being between the line drawn along the endocranial surface of the frontal bone, traversing the anterior clinoid processes and a second line drawn along the hard palate through the anterior nasal spine. The SPA used by Carrie *et al*. (2000) and the vomerine and sphenopalatine angles of this study essentially describe the same bony relationships in the mid-face region and can be compared. Carrie *et al*. (2000) noted that in those cleft palate children with hearing loss the SPA was smaller than in normal hearing groups ($p=0.01$). They suggested there was compression of structures, including the eustachian tube, between the lateral walls of the pharynx and side-walls of the cranium, and concluded that the anatomical differences in the skull

base between normal and cleft palate subjects contributed to the incidence of hearing loss as well as being reflected in the different SPA values. The authors further suggested that a greater SPA value was associated with better eustachian tube function in control and cleft palate group without hearing loss. Although different methodology was applied, the findings in the present study are consistent with those of Carrie *et al*.

An anatomically based explanation of tensor veli palatini (TVP) function requires not only knowledge of its origin and insertion, but also its angle of action (Swarts and Rood 1990). The angle of action of the TVP relative to the medial lamina of the cartilage and its attachment to the cranial base has implication for efficient functioning. Cartilage rotation can be accomplished most effectively by a force vector directed inferiorly and anteriorly (i.e., toward the hamulus). Any distortion of these relationships (e.g., cleft palate) will alter the effectiveness of the TVP action and hence Eustachian tube function. The alteration of the position of the hamulus noted in CLP subjects in the present study provides a partial explanation for the Eustachian tube dysfunction presented in many cleft subjects.

6.5 Conclusion

The results of the present study show that there is an increased nasopharyngeal space in cleft lip and palate that may lead to compression of the nasopharyngeal structures, including the Eustachian tube. Alterations of the medial pterygoid plate and the hamulus may lead to an alteration in the origin and orientation of the TVP muscle leading to alteration in its function. These anatomical variations may compromise the

dilatory mechanism of the Eustachian tube leading to recurrent middle ear infections in cleft children and subsequent loss of hearing.

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CHAPTER 7

THE CRANIAL BASE IN INFANTS WITH CLEFT LIP AND PALATE

7.1 Introduction

The cranial base is a border structure between the neurocranium and facial skeleton (Sperber, 2001). Thus the development and growth of the cranial base can interact both with the neurocranial and facial skeletal development (Ford, 1958; Lieberman *et al.*, 2000). Unlike the rest of the skull, which develops intramembranously from neural crest-derived tissue, the cranial base grows from endochondral ossification processes in which mesodermally-derived cartilaginous precursors (the chondrocranium) develop in utero and are gradually replaced by bone after birth. The formation of the chondrocranium commences from the fourth week of intra-uterine life (Sperber, 2001). The cranial base is the first region of the skull to reach adult size, and it is the structural foundation of many aspects of craniofacial architecture. As the cranial base grows, it elongates and flexes in the spheno-ethmoid, mid-sphenoid, and spheno-occipital synchondroses (SOS) (Lieberman *et al.*, 2000).

The body of the sphenoid consists of two anterior-posterior portions, presphenoid and postsphenoid (basisphenoid), that are derived from the cartilaginous basicranium. The midsphenoidal synchondrosis between the pre- and post-sphenoid fuses shortly before birth and the spheno-occipital synchondrosis fuses in adolescence. The

basioccipital bone anterior to the foramen magnum is derived from basicranial endochondral ossification. Postnatally, the endocranial surfaces of the occipital bone are predominantly resorptive, and the ectocranial surfaces are depository, resulting in the downward displacement of the floor of the posterior cranial fossa to accommodate the enlarging brain (Sperber, 2001).

The development of the craniofacial skeleton in CLP has been widely studied using cephalometric radiographs, with most of the data derived from the lateral view (Ross, 1993). Although much effort has been expended to determine the mechanisms and factors involved in facial development in CLP, the possibility of intrinsic maldevelopment in the cranial structures remains a controversial (Horswell and Gallup, 1992). Many researchers have concentrated on the basicranium in an attempt to determine whether maldevelopment in this region exists in CLP and whether these abnormalities influence subsequent midfacial development. Some investigators have found abnormalities in the size and shape of the cranial base in their cleft patients (Krogman *et al.,* 1975; Hayashi *et al.,* 1976), whereas others have observed essentially 'normal' cranial base structures (Ross RB, 1965; Bishara and Iversen 1974; Bishara *et al.,* 1976). Thus, the literature still reflects controversy and confusion regarding cranial base abnormalities in CLP patients.

Previous studies of cleft lip and palate have applied two-dimensional lateral cephalometric methods but these have significant limitations, such as superimposition of structures, difficulty in identifying landmarks and poor visualization of 3D structures (Moyers and Bookstein, 1979; Cohen, 1984; Maue-Dickson, 1979; Fisher *et al.,* 1999; Singh *et al.,* 2004). Furthermore, the subjects of these studies have been older children and adults, limited to specific ethnic groups. Researchers investigating

CLP have recognized the potential advantages of applying 3D CT to clarify whether CLP is associated with other craniofacial malformations or is a localized anomaly (Maue-Dickson and Dickson, 1980). Schendel and Delaire, (1982) investigated the cranio-orbital morphology of the cranial base using CT in CLP infants but the sample size was small, few landmarks were defined and the methodology was different to the present study. However, this earlier investigation indicated that CLP is not an isolated malformation localised to the jaws, but involves other closely related embryologic structures.

Therefore, the main aim of this study was to use CT imaging to compare skeletal components of the cranial base and to quantify anatomical variation between a unaffected group (NC) and four groups of infants with clefts: unilateral cleft lip palate (UCLP); bilateral cleft lip and palate (BCLP); isolated cleft palate (ICP); and cleft lip primary palate/alveolus (CL). Other aims were to compare the ICP group with the other affected groups, as previous embryological studies have indicated that CLP infants are etiologically and developmentally distinct from ICP group (Johnston and Bronsky, 1995; Hart *et al.,* 2000), and to compare males and females.

7.2 Materials and Methods

The methods of data collection and statistical analysis have already been outlined in Chapter 3.

7.2.1 Data Collection

The sources of patients selected for this study, the breakdown by age, gender and cleft (CLP) or non-cleft (NC) group, and the problems encountered in collecting this information are detailed in Section 3.5.

7.2.2 CT Protocol

Axial scans were obtained with a GE Lightspeed Plus CT Scanner System at the Department of Radiology, Hospital Universiti Sains Malaysia. The protocol used is detailed in Section 3.6.

7.2.3 Cranial Base Variables

Linear and angular variables were computed from selected landmarks to enable cranial base size and length, height and cranial base angle to be determined. Definitions were as follows:

7.2.3.1 Cranial base height

The height of the basi-sphenoid was measured from the superior to inferior points on both sides of the sphenoid border of the spheno-occipital synchondrosis (Fig. 7.1). The height of the basi-occipital was measured from the superior to inferior points on both sides of the occipital border of the spheno-occipital synchondrosis (Fig 7.1).

7.2.3.2 Cranial base length

Cranial base length dimensions were determined as follows: anterior cranial base length (nasion, N to sella, S); posterior cranial base length (basion, Ba to sella, S) (Fig. 7.2); and total cranial base length (basion, Ba to nasion, N) (Fig. 7.3).

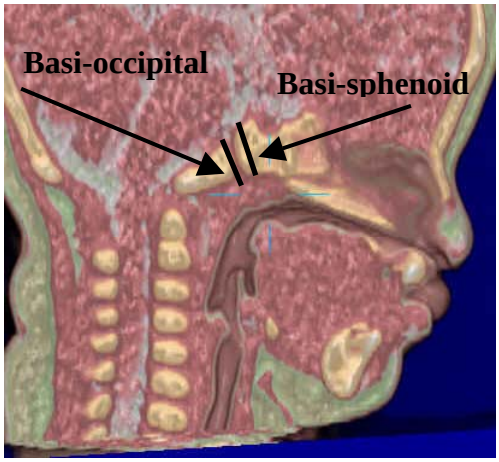

Figure 7.1 3D CT reconstruction of the sagittal view showing that the heights of the basi-sphenoid and basi-occipital of the left and right were measured from the superior points to the inferior points bordering the SOS.

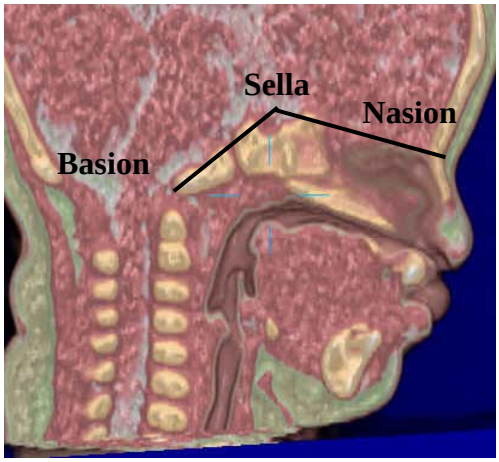

Figure 7.2 3D CT reconstruction of the sagittal view showing the measurement of the anterior cranial base length (sella to nasion) and the posterior cranial base length (basion to sella).

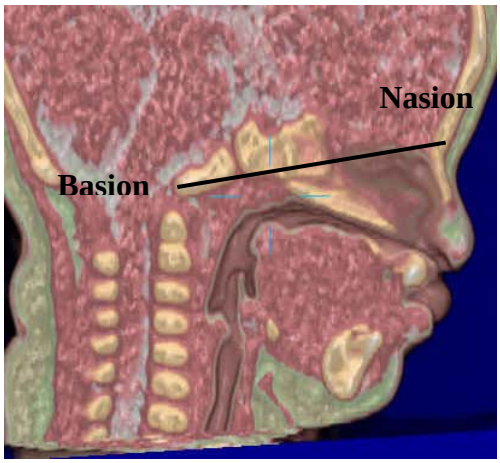

Figure 7.3 3D CT reconstruction of the sagittal view showing that total cranial base length was measured from the basion to sella.

7.2.3.3 Sella distance

The sella distance was measured from sella (the centre of sella turcica) to the superior part on both sides of the sphenoid border of the spheno-occipital synchondrosis (Fig. 7.4).

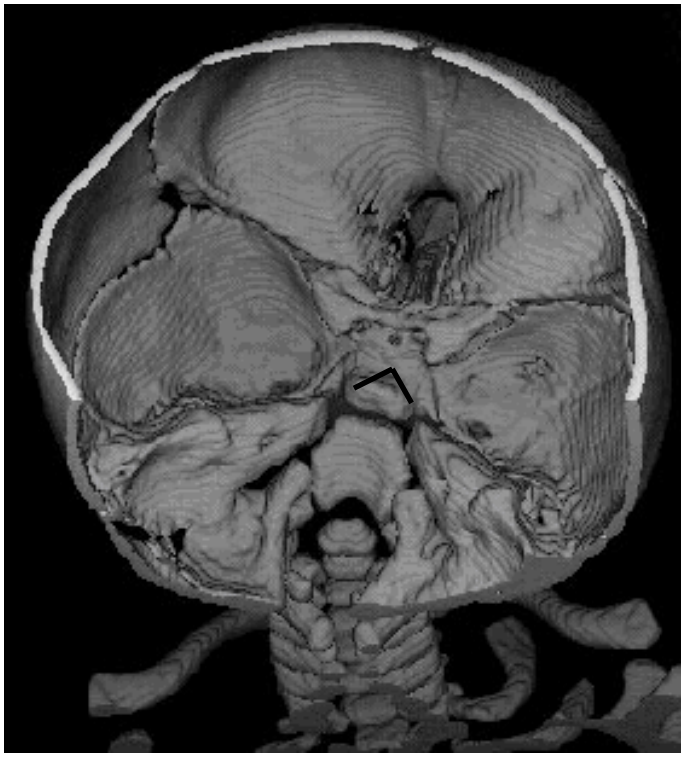

Figure 7.4 3D CT reconstruction of the P-A view showing the distance of the sella to superior left and right of the basi-sphenoid.

7.2.3.4 Clivus length

Clivus length was determined by measuring the distances from the basion (most posterior-inferior point on the clivus) to the superior and inferior parts of both sides of the occipital border of the spheno-occipital synchondrosis (Fig. 7.5).

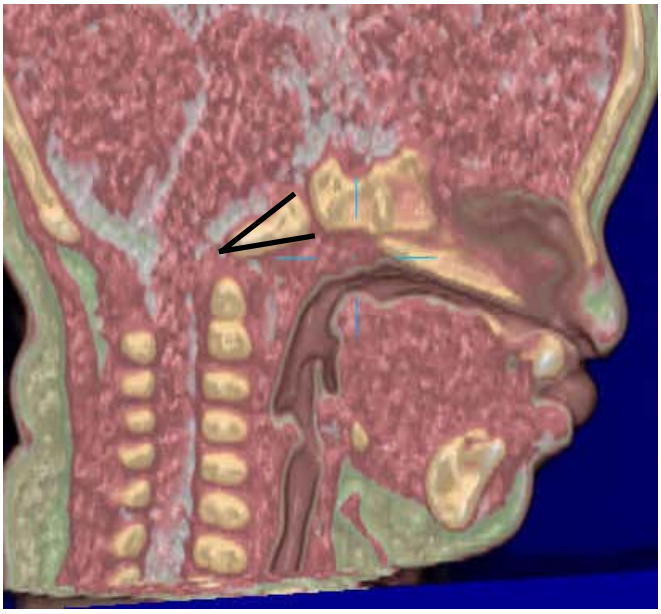

Figure 7.5 3D CT reconstruction of the sagittal view showing that clivus length was measured from the basion to the superior and inferior point of the basi-occipital bone bordering the SOS.

7.2.3.5 Angle

The cranial base flexure angle was measured form nasion-sella-basion to determine the cranial base angle (Fig. 7.6).

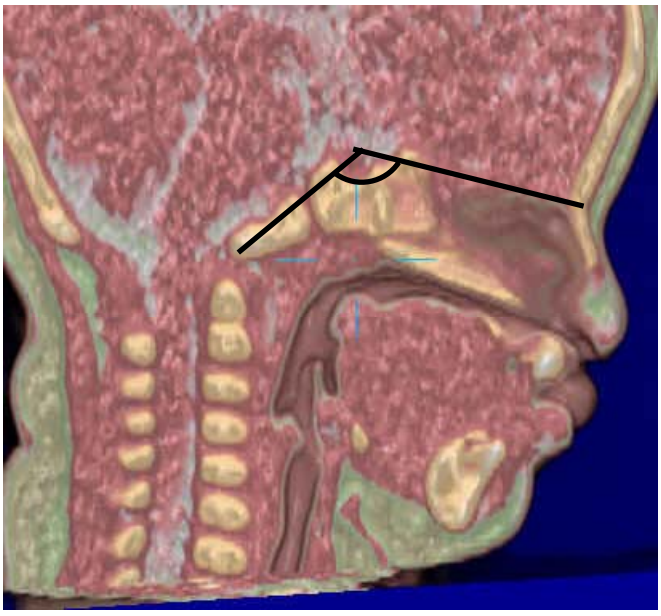

Figure 7.6 3D CT reconstruction in the sagittal view showing that the cranial base angle was measured from basion-sella-nasion.

7.2.3 Statistical Analysis

The statistical model used to analyse the cranial base data has already been described in Section 3.11.

7.2.4 Errors of the Method

The methods for determining errors in the landmark determination and anthropometric variables derived from these landmarks by the use of repeated determinations are outlined in Section 3.12. Systematic errors in landmark location were tested using Hotelling's T^2 statistic. For anthropometric variables Student's paired t-tests were used to detect systematic errors (i.e. to ascertain whether the mean difference between repeated measures deviated significantly from zero) and Dahlberg's (1940) method of double determination was used to quantify the magnitude of random errors.

7.3 Results

The relocation error for individual landmarks ranged from 0.2mm for basi-occipital synchondrosis superius right to 0.7mm for basi-occipital synchondrosis superius left. None of the paired t-tests between repeat determinations disclosed significant differences, indicating that there were no marked systematic errors. The maximum mean measurement error was only 0.1mm for posterior cranial base length from basion to sella. The Dahlberg statistic for cranial base variables ranged from 0.2mm for right superior clivus length (basion to basi-occipital superior synchondrosis right) to 0.5mm for right sella sphenoid length. These findings indicated that errors in the method were small and unlikely to bias the results.

Table 7.1 shows descriptive statistics, including the unadjusted means, standard deviations and coefficients of variation. Table 7.2 shows the adjusted means and their standard errors using PROC GLM SAS 2001 statistical package.

Table 7.1 Unadjusted means ($\bar{x}$), standard deviations (SD) and coefficients of variation (CV) of the cranial base variables (in mm and degrees).

Variable	**Groups**														
Cranial Base	**NC (n=12)**			**UCLP (n=10)**			**BCLP (n=4)**			**CL (n=7)**			**ICP (n=8)**		
	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**
Lt sphenoid height	8.2	1.21	16.4	6.5	0.45	6.8	6.4	1.23	19.2	6.7	1.59	23.8	6.3	1.38	21.8
Rt sphenoid height	7.9	1.46	20.2	6.2	0.44	7.1	6.2	1.07	17.3	6.8	1.35	19.8	6.2	1.73	28.2
Lt basioccipital height	8.0	0.89	13.3	7.0	0.44	6.3	6.3	2.06	32.5	7.3	1.57	21.5	7.1	1.12	15.7
Rt basioccipital height	7.9	0.86	12.3	6.8	0.69	10.1	6.4	1.86	29.3	7.3	1.34	18.4	7.2	1.22	17.0
Basion – nasion	65.5	7.95	11.1	61.2	3.70	6.0	60.6	6.89	11.4	61.7	5.40	8.8	62.1	4.98	8.0
Basion – sella	26.4	2.73	8.8	25.3	1.40	5.5	24.0	5.20	21.7	26.3	2.06	7.8	26.5	2.44	9.2
Sella - nasion	44.9	5.44	11.7	41.2	2.23	5.4	41.5	3.86	9.3	41.0	4.83	11.8	41.9	3.38	8.1
Sella - superior sphenoid lt	9.4	1.51	14.8	9.6	0.73	7.6	9.2	2.33	25.5	10.1	0.85	8.4	9.9	1.81	18.2
Sella - superior sphenoid rt	9.5	1.52	15.3	9.8	1.10	11.3	9.3	2.25	24.2	10.2	1.17	11.4	9.9	1.37	13.8
Basion – sup. basioccipital lt	15.6	1.53	9.9	15.2	0.76	5.0	14.4	3.55	24.7	15.7	1.18	7.5	16.1	1.56	9.7
Basion – sup. basioccipital rt	15.8	1.30	8.0	15.0	0.77	5.1	14.0	4.07	29.2	15.7	1.18	7.6	16.2	1.64	10.1
Basion – inf. basioccipital lt	13.4	1.25	8.0	13.9	1.08	7.8	13.4	2.71	20.3	13.8	1.36	9.8	14.5	1.17	8.0
Basion – inf. basioccipital rt	13.7	1.38	9.5	13.8	0.73	5.3	12.9	3.01	23.4	13.8	1.20	8.7	14.4	1.23	8.5
Cranial base angle	131.6	6.30	4.2	132.8	5.07	3.8	135.2	10.45	7.7	132.4	5.36	4.0	130.0	8.58	6.6

Table 7.2 Adjusted means and standard errors of the cranial base variables (in mm and degrees).

Variables	Groups									
Cranial Base	**NC (n=12)**		**UCLP (n=10)**		**BCLP (n=4)**		**CL (n=7)**		**ICP (n=8)**	
	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**	$\bar{x}$	**SE**
Lt sphenoid height*	8.1	0.29	6.8	0.29	6.9	0.46	6.8	0.33	5.9^{+}	0.34
Rt sphenoid height *	7.9	0.26	6.7	0.27	6.8	0.42	7.0	0.31	5.7^{+}	0.32
Lt basioccipital height*	7.9	0.27	7.3	0.27	6.7	0.42	7.4	0.31	6.7	0.32
Rt basioccipital height*	7.8	0.25	7.1	0.24	6.7	0.40	7.4	0.29	6.8	0.29
Basion - nasion	64.1	1.31	62.2	1.41	61.8	2.19	62.0	1.63	60.5	1.66
Basion - sella	25.9	0.59	25.8	0.64	24.6	0.99	26.4	0.74	25.8	0.75
Sella - nasion*	44.9	0.92	42.0	0.98	42.5	1.53	41.3	1.14	40.7	1.16
Sella – sup. sphenoid lt	9.2	0.34	9.9	0.34	9.5	0.54	10.2	0.40	9.5	0.41
Sella to sup. sphenoid rt	9.2	0.36	10.0	0.36	9.5	0.57	10.3	0.42	9.5	0.43
Basion – sup. basioccipital lt	15.5	0.43	15.5	0.44	14.9	0.68	15.8	0.50	15.6	0.51
Basion - superior basioccipital rt	15.7	0.47	15.3	0.47	14.4	0.73	15.8	0.54	15.7	0.55
Basion – inf. basioccipital lt	13.3	0.42	14.0	0.42	13.5	0.66	13.8	0.49	14.3	0.50
Basion – inf. basioccipital rt	13.7	0.42	14.0	0.43	13.1	0.67	13.8	0.50	14.1	0.50
Cranial base angle	131.4	2.00	131.9	2.13	134.1	3.34	132.1	2.48	130.7	2.51

*Significant difference at $p<0.05$ between all cleft groups and non-cleft

$^{+}$ Significant difference at $p<0.05$ between ICP and other combined cleft groups

When the GLM model was applied to the height data for the basi-sphenoid and basi-occipital bones, statistically significant differences were found between the CLP and

NC groups (Table 7.2). The heights of the bones on both sides in CLP infants were significantly smaller when compared to the NC ($p<0.05$). Furthermore, the heights of the basi-sphenoid in the ICP group on both sides were significantly smaller when compared with the other cleft groups ($p<0.05$) (Figs. 7.7 and 7.8).

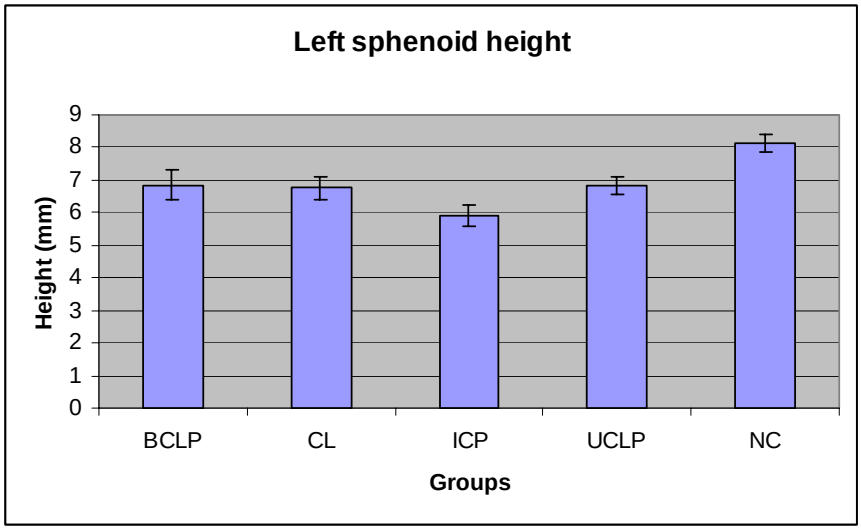

Figure 7.7 Adjusted mean values and standard errors for left sphenoid height. The CLP groups were significantly smaller than the NC group. The ICP group was significantly smaller when compared to the other cleft groups.

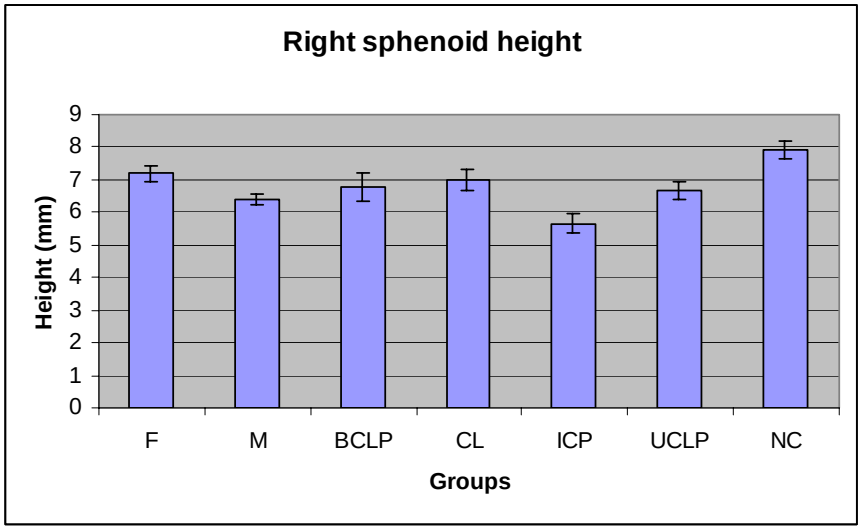

Figure 7.8 Adjusted mean values and standard errors for the height of the right sphenoid bone. The CLP groups were significantly smaller than the NC group. The ICP group was significantly smaller when compared to the other affected cleft groups. The height in females (F) was significantly larger than in males (M).

There was no difference in the height of the basi-occipital between the ICP group and the other cleft groups (Figs. 7.9 and 7.10). There was a significant difference between males and females in right sphenoid height, the females being significantly larger than the males.

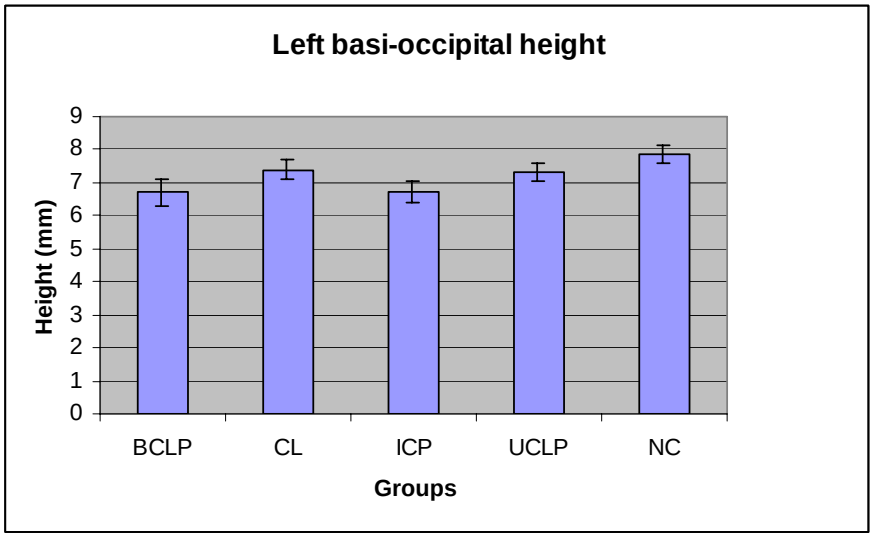

Figure 7.9 Adjusted mean values and standard errors for the height of the left basi-occipital bone. The CLP groups were significantly smaller than the NC group. The ICP group was not significantly different when compared to the other affected cleft groups.

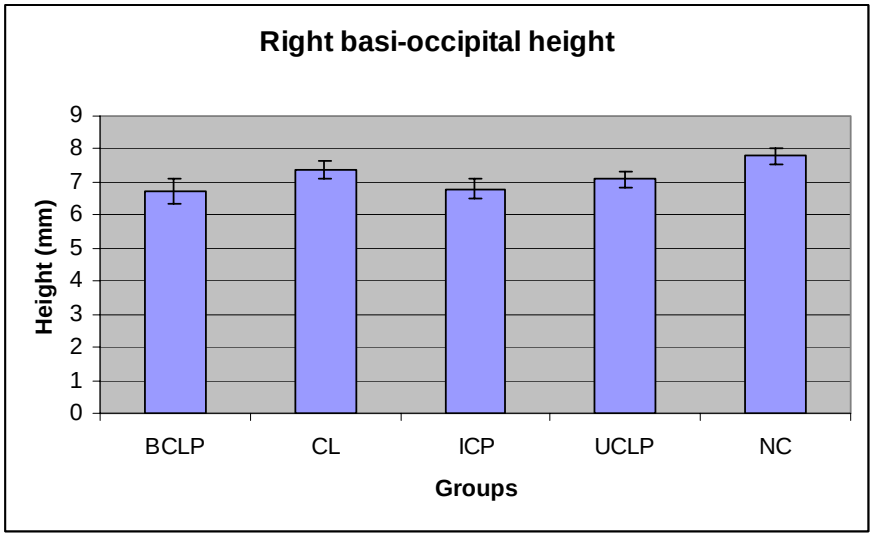

Figure 7.10 Adjusted mean values and standard errors showing the height of the right basi-occipital bone. The CLP groups were significantly smaller than the NC group. The ICP group was not significantly different when compared to the other affected cleft groups.

In terms of cranial base length dimensions, the anterior cranial base distance from sella to nasion (s-na) in CLP infants was significantly smaller than in the NC ($p<0.05$) (Fig. 7.11). The posterior cranial base length (basion to sella) and total cranial base length in CLP infants did not differ significantly when compared to the NC infants. There was no significant difference in the lengths of the cranial base between the ICP group and other cleft groups. There was no difference in the distance between sella to the superior part of the sphenoid bone on both sides between the CLP infants and NC infants and ICP and other cleft groups. The clivus lengths from basion to the superior and inferior parts of the basi-occipital were not significantly different in CLP infants when compared to the NC infants, or between ICP and the other cleft groups.

The cranial base angle (n-s-ba) was not significantly different in CLP infants when compared to the NC infants, or between ICP and the other cleft groups.

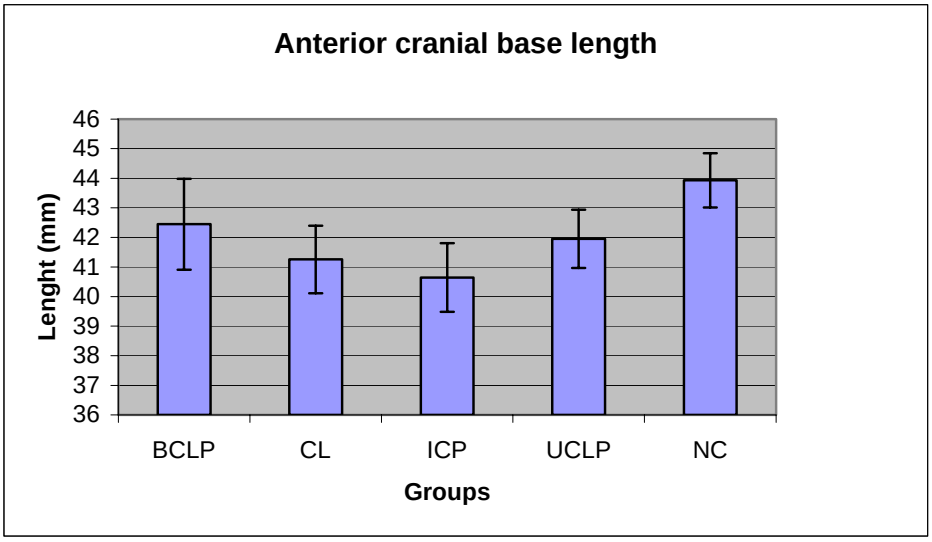

Figure 7.11 Adjusted mean values and standard errors of the length of the anterior cranial base. The CLP groups were significantly smaller than the NC group. The ICP group was not significantly different when compared to the other affected cleft groups.

7.4 Discussion

When the GLM model was applied to the heights of the basi-sphenoid and basi-occipital bones, statistically significant differences were found between the CLP and NC groups. The heights of the bones on both sides in CLP infants were significantly smaller than in the NC group ($p<0.05$). The heights of the basi-sphenoid in the ICP group on both sides were also significantly smaller when compared with the other combined cleft groups ($p<0.05$). There was no difference in the height of the basi-occipital between the ICP group and the other cleft groups. Molsted *et al.* (1993) found the height of spheno-occipital synchondrosis bordering the basi-sphenoid and basi-occipital bones was not significantly different in a CLP group compared to a cleft lip control group.

In another study, Molsted *et al.* (1995) noted a significant increase in the cranial base and maxillary widths in CLP but the findings did not include the height and length of the basisphenoid and basioccipital bones. Smahel *et al.* (1991) reported on the reduction in the height of the body of the sphenoid bone in adult patients and suggested adult CLP patients had a certain degree of hypoplasia of the sphenoidal sinus. However, in these studies the landmarks were different from this study and this 3D study was able to investigate in considerable detail the bony landmarks of the area with enhanced imaging that permitted description of subtle changes not observed with earlier technology. There was only one significant difference between males and females, for right sphenoid height. The height in females was significantly larger than in males. It is possible that with larger sample sizes, clearer findings about gender differences would be found.

In terms of cranial length dimensions, the anterior cranial base distance from sella to

nasion (s-na) was significantly smaller in CLP infants than in the NC group. In contrast to this study, Herman *et al.* (1999) found that the lengths of the anterior (n-s) and posterior (s-ba) cranial base were both within normal limits but total length of the external cranial base (ba-n) was slightly, but not significantly, shorter in infants with UCLP compared to the unilateral incomplete cleft lip and palate group. In this study, there was no difference in the distances of the cranial base between the ICP group and the other cleft groups but Dahl *et al.* (1982) reported ICP infants showed short anterior cranial base length when compared to a cleft lip group. The difference in results could be due to the larger sample size in Dahl's study. Ross (1965) studied the morphology of the cranial base in older children with CLP and compared them to non-cleft children using cephalometric tracings. He reported that cranial base length and angular measurements were smaller in children with clefts than normal. Ross (1987) reported that abnormal facial morphology in UCLP related to intrinsic developmental deficiencies. However, in contrast to Ross, Maue-Dickson (1979) proposed that intrinsic tissue abnormalities could not only contribute to maldevelopment in the immediate cleft area in the midfacial region but also extend to involve the cranial base.

The distances from sella to the superior part of the sphenoid bone on both sides in CLP infants were not significantly different to those in NC infants. These findings contrast with Herman *et al.* (1999) who measured the distance from sella to SOS using lateral cephalometric radiographs and reported a significantly shorter distance in a CLP group compared to a CL group. The clivus lengths from basion to the superior and inferior parts of the basi-occipital on both sides did not differ significantly in CLP infants when compared to the NC infants or when comparing ICP with the other cleft groups. This is consistent with Hermann *et al.* (1999) who found no differences in

clivus length, when comparing UCLP with cleft lip. Sandham and Cheng (1988), in their study comparing CLP patients with non-cleft orthodontic patients, reported that cranial base angulation did not differ significantly but significant difference was demonstrated for clivus length (S-Ba) which was smaller. Most of the these studies applied lateral cephalometric radiography and used different landmarks, for example sella to basion and SOS to basion for cranial base length. Therefore, these results must be interpreted with caution when compared to the findings in the present study.

When the cranial base angle (n-s-ba) of CLP infants was compared with the controls, no significant difference was disclosed. This is in accord with the findings of Dahl *et al.* (1982) and Hermann *et al.* (1999) who also noted no significant difference in the shape of the cranial base between CLP and NC groups. Dahl *et al.* (1982) urged caution in drawing comparisons between findings in young children and older children and adults because of differences in growth during post-natal life.

When studying unoperated adults to see whether cranial base abnormalities persist until adult life, previous studies have (Mars and Houston, 1990; da Silva Filho *et al.,* 1998) observed that the cranial base dimensions were smaller in unoperated CLP adults when compared to non-cleft controls. Smaller craniofacial dimensions were also observed in operated CLP individuals (Sandham and Cheng, 1988; Horswell and Gallup, 1992).

Previous studies (Tessier, 1981; Kreiborg, 1981; Kreiborg and Pruzansky, 1981; Kreiborg and Aduss, 1986) on craniosynostoses have shown that congenital malformations of the cranial vault and facial skeleton are associated with the base of the cranium. These investigations have reinforce the view that this developmental

relationship is important for 'normal' growth to proceed; if the cranial base is 'abnormal', it follows that midfacial development may be adversely affected.

In contrast to this 3D CT study, Krogman *et al.* (1975) in his cross-sectional study from newborn to 6 years noted that cranial base length (n-s) and clival length (s-ba) were greater than normal in CLP and there was a greater flexion of the sellar angle (n-s-ba angle). One of the statements made by these authors is worthy of direct quotation: " We feel that all of these points to basion and foramen magnum as the major areas of adjustments to CL(P) and CP clefting." The authors further suggested that there is a close relationship between the various structural components of the craniofacial midline and, specifically, that palatal clefting may have repercussions in adjacent bony structures in both the cranial base (occipital, sphenoid, and ethmoid bones) and facial areas (involving the midfacial complex). The authors concluded that palatal clefting has growth and / or developmental repercussions in the associated cranial base and facial structures, probably a reflection of embryogenic growth-timing, i.e., palatal clefting may be associated with associated growth dysplasia of basi-facial structures in their formative stages at the time when palatal clefting occurred.

A recent study by Singh *et al.* (2004) showed that deficiencies in the cranial base region may only become apparent in CLP patients with Class III malocclusion during 13 – 16 year interval. This finding supports the view that later environmental effects may modify the template for post-natal maxillary and mandibular growth provided by the cranial base (Martone, 1992).

7.5 Conclusion

Analysis of data on the cranial base provides further insight into the aetiology of the observed midface hypoplasia in CLP. The shorter cranial base could lead to deficient associated downward and forward translation of the midfacial region.

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CHAPTER 8

THE SPHENO-OCCIPITAL SYNCHONDROSIS IN INFANTS WITH CLEFT LIP AND PALATE

8.1 Introduction

The spheno-occipital synchondrosis (SOS) is a cartilaginous joint between the basisphenoid and the basioccipital bones of the cranial base (Sperber, 2001). A synchondrosis is a primary cartilaginous joint in which cartilage is ultimately replaced by bone. The SOS is regarded as an important maturity and growth centre of the facial skeleton (Ford, 1958; Stramrud, 1959; Thilander and Ingervall, 1973; Melsen, 1974). Post-natal growth in the SOS is the major contributor to growth in the cranial base, persisting into early adulthood. This prolonged growth period allows for continued posterior expansion of the maxilla to accommodate future erupting molars and provides space for the growing nasopharynx.

Previous studies have concentrated upon growth and closure of the SOS by examining non-cleft human autopsy specimens (Ford, 1958; Thilander and Ingervall, 1973; Melsen, 1974). The basicranium is also the first region of the skull to reach adult size, and it is the structural foundation of many aspects of craniofacial architecture. As the basicranium grows, it elongates and flexes in the spheno-ethmoid, mid-sphenoid, and spheno-occipital synchondroses (Lieberman *et al.,* 2000).

The width of the SOS is not well described in the literature on orofacial clefting. This paucity of data may relate to difficulties in visualizing the SOS using conventional radiographic techniques. Only one study (Molsted *et al.,* 1993) has compared the width of the SOS in patients with cleft lip and palate (CLP) to cleft lip infants using lateral cephalometric techniques. In this study, the authors mentioned about the difficulty of recognising the SOS on lateral cephalometric radiographs, as the ear rods and the overlapping structures in adjacent regions can blur the image. In cases where there was doubt, the radiographs were excluded from the study. Researchers investigating CLP have recognized the potential advantages of applying 3D CT to clarify whether CLP is associated with other craniofacial malformations or is a localized anomaly (Maue-Dickson and Dickson, 1980). However, the author is not aware of any previous CT studies of the SOS in CLP infants during their first year of life before any surgical intervention.

The aims of this study were to use CT imaging and computer technology to compare the width of the SOS between four groups of infants with clefts: unilateral cleft lip palate (UCLP); bilateral cleft lip and palate (BCLP); isolated cleft palate (ICP); and cleft lip primary palate/alveolus (CL) with an unaffected NC group. The ICP group was also compared with the other affected groups, as previous embryological studies have indicated that ICP infant is morphological different group (Johnston and Bronsky, 1995; Hart *et al.,* 2000). Another aim was to see whether there was any difference in the width of the SOS between males and females.

8.2 Materials and Methods

The methods of data collection and statistical analysis have already been outlined in Chapter 3.

8.2.1 Data Collection

The sources of patients selected for this study, the breakdown by age, gender and cleft (CLP) or non-cleft (NC) group, and the problems encountered in collecting this information are detailed in Section 3.5.

8.2.2 CT Protocol

Axial scans were obtained with a GE Lightspeed Plus CT Scanner System at the Department of Radiology, Hospital Universiti Sains Malaysia. The protocol used is detailed in Section 3.6.

8.2.3 Spheno-occipital Synchondrosis Variables

In this study, the width of the synchondrosis was measured in the most superior part and inferior part on the left and right sides (Fig. 8.1). The values obtained were then averaged for the width of the superior and inferior synchondrosis. One of the advantages of 3D CT is that the SOS can be examined in a variety views compared to the single view available using lateral cephalometric techniques (Figs. 8.2 and 8.3).

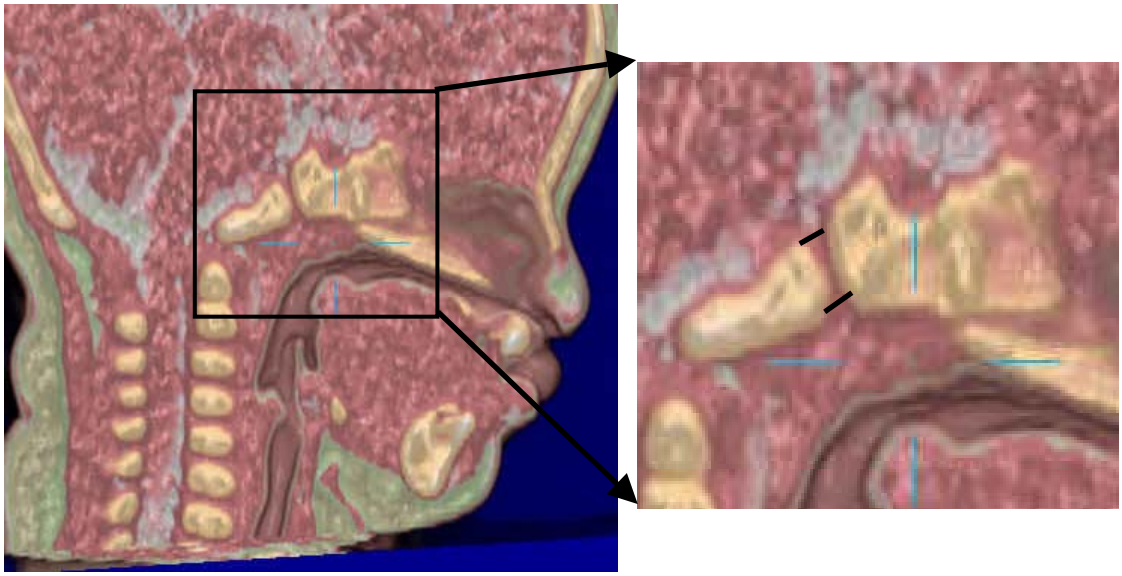

Figure 8.1 3D CT reconstruction showing the width of the synchondrosis measured from the superior and inferior parts (sagittal view).

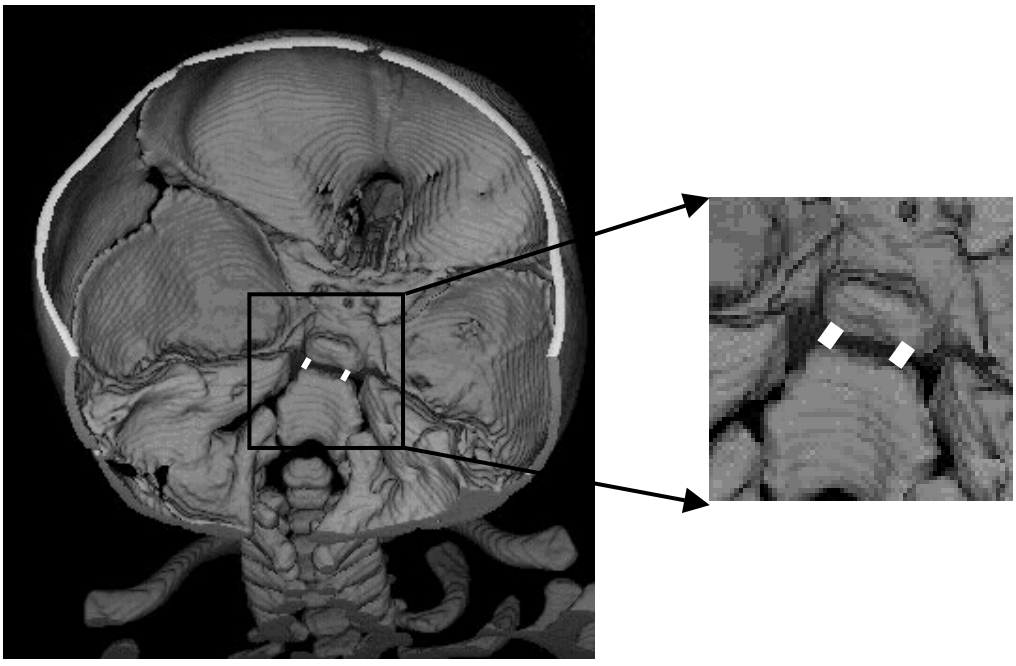

Figure 8.2 3D CT reconstruction in P-A view showing the width of SOS measured from the superior view.

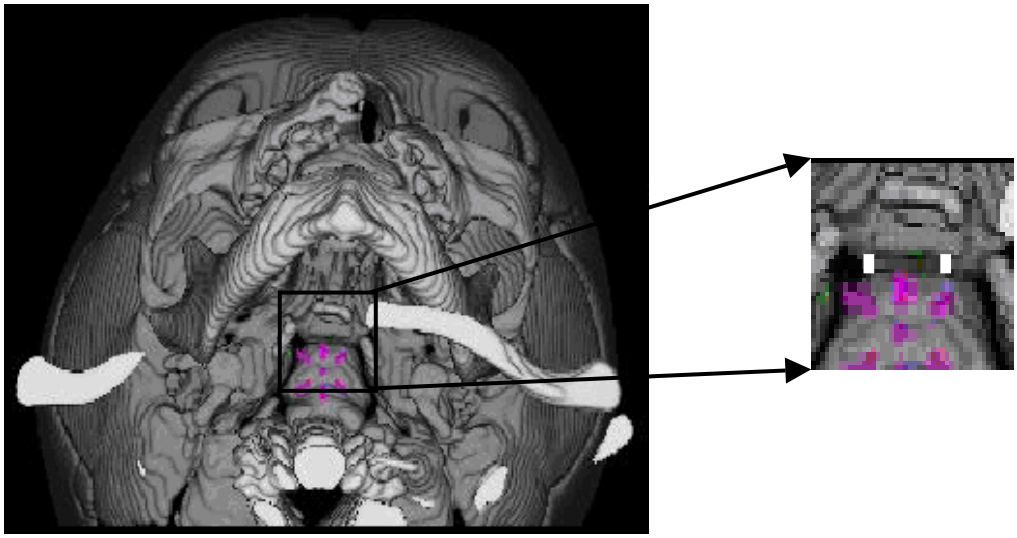

Figure 8.3 Width of SOS measured from the inferior view.

8.3 Statistical Analysis

The statistical model used to analyse the cranial base data has already been described in Section 3.11.

8.4 Errors of the Method

The methods for determining errors in the landmark determination and anthropometric variables derived from these landmarks by the use of repeated determinations are outlined in Section 3.12. Systematic errors in landmark location were tested using Hotelling's T^2 statistic. For anthropometric variables Student's paired t-tests were used to detect systematic errors (i.e. to ascertain whether the mean difference between repeated measures deviated significantly from zero) and Dahlberg's (1940) method of double determination was used to quantify the magnitude of random errors.

8.5 Results

The paired t-tests between repeat determinations disclosed only one significant difference at $p<0.05$ level. However, the mean measurement error of this variable, the width of the superior synchondrosis right, was small (0.1mm) with the standard deviation of 0.2mm. The error in this case could be due to difficulty in locating the landmark. The Dahlberg statistic for SOS variables was 0.2mm for all the variables. The landmark relocation errors for the individual landmarks were also small; ranging from 0.2mm for the landmarks left inferior spheno-occipital synchondrosis to 0.5mm for landmark right basioccipital synchondrosis superior. These findings indicated that errors in the method were small and unlikely to bias the results.

Table 8.1 shows descriptive statistics, including the unadjusted means, standard deviations and coefficients of variation. Table 8.2 shows the adjusted means and standard errors using PROC SAS 2001 statistical package.

Table 8.1 Unadjusted means ($\bar{x}$), standard deviations (SD) and coefficients of variation (CV) of the spheno-occipital synchondrosis variables (in mm and degrees).

Variable	**Groups**														
SOS	**NC (n=12)**			**UCLP (n=10)**			**BCLP (n=4)**			**ICP (n=8)**			**CL (n=7)**		
	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**	$\bar{x}$	**SD**	**CV**
Inferior SOS	1.3	0.41	33.9	1.4	0.42	32.3	1.7	0.43	26.2	1.7	0.42	29.9	1.5	0.61	40.9
Superior SOS	1.3	0.38	39.2	1.4	0.46	34.6	1.9	0.83	44.9	1.7	0.28	26.8	1.3	0.65	42.7

Table 8.2 Adjusted means and standard errors of the spheno-occipital synchondrosis variables (in mm and degrees).

Variables	Groups									
SOS	NC (n=12)		UCLP (n=10)		BCLP (n=4)		ICP (n=8)		CL (n=7)	
	$\bar{x}$	SE	$\bar{x}$	SE	$\bar{x}$	SE	$\bar{x}$	SE	$\bar{x}$	SE
Inferior SOS width*	1.2	0.15	1.3	0.15	1.6	0.23	1.5	0.16	1.7	0.17
Superior SOS width	1.2	0.15	1.2	0.15	1.7	0.24	1.4	0.17	1.6	0.17

* Significant difference at $p<0.05$ between all cleft groups and non-cleft

When the GLM model was applied to the width of the spheno-occipital synchondrosis, statistically significant differences were found between the CLP and NC groups. Greater width was found in the inferior part of the spheno-occipital synchondrosis in CLP infants than in the NC group ($p<0.05$) (Fig 8.4). The width of the inferior SOS in females was narrower than in males ($p=0.09$). The width of the superior SOS was not significantly different between CLP and NC groups ($p=0.09$) (Fig. 8.5). However, there was a significant difference between males and females in the width of superior SOS ($p<0.05$). The SOS in females was narrower than in males.

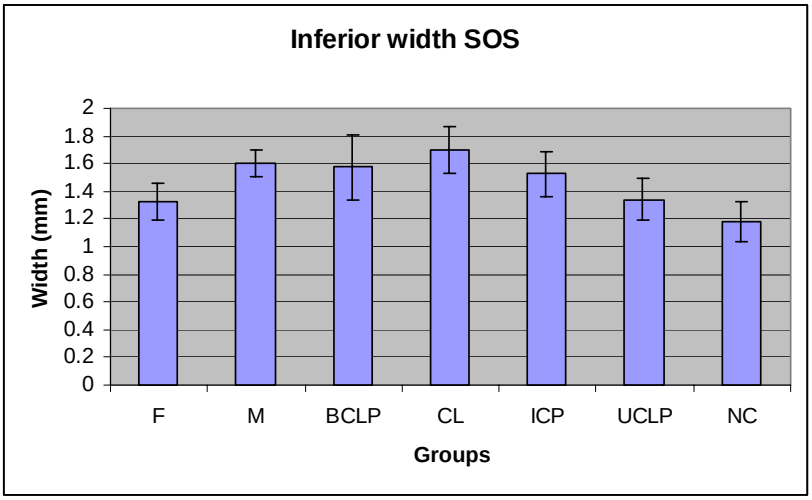

Figure 8.4 Adjusted mean values and standard errors showing the width of the inferior SOS. The CLP group was significantly wider than the NC group.

The ICP group was not significantly different to the other cleft groups. There were no significant differences between males and females.

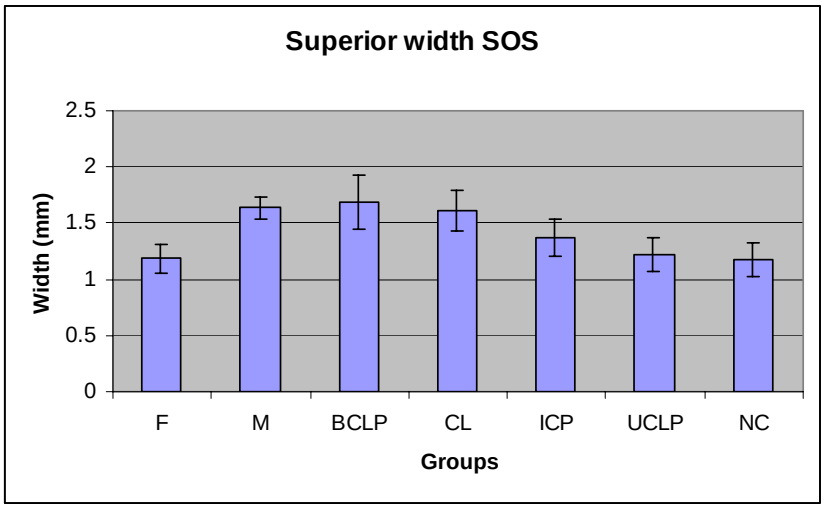

Figure 8.5 Adjusted mean values and standard errors showing the width of superior synchondrosis. The CLP groups were not significantly different to the NC group. The ICP group was not significantly different to the other affected cleft groups. The width in males (M) was significantly larger than in females (F).

8.6 Discussion

Significantly greater width was found in the inferior part of the SOS in CLP infants than in the NC infants. This is in contrast with Molsted *et al.* (1993), who found a greater width in the superior and inferior part of SOS in CLP infants compared to a cleft lip group by applying lateral cephalometric techniques. His finding is not consistent with this study but comparisons must be made with caution because of methodological differences.

In the present study, there was a significant difference between males and females in the width of superior SOS. The SOS in females was narrower than in males. Previous studies on autopsy specimens have shown that the SOS starts to fuse, beginning on its cerebral surface, at 12 –13 years of age in girls and 14-15 of age in boys; with ossification of the external aspect complete by around 20 years of age (Thilander and Ingervall, 1973; Melsen, 1974)). It can be speculated that the narrower SOS could be due to earlier fusion on the superior part in females.

The morphological appearance of the cranial base and changes in its shape during growth have been the focus of reports based on standard cephalometric methods. Previous studies have also applied histological techniques to examine the mid-sagittal structures of cranial base in normal human autopsy material. Thilander and Ingerval (1973) noted that the central zone on the cranial base at the SOS was wide and very cellular with abundant cartilage at birth. With age the structural organization of the synchondrosis changed. The cells which were initially elongated and arranged perpendicular to the longitudinal direction of the clivus, became narrower, decreased in number, and became round. Melsen (1974) examined the mid-sagittal structures of cranial base in normal human material (non-cleft/autopsy) from birth to 20 years of age. She concluded that structural variations observed in the synchondrosis suggested that differentiated growth occurs, which could give rise to a tilting of the basilar part of the occipital bone upwards and backwards in relation to the sphenoid bone leading to flattening of the cranial base.

Whether the dimensional changes registered in the cranial base of CLP newborns in this study are caused by primary defects in the early cartilaginous cranial base, or are secondary to the deficiency in palatal closure and growth, cannot be concluded. Kjaer

(1992) examined the osseous maturation of the cranial base at the time of palatal closure based on human embryos and fetuses. The cranial base was dissected and skeletal maturity was determined radiographically. Her study showed that palatal closure occurred before ossification began in the cranial base. Kjaer's (1992) study (by charting prenatal ossifications in the cranial base) has created a basis for understanding normal and pathological neonatal and postnatal deviations in cranial maturation, shape and growth.

In another study Kjaer (1990) investigated the pattern of skeletal maturity of the cranial bones in the mid-sagittal region anterior to the foramen magnum based upon radiographic and histological investigations of human foetuses derived from first half of the prenatal period. It was observed that ossification started in the frontal bone and was followed by the occipital bone, basisphenoid, preshenoid, and ethmoid bone. Furthermore, the development of the maxillary, palatal, vomer and nasal bones and the pterygoid plates was coordinated with cranial base development.

Kjaer *et al.* (1991) have shown that in cases with holoprosencephaly, which is a polytopic field defect that also affects the cartilaginous skeleton in the cranial base anterior to the sella turcica, the premaxilla and the presphenoid bone were affected in all cases. The spheno-occipital junction thus seems to be a border between the abnormal and normal basicranial development in holoprosencephaly. Kjaer *et al*. (1991) proposed that the facial abnormality in holoprosencephaly is secondary to abnormalities in the basal cranium.

Jenson and Kreiborg (1993) examined CT scans of the skull of cleidocranial dysplasia patients with 3D reconstructions. One of the findings of this study was the increased width of the spheno-occipital synchondrosis in the cranial base. The authors suggested

that this finding may contribute to the craniofacial dysmorphology in cleidocranial dysplasia patients at a later age.

Kreiborg *et al.* (1993) also analyzed Apert and Crouzon cases ranging in age from 0 to 23 years from 3D reconstruction of CT scans. The primary abnormality in Crouzon syndrome appeared to be premature fusion of the spheno-occipital synchondrosis. Based on findings at birth and early infancy it would seem that such fusion occurs relatively late in fetal life. However, closure of the fontanelles and spheno-occipital synchondrosis were observed in Apert syndrome by early childhood. They speculated that the fusion of the synchondrosis could result in the basilar kyphosis and thinning of the clivus which was frequent in Crouzon syndrome, and narrowing of the floor of the sella turcica. Thus the temporal bones could not drift laterally as in normal development of the cranial base. The authors suggested that cartilaginous abnormalities played a primary role in abnormal cranial base development in Apert and Crouzon syndrome. Sperber (2001) reported that the SOS normally fuses at adolescence; its premature fusion in infancy results in a depressed nasal bridge and dished faced that characterises many craniofacial anomalies.

In this study infants with CLP tended to have a wider SOS, in contrast to the narrower SOS reported previously in Crouzon syndrome and Apert syndrome. A wider SOS could possibly cause dysmorphic and compensatory growth changes in later age.

8.7 Conclusion

Since the cranial base develops from the chondrocranium, it is possible that alteration in growth, or delayed maturation of the early development of the cartilaginous cranial

base may affect the width of the SOS in CLP infants. For example, deficient ossification or continuous chondroblastic proliferation of the SOS may alter the dimensions of the cranial base and in turn affect the merging of the facial processes. Further studies on the SOS with larger sample sizes using 3D CT should lead to a more definitive answer about the nature of the relationship between cranial base morphology and clefting.

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CHAPTER 9

GENERAL DISCUSSION AND CONCLUSION

9.1 Introduction

Cleft lip and palate represents one of the most common forms of facial deformity affecting one in every 500 to 1000 live births worldwide. It affects individuals in all societies and has been the subject of considerable research. The focus of previous studies has been on the aetiology, investigating the implications and consequences for affected individuals, and surgical management.

The results of embryological studies have provided a clearer picture of what happens during craniofacial development. This was highlighted by Diewert (1983) who reported changes in craniofacial dimensions, proportions, and spatial relations during the development of the secondary palate. Movements of the palatal shelves to the horizontal position involve a complex interaction between the shelves and the tongue that is influenced by developmental events in the shelves and the surrounding craniofacial complex. Normal facial growth tends progressively to separate the palatomaxillary processes from the tongue-mandibular complex as the naso-maxillary complex lifts upward and the tongue shifts forward prior to shelf elevation. This positional change may enhance palatal shelf elevation.

In addition to studies in humans, investigations using animal models show that, during the period of shelf elevation, there is almost no growth in head width, but constant

growth in head height. This means that the position of least resistance for the expanding palatal shelves is to occupy the space above the tongue (Ferguson, 1988).

Our understanding of the cellular and molecular events involved in craniofacial development has improved greatly because of rapid advances in molecular biology (Cox, 2004). During recent years, enormous progress has been made in our understanding of normal and abnormal development of the head and neck. This progress has been made possible through technical developments, particularly the application of molecular techniques, and the development of animal models for studying the roles of genetic and environmental factors relevant to human CLP formation. The application of precise cell marking procedures has led to a much better appreciation of the cell movements and interactions involved in germ layer formation. The techniques of scanning electron microscopy and *in situ* hybridisation methods for studying gene expression have demonstrated the extensive contributions of neural crest cells to craniofacial development.

In CLP studies, anatomical differences have been observed. Excessive separation of structures formed lateral to the tongue was observed by Maue-Dickson and Dickson (1980) in a 15-week-old human foetus with cleft palate. Subtelny (1955) also found that the nasopharynx was abnormally wide and the width between the maxillary tuberosities was increased in unoperated CLP subjects.

Malformation resulting in CLP results from perturbations or insults during embryonic development between the fourth and tenth weeks of gestation. Cleft lip and cleft of the primary palate results from a failure of merging of medial nasal, lateral nasal and maxillary processes on either left, right or both sides of the forming craniofacial complex. After primary palate merge, secondary palate merge takes place during the

ninth week to tenth week of gestation. Cleft palate may result from disturbances at any stage of palate development: defective palatal shelf growth, delayed or failed shelf elevation, defective shelf merging, failure of medial edge cell death, post-merging rupture and failure of mesenchymal consolidation and differentiation (Ferguson, 1988).

Cleft lip and palate can occur in syndromic and non-syndromic forms. This study concentrated on non-syndromic forms as they are less likely to have other pathological problems that can affect the results. However, there may be some common mechanisms in both types. Non-syndromic clefts of the oral cavity seem to be aetiologically distinctive, however, clinically they make up the majority of cleft cases in the human population. The non-syndromic forms of CLP have a multifactorial mode of inheritance with both genetic and environmental factors operating. Currently, genes implicated in CLP have been identified on different chromosomes, including chromosomes 6 and 11 (Juriloff and Mah, 1995; Eiberg *et al.*, 1987; Chenevix-Trench *et al*., 1992). Genetic analyses of non-syndromic oral clefts have produced significant results such as association studies that point to polymorphisms at the TGF alpha locus playing a key role in the aetiology of oral clefts. There is a suggestion that this locus may interact with exposure to maternal smoking to influence the risk oral clefting (Shaw *et al.*, 1996). The lack of consistent results from family studies highlights the fact that non-syndromic CLP is a heterogenous condition, undoubtedly caused by more than one factor.

Many affected individuals appear as spontaneous events with no affected family members. Multiple ‘chance’ combinations of genetic and environmental factors (multifactorial aetiology) appear to be responsible for most of these CLP cases.

The most implicated environmental factors for human CLP have been cigarette smoking, alcohol and nutritional factors such as folate deficiency (Wyszynski *et al*., 1996).

This aetiology suggests that it is unlikely that the phenotypic effects will be limited only to the cleft. It is likely that other structures will also be affected. It is also likely that there will be a range of expressions of CLP, in other words phenotypic heterogeneity.

The overall phenotypic pattern in CLP has not been well understood. The structures affected in the cranio-cervical region have not been well described previously. The present study reports several anatomical anomalies not previously recognised. It is not known whether these changes are a result of the CLP, a cause, or simply pleiotropic effects associated with the clefting.

Further help in addressing these questions has been provided by development of a knockout mouse for MSX1 (Satokata and Maas, 1994). Clefting may be a secondary consequence of this gene mutation that lead to a lack of mesenchyme and deficient tooth development. In other words, MSX1 may be involved in the proliferation of dental papilla and dental follicle mesenchyme cells and also the cells that contribute to the mesenchyme of the forming palate. Given that MSX1 is not normally expressed during palate development, the two most likely explanations are that either dental mesenchyme cells contribute to palate formation, or that disruption of dental development causes geometric alterations in the jaw relationships, resulting in cleft palate as a consequence. Furthermore, this animal study by Satokata and Maas (1994) represents a valuable new experimental model, opening up many exciting possibilities to investigate the role of various factors during dental and craniofacial development.

It has only been relatively recently that imaging techniques and 3D analytic techniques have enabled a detailed assessment of the skeletal structures in CLP patients. Most early knowledge has come from analyses of conventional radiographs eg lateral head and AP views, which have several limitations such as superimposition of structures, difficulty identifying landmarks and poor visualization of 3D structures.

The availability of 3D methods allows better opportunities to evaluate craniofacial structures. There is now an opportunity of exploring the phenotypes of CLP individuals in much more detail and to describe links, in terms of understanding the mechanisms involved between what is happening at a molecular level and what happens at the phenotypic level. There is a much better opportunity to link the genotype, the molecular mechanisms and the phenotype.

By using 3D CT approaches, variables can now be defined that describe the size and shape of bones and regions. Statistical analyses enable comparisons to be made and help to clarify associations between structures. Multivariate analyses and morphometric analyses are now possible with sophisticated computer software.

The particular advantage offered by this study is that CT data were obtained from CLP individuals at infancy before they had been operated, and records were available for unoperated NC children, matched for age, for comparison. This study also used a sophisticated software package that enabled accurate and reproducible location of landmarks from which variables could be derived thereby offering advantages over conventional radiographs. This has allowed views that are not possible with a conventional approach, including images of the hyoid bone, cervical spine, nasopharynx, cranial base and spheno-occipital synchondrosis (SOS).

The description of the associations between the hyoid bone, cervical spine, nasopharynx, cranial base, spheno-occipital synchondrosis (SOS) and CLP, which have not been detailed in previous studies, is possibly the most important contribution of this thesis. These areas were also selected because of their clinical importance to swallowing, hearing, and speech in CLP. This study focussed on the areas more distant from the cleft but within the craniofacial/cervical region. The selection was also based on the hypothesis that CLP reflects part of a broader problem, not just one in the region of the cleft. Previous studies have indicated that CLP is associated with a variety of other anomalies (Maue-Dickson, 1979; Maue-Dickson and Dickson, 1980; Horowitz *et al.*, 1976; Krogman *et al.*, 1975; Molsted *et al.*, 1993, 1995).

9.2 3D CT Analysis of the Morphology of Cleft Lip and Palate

After detailed analysis of the data collected for this study, several differences between the CLP and NC groups became apparent. These differences pertained to the five main areas of interest described above:

9.2.1 Hyoid Bone

This 3D CT study has shown, for the first time, details of the abnormalities of the hyoid bone in CLP. The hyoid bone is smaller and in some cases there is no ossification of the body of the hyoid bone. The hyoid is further from the cranial base. There is smaller angulation and also it is at a low level in relation to the cervical vertebrae.

These phenotypic changes in the hyoid bone relate to structures derived from the first, second and third branchial arches. The hyoid bone is a composite endochondral bone

that develops from cartilage of the second and third branchial arches – lesser horn from the second branchial arches; greater horn from the third branchial arches; body from both second and third branchial arches (Koebke, 1978). In terms of embryology, this finding indicates that the underlying factors associated with clefting anomalies not only affect the labiomaxillary and palatine structures of the first arch, but also appear to influence the development of structures derived from the second and third branchial arches.

The precise nature of the developmental mechanism responsible for the alterations in the morphology of the hyoid bone in infants with CLP remains to be determined. Clinically there is an association between the low level of the epiglottis and the level of the hyoid in relation to the cervical vertebrae with aspiration pneumonia. Alteration in the position of the hyoid also presents significant potential problems in terms of breathing, swallowing and head posture, because of alterations in attachments of the muscles responsible for these functions.

In terms of clinical problems presented by the CLP groups 4/29 had aspiration pneumonia and 6/29 had upper respiratory tract infections causing surgical intervention to be deferred. When two or more anomalies present together, medical complications can result and their coincidence carries implications for morbidity and prognosis (Azmi *et al.*, 1983). Pandya and Boorman (2001) found failure to thrive (FTT) in babies with CLP, but with a feeding support nurse and airway management it improved. It may also be that neonatal nurses may be able to provide more effective care by understanding more of the nature of CLP and its effects on feeding.

The multidisciplinary nature of effective care of CLP infants also involves speech pathology. A greater understanding of the differences in the morphology of the hyoid

bone may improve the approaches to speech therapy in CLP infants. Therapy based on current knowledge entirely overlooks the hyoid malformation. It is hoped that the findings of this study may lead to new approaches to CLP speech therapy.

9.2.2 Cervical Spine

The cervical spine showed smaller vertebral body heights and greater intervertebral spaces and smaller cervical angle. The presence of cervical spine anomalies was noted and delayed ossification of the anterior arch of C1. There was also an association between the occurrence of CLP and the presence cervical spine anomalies.

Endochondral ossification of the upper cervical vertebrae commences by the eight week of foetal life and is completed by about three to six years of post-natal life (Farman and Escobar, 1982; Sandham, 1986). Although no significant difference was found in the overall length of the cervical spine, the smaller vertebral bodies and greater intervertebral spaces suggest that there may be a difference in the pattern of skeletal ossification or that maturation is delayed or altered in CLP compared with the NC infants. This delay in maturation may influence the lifting of the head (during the sixth – tenth weeks *in utero*) and could also possibly be associated with the failure of the elevation of the palatal shelves to meet leading to clefting of the palate. These limitations of the extension of the head of the foetus could also interfere with the descent of the glosso-mandibular complex. The wedging position of the tongue in between the palatal shelves has been shown to be a major factor contributing to failure of shelf elevation and clefting of the secondary palate (Diewert, 1983).

Abnormalities of the cervical spine in CLP, such as synostosis of the posterior upper arch and short posterior arch of C1, tilting of the atlas (C1) and anterior arch

anomalies of C1 which included two anterior arches instead of one and an asymmetric anterior arch to the right, have not been demonstrated before the use of 3D CT.

The reduced cervical angle in CLP may be associated with postural changes to facilitate airway maintenance. Anderson (1997), in his study on craniosynostosis patients, reported that cervical spine synostosis, particularly those affecting the higher levels, may also have important consequences for head posture with resulting influences on craniofacial growth and dental occlusion. Other researchers have also proposed that cervical spine anomalies may alter head posture (Solow et al., 1984; Solow and Siersbaek-Nielsen, 1986; Hellsing et al., 1987; Solow and Siersbaek-Nielsen, 1992; Nevard, 1994). These previous studies have also demonstrated associations between head posture and craniofacial morphology. This study's findings suggest that upper cervical spine anomalies may be more common in Malaysian children with CLP (24%) than in American children (22%) (Horswell, 1991), Scottish children (13%) (Sandham, 1986), and Norwegian children (18%) (Ugar and Semb, 2001). However, it must be stressed that the study groups referred to include different proportions of cleft types so comparisons of incidence should be undertaken with some caution. Furthermore, the present study was based upon 3D CT scans of subjects while earlier studies were based upon 2D cephalometric radiographs. The enhanced clarity offered by CT images may well display anomalies more clearly and thereby facilitate the diagnosis of CLP associated defects. Previous studies have reported similar frequencies of synostosis in NC groups or in the general population, ranging from 0.5 – 5% (Gray et al., 1964; Brown et al., 1964; Farman and Escobar, 1982). In contrast, the author did not find any synostosis anomalies, probably due to the small sample size of the NC group. However, ethnicity cannot be ruled out as an explanation.

Osborne *et al*. (1971) suggested a smaller than normal anterior arch of the atlas could have a direct effect on the anterior-posterior dimension of the pharynx. The anterior arch of C1 is suggested to play a significant role in the establishment of adequate velo-pharyngeal function and speech in children with CLP (Osborne *et al*., 1971; Sandham, 1986). These findings suggest that the ossification of anterior arch of C1 may be compromised in patients with CLP and this may later contribute to problems in speech. The importance of the anterior arch of C1 and upper cervical vertebrae was highlighted by Berkowitz (1996) in achieving adequate velopharyngeal closure and speech.

The finding of short vertebral bodies in the cervical spines of infants with clefts is consistent with a delay in growth in infancy. Previous studies have shown a delayed growth in children with clefts of the lip and palate but further studies are needed to clarify the developmental mechanism involved (Bowers *et al.*, 1987; Seth and McWilliams, 1988; Harris and Hullings, 1990; Lilius and Nordstrom, 1992; Neiman and Savage, 1997; Grippaudo and Kennedy, 1999; Spyropoulos and Burdi, 2001).

9.2.3 Nasopharynx

The findings in relation to the nasopharynx showed that there were increases in the nasopharyngeal space, maxillary tuberosity, the zygoma, and a greater height of the nasopharynx from the posterior part of the vomer (hormion) to hamulus left and right in CLP.

The increased nasopharyngeal space may be associated with compression of nasopharyngeal structures including the eustachian tube. The alteration of the medial pterygoid plate and hamulus may alter the origin and orientation of the tendon of tensor veli palatini, affecting its function and pull, and lead to eustachian tube

dysfunction. These anatomical variations may compromise the dilatory mechanism of the eustachian tube leading to clinical problems such as otitis media and hearing loss. These anatomical variations could also play a possible role in the production of velopharyngeal incompetence, hypernasality and upper respiratory tract infection.

9.2.4 Cranial Base

Maxillary hypoplasia is commonly associated with CLP. The cranial base in the CLP group demonstrated smaller heights of the basisphenoid and basioccipital bones and a smaller anterior cranial base distance from sella to nasion which may provide a clue as to the origin of this facial feature. In a normal foetus the cranial base is a border structure between the neurocranium and the facial skeleton. Thus, the development and growth of the cranial base can interact both with the neurocranial and facial skeletal development. The cranial base is derived from the chondrocranium (Sperber, 2001) and the formation of the chondrocranium starts around the fifth foetal week. The elevation of the merging of the palatal shelves takes place around 7-10 weeks gestational age. At this time no ossification has occurred in the occipital, sphenoid, ethmoid and frontal (Kjaer, 1990, 1992). Kjaer *et al.* (1993) have shown that the human basal cranium undergoes dimensional changes when the palatal processes are elevated, and the primitive face, with its widely-spaced eyes, changes to a face with the eyes closer together.

Since the cranial base develops from the chondrocranium, the possibility cannot be excluded that an inborn alteration or a delayed maturation of the early development of the cartilaginous cranial base affects not only the height of the basisphenoid and basioccipital bones, but also the length of the cranial base, the width of the nasopharynx, and the width of the cranial base and SOS, as all these structures

develop from the same basic structure. There may deficient ossification or continuous chondroblastic proliferation of the chondrocranium at the time of cleft formation in infants with CLP.

9.2.5 Spheno-occipital synchondrosis (SOS)

The main difference noted in the spheno-occipital synchondrosis in CLP was a greater inferior width.

The SOS is regarded as an important maturity and growth centre of the facial skeleton (Ford, 1958; Stramrud, 1959; Thilander and Ingervall, 1973; Melsen, 1974). Post-natal growth in the SOS is the major contributor to growth in the cranial base, persisting into early adulthood. This prolonged growth period allows for continued posterior expansion of the maxilla to accommodate future erupting molars and provides space for the growing nasopharynx.

Previous studies have concentrated upon growth and closure of the SOS by examining non-cleft human autopsy specimens (Ford, 1958; Thilander and Ingervall, 1973; Melsen, 1974). The basicranium is also the first region of the skull to reach adult size, and it is the structural foundation of many aspects of craniofacial architecture. As the basicranium grows, it elongates and flexes in the spheno-ethmoid, mid-sphenoid, and spheno-occipital synchondroses (Lieberman *et al.*, 2000).

The greater width found in the inferior part of the spheno-occipital synchondrosis could be related to a defect in the chondrocranium of the cranial base. In the present study, there was a significant difference between males and females in the width of superior SOS. The SOS in females was narrower than in males. Previous studies on autopsy specimens have shown that the SOS starts to fuse, beginning on its cerebral

surface, at 12 –13 years of age in girls and 14-15 of age in boys; with ossification of the external aspect complete by around 20 years of age (Thilander and Ingervall, 1973; Melsen, 1974)). It is possible that a delay in skeletal maturation in CLP contribute to its greater width in the inferior region where fusion normally occurs at a later stage. The narrower SOS in CLP females compared with males might then reflect a tendency to earlier skeletal maturation in females.

In this study infants, with CLP tended to have a wider SOS, in contrast to the narrower SOS reported previously in Crouzon syndrome and Apert syndrome Kreiborg *et al.* (1993). A wider SOS could be associated with dysmorphic and compensatory growth changes at a later age.

9.2.6 Summary of Findings

The fact that several craniocervical structures are affected at the same time suggests that clefting may be one aspect of a more general problem. While this study cannot clarify whether the main aetiological factor is genetic or environmental, the reporting of these common features should assist future researchers. This phenotypic study should also assist molecular biologists searching for a molecular basis of CLP by highlighting the fact that several regions of the developing craniofacial complex are affected in CLP.

The phenotypic changes relate to structures derived from the first, second and third arches and may reflect alterations in cartilage growth and/or ossification. The findings of this study suggest there could be a common underlying defect or delay in endochondral ossification. Development of the hyoid bone, cervical spine, nasopharynx, cranial base and SOS all involve endochondral ossification.

This also could explain, in general, the reduced growth potential in CLP. Previous studies have shown a delayed growth in children with clefts of the lip and palate (Bowers *et al.,* 1987; Seth and McWilliams, 1988; Harris and Hullings, 1990; Lilius and Nordstrom, 1992; Neiman and Savage, 1997; Grippaudo and Kennedy, 1999; Spyropoulos and Burdi, 2001).

The principal feature of skeletal and connective tissue in the face is its dual origin from neural crest cells and mesoderm. These cells establish the origins of the skeletal and connective tissues. The cartilages are the first skeletal elements to develop. The induction of cartilage from neural crest cells is often promoted by the product of the epithelium. In the branchial region the morphology of the cartilages is dependent on Homoebox gene activity. Most of these cartilages undergo endochondral ossification (Johnston and Bronsky, 1995).

Two genes, core-binding factor alpha 1 (Cbfa-1) and Indian hedgehog (IHH), have been shown to control osteoblast differentiation. Bone morphogenetic proteins (BMP), members of the transforming growth factor-beta, and fibroblast growth factors (FGR) and their receptors (FGFR) induce bone formation at genetically designated sites (ossification centers) (Sperber, 2001). Delayed onset of osteogenesis will reduce the final size of a bone, and premature onset of osteogenesis will increase its final size. During the seventh week of intra-uterine life, mesenchymal cells condense as a prelude to both intramembranous and endochondral bone formation. Although the basic shape and size of bones may be genetically determined, extrinsic functional or environmental factors become the predominant determinator of bone form.

Alterations in cartilage growth can lead to a reduced cranial base. Such a defect of the chondrocranium will then have an inhibiting effect on the midface and maxilla producing a dish-faced deformity of the middle third and dental malocclusion (Sperber, 2001). Recently Singh *et al.* (2004) have shown that Class III malocclusion in CLP patients is associated clinically with deficient cranio-maxillary growth.

Overall, the 3D analysis has disclosed new information about phenotypic variation in CLP and shown several significant differences from NC infants. It has also helped to explain the possible reasons for the clinical problems faced by affected children such as aspiration pneumonia, speech problems, otitis media and upper respiratory tract infection.

The question of whether the phenotypic findings in the craniocervical structures are the cause of the CLP, reflect a common underlying aetiological problem, or are an effect cannot be answered definitively. However, the fact that there are several structures affected together suggests that the clefting may be one aspect of a more general problem.

9.3 Summary of the Findings for Isolated Cleft Palate (ICP)

In this study different CLP groups (CL, UCLP, BCLP and ICP) were compared with an NC group. In addition the ICP group was also compared to the other three affected groups. This was based on the fact that ICP seems to result from a different mechanism and the defect occurs at a later time during embryogenesis.

The findings for the ICP group compared with the other CLP groups included smaller length of the left greater horn, smaller intervertebral spaces, smaller nasopharyngeal

width at various levels, a greater right hamulus angle, a larger vomer-basion distance and a smaller basisphenoid height.

These differences indicate that ICP is a related but developmentally different condition from CLP.

9.4 Comparison between Males and Females

In this study it was found that four variables were larger in the CLP and NC group males than females; lateral pterygoid width, vomer to lateral pterygoid right, interzygomatic distance and superior SOS width.

These findings show that, even in the infant stage, there is a tendency for some craniofacial structures in males to be generally larger than females.

9.5 Limitations

One of the limitations of this study is the relatively small sample size. The 29 subjects were derived from an initial group of 40 possible cases based on preliminary power studies. This limits the statistical power of the analysis and hence, caution must be used when drawing inferences or conclusions from the data.

Also, while numerous craniofacial landmarks were located, not all of them were included in subsequent analyses due to time constraints. The selection of the variables that were studied was based on three main factors: firstly, 3D imaging made structures such as the hyoid bone clearly visible for the first time, secondly, the clinical importance of the areas chosen, eg. the relationship between the hyoid bone

and swallowing, and thirdly, absence of any detailed analysis of the particular areas selected in the literature.

Another limitation of this study is that it is cross-sectional, not longitudinal. This means that changes over time cannot be assessed and nor can any correlation between age and growth be drawn.

This study also only provides indirect evidence concerning the aetiology of cleft lip and palate. However, detailed analysis of the phenotype in CLP can only be of benefit to future researchers.

9.6 Future Studies

The present investigation has opened the way for further studies into the quantification and analysis of cleft lip and palate in three dimensions. Several avenues of future research have been suggested by the findings reported here, including the use of more sophisticated morphometric shape analyses that should further improve understanding of CLP and also improve management approaches for affected infants.

Singh *et al*. (2004) have recently undertaken a comprehensive longitudinal craniofacial growth study of orofacial clefts involving morphometric analysis. Similarly, it is intended to follow the children in this study over time to allow pre- and post-surgical comparisons and to evaluate the effect of growth and development on the structures assessed in the present study. It is also planned to extend the area of study to include other craniofacial variables such as the orbit and cribriform plate. It is hoped that, with time, increasing numbers of patients will be added to the current

sample, thereby allowing the use of more sophisticated methods of analysis such as those developed by Singh and colleagues.

Future studies could include morphometric analyses of asymmetry in CLP by considering variables in 3D, thereby overcoming the problem of defining midlines. It is also planned to explore the topic of fluctuating asymmetry in CLP and its association with decreased developmental homeostasis.

The future will also provide opportunities to investigate molecular/cellular events and genetic make-up in CLP. As the genotype of CLP becomes better understood so too will its phenotype leading to better management of the condition and better outcomes for the patients.

9.7 General Conclusion

From the findings of the present and previous studies, it can be concluded that there are significant differences in the craniofacial-cervical morphology of infants with CLP compared with NC infants, between infants with ICP and other affected cleft infants, and between affected males and females. These differences need to be recognised since they can improve our understanding of developmental associations in CLP and also assist in the management of individuals with CLP.

It seems justifiable to assume that the major part of the observed morphological aberrations in CLP reflect abnormalities in early embryonic development. This study has identified a wide range of anomalies, affecting sites of the extracranial skeleton, that have not been well described in the literature.

There are several consequences that follow as a result of this research.

Firstly, the new knowledge of the extent of the range of extracranial anomalies associated with CLP will assist those attempting to make a diagnosis on clinical features of CLP.

Secondly, knowledge of the wider range of anomalies associated with CLP will alert clinicians involved in the care of individuals to be aware of the potential problems that may arise during a child's development.

Thirdly, this study has highlighted the extent of biological associations in CLP, apart from those in the region of the defect.

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