Lateral Deviation Pattern of the Nasopalatine Canal in Patients Exhibiting Alveolar Cleft Defects

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Dedication

To my parents Hélène and Michel Vachon

To my husband Pierre-Paul Gros.

Abstract

Patients with facial cleft defects, such as alveolar clefts, represent quite a challenge for the dental practitioner. These patients require a multidisciplinary care approach from the time they are born up until the anomaly is completely repaired. Many guidelines have been established to improve the treatment and closure of cleft defects. To this day, little is known about the trajectory taken by the nasopalatine canal (NPC) in cleft patients.

The aim of this study is to describe the lateral deviation pattern of the NPC in alveolar cleft patients as compared to sex- and age-matched controls without such defects. Cone Beam Computed Tomography images (CBCT) of 29 unilateral cleft patients were evaluated and compared to a control group. The dimensions of the NPC and of the buccal alveolar process overlying the canal itself were also assessed.

Among the 29 unilateral alveolar cleft patients observed in this investigation, 59% occurred in males while 20 of 29 were on the left side. The NPC was significantly wider in a bucco-lingual dimension and slightly greater in a mesio-distal dimension in cleft patients than non-cleft patients. The width of the buccal alveolar process overlying the NPC was similar in both groups. Age was significantly and inversely associated with buccal alveolar bone width overlying the NPC in cleft patients, but not in control patients. The mean lateral deviation of the NPC was non-significant when compared between the groups. However, the absolute mean deviation of the NPC was statistically different between the 2 groups. Our data suggests there is a strong tendency for the NPC to be positioned on the opposite side of the cleft defect in patients exhibiting cleft alveolus.

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I. Review of the Literature

Craniofacial anomalies (CFA) are a particularly diversified ensemble of complex congenital anomalies. They overall affect a remarkable proportion the global society and show tremendous variability across ethnic groups and geographic regions. Their significant impact on hearing, speech, appearance and cognition has a long-term negative influence on health and social integration. Considerable morbidity, healthcare costs, emotional disturbances, and possible social exclusion can also be associated with CFAs, which underlines the importance of research in this field (WHO, 2004).

A) Types of Clefts/Definition

Cleft defects of the lip (cheiloschisis or labioschisis) and/or of the palate (palatoschisis) are among the most common congenital anomalies in newborns (Gorlin et al., 2001). About 6,800 infants each year are affected by this condition in the USA (CDC, 2006).

Great heterogeneity exists in the types and severity of oral cleft defects, which can involve the primary palate (lip and alveolus), the secondary palate (hard and soft palate, posteriorly to the incisive foramen), or both structures at the same time (Tessier, 1976). Defects can also be subcutaneous, making them difficult to detect clinically (Gosain et al., 1996; Heckler et al., 1979; Shapira et al., 1999; Thornton et al., 1996). These malformations result from an interruption in embryonic development and failure of certain facial structures to fuse (Nanci, 2003). They can occur unilaterally or bilaterally, and can be complete or incomplete (Thornton et al., 1996).

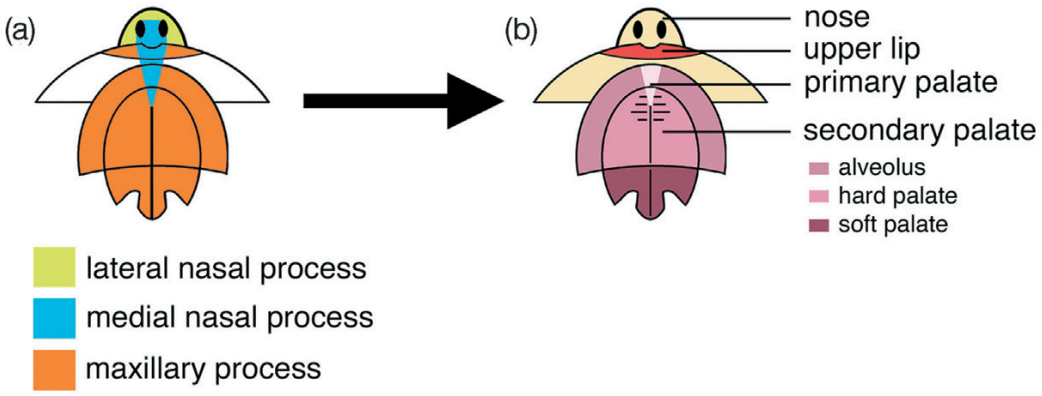

Figure 1 a), b). Embryological origins of the midline facial structures. The lateral nasal processes form the alae and sides of the nose, while the medial nasal processes form the intermaxillary segment, composed of the upper philtrum, the primary palate and the four incisor teeth. The maxillary process forms the remainder of the upper lip and secondary palate consisting of the hard palate and associated dentition anteriorly and posteriorly, and the soft palate.
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Over the years, many different classifications systems have been elaborated in order to describe cleft defects (Losee and Kirschner, 2009). Initial classifications systems based on observed defect morphology, i.e. those by Davis and Ritchie in 1922 (Davis, 1922) and by Veau in 1931 (Veau, 1931) were used for descriptive purposes. Fogh-Anderson later modified Veau's classification and divided clefts into 3 main groups based on affected anatomy and using the incisive foramen as a landmark. A 4th group involves microforms of the anomaly, i.e. minimal expressions of cleft lip or cleft palate anomalies, and is not an integral part of this classification system (Fogh-Anderson, 1942):

Cleft lip (CL) group

Involves cleft of the primary palate (including lip, alveolus, and incisive foramen)

Cleft lip and palate (CLP) group

Unilateral and bilateral clefts (complete or incomplete) of the lip extending into the hard palate

Cleft palate (CP) group

Midline clefts of the secondary palate, posteriorly to the incisive foramen, without any involvement of the lip

Microforms of clefts

Including cleft uvula and submucous palatal cleft

Besides Fogh-Anderson's classification, Tessier's classification was also widely accepted and used to describe orofacial clefts (Tessier, 1976). A major drawback of these classifications is that they do not identify the etiopathogenesis of clefts. Luijsterburg and associates recently suggested a classification system based on the pathoembryological events that ultimately result in various subtypes of cleft defects. The 3 major categories previously outlined by Fogh-Anderson, i.e. CL, CLP and CP are divided into 3 new subgroups: fusion defects, differentiation defects, and fusion and differentiation defects. This new classification provides new cleft subgroups that may be used for future clinical and fundamental research (Luijsterburg et al., 2013).

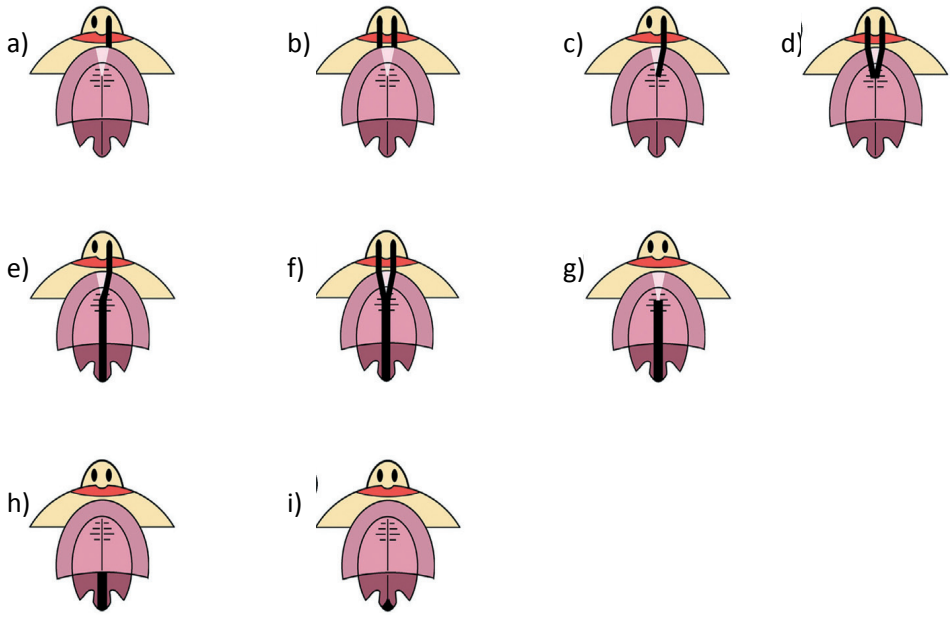


Figure 2. Various types of clefts

a) Unilateral cleft lip

b) Bilateral cleft lip

c) Unilateral cleft lip and primary palate

d) Bilateral cleft lip and primary palate

e) Complete unilateral cleft of the lip and palate

f) Complete bilateral cleft of the lip and palate

g) Isolated cleft of the secondary palate

h) Isolated cleft of the soft palate

i) Submucous cleft of the soft palate

(Reprinted with permission form (Cobourne, 2004))

B) Prevalence & Distribution

Although most orofacial clefts are isolated developmental anomalies, as many as 250 syndromes of the head and neck include clefts as one of their characteristics (CL +/- CP, or isolated CP), and apparently account for 3-8% of all orofacial clefts (Neville et al., 2002). Cleft defects show varied distributions and severity within the population. In general, unilateral clefts seem to occur 4 times more frequently than bilateral clefts (Shapira et al., 1999).

CL, which results from a defective fusion between the medial nasal process and the maxillary process, represents about 25% of all cleft defects. This anomaly is more prevalent in males than in females, with a 1.5:1 ratio (Neville et al., 2002). It can involve the lip only by creating a slight notch into the vermilion border, or it may extend to the nostril. Eighty percent of CL cases are unilateral, of which about 70% show a predilection for the left side of the face. The residual 20% of CL cases are of bilateral nature (Moller and Glaze, 2009; Neville et al., 2002).

CLP is by far the most common cleft defect. This anomaly represents ~45-50% of the total cleft population, and occurs twice as frequently in males than in females (Shapira et al., 1999). CLP results in a failure to fuse of both the palatal shelves and the medial nasal process with the maxillary process (Nanci, 2003; Neville et al., 2002). Left-sided predominance has been associated with this specific anomaly. Indeed, the left side is affected approximately 50% more than the right side or both sides (Shapira et al., 1999).

CP results only from a failure of the palatal shelves to fuse. Therefore, it is considered a separate entity from CL and CLP defects. CP defects represent another ~25% of the

cleft population. In contrast with the other defect types, CP occurs more frequently in females than in males, with a 2:1 to 3:1 ratio for complete clefts of the hard and soft palate (Neville et al., 2002; Shapira et al., 1999). However, the ratio approaches 1:1 for defects involving the soft palate only (Moller and Glaze, 2009).

Microforms include defects such as the bifid uvula, submucous palatal cleft, hairline indentation and lateral congenital sinus of the upper lip. Bifid uvula anomalies vary in completeness, with incomplete clefts being the most common (Heckler et al., 1979). As for submucous cleft palate anomalies, they occur as a result of an incomplete muscle union across the soft palate underlying the mucous membrane (Gosain et al., 1996).

It is also interesting to notice that prevalence varies with race and ethnicity. Native Americans show the highest prevalence of CL +/- CP defects, with about 3.6 affected individuals per 1000 births. Japanese and Chinese follow with decreasing prevalence values for oral cleft defect occurrence. In contrast, Whites show much lower values, with about 1 Caucasian over 1000 births affected and African-Americans show the lowest prevalence of all (Vanderas, 1987). The latest data in the Indian population of Baroda, Delhi and Mumbai show a frequency of CL+CP 0.93 per 1000, and CP alone of 0.17 per 1000. Unfortunately, there are still many parts of the world where little or no information on the frequency of OFCs is available, in particular in most of Africa, Central Asia, Eastern Europe, Indian sub-continent and the Middle East (Mossey and Little, 2009).

The International Perinatal Database of Typical Oral Clefts (IPDTOC) conducted a study to evaluate the prevalence at birth of cleft lip with or without cleft palate. Their data suggest an overall prevalence of cleft lip with or without cleft palate of 0.99 in 1000 in

births. The prevalence for cleft lip was 0.33 per 1000, and that of cleft lip and palate was 0.66 per 1000. About 76.8% of cases were isolated, while 15.9% showed malformations in other systems, and 7.3% were syndromic (IPDTOC, 2011).

C) Embryology

Cleft formation is a process that starts early during the embryologic growth. After fertilization of the egg, a rapid proliferation and migration of cells occurs to form the morula, which soon transforms into a blastocyst. This blastocyst transforms into a bilaminar germ disk, and eventually into a 3-layered embryo, i.e. the trilaminar disk (ectoderm, mesoderm, endoderm). All this occurs during the first 3 weeks of development. During the subsequent 3 to 4 weeks the head, face and the tissue that will lead to formation of the teeth develop (Nanci, 2003).

The thickening of the ectoderm leads to the formation of the neural tube, which soon undergoes massive expansion to form the forebrain anteriorly, the midbrain, and the hindbrain posteriorly. The hindbrain divides itself into 8 rhombomeres, which are very important in the development of the head. The first 2 rhombomeres as well as the midbrain contribute to the formation of the neural crest, which plays a crucial role in craniofacial development. Neural crest cells then migrate to form the branchial arches (Merritt, 2005a; Nanci, 2003).

At 24 days, the embryo begins folding in a caudocephalic direction. At this stage, the stomatodeum (or primitive mouth) is bounded by the neural plate posteriorly, the developing cardiac plate inferiorly and the frontal eminence superiorly. The

buccopharygeal membrane separates the stomatodeum from the foregut. It eventually undergoes selective cell apoptosis and ruptures (Moller and Glaze, 2009; Morriss-Kay and Tucket, 1991). The stomatodeum is also lined laterally by the branchial arches, which are each formed of mesoderm, cartilage, an artery and a nerve. As the embryo evolves, the branchial (or pharyngeal) arches separate the stomatodeum from the developing heart. Each arch gives rise to various structures, i.e muscles, bones and cranial nerves (Merritt, 2005a; Nanci, 2003).

Overall, the face of the embryo forms by the merging and fusion of various facial processes during the 5th to the 10th weeks after conception. The face is formed by derivatives of the first and second branchial arches. On each side of the frontal eminence, the thickening of the ectoderm leads to the formation of the olfactory placodes. Cell proliferation and selective apoptosis soon leads to the formation of olfactory pits and the alae of the nose. The medial nasal processes fuse to the maxillary processes on each side to form the upper lip and the primary palate around 7 weeks after conception. The formed segment is therefore referred to as the intermaxillary segment. This segment is divided into 2 portions: one labial component, which forms the philtrum of the upper lip, and one triangular palatal component, which forms the premaxilla and includes the 4 anterior incisors. The primary palate extends posteriorly to the incisive foramen, through which the nasopalatine nerve will exit (Merritt, 2005a; Nanci, 2003).

The secondary palate makes up the remainder of the hard and soft palate, which account for about 90% of the whole palatal area. It starts forming around 7 to 8 weeks post conception and continues up until the end of the 1st trimester, i.e. 3 months post

conception. Prior to that developmental stage, the oral and nasal cavities are not yet separated from one another. At the 6th week post-conception, small prominences extend from the medial portion of the maxillary processes on each side. These eventually form the palatal shelves and are initially in a vertical position. The tongue separates them at this point in time. As the embryo develops, the palatal shelves grow downward and become horizontal, the tongue is displaced inferiorly and the mandible widens and grows in a forward direction. The epithelium overlying each palatal shelf undergoes degeneration when they finally contact as a result of their horizontal elevation. This allows for a flow of the underlying ectomesenchyme to close the gap from each side. Complete fusion takes place by the 10th week, in an antero-posterior direction (Merritt, 2005a; Moller and Glaze, 2009; Nanci, 2003). The mechanism that drives the elevation of the palatal shelves around the 7th week is referred to as intrinsic shelf force and has a complex biochemical and physiochemical basis (Gorlin et al., 2001). Failure of any of these precisely timed events to occur will result in the development of palatoschisis, labioschisis, or both (Sperber, 1992).

D) Mechanisms of Clefts

A multifactorial etiology has been suggested for both palatoschisis and labioschisis (Kohli and Kohli, 2012; Murray and Schutte, 2004). Clefting mechanisms are very complex in nature and our understanding of these is at best sparse. The fusing tissues of the head develop as a result of cell proliferation, vascular expansion, extracellular matrix production, and fluid accumulation, all of which are subject to variations that may

predispose individuals to cleft defects (Losee and Kirschner, 2009). Exact timing and precise positioning of each facial structure play crucial roles in the facial development of the embryo (Sperber, 1992). Migration of cells originating from the neural tube is greatly affected not only by key genetic factors, but also by environmental factors (such as teratogenic substances) (Gorlin et al., 2001).

Mice and human studies have suggested various clefting mechanisms for both the primary and secondary palate (Amin et al., 1994; Bronsky et al., 1986; Johnston and Sulik, 1979; Millicovsky et al., 1982). Depending on the nature of the defect, cleft mechanisms such as vascular interruption, alteration in growth of the nasal placodes and wedging of the tongue between the palatal processes act unilaterally or bilaterally on the primary palate, the secondary palate, or both structures at once (Thornton et al., 1996).

Differences in the vascular patterns among cleft and non-cleft subjects seems to indicate that discontinuation of the palatine artery may occur in the premaxilla of cleft subjects at an early embryonic stage. Such an alteration in blood supply might be a contributing factor to the formation of cleft defects in the primary palate (Amin et al., 1994).

Alterations in growth and positioning of nasal placodes, as well as abnormal positioning of facial prominences have been suggested as being potentially responsible for clefting of the primary palate (Johnston and Sulik, 1979). Other investigators have suggested that primary palate clefting could be caused by wedging of the tip of the tongue between the nasal median and the maxillary processes (Trasler and Fraser, 1963) . However, controversy remains even to this date.

Clefting mechanisms for the secondary palate remain unclear. The presence of a large tongue that could prevent the palatal shelves to fuse has been postulated but this explanation appears too simplistic (Gorlin et al., 2001). Diminished mandibular growth has also been proposed as a mechanism. This would inhibit maxillary growth and impinge on the downward trajectory of the tongue, as observed in the Pierre-Robin Sequence (Evans et al., 2011; Shprintzen, 1988). Secondary palate cleft defects are more likely to occur as a result of hypoplasia of the palatal structures, or delay in the timing of the palatal shelves elevation (Johnston and Sulik, 1979).

E) Genetics

The etiology of oral cleft defects is extremely complex. Most cases of palatoschisis and labioschisis have a multifactorial inheritance, as they are caused by multiple gene mutations and environmental insults (Murray and Schutte, 2004).

Genetic plays a major role in the occurrence of cleft defects, with family history remaining one of the most important factors for labioschisis and/or palatoschisis (Moller and Glaze, 2009). Many genes have been associated with both syndromic and non-syndromic cleft cases, such as TBX22, PVRL1, and IRF6. Mutations in candidate genes have also been associated with cleft defects (Cobourne, 2004; Kohli and Kohli, 2012). Nonetheless, cleft defects cannot be solely explained by genetic factors, and are also greatly influenced by environmental factors. Our understanding of clefting anomalies is still poor and necessitates further research (Cobourne, 2004; Gorlin et al., 2001; Kohli and Kohli, 2012; Losee and Kirschner, 2009; Thornton et al., 1996).

F) Environment

In addition to genetic risks, many environmental and behavioral risk factors have been suggested as potentially involved in clefting mechanisms, such as teratogenic agents (Kohli and Kohli, 2012; Merritt, 2005a). Considering that the palate and upper lip complete their development between the 7th and 9th weeks post-conception, these risk factors must be present prior to that time to contribute to cleft defect formation (Losee and Kirschner, 2009).

Tobacco smoking by pregnant women has been extensively discussed and appears to be associated with an increased risk of facial malformations for newborns (including CPL and CP) as well as pregnancy complications. A meta analysis of 24 studies revealed that pregnant smokers were 1.3 times more likely to have offsprings with CL +/- CP, and 1.2 times more likely to have their child develop CP than non-smokers (Little et al., 2004). Although this risk increase is modest, it is considered significant, especially if combined with a positive family history (Lebby et al., 2010).

Substantial intake of alcohol during pregnancy, apart from causing fetal alcohol syndrome, also increases the risk for cleft defects in the neonatal by 1.5 to 4.7 times. Indeed, a dose-dependent relationship seems to exist between the occurrence of cleft defects and maternal drinking (Munger et al., 1996). Shaw and Lammer supported those results, by showing that pregnant women who consumed more than five drinks per occasion had 3.4 times increased risk of delivering an infant with CLP (Shaw and Lammer, 1999). However, low-level alcohol ingestion did not seem to increase the risk CLP (Natsume et al., 2000). Other potentially harming behavioral factors for the fetus/

embryo include obesity and stress in pregnant women (Blomberg and Kallen, 2010; Stothard et al., 2009).

Using certain medications during pregnancy has also been associated with greater risks of cleft defects. For example, increased intake of retinoids, anticonvulsivants, folate antagonists, benzodiazepines and corticosteroids during pregnancy is correlated with a slightly increased risk of developing these anomalies (Carmichael and Shaw, 1999; Carmichael et al., 2007; Merritt, 2005a; Puho et al., 2007). However, more research is needed to fully determine the impact of these drugs on fetal development.

The role of folic acid supplementation in the prevention of CLP has been investigated several times. An adequate intake of folic acid by expecting mothers considerably reduces the risk of neural tube defects in the newborn, such as spina bifida (Carmichael et al., 2012; Jia et al., 2011). However, Ray and associates reported that a low-dose folic acid supplementation cannot protect against CLP (Ray et al., 2003). As a matter of fact, insufficient daily intake of folic acid has been demonstrated to triple the risk for CLP (Shaw et al., 2002). In contrast, using a very high dose of supplementary folic acid (10 mg/day) was reported to reduce the risk of CLP by 65.4%, according to Tolarova (Tolarova and Harris, 1995). These results all confirm why the NHI has implemented guidelines for folic acid intake in pregnant mothers, as seen below (NIH, 2009):

Table 1. Recommended Dietary Allowances for Folate for Children and Adults

Age (years)	Males and Females (μg/day)	Pregnancy (μg/day)	Lactation (μg/day)
1–3	150	N/A	N/A
4–8	200	N/A	N/A
9–13	300	N/A	N/A
14–18	400	600	500
19+	400	600	500

*1 DFE = 1 μg food folate = 0.6 μg folic acid from supplements and fortified foods (Modified from (NIH, 2009)

Maternal excessive intake of vitamin A has been shown to cause patterns of malformations in the neonatal, including an increased risk for cleft occurrence if very high doses of this vitamin (over 25,000 IU/day), when consumed on a daily basis (Kohli and Kohli, 2012; Losee and Kirschner, 2009). Healthy dietary patterns and the use of pre-conceptional vitamins should be encouraged in pregnant mothers, as long as they follow the dietary guidelines established by major health organizations such as the NIH. Maternal diet of high quality is strongly associated with reduced risks of neural tube defects and cleft defects in fetuses (Carmichael et al., 2012).

Maternal systemic conditions such as pregestational diabetes, gestational diabetes, and diabetes mellitus in expecting mothers have been associated with increased risks of developing palatoschisis and labioschisis in the embryo (Losee and Kirschner, 2009). However, other investigators have found this association to be insignificant, as too many co-founding factors exist (Lebby et al., 2010). Many exogenous exposure factors such as lead, pesticides, and hazardous waste have also been associated with a greater occurrence

of cleft defects, but the research on these topics remains incomplete (Kohli and Kohli, 2012).

G) Related Anomalies (including dental anomalies)

Numerous congenital anomalies have been reported to occur alongside cleft defects (Sekhon et al., 2011). Although many cleft defects may occur as isolated anomalies, oral clefts occurring in association with a syndrome including other anomalous findings, account for approximatively 3% to 8% of clefts (Bixler, 1981; Fraser, 1970). Patients affected with one of these conditions can present a wide range of anomalies, such as growth retardation, organ, bone or limb malformations, cleft defects, and dental anomalies (Gorlin et al., 2001; Shprintzen et al., 1985). In fact, previous studies have estimated that about 63.4% of cleft patients also presented other congenital anomalies (Shprintzen et al., 1985).

A wide range of dento-facial anomalies have been associated with cleft defects. Given that the facial clefting process and the development of both deciduous and permanent dentition occur concurrently, it is not surprising that abnormal tooth development can occur in the area of the cleft. Indeed, dental anomalies are more frequently found both in syndromic and non-syndromic cleft patients than in the unaffected populations. Schroeder and Green have compared the incidence and types of dental trait anomalies found in individuals with cleft lip or cleft palate or both (cleft group), in siblings of the cleft subjects, and in a group of individuals without cleft lip or cleft palate (noncleft group).

Overall, cleft subjects had 1.02 anomalies per individual, while the sibling group had 0.38, and the noncleft group only had 0.17 (Schroeder and Green, 1975).

Alveolar cleft formation leads to malformation of the maxillary bone and collapse of the maxillary arch with subsequent malposition and/or malformation of the dentition (Moller and Glaze, 2009). The incidence of hypodontia among patients affected by palatoschisis, labioschisis, or both was reported as high as 77% (Shapira et al., 2000), which is significantly greater than the 1.6 to 9.6% reported for a non-clefted population (Graber, 1978). Hypodontia was found significantly more often on the left side in both the maxilla and mandible, reflecting the predilection of cleft defects for this side of the face. The teeth reported to be missing most frequently were the maxillary lateral incisors on the side of the cleft, followed by the maxillary and mandibular second premolars. These teeth are also sometimes missing on the opposite side of the cleft, but this occurs much less often (Shapira et al., 2000). Tortora noted an incidence of missing lateral incisors on the same side as the cleft 45 to 48% of the time in unilateral and bilateral cleft subjects while the incidence of missing laterals outside of the cleft area has been reported with an occurrence frequency of only 6.1% (Tortora et al., 2008).

Dental anomalies such as peg shaped lateral incisors, malformed roots, supranumerary and rotated teeth have also been reported as anomalies associated with cleft defects. Once again, these findings are most commonly seen on the side of the defects (Tortora et al., 2008). A delay in tooth development has also been documented in cleft subjects by previous investigators (Borodkin et al., 2008). In addition to osseous malformations caused by the cleft process itself, all previously stated dento-facial

anomalies contribute to creating a significant discrepancy between the mandible and the maxilla, leading to moderate to severe malocclusion, and possible speech and language impediment (Moller and Glaze, 2009; Neville et al., 2002). Facial growth and dental eruption can be significantly delayed in such patients (Corbo et al., 2005).

H) Management of Palatoschisis & Labioschisis

Children with craniofacial birth defects, including labioschisis and palatoschisis, obviously have special health care needs. Such an anomaly can be detected as early as before birth or as late as early adulthood. These patients require the multidisciplinary attention of a complete team of craniofacial specialists: a plastic surgeon, an oral maxillofacial surgeon, an orthodontist, a pediatric dentist, a prosthodontist, a speech therapist, a psychologist, a nutritionist, and in most cases, a social worker to assist in the facilitation of services (Thornton et al., 1996). Treatment must be tailored to each patient's needs and staged over a period of several years (ACPA, 2009).

The patient's first evaluation by a craniofacial team should be done as early as a few days to a few weeks after birth. Preliminary lip adhesion and maxillary orthopedics may be used as pre-surgical therapies to improve the position of the premaxillary segment. Primary surgical repair of the defect is intended to regain normal functional and anatomic features. It can be initiated as soon as deemed safe for the child and is usually performed within the patient's first 12 months of life. Nasal deformities may be treated at the time of primary lip and palate repair (ACPA, 2009; Daw and Patel, 2004; Merritt, 2005b).

Secondary surgical repair procedures of the lip, nose, palate and jaws, may be performed later in the patient's life in order to improve esthetics and function. This includes rehabilitation of the edentulous space in the area of the alveolar cleft with a partial denture, a tooth-retained bridge, by orthodontic closure, or with a dental implant.

Failure to replace a missing tooth has been implicated with several adverse consequences. These include the supra eruption of the opposing tooth or teeth, tilting or drifting of the adjacent teeth, and loss of proximal contacts, which negatively impact the health of the supporting structures and the occlusion. These adverse consequences may ultimately result in the loss of 1 or more of the teeth adjacent to the edentulous space (Rosenteil et al., 1995). Therefore, missing teeth should ideally be replaced in cleft patients.

Although many options exist to replace missing teeth, some alternatives may involve more complications and risks than others. Aquileno conducted a retrospective cohort study on the fate of teeth adjacent to a nonreplaced missing posterior tooth. A significant difference was observed in the 10-year survival rate for teeth adjacent to a posterior edentulous space being 92% for a fixed partial denture, 81% for untreated teeth and 56% for removable partial dentures (Aquilino et al., 2001). Although this study was conducted on posterior teeth, it can be assumed that failure to replace anterior teeth will lead to a comparable outcome in addition to many psychological issues (Misch, 2008; Moller and Glaze, 2009). Also, we can conclude from Aquileno's study, that a conventional removable prosthesis may not be the most reliable and durable restorative option and that a fixed restoration may be more appropriate (Budtz-Jorgensen, 1996; Sadan et al., 2004).

While a fixed partial denture seems to have a better long-term prognosis than a removable partial denture,, there are still considerable risks involved. Goodacre reported the 3 most common complications associated with fixed partial dentures were caries (18% of abutments), need for endodontic treatment (11% of abutments), and loss of retention (7% of prostheses) (Goodacre et al., 2003).

A good alternative to both traditional fixed and removable prosthodontics options is an implant-retained restoration (crown or bridge). Indeed, this option has been proven to be very predictable in the general population as well as in cleft patients, yielding high success rates with fewer complications to adjacent teeth (Cune et al., 2004; Fugazzotto et al., 1993; Lekholm et al., 1999; Lindh et al., 1998; Matsui et al., 2007; Pjetursson et al., 2004; Priest, 1999; Sullivan et al., 2001). The longevity of implant-retained restorations is of about 95-97% at 20 years compared to 69-89% at 10-15 years for fixed partial prostheses, and 50% for removable partial dentures at 10 years (Budtz-Jorgensen, 1996; Sadan et al., 2004). However, such treatment obviously requires extensive treatment planning and surgical preparation of the implant site prior to implant placement (Daw and Patel, 2004). Careful site assessment must be undertaken prior to performing any surgical procedure to insure that treatment is tailored to each patient's needs (Tyndall et al., 2012).

I) Radiographic Assessment

Initial examination of each implant patient and site should begin with a clinical evaluation accompanied by intra-oral radiographs as well as with a panoramic image (Tyndall et al., 2012). An intra-oral exam and radiographs enables the clinician to

establish an adequate diagnose, including periodontal disease, caries and other intra-oral conditions. Panoramic images can serve as an initial assessment tool for extra-oral structures and pathologies for patients seeking implant treatment (Tyndall et al., 2012; White and Pharaoah, 2004). Panoramic images can no longer be considered sufficient to assess implant sites given their 10-30% image distortion and incapability to provide buccal-lingual measurements (Carranza et al., 2011). Indeed, panoramic images tend to show a certain degree of magnification of both horizontal and vertical measurements, and the degree of magnification is not necessarily uniform throughout the same panoramic image. Horizontal measurements are more unreliable than vertical measurements on these radiographic views (Truhlar et al., 1993). Cephalometric images are also of limited value in implant dentistry (Carranza et al., 2011).

Cross-sectional (3D) imaging is now frequently recommended for implant site assessment, and is considered the tool of choice for pre-operative implant planning. Cone Beam Computed Tomography (CBCT) images allow the clinician to correctly assess anatomical variations in each patient, including location of nerve canals, residual alveolar height and width, location of the sinusal and nasal floors, as well as potential pathologies, etc. (Tyndall et al., 2012). CBCT images have been shown to provide more precise measurements than conventional 2D cephalometric assessment (Chien et al., 2009). CBCT images can provide reliable and reproducible data for identification of three-dimensional landmarks (de Oliveira et al., 2009).

J) Nasopalatine Canal

The nasopalatine canal (NPC) is one of many structures that should be assessed by radiographic imaging prior to placement of a dental implant (Tyndall et al., 2012).The NPC may impinge upon the potential implant site and necessitate bone grafting may help to facilitate a successful outcome. Presence of pathologies such as a nasopalatine cyst within the NPC may require enucleation of the lesion and bone grafting prior to implant placement. Kraut and Boyden utilized CBCT scan images to examine parameters of the incisive canal in 30 patients ranging in age from 21 to 78 years old with both central incisors present. They concluded that the average length of the incisive canal was of 9 mm with a range going from 3 to 14 mm. The volume of the incisive canal averaged 103 cm^3, with a range going from 14.3 to 656 cm^3 (Kraut and Boyden, 1998). In another study examining a non-cleft population, the nasopalatine nerve and canal were shown to be within 3-5mm of the patient's midline between the central incisors (Chatriyanuyoke et al., 2012). Likewise, we noticed some variation in NPC positioning in non-cleft patients included in this investigation, as seen in figure 3. Patients who exhibit cleft defects at birth are expected to have greater deviations in this anterior segment than a non-cleft population. However, no study has ever evaluated the anatomy of this region to see if a trend existed in the positioning of the NPC and incisive nerve, in relationship to the cleft defect.

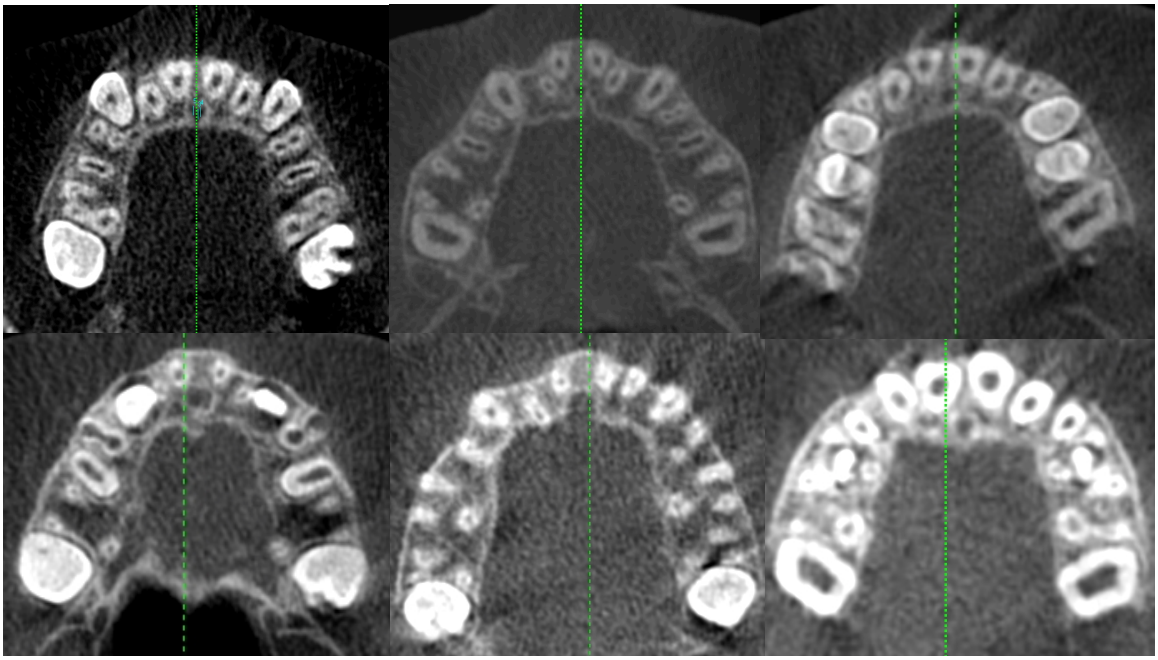


Figure 3. NPC variations in non-cleft patients (control patients)

K) Implant Placement Considerations

Implant-retained crowns have been shown to be very acceptable and reliable treatment options for both cleft and non-cleft patients (Cune et al., 2004; Fugazzotto et al., 1993; Lekholm et al., 1999; Lindh et al., 1998; Matsui et al., 2007) (Pjetursson et al., 2004; Sullivan et al., 2001). However, implant placement should be delayed until the patient's growth period is completed since implant surgery done during childhood can lead to serious complications such as poor implant positioning, burying of the implant into the bone, malocclusion, or even loss of the implant. An implant can be compared to an ankylosed tooth in that neither an implant nor a non-ankylosed tooth moves or

continue to erupt as natural teeth do (Cronin and Oesterle, 1998; Oesterle et al., 1993; Oesterle and Cronin, 2000; Op Heij et al., 2003).

Growth patterns in both genders should be carefully assessed during treatment planning. Both the maxilla and mandible undergo significant growth and development in girls until they reach the age of ~15 years, while boys continue to develop until they reach the age of ~18 years. However, many patients may continue to grow for a few more years after this age. Most women show very little growth during the ages of 17 and 20 years yet it is not unlikely for men to continue growing between years 15 to 25 (Oesterle and Cronin, 2000). Therefore, patients should not receive dental implants until they have reached the end of their growth period.

Although the main growth period may be over after adolescence, recent studies have shown that jaw growth occurs over many decades throughout adulthood for both soft and hard tissues. While this growth is minimal and extremely variable between individuals, it could still potentially affect the long-term esthetic and functional outcome of the implant (Oesterle and Cronin, 2000). The maxilla and mandible for both genders continue to grow in an anterior and downward direction during life and throughout the 6th decade, while the magnitude of this change decreases as the patient ages (Behrents, 1985; Bishara et al., 1994; Cronin and Oesterle, 1998; Dager et al., 2008).

In order to obtain satisfactory esthetic and functional outcomes, critical surgical guidelines must be respected during the implant placement. The implant should ideally be placed in the position of the pre-existing tooth. It should be centered in both mesio-distal and bucco-lingual dimensions. The implant shoulder should be positioned about 1-3mm

apically when compared to the cement-enamel junction of the adjacent teeth. Bony plates overlying the implant should ideally be 1-2mm in thickness, and vital structures such as nerves, blood vessels and sinuses should be avoided. Additional bone grafting should be performed if these criteria can't be fulfilled at the time of implant placement because insufficient bone support can compromise the long-term surgical outcomes, and impingement of dental implants on vital structures can create further complications. Soft tissue grafting can also be performed at the time or after implant placement to improve final esthetic outcomes (Al-Sabbagh, 2006; Buser et al., 2004; McAllister and Haghighat, 2007). The lack of bone at the cleft site represents a considerable challenge for the placement of dental implants in the cleft population. Therefore, these patients must always undergo cleft repair and bone grafting procedures prior to their implant surgery.

L) Bone Augmentation

Significant ridge deficiencies occur as a result of alveolar cleft defects, and their extent is extremely variable from one patient to another (Daw and Patel, 2004). Deficient ridges can be well described with the Seibert ridge classification system, where class I defects show horizontal (buccal-lingual width) deficiency, class II defects show vertical height deficiency, and class III defects display ridges usually deficient in both width and height (Seibert, 1983). Depending on the extent of the cleft defect, patients must undergo considerable bone reconstruction procedures prior to receiving orthodontic treatment with or without an implant-retained prosthesis to replace the congenitally missing teeth (Duskova, 2007). Otherwise, the surgical guidelines for implant placement can't be

respected completely (Al-Sabbagh, 2006; Buser et al., 2004; McAllister and Haghighat, 2007). Treatment needs to be sequenced appropriately by the surgeon and in conjunction with anticipated prosthodontics therapy.

Nowadays dental surgeons can choose from a variety of bone graft materials to reconstruct contour and/or volume of a deficient ridge. Bone grafts fall into four general categories: autografts, allografts, xenografts, and alloplasts. Selection of these materials for use in regenerative procedures is based on the assumption that they contribute to bone formation. The ideal bone graft should be osteogenic (contain bone-forming cells), osteoinductive (contain bone-inducing substances), osteoconductive (serve as a scaffold for bone formation) and yield a stable outcome by repairing the osseous defect (McAllister and Haghighat, 2007).

Autogenous bone grafts originate from the patient himself, and can be harvested from intra-oral or extra-oral donor sites. Autogenous bone remains the gold standard by which all other materials are judged. It is the most predictable osteogenic organic graft for osseous tissue regeneration due to its osseoinductive and osseoconductive properties (Palmer and Palmer, 1999).

Allografts are obtained from a donor of the same species but with a different genetic make-up from the graft recipient. They can be obtained in the form of freeze dried bone (FDBA) or demineralized freeze dried bone (DFDBA). The graft is harvested from cadavers, processed and sterilized. It is available in a wide range of forms including particles or blocks. They are predominantly used for their osteoconductive and resorbable

properties but often remain integrated at the graft site long after the surgery (Palmer and Palmer, 1999).

Xenografts are graft materials derived from a different species than the receiver. They are widely used as a scaffold for bone to grow into and don't resorb as the allografts do. Instead, they seem to remain integrated into the graft site. When processed, the organic component is completely removed from xenografts to leave the mineralized bone architecture. This process makes xenografts non-immunogenic and presumably safe (Palmer and Palmer, 1999).

Alloplasts are synthetic graft materials such as calcium sulfate and calcium phosphate. They can be used alone or most frequently in combination with other types of grafts for their osseoconductive capacities (McAllister and Haghighat, 2007).

Although different bone graft sources have been used to repair cleft defects cancellous autogenous bone remains the preferred material when orthodontic movement of the teeth through the graft is anticipated because of its osteogenic, osteoinductive and osteoconductive characteristics (ACPA, 2009; Daw and Patel, 2004). The graft is usually harvested from the anterior iliac crest which represents the source of choice for most patients (Murthy and Lehman, 2005). Nonetheless, bone grafts can also be harvested from the cranium, the tibia, the symphysis, ribs, and other donor sites (Losee and Kirschner, 2009). Unfortunately, significant morbidity is associated with harvesting donor tissue from these sites (Laurie et al., 1984). Hopefully, novel grafting procedures using allogenic bone grafts or use of stem cells will be developed in the future to decrease the

morbidity associated with these procedures (Gimbel et al., 2007; McAllister and Haghighat, 2007).

Grafting of alveolar cleft defects provides multiple advantages. First, grafting the alveolar cleft with a bone graft unites the alveolar segments on each side of the defect and helps to prevent arch collapse and constriction of the maxillary arch. Secondly, the bone graft provides adequate bone support for the erupting maxillary teeth, and can be used to close any remaining oronasal fistula. Third, a dental prosthesis can be better adjusted with adequate bone support in the cleft area. Finally, both the bone graft and the prosthesis can provide adequate lip and nose support, thereby enhancing the patient's esthetics and self-esteem (Hupp et al., 2008).

Grafting procedures should be coordinated with orthodontic treatment. Teeth adjacent to the cleft defect may be re-aligned to close the space without the use of a prosthetic appliance. Otherwise, teeth adjacent to the cleft defect may be re-aligned properly to allow for the replacement of the missing teeth with a prosthetic device such as an implant or a bridge (Losee and Kirschner, 2009). Ideally, grafting takes place prior to the eruption of the permanent maxillary teeth in the cleft region. Grafting during the mixed stage of dentition is referred to as secondary grafting and insures sufficient periodontal support to the teeth in the cleft area once they erupt (Daw and Patel, 2004; Semb, 2012). In contrast, tertiary grafting of the alveolar cleft is performed after completion of the second stage of dentition. When compared, secondary osteoplasty seems to provide better outcomes than its alternative, as the lateral or canine teeth can grow into the bone transplant, and

eventually exert functional stress on the transplanted bone. Less bone resorption has been noticed with this technique than with tertiary osteoplasty (Dempf et al., 2002).

M) Hypotheses

1) Compared to patients without alveolar cleft defects, patients presenting with alveolar clefts will exhibit a lateral deviation pattern of the nasopalatine nerve and canal towards the side of the anatomical anomaly.

2) Alveolar cleft patients will have similar dimensions of the NPC as those of control patients.

3) Compared to patients without cleft defects, alveolar cleft patients will exhibit a significant deficiency in the width of the buccal alveolar bone overlying the NPC (if the NPC is deviated towards the side of the cleft defect.)

N) Statement of purpose

The purpose of this study is to:

i) Identify variations of the NPC anatomy in patients with alveolar cleft defects.

ii) Compare the dimensions and position of the NPC in a cleft population compared to age- and gender-matched controls without cleft defects.

iii) Relate these findings to the position of the cleft defect.

II. Materials and Methods

A) Study Population

The study protocol was reviewed and approved by the University of Minnesota Institutional Review Board, Minneapolis, Minnesota. All subjects remained anonymous, and none were exposed to additional radiation since all CBCT images were previously collected for therapeutic evaluation purposes and archived at the University of Minnesota Dental Clinics.

A total of 89 patients with craniofacial defects who had been referred from the University of Minnesota Cleft and Craniofacial Clinic and to the University of Minnesota Oral and Maxillofacial Radiology Clinic between 2009 & 2012 were initially screened for selection in this study. Following review of CBCT images from all patients, images for 29 unilateral alveolar cleft subjects were retained for analysis. Patients with various orofacial syndromes and / or bilateral cleft defects were excluded. A control group of 29 pre-orthodontic patients from the University of Minnesota Orthodontics Clinics were utilized as controls for comparison. All subjects were matched for age and gender.

B) Data Collection

CBCT scans were taken using a Next Generation i-CAT® (Imaging Sciences, Hatfield, PA). Voxel size in the study population ranged from 0.25 mm to 0.40 mm. Total volume of the acquired data was available to the observers. The scans were on a Dell 24-inch non-glossy monitor (1920 X 1200 resolution), with a Dell Precision Workstation using iCATVison software (Imaging Sciences). Each scan was reviewed in axial, coronal

and sagittal sections, and in ‘implant’ view for assessing the cleft area. Study patient’s age, gender, exam date and defect type (right or left cleft alveolus) were recorded. CBCT images were examined for 4 key parameters to be measured. All parameters were measured (in millimeters) 3 times in each patient by the same investigator (E.V), and the mean of those 3 values for each parameter was used for final analysis:

1) Average bucco-lingual width of the NPC.

2) Average mesio-distal width of the NPC.

3) Average distance from the buccal bony alveolar plate to the most buccal aspect of the NPC (alveolar width)

4) Average deviation of the NPC from the patient’s midline.

C) Midline determination / Landmarks

Each patient’s midline was used as a reference point to measure the lateral deviation of the NPC. Each CBCT was first examined in a panoramic view to determine which side was affected by the cleft defect. Subsequently, the patient’s occlusal plane was placed parallel to the floor, and the head was positioned at a neutral angle when viewed from a facial aspect. In a cross-sectional sagittal view, the sella turcica was first identified. In a cross-sectional coronal (frontal) plane, the osseous floor of this cranial structure was measured and divided in half which provided us with our first midline landmark. Subsequently, the foramen magnum was outlined in a cross-sectional transverse plane. This structure was also divided in half, and served as a second midline landmark. The

mean of these 2 landmarks was identified as the patient's true midline from which any deviation could be measured.

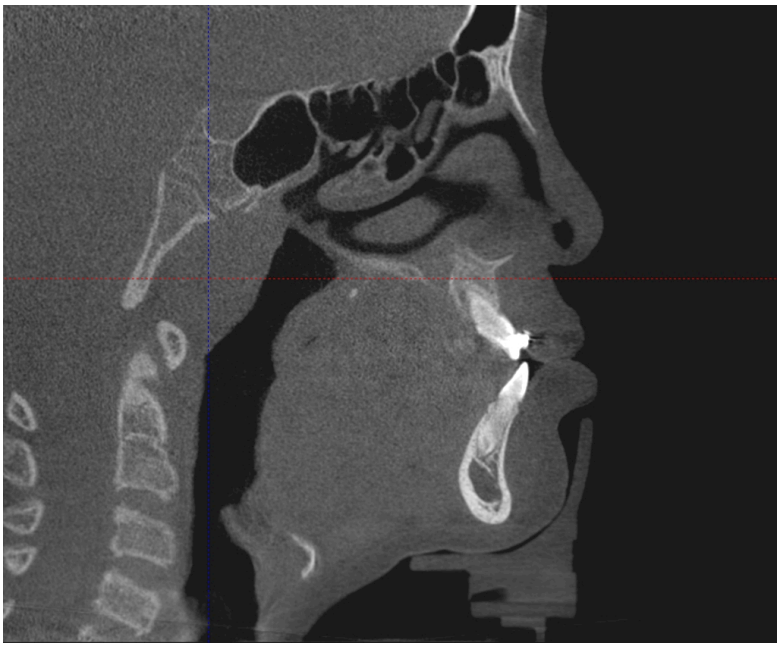


Figure 4. Identification of the sella turcica in a cross-sectional sagittal plane (cleft patient)

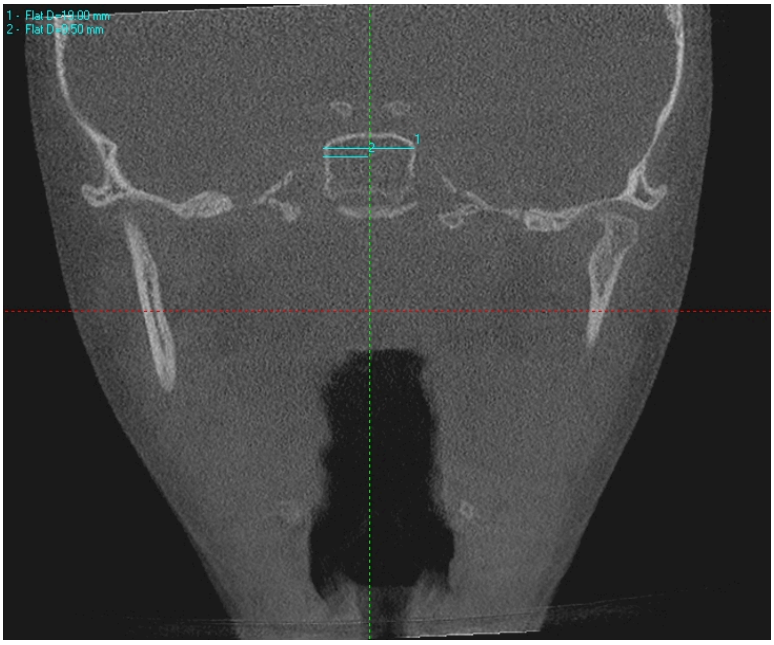


Figure 5. Cross-sectional coronal view showing identification of the midline by using the sella turcica as a landmark (cleft patient)

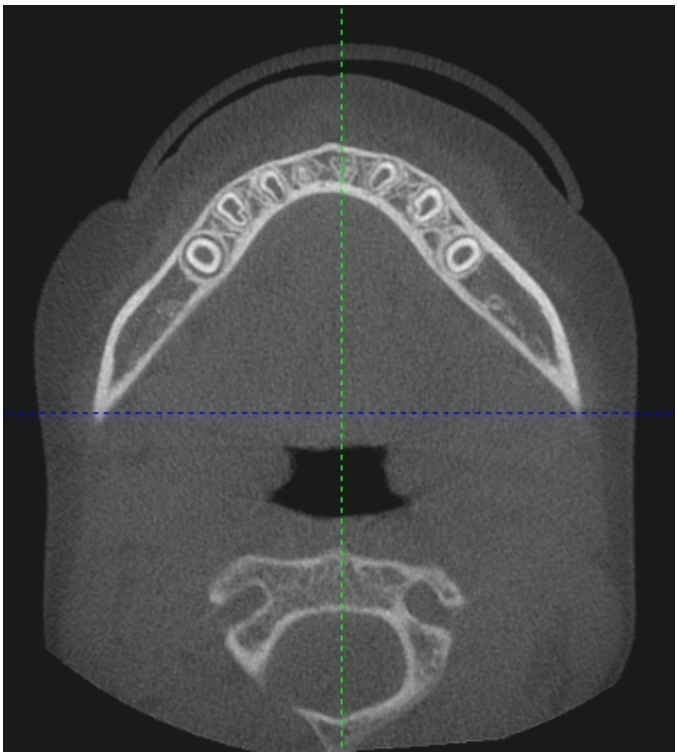


Figure 6. Cross-sectional transverse plane showing the identification of the foramen magnum (cleft patient)

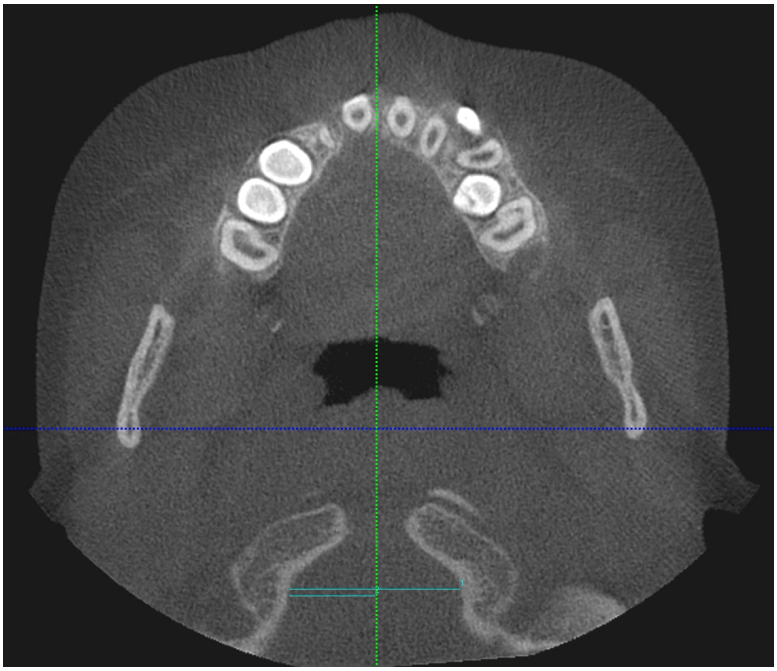


Figure 7. Cross-sectional transverse view showing identification of the midline by using the foramen magnum as a landmark (cleft patient)

D) Identification of the NPC and Measurements

The location of the NPC was identified and confirmed in coronal, sagittal and transverse planes. A cross-sectional transverse plane allowed us to measure the bucco-lingual width as well as the mesio-distal width of the NPC. Employing the same cross-sectional view, the lateral deviation of the NPC from the midline was determined by measuring the distance between the center of the NPC and the patient's midline. Finally, the distance between the buccal bony alveolar plate and the most buccal aspect of the NPC was also measured in a transverse view (alveolar width). This measurement was taken perpendicularly to the NPC which had to be visualized entirely with its cortical walls.

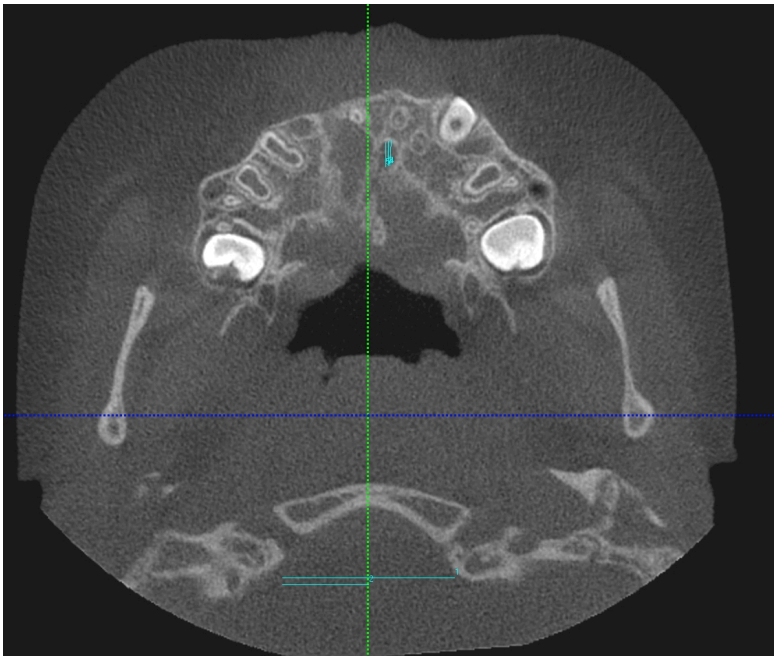


Figure 8. Cross-sectional transverse view showing bucco-lingual width measurements of the NPC (cleft patient)

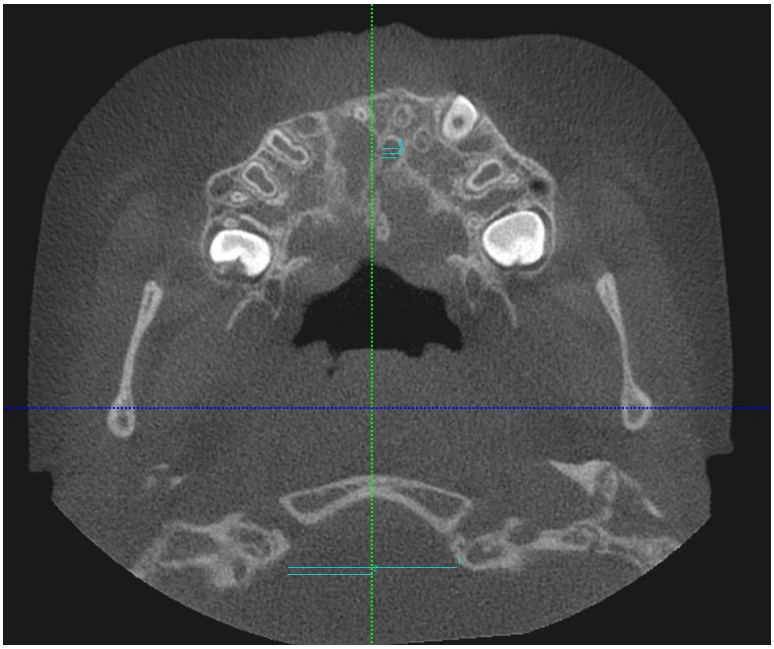


Figure 9. Cross-sectional transverse view showing medio-distal width measurements of the NPC (cleft patient)

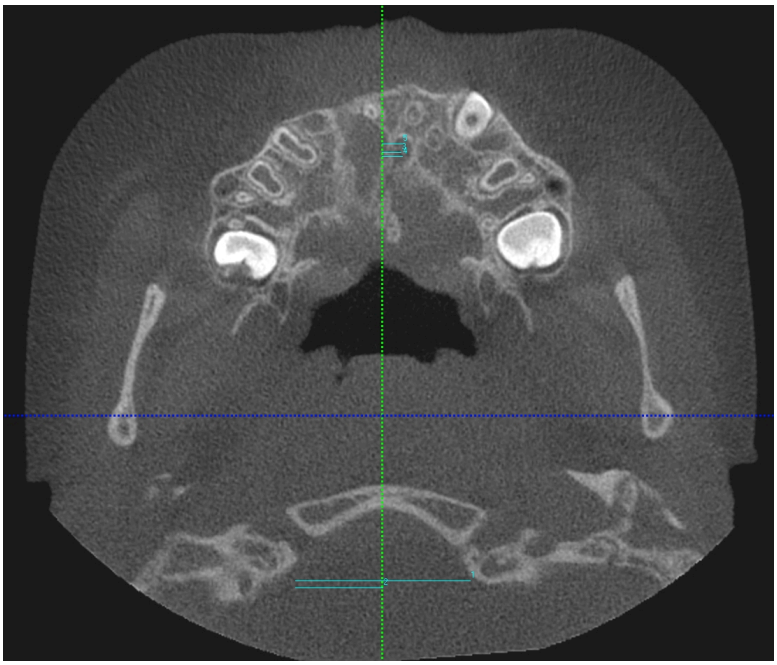


Figure 10. Cross-sectional transverse view showing lateral deviation measurements of the NPC (cleft patient)

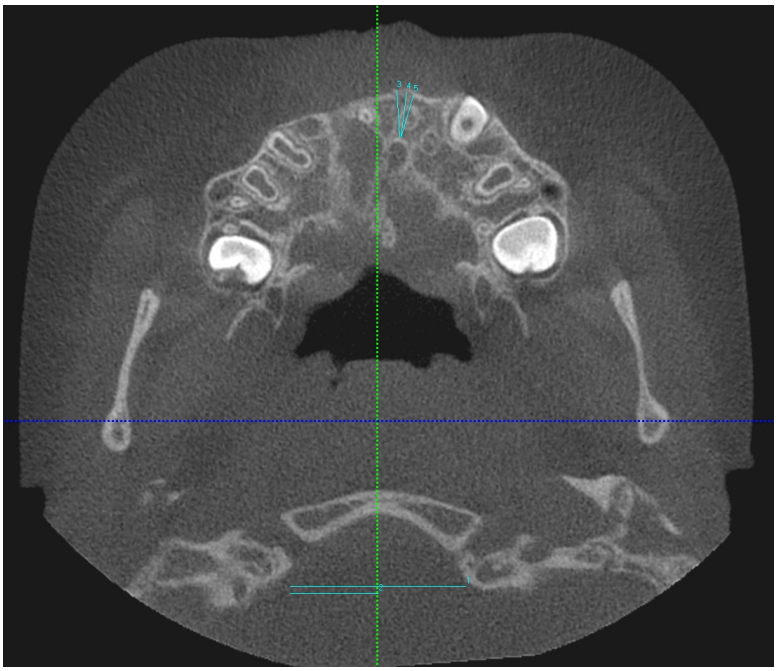


Figure 11. Cross-sectional transverse view showing width measurements of the alveolar plate, between the buccal alveolar plate itself and the most buccal aspect of the NPC (cleft patient)

E) Statistical analysis

Means and standard deviations of each measurement were calculated for both groups. T-tests were used to compare the mean measurements and age at exam between the groups. Among those participants exhibiting alveolar cleft defects, lateral deviation measures were compared between the two types (right and left). Additionally, multiple linear regression models were used to compare the measures between the groups while controlling for age at exam and gender. The differences between the means and 95% confidence intervals were also calculated. P-values less than 0.05 were considered statistically significant. No adjustments were made for multiple comparisons.

III. Observations & Results

Eighty-nine craniofacial patients were initially selected from the University of Minnesota's Cleft and Craniofacial Clinic. Out of these 89 cases, 29 were retained for analysis. Subsequently, 29 age and gender-matched controls were selected from the University of Minnesota's orthodontic clinic. Of these 29 cases, 20 exhibited a cleft defect on the left side, while 9 were positioned on the right side. At the time exam the differences in age and gender between the 2 groups were not statistically significant ($p>0.05$). Indeed, the mean age ($\pm$sd) for the cleft group was 11.59 (6.24) years and composed of 12 females and 17 males. The control group's mean age was 13.00 (5.69) years and included 13 females and 16 males. The gender differences between the 2 groups were also considered to be statistically insignificant ($p>0.05$).

Table 2. Summary of Demographics and Measurements

	Alveolar Cleft Defects N=29	No Alveolar Cleft Defects N=29	P-value†
Age at exam, mean (sd)	11.59 (6.24)	13.00 (5.69)	0.37
Female, n (%) Male, n (%)	12 (41) 17 (59)	13 (45) 16 (55)	1.00
Bucco-lingual width, mean (sd)	3.23 (1.31)	2.61 (0.76)	0.03
Mesio-distal width, mean (sd)	2.61 (1.18)	2.51 (0.81)	0.71
Buccal alveolar bone width overlying the NPC, mean (sd)	8.60 (3.32)	7.69 (1.36)	0.18
Lateral deviation, mean (sd) Left defect(n=20) Right defect (n=9)	1.11 (3.62) 2.73 (2.40) -2.51 (3.29)	0.37 (1.48)	0.31
Absolute lateral deviation, mean (sd) Left defect(n=20) Right defect (n=9)	3.18 (1.98) 3.07 (1.91) 3.40 (2.22)	1.01 (1.12) - -	<0.0001

mm: millimeters

† Two group t-test for continuous measures; Fisher's exact test for gender

The absolute lateral deviation is the absolute value of the lateral deviation measures.

+ value: deviation measured to the right of the midline

+ - value: deviation measured to the left of the midline

The mean bucco-lingual (BL) widths of the NPC were statistically different between the two groups ($p < 0.05$). The mean BL width of the NPC in the cleft group was of 3.23 (1.31) mm, while this same parameter had a value of 2.61 (0.76) mm in the control group ($p=0.3$). Although statistically significant at the 0.05 level, a Bonferroni correction for multiple comparisons would yield a non-significant result.

In contrast to the previous measurement, the mean mesio-distal (MD) width of the NPC between the 2 groups did not show any statistically significant difference ($p>0.05$), although slightly greater in the cleft than in the non-cleft group. The cleft group exhibited

a mean MD width of 2.61 (1.18) mm while the control group's mean MD width was 2.51(0.81) mm (p=0.71).

The mean width of the alveolar process overlying the canal was also measured during this cross-sectional experiment by tracing a direct line from the buccal aspect of the NPC to the buccal plate of the maxilla itself. The cleft group had a mean alveolar width width of 8.60 (3.32) mm, while the control group had a mean alveolar width of 7.69 (1.36) mm. The difference between these 2 values was not statistically significant (p=0.18).

The last parameter measured was the lateral deviation of the NPC in relationship with each patient's own midline. Among those patients with alveolar cleft defects, lateral deviation measures were compared between the two types (right and left). A negative value was associated with a deviation of the NPC towards the left while a deviation towards the right was associated with a positive value. The difference between the cleft and control groups regarding the mean lateral deviation of the NPC was not statistically significant (p>0.05). The cleft group showed an overall mean lateral deviation of the NPC of 1.11 (3.62) mm. The subgroup of patients exhibiting a left cleft defect had a mean deviation of the NPC from the midline of 2.73 (2.40) mm (+ value = deviation to the right of the midline). The subgroup of patients with a right cleft defects showed a mean deviation of the NPC from the midline of -2.51 (3.29) mm (- value = deviation to the left of the midline). In contrast, the control group exhibited a mean lateral deviation of the NPC from the midline of 0.37 (1.48) mm. The difference between the cleft and control groups was therefore not statistically significant at the 0.05 level (p=0.31).

Although there was no significant difference between the mean lateral deviation values for the cleft and non-cleft groups, the difference between the mean for the absolute lateral deviations were significantly different between the groups. The cleft groups exhibited an absolute lateral deviation value of 3.18 (1.98) while the non-cleft group had a value of 1.01(1.12) for the same parameter. This was statistically significant ($p<0.0001$).

The lateral deviation pattern of the NPC veered away from the side of the anatomical anomaly. However, the magnitude of these deviations was not significantly different between right and left deviations ($p=0.69$). Patients with a left-sided defect showed a 3.07(1.91) mm deviation of the NPC away from the defect while patients exhibiting a right-sided defect showed 3.40(2.22) mm deviation of the NPC away from the defect.

Adjusting for age and gender yielded similar results (Table 3). The BL width of the NPC was statistically different between the 2 groups ($p=0.04$) while the absolute lateral deviation of the NPC between the 2 groups was highly statistically significant ($p<0.0001$).

Table 3. Differences Between Group Means (mm), Adjusting for Age and Gender

	Difference* between group means (95% CI) N=29	**P-value†**
Buccolingual width	0.61 (0.04, 1.19)	0.04
Mesio-distal width	0.11 (-0.42, 0.65)	0.67
Buccal alveolar bone width overlying the NPC ‡	0.63 (-0.58, 1.83)	0.30
Lateral deviation	0.69 (-0.79, 2.18)	0.35
Absolute lateral deviation	2.14 (1.29, 2.99)	<0.0001

*(ACD – Control)

†Age and gender included in a multiple linear regression model

‡Age was associated with buccal alveolar width (p=0.0012).

A multiple linear regression model included age and gender and revealed that age was inversely associated with buccal alveolar bone width overlying the NPC in cleft patients (p=0.0012) (figure 12). The same trend could not be observed in the control group (figure 13).

Figure 12: Buccal alveolar width according to the patient's age; Cleft group

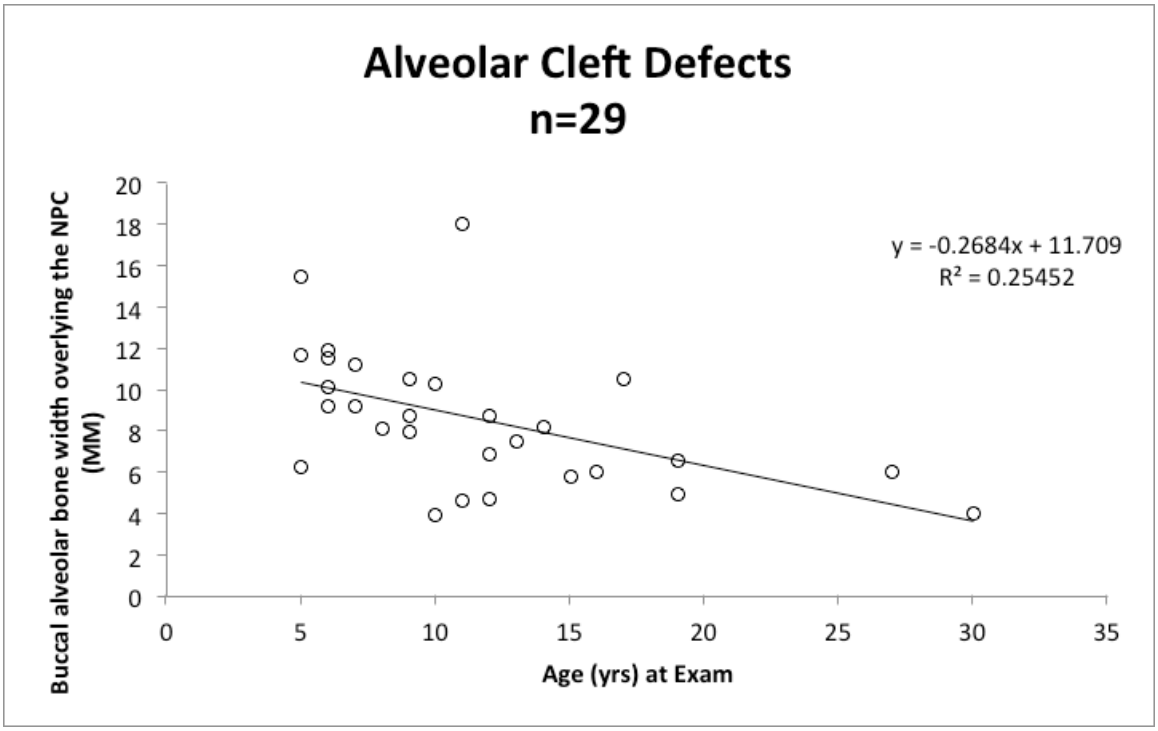
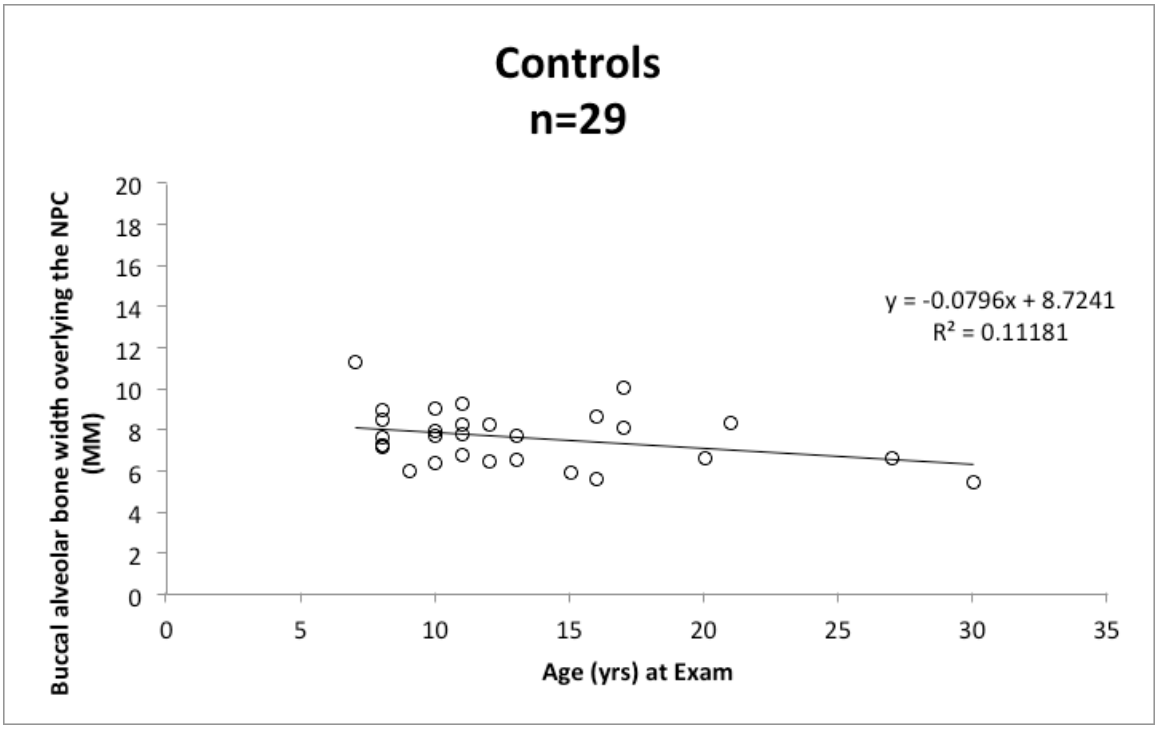


Figure 13: Buccal alveolar width according to the patient's age; Control group



Discussion

This investigation aimed to describe the lateral deviation pattern and the size of the NPC in cleft patients as compared to sex and age-matched controls. The present findings revealed a significant difference in BL dimensions of the NPC between cleft and non-cleft patients. A significant difference was also noticed for the absolute lateral deviation of the NPC between the same groups of patients. However, no significant differences were found for the MD dimensions of the NPC, as well as for the width of the buccal alveolar process overlying the NPC.

Two-thirds of cleft patients exhibited left-sided defects, while the other third exhibited right-sided defects. This suggests that a predilection exists for left cleft defects over right cleft defects (Moller and Glaze, 2009; Neville et al., 2002; Shapira et al., 1999). Also, both examined groups included more males than females, which confirms that males are at greater risks of developing such defects than female patients (Neville et al., 2002; Shapira et al., 1999).

Although BL dimensions of the NPC were reported to be greater in cleft patients than in non-cleft patients this was not the case when it came to MD measurements of the NPC. Therefore, clinicians treating cleft patients should expect to see greater NPC dimensions than in a non-affected population. To our knowledge, this had not been reported previously in other studies. This may present a challenge when planning for implant placement in the anterior segment, as a dental implant could potentially impinge on the NPC and potentially create complications such as nerve damage or suboptimal implant stability.

Previous investigators have suggested clinical guidelines for adequate implant placement around nerve structures without complications. Taking 3D images to assess the future implant site and keeping a 2 mm safety margin between the implant and the nerve are an example of these guidelines(Greenstein and Tarnow, 2006). However, placement within the NPC space has been reported in previous case reports without creating any post-operative complications such as lack of implant stability, compromised esthetics, and nerve injury. In this specific case-report, an implant was placed at site #8 in a 19 year old patient, who exhibited a large NPC at the site of future implant placement. As the osteotomy was prepared, a communication occurred with the NPC. The implant was placed, along with the obstruction of the NPC communication with a bone graft form the chin area. At 9 months re-entry, the implant showed great bone-to-implant contact, excellent stability, and the NPC had been deviated posteriorly. No nerve damage occurred, as sensation was normal at all times during the healing period (Artzi et al., 2000). Therefore, repositioning of the NPC may be an alternative to allow adequate implant positioning. Adequate visualization of the NPC area is strongly advised by reflecting a full thickness palatal flap (Artzi et al., 2000).

In the present investigation, we report a strong tendency for the NPC to be deviated to the opposite side of the alveolar cleft defect. This would explain why the width of the alveolar bone overlying the canal was unaffected when cleft and non-cleft patients were compared since the NPC was usually not found on the side of the cleft defect. This contradicts our initial hypothesis whereby we anticipated that the NPC would be deviated towards the side of the cleft defect.

Multiple challenges were encountered during this investigation. Although we started out with 89 cleft subjects, only 29 were retained for analysis. Many subjects had to be excluded from this study in reason of a bilateral cleft defect or because of a syndromic cleft, which significantly decreased our number of potential study candidates. Determining the midline in each patient turned out to be a true challenge mostly in the cleft group, because of considerable facial asymmetry. The fact that many age groups were examined in this study also made the midline determination a challenge, as we had to choose landmarks that would be reproducible regardless of the age group. Therefore, the sella turcica as well as the foramen magnum were chosen as key landmarks for midline determination.

Findings from our present investigation should enhance a clinician's ability to establish a comprehensive treatment planning for patients exhibiting alveolar cleft defects by minimizing complication with the NPC and maximizing a successful clinical outcome.

Conclusions

The following conclusions were made based on the results and discussion of our investigation:

1- Predilection exists for left defect over right defects.

2- Males more frequently exhibit cleft alveolus than females.

3- The NPC has significantly greater BL dimensions in cleft patients than in non-cleft patients.

4- The NPC seems to have a tendency for greater MD dimensions in cleft patients than in non-cleft patients. However, the difference seems to be minimal and non-statistically significant.

5- The buccal alveolar width overlying the NPC is similar in both cleft and non-cleft populations.

6- Age was significantly and inversely associated with buccal alveolar bone width overlying the NPC in cleft patients, but not in control patients.

7- The mean lateral deviation of the NPC is non-significant when compared between the cleft and non-cleft groups.

8- The absolute mean deviation of the NPC is significant between the cleft and non-cleft groups. This suggests a strong tendency for the NPC to be positioned on the opposite side of the cleft defect in patients with cleft alveolus.

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