The Cleft Palate–Craniofacial Journal 54(3) pp. 338–342 May 2017

ORIGINAL ARTICLE

Clinical Finding and Management of 12 Orofacial Clefts Cases With Nevoid Basal Cell Carcinoma Syndrome

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Objective: **To study the phenotype and overview the clinical management on Cleft Lip and/or Palate (CL/P) with Nevoid Basal Cell Carcinoma Syndrome (NBCCS) patients in Peking University School and Hospital of Stomatology.**

Design: **Case series study.**

Main Outcome Measures: **To describe the clinical phenotype of 12 CL/P with NBCCS patients who fulfilled the diagnostic criteria as well as to explore clinical management.**

Results: **Seven cases (7/12, 58.33%) were classified as bilateral complete cleft lip and palate (BCCLP). Two cases (2/12, 16.67%) were classified as unilateral complete cleft lip and palate (UCCLP). Three cases (1/12, 8.33%) were classified as unilateral complete cleft lip (UCCL), submucosa cleft uvula (SCU), and bifid uvula (BU), respectively. The ratio of male/female was 9/3. Keratocystic odontogenic tumors (KCOTs) were presented in all 12 cases. The most common site was the mandible region (12/12, 100%) followed by the maxilla region (7/12, 58.33%). The diagnostic age of 12 NBCCS with CL/P ranged from 11 to 42 years old (usually postponed to the occurring of KCOTs). The delayed diagnosis of NBCCS can be attributed to its complicated clinical manifestations. In some cases, the mutual effect between the surgical therapy of removing KCOTs and alveolar bone grafting made the team approach (TA) of CL/P more complicated.**

Conclusion: **CL/P may become important clinical phenotype in NBCCS. The type of cleft varied, with bilateral cleft lip and palate comprising above 50%. Larger sample sizes are needed to study and confirm this result. KCOTs, as one of the most common clinical feature of NBCCS, make the diagnosis delayed and the TA more difficult because of the occurring time and site. This compels us to improve the diagnostic criteria to make an early diagnosis and explore a better therapeutic protocol for CL/P.**

KEY WORDS: *nevoid basal cell carcinoma syndrome, cleft lip and palate, keratocystic odontogenic tumors*

Cleft lip and/or palate (CL/P) is one of the common congenital craniofacial defects. The incidence of CL/P for Chinese was reported to be 1.82 per 1000 live births (Wang, 1995). Based on isolated craniofacial defects or their specific malformative forms, they can be classified as nonsyndromic cleft lip and palate (NSCLP) or syndromic cleft lip and palate (SCLP), respectively; 30% to 50% of CL/P is considered as SCLP (Croen et al., 1998; Stoll, 2000).

Nevoid Basal Cell Carcinoma Syndrome (NBCCS) is one of the syndromes associated with CL/P. It also called as Gorlin-Goltz Syndrome, first reported by Jarish (1894) and delineated by Robert J. Gorlin and Robert W. Goltz (1960). NBCCS is characterized by basal cell carcinoma (BCC), keratocystic odontogenic tumors (KCOTs), and skeletal abnormalities. NBCCS associated with CL/P was first reported by Kirsch (1956). Subsequently, as a minor phenotype, CL/P was reported increasingly in NBCCS by Taicher (1978), van Dijk (1980), Soekermann (1991), and Ruprecht et al. (1987). According to the reviews, the frequency of CL/P in NBCCS is about 2% to 9.1% (Evans et al., 1993; Shanley et al., 1994; Lambrecht et al., 1997; Kimonis et al., 1997; Lo Muzio et al., 1999; Ahn et al., 2004; Endo et al., 2012). Although there are considerable literature

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This study was presented at the 12th International Congress on Cleft Lip/Palate and Related Craniofacial Anomalies, Lake Buena Vista, Florida, May 5–10, 2013.

There are no conflicts of interest.

Submitted December 2014; Revised July 2015, October 2015; Accepted December 2015.

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DOI: 10.1597/14-323

TABLE 1 Diagnostic Criteria of NBCCS Taken From Kimonis et al.

Major Criteria	*Minor Criteria*
1. More than two BCCs or one BCC in patients younger than 20 years of age	1. Macrocephaly
2. KCOTs of the jaw (proven by histologic analysis)	2. Congenital malformations (e.g., CL/P, frontal bossing, coarse faces, and moderate or severe hypertelorism)
3. Three or more palmar or plantar pits	3. Other skeletal abnormalities (e.g., sprengel deformity, marked pectus deformity, and marked syndactyly of the digits)
4. Bilamellar calcification of the falx cerebri	4. Radiological abnormalities (e.g., bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet)
5. Bifid, fused, or markedly splayed ribs	5. Ovarian fibroma or medulloblastoma
6. A first-degree relative with NBCCS	

If the patient meets at least 2 major or 1 major and 2 minor criteria, it can be diagnosed as NBCCS.

reports about NBCCS from different countries, the syndrome with CL/P has rarely been thoroughly documented or analyzed.

The current work presents a preliminary study about the phenotype and overview of the clinical management of 12 CL/P with NBCCS patients in the Peking University School of Stomatology.

Materials and Methods

Twelve cases of CL/P with NBCCS were included between January 2001 and January 2013. The medical notes of patients with NBCCS were reviewed and the clinical phenotype, diagnostic age, and therapeutic process, and radiographic and pathological findings were recorded and analyzed. The diagnostic criteria of Kimonis et al. (1997) was applied, including at least two major or one major and two minor criteria (Table 1).

All the patients had agreed to and signed the informed consent for their clinical information to be used in research. This study was granted exemption by the Institutional Review Board of Peking University School and Hospital of Stomatology.

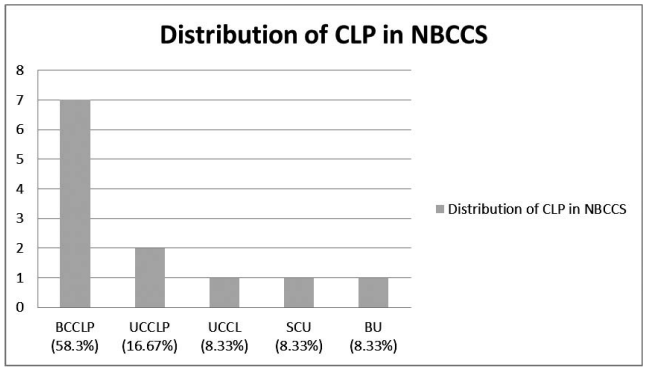

FIGURE 1 The classification and distribution of CLP in NBCCS. BCCLP = bilateral complete cleft lip and palate; UCCLP = unilateral complete cleft lip and palate; UCCL = unilateral complete cleft lip; SCU = submucosa cleft uvula; BU = bifid uvula.

Results

Phenotype of CL/P in NBCCS

Seven cases (7/12, 58.33%) were classified as bilateral complete cleft lip and palate (BCCLP), and two cases (2/12, 16.67%) were unilateral complete cleft lip and palate (UCCLP). One case (1/12, 8.33%) was unilateral complete cleft lip (UCCL), one case (1/12, 8.33%) was submucosa cleft uvula (SCU), one case (1/12, 8.33%) was bifid uvula (BU), and 10 cases (10/12,83.33%) were classified as complete cleft lip and/or palate (CCL/P) (Fig. 1). The ratio of male/female was 9:3.

Diagnostic Age of NBCCS with CL/P

Among 12 NBCCS with CL/P patients, the age of KCOTs onset ranged from 8 to 29 years old. The age of NBCCS diagnosis ranged from 11 to 42 years old. The median age of NBCCS diagnosis was 26 years old (Table 2).

Surgical Treatment Management of NBCCS With CL/P

The detailed information of 12 NBCCS with CLP patients' surgical treatment is shown in Table 3. Their

TABLE 2 Diagnostic Age Information of 12 NBCCS With CL/P Patients

Case No.	*Cleft Form*	*Age of KCOTs Onset (y)*	*Diagnostic Age of NBCCS (y)*
1	BU	8	26
2	BCCLP	11	11
3	BCCLP	12	12
4	BCCLP	13	13
5	BCCLP	14	14
6	BCCLP	18	18
7	BCCLP	20	42
8	UCCLP	21	21
9	UCCLP	25	25
10	BCCLP	27	27
11	UCCL	28	28
12	SCU	29	29

TABLE 3 Surgical Treatment of 12 NBCCS With CL/P Patients

	Surgical Age (m/y†)*					
Case No.	*Cheiloplasty*	*Palatoplasty*	*Alveolar Bone Graft*	*Pharyngoplasty*	*Secondary Deformity Repair*	*Enucleation of KCOTs*
1	(–)‡	(–)	(–)	(–)	(–)	8 y, 14 y, 15 y, 23 y, 24 y
2	3 m	3 y	7 y	8 y	(–)	11 y
3	5 m	9 m	10 y	6 y	14 y	12 y, 13 y, 15 y
4	4 m	1 y	9 y	(–)	11 y	13 y
5	3 m	1 y	(–)	4 y	15 y	14 y
6	1 y	4 y	(–)	(–)	9 y, 18 y	UN§
7	1 y	7 y	(–)	9 y	(–)	11 y, 20 y, 21 y, 32 y, 37 y, 41 y, 45 y
8	1 y	6 y	14 y	(–)	26 y	14 y, 21 y, 26 y
9	9 m	19 y	(–)	(–)	19 y	25 y
10	UN	UN	UN	UN	UN	27 y
11	5 y	5 y	(–)	(–)	(–)	28 y, 31 y
12	(–)	(–)	(–)	(–)	(–)	29 y

* m = month; † y = years; ‡ (–) = no operation; § UN = unknown.

number of surgeries ranged from 1 to 10 times. KCOTs presented in all 12 cases, with occurrence of KCOTs in 12 cases ranging from 1 to 7 times. The most common site of KCOTs was the mandible region (12/12, 100%) followed by the maxilla region (7/12, 58.33%). Most patients had undergone both TA of CL/P and enucleation of KCOTs.

In one case, KCOTs were occurring in the same site of an alveolar cleft that still needed bone grafting therapy (Fig. 2A). After considering the high recurrence rate of KCOTs, we used bi-arrangement teeth arch as a transitional therapy instead of bone grafting therapy.

Discussion

NBCCS is a hereditary condition transmitted as an autosomal dominant trait with high penetrance. It is an infrequent multisystemic disease (Evans et al., 1993; Kimonis et al., 1997; Lo Muzio et al., 1999). Clinical manifestations of NBCCS are complicated because of two characteristics: The first is its variability of expressivity. It is reported that more than 100 features have been described in NBCCS (Cohen et al., 1999; Endo et al., 2012). This variability is characterized by tumorigenesis and developmental abnormalities. Tumors in NBCCS include BCC, KCOTs, medulloblastomas, meningiomas, ovarian fibromas, cardiac fibromas, and so on. In addition, developmental abnormalities—such as congenital skeletal anomalies, macrocephaly with frontal bossing, ocular anomalies, and CL/P—are also NBCCS complications. However, these manifestations have different frequencies (Evans et al., 1993; Gorlin, 2004). KCOTs were estimated present in 75% of patients with NBCCS. The frequencies of

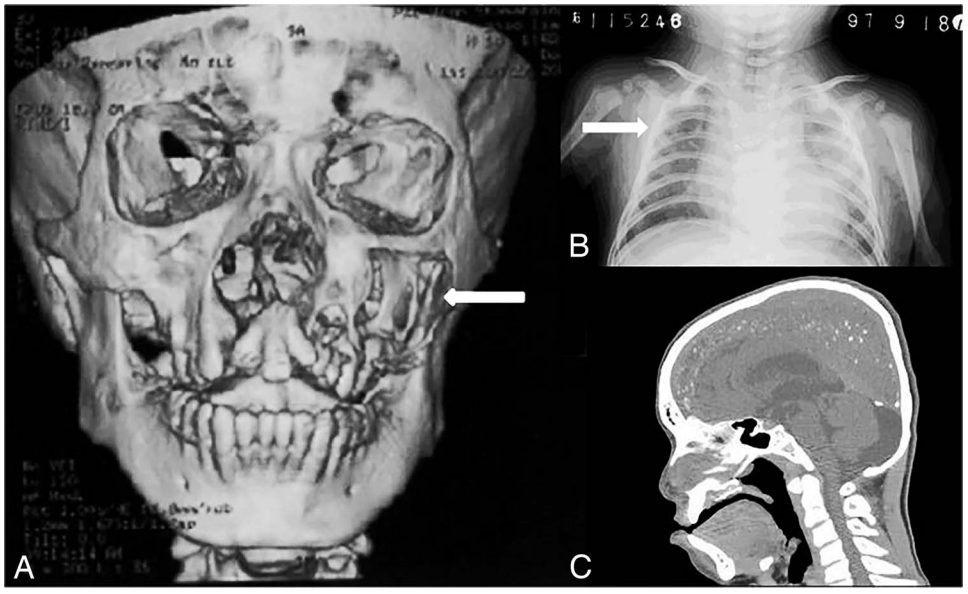

FIGURE 2 Radiographic examination of NBCCS with CL/P patient. A (left): CT shows us the patient suffered from KCOTs, which presented at the same position of alveolar cleft. B (upper right): Chest X-ray shows us bifid rib on the right side of the case. C (lower right): Cephalometrical film shows us calcification of falces of the case.

TABLE 4 Literature of Frequency of CL/P in NBCCS

Country	*Author and Publication (y*)*	*Frequency of CLP*	*Time Span of Study (y)*	*Research Area*
United Kingdom	Evan (1993)	5.7% (4/70)	1982–1992	Dermatology, oral, plastic surgery departments in the North West Regional Health Authority area
Australia	Shanley (1994)	3.7% (4/107)	Unknown	Dermatology, oral, plastic surgery, ophthalmology, radiology department in Royal Australian College
America	Kimonis (1997)	2.8% (3/103)	1985–1997	National Institutes of Health
Germany	Lambrecht (1997)	8.5% (61/719)	1993–1997	Oral department in Christian Albrechts University Hospital and reviews of literature before 1997
Italy	Lo Muzio (1999)	2.7% (1/37)	1978–1997	Division of Oral Pathology and Medicine at the University Federico II of Naples, the University of Bari and the Division of Oral Surgery at the University of Verona
Korea	Ahn SG (2004)	9.1% (3/33)	1981–2002	Reviews of Korean dental and medical literature
Japan	Endo M (2012)	9.0% (12/133)	Unknown	Departments of Pediatrics, Genetics, Neurosurgery, Dermatology, and Oral Surgery of University Hospitals, Regional Children's Hospitals, and large Municipal Hospitals with 500 or more beds in Japan

* y = year.

BCC, Palmar and/or plantar pits (PPP), and calcification of falces were 97%, 90%, and 79%, respectively (Manfredi et al., 2004). The second characteristic of NBCCS is its different ages of onset for the different traits. Medulloblastoma presents during the first two years of life in NBCCS compare to seven to eight years old in the general population. PPP may present in children, and the amount of PPP may increase as age increases. The calcification of the falx cerebri can also present very early in life; it is often apparent from late childhood. The median age of KCOTs onset is about 15 years old. BCC—the most difficult to treat aspects of the syndrome—also develops much earlier in life (Shanley et al., 1994; Gorlin, 2004; Manfredi et al., 2004; Amezaga et al., 2008); thus, early diagnosis of NBCCS is difficult due to its feature of complicated clinical manifestations.

The frequency of CL/P, one of the minor phenotypes of NBCCS, is estimated about 2% to 9.1% (Evans et al., 1993; Shanley et al., 1994; Lambrecht et al., 1997; Kimonis et al., 1997; Lo Muzio et al., 1999; Ahn et al., 2004; Endo et al., 2012) (Table 4). Few studies have analyzed and recorded the cleft form of CL/P in NBCCS. According to our study, seven of our NBCCS with CL/P cases were BCCLP (7/12, 58.33%), and 10 of the cases were CCL/P (10/12, 83.33%). The cleft type of NBCCS with CL/P seems more severe. However, Lambrecht and Kreusch (1997) reviewed 719 NBCCS cases cited in literature published before 1997. Consequently, 61 cases were associated with CL/P, with 21 being UCLP and 6 being BCLP. Others were not documented. Based on the data, we still did not find any specificity in the type of orofacial cleft in NBCCS. The reason the cleft type of NBCCS with CL/P is more severe is still unknown. To explore the characteristic of NBCCS with CL/P, larger proportions of cases are needed.

In our study, the age of NBCCS diagnosed ranged from 11 to 42 years old. The median age of NBCCS diagnosed was 26 years old. None were diagnosed as NBCCS in the early stage of infancy when they presented with CL/P deformity alone. The diagnostic time of all 12 cases were postponed due to the occurrence of KCOTs. The reason for delayed diagnosis was that they did not fulfill the diagnostic criteria when they presented just minor phenotype alone. For example, one of our cases presented with only orofacial cleft and bifid rib (Fig. 2B) during infancy. Gradually, with age, he started to develop basal cell nevi, PPP, calcification of falces (Fig. 2C) and KCOTs (Fig. 2A). How can we diagnose the newborn as NBCCS who presents only with orofacial cleft in babyhood without family history or genetic examination? Here, we have to point out that any bifid ribs or other skeleton anomalies found in preoperative chest X-ray examination as a clefts baby come for cheiloplasty, NBCCS should be highly suspected. Early diagnosis of NBCCS, especially with CL/P patients, is significant because it is a tumorigenic syndrome. CL/P may conceal other clinical signs of NBCCS that may not be detected in early life. Early diagnosis may have great impact on affected individuals. It can be beneficial for the patient to receive prompt access to genetic counseling, receive early treatment, reduce the risk of recurrence rate in the family or future, and obtain a good prognosis. Hence, future study should also be focused on improving the diagnostic criteria available for early diagnosis.

Moreover, KCOT is one of the major phenotypes of NBCCS with high frequency. The youngest case of NBCCS with KCOTs reported in the literature was five years old (Dowling et al., 2000). KCOTs were presented in all 12 cases in our study. The occurrence of KCOTs in 12 cases ranged from 1 to 7 times. The most common sites of KCOTs were the mandible region (12/12, 100%) followed by the maxilla region (7/12, 58.33%). The frequency and occurring site of KCOTs conformed to the previous study. One of our NBCCS with BCCLP cases suffered from KCOTs, which presented at the same position of alveolar cleft (Fig. 2A). Obviously, the TA of NBCCS with CL/P is completely different from the traditional TA of CL/P. It was difficult for us to decide on a surgical plan as to whether we should have KCOTs enucleated and alveolar

bone grafting concurrently or perform the reconstruction in stages. After considering the long-term effect of bone grafting and the possibility of KCOTs recurrences, we have removed KCOTs only in the first surgical stage and used a bi-arrangement teeth arch as a transitional therapy instead of bone grafting therapy. Further follow-up on patients is necessary in case of any recurrences of KCOTs or occurrences of malignant tumor. In addition, whether we should list the therapy of KCOTs into NBCCS with CL/P patients' TA and the surgical timing still require long-term exploration.

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