Van der Woude Syndrome: a report of two cases

NM King* / CHL Cheong** / AME Sanares***

Van der Woude syndrome is a rare autosomal dominant condition with high penetrance and variable expression. It consists of a cleft lip and/or palate pits on the vermilion of the lower lip, and hypodontia. Two cases of congenital lip pits with cleft lip and alveolus and an isolated cleft palate are described to illustrate the variable presentation of the clinical features and the importance of early recognition of Van der Woude syndrome because of the genetic implications.
J Clin Pediatr Dent 28(3): 267-272, 2004

INTRODUCTION

First described in 1954, Van der Woude Syndrome (VWS) was recognized as a rare autosomal dominant condition in which the primary clinical manifestations were pits on the lower lip, and cleft lip and/or cleft palate.[1,2] Later, hypodontia was included as a feature of the syndrome.[3,4] Most linkage studies have identified the loci on chromosome 1q32-q41,[5,6] but a second VWS locus has been mapped to 1p34.[7] Kondo and co-workers identified that the gene encoding interferon regulatory factor-6 was located in the critical region for the VWS locus at chromosome 1q32-41 and demonstrated that a mutation in IRF6 were pathogenic for both VWS and popliteal pterygium syndromes. [8]

The autosomal dominant gene for VWS has been found to have an 80% to 92% penetrance,[2,9] indicating that 3% to 20% of VWS genotypes were missed because they were clinically asymptomatic. However, a higher penetrance of 97% to 100% was attained when hypodontia and submucous clefts were included as manifestations of the syndrome.[10,11]

A wide variety of expressions can be observed within the pedigree of the syndrome. The cardinal features are lip pits and/or clefts only, or lip pits in combination with clefts. The full range of expression of clefts may be evident; including unilateral, bilateral, complete or incomplete cleft lip and cleft palate. Although to a lesser extent submucous cleft palate and cleft uvula have also been identified.[10-12]

The classical clinical appearance of the lip pits are that they are symmetrically located, asymptomatic paramedian sinuses, or fistulae on the vermilion of the lower lip. However, unilateral, median, and bilateral asymmetric pits have also been reported.[13-15] The depth varies from mere depressions, to 25mm deep channels with circular or slightly flattened openings which can communicate with the excretory ducts of mixed acinar glands. Another clinical variant is the microform type, which presents with only paramedian conical elevations or protrusions without any openings.[15-17]

The incidence of lip pits among cleft patients is approximately 2%.[16] Other studies show an incidence of 24% to 31% with the classical combination of lip pits and cleft lip and/or palate.[2,18] In a study of eleven families, an incidence of 60% was found by Sphrintzen and his co-workers when submucous clefts were also included.[10] Lip pits were the most common manifestation of the syndrome and were the only manifestation in 30% to 52% of cases.[2,11,18] In Finland, it was estimated that the incidence of genotypes among live births was 1:33,600 while the prevalence among the general population was approximately 1:60,000.[16]

A number of hypotheses have been postulated regarding the etiology of the congenital lip pits. The remnants of the lateral sulci of the lip during the fetal

* Send all correspondence to N.M. King, BDS, MSc, PhD, FCDSHK, FHKAM, LDSRCS, Professor in Paediatric Dentistry, Paediatric Dentistry and Orthodontics, Faculty of Dentistry, The University of Hong Kong, Prince Philip Dental Hospital, 34 Hospital Road, Hong Kong SAR, China.
Voice: (+852) 2859 0253
Fax: (+852) 2859 3803
E-mail: kingnm@glink.net.hk

** Celine HL Cheong, BDS, MDS, Adv. Dip (Paed Dent), M (Paed Dent) RCS (Edin), FRACDS, Honorary Clinical Assistant Professor, Paediatric Dentistry and Orthodontics, Faculty of Dentistry, The University of Hong Kong, Prince Philip Dental Hospital, 34 Hospital Road, Hong Kong SAR, China.
Voice: (+852) 2859 0447
Fax: (+852) 2559 3803
E-mail: cheongch@hkusua.hk

*** Anna Marie E. Sanares, DDM, MDS, Adv. Dip. (Paed Dent), M (Paed Dent) RCS (Edin), Department of Paediatric Dentistry, Westmead Centre for Oral Health, Darcy Road, Westmead 2145, NSW, Australia.
Voice: (+61 2) 9845 8306
Fax: (+61 2) 9845 7450
E-mail: amesanhk@yahoo.com

period, which are usually obliterated at the same stage of development as the completion of the primary palate of the maxillary arch, have been regarded as the most probable cause,[19] while failed fusion of the inferior part of the first branchial arch, resulting in a cleft of the lower lip and the other structures that originate from the this branchial arch have also been suggested.[20,21]

Lip pits are also manifestations of with several other syndromes such as popliteal pterygium syndrome, orofacial digital syndrome, and ankyloblepharon filiform adnatum. In addition, they can be associated with other anomalies such as median cleft of the lower lip,[22] adhesion between the maxilla and mandible,[23] commissural pits,[24] anomalies of the genitourinary system,[15] ankyloglossia[25] and Pierre Robin Syndrome were also reported to be associated with lip pits of the lower lip.[26]

Hypodontia, or congenitally missing teeth, were not mentioned in the early literature reporting VWS. Then, in 1973 Schneider suggested that hypodontia was a feature and that it had been overlooked and that it should be included as a characteristic of the VWS syndrome.[3] A subsequent study showed that the prevalence of hypodontia was significantly higher in children with cleft palate and conical elevations of the lower lip (40%) than those without lower lip elevations (25%).[4]

Studies have shown that the incidence of congenitally missing teeth, excluding third molars, in subjects with VWS was 10% to 20%.[3,10] The most commonly affected teeth have been found to be the lateral incisors and the second premolars. It was speculated that the same etiologic factors were responsible for the formation of the cleft, for the defects on the lower lip and for the hypodontia which was found in children with isolated cleft palate.[4]

The high degree of penetrance and variable expression of VWS serves to emphasize the need to recognize the condition even in its most subtle form, and once recognized, awareness of the implications through genetic counseling of affected individuals and their families is important to assess the likelihood of occurrence of the syndrome in subsequent siblings and future generations.

This paper presents two cases of Van der Woude syndrome with varying penetrance, expression and heredity as a means of demonstrating the importance of early accurate diagnosis of this condition.

CASE REPORT

Case 1

A 19-day-old Caucasian male was referred because of the presence of a cleft palate. A review of his medical history revealed a normal full-term pregnancy and delivery with a birth weight of 2.78 kg.

The extraoral examination revealed two paramedian symmetrical elevations on the vermilion border of the lower lip. Examination of the oral cavity showed a cleft involving the soft palate and the posterior 4-5mm of the hard palate with the nasal septum visible intraorally. All other oral structures were considered to be normal.

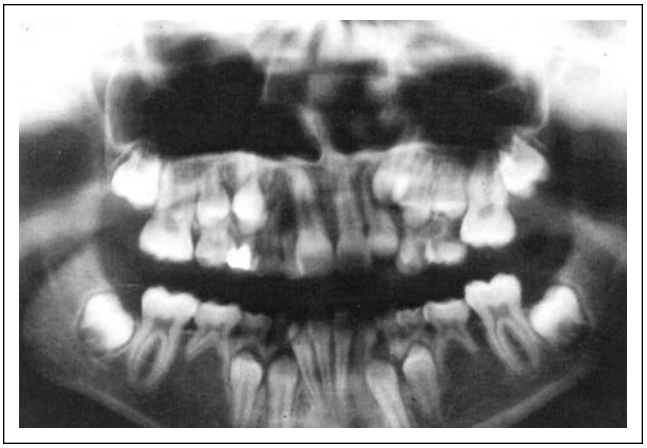

Figure 1. Panelipse of Case 1 showing congenitally missing permanent maxillary right lateral incisor and two mandibular second premolars.

The father was unaffected, while his mother was found to have a repaired unilateral complete cleft lip and palate on the left side, and evidence of scoring on the lower lip, which was consistent with surgical removal of two symmetrical paramedian indurated elevations, as reported by the subject mother. Further detailed investigation of the mother's siblings was impossible, but the maternal grandmother, who was asymptomatic reported nothing of significance in any other siblings or relatives.

Examination of the elder sister of the propositus showed a complete permanent dentition with no oral anomalies. The elder brother was found to have a full permanent dentition except for one mandibular third molar. However, his primary maxillary second molars had two accessory palatal cusps.

Clinical examination of the primary teeth of the propositus revealed two supplementary cusps on the primary maxillary second molars, similar to his elder brother. Although the propositus had a full complement of primary teeth, the panelipse radiograph revealed that the permanent maxillary right lateral incisors and two mandibular second premolars were congenitally missing (Figure 1). Transposition of the maxillary right first premolar and canine teeth was also observed. All of the other permanent teeth were developing normally except for the third molars, of which there was no evidence, by the age of twelve years.

Speech development and communication skills were considered, by the speech therapist, to be normal. Apart from recurrent bouts of otitis media, which had led to temporary loss of hearing in early infancy, the boy was generally healthy. The cleft palate was subsequently surgically repaired and a residual naso-palatine fistula gradually narrowed down to a pinhole-sized defect as the child grew older. As the child found the elevations on

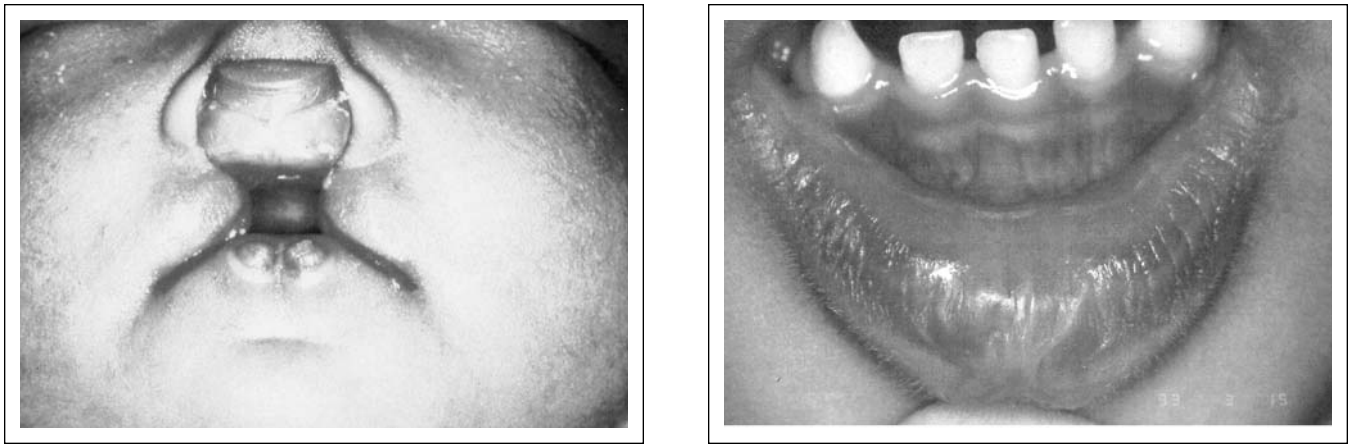

Figure 2. Case 2 with bilateral cleft lip and symmetrical paramedian dome-shaped elevations with fistulae on the vermilion border of the lower lip.

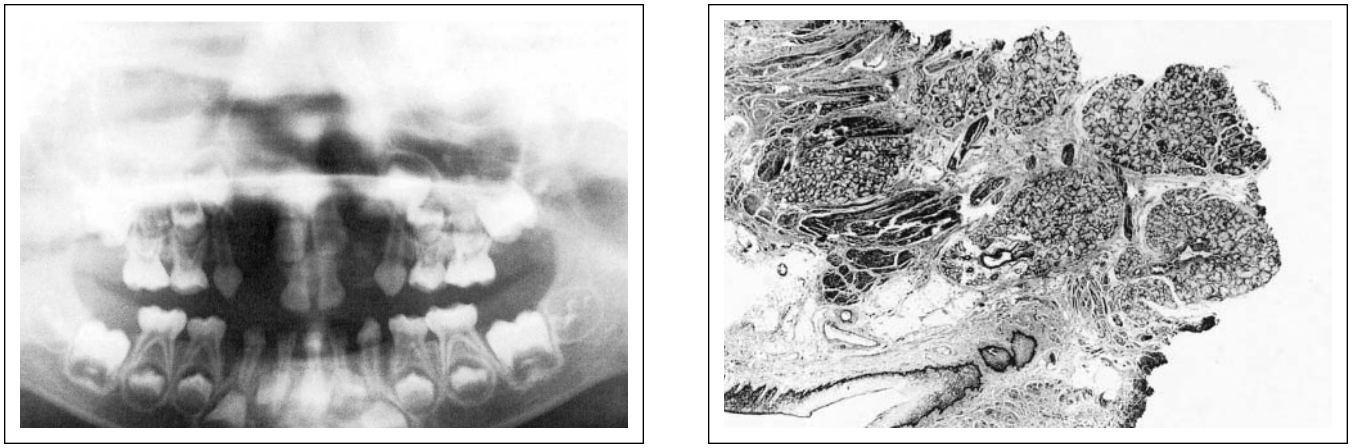

Figure 3. Panelipse of Case 2 showing congenital absence of both primary and permanent maxillary lateral incisors and one mandibular incisor in the primary and permanent dentitions.

Figure 4. Histological examination of the excised lesion from Case 2, showing lip pits lined with squamous epithelium with unremarkable infiltration of salivary glandular tissue.

the lower lip irritating and had bitten them repeatedly, surgical excision was performed under local anesthesia.

Case 2

An 11-day-old southern Chinese boy was found to have bilateral cleft lip and alveolus. The hard palate was normal, while the soft palate was short and the uvula diminutive. Two symmetrical paramedian dome-shaped elevations with fistulae were present on the vermilion border of the lower lip. There was saliva at the base of the pits even when the remainder of the lip was dry (Figure 2). Subsequent radiographic examination revealed congenital absence of both primary and permanent maxillary lateral incisors and one mandibular incisor in both dentitions (Figure 3).

Surgical repair of the cleft lip was performed at the age of 4 months together with excision of the lower lip elevations. Histological examination showed that the pits were lined with squamous epithelium with unremarkable infiltration of salivary glandular tissue (Figure 4).

Examination of the parents of the propositus and his three elder sisters revealed that they were unaffected by the syndrome. Investigations were also performed on all close relatives and construction of a pedigree revealed this to be a sporadic case of Van der Woude syndrome (Figure 5).

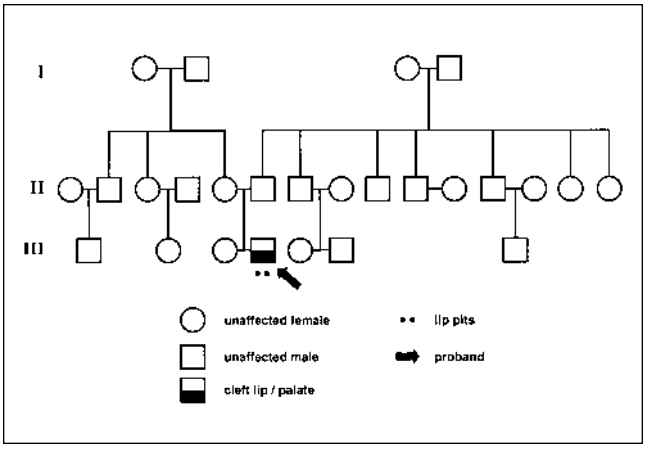

Figure 5. Pedigree of Case 2 showing spontaneous mutation of Van der Woude syndrome.

DISCUSSION

Van der Woude syndrome, which is an autosomal dominant inherited condition, with high penetrance and variable expression can thus easily occur in the offspring of affected parents.

This association was particularly relevant in Case 1 as the proband's mother, who was as a consequence of her son, diagnosed as being affected by the VWS, was planning another pregnancy. Previous studies have shown that the risk of a cleft occurring in the offspring is between 31% and 48% when a parent has lip pits and cleft lip and/or palate, and 22% when the parent has lip pits alone, while the risk of having a cleft in the offspring of a parent with a facial cleft is less than 10%.[2] Genetic counseling is therefore mandatory for members of affected families.

The syndrome is said to result from fresh mutations in one third of cleft cases.[16] The Pedigree analysis of Case 2 revealed that this was a sporadic occurrence of VWS. The mutation rate of the VWS gene has been estimated, by Burdick and co-workers, to be 1.8 x 10.[5,8]

Pits on the lower lip were first mentioned in 1845 by Demarquay and subsequently reported under many different names, such as fistula labii inferioris, labial humps, labial cysts, labial fistulae and paramedian sinuses of the lower lip. They can be bilateral, unilateral, or mixed types of congenital pits associated with cleft lip with or without cleft palate.[2,16,17,27] Microforms or conical elevations in contrast are almost exclusively associated with cleft palate.[12,28,29] The reported cases exhibited the tendency for variable forms of presentation of the lip condition.

The treatment of the lip pits is usually performed because of functional (trauma or discomfort) or esthetic disturbances.[11,28,29] Excision of the sinus is by a longitudinal transverse, or by a wedge resection. Excision of the lip pits were not performed in Case 1 until 6 years of age because repeated biting of the lip resulted in the growth of redundant mucosa, so causing further irritation. For Case 2 removal of the lip pits was performed at age 4 months at the time of the repair of the cleft lip. The histmorphological features of the fistulae of the lower lip were consistent with VWS in which there was stratified nonkeratinized squamous epithelium, lamina propria of connective tissue and salivary glands.[30]

Hypodontia, which was not initially considered to be a manifestation of the syndrome has been found to have an increased prevalence in children with cleft palate and conical elevations of the lower lip. The teeth most frequently missing are maxillary lateral incisor and second premolars in both arches.[4] In the Caucasian proband, hypodontia involved the permanent maxillary incisor and mandibular second premolars, while in the Chinese proband, there was an absence of a mandibular incisor in addition to the maxillary lateral incisors in both the primary and permanent dentitions.

The congenital absence of one of the third molars in the elder brother of Case 1 cannot be totally dismissed as being a minimum expression of the syndrome.

Although it has been demonstrated that the size of the primary teeth in males with isolated cleft palate and complete unilateral cleft lip and palate is reduced in the bucco-lingual dimension,[31] Case 1 showed contrary characteristics, he had larger maxillary primary second molars due to the presence of accessory disto-palatal cusps.

It has been claimed that the frequency of VWS has been under-diagnosed and under-reported by both parents and clinical personnel.[11,17,32] Individuals affected only by a submucous cleft palate, a category which was not present in many previous studies, and who are otherwise asymptomatic, can easily be overlooked. Neonates should be carefully examined for microform variations of the defect on the lower lip regardless of the presence of a cleft of the lip or palate because they may represent a weak expression of VWS. A thorough examination of a child with a cleft lip and/or palate is important, because of the autosomal mode of inheritance of VWS which means that siblings of an affected parent can be predicted as being likely to manifest this syndrome and this may affect family planning.

The early diagnosis of any syndrome is important but more especially when it has an autosomal dominant mode of inheritance with a high degree of penetrance. The mother of Case 1 should have been diagnosed post-partum and subsequently counseled about the likelihood of her children being affected, so that she and the father would have been prepared for the occurrence of the syndrome in their children.

SUMMARY

Two cases of Van der Woude syndrome were presented with varying degrees of penetrance, expression and heredity. Case 1 which exhibited paramedian symmetrical elevations on the vermilion border of the lower lip and a cleft involving the soft palate and the hard palate was inherited from the mother who had a repaired left unilateral cleft lip and palate, and lip pits while Case 2 which had a bilateral cleft lip and alveolus and symmetrical paramedian dome-shaped elevations with fistulae on the vermilion border of the lower lip was a spontaneous gene mutation.

REFERENCES

1. van der Woude A. Fistula labii inferioris congenital and its association with cleft palate. Am J Hum Genet 6: 244-256, 1954
2. Cervenka JR, Gorlin J, Anderson VE. The syndrome of pits of the lower lip and cleft lip and/or palate. Genetic considerations. Am J Hum Genet 19: 416-432, 1967.
3. Schneider EL. Lip pits and congenital absence of second premolars. Varied expression of the lip pit syndrome. J Med Genet 10: 346-439, 1973.
4. Ranta R, Stegards T, Rintala AE. Correlations of hypodontia in children with isolated cleft palate. Cleft Palate J 20: 163-165, 1983.
5. Bocian M, Walker AP. Lip pits and deletion 1q32——41. Am J Med Genet 26: 437-443, 1987.

6. Sander A, Schmelzle R, Murray J. Evidence for a microdeletion in 1q32-41 involving the gene responsible for Van der Woude syndrome. Hum Mol Genet 3: 575-578, 1994.
7. Koillinen H, Wong FK, Rautio J, Ollikainen V, Karsten A, Larson O, The BT, Huggare J, Lahermo P, Larsson C, Kere J. Mapping of the second locus for the van der Woude syndrome to chromosome 1p34. Europ J Hum Gene 9: 747-752, 2001.
8. Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, Howard E, Ferreira de Lima RLL, Daack-Hirsch S, Sander A, McDonald-McGinn DM, Zackai EH, and 14 others. Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. Nature Genet 32: 285-289, 2002.
9. Burdick AB, Bixler D, Puckett CL. Genetic analysis in families with van der Woude syndrome. J Craniofac Genet Dev Biol 5: 181-208, 1985.
10. Janku P, Robinow M, Kelly T, Bralley R, Baynes A, Edgerton MT. The van der Woude syndrome in a large kindred: variability, penetrance, genetic risks. Am J Med Genet 5: 117-123, 1980.
11. Shprintzen RJ, Goldberg RB, Sidoti EJ. The penetrance and variable expression of the Van der Woude syndrome: implications for genetic counseling. Cleft Palate J 17: 52-57, 1980.
12. Rintala AE, Lahti AY, Gylling US. Congenital sinuses of the lower lip in connection with cleft lip and palate. Cleft Palate J 7: 336-346, 1970.
13. Watanabe YM, Igaku-Hakushi MD, Tomida K. Congenital fistulas of the lower lip. Oral Surg 4: 709-722, 1951.
14. Sato K. Three case of congenital fistulas of the lower lip. Jap J Orthod 13: 581-584, 1938.
15. Wang MK, Macomber WB. Congenital lip sinuses. Plast Reconstr Surg 18: 319-328, 1956.
16. Rintala AE, Ranta R. Lower lip sinuses: I. Epidemiology, microforms and transverse sulci. Br J Plast Surg 34: 26-30, 1981.
17. Ranta R, Rintala AE. Correlations between microforms of the Van der Woude syndrome and cleft palate. Cleft Palate J 20: 159-162, 1983.
18. Burdick AB. Genetic epidemiology and control of genetic expression in Van der Woude Syndrome. J Craniofac Genet Dev Biol Suppl 2: 99-105, 1986.
19. Warbrick JG, McIntyre JR, Girwood Fergusson A. Remarks on the etiology of congenital bilateral fistula of the lower lip. Br J Plast Surg 4: 254, 1952.
20. Monroe CW. Midline cleft of the lower lip, mandible and tongue with flexion contracture of the neck: case report and review of the literature. Plast Reconstr Surg 38: 312-319, 1966.
21. Grabb WC, Rosenstein SW, Bzoch KR. Cleft lip and palate. Surgery Dental and Speech Aspects, Boston: Little, Brown and Co; 1971.
22. Gorlin RJ et al. Syndromes of the Head and Neck. 3rd ed, New York, McGraw-Hill, 738-739, 1990.
23. Baker BR. Pits of the lip commissures in Caucasoid males. Oral Surg Oral Med Oral Pathol 21: 56-60, 1966.
24. Taylor WB, Lane DK. congenital fistulas of the lower lip: Associations with cleft lip- and palate and anomalies of the extremities. Arch Dermatol 94: 421-424, 1966.
25. Neuman Z, Shulman J. Congenital sinuses of the lower lip. Oral Surg 14: 1415-1420, 1961.
26. Denion E, Capon N, Martinot V, Pellerin P. Neonatal permanent jaw constriction because of oral synechiae and Pierre Robin seqence in a child with van der Woude syndrome. Cleft Palate Craniofac J 39: 115-119, 2002
27. Onofre MA, Brosco HB, Taga R. Relationship between lower-lip fistulae and cleft lip and/or cleft palate in Van der Woude syndrome. Cleft Palate Craniofac J 34: 261-265, 1997.
28. Schinzel A, Klausler M. The Van der Woude syndrome(dominantly inherited lip pits and clefts). J Med Genet 23: 291-294, 1986.
29. Srivastava S, Bang RL. Congenital sinuses of the lower lip: reappraisal of Van der Woude syndrome on the basis of nine patients. Ann Plast Surg 22: 316-320, 1988.
30. Onofre MA, Brosco HB, Brosco JU, Taga R. Congenital fistulae of the lower lip in Van der Woude syndrome: A histomorphological study. Cleft Palate Craniofac J 36: 79-85, 1999
31. Peterka M, Mullerova Z. Tooth size in children with cleft lip and palate. Cleft Palate J 20: 307-313, 1983.
32. Tan KL, Wong TT, Ong ES, Chiang SP. Congenital lip pits with cleft lip or palate. J Singapore Paediatr Soc 13: 75-78, 1971.