JBR Journal of Interdisciplinary Medicine and Dental Science

Htun et al., J Interdiscipl Med Dent Sci 2016, 4:1
DOI: 10.4172/2376-032X.1000188

Research Article Open Access

Interlink of Two Syndromes - Demarquay-van der Woude and Popliteal Pterygium in One Family Group

Su Yin Htun[1], Kurt-W Bütow[*2], Hanlie Engelbrecht[3] and Engela Honey[4]

[1]Department of Cranio Maxillofacial Surgery, University of Technology, Jamaica
[2]Department of Maxillofacial Surgery, University of Kwazulu-Natal, South Africa
[3]Department of Cranio Maxillofacial Surgery, University of Melbourne, Australia
[4]Department of Genetics, University of Pretoria, South Africa

Abstract

Background and Objective: Demarquay-van der Woude (DVWS) and Popliteal Pterygium (PPS) syndromes are distinct autosomal dominant conditions generally presenting with a cleft lip and/or cleft palate. Both syndromes are genetically associated with mutations of the gene coding for Interferon Regulatory Factor 6 (IRF6) and grouped together as the IRF6-Related Disorder. In addition to a cleft, DVWS characteristically includes generally two labial pits on the lower lip. The pits may be symmetrical or asymmetrical, with saliva draining from them, or may also be abnormally flabby or conical-shaped mucosal elevations without distinct pitting. In PPS, the cleft patient commonly presents with an extensive single lower lip pit with salivary drainage, as well as popliteal webs/pterygia of the lower limb/limbs. Additional defects may include intraoral synechial web, syndactyly and genito-urinary malformations.

Methods: One case (infant) with two family members presented with overlapping deformities associated with DVWS, as well as PPS. Sequencing of the IRF6- gene was performed on one of the members.

Results: The surgical records of 4182 patients of a major cleft lip and palate clinic recorded 71 (1.70%) patients diagnosed with DVWS, 12 (0.29%) with PPS and one infant (0.02%) as an interlinked DVWS-PPS. In the family of the baby presented in this paper, all three affected individuals are females and each the third child in the family, who have lip pits typically associated with DVWS that are both bilateral and symmetrical. The grandmother and grandchild, but not the mother, has underdeveloped or minor unilateral popliteal webs. All three have syndactyly of their feet with hypoplastic toenails (involving one to three phalanges) and pyramidal-shaped (or redundant) skin above the hallux nail of the main phalanges.

Conclusion: The infant and two family members are identified as interlinked DVWS-PPS.

Keywords: Cleft lip and palate; Demarquay-van der Woude; Popliteal Pterygium syndrome; IRF6-Related disorder

Introduction

Although Demarquay first described the Fistula labia inferioris congenua in 1845 [1], Van der Woude [2] reviewed these features and established a relationship between lower lip pits and cleft lip or palate. Demarquay-van der Woude Syndrome [3] (DVWS) (OMIM 119300) is an autosomal dominant condition that affects embryologic facial development and is characterized by the usual two labial pits (fistulae) or elevations in the lower lip, cleft lip with or without cleft palate. Dental agenesis is seldom. Lip pits or sinuses are usually symmetrically and bilaterally located on the vermilion portion of the lower lip on either side of the midline (Figure 1). They are less unilaterally, medially or bilaterally asymmetrical [4]. The sinuses penetrate the orbicularis oris muscle and mostly communicate with the underlying minor salivary glands, and are usually asymptomatic with intermittent or continuous drainage of watery or salivary secretions. Hypotonia of the muscles of the lower lip has also been described in DVWS, leading some authors to suggest the existence of real central lip dysplasia [5].

Most reported cases of DVWS have been linked to the chromosome 1q32-q41 (DVWS 1), however, a second locus (DVWS 2) has been mapped to the chromosome 1p34 [6-9]. Kondo et al. have demonstrated that mutations in the gene encoding of the transcription factor interferon regulatory factor 6 (IRF6) cause DVWS. The IRF6-protein, which plays a predominant role in embryological facial development, is found in the medial edges of the paired palatal shelves around the time of fusion [10].

The popliteal pterygium syndrome (PPS) (OMIM 119500) is an uncommon malformation syndrome, which includes multiple defects of the extremities, face and mouth and the genito-urinary system. This uncommon disorder is considered to be autosomal dominant, though autosomal recessive inheritance has been suggested [10]. The most consistent malformations of this syndrome, in descending order of frequency, are the popliteal pterygium (webbing of the skin extending from the ischial tuberosities to the heels), cleft palate and/or lip, mostly an extensive single lower lip pit with salivary drainage, genital anomalies and synechia or syngnathia. The pterygium disorder presents with an intra-familial variability [11-13].

Although the IRF6-related disorders span a spectrum from isolated cleft lip and palate to severe end of webbing of ischial skin [13], and even the popliteal pterygium syndrome share some cranio-facial features with

***Corresponding author:** Kurt-W Bütow, Professor and Head of the Facial Cleft Deformity Clinic, University of Pretoria, Honorary Professor, University of Kwazulu-Natal, South Africa, P. O. Box 345, Wapadrand 0050, South Africa, Tel: +0027- 12-8073065; Fax: 0027- 12- 8073064; E-mail: kurt@butow.co.za

Received: January 08, 2016; **Accepted:** January 22, 2016; **Published:** February 01, 2016

Citation: Htun SY, Bütow KW, Engelbrecht H, Honey E (2016) Interlink of Two Syndromes - Demarquay-van der Woude and Popliteal Pterygium in One Family Group. J Interdiscipl Med Dent Sci 4: 188. doi: 10.4172/2376-032X.1000188

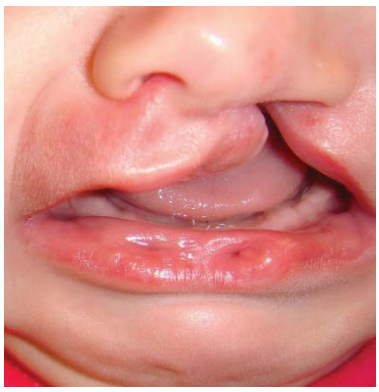

Figure 1: Bilateral and symmetrical lower lip pit with unilateral complete cleft lip and palate.

DVWS as part of this disorder, it is distinctly different. The clinical case presented in this paper has features of both DVWS and PPS. The infant and her two family members present with anomalies not previously described in the literature. The management of this condition, based on the protocol of the Facial Cleft Deformity Clinic, is presented in this paper.

Epidemiology

DVWS has a variable expressivity and a high penetrance ranging from 89% to 99%. The prevalence in general population varies from 1:35,000 to 1:100,000 live births [14]. This syndrome has been reported as the most frequent chromosomal malformation in facial deformity connected to clefts, accounting for 2% of all cleft lip and palate cases. Clefts without mandibular lip pits occur in 5%, while pits without clefts manifest in 64 % [8]. Lower lip pits, with or without cleft lip or palate, is a cardinal sign of DVWS and present in 90 % of the cases [15].

Cleft palate with or without cleft lip presents in almost all cases of PPS [12,16] and is most frequently accompanied by mandibular lip pits [17,18]. Congenital synechia is a rare phenomenon with only a few documented cases as an intraoral web [19]. The most striking feature is the popliteal web of the lower leg, occurring in 57% to 84% of cases. The pathognomonic deformity of the great toe consisting of a triangular pterygium extending from the nail fold to the middle of the free margin of the nail maybe found in 30% of the patients. Syndactyly is described in 50% of the patients in PPS [12,16].

Patients and Methods

The medical and surgical records of 4182 cleft patients of the Facial Cleft Deformity Clinic were reviewed. Data collection included sex, family history concerning lip pits and cleft lip or palate and its variation, as well as other associated malformations.

Seventy-one (1.70%) patients were diagnosed with DVWS, whereas twelve (0.29%) with PPS and one patient (0.02%) as an interlinked DVWS-PPS.

The interlinked DVWS-PPS patient's family presented with the clinical features of both DVWS and PPS and the malformations are partially expressed in three females of different generations. The features of the three affected individuals in this family, all females and each the third and only child in the family, are summarized in Table 1.

	Grandmother	Mother	Child
Gender	Female	Female	Female
Position	3rd child (1)	3rd child (1)	3rd child (1)
Cleft palate	+	+	+
Cleft lip (b=bilat; u=unilat)	+(b)	+(b)	+(u)
Lip pits (double,symmetrical)	+	+	+
Synechia or syngnathia	-	-	-
Popliteal web (minor,one leg)	+	-	+
Syndactyly (foot)	+	+	+
Nail anomalies (foot)	+	+	+
Ankyloblepharon	-	-	-
Digital reduction	-	-	-
Intercrural web	-	-	-
Genital anomalies	-	-	-

Table 1: Features of family group with interlinked DVWS-PPS

The infant girl was born with a complete unilateral left-sided cleft lip and palate, bilateral symmetrical lip pits on the vermilion portion of the lower lip on either side of the midline and a contracture at the right knee resulting from an underdeveloped or minor popliteal web (Figure 2).

The mother of the index case was examined and revealed scars of a repaired bilateral cleft lip and palate as well as excised lower labial pits. However, she presented with no popliteal web.

The physical examination of the grandmother revealed lip scars due to the repaired bilateral cleft lip, scars at the repaired hard and soft palate, and scars due the surgical removal of the lower labial pits. In addition, a triangularly shaped redundant tissue was noted above the great toe. A history of an underdeveloped or minor pterygium of one leg, extending from the ischial tuberosity to the heel, which led to a minor flexion contracture of the knee, was reported. A clubfoot was operated on several times.

All three family members presented with a partial syndactyly between the second and third toe, as well as with hypoplastic toenails, involving one or three toes. A pyramidal-shaped (or redundant) skin above the hallux nail of the big toe is present in all three generations (Figure 3).

The grandmother, the mother and the infant girl were all third sibling of each family unit in which no other family members were affected. There was no apparent consanguinity between the grandmother and husband and between the mother and her husband.

Molecular genetic analysis of the IRF6-gene performed in the mother revealed a novel single copy sequence variant c.1270T>C; p.Ser424Pro in the heterozygous state in exon 9 believed to be disease causing. In-silico analysis and pathogenicity indicators of this variant using Alamut Interactive Biosoftware indicated a highly conserved nucleotide (amino acid). The other two affected family members were not tested due to financial constraints.

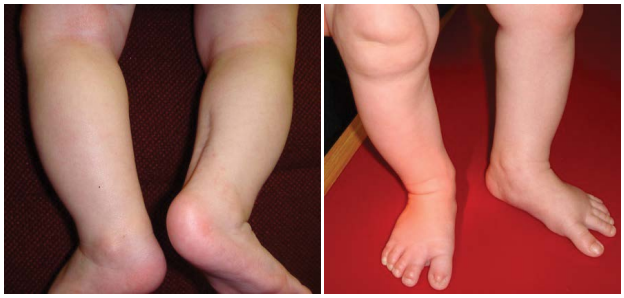

Figure 2: The popliteal web on the right leg and pyramidal-shaped (or redundant) skin above the big toe of the baby infant.

Figure 3A: Grandmother and mother with scars of repaired bilateral cleft lip and lip pits and the baby girl with unilateral complete cleft lip with bilateral symmetrical lower labial lip pits.

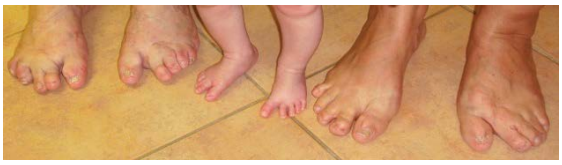

Figure 3B: All three have partial syndactyly of their feet including hypoplastic toe nails.

Treatment

The soft palate cleft of the baby girl was repaired at five months of age. The hard palate cleft anterior nasal floor and unilateral cleft lip, as well as lower labial lip pits were operated upon seven months of age. Simple bi-elliptic excision of the labial lip pits was performed. Special care was taken during the dissection not to damage the orbicularis muscle. An optimal cosmetic result was achieved. Although the DVWS and PPS are rare, the paediatric maxillofacial and paediatric orthopedic surgeon should be involved in planning the care of patients with these syndromes.

Discussion

Demarquay-van der Woude (DVWS) and Popliteal Pterygium (PPS) syndromes are uncommon syndromes resulting from the mutations of genes mapped to the chromosome 1q32-q41 or 1q34 [6-9]. The genetic origin is traced to IRF6-gene which plays a predominant role in embryological facial development and as such these two syndromes are grouped under the description of IRF6-Related Disorders [13].

The medical and surgical records of 4182 patients of a large cleft lip and palate clinic were reviewed. Data collected consisted of cleft type, gender, associated mandibular lip pits and its appearances, family history and other associated malformations.

Bocian and co-workers [8] reported an incidence of 2% DVWS of all cleft lip and palate cases. This percentage can be confirmed for DVWS and PPS together at 2.01% for this facial cleft deformity clinic with 71 (1.70%) patients as DVWS, 12 (0.29%) as PPS and one (0.02%) as an interlinked DVWS-PPS.

Facial cleft deformity data of the clinic revealed 2537 (60.6%) White Caucasians, 1389 (33.2%) Black Africans, 110 (2.6%) Cape Coloured, 134 (3.2%) South Asians and 12 (0.3%) East Asians. Furthermore, the data was evaluated for the isolated cleft lip (CL), the cleft lip and alveolus (CLA), the cleft lip, alveolus and palate (CLAP), the isolated hard palate cleft (hP), the hard palate and soft palate cleft (hPsP), the isolated soft palate cleft (sP) the COMBI cleft (i.e. isolated cleft lip and isolated soft palate or partial hard and soft palate, with a bridged fusion in between) and the oblique facial cleft. The data for the DVWS was as follow: 14.1% (10) cleft lip and alveolus, 39.4% (28) cleft lip, alveolus and palate, 33.8% (24) hard palate and soft palate cleft and 12.7% (9) isolated soft palate cleft, whereas for the PPS the following was recorded 33.3% (4) cleft lip, alveolus and palate, 25.0% (3) hard palate and soft palate cleft, 25.0% (3) isolated soft palate cleft and 16.7% (2) COMBI cleft (Table 2). No isolated cleft lip is recorded for the DVWS and PPS. All PPS cases had an involvement of the cleft palate with or without a cleft lip, whereas in DVWS cases 85.9% had a cleft palate with or without cleft lip involvement and 14.1% a cleft lip and alveolus. The interlink case presented with a cleft lip, alveolus and palate.

The overall male to female ratio is 1.10: 1, however, for DVWS 1: 1.09 and for the PPS 1: 1.40. 16.4% (685) of facial cleft deformity patients were diagnosed with a syndrome and 13.3% (555) have other genetic variations that cannot be allocated to a specific syndrome. DVWS and PPS together present 12.3% of all recorded syndromic patients.

The interlinked DVWS-PPS case in the family group of three presented as a unilateral complete cleft lip, alveolus and palate of the left side with bilateral symmetrical lower labial lip pits. In this family group, an underdeveloped (minor) popliteal web was diagnosed in one leg only in two of the three females, while a partial syndactyly was present in all of them. This infant girl presented with features that are common to both syndromes. There were overlapping deformities associated with both DVWS and PPS in all three affected individuals who are females. Lip pits typically associated with DVWS, bilateral and symmetrical, were present in all three. The grandmother and the grandchild, but not the mother has underdeveloped (minor) unilateral popliteal webs. All three generations have partial syndactyly of the 2nd and 3rd toes and hypoplastic toenails. The patient's condition is an interlink between two syndromes (Table 1).

DVWS and PPS are both associated by mutations in IRF6 which belongs to a family of nine transcription factors [6]. More than 300 mutations associated with the clinical phenotype have been reported up to date [21]. Mutations in patients with DVWS are missense mutations in the DNA-binding domain, truncating mutations including whole gene deletions and splicing mutations causing haploinsufficiency of the IRF6-gene. PPS on the other hand are strongly correlated with missense mutations involving the DNA-binding domain without affecting the protein – binding activity or mutations causing the creation of cryptic

Ciefts	Clinic numbers	DVWS	PPS	Interlink
Total	4182	71 (1.70%)	12 (0.29%)	1 (0.02%)
CL	5.8% (244)	-	-	-
CLA	13.5% (566)	14.1% (10)	-	-
CLAP	38.2% (1599)	39.4% (28)	33.33% (4)	100% (1)
hP	0.9% (39)	-	-	-
hPsP	17.2% (717)	33.8% (24)	25.0% (3)	-
sP	18.5% (772)	12.7% (9)	25.0% (3)	-
COMBI	4.1% (172)	-	16.7% (2)	-
Oblique facial	2.0% (85)	-	-	-

Table 2: Cleft type distribution for DVWS and PPS.

splicing sites, which produce a dominant negative effect [22]. This suggests that PPS-causing mutations have a different effect of IRF6 function than DVWS causing mutations. The majority of mutations in DVWS are located in exons 3, 4, 7, and 9 and in PPS mutations are present in exons 2, 4 and 9 [6]. The severity of the PPS phenotype could also be partly due to other genetic and environmental factors. Families with individuals with only DVWS and other members with the additional features of PPS have been described [23]. As such, one should consider whether the DVWS and PPS might be interlocked as a single syndrome, connected to the chromosomes 1q32 and 1q34, with variable expressions of features common to both syndromes.

Conclusion

The infant, in a family group of three females, and each the third child in the family, has been identified as an interlinked DVWS-PPS. This appears to be only the second report in the literature. This case, including the description of the mother with her genetic test and the grandmother, is of significant clinical importance since unique features are found which combine DVWS and PPS, as well as the additional not formerly described skeletal and facial anomalies. Furthermore the molecular genetic analysis of the IRF6-gene performed in the mother revealed a novel single copy sequence variant. It may well be that the DVWS and PPS may be interlocked as single syndrome with various expressions.

Acknowledgement

Dr Nico de Villiers, PathCare, Cape Town, for the testing of the genetic material.

Concent

Consent was signed, including for photographs and genetic test.

References

1. Demarquay JN (1845) Quélques considérations sur le bec-de-lièvre. Gaz Méd 13: 52.
2. Van der Woude A (1954) Fistula labii inferioris congenita and its association with cleft lip and palate. Am J Hum Genet 6: 244.-256.
3. Redelinghuys IF, de Witt TW (1994) Demarquay-van der Woude syndrome: Incidence and surgical treatment of lower lip. Hands-On 6: 37-39.
4. Bütow K W (2007) Construction of congenitally missing columella in midline clefts. J Cranio-Maxfac Surg 35: 287-292.
5. Capon-Degardin N, Martinot-Duquennoy V, Auvray G, Pellerin P (2003) Lower lip repair in Van der Woude syndrome. Eur J Pediatr Surg 13: 92-96.
6. Kondo S, Schutte BC, Richardson RJ Bjork BC, Knight AS, et al. (2002) Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. Nat Genet 32: 285-289.
7. Beiraghi S, Miller CA, Kimberling WJ, Sun CE, Wang YF, et al. (1999) Confirmation of linkage of Van der Woude syndrome to chromosome 1q32: Evidence of association with STR alleles suggests possible unique origin of the disease mutation. J Craniofac Genet Dev Biol 19: 128-134.
8. Bocian M, Walker AP (1987) Lip pits and deletion 1q32-q41. Am J Med Genet 26: 437-443.
9. Koillinen H, Wong FK, Rautio J, Ollikainen V, Karsten A, et al. (2001) Mapping of the second locus for the Van der Woude syndrome to chromosome 1p34. Eur J Hum Genet 9: 747-752.
10. Papadia F, Zimbalatti F, La Rosa CG (1984) The Bartsocas-Papas syndrome: Autosomal recessive form of popliteal pterygium syndrome in a male infant. Am J Med Genet 17: 841-847.
11. Khan SN, Hufnagle KG, Pool R (1986) Intrafamilial variability of popliteal pterygium syndrome: A family description. Cleft Palate J 23: 233-236.
12. Hall JG, Reed SD, Rosenbaum KN, Gershanik J, Chen H, et al. (1982) Limb pterygium syndrome: A review and report of eleven patients. Am J Med Genet 12: 377-409.
13. SchutteBC, Saal HM, Goudy S, Leslie E (2014) IRF6-Related Disorders. GeneReviews
14. Burdick AB (1986) Genetic epidemiology and control of genetic expression in Van der Woude syndrome. J Craniofac Genet Dev Biol 2: 99-105.
15. Schinzel A, Klaüssler M (1986) The Van der Woude syndrome (dominantly inherited lip pits and clefts). J Med Genet 23: 291-294.
16. Froster-Iskenius UG (1990) Popliteal pterygium syndrome. J Med Genet 27: 320-326.
17. Koch H, Grzonka M, Koch J (1992) Popliteal pterygium syndrome with special consideration of the cleft malformation: Case report. Cleft Palate-Craniofac J 29: 80-84.
18. Gorlin RJ, Cohen MM, Levin LS (1990) Syndromes of the head and neck. Oxford University Press 629.
19. Naidoo S, Bütow K-W (2015) Nonsyndromic palate synechia with floor of mouth. Ann Maxillofac Surg 5: 100-103.
20. Ranta R, Rintala AE (1983) Correlations between microforms of the Van der Woude syndrome and cleft palate. Cleft Palate J 20: 158-162.
21. Leslie EJJ, Standley J, Compton S, Bale S, Schutte BC, et al. (2013) Comparative analysis of IRF6 mutations in families with Van der Woude syndrome and popliteal pterygium syndrome using public whole-exome databases. Genet Med 15: 338-344.
22. Ferreira de Lima RLL, Hoper SA, Ghassibé M, Cooper ME, Rorick NK, et al. (2009) Prevalence and nonrandom distribution of exonic mutations in interferon regulatory factor 6 in 307 families with Van der Woude syndrome and 37 families with popliteal pterygium syndrome. Genet Med 11: 241-247.
23. Ghassibé M, Revencu N, Bayet B, Gillerot Y, Vanwijck R, et al. (2004) Six families with Van der Woude and/or popliteal pterygium syndrome: All with a mutation in the IRF6 gene. J Med Genet 41: e15.

Citation: Htun SY, Bütow KW, Engelbrecht H, Honey E (2016) Interlink of Two Syndromes - Demarquay-van der Woude and Popliteal Pterygium in One Family Group. J Interdiscipl Med Dent Sci 4: 188. doi: 10.4172/2376-032X.1000188