(Jurnal Plastik Rekonstruksi, 2025; Vol 12, No 2, 113-118) RECONSTRUCTIVE

Case Report

THE MANAGEMENT OF CLEFT LIP AND PALATE IN FOUR SIBLINGS WITH VAN DER WOUDE SYNDROME IN A DEVELOPING COUNTRY: A CASE REPORT

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ABSTRACT

Introduction: Van der Woude syndrome (VWS) is a rare genetic disorder characterized by cleft lip and/or palate and congenital lower lip pits. It is an autosomal dominant condition with high penetrance, affecting 0.5-2% of all cleft lip/palate cases. VWS is caused by mutations in the IRF6 gene and is associated with hypodontia and dental anomalies. Lip pits, which can cause aesthetic or functional problems, may intermittently drain saliva. VWS is diagnosed using genetic testing and bioinformatics tools, providing more accurate predictions. Treatment requires multidisciplinary care, including surgical removal of lip pits and cleft correction. This study describes a rare case of VWS family, including management strategies in low resource settings.
Case presentation: A 42-year-old man from a non-consanguineous marriage presented with four out of five children affected by VWS, characterized by cleft lip and palate. All four children underwent labioplasty. The family history revealed no congenital defects in the father's and the first wife's lineage, except for the second wife.
Conclusion: Early identification of familial patterns and clinical presentation is essential in Van der Woude Syndrome, as it significantly impacts the management and quality of life of affected individuals, particularly in resource-limited settings.
***Keywords**: Cleft Lip and Palate, Van der Woude Syndrome, Familial Genetic*

Pendahuluan: *Sindrom Van der Woude* (VWS) merupakan kelainan genetik langka yang ditandai dengan adanya celah bibir dan/atau palatum serta pit bibir kongenital. Kondisi ini bersifat autosomal dominan dengan penetransi tinggi, mencakup sekitar 0,5–2% dari seluruh kasus celah bibir/palatum. VWS disebabkan oleh mutasi pada gen *IRF6* dan sering berkaitan dengan hipodonsia maupun kelainan gigi lainnya. Pit bibir, yang dapat menimbulkan masalah estetik maupun fungsional, kadang-kadang mengeluarkan saliva secara intermiten. Diagnosis VWS dilakukan melalui pemeriksaan genetik dan penggunaan perangkat bioinformatika, yang memberikan prediksi lebih akurat. Penatalaksanaan membutuhkan perawatan multidisipliner, termasuk eksisi pit bibir serta koreksi celah bibir dan palatum. Studi ini melaporkan kasus langka keluarga dengan VWS, sekaligus membahas strategi penanganan dalam kondisi sumber daya terbatas.
Presentasi Kasus: Seorang pria berusia 42 tahun dari pernikahan non-konsanguinitas memiliki empat dari lima anak yang terdiagnosis VWS, ditandai dengan celah bibir dan palatum. Seluruh anak yang terdampak telah menjalani labioplasti. Riwayat keluarga menunjukkan tidak terdapat kelainan kongenital pada pihak ayah maupun istri pertama, kecuali pada garis keturunan istri kedua.
Kesimpulan: Identifikasi dini pola familial dan manifestasi klinis sangat penting dalam Sindrom Van der Woude, karena hal ini berpengaruh signifikan terhadap strategi penatalaksanaan serta kualitas hidup penderita, terutama pada lingkungan dengan keterbatasan sumber daya.
Kata Kunci: *Celah Bibir dan Palatum, Sindrom Van der Woude, Genetik Familial*

Conflicts of Interest Statement:
The author(s) listed in this manuscript declare the absence of any conflict of interest on the subject matter or materials discussed

Received: 11-02-2025, Revised: 27-08-2025, Accepted: 28-09-2025

INTRODUCTION

Van der Woude syndrome (VWS) is a rare genetic disorder characterized by cleft lip and/or palate, as well as congenital lower lip pits [1]. It is an autosomal dominant developmental condition with high penetrance, ranging from 61% to nearly 100% when including individuals with submucous cleft palate and lip pits [2].

The hallmark features of VWS include cleft lip and/or palate, as well as lower lip pits, which range from small cavities to large midline structures. These pits may be bilateral, asymmetric, or single and are most commonly located in the lower lip vermillion border. Hypodontia, particularly involving maxillary incisors, canines, and premolars, is frequently observed, along with other dental anomalies that may cause malocclusion. While lip pits are generally asymptomatic, they may intermittently or continuously drain saliva, and their appearance can sometimes lead to social or functional challenges, such as lip protrusion or feeding difficulties in children [3].

Congenital lip pits were first described by Demarquay in 1845 as pits ranging from minor cavities to large structures. In 1954, Anne Van der Woude established the association between lip pits and cleft lip and palate, solidifying the syndrome's identification [4].

VWS is the most common syndromic form of clefting, accounting for 0.5–2% of all cases of cleft lip and/or palate [5,6]. Its prevalence ranges between 1.65 per 100,000 and 1 per 75,000 individuals [3]. This condition affects males and females equally, and it is estimated to occur in 1 in 40,000 to 1 in 100,000 live births [7]. VWS is caused by mutations in the *IRF6 gene*, located on chromosome 1q32.2-q32.3 [8]. This gene plays a crucial role in orofacial development, and mutations disrupt processes essential for normal craniofacial morphology. IRF6 is the only member of its gene family involved in craniofacial development and is characterized by highly conserved DNA-binding and protein-binding domains [9]. Approximately 70% of VWS cases are linked to mutations in these regions [10]. Mutations in the *GRHL3 gene* have also been implicated in VWS and related conditions, further emphasizing the syndrome's genetic complexity [11].

Various bioinformatics tools, including SIFT, PolyPhen, and HOPE, are used to predict the pathogenicity of genetic mutations [12]. However, their limitations prompted the development of the Combined Annotation Dependent Depletion (CADD) score. CADD integrates over 60 algorithms to predict the clinical implications of genetic variants, providing a unified and robust measure of their deleterious effects [13].

Management of VWS requires a multidisciplinary approach to address its various anomalies. Treatment includes surgical correction of clefts and removal of lip pits if they cause aesthetic or functional concerns, as well as interventions by dermatology, psychiatry, orthodontics, pediatric dentistry, speech therapy, and other specialties [14]. The surgical removal of lip pits is indicated in cases of persistent salivary secretion, chronic inflammation, or significant aesthetic issues. Techniques such as surgical excision, diathermy, or electrocautery have been used, though complete removal of the pits is necessary to prevent recurrence. Surgical removal of lower lip pits in VWS is more effective using advanced techniques (e.g., inverted-T lip reduction, Mutaf-Goldstein) rather than simple excision, which risks recurrence or mucocele formation. Deep pits (>6 mm) require complete fistula pathway removal, especially when involving areas beyond the lip vermillion border, for better outcomes [3].

This case report aims to present a rare instance of a family in which four out of the five children inherited cleft lip and palate associated with VWS.

CASE REPORT

The proband was a 42-year-old man in a nonconsanguineous marriage, referred to as “the father,” who visited our plastic surgery department to seek consultation regarding his four children, all born with congenital orofacial defects. Both the father and his wives belong to the “Minahasa” ethnic group, an indigenous Austronesian community. The father reported no family history of congenital orofacial defects or other congenital conditions on his side of the family. However, his second wife had a personal history of cleft lip and palate.

Four children from two families with the same father were reported with clefts in the lip

P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v12i2.26

and palate (Figure 1). Two of the children are from the first marriage. The first child is a 16-year-old boy with complete unilateral labiognathopalatoschisis, accompanied by bilateral lower lip pits. Labioplasty was performed at the age of 13. The second child is a 14-year-old boy who also presents with complete unilateral labiognathopalatoschisis, accompanied by bilateral lower lip pits (Figure 2). Labioplasty was performed at the age of 11.

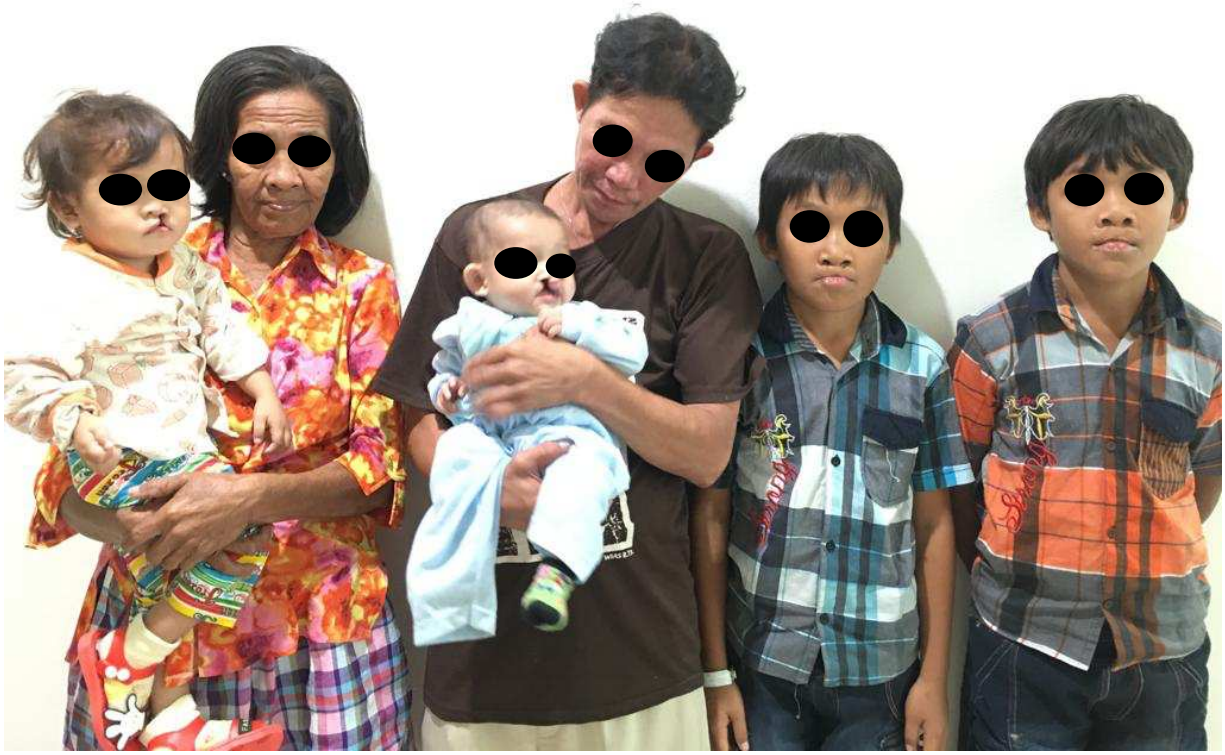

Figure 1. From the left: The grandmother from the father's side holding the second child form second marriage, the father holding the third child from the second marriage, second child from the first marriage, and the first child from the first marriage.

From their second marriage, they have three children. The first is a 12-year-old girl with no malformations around the lip area. The second is a 6-year-old girl with complete unilateral labiognathopalatoschisis (Figure 3A). She underwent labioplasty at the age of 3. The third is a 4-year-old boy with complete bilateral labiognathopalatoschisis (Figure 3B). This child had labioplasty at the age of 10 months.

On the family tree of the patient, it can be seen that out of the five children of this father, four were born with orofacial congenital disorders (Figure 4). Only the first child from the second marriage was born without a congenital disorder.

The eldest child from the first marriage underwent labioplasty at the age of 13, followed by palatoplasty at 14. Post-surgical follow-ups were conducted every three months for a year at the surgical outpatient clinic. Additionally, at 15 years old, the patient underwent scar revision surgery to address a bothersome post-operative scar.

P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: DOI: 10.14228/jprjournal.v12i2.26

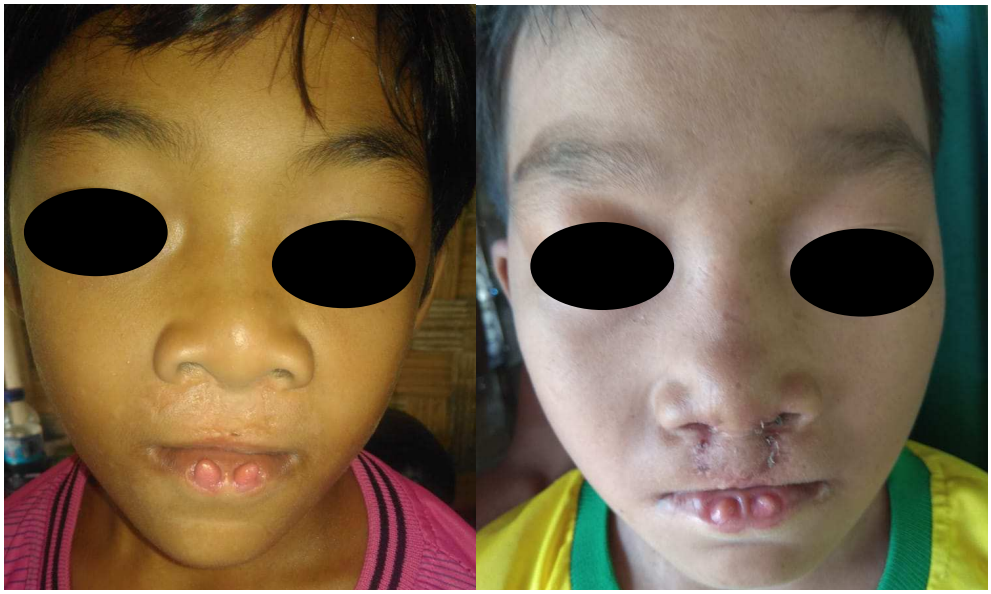

Figure 2. Children from the first marriage.

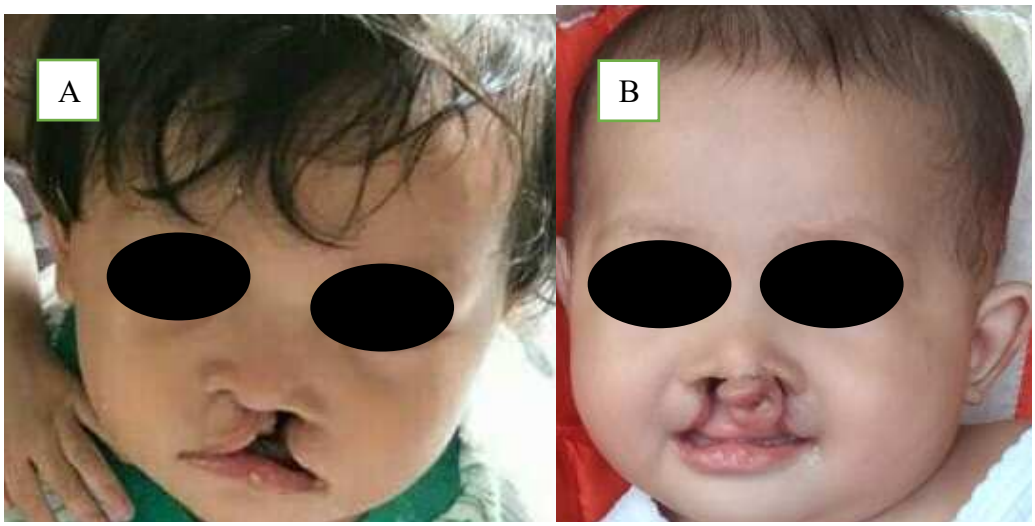

Figure 3. Children from the second marriage.

The second child from the first marriage had labioplasty performed at 11 years old, with palatoplasty following at the age of 12. Routine follow-ups were scheduled every three months for a year after the operation at the surgical outpatient clinic. At the age of 13, the patient also underwent scar correction to improve the appearance of a noticeable post-surgical scar.

The second child from the second marriage first visited the clinic at the age of 2. Labioplasty was performed at the age of 3, and palatoplasty was carried out the following year. The patient attended regular post-operative check-ups at the surgical outpatient unit.

The youngest child from the second marriage was brought to the clinic for the first time at the age of 8 months. Labioplasty was performed when the child was 10 months old, followed by palatoplasty at 1 year. Post-surgical follow-up appointments were conducted periodically at the surgical outpatient clinic.

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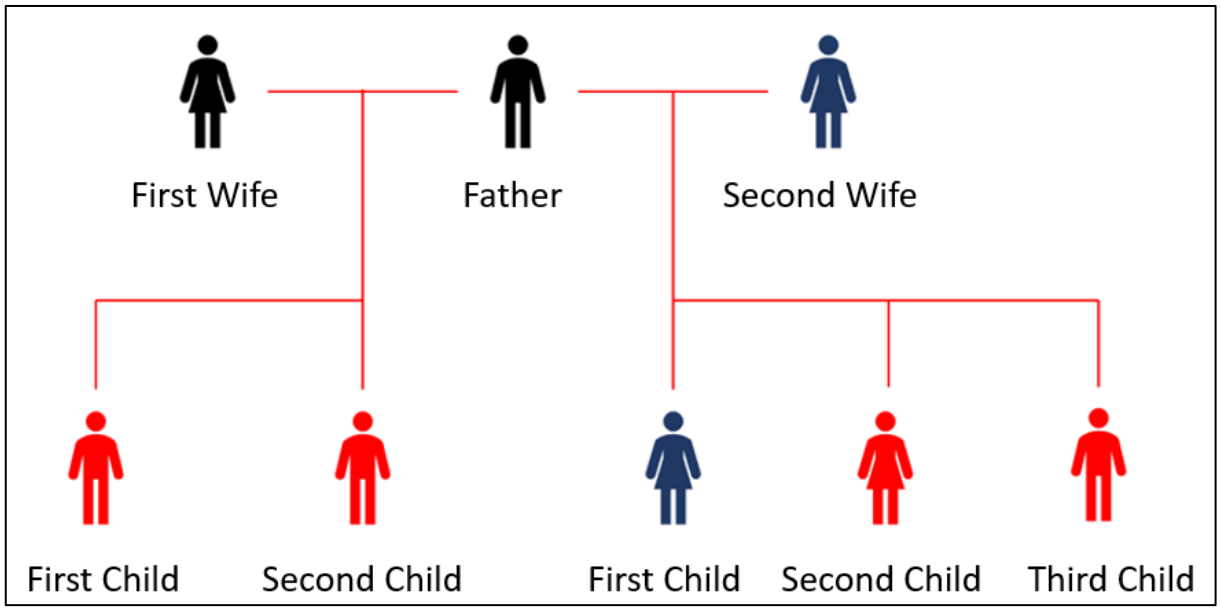

Figure 4. Family tree of the patient (red indicates the presence of orofacial congenital anomalies)

DISCUSSION

VWS is a congenital disorder characterized by a set of clinical symptoms marked by the presence of a connection between a fistula on the lower lip and a cleft in the lip with or without the palate [15].

In Indonesia, the number of cleft lip and palate patients occurs at 3000-6000 births per year or 1 baby per 1000 births. The most common cases are cleft lip and palate at 46%, isolated cleft palate at 33%, and cleft lip only at 21%. Unilateral clefts are 9 times more frequent than bilateral clefts, and left-sided clefts are twice as common as right-sided clefts. Males are more dominant in cleft. However, there is no epidemiology statistics available yet of VWS in Indonesia [16].

Diagnosing VWS involves using several computational tools, including SIFT, PolyPhen, and HOPE, to evaluate the pathogenicity of genetic mutations [12]. However, access to these tools is often limited in developing countries. Despite conducting an extensive search for laboratories in North Sulawesi, Jakarta, and neighboring regions, we were unable to locate any that provide this genetic diagnostic service. As a result, diagnosis is primarily based on clinical presentation and the family history of similar conditions.

Management of VWS involves a multidisciplinary approach, including surgical correction of clefts, lip pit removal, and interventions from various specialties. Surgical techniques like excision, diathermy, or electrocautery are used, with advanced methods preferred to prevent recurrence and complications, especially for deeper pits [3]. In our study, we treat the patients by correcting the malformation that is present in the patient with with labioplasty and palatoplasty, followed bty regular post operative checkup in the outpatient unit.

All parents with VWS should be warned that they have a 50% risk of having a child with a cleft lip with or without a cleft palate because this type of disease is inherited in an autosomal dominant manner [17].

CONCLUSION

Early recognition of family history in cases of cleft lip and palate is crucial for managing orofacial clefts, as it can significantly impact the individual's quality of life. Understanding the genetic basis and potential familial patterns of VWS helps guide appropriate treatment and care strategies.

P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: DOI: 10.14228/jprjournal.v12i2.26

ACKNOWLEDGEMENT

None

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