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Case Report / Olgu Sunumu

Oral and Dental Findings of A Child with Weill-Marchesani Syndrome Type II: A Case Report with 3-Year Follow-up

Weill-Marchesani Tip II Sendromlu Bir Çocuk Hastanın Oral ve Dental Bulguları: 3 Yıllık Takipli Olgu Sunumu

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ABSTRACT

Weill-Marchesani syndrome (WMS, OMIM# 227600) is a genetically determined, rare systemic connective tissue disorder. The syndrome is divided into four types according to mutations in related genes. Given the limited number of individuals with WMS in the literature, no genotype-phenotype correlations for ADAMTS10, ADAMTS17, FBN1, or LTBP2 have been identified. In the accessible literature, none of the limited studies were focused on the oral and dental anomalies of WMS. The present case report describes oral and dental findings of a 63 months old female patients with WMS2.

Keywords: *Weill-Marchesani Syndrome, FBN-1 Gene Mutation, Dental Anomalies*

ÖZ

Weill-Marchesani sendromu (WMS, OMIM# 227600) genetik olarak tanımlanmış, nadir görülen bir sistemik bağ dokusu hastalığıdır. Sendrom, ilgili genlerdeki mutasyonlara göre dört tipe ayrılmaktadır. Literatürde WMS'li sınırlı sayıda birey göz önüne alındığında, ADAMTS10, ADAMTS17, FBN1 veya LTBP2 için genotip-fenotip korelasyonu tanımlanmamıştır. Erişilebilir literatürde, sınırlı çalışmaların hiçbiri WMS'nin ağız ve diş anomalilerine odaklanmamıştır. Bu vaka raporu, WMS2'li 63 aylık bir kız hastanın ağız ve diş bulgularını tanımlamaktadır.

Anahtar Kelimeler: *Weill-Marchesani Sendromu, FBN-1 Gen Mutasyonu, Dental Anomaliler*

Introduction

Weill-Marchesani syndrome (WMS, OMIM# 227600) is a genetically determined, rare systemic connective tissue disorder which was also named spherophakia-brachymorphia syndrome or mesodermal dysmorphodystrophy.[1,2] The reported worldwide prevalence of WMS is 1:100,000.[3] The syndrome is characterized by eye anomalies, proportionate short stature, cardiovascular defects, joint stiffness, and brachydactyly. Other findings are thickened skin, pseudomuscular build, shortened long tubular bones, delayed bone age, depressed nasal bridge, brachycephaly, and broad proximal phalanges. Among findings, maxillary hypoplasia, highly arched and narrow palate, malaligned and malformed teeth were also reported.[1-4]

The diagnosis of WMS is based on the characteristic clinical manifestations. Pathogenic variants in *FBN1* are inherited in an autosomal dominant manner while pathogenic variants in *ADAMTS10*, *ADAMTS17*, or *LTPBP2* are inherited in an autosomal recessive manner.[3,5] The syndrome is divided into four types according to mutations in related genes. In the limited literature, no genotype-phenotype correlations for *ADAMTS10*, *ADAMTS17*, *FBN1*, or *LTBP2* have been identified in patietns with WMS. WMS type II (WMS2) is an autosomal dominant form of a syndrome caused by mutations in the *FBN1* gene.[3]

In the accessible literature, none of the limited studies were focused on the oral and dental anomalies of WMS. In this case report, oral and dental findings of a child with WMS2 were presented.

Case Report

The patient had informed consent and permission for data usage from their parents, and the study was carried out in compliance with the principles of the Declaration of Helsinki.

A 32 months-old girl was referred by the Department of Medical Genetics to the Department of Pediatric Dentistry for delayed primary tooth eruption. The patient was born at term (38 weeks) by normal delivery. Her weight was 2290 gr, length was 50 cm. The maternal age at conception was 20 years. Consanguineous marriage (second degree) was found among parents. She was able to walk at 15 months, babble at 24 months, and her first primary tooth erupted at 11 months. At the time of examination, her weight was 5.5 kg, height was 68 cm (BMI was 11.9, less than 1st percentile) and head circumference was 40 cm (<3rd centile). In the clinical examination at the age of 32 months, atypical face features, thin upper lip, and thick skin were noted. In an intraoral examination, it was found that only two primary teeth (FDI #74, #84) erupted. Since the child was uncooperative in the clinic, the radiographical examination could not be done so, it was decided to follow up with the child in a multidisciplinary manner with the genetics department at 3-month intervals to diagnose the syndrome. Panoramic radiograph taken when the patient was 50 months old in **Figure 1.A**.

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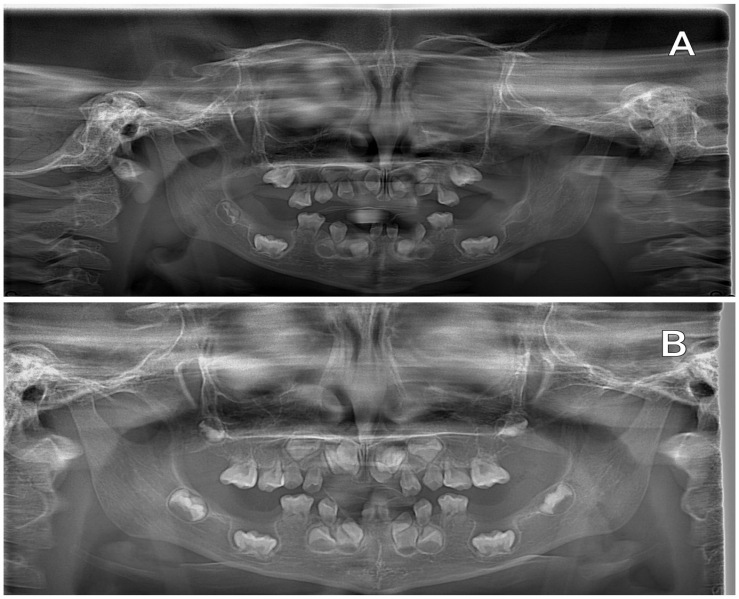

Figure 1.(**A**) The panoramic radiograph taken when the patient was 50 months old, (**B**) 63 months old.

Because a specific group of diseases could not be considered for pre-diagnosis, Whole Exome Sequencing (WES) was performed. As a result of this analysis, the heterozygous NM_000138.4 c.5510C>G p.Pro1837Arg rs752008146 novel mutation in the *FBN1* gene was detected. According to the American College of Medical Genetics (ACMG) criteria, this mutation has been reported as a"Variant of Insignificance". It has been reported that this mutation can cause disease by insilico analysis programs such as mutation tester, polyphene, and shift. This is caused to Weill-Marchesani syndrome type 2. Because of the genotype-phenotype similarity of the patients in the literature and our patients, we decided that the diagnosis was WMS. The genetic diagnosis of the patient was reported at the age of 54 months.

Genetic consultation was done for her parents and brother after her diagnosis. As a result of WES analysis, the heterozygous NM_000138.4 c.5510C>G p.Pro1837Arg rs752008146 novel mutation in the *FBN1* gene was detected in her father. However, in the intraoral examination and radiographic examination of the father of the patient, no similar dental findings were found.

In the dental examination of her parents and brother, no dental anomalies were found. After the diagnosis of the syndrome, the ophthalmologic consultation was done, and learned that no pathology was found. In her cardiology consultation, echocardiography of the patient also revealed aortic valve insufficiency and patent foramen ovale. Extraoral and intraoral findings of the patient at the age of 63 months old were given in **Table 1**.

Table 1. Extraoral and intraoral findings of the patient at the age of 63 months old

INTRAORAL EXAMINATION	
Gingiva, oral mucosa	Normal
Palate	Deep palate
Tongue	Normal
Tooth number	Both primary and permanent teeth agenesis Agenesis of four primary teeth: FDI #55, #65, #75, and #85 (At the age of 5.5) Agenesis of twelve permanent teeth: FDI #12, #14, #15, #22, #24, #25, #31, #34, #35, #41, #44 and #45 (At the age of 5.5)
Oral hygiene	Oral hygiene was fair with no clinical and radiographic evidence of dental caries
Tooth shape	Microdontia (FDI #16, #26) Talon cusp (FDI #52, #62, #11, #21)
Tooth structure	There is no evidence of hypoplasia or hypomineralization (clinical examination)
Root and root canal	Short roots, lack of some roots Open apices of primary molars
Eruption pattern	Delayed eruption of primary teeth Impacted primary incisors (FDI #51, #61, #82, #72)
Occlusion	Anterior cross-bite
EXTRAORAL EXAMINATION	
Temporomandibular joint	The bone structure of TMJ was normal but the joint limitation was seen. The mouth opening of the patient was limited (23 mm).
Head and face	Brachycephaly Broad skull Maxillary hypoplasia Depressed nasal bridge Small shallow orbits Prominent ear Thin upper lip

Especially for superposition in the anterior maxilla, CBCT was taken and radiographic examination was detailed. Panoramic radiographs of the patient (63 months-old) in follow-up appointments were seen in **Figure 1.B**. CBCT images taken to examine the morphology of the patient's teeth are shown in **Figure 2**. Intraoral photographs of the patient are shown in **Figure 3**.

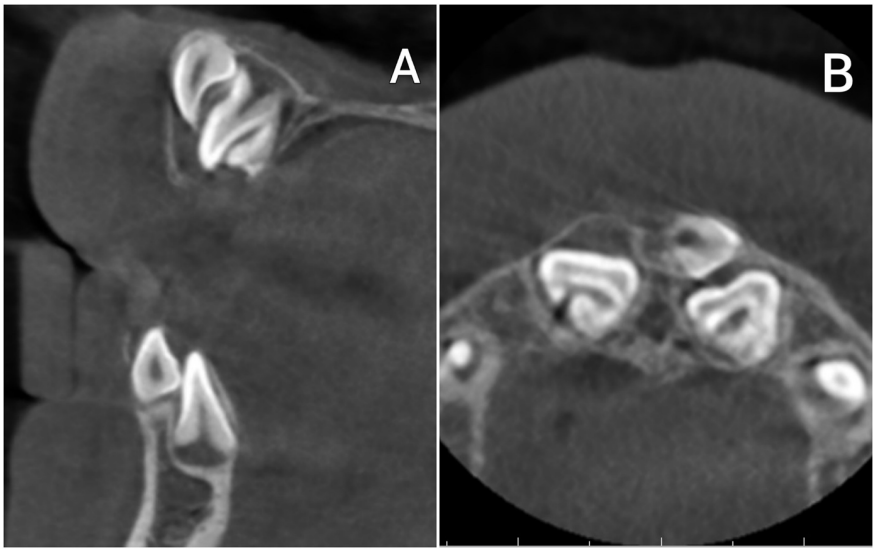

Figure 2. The CBCT images taken to examine the morphology of the patient's teeth are shown. Sagittal(**A**) CBCT sections demonstrating maxillary impacted primary central incisors and impacted permanent central incisors with talon cusps, and mandible impacted primary incisors and impacted permanent incisors. Axial(**B**) CBCT sections demonstrating maxillary impacted primary incisor, impacted permanent central incisors with talon cusps and impacted primary lateral incisors.

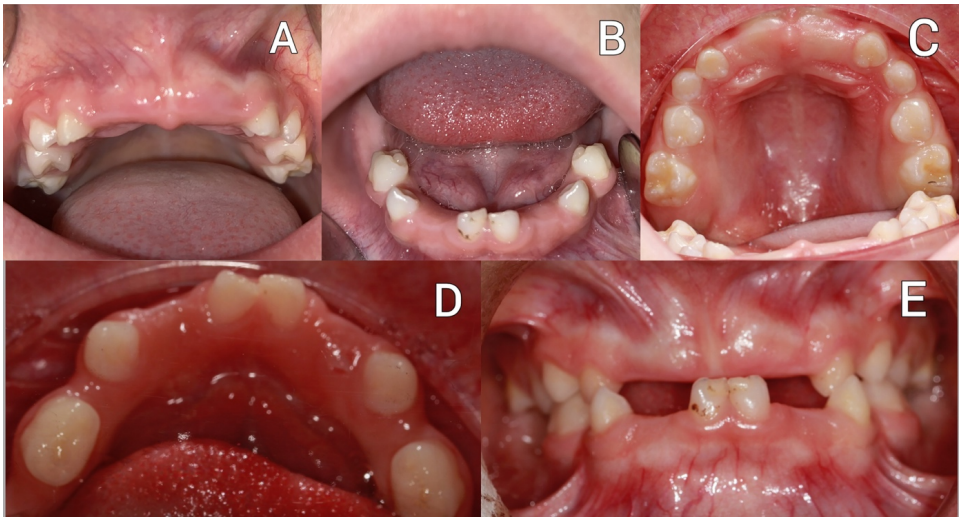

Figure 3. The clinical photographs of the oral condition of patient with WMS2. When the patient 50 months old (A,B) ; When the patient 63 months old.(C,D,E)

Follow-up appointments will be given to the patient in the pediatric dentistry department and comprehensive oral rehabilitation will be planned once the growth of the craniofacial skeleton is complete.

Discussion

In 1932, Weill described a patient with dislocated lenses, short stature, brachydactyly, and stiff joints, within a group of patients with Marfan syndrome.[1] Marchesani, in 1939, recognized this to be a separate entity.[2] The diagnosis of WMS syndrome may be confirmed by clinic findings, in addition to genetic tests and the condition has to be differentiated from isolated autosomal dominant lens dislocation, Marfan syndrome, and Moore-Federman syndrome.[3,6]

Considering the limited number of individuals with WMS in the literature, only maxillary hypoplasia, poorly aligned and malformed teeth were reported among the oro-dental findings, and it was observed that a detailed dental examination was not included.[7] Best of our knowledge, this is the first report which presented the oral and dental findings of WMS2.

Weill-Marchesani syndrome is a rare connective tissue disorder caused by defects in multiple genes and divided into four types. The difference of WMS2 from other types is that there is a mutation in the FBN1 gene which is located on chromosome 15q21.1 and it is inherited as an autosomal dominant.[3,5,8] There was a heterozygous mutation of the FBN1 gene in our patient and her disease was an autosomal dominant form of WMS. Her father has a heterozygous mutation in the same gene but, her mother and brother were healthy individuals. Her father has no clinical symptoms of the syndrome. Also, no dental anomaly was detected in any of the family members except our patient in clinical and radiographic examinations.

Among skeletal findings of WMS type II, joint stiffness and joint limitations were reported in hands, shoulder, knees, elbows, and ankles.3 In our patient, the joint limitation was seen also in the temporomandibular joint and her mouth opening was limited. Karabiyik7, reported that limited mouth opening made it difficult to intubate and airway control in patients with WMS. Limited mouth opening was also important for speech, food intake, oral hygiene, and dental procedures. Therefore, it might be recommended that dental examinations should be performed regularly, and preventive treatments should be performed with topical fluoride applications. An appropriate protective program was scheduled for the patients, and education regarding oral hygiene was given to parents.

Primary tooth eruption, which is a part of the general somatic growth and development of infants, may be influenced by genetic and exogenous factors. Delayed eruption of primary teeth might be the primary or sole manifestation of local or systemic pathology. It is a feature in many genetic disorders and syndromes.[8] Our patient was first referred to us by the genetics department due to the delay in the eruption of primary teeth, and the patient was followed up in a multidisciplinary manner for two years until the diagnosis of the syndrome.

Short roots can be caused by malignancy, chemotherapy, environmental factors, or syndromes such as Scleroderma, Steven Johnsons, Down syndrome, Laurence–Moon–Bardet–Biedl syndrome, Aarskog syndrome, and Seckel's dwarfism. Short roots can also be seen in patients with short stature.[3] In our patient, short roots were observed in all teeth, and some of them also had root deficiencies. The fibrillin-1 glycoprotein encoded by the FBN1 gene is essential for the formation of elastic fibers in connective tissue. Therefore, mutations of the FBN1 gene could cause structural or functional abnormalities in microfibrils.[9] Microfibrils play important roles in development of root and formation of dentin by activation of transforming growth factor-ß (TGF-ß) in the dental epithelium and mesenchyme.[10] The root deformity and delayed eruption can be explained by abnormal growth modeling forces that are generated by the microfibrils in the stroma, periosteum, and periodontal ligament cells surrounding the developing tooth germ.[11] In addition, considering that FBN1 activates certain matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, which play an important role in dentin formation, it can be thought that mutations in this gene may impair radicular dentin formation.[12] To illuminate this issue and to examine the dentin formation of our patient in detail, it is also planned to perform the necessary histological examinations on a primary tooth that may be exfoliated or extracted in the future.

The agenesis of tooth germ may result from disorders in the early stages of odontogenesis, such as failure to initiate tooth formation, reduced odontogenic potential of the dental lamina, or premature arrest of tooth development.[13] In our patient, agenesis of four primary teeth and twelve permanent teeth were seen. In the limited literature, a relationship between tooth agenesis and WMS has not been reported before, and our case is the first also in this respect. Especially in pediatric patients, tooth agenesis can cause physical, functional and psychological negative impacts. Multidisciplinary approaches which include orthodontic, prosthetic or restorative treatments can be choosed. In our patient, since the teeth are not mobile despite root deformities the primary goal is to keep and protect the existing primary teeth. Therefore, routine follow-ups will be continued.

In our patient, in addition to dental number anomalies, shape anomalies such as microdontia and talon cusps were seen. Talon cusp has been widely diagnosed with other developmental pathologies or genetic syndromes and they may cause soft and hard oral tissue damages.[14] The talon cusps in the primary teeth of our patient did not cause any clinical or radiographic problems, but permanent anterior teeth should be followed up.

Conclusion

In conclusion, this case report will provide valuable data for our understanding of the oral and dental characteristics of this rare condition that has not been previously published in the literature. It is important for clinicians seeing patients with severe tooth agenesis, root deformities, maxillary hypoplasia, tooth shape anomalies, and delayed eruption of primary teeth to refer them for genetic consultation to look for syndromes such as WMS in addition to other characteristic clinical features. Early prevention and a multidisciplinary approach to the care of patients with WMS are essential.

Değerlendirme / Peer-Review

İki Dış Hakem / Çift Taraflı Körleme

Etik Beyan / Ethical statement

Bu çalışma Selçuk Üniversitesi 3. Uluslararası Yenilikçi Diş Hekimliği Kongresi'nde (25-27 Kasım 2022, Konya, Türkiye) sözlü bildiri olarak sunuldu.

Çalışma herhangi bir tez çalışması değildir.

Bu çalışmanın hazırlanma sürecinde bilimsel ve etik ilkelere uyulduğu ve yararlanılan tüm çalışmaların kaynakçada belirtildiği beyan olunur.

This study was presented as an oral presentation at Selcuk University 3rd International Congress of Innovative Dentistry (25-27 November 2022, Konya, Turkey).

The study is not any thesis work.

It is declared that during the preparation process of this study, scientific and ethical principles were followed and all the studies benefited are stated in the bibliography.

Benzerlik Taraması / Similarity scan

Yapıldı – ithenticate

Etik Bildirim / Ethical statement

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Finansman / Grant Support

Bu çalışma sırasında, yapılan araştırma konusu ile ilgili doğrudan bağlantısı bulunan herhangi bir ilaç firmasından, tıbbi alet, gereç ve malzeme sağlayan ve/veya üreten bir firma veya herhangi bir ticari firmadan, çalışmanın değerlendirme sürecinde, çalışma ile ilgili verilecek kararı olumsuz etkileyebilecek maddi ve/veya manevi herhangi bir destek alınmamıştır. | The authors declared that this study has received no financial support.

Çıkar Çatışması / Conflict of Interest

Bu çalışma ile ilgili olarak yazarların ve/veya aile bireylerinin çıkar çatışması potansiyeli olabilecek bilimsel ve tıbbi komite üyeliği veya üyeleri ile ilişkisi, danışmanlık, bilirkişilik, herhangi bir firmada çalışma durumu, hissedarlık ve benzer durumları yoktur.| The authors have no conflict of interest to declare.

Yazar Katkıları / Author Contributions

Çalışmanın Tasarlanması | Design of Study: BGT 50%, ME 30 %, MT % 20%
Veri Toplanması | Data Acquisition: BGT 40%, ME 30%, MT 30%
Veri Analizi | Data Analysis: BGT 50%, ME 30%, MT 20%
Makalenin Yazımı | Writing up: BGT 60%, ME 20%, MT 10%
Makale Gönderimi ve Revizyonu | Submission and Revision: BGT 60%, MT 40%

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