REVIEW ARTICLE

WEILL-MARCHESANI SYNDROME: A COMPREHENSIVE REVIEW OF PATHOGENESIS, CLINICAL FEATURES, AND MANAGEMENT

Zespół Weilla-Marchesaniego: kompleksowy przegląd patogenezy, cech klinicznych i postępowania

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Abstract

Weill-Marchesani syndrome is a rare genetic connective tissue disorder, with an estimated prevalence of approximately 1 in 100,000 individuals. It is characterized by a pleiotropic set of manifestations, including short stature, brachydactyly, joint stiffness, ocular abnormalities, and cardiovascular complications. The syndrome follows either an autosomal recessive or autosomal dominant inheritance pattern, with pathogenic variants identified in the FBN1, ADAMTS10, ADAMTS17, and LTBP2 genes. This review examines the current understanding of Weill-Marchesani syndrome pathogenesis, clinical presentation, diagnostic approaches, and treatment strategies. Diagnosis relies on a combination of genetic testing and clinical evaluation. The autosomal dominant form, primarily associated with FBN1 mutations, is typically characterized by lens ectopia and joint stiffness. In contrast, the autosomal recessive form, resulting from mutations in ADAMTS10, ADAMTS17, or LTBP2, is predominantly linked to microspherophakia and cardiovascular abnormalities. Ophthalmological manifestations, including severe myopia and an increased risk of angle-closure glaucoma, are crucial for diagnosis. Management requires a multidisciplinary approach, incorporating ophthalmological interventions such as iridotomy or lensectomy, cardiological monitoring, and orthopedic care. This review synthesizes findings from literature published between 2015 and early 2025, highlighting the ongoing challenges in establishing definitive diagnostic criteria. The analysis underscores the need for further research into the molecular mechanisms underlying Weill-Marchesani syndrome and the development of targeted therapeutic strategies.

Streszczenie

Zespół Weilla-Marchesaniego to rzadka genetyczna choroba tkanki łącznej, występująca z częstością 1:100 000 osób. Charakteryzuje się plejotropowym spektrum objawów, obejmujących niskorosłość, brachydaktylię, sztywność stawów, wady wzroku oraz powikłania sercowo-naczyniowe. Choroba dziedziczona jest autosomalnie recesywnie lub dominująco, z różnymi mutacjami w genach FBN1, ADAMTS10, ADAMTS17 i LTBP2. W pracy omówiono patogenezę, obraz kliniczny, diagnostykę oraz leczenie zespołu Weilla-Marchesaniego. Diagnostyka opiera się na badaniach genetycznych oraz ocenie klinicznej. Wariant autosomalny dominujący związany jest głównie z mutacjami w FBN1 i objawia się ektopią soczewki oraz sztywnością stawów. Wariant recesywny wynika z mutacji w ADAMTS10, ADAMTS17 lub LTBP2 i wiąże się z mikrosferofakią oraz nieprawidłowościami kardiologicznymi. Objawy okulistyczne są kluczowe dla rozpoznania i obejmują m.in. wysoką krótkowzroczność oraz ryzyko jaskry zamkniętego kąta. Leczenie wymaga interdyscyplinarnego podejścia – okulistycznego (np. irydotomia, lensektomia), kardiologicznego i ortopedycznego. W pracy przedstawiono aktualny stan wiedzy na temat zespołu Weilla-Marchesaniego na podstawie przeglądu literatury z lat 2015–2025. Wyniki wskazują na brak jednoznacznych kryteriów diagnostycznych oraz konieczność dalszych badań nad patogenezą i terapią tej choroby.

Keywords: Weil-Marchesani syndrome; FBN1 mutation; fibrillins; Marfan syndrome

Słowa kluczowe: zespół Weilla-Marchesaniego; mutacja FBN1; fibryliny; zespół Marfana

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Introduction

Weill-Marchesani syndrome (WMS, spherophakia-brachymorphia syndrome) is a rare genetic connective tissue disorder, with an estimated prevalence of approximately 1 in 100,000 individuals. It is characterized by short stature, brachydactyly, joint stiffness, cardiovascular complications, and ocular abnormalities, including microspherophakia, lens ectopia, severe myopia, and secondary glaucoma [1]. First described in the early 20th century by Weill and later by Marchesani [2], the syndrome follows both autosomal recessive (more common) and autosomal dominant inheritance patterns. The autosomal recessive form is primarily associated with microspherophakia and cardiovascular abnormalities, whereas the autosomal dominant variant is predominantly linked to lens ectopia and joint stiffness [1].

This study aims to review current knowledge and recent discoveries regarding Weill-Marchesani syndrome, with a focus on its pathogenesis, clinical presentation, diagnostic approaches, and treatment strategies.

Materials and methods: A systematic literature review was conducted using PubMed, analyzing case reports and studies published between 2015 and early 2025.

Etiology

The genetic basis of Weill-Marchesani syndrome is attributed to pathogenic variants in the *FBN1*, *ADAMTS10*, *ADAMTS17*, and *LTBP2* genes. There are two primary modes of inheritance: autosomal dominant, associated with pathogenic variants in *FBN1*, and autosomal recessive, linked to mutations in *ADAMTS10*, *ADAMTS17*, and *LTBP2*. Regardless of the inheritance pattern, these mutations exhibit complete penetrance (100%). However, the severity of clinical manifestations varies significantly, even among individuals carrying the same mutated gene, including members of the same family [3]. In cases of autosomal dominant inheritance, at least one parent is typically affected, although the mutation may also arise de novo. The exact proportion of individuals who inherit the disorder from an affected parent versus those in whom it results from a de novo mutation remains unknown. However, the autosomal recessive form is more frequently inherited [1, 4]. In this inheritance pattern, both parents may be affected, one parent may have WMS while the other is a heterozygous carrier, or both parents may be heterozygous carriers of pathogenic variants in *ADAMTS10*, *ADAMTS17*, or *LTBP2*. It is important to note that heterozygous individuals do not exhibit any clinical symptoms of the disease [1, 5, 6].

Genetics

The autosomal dominant form of WMS is caused by mutations in the *FBN1* gene, which encodes fibrillin-1 [7, 8]. Fibrillins are structural proteins that constitute microfibrils within the extracellular matrix of both elastic and non-elastic tissues [9]. Three types of fibrillins have been identified: fibrillin-1, encoded by the *FBN1* gene on human chromosome 15; fibrillin-2, encoded by the *FBN2* gene on chromosome 5; and fibrillin-3, encoded by the *FBN3* gene on chromosome 19 [10]. Microfibrils exhibit a distinctive morphology, characterized by alternating light and dark – or hollow – regions, giving them a railroad track-like appearance. They are found as large microfibril bundles, as single short microfibrils (often near basement membranes, such as in glomerular endothelial cells), and as a peripheral microfibrillar sheath surrounding elastin in elastic fibers. Microfibrils serve as scaffolds that adapt to the functions of specific tissues to maintain their integrity. For example, in the skin, elastic fiber microfibrils form a loose network of interconnected pathways. In the dermis, they run parallel to the epidermis, with branches extending perpendicularly upwards – from the deeper elastic fiber layers to the basement membrane at the dermo-epidermal junction, where microfibril bundles cross the lamina densa. In tendons and the perichondrium, elastic fibers align parallel to the longitudinal axis, whereas in muscular arteries, they encircle the vascular lumen [11]. Additionally, microfibrils regulate the bioavailability of potent growth factors from the TGF-β superfamily.

In contrast, the autosomal recessive form of WMS is associated with mutations in the *ADAMTS10*, *ADAMTS17*, or *LTBP2* genes. The ADAMTS (A Disintegrin-like and Metalloproteinase with Thrombospondin motifs) family consists of extracellular matrix metalloproteinases capable of degrading matrix proteins. ADAMTS proteins participate in various biological processes, including angiogenesis, coagulation, morphogenesis, and development, as well as pathological conditions such as cancer, arthritis, and extracellular matrix disorders. *ADAMTS10*, in particular, is crucial for microfibrillar fiber organization: it accelerates microfibril assembly in fibroblast cultures, facilitates cell-cell adhesion in epithelial tissues, binds heparan sulfate, and supports focal adhesion formation [12]. Dysfunction of fibrillin or ADAMTS family proteases in WMS results in connective tissue abnormalities, which clinically manifest as the characteristic syndrome [1].

Symptoms

Weill-Marchesani syndrome is characterized by a pleiotropic spectrum of clinical manifestations affecting multiple organ systems. According to the available literature, no clear genotype-phenotype correlation has been established. The disorder involves musculoskeletal, ocular, cardiovascular, and psychiatric abnormalities. Typical features include short stature (average height 142–169 cm in males and 130–157 cm in females), brachydactyly (short fingers), joint stiffness, and ocular anomalies [1]. Ophthalmologic complications often present in childhood, with key manifestations including microspherophakia, high myopia, and angle-closure glaucoma, which can lead to vision loss. Additional ocular findings may include lens dislocation, cataracts, and a recently described feature – corneal thickening. The spherical, subluxated lens appears as a "golden ring" under slit-lamp examination [4, 13–15]. Some patients with WMS also exhibit cardiovascular anomalies such as patent ductus arteriosus, pulmonary valve stenosis, aortic valve stenosis, and mitral valve regurgitation. Less common but clinically significant features include restricted mouth opening and difficulties with intubation, highlighting the need for thorough preoperative assessment. Intellectual disability has been reported in a subset of patients. Rare cases in the literature describe severe supravalvular pulmonary artery stenosis, mitral supravalvular stenosis, and subaortic stenosis. In mildly symptomatic individuals, Weill-Marchesani syndrome type 4 (WMS4) may be diagnosed. Awareness of these clinical features is crucial for pediatricians to ensure early referral for further evaluation and timely diagnosis. Interestingly, most pathogenic variants in *FBN1*, the gene encoding fibrillin-1, are associated with Marfan syndrome, which in many aspects presents as a phenotypic opposite of Weill-Marchesani syndrome [6]. Table 1 provides a comparative overview of the clinical features and genetic mutations observed in WMS and Marfan syndrome [1, 7, 16, 17].

Diagnosis

There are no official, widely accepted diagnostic criteria for WMS, unlike Marfan syndrome (e.g., Ghent criteria). Diagnosis is primarily based on clinical evaluation, imaging studies, and genetic testing. WMS does not present a pathognomonic sign that allows for definitive diagnosis; genetic testing remains the only reliable method. In cases where the autosomal dominant form is suspected, serial testing of a single gene, including sequential analysis of *FBN1*, is performed. Genetic testing including *ADAMTS10*, *ADAMTS17*, *FBN1*, *LTBP2*, and other relevant genes helps identify the condition and exclude uncertain variants. Commonly used diagnostic methods include sequence analysis, deletion analysis, and duplication testing [1]. The primary symptoms of WMS that prompt patients to seek medical consultation, such as short stature, brachydactyly, and musculoskeletal abnormalities, are diagnosed using standard radiographic imaging. This allows for the identification of shortened long bones, delayed bone age, and widening of the proximal phalanges, as well as the assessment of skeletal dysplasia [1]. Ophthalmological examination is critical, as WMS affects the lens and supportive structures of the eye. Techniques such as biomicroscopy help detect lens ectopia, as well as changes in the cornea and anterior chamber. Tonometry is used to assess the risk of glaucoma, while gonioscopy aids in identifying anatomical abnormalities in the filtration angle. Ultrasound biomicroscopy is a valuable tool for detailed analysis of Zinn's ligaments and the degree of lens subluxation. Furthermore, due to the high prevalence of significant myopia in WMS patients, keratometry and skiascopy are also essential [18, 19]. In the evaluation of cardiovascular symptoms, electrocardiography may reveal a prolonged QT interval, while echocardiography helps identify valvular heart diseases [20]. For the differential diagnosis, other connective tissue disorders, such as Marfan syndrome, as well as acromelic dysplasias, which are a group of genetic bone dysplasias, should be considered. These dysplasias are characterized by abnormalities in bone development, especially in the distal parts of the body, including the hands, feet, and face, leading to characteristic deformities [1]. Among the conditions to be considered in the differential diagnosis of WMS are gelatinous-physical dysplasia (GD), acromicrodysplasia (AD), and Myhre syndrome [21, 22]. A comparison of common and distinguishing features is presented in Table 2.

Table 1. Comparison of clinical features between Marfan syndrome and Weill-Marchesani syndrome [1, 7, 16, 17].

Feature	Weill-Marchesani syndrome	Marfan syndrome
Genetic cause	Mutations in *FBN1* (less common than in Marfan syndrome), *ADAMTS10*, or *LTBP1*	*FBN1* gene mutation encoding fibrillin-1
Phenotypic features	Short stature, short fingers and toes (brachydactyly), joint stiffness	Tall stature, long and slender limbs (arachnodactyly), joint hypermobility
Height	Below average	Above average
Digits (fingers/toes)	Short and broad (brachydactyly)	Long and slender (arachnodactyly)
Joint involvement	Restricted mobility, joint stiffness	Increased joint flexibility (hypermobility)
Ocular manifestations	Downward lens dislocation, severe myopia, secondary glaucoma	Upward lens dislocation, myopia
Cardiovascular involvement	Less frequently associated with severe cardiac abnormalities	Aortic aneurysm, aortic dissection, mitral valve prolapse
Cognitive function	Typically normal, although learning difficulties may occur	Typically normal
Additional features	Small, spherical lenses, accommodation difficulties	Chest wall deformities (pectus excavatum or carinatum), skin laxity, striae distensae

Table 2. Comparative features of Weill-Marchesani syndrome (WMS), gelatinous-physical dysplasia (GD), acromicrodysplasia (AD), and Myhre syndrome

Common features of WMS, GD, AD	Short stature, short hands and feet, joint restrictions, thickened skin, mild facial anomalies, and specific radiological findings including delayed bone age, shortened long bones, oval-shaped vertebral bodies
Characteristic features of WMS	Lenticular myopia, lens ectopia, glaucoma, spherophakia
Characteristic features of GD	Valvular heart abnormalities, progressive hepatomegaly, tracheal stenosis
Characteristic features of AD	Progressive hepatomegaly and tracheal stenosis
Common features of WMS and Myhre syndrome	Intrauterine growth restriction (IUGR), short stature, brachydactyly, joint stiffness, thickened skin, heart disease
Characteristic features of Myhre syndrome	Hearing loss, characteristic facial features, varying degrees of cognitive dysfunction, absence of lens abnormalities

Treatment

Following the diagnosis of WMS, it is essential to conduct comprehensive and interdisciplinary evaluations to assess potential manifestations of the disease. Such an approach allows monitoring of disease progression, detection of complications, and initiation of appropriate treatment. Ophthalmic management in WMS is complex and requires an individualized approach, taking into account the unique characteristics of each case. In the early stages of WMS, glaucoma prophylaxis is crucial. Peripheral iridotomy is recommended as a preventive measure to avert closure of the drainage angle. However, closed-angle glaucoma represents a severe complication of WMS, and is often resistant to standard treatments. Available studies indicate that although laser iridotomy is commonly used, it may prove ineffective in deepening the anterior chamber and opening the drainage angle in WMS patients. In such cases, more invasive interventions are necessary. For advanced, chronic closed-angle glaucoma, the following combined procedures may be effective:

- **Lensectomy:** Removal of the lens, which often exhibits abnormal structure and positioning in WMS, contributing to closure of the drainage angle.
- **Anterior vitrectomy:** Removal of the vitreous body from the anterior chamber to improve aqueous humor flow.
- **Combination of vitrectomy and lensectomy:** A combined approach to address the underlying issues.
- **Intraocular lens (IOL) implantation:** Implantation of an artificial intraocular lens following lensectomy.
- **Molteno tube shunt implantation:** Use of a drainage system to reduce intraocular pressure.
- **ExPress shunt implantation:** Another method to reduce intraocular pressure.

In addition to essential ophthalmologic care, patients with WMS require the involvement of specialists from various medical fields. Given the broad range of symptoms and complications associated with this syndrome, the multidisciplinary management team should include a pediatrician, cardiologist, endocrinologist, orthopedist, and physiotherapist [1, 15, 23–26].

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