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Case Report

Undiagnosed Marfan syndrome during military enlistment: Challenges for medical qualification and a brief clinical review

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ABSTRACT

Introduction: Marfan syndrome, an inheritable connective tissue disorder, engenders multifaceted systemic effects, impacting the musculoskeletal, ocular, cardiovascular, neurological, cutaneous, and respiratory systems. Its prevalence ranges from 1 : 5000 to 1 : 10,000 individuals, with approximately 25% of cases attributed to spontaneous genetic mutations. In the United States, an estimated 50,000 individuals are affected, and an additional 200,000 individuals exhibit related connective tissue disorders.

Aim: Here, we present a compelling case of a young soldier who enlisted in our Military Training Center, wherein a previously undiagnosed Marfan syndrome came to light.

Case study: Notably, a strong family history of the syndrome was evident. Clinical manifestations included pectus excavatum necessitating surgical intervention, an upper-to-lower segment ratio (ULSR) less than 0.86, a span-to-height ratio exceeding 1.05, wrist and thumb signs, scoliosis exceeding 20°, and mitral valve prolapse. Notably, no clinical anomalies about the patient's pulmonary or cutaneous systems were detected.

Results and discussion: While considerable advancements have been made in comprehending the pathogenesis, the diagnostic protocol for Marfan syndrome remains rooted in the Ghent criteria, mandating a thorough evaluation of multiple organ systems.

Conclusions: Consequently, the patient was deemed unsuitable for Special Forces deployment and was enlisted as an auxiliary service member, overseen by the Medical Department of the Military Center. Post-discharge, we strongly advocate routine follow-up visits with a family physician to ensure comprehensive medical surveillance.

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1. INTRODUCTION

1.1. Epidemiology

Marfan syndrome is a highly variable autosomal dominant multisystem disorder primarily affecting connective tissue, with an estimated prevalence of 1 in 10,000 to 1 in 20,000 individuals.[1–4] The estimated birth incidence is approximately 1 in 9,800. The syndrome shows no predilection for specific geographic regions, ethnic groups, or genders.[4]

1.2. Historical aspects

Historical accounts suggest that notable figures such as Liu Bei (A.D. 161–223), founder of the Shu Han dynasty, former U.S. President Abraham Lincoln (1809–1865), and British poet Edith Louisa Sitwell (1887–1964) may have exhibited features of Marfan syndrome (Figure 1).[4,5] The first formal description of the syndrome was provided by French pediatrician Antoine Bernard-Jean Marfan in 1896, based on the case of a 5.5-year-old girl (Figure 2).[3] Earlier evidence, however, points to a report by ophthalmologist E. Williams from Cincinnati, Ohio, nearly two decades before, describing siblings with congenital ectopia lentis, remarkable height, and joint hypermobility.[6]

Cardiac involvement in Marfan syndrome was first documented in 1912 by Salle, who reported mitral valve alterations in a 2½-month-old infant.[7] Rados later confirmed the cardiac manifestations through a comprehensive review in 1942, highlighting the prevalence of mitral valve regurgitation.[8] The association with aortic aneurysms and dissections was first reported in 1943 by Etter, Glover, Baer, and colleagues.[6] In 1955, Victor McKusick significantly advanced the understanding of Marfan syndrome by elucidating its hereditary nature and emphasizing cardiovascular complications, such as aortic root dilation and regurgitation.[6]

Figure 1. Historical figures associated with Marfan syndrome: (a) Liu Bei (A.D. 161–223); (b) young Abraham Lincoln (1809–1865), and (c) Edith Louisa Sitwell (1887–1964) are historical individuals presumed or known to have exhibited characteristics consistent with Marfan syndrome.

Figure 2. Depiction of the French pediatrician Antoine Bernard-Jean Marfan (1858-1942), who first described the syndrome in 1896.

1.3. Genetic background

Marfan syndrome is primarily caused by mutations in the fibrillin-1 (FBN1) gene, located on chromosome 15q21.1. Fibrillin-1 is a large glycoprotein (350 kDa) secreted by fibroblasts and incorporated into the extracellular matrix as insoluble microfibrils, providing a framework for elastin deposition and ensuring the elasticity of connective tissues. Approximately 27% of cases arise from de novo mutations.[9]

In addition to FBN1 mutations, alterations in the TGFbR1 or TGFbR2 genes may also contribute to the syndrome; TGFbR1 and TGFbR2 mutations are associated with Loeys-Dietz syndrome, and TGFbR2 mutations with familial thoracic aortic aneurysm.[1] Advances in molecular genetics now allow for the diagnosis of Marfan syndrome in many families through genetic linkage analysis.[10]

1.4. Manifestations

Marfan syndrome is a hereditary connective tissue disorder that affects multiple organ systems, including the musculoskeletal, ocular, cardiovascular, neurological, respiratory, and cutaneous systems.[11] Key clinical features include myxomatous degeneration of the aortic valve, aortic dilation, lens dislocation, pectus excavatum, and arachnodactyly. Musculoskeletal manifestations such as scoliosis, dural ectasia, protrusio acetabuli, and ligamentous laxity are also common.[6]

The prognosis has historically been poor, with an average life expectancy around 32 years, mainly due to aortic dissection, rupture, or cardiac failure.[3] Generalized aortic root dilation is a major predictor of subsequent aortic complications.[12] However, improvements in diagnosis, surveillance, and medical management have significantly extended survival, allowing many individuals to lead longer and more active lives.[6]

The leading causes of morbidity and mortality are progressive aortic root enlargement and aortic dissections. Ap-

proximately 90% of patients exhibit cardiovascular involvement, and around 40% of deaths are attributed to aortic rupture and hemorrhage. Cardiovascular complications include aortic valve regurgitation, aortic aneurysm formation, and aortic rupture.[12,13]

Current guidelines from the American College of Cardiology and the American Heart Association recommend precise measurement of both external and internal aortic diameters, perpendicular to the blood flow axis, using imaging modalities such as computed tomography, magnetic resonance imaging, or echocardiography.[13]

1.5. Diagnostic criteria

The diagnostic understanding of Marfan syndrome has evolved considerably over time. In 1986, the Berlin nosology introduced standardized clinical criteria, but ambiguities and inconsistent application often led to overdiagnosis, particularly in tall, slender individuals.[14] To improve diagnostic accuracy, the revised Ghent criteria (Table 1) were established in 1996, incorporating molecular genetic findings and family history into the assessment.[15] Clinical diagnosis in adults should adhere to the Ghent criteria, although their reliability in pediatric populations remains limited.[1]

2. AIM

We present the case of a 23-year-old male with a strikingly tall stature who was diagnosed with previously unrecognized Marfan syndrome during military enlistment.

Table 1. The Ghent Criteria for Diagnosing Marfan Syndrome. Major and minor criteria are used in diagnosing Marfan syndrome according to the Ghent criteria, which encompass various organ systems to make an accurate diagnosis.

	Criteria	
Category	Major	Minor
Skeletal	Pectus carinatum	Pectus excavatum of moderate severity
	Pectus excavatum requiring surgery	Joint hypermobility
	Reduced upper to lower segment ratio OR arm span to height ratio >1.05	High arched palate with crowding of teeth
	Wrist and thumb signs	Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, downslanting palpebral fissures)
	Scoliosis of >20° or spondylolisthesis	
	Reduced extension at the elbows (<170°)	
	Medial displacement of the medial malleolus causing pes planus	
	Protrusio acetabulae of any degree	
Ocular	Ectopia lentis	Abnormally flat cornea
		Increased axial length of the globe
		Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis
Cardiovascular	Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva	Mitrat valve prolapse with or without mitral valve regurgitation
	Dissection of the ascending aorta	Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis below the age of 40 years
		Calcification of the mitral annulus below the age of 40 years
		Dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years
Pulmonary		Spontaneous pneumothorax
		Apical blebs
Skin		Striae atrophicae
		Recurrent or incisional hernias
Dura	Lumbosacral dural ectasia	
Family history	First degree relative who meets the diagnostic criteria	
	Presence of mutation in FBN1 known to cause Marfan syndrome	
	Presence of haplotype around FBN1 inherited by descent and unequivocally associated with diagnosed Marfan syndrome in the family	

3. CASE STUDY

The patient, a 23-year-old male from a socioeconomically disadvantaged background, was diagnosed with previously undetected Marfan syndrome during military enlistment. The enlistment interview revealed a strong family history of the condition.

Physical examination showed a height of 196 cm, an arm span of 202 cm, and a weight of 65 kg (Figure 3). The patient reported a history of weakness during defecation that had previously led to hospitalization without significant improvement.

Although no cardiac symptoms were evident, echocardiography demonstrated aortic root dilatation and mitral valve prolapse. Musculoskeletal findings included elongated, slender digits (arachnodactyly) with positive Walker's and Steinberg signs (Figure 4). Additional skeletal abnormalities included pectus excavatum requiring surgical intervention, scoliosis greater than 20°, a reduced lower-to-upper body segment ratio (<0.85 for Caucasians), and an increased arm span-to-height ratio (>1.05).

Craniofacial features were consistent with the Marfan phenotype, and ocular examination revealed increased axial globe length, resulting in myopia. No pathological respiratory findings were observed. A psychiatric evaluation found no clinically significant abnormalities.

Military enlistment is mandatory for all eligible young men in Greece. Although the patient initially aspired to join the Special Forces, he was deemed medically unsuitable and served in an auxiliary, non-combatant role for nine months. Throughout his service, he was restricted from strenuous physical activity and was monitored regularly by the Medical Department of the Military Center. Upon discharge, regular follow-up with a family physician was strongly recommended to ensure ongoing medical oversight and management.

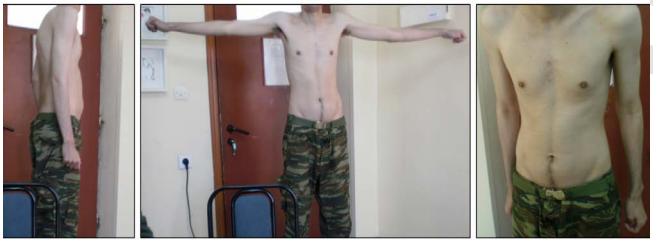

Figure 3. The characteristic body structure of a 23-year-old recruit diagnosed with Marfan syndrome.

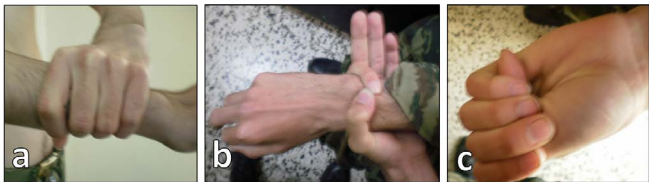

Figure 4. Positive wrist and thumb signs in the young recruit: (a) Positive Walker's Sign: The fingers wrap around the opposite wrist, (b) Positive Walker's Sign (alternative view), and (c) Positive Steinberg Sign: The thumb protrudes beyond the ulnar border when clenched within the fist.

4. RESULTS AND DISCUSSION

The diagnosis of Marfan syndrome in our patient was established using the revised Ghent criteria, which integrate major and minor features across musculoskeletal, ocular, cardiovascular, respiratory, and integumentary systems, along with family history.[6] In the absence of a familial history, diagnosis requires major criteria in two distinct systems and involvement of a third.[16] In this case, a positive family history supported the diagnosis, along with significant findings in multiple organ systems.

Differential diagnosis can be challenging, particularly in younger patients who may present with non-specific connective tissue signs. In adults, Marfan syndrome must be differentiated from conditions such as ectopia lentis syndrome, the MASS phenotype (Myopia, Mitral valve prolapse, Aortic root dilatation, Striae, Skeletal findings), and mitral valve prolapse syndrome (MVPS).[10]

Although the clinical presentation was characteristic, this case is distinguished by the late diagnosis during mandatory military enlistment screening. The patient's socioeconomic background likely contributed to the delayed recognition of Marfan syndrome, highlighting disparities in access to early healthcare. Structured screenings during military service, educational enrollment, or occupational health evaluations can provide critical opportunities for the identification of undiagnosed genetic disorders in vulnerable populations.

Importantly, the diagnosis has significant implications for career planning and physical activity. In this case, the patient's aspiration to serve in the Special Forces was precluded due to the high cardiovascular risks associated with intense physical exertion. Individuals with Marfan syndrome are advised to avoid occupations and activities involving strenuous effort or heavy lifting, given the elevated risk of aortic dissection or rupture. Early diagnosis is thus essential not only for medical management but also for guiding appropriate occupational and lifestyle choices.

Historically, individuals with Marfan syndrome faced a severely reduced life expectancy, averaging around 32 years, primarily due to aortic complications.[3] Advances in early diagnosis, medical therapy, and surgical techniques have significantly improved outcomes, with life expectancy now frequently exceeding 70 years.[6,13,17] However, these gains also bring new challenges, including the management of delayed-onset complications such as joint degeneration and aneurysms of the descending thoracic aorta.[6]

Contemporary research has expanded the understanding of Marfan syndrome's genetic underpinnings. Studies exploring the relationship between FBN1 haploinsufficient genotypes and therapeutic responses to angiotensin receptor blockers (ARBs) offer the potential for more personalized management strategies.[6,17]

This case underlines the importance of systematic early diagnosis, vigilant long-term follow-up, and health education initiatives. Raising awareness among healthcare providers and within structured screening programs is crucial,

particularly for socioeconomically disadvantaged groups. Organizations such as the Greek Marfan Syndrome Society, established in 2002, provide valuable support and advocacy for affected individuals and their families.

Finally, proactive cardiovascular surveillance, including regular follow-up with a family physician, is critical to monitoring aortic dimensions and preventing life-threatening complications. Early intervention and tailored guidance regarding physical activity can substantially enhance the quality of life and long-term prognosis for individuals with Marfan syndrome.

6. CONCLUSIONS

(1) Marfan syndrome is a multisystemic disorder that requires early diagnosis to prevent life-threatening complications.
(2) Structured screenings during military service or similar settings can help identify undiagnosed cases, particularly in socioeconomically disadvantaged populations.
(3) Diagnosis has important implications for career planning and restrictions on physical activity.
(4) Advances in medical care have significantly improved the life expectancy and quality of life of individuals with Marfan syndrome.
(5) Continuous medical follow-up, patient education, and genetic counseling are essential for optimal management.

Conflict of interest
None declared.

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