

OCULAR FEATURES OF MARFAN SYNDROME

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Summary. *Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder involving the cardiovascular, skeletal and ocular systems. In 90–93 % of cases, MFS is caused by a mutation in fibrillin-1 (FBN1) on chromosome 15. The prevalence of MFS is at least 1/ 5000. The disease has no ethnic or gender predilection and shows an extremely high penetrance but marked inter- and intra-familial variability. The diagnosis of Marfan syndrome requires a multidisciplinary team approach, in view of its multisystem effects and phenotypic variability. The paper presents two twelve-year-old girls who, owing to the problem of nearsightedness, were sent to a consultational examination to the Orthoptic and Pleoptic Cabinet of our clinic. Both of them are typically high, gracious, with long limbs, and with a deformity of the spinal column and chests. They are quiet, reserved and shortsighted with a myopic refraction of the eye, the temporal and upper-bilateral subluxation of the lens, as well as with the enlarged axial diameter of the eye. Suspected to suffer from Marfan syndrome, they were sent to a pediatrician and neuropsychiatrist for further examinations. Marfan syndrome requires early integral and update management by a multidisciplinary group, to obtain the best quality of life and survival.*

Key words: *Marfan syndrome, ocular features.*

Introduction

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder involving the cardiovascular, skeletal and ocular systems. Additionally, the skin, integument, lung, muscle, adipose tissue and dura can also be affected (1,2). Cardinal manifestations include aortic aneurysm and dissection, ocular lens dislocation and long bone overgrowth (1).

It was first described by Antoine – Bernard Marfan in an 1896 case report of a young girl with unusual musculoskeletal features (2), while Bürger first described ophthalmological features of MFS in 1914 (3).

MFS occupies a special place in the history of medicine and science owing to the number of seminal discoveries and conceptual breakthroughs that have been associated with this disorder. A 50-year-long analysis of the clinical and genetic features of MFS ultimately led Victor Mc Kusick to delineate it as the founding member of a larger group of congenital conditions that he defined as the heritable disorders of the connective tissue. He predicted it to be the result of structural or metabolic dysfunctions of extracellular matrix proteins (2).

In 1991 McKusick demonstrated that a mutation in the fibrillin-1 gene (FBN1) on chromosome 15 causes Marfan syndrome (2). In 90 – 93 % of cases (1) or 66 – 91% cases (4) MFS is caused by a mutation in FBN1. Fifteen years later, the unexpected finding that the increased transforming grown factor beta (TGF β) signaling is part of the molecular pathogenesis of deficient

mice paved the way to a new drug strategy against the life-threatening manifestations MFS (2). Mutations in the transforming grown factor β - receptor 2 (TGFBR2) gene on chromosome 3 and in the TGFBR1 gene on chromosome 9 were found in some families with apparent MFS (MFS2), but these families seem less likely to have ectopic lentis (4).

The prevalence of MFS is at least 1/ 5000 (1), 2-3 per 10000 individuals (2) or 1 in 9800(4) and > 25% of cases are sporadic (1,4). The disease has no ethnic or gender predilection and shows an extremely high penetrance but marked inter-and intra-familial variability (2). Isolated cases with no family history are often more severely affected. Each child of an affected parent has a 50 % chance of inheriting a disease – causing gene mutation, with males and females equally at risk (1).

Clinically affected individuals often have tall stature and dolichostenomelia, lens dislocation, aortic dilatation, skeletal manifestations as precuts deformities and /or scoliosis. MFS is usually associated with normal intelligence.

Clinical examination should include: AP X - ray of spine for scoliosis of > 20° or spondylolisthesis, AP X-ray of pelvis for protrusio acetabulae, lumbosacral MRI or CT for dural ectasia, ophthalmological examination, cardiological evaluation, accurate height and weight measurements, use of appropriate nomograms for plotting aortic root dimension, urine metabolic screen or fasting plasma amino acids to exclude homocystinuria, chromosome karyotype to exclude Klinefelter syndrome in any individuals with predominant skeletal features

and screening of first-degree relatives with echocardiogram +/- ophthalmological examination(1).

The diagnosis and management of Marfan syndrome requires a multidisciplinary team approach, in view of its multisystem effects and phenotypic variability. A DNA diagnostic service for FBN1 gene testing for MFS and related clinical entities is available (1).

Prophylactic medical (eg β -blockade) and surgical intervention is important in reducing the cardiovascular complications of Marfan syndrome (4).

A Case Report

The paper presents two twelve-year-old girls who, owing to the problem of porsightedness, were sent to a consultational examination to the Orthoptic and Pleoptic Cabinet of our clinic. Both girls are tall, of thin stature, with scoliosis and prominent sternal deformity. They have disproportionately long limbs compared with the trunk, long spider-like fingers (arachnodactyly) and mild joint hypermobility. The skin is fragile and bruising easily.

Ophthalmic features of the first girl: Visual acuity 3/60 with temporal and upper subluxation lentis billateralis, iridodonesis, myopia. The objective refraction of both eyes (Sol. Homatropin 2%) points to myopia of -16,0 D on the right eye and -13,25 D on the left eye. Intraocular pressure determined by the impression method was bilaterally normal. Biometrics: Lax = 29,5mm on the right eye and Lax = 28,0mm on the left eye, B-scan bilaterally - blurring in the glassy body, the retina in the proper position. There is an observable facial asymmetry, with slanting rima oculi; motility and convergence are normal, while there is an exodeviation with hypertrophy in the right eye in the primary position. The girl's aunt gives heteroanamnestic information: the first-born child from the first regular pregnancy completed with a C-section at the full term, as the girl's mother has „a problem with the pelvis" (a shorter leg and she is limping). The girl's father is also tall. Both parents are short-sighted. The girl is quiet, reserved, with an irregular menstrual cycle (with the menarche at the age of 11). After being given a suitable correction of the refraxional anomaly and advice, the girl was sent to a further consultational examination to the pediaticirician, gynecologist and neuropsychiatris.

Ophthalmic features of the second girl: Visual acuity 1/60 with subluxatio lentis bilateralis, iridodonesis, myopia (-10,0 D). Intraocular pressure (IOP) determined by the impression method points to somewhat higher values in the right eye. Biometrics is bilaterally Lax - 26 mm, B scan - without blurring in the glassy body, the retina in the proper position. Gonioscopy bilaterally: without the underdeveloped mesodermal tissue over the chamber angle. The girl is quiet, reserved, suspicious of her surroundings. After being given an appropriate local antiglaucoma therapy on the right eye, the correction of the refraction anomaly and advice, the girl was sent to a consultational examination to the pe-

diatrician, neuropsychiatrist and further check-ups to the ophthalmologist in charge.

Discussion

Marfan syndrome is a systemic disorder caused by mutations in fibrillin -1. Fibrillin - 1 is a multidomain cysteine-rich glycoprotein containing 43 calcium - binding EGF (cbEGF) - like domains and 78 cystein - containing TB motifs. Fibrillin microfibrils of the extracellular matrix (ECM) which associate with elastic fibres are implicated in the regulation of TGF β in large latent complex (5). The phenotype of MFS typically involves manifestations in the cardiovascular, skeletal and ocular systems.

Cardiovascular manifestations include progressive aortic root enlargement and abnormally thick and elongated valve leaflets. Ascending aortic aneurysm can precipitate life-threatening complications such as aortic regurgitation, dissection or rupture (2). Marfan syndrome mortality from aortic complication has decreased (70% in 1972, 48% in 1995) and life expectancy has increased (mean age at death 32 ± 16 years in 1972 versus 45 ± 17 years in 1998) associated with the increased medical and surgical intervention (4).

The most striking and immediately evident manifestation in MFS patients often involves a disproportion or increase in linear bone growth that causes overt malformations of the digits, limbs and anterior chest wall as well as craniofacial abnormalities, scoliosis and joint hypermobility (2). Scoliosis affects around 60% of Marfan patients and may progress rapidly during growth spurts, leading to marked deformity, pain and restricted ventilatory deficit. Joint hypermobility affecting 85% of children under 18 and 56% of adults with many patients suffering arthralgia, myalgia or ligamentous injury. Pectus excavatum occurs in approximately two-thirds of patients with Marfan's syndrome and, when severe, can be associated with a restrictive ventilatory defects (4).

Ocular features of MFS include bilateral ectopia lentis (40 - 56 %), myopia (28%) and retinal detachment (0,78%). Subluxatio usually develops in early childhood, but may first appear in the second decade. Lens dislocation into the anterior chamber may occur (4). Hypoplasia of dilatator pupillae, angle anomaly is common, but microspherophakia, keratokonus, cornea plana megalocornea are uncommon features (6). Myopia is associated with an increased length of the globe and an increased risk of retinal detachment. Anisometropia and the possible anterior chamber abnormalities are further important considerations for management. Vitreolensotomy with laser prophylaxis to prevent detachment can be effective in improving visual acuity in some patients. Early detection and correction of refractive errors prevents amblyopa - correction after the age of 12 years is unlikely to restore visual acuity (4).

For better understanding, the ocular manifestations of the Marfan syndrome, we must know the distribution of fibrillin in normal human ocular tissues. Fibrillin is

widely distributed in ocular connective tissues. In the anterior segment, the following exhibited positive staining for fibrillin: the lens capsule and zonules, connective tissues of the iris, ciliary body, ciliary processes, and conjunctiva, as well as the basement membrane regions of the corneal epithelium and endothelium of Schlemm's canal. Posteriorly, fibrillin localized to the lamina cribrosa, sclera, choroid, and Bruch's membrane. Defects in these tissues result with ocular abnormalities in the Marfan syndrome such as ectopia lentis, glaucoma, myopia (7).

Marfan patients report fatigue as a major subjective complaint. Self-reported fatigue is comparable with fatigue in other severe chronic diseases and disabilities and is primarily in the mental/psychological domain. Psychological distress is higher compared with the population at large. Fatigue seems related to some areas of cognitive functioning and slightly reduced speed of information processing. Reduced visio-motor coordination could be explained by impaired visual acuity (8).

The diagnosis of MFS in adults is based on the Ghent criteria, which requires the presence of major criteria in two organ systems and involvement of a third. Berlin diagnostic criteria of 1988 were revised and the clinical features codified as the Ghent nosology in 1996. Scottish clinical guideline for management of Marfan patients was devised by a consensus group in 1999 using SIGN methodology (4).

In the Ghent nosology, clinical features are assessed within seven body "systems", to determine whether that system provides a major criterion, or only system involvement. The cardiovascular, ocular and skeletal system can provide major criteria, or system involving the pulmonary system and skin-integument can provide only system involvement, the dura and family-genetic history provide only major criteria organ system(4). However, this cannot always be applied to pediatric patients and it is particularly true of children with sporadically occurring disease. Many features of MFS such as mitral valve prolapse or scoliosis are also common in

the general population or may occur in other connective tissue disorders (1).

A DNA diagnostic service for FBN1 gene testing for MFS and related clinical entities is available (1). Prenatal diagnosis is available where a familial mutation is known, but disease severity cannot be predicted. In the absence of a FBN1 mutation in a "Ghent Positive" case, TGFBR 2 screening may be appropriate. A detailed family history and a high level of clinical suspicion are essential too. All family members potentially at risk should receive genetic counseling, lifestyle modification advice and where appropriate, counseling with regard to career options (1).

Prophylactic medical (eg β -blockade) and surgical intervention is important in reducing the cardiovascular complications of Marfan syndrome. Ophthalmological assessment is important and regular orthoptic review is recommended, particularly in childhood (4).

Marfan syndrome requires early integral and update management by a multidisciplinary group, to obtain the best quality of life and survival (9).

Conclusion

Marfan syndrome is a widespread disorder of connective tissue associated with mutation of the fibrillin gene on chromosome 15q. Inheritance is AD with variable expressivity. Although neonatal and infant forms of the disease exist, the classic MFS is the most frequent form of presentation in childhood and adolescence. Due to the natural evolution of the disease there is a progressive involvement of different organs or systems, which means that the suspicion must arise on skeletal clinical aspects which are the first evident signs. The cardiovascular involvement appears later but is the major life threatening complication. Ophthalmological assessment is important and regular orthoptic review is recommended, particularly in childhood.

Marfan syndrome requires early integral and update management by a multidisciplinary group, to obtain the best quality of life and survival.

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OČNE KARAKTERISTIKE U MARFANOVOM SINDROMU

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Kratak sadržaj: *Marfanov sindrom (MFS) je autozomno dominantni poremećaj vezivnog tkiva koji zahvata kardiovaskularni, skeletni sistem i oči. U 90-93% slučajeva MFS je uzrokovan mutacijom fibrilina -1(FBN1) na hromozomu 15. Prevalenca MFS je 1 /5000. Bolest nema etničku ni polnu predilekciju i pokazuje ekstremno visoku penetraciju sa značajnom inter – i intra – familijarnom varjabilnošću. Dijagnoza Marfanovog sindroma zahteva multidisciplinarni timski pristup, obzirom na multisistemske efekte i fenotipske razlike. Radom se prikazuju dve dvanaestogodišnje devojčice koje zbog slabog vida bivaju upućene na konsultativni pregled u Kabinet za ortoptiku i pleoptiku naše klinike. Obe su tipičnog visokog rasta, dugih ekstermiteta, gracilne, sa deformitetom kičmenog stuba i grudnog koša, tihe, povučene, slabovide sa miopnom refrakcijom oka, subluksacijom sočiva temporalno i gore obostrano, uvećanim aksijalnim prečnikom oka. Pod sumnjom na Marfanov sindrom upućene su pedijatru i neuropsihijatru na dodatne preglede. Marfanov sindrom zahteva rani, integralni i blagovremeni multidisciplinarni tretman, kako bi se pružio najbolji kvalitet života i opstanaka obolelih.*

Ključne reči: *Marfanov sindrom, očne promene*