Marfanov sindrom u oftalmologiji

Marfan Syndrome in Ophthalmology

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PRIMLJEN 11.12.2013.
PRIHVACEN 16.06.2014.

RECEIVED 11.12.2013.
ACCEPTED 16.06.2014.

SAŽETAK

Autori prikazuju slučaj 59-godišnje pacijentkinje sa obostranom zadnjom luksacijom sočiva u staklasto telo, klinički kontrolisanim glaukomom i adherentnim leukomom rožnjača sa vaskularizacijom, a sa klinički dijagnostikovanim Marfanovim sindromom. Pacijentkinja je klinički kompletno obrađena u smislu očnih i sistemskih ispitivanja, kao i verifikacije genetske mutacije na fibrilin1-genu (FBN1). Pacijentkinji je postavljena dijagnoza Marfanovog sindroma na osnovu kliničke i genetske analize heterozigotne mutacije FBN1 gena, uz kliničke znake od strane oči. Pacijentkinji je predlagana pars-plana vitrektomija sa lensektomijom, ili antiglaukomna operacija sa ugradnjom Ahmedove valvule u cilju kontrole sekundarnog glaukoma, ali krajnja odluka o terapiji je isključila hirurške module od strane referentnog tima experata. Kod naše pacijentkinje sekundarni glaukom je bio pod kliničkim, terapijskom kontrolnom.

Ključne reči: Marfanov sindrom; dislokacija sočiva; dijagnoza; terapija

ABSTRACT

Authors report the case of a 59-year old woman with bilateral posterior lens luxation in vitreous, medically controlled glaucoma and corneal adherent leucoma with vascularization in whom Marfan syndrome was diagnosed. The patient underwent complete clinical eye and systemic examinations and blood samples were drawn for mutational screening of fibrillin1 gene (FBN1). The patient was diagnosed with Marfan syndrome on clinical basis do to genetic testing revealed a new heterozygous mutation in the FBN1 gene and described with ocular signs. The patient required pars plane vitrectomy with lensectomy, or Ahmed valve implantation in vitreous to control glaucoma secondary, but the finally treatment was without surgical modules from recommendation of referent expert team. In our patient glaucoma secondary was under therapy control.

Keywords: Marfan syndrome; lens subluxation; genetics; diagnosis; therapeutics.

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INTRODUCTION

The incidence of the Syndrome is 6 - 10 per 100,000 of population by year.

Marfan syndrome is the autosomal dominant connective tissue disorder characterized by ocular anomalies, skeletal, cardiovascular and other clinical problems. The cause is mutation in the gene for fibrillin1, due to the lack of elastic connective fibers and fiber mikrofibrilae lack the necessary strength. Luxation lentis is the most common ocular manifestation in 70 - 80 % of cases, but bilateral posterior dislocation is the rare feature. Syndrome is a connective tissue disorder with mitral valve prolapsed, aortic dilatation and dissection.

Ocular changes are myopia, glaucoma, and ectopic lentis, flattening the cornea, cataract, iris and ciliary muscle hypoplasia, retinal detachment, with subsequent loss of vision. More than half of patients have dislocation of one or both lenses. Retinal detachment is one of the most severe complications, which can lead to blindness. Of affected, most individuals are heterozygous carriers of pathological genes.

Genetic cause of mutation of FBN1 encoding fibrillin synthesis and the locus of the gene located on long arm of 15th chromosome (15q21.1). The glycoprotein fibrillin is the main component of ligaments suspensors eye as elastin in the aorta and the second binder¹.

In some patients, the disease can be very mild, while others severe and progressive.

Diagnosis is based on clinical examination, ophthalmologic examination, X-ray, ultrasound, CT, NMR and the genetic testing.

The treatment is symptomatic, use of local and systemic medicaments and if necessary, surgical therapy.

METHODS

A 59-year old female was directed in Clinic of Ophthalmology in Kragujevac with decreased visual acuity of both eyes; with posterior luxation lentis of the both eyes. Anamnesis' dates indicated that our patient is diagnosed with Marfan syndrome for many years. Best corrected visual acuity (with +9.00 Dsph) of the right eye was 0.02, and of the left eye 0.001 (by Snellen test).

Intraocular pressures of the both eye were irregular, 22 mm Hg of the right eye and 23 mm Hg of the left eye, with anti-glaucomatous therapy. Having in mind that use of mi-

otic treatment can cause rotation of the lens-iris diaphragm anteriorly and may also contribute to the formation of such adhesions, we didn't use topical miotics. Secondary glaucoma was under clinical control with optimal topical therapy.

Slit examination of both eyes showed discrete corneal adherent leucoma with superficial vascularization and iris atrophy, figure 1. Careful slit-lamp examination of anterior segment should be conducted in patient with posterior dislocated lenses.

Figure 1. Ultrasound of luxation lens with ablation retina of the left eye

Indirect clinical ophthalmoscope of the both eyes showed posterior sub capsular opacities and exudation of vitreous. Fundus examination showed attenuated retinal vessels, macular atrophy with occasional pigment accumulation as clumps.

The both visual field were constricted. Ultrasound showed bilateral spontaneous complete posterior lens dislocation without ablation retina of the right eye, and with ablation retina of the left eye, figure 2.

Figure 2. Leucoma corneae - vascularisata and subatrophia - iridis in Marfan syndrome

Complete blood, immunological and necessary clinical examinations were performed. Our patient has long limbs, chest deformity, hip deformity, flat feet and increased joint mobility. Characteristic of the patient's eyeball recessed, recessed lower jaw, elongated head and thick teeth. She also presented cardiovascular disorders such as aortic dilatation, dilatation of the pulmonary artery and thoracic aorta. Skin changes occur in form of stretch marks on the shoulders. One of her soon died from aortic dilatation rupture, and other son has the same clinical manifestations as his mother.

DISCUSSION

Marfan syndrome is condition which affects ocular, musculoskeletal and cardiovascular system, in its bases is connective tissue disorder caused by mutations in fibrillin1 which is the major constituent of extracellular micro-fibrils. Many studies have established that syndrome is part of group of developmental disorders with complex effects on morphogenesis, homeostasis and organ functions¹.

Many of other authors have described genotype-phenotype relationship of cohort in consecutive patients with isolated ectopic lentis secondary to ADAMTSL4 and FBN1 mutations. Their patients underwent detailed ocular, cardiovascular, skeletal examination and their ophthalmic features, including corneal problems, poor visual acuity, and direction of lens displacement, some of which we examined in our patient².

The condition can cause the aggressive secondary glaucoma that requires surgical treatment with lensectomy, vitrectomy, and drainage device implantation in order to avoid its devastating progression into glaucomatous optic atrophy³. But in our opinion surgical treatment may represent high risk for our patient, due to her existing condition and secondary glaucoma which was under control.

Circulating TGFβ1 is not diagnostic and therapeutic marker for Japanese patients with Marfan syndrome, although findings don't eliminate the possible association of TGFβ with the pathogenesis of Marfan syndrome, what we have not been able to confirm nor exclude, due to technical limits in genetic examinations⁴.

The Marfan syndrome shows symptoms in ophthalmology assessment are refractive errors and ectopic lentis. Pregnancy is time of increased cardiovascular and other risk for women with Marfan syndrome, particularly if aortic root exceeds 4 cm in the beginning of pregnancy. The diagnosis and management of Marfan syndrome requires multidisciplinary team approach, in view of its multisystem effects and phenotypic variability, which was our guideline in management of this condition in our patient⁵.

Pars plane lensectomy - vitrectomy and anterior chamber intraocular lens implantation appears to be an excellent technique for the management of ectopic lentis associated with Syndrome. A bimanual, closed-system endue-surgical technique avoids many of complications previously associated with surgery for ectopic lentis⁶. After performing an examination on our patient, vitreo retinal-surgical team, from Belgrade, gave opinion not to perform any surgery, due to high risk for our patient caused by a connective tissue disorder.

Marfan syndrome is result from mutation of the FBN1 gene on human chromosome 15. It is still difficult to use modern genetic testing for diagnosis because Marfan Syndrome can be caused by many different mutations in FBN1, a large gene with 65 coding segments, while mutations in other genes can cause overlapping phenotypes⁷.

Although historically Marfan syndrome has been considered as condition caused by the deficiency of structural extracellular matrix protein, fibrillin1, the study of Marfan mouse models and Marfan-related conditions has shifted our current understanding to pathogenic model that involves dis-regulation of the cytokine-transforming growth factor beta (TGF-β) signaling. The recent insights into pathogenesis of syndrome and related disorders have offered prime example of translational medicine with immediate bridge between molecular findings and therapeutic options, and we set high hopes in these future, from gene to therapy⁸.

Other authors have examined the development, composition, and structural organization of ciliary zonule of the mouse. The large glycoprotein enriched in force-bearing tissues, fibrillin1, is prominent constituent of the mouse zonule (characterized by lens dislocation). The development and arrangement of the murine ciliary zonule are similar to those of humans, and consequently the mouse eye may be the useful model in which to study ocular complications of Marfan syndrome, which can be subject of our future researches⁹.

Retinal detachment in Marfan syndrome is complete in 75% of the eyes. More than half, 56% had a retinal break in temporal half of the retina, and 83% had at least a break in temporal half of the retina, which coincides with our data. Currently available vitreous retinal surgical techniques result in successful reattachment of the retina in approximately 86% of the eyes, whose surgical experience we don't have for now, because our patient already had reattachment surgery which resulted in repeated ablation, but the clinical characteristics are the same¹⁰.

CONCLUSION

The patient was diagnosed with Marfan syndrome on clinical basis do to genetic testing revealed a new heterozygous mutation in the FBN1 gene and described with ocular signs. In our patient glaucoma secondary was under topical therapy control.

The patient required pars plane vitrectomy with lensectomy or Ahmed valve implantation in the vitreous cavity to establish long-term control in her glaucoma, but the finally treatment was without surgical modules from recommendation of referent expert team.

REFERENCES

1. Ramirez F, Dietz HC. Marfan syndrome: from molecular pathogenesis to clinical treatment. *Curr Opin Genet Dev* 2007; 17(3):252-8.
2. Chandra A, Aragon-Martin JA, Hughes K, et al. A genotype-phenotype comparison of ADAMTSL4 and FBN1 in isolated ectopic lentis. *Invest Ophthalmol Vis Sci* 2012; 53(8):4889-96.
3. Milla E, Leszczynska A, Rey A, Navarro M, Larena C. Novel FBN1 mutation causes Marfan syndrome with bilateral ectopia lentis and refractory glaucoma. *Eur J Ophthalmol* 2012; 22(4):667-9.
4. Ogawa N, Imai Y, Nishimura H, et al. Circulating transforming growth factor β -1 level in Japanese patients with Marfan syndrome. *Int Heart J* 2013; 54(1):23-6.
5. Dean JC. Marfan syndrome: clinical diagnoses and management. *Eur J Hum Genet* 2007; 15(7):724-33.
6. Koenig SB, Mieler WF. Management of ectopia lentis in a family with Marfan syndrome. *Arch Ophthalmol* 1996; 114(9):1058-61.
7. Summers KM, West JA, Hattam A, Stark D, McGill JJ, West MJ. Recent developments in the diagnosis of Marfan syndrome and related disorders. *Med J Aust* 2012; 197(9):494-7.
8. Bolar N, Van Laer L, Loeys BL. Marfan syndrome: from gene to therapy. *Curr Opin Pediatr* 2012; 24(4):498-504.
9. Shi Y, Tu Y, De Maria A, Mecham RP, Bassnett S. Development, composition and structural arrangements of the ciliary zonula of the mouse. *Invest Ophthalmol Vis Sci* 2013; 54(4):2504-15.
10. Sharma T, Gopal L, Shanmugam MP, et al. Retinal detachment in Marfan syndrome: clinical characteristics and surgical outcome. *Retina* 2002; 22(4):423-8.