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Case report

OCULAR ASPECTS OF USHER SYNDROME

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Abstract: **Introduction:** Usher Syndrome is a rare syndrom, which typical expressions are hearing loss, retinitis pigmentosa and in some cases impairment of balance and congenital cataract. It is inherited autosomal recessive. Nine genes whose mutation are associated with this condition have been isolated. It is diagnosed on the basis of clinical and genetic testing. The therapy is aimed at facilitating the functioning of these patients in the environment. Gene therapy is promising in treatment.

The purpose of this paper is to focus attention on the specificity and multiplicity of the disease, which would be of educational significance to ophthalmologists and otorhinolaryngologists, through the use of the case report of Usher syndrome.

Case report: We present the case of gene confirmed Usher syndrome with 85% hearing loss, retinitis pigmentosa and congenital cataract. Female at the age of 39, pregnant at 26 gestational week, second pregnancy. Genetic investigation by Macedonian Academy of Sciences and Arts (MANU) confirmed double heterozygosity for pathogenic changes c.13010C > T. p. (Thr4337Met) and c.13137delC; p. (Thr4380GinfsTer11) in the USH2A gene, a genotype that confirmed the diagnosis of autosomal recessive disease Usher syndrome type 2A (Usher syndrome 2A).

Conclusion: Detailed anamnesis is always required in patients with retinitis pigmentosa, who are referred to an ophthalmologist for hearing and vice versa for patients with hearing loss that are examined by an otorhinolaryngologist. Early diagnosis is important in terms of quality of life, i.e. timely diagnosing and undertaking measures for genetic testing in the family, in order to inform them about the type of the disease and the earlier involvement in educational programs designed for these conditions.

Key words: Usher syndrome, retinitis pigmentosa, deafness, gene therapy.

INTRODUCTION

Usher syndrome (USH) is a hereditary syndrome, usually detected before adolescence and causes hearing and vision loss. Patients with this syndrome may also have balance problems.

Gene mutations that affect the retina and cochlea are responsible for hearing loss. Several studies have shown that up to 25,000 people in the United States have some form of this syndrome. Generally, Usher syndrome is a main cause of linked deafness and blindness (1).

Nearly thirty percent of patients with retinitis pigmentosa reported hearing impairment, and almost 50 % of them are confirmed as USH (1).

Hearing loss is classified as sensory. Visual loss is due to involvement of photoreceptor cells. It first begins with peripheral scotomas in the visual field, and after a period of time it remains only a tubular vision. In some cases, the vision is further reduced due to lens clouding i.e. cataract (2).

Usher syndrome is classified into three main types: type I, II and III. While all three types involve progressive vision loss due to retinitis pigmentosa (RP), the categorization is by the genes responsible for the disease and the onset and severity of the signs and symptoms.

Type I of USH that is manifested by severe deafness, RP and absence of vestibular function is the most severe clinical presentation of the disease.

Type II of USH is less severe with moderate congenital deafness, retinitis pigmentosa without vestibular damage. Usher syndrome type III includes profound deafness, retinitis pigmentosa and varying degrees of vestibular impairment. This type typicaly occurs in the second to fourth decade of life. These patients tend to have better vision than the other two types (3, 4).

CASE REPORT

We present the case of gene confirmed Usher syndrome. Female at the age of 39, pregnant at 26 gestational week, second pregnancy.

She first came at the University Eye Clinic in Skopje in 2013, when she was diagnosed with retinitis pig-

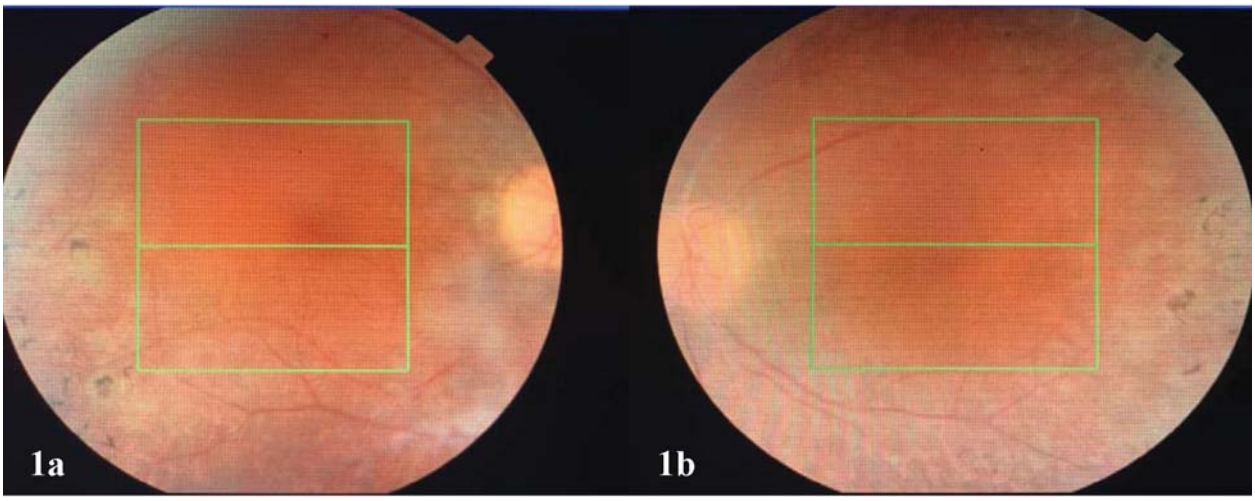

***Figure 1a and 1b**. Fundus photo, right and left eye*

mentosa (RP) and BCVA 0.1 of both eyes. Her next examinations were in 2014 and 2016, without worsening of visual acuity and no significant progression of the visual field.

After three years, at the examination in October 2019, the patient had a BCVA of 0.05 on both eyes, and a significantly narrowed visual field, i.e. tubular vision.

The biomicroscopy of the anterior segment of the eye showed a congenitally clouding of the posterior lens capsule. The fundus examination showed hyaloid membrane remnant, large opacity floating in the vitreous body of the right eye, pale papilla with narrow blood vessels, thin layers of the retina and osteoclastic changes throughout the whole medioretina and peripheral retina (Figures 1a, 1b).

Optical coherence tomography (OCT) of the posterior segment of the eye showed a posterior hyaloid membrane detachment, thinning of the retinal layers, more pronounced to the right eye, with changes in the retinal pigment epithelium (Figures 2a, 2b).

In medical history, the patient reported hearing loss, which began in childhood. Audiological tests found an 85% reduced hearing, according to the Fowler-Sabinau scale and no impairment of vestibular function.

Further genetic and intrauterine examinations of fetus were assigned to the patient.

Genetic investigation by Macedonian Academy of Sciences and Arts (MANU) confirmed double heterozygosity for pathogenic changes c.13010C > T. p.(Thr4337Met) and c.13137delC; p. (Thr4380GinfsTer11) in the USH2A gene, a genotype that confirmed the diagnosis of autosomal recessive disease Usher syndrome type 2A (Usher syndrome 2A).

While analysis for determining the presence of changes in c.13010C > T and c.13137delC in the USH2Agene in the patient's fetus has shown that the fetus is the carrier of the change c.13010C > T.

But the fact that the partner of this patient is unaffected and untested and there is a risk of being a carrier of the disease, taking into account the prevalence of Usher syndrome type 2A in the general population is 1-9/100000, the risk that the fetus will develop Usher syndrome is from 1/118 to 1/354 in this pregnancy (1, 5, 6).

DISCUSSION

Usher syndrome is a gene determinate disease, in most cases genetically heterogeneous. Nine genes have been identified whose mutations are responsible for USH. Because proteins, which are encoded by these genes, are believed to interact with each other in order

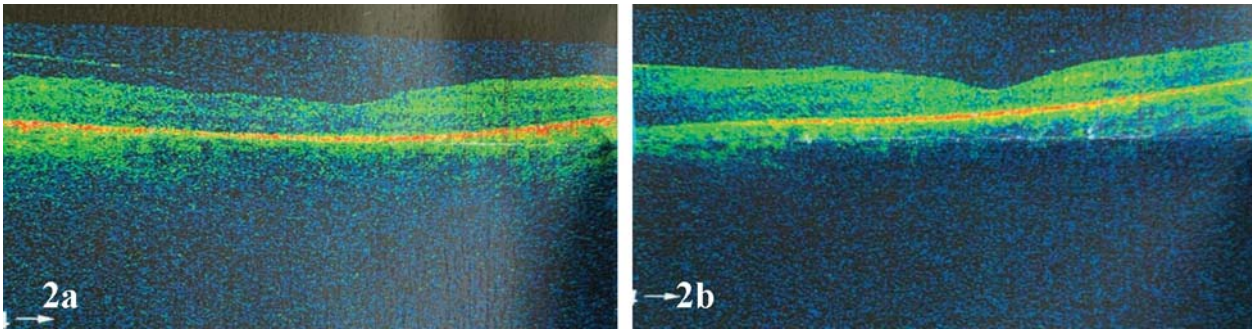

***Figure 2a and 2b.** OCT findings of the macula, right and left eye*

to form a network in the sensory cells of the inner ear and the retina (7).

Sixteen loci were found which are associated with the appearance of USH and atypical USH. Twelve of them were proven to be causative genes and one is proven to be a modification gene.

According to research on the proteins encoded by these USH genes, it seems that the USH proteins interact and operate as a multiprotein complex.

Even though their precise role remains an enigma in terms of the retina, it has been shown that these proteins are necessary for the development, maintenance, and function of hair fiber bundles, which are the main mechanosensitive structure of the inner ear fiber cells (8).

Genetic testing is necessary for the diagnosis Usher syndrome. So far, researchers have found nine genes responsible for the syndrome. Genetic testing is available for all of them: Usher type 1 syndrome: MY07A, USH1C, CDH23, PCHD15, USH1G, Usher type 2 syndrome: USH2A, GPR98, DFNB31 and Users type 3 syndrome CLRN1 (9).

USH2A gene, confirmed by our case and presented in the paper, is located on chromosome 1and it encodesa protein called usherin. This protein is a key component of the basal cell membrane, which separates and supports cells in a multitude of tissues. Usherin exists in the basal cell membranes of the inner ear and retina and plays major role in the development and maintenance of cells in the same tissues.

Pathogenic alterations in USH2A have been shown to be associated with retinitis pigmentosa type 39 and Usher syndrome type 2A, which was confirmed in our patient (1, 5, 6).

In terms of the treatment of retinitis pigmentosa, a study was performed from 1979 to 1983 with four control groups, where patients were given high doses of vitamin A, high doses of vitamin A and vitamin E, low doses of vitamin A and vitamin E, and only high doses of vitamin E, respectively.The results, measured by electroretinogram (ERG), showed a slowing of the course of the disease in the vitamin A-treated group and an acceleration of the disease in the vitamin E-treated group. The recommendation of this study is the daily use of vitamin A palmitate 15,000 IU, under medical supervision and avoiding vitamin E in high doses (10).

In another study done to examine the incidence of Usher syndrome in children with hearing loss and total deafness it was shown that the incidence was 11.3% (15/133). The prevalence is thought to be 1/6000 (1, 5). Usher syndrome is far more common than what had been observed prior to the age of genomic research. The early diagnosis of the Usher syndrome is highly beneficial for the safety of children, prior planning for their education, genetic counseling and treatment (11).

Currently, no cure is available for Usher syndrome or retinitis pigmentosa. Early diagnosis is the best advantage thus far, so that educational programs can start earlier, depending on the severity of vision loss, age and the ability of the child.

Treatment includes learning to read Braille and making use of devices and techniques intended for the visually impaired and blind. Some research suggests that the progress of certain forms of RP can be slowed down, however the high intake of vitamin A can cause deterioration of other eye conditions.

It is thought that gene therapy will take an important place in the treatment of this syndrome (9). This therapy does not compensate lost photoreceptor cells, but recent studies suggest that it slows the degeneration (12).

CONCLUSION

Usher syndrome is definitely more common than it is presumed. As many as 30% of patients with retinitis pigmentosa report hearing loss and 50% of them are diagnosed with Usher syndrome. Detailed anamnesis is always required in patients with retinitis pigmentosa, who are referred to an ophthalmologist for hearing and vice versa for patients with hearing loss that are examined by an otorhinolaryngologist.

Additional ophthalmic examinations, beside a detailed examination of fundus in mydriasis, which need to be made are perimetry and electroretinogram (ERG). Furthermore, if there is a positive history of hearing loss, a consultation with an otorhinolaryngologist and an auditory examinations are needed. Early diagnosis is important in terms of quality of life, i.e. timely diagnosing and undertaking measures for genetic testing in the family, in order to inform them about the type of the disease. Progress is also expected in the field of gene therapy in the treatment of this syndrome.

Abbreviations

MANU — Macedonian Academy of Sciences and Arts

USH — Usher syndrome

RP — retinitis pigmentosa

OCT — Optical coherence tomography

ERG — electroretinogram

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Licensing

Sažetak

OKULARNI ASPEKTI USHER-ovog SINDROMA

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Uvod: Usher sindrom je redak sindrom, koji se karakteriše gubitkom sluha, retinitis pigmentosom i u pojedinim slučajevima poremećajem ravnoteže, i kongenitalnom kataraktom. Nasleđuje se autozomno recesivno. Mutacije devet gena se mogu dovesti u vezu sa ovim stanjem. Dijagnoza se postavlja na osnovu kliničke slike i genetskog testiranja. Terapija ima za cilj da omogući funkcionisanje ovih pacijenata u okolini. Genetska terapija obećava kao terapija izbora. Cilj rada je da podseti na specifičnost ove bolesti, i da kroz prikaz slučaja Usher-ovog sindroma ima i edukativni značaj za oftalmologe i otorinolaringologe.

Prikaz slučaja: Prikazujemo pacijentkinju kod koje je genetički potvrđeno postojanje Usher-ovog sindroma, sa oštećenjem sluha, retinitis pigmentosom i kongenitalnom kataraktom. Pacijentkinja starosti 39 godina, u 26.oj gestacijskoj nedelji, kojoj je ovo druga trudnoća, genetskim ispitivanjem, Makedonsko društvo za nauku i umetnost (MANU) potvrdilo je duplu heterozigomatičnost za patogene promene c.13010C > T. p.(Thr4337Met) ic.13137delC; p. (Thr4380GinfsTer11) u genu USH2A, a genotip potvrđuje dijagnozu autozomno recesivne forme Usher-ove bolesti tip 2A.

Zaključak: Detaljna anamneza je uvek neophodna za pacijente sa retinitis pigmentosom, koji se šalju na konsultativni pregled oftalmologa zbog gubitka sluha, kao i obrnuto da se pacijenti sa oštećenjem sluha šalju kod otorinolaringologa. Rana dijagnoza je veoma bitna u smislu kvaliteta života i.e. na vreme postavljena dijagnoza i preduzimanje mera za genetsko testiranje u porodici, ima velikog smisla radi informisanja porodice o mogućoj transmisiji i naslednosti bolesti, kao i adekvatnoj terapiji i uključivanje u edukativni program, koji je dizajniran za ovu bolest.

Ključne reči: Usher-ov sindrom, retinitis pigmentosa, gluvoća, genska terapija.

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