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MUTATION OF ABCA4 GENE AS A CAUSE OF AUTOSOMAL RECESSIVE FORM OF STARGARDT DISEASE - CASE REPORT

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Abstract

Stargardt disease is the most common type of juvenile macular dystrophy. It is inherited autosomal recessively, although autosomal dominant forms have also been described. It affects both sexes equally, without racial predisposition. Patients experience a progressive deterioration of the macular region and loss of central vision, leading to legal blindness in the majority of affected individuals.

In this paper, we describe the case of an 11-year-old boy who presented for an ophthalmological evaluation due to a progressive decrease in visual acuity. The fundoscopic examination supplemented with imaging ophthalmological methods were sufficient to establish a working diagnosis of Stargardt disease. The diagnosis was confirmed by genetic testing, a mutation of the ABCA4 gene, which is associated with this dystrophy. The importance of this case report is that it is one of the first documented cases of Stargardt disease with ABCA4 mutation in Macedonia.

Keywords: Stargardt disease, autosomal recessive disease, optical coherence tomography, autofluorescence, macular dystrophy

Introduction

Stargardt disease is the most common form of juvenile macular dystrophy in the human population. The incidence of the disease is estimated to be between 1:8,000 to 1:10,000 live births[1]. The disease usually begins in the first decades of life, although cases with late onset have also been described. For the first time, seven cases with this dystrophy were described in 1909 by Karl Stargardt, after whom the disease was later named[2].

Over time, a loss of central vision occurs in the affected patient, with the appearance of creamy spots in the macular region and middle periphery of the retina, accompanied by progressive atrophy of the retinal pigment epithelium (RPE). Mainly visual acuity in patients ranges between 6/18 to 6/60 although initial visual acuity can be 6/6 and final visual acuity can reach 20/200 or worse making these patients legally blind[3]. The disease is genetic with an autosomal recessive pattern of inheritance. There are also cases with an autosomal

dominant pattern of inheritance, with a mutation in the ELOVL4 gene - Stargardt-like macular dystrophy[4]. Stargardt disease with late onset and milder clinical course is also known as fundus flavimaculatus which has quite common phenotypic features but better final visual acuity than the juvenile form[5].

Case report

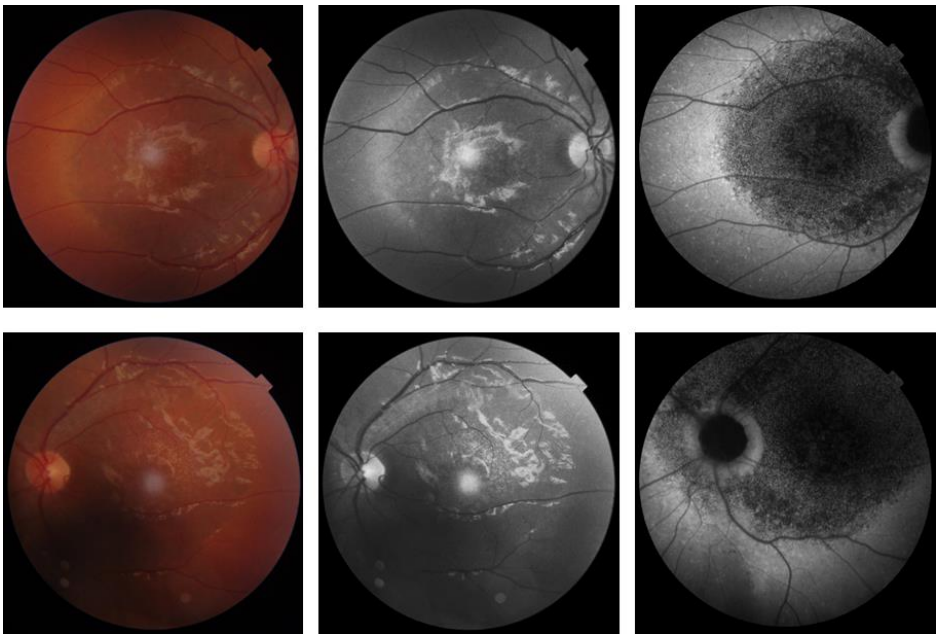

Fig. 1. Fundus photograph, red-free photograph and autofluorescence of the right (top) and left (bottom) eye. The native fundus photograph shows a zone in the macular region up to the level of the arcades with a darker color and a beaten bronze metal appearance. The boundaries of the change are more clearly delineated on a red-free photo. Autofluorescence - a wide zone of granulated hypo-hyperautofluorescence is observed in the maculo-papillary region that reaches the temporal vascular arcades. Punctiform hyperautofluorescent flecks are seen on the medioretina all the way to the equator.

An 11-year-old child was sent to the University Clinic for Eye Diseases in Skopje by a pediatrician due to a decrease in vision in the past period. Best-corrected visual acuity was 0.08 bilaterally. The intraocular pressure was 12 mmHg in the right and 14 mmHg in the left eye. The motility of the bulbs was arranged in all directions. Stereo vision was absent when tested with the Lang test, and the patient also exhibited green-red dyschromatopsia when tested with the Ishihara chart. A funduscopic examination was performed, during which granulation with a beaten bronze metal appearance was noted in the macular region and individual creamy flecks were present at the posterior pole and near the vascular arcades. Changes were also observed using fundus photography, autofluorescence and red-free camera (Figure 1).

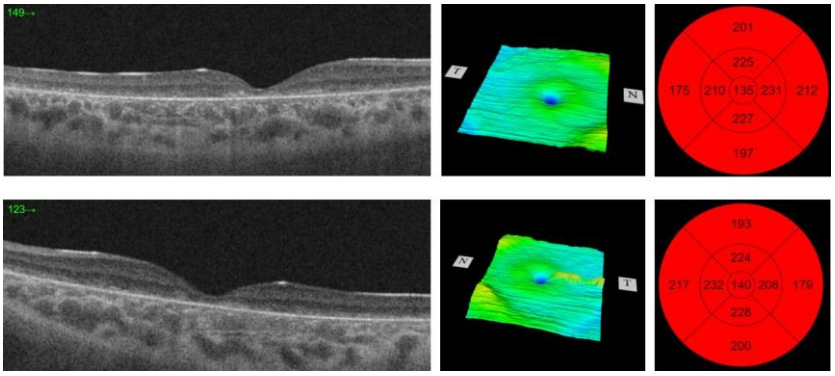

Fig. 2. Optical coherence tomography and macular topography of the right (top) and left (bottom) eye. Neurosensory retinal thinning and deepened foveolar depression. Quantitative data for macular thickness in the right and left eye, respectively.

Anamnestically, no data were obtained about vision problems in another family member, as well as any other disease in the patient. Also, the parents denied the existence of consanguinity in the family. An optical coherence tomography (OCT) of the macula was performed where thinning of the neurosensory retina, disturbance of foveal depression, central macular thickness of 135 um on the right and 140 um on the left eye were observed, respectively. Thinning was also observed at the level of the ganglion layer in the neurosensory retina (GCL+ 53 um right and 54 um left) as well as irregularities at the level of the RPE and photoreceptor cells (Figure 2). Based on the clinical findings supplemented by OCT data, a working diagnosis of juvenile macular dystrophy, possibly Stargardt disease, was made, and genetic testing was indicated.

In the Research Center for Genetic Engineering and Biotechnology at the Macedonian Academy of Sciences and Arts, targeted massive parallel sequencing of the exons of protein coding genes in the human genome was performed. Illumine second-generation sequencing technology and bioinformatic processing of genes associated with the patient's condition were used. It was found that the patient was homozygous for a pathogenic variant c.5917del, (p.Gly1972_Val1973insTer) in the ABCA4 gene inherited from both parents. The pathogenic variant in heterozygous form was present in both parents of the patient. The clinical picture complemented by the genetic analysis confirmed the diagnosis of Stargardt macular degeneration. The condition was explained to the patient's parents, the impossibility of its therapeutic treatment, and advice was given for regular follow-up and monitoring by an ophthalmologist.

Discussion

The ATP-binding cassette (ABC) transporter superfamily is a broad and heterogeneous group of proteins specialized in the active transport of various substances across the cell membrane against a concentration gradient[6]. These proteins are found in almost all living organisms, including humans. A subclass of these transport proteins known as ABCA4 is found only in the retina. Their gene is located on the first chromosome[7]. This protein molecule is located on the membrane of the discs of the outer segments of cons and rods and is involved in the retinoid cycle. In patients in whom this membrane protein is dysfunctional, there is a disruption of the retinoid cycle and accumulation of degenerative material-lipofuscin at the level of the RPE. This pathophysiological mechanism is considered to be the basis for Stargardt disease[8]. New knowledge indicates that mutations of the ABCA4 gene are also the cause of other retinal diseases such as: with a small proportion of AMD cases, some cone-rod dystrophies and some forms of retinitis pigmentosa[8-10].

Stargardt disease is characterized by slow but progressive damage to the retinal pigment epithelium and photoreceptor cells. It leads to an irreversible decrease in central vision, color vision and dark adaptation. Dysfunction of the ABCA4 protein results in the accumulation of lipofuscin in the RPE, causing its dysfunction, atrophy and destruction. The macular region takes on a beaten bronze appearance, accompanied by a large number of creamy flecks in the surrounding area. The progression of the disease takes a centrifugal pattern[11].

The diagnosis in patients is established with the help of anamnestic data, complemented by examinations of visual acuity and color vision, fundoscopic examination, examination of the visual field, as well as fluorescein angiography (FFA), fundus autofluorescence (FAF), electroretinogram and optical coherence tomography[12]. Genetic analysis is not always necessary to establish the diagnosis, but it is needed especially in patients with an atypical clinical picture. For example, other macular degenerations and dystrophies such as: multifocal pattern dystrophy, central areolar choroidal dystrophy, achromatopsia, cone dystrophy and cone rod dystrophy, can present in a similar way as Stargardt disease. These diseases can sometimes pose significant differential diagnostic challenges. However, modern imaging technologies in ophthalmology (OCT, FAF and FFA), electrophysiological tests such as electroretinography, supplemented with genetic analyses can help in these situations[10,12].

The variant c.5917del (p.Gly1972_Val1973insTer) in exon 43 of the ABCA4 gene, which is present in our case, is a nonsense mutation that results in a stop signal during translation of the genetic material at position 1973. This variant is known in the literature as pathogenic and is associated with autosomal recessive eye diseases such as Stargardt disease and other retinal dystrophies[13].

In the beginning, the fundus in patients may have normal morphological characteristics, although accompanied by a significant reduction of central vision. In the advanced stages, relative and then absolute central scotomas are observed. It should be noted that at the beginning of the disease, the visual field may be without pathological changes[14]. Typically, patients with Stargardt disease preserve their peripheral visual field even in the late stages of the disease. On fluorescein angiography in these patients, the pathognomonic finding is "dark choroid", covered with hyperfluorescent small irregular lesions - fundus flecks[15]. However, angiography is not necessary in establishing the diagnosis and can be replaced by the non-invasive procedure - autofluorescence. Changes in fundus autofluorescence correspond accordingly to the degree of damage to the RPE and photoreceptors. Areas of atrophy and photoreceptor loss appear as hypoautofluorescent zones, while areas with lipofuscin accumulation appear as hyperautofluorescent[16].

Electrophysiological tests are essential in the evaluation of patients with Stargardt disease, both for their diagnosis and for monitoring the progression of the disease. Most often these patients present with a normal or subnormal full-field electroretinographic scotopic or photopic response. In those with advanced disease, there is a pronounced abnormality in both responses during full-field electroretinogram[17]. Optical coherence tomography, on the other hand, offers the possibility of detailed analysis of retinal layers, detection of lipofuscin accumulation in the RPE, as well as examination of damaged and lost photoreceptor cells, which makes this tool quite useful in the modern diagnosis and monitoring of patients with this dystrophy[12].

In our case, during the clinical evaluation of the condition, optical coherence tomography, fundus photography and autofluorescence were performed, which, in addition to the genetic analysis, were sufficient to establish the patient's diagnosis. Electrophysiological tests were not performed due to their unavailability. The patient has been followed for three

years at the University Clinic for Eye Diseases in Skopje; until the moment of publication of this paper, there is no further decline in visual acuity and funduscopic findings.

To this day, Stargard disease is still an incurable condition. Current therapeutic options include photoprotection, avoidance of foods rich in vitamin A and vitamin A supplementation, as well as low vision aids[18]. Several possible therapeutic modalities are under development, such as pharmacological slowing of the visual cycle and gene therapy, which aim to prevent the accumulation of lipofuscin, thus enabling longer-term preservation of functional vision[18,19].

Conclusion

In this paper, we have presented a case of a patient with Stargardt disease in whom a genotypic-phenotypic correlation was confirmed. Although this disease is still without adequate therapy, modern medicine is making efforts to overcome this obstacle. However, the timely recognition of such patients is important for appropriate genetic counseling and planning of future offspring for people affected by this condition.

Conflict of interest statement. None declared

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