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Current Trends in Ophthalmology and Visual Science

Hartnett M and Kaufman EJ. Curr Trends Ophthalmol and Vis Sci: CTOVS-101.

DOI: 10.29011/CTOVS-101. 100001

Case Report

Ocular Findings and Implications of Genetic Testing for Papillorenal Syndrome

Magen Hartnett[1], Evan J. Kaufman2[*]

[1]Department of Optometry Extern, New England College of Optometry, Virginia, USA

[2]Department of Ophthalmology, University of Virginia Health System, Virginia, USA

[*]**Corresponding author:** Evan J. Kaufman, Department of Ophthalmology, University of Virginia Health System, Virginia, USA. Tel: +14349720070; Fax: +14349245180; Email: EK2CZ@hscmail.mcc.virginia.edu

Citation: Hartnett M, Kaufman EJ (2018) Ocular Findings and Implications of Genetic Testing for Papillorenal Syndrome. Curr Trends Ophthalmol and Vis Sci: CTOVS-101. DOI: 10.29011/CTOVS-101. 100001

Received Date: 17 March, 2018; **Accepted Date:** 04 May, 2018; **Published Date:** 11 May, 2018

Abstract

Renal coloboma syndrome, also referred to as papillorenal syndrome, is a rare hereditary disorder that causes bilateral malformation of the optic nerve heads as well as a form of renal impairment [1,2]. It generally is acquired through autosomal dominant family inheritance, but cases of mutated forms have been reported in the absence of a family history.

A 19-year-old female was seen at the University of Virginia's Eye Clinic with bilateral optic disc anomalies and documented end stage renal disease (ESRD). She presented with a complaint of persistent blurring in both eyes that had not been treated previously. Clinical examination revealed refractive error, optic nerve dysplasia, and macular schisis of both eyes. This case outlines the clinical findings associated with apparent renal coloboma syndrome and its relation to genetic disorder.

Three types of genetic testing are used to examine a person's biological makeup: molecular, chromosomal, and biochemical. Molecular testing is used most commonly to test for specific diseases with known genetic markers, and the PAX2 gene has been found to cause papillorenal syndrome [3,4]. Reasons for choosing to have a patient evaluated for a genetic work-up vary. This paper describes the benefits and availability of genetic testing for patients with implied renal coloboma syndrome.

Keywords: Autosomal Dominant; Coloboma; ESRD; Hereditary; Papillorenal; PAX2; Mutation

Case Report

A 19-year-old female who recently emigrated from the Philippines was referred for a comprehensive eye exam to the University of Virginia Eye Clinic with complaints of long standing, severe bilateral blurred vision at distance. The patient denied sustaining any trauma to either eye. Her last comprehensive ocular examination was reported to be at age 7. Details of personal and family history were difficult to acquire because the patient was unable to provide a detailed history. She was known to have chronic End Stage Renal Disease (ESRD), for which she was receiving dialysis treatment 3 times per week. She denied taking any systemic or ocular medications. Her social history was negative for tobacco, alcohol, and recreational drug abuse. She had no known drug allergies

The patient's entering visual acuity was reduced to right eye: 20/100-1 left eye: 20/200 upon entering and best corrected to right eye: 20/25+1 left eye: 20/30-1 after manifest refraction. Her pupils were equal, round, and reactive to light; no afferent pupillary defect was noted. Finger counting confrontation fields were full in both eyes. Extra-ocular muscles were unrestricted in all gazes without pain or diplopia. Color testing was not performed at this visit. Goldmann applanation tonometry measured within normal limits. No staining or corneal defects were observed on slit lamp evaluation. The lids and lashes were clear with no signs of Meibomian gland dysfunction or blepharitis, in each eye. Anterior chambers appeared quiet without evidence of cells or flare both eyes; estimation of the chamber angles was 1:1 using the Von Herrick method. The anterior segment was unremarkable in both eyes. The funds exam revealed anomalous optic discs in both eyes that resembled morning glory abnormalities. Clinical estimation

of cup to disc ratios was difficult; however, upon visualization, they were approximated to be 0.80 both eyes. There was abnormal arterial/venous crossing inferiorly in the left eye, and both eyes showed angioid streaks radiating from the disc area. The imaging ordered included funds photography, red-free funds photography, disc photos, and both macular/retinal nerve fiber layer optical coherence tomography. See analysis below.

Morning Glory Disc Anomaly (MGDA) is a congenital malformation of the optic nerve disc characterized by the presence of a cone-shaped macropapilla with neuroglial remnants in its center surrounded by chorioretinal ring [5,6].

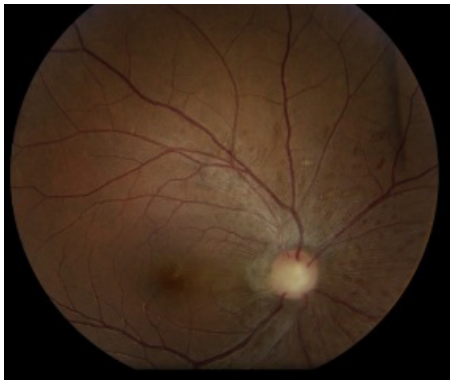

Figure 1: Fundus Photography OD and OS.

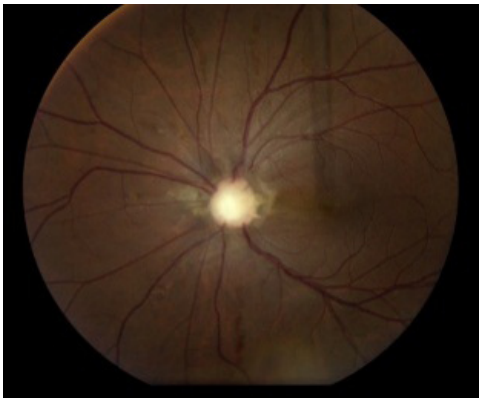

Figure 2: Bilateral Funduscopic View of Morning Glory Discs.

Funds photography revealed severe optic nerve abnormalities and micro vascular retinopathy.

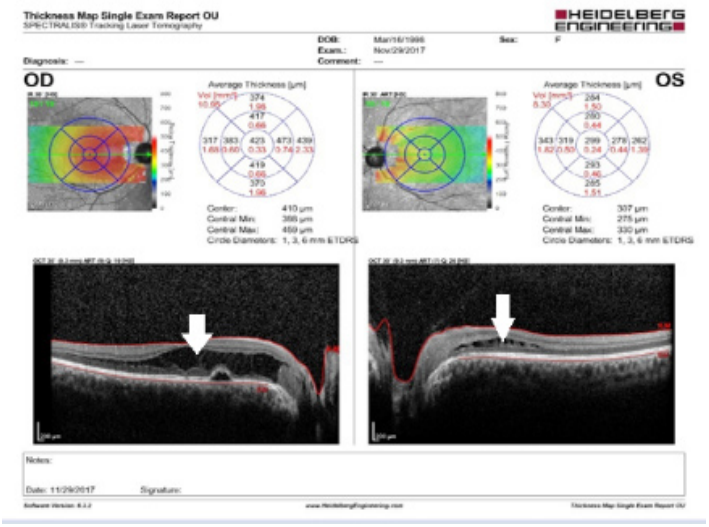

Figure 3: Spectralis: Optical Coherence Tomography; Macular with Bilateral macular edema.

Macular optical coherence tomography revealed intra-retinal fluid in both eyes and a focal area of sub-retinal fluid of the left eye. Remarkably, the patient was able to obtain right eye 20/25 and left eye 20/30 vision, respectively. Central macula thickness exhibited right eye 423 um left eyes 299 um. The patient was referred to specialty retina for further consultation and possible treatment.

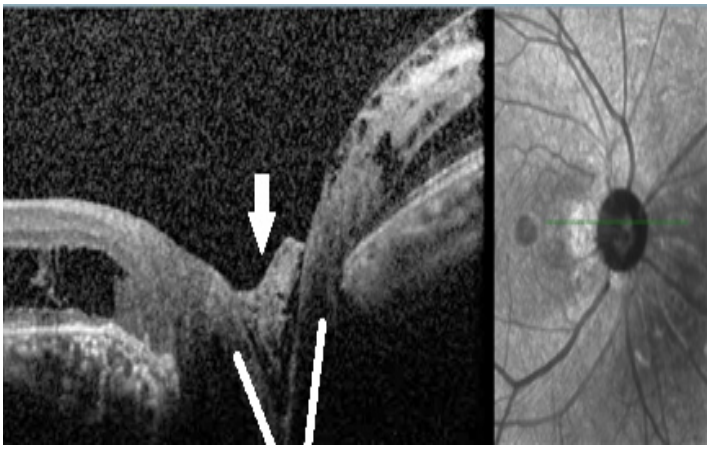

Figure 4: Right Optic Nerve: Optical Coherence Tomography Cone-Shaped Macro Papilla with Neuroglial Remnants.

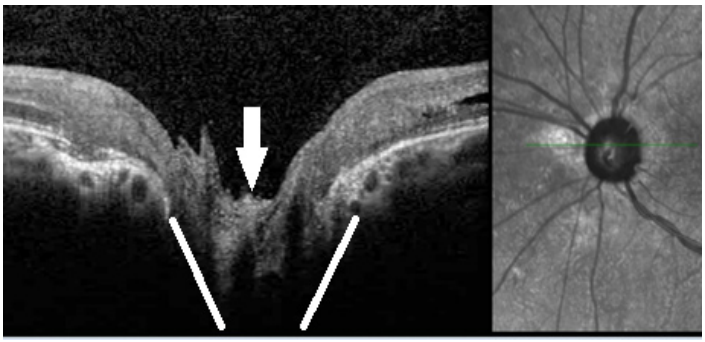

Figure 5: Left Optic Nerve Optical Coherence Tomography Cone-Shaped Macro Papilla with Neuroglial Remnants.

Optic nerve head and retinal nerve fiber layer analysis revealed nerve asymmetry and areas of thinning.

The patient was referred to a retinal specialist for further consultation. Her return protocol after retinal examination was a 3-month follow-up for serial field testing and optical coherence tomography. No treatment was indicated at the time of that visit.

Background

Papillorenal syndrome is characterized by renal hyperplasia and abnormal optic nerves. Because of the variations in the mutations, patients can present with mild to severe ocular and/or systemic manifestations. For example, patients can express mild kidney insufficiency through ESRD. Similarly, they can express mild optic disc dysplasia to optic aplasia [7].

The mutations that cause papillorenal syndrome have been isolated to the PAX2 gene, which is located on chromosome number 10q24.31 [3]. PAX2 is an important embryogenic gene and plays a role in the development of many ocular and renal structures. Abnormal renal function is noted in 92% of affected individuals with a mutated PAX2 gene. Ophthalmologic abnormalities are noted in 77% of theses affected individuals [8].

A grading scale to classify optic nerve anomalies in papillorenal syndrome follows:

The optic disc coloboma was scored according to a 5-point scale. 0 = normal; 1 = optic disc dysplasia with an unusual pattern of retinal vessels and cilioretinal arteries; 2 = optic disc pit associated with vascular abnormalities and a cilioretinal artery; 3 = large coloboma involving the entire surface of the optic disc; 4 = large coloboma of the optic disc and adjacent retina or morning-glory anomaly (with radial emergence of the retinal vessels).

The patient in this case presented with a score of 4 bilaterally. Both nerves showed deep excavation and radial vessels emerging along the very edge. Many ocular manifestations are associated with papillorenal syndrome, the most common of which are optic nerve dysplasia, scleral staphyloma, macular abnormalities including cystic changes and hyper pigmentation, optic nerve cysts, and lens abnormalities, including lens opacities and luxation [8].

Currently, there is no treatment for papillorenal syndrome; however, management of symptoms of underlying ocular and systemic pathology provides the best opportunity for optimal health. Genetic testing does not alter the treatment plan for congenital optic nerve anomalies and is costly; it is not part of the current gold standard for management in these patients. Treatment for macular schisis includes anti-VEGF injections to reduce fluid accumulation, while treatment for refractive error includes careful refraction and complete correction. If possible, it is ideal to have equal visual acuity potential between the eyes. Surgical care is indicated for cataracts that impair vision and retinal pathologies when genetic testing becomes affordable and available more readily, it is likely to help improve patients' quality of life through earlier diagnosis and appropriate systemic referrals.

Discussion

There are many congenital anomalies of the optic nerve. However, advanced technologies have made it increasingly easier to differentiate between specific presentations and etiologies. The most common congenital anomalies include optic nerve hypoplasia, Morning glory disc anomaly, optic disc coloboma, Renal Coloboma Syndrome (RCS), peripapillary staphyloma, optic pit, congenital tiled disc syndrome, and optic nerve drusen [9].

Since the completion of the human genome project in 2003, more than 20,000 genes have been identified [10]. Continued research and advanced methods have created faster sequencing techniques, which offer clinicians more opportunities to use genetic testing throughout their treatment and management plans. Indications for genetic testing for papillorenal syndrome specifically include differentiation of renal-coloboma syndrome from other coloboma-associated disorders, improved medical management and prenatal diagnosis in pregnancies [11].

Conclusion

This case illustrates the significance of symptom management as well as the importance of current genetic research. Papillorenal syndrome has been found in approximately 200 cases worldwide [8]. Mutations in the PAX2 gene cause embryonic malformations in renal and ocular structures, primarily the optic nerve.

There is no current cure for papillorenal syndrome, and therefore, we can only manage its symptoms. Patients should be educated about the importance of dilated eye exams, visual field testing, and optical coherence tomography to track nerve and macular damage. Further, patients with suggestive optic nerve findings should have their kidney function screened and treated appropriately.

Each individual case must be assessed for any additional anterior and posterior involvement. All ocular manifestations must be treated at an appropriate level to ensure the best possible visual acuity and eye health overall. The patient seen in this case was atypical, in that her best-corrected visual acuity was Right eye: 20/25- Left eye: 20/30. With such a good visual acuity, treatment of her schisis can be more conservative, and we elected to monitor her carefully by serial visual field screening and optical coherence tomography imaging together with dilation.

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