Oculodentodigital Dysplasia

New Ocular Findings and a Novel Connexin 43 Mutation

Luis A. Rassi Gabriel, MD; Reccha Sachdeva, MD; Andreas Marcotty, MD; Edward J. Rockwood, MD; Elias I. Traboulsi, MD

Objectives: To describe new ocular findings associated with oculodentodigital dysplasia (ODDD) and a novel mutation in the connexin 43 transmembrane domain.

Design: Oculodentodigital dysplasia is a rare autosomal dominant disease characterized by multiple systemic abnormalities, most commonly of the ocular, nasal, dental, and limb structures. Herein, we studied 2 patients with ODDD. We describe their clinical findings and 2 ocular abnormalities not previously emphasized or reported.

Results: Optic nerve and retinal dysplasia was observed in both patients, and ciliary body cysts were observed in 1 patient. Both patients carried isolated in-frame deletion and missense mutations of the GJA1 gene on chromosome 6.

Conclusions: Optic nerve and retinal dysplasia had not been emphasized as ocular manifestations of ODDD. Ciliary body cysts have not previously been reported in association with ODDD.

Clinical Relevance: Our findings support the potential significance of connexin 43 in the retina, optic nerve, and ciliary body. Retinal and optic nerve dysplasia may be more common than previously appreciated and may be associated with reduced vision. In addition, the ciliary body cysts observed in 1 patient may be secondary to weakened cellular adhesions between ciliary body pigmented and nonpigmented epithelium associated with the in-frame deletion identified in the affected patient. The presence of these cysts may exacerbate glaucoma or complicate its management.


OCULODENTODIGITAL DYSPLASIA (ODDD) is a rare autosomal dominant disease characterized by abnormalities of the ocular, nasal, dental, and limb structures. Rare findings include spastic paraplegia, deafness, and cardiac abnormalities. The disease results from mutations in the gap junction alpha 1 gene (GJA1). The gene is composed of 2 exons and 1 intron and is located at chromosome 6q21-q23.2,1,2 Under physiological conditions, the gene codes for a transmembrane protein, connexin 43 (Cx43). Cx43 molecules hexamerize to form a hemichannel called connexon that apposes itself with another connexon in another cell membrane to form a gap junction.2

To date, 62 Cx43 mutations resulting in ODDD have been identified. Of these, 85% have consisted of dominant missense mutations. The remaining mutations are made up of several duplications, 2 deletions resulting in frameshift mutations, a recessive nonsense mutation, a recessive missense mutation, and a compound heterozygote missense mutation.2 Most ODDD cases have been in patients of white race/ethnicity and are apparently associated with advanced paternal age in sporadic cases.1 There is no sex predilection.3

Herein, we studied 2 patients with ODDD to examine the relationship between previously undescribed clinical findings and the underlying molecular defects. The combination of clinical findings and identified mutations, along with previous studies of the Cx43 function, allows us to hypothesize the behavior of the altered protein in these patients and its clinical relevance.

METHODS

We examined 2 patients with characteristic systemic clinical findings of ODDD. Testing for...
GJA1 (OMIM 121014) mutations was performed in a Clinical Laboratory Improvement Act–certified laboratory.

**REPORT OF CASES**

**CASE 1**

A 2-year-old girl with a family history of ODDD in her father, paternal grandmother, and paternal aunt was seen with facial, nasal, dental, and hair abnormalities typical of this condition. She also had characteristic digital anomalies consisting of bilateral clinodactyly. Her visual acuity was estimated at 20/170 using Teller acuity cards. Bilateral microcornea and pupillary membrane remnants were present on examination. Her intraocular pressure (IOP) was normal in both eyes. She also had an accommodative esotropia. Dilated fundus examination revealed diffuse hypopigmentation, most notable in the peripapillary and macular areas and associated with linear pigment mottling (Figure 1). A distinct foveal reflex was absent in both eyes (Figure 2).

Subsequent examination under anesthesia at age 3 years revealed IOPs of 43 mm Hg in the right eye and 39 mm Hg in the left eye. There were circumferential iris vessels that were close together and ran into the angle. Lenses were clear in both eyes. She was placed on a combination of pressure-lowering topical medications that was effective in controlling the IOP consistently below 30 mm Hg in both eyes. Visual acuity measurements using Allen cards improved to 20/60 OD, but visual acuity remained at 20/200 OS. Patching of the right eye was initiated to treat possible amblyopia in the left eye. Follow-up examinations revealed deep anterior chambers with iridocorneal and iridolenticular synechiae.

Approximately 4 years following the initiation of topical glaucoma management, the patient's IOP became uncontrolled, despite maximum topical medication. At age 6 years, she underwent trabeculectomy in the left eye with intraoperative mitomycin C therapy, which led to acceptable control of IOP. Approximately 1 year later, iris bulging was identified on slitlamp examination in the left eye. To elucidate the nature of this finding, ultrasonographic biomicroscopy was performed and revealed iridociliary cysts that involved the total circumference of the iris in the unoperated right eye and were present at the 7-o’clock and 9-o’clock positions in the left eye (Figure 2). The IOP in the left eye again became elevated, despite topical medications, and the patient underwent a pars plana lensectomy and vitrectomy with glaucoma shunt valve implant. The patient’s current visual

![Figure 1. Case 1. Anomalous right optic nerve head (A) and dysplastic posterior fundus (B).](image1)

![Figure 2. Case 1. Ultrasonographic biomicroscopy reveals iridociliary cysts of the right (A) and left (B) eyes.](image2)
acuity is 20/100 OD and 20/200 OS, and her IOP remains controlled.

Full sequencing of the GJA1 gene in a Clinical Laboratory Improvement Act–certified commercial laboratory revealed a novel heterozygous in-frame deletion, Nt120delGGTTGAGTCAGC, in the open reading frame of exon 2, leading to the elimination of the amino acids valine, glutamic acid, serine, and alanine in the first transmembrane domain of the protein in positions 41, 42, 43, and 44, respectively. This test has a clinical sensitivity of 99% and an analytic sensitivity of at least 97% accuracy for the nucleotides evaluated. Although the patient’s father, paternal grandmother, and paternal aunt were known to have ODDD based on clinical examination, they did not agree to molecular testing.

CASE 2

A 13-year-old girl was seen with an established clinical diagnosis of ODDD and had many of its typical features, including hypoplastic ala nasae micrognathia, dental enamel hypoplasia, thin and sparse hair, conductive hearing loss, mild peripheral pulmonary stenosis (spontaneously resolved), bilateral mild syndactyly of the fourth and fifth digits without bone fusion (repaired surgically), and fifth-digit clinodactyly. She had had strabismus since age 2 years, with amblyopia treated with patching. She was referred for the management of elevated IOP.

On initial examination, her Snellen visual acuity was 20/20 OD and 20/50 OS. She was anisometropic, with mild hyperopia in the right eye and myopic astigmatism in the left eye. Examination was remarkable for bilateral microcornea of 9 mm in both eyes. Her IOP at the initial visit was 34 mm Hg in the right eye and 33 mm Hg in the left eye, with corneal thicknesses of 665 and 646 µm, respectively. Dilated fundus examination revealed nasally dragged and tilted dysplastic discs in both eyes, as well as diffuse blood vessel tortuosity, prominent choroidal vessels, and poorly developed retinal pigment epithelium (RPE) (Figure 3). She was initially treated using topical medications but eventually underwent a trabeculectomy with intraoperative mitomycin C therapy in the right eye at age 14 years. Two years later, she required the same surgical procedure in the left eye. She has since maintained normal IOP in both eyes for the last 2 years. Slitlamp examination and ultrasonographic biomicroscopy failed to identify any ciliary body or iris cysts.

Mutation analysis of the GJA1 gene revealed a heterozygous missense mutation Nt31C>T, leading to the substitution of a leucine for a phenylalanine at position 11 in the first intracellular domain of Cx43. Although her family members did not undergo molecular testing, there was no clinical evidence of a familial history of ODDD, and this mutation was considered de novo. In addition, this Nt31C>T missense mutation has been previously described in a patient with dissimilar ocular findings.

COMMENT

Glaucoma is the most common ocular complication of ODDD. The mechanisms are varied but usually relate to anterior segment malformations that range from microcornea to iridocorneal angle dysgenesis. Patients may be seen with infantile glaucoma or with IOP elevation as adults. Our patients developed childhood glaucoma in the setting of a small anterior segment. In addition, there was evidence of anterior segment dysgenesis in patient 1. Both patients required surgical interventions to control IOP.

Optic nerve and retinal dysplasia had not been emphasized as ocular manifestations of autosomal dominant ODDD. A recessive form of the disease probably exists, and patients with recessive ODDD seem to have more severe ocular findings, including microphthalmia, persistent hyperplastic primary vitreous, and anterior segment malformations. Patient 1 had foveal hypoplasia and diffuse RPE hypopigmentation, as well as dysplastic optic nerve heads. The appearance of the optic nerve heads was even more unusual in patient 2, with tilting and nasal dragging of the blood vessels. Patient 1 developed ciliary body cysts in both eyes, which we believe are due to weakened and abnormal cellular adhesions between the ciliary body pigmented and nonpigmented epithelium as...
a result of the mutated Cx43 protein and poor cellular adhesions.

The distribution of Cx43 has been widely studied in human and animal tissues. It is found in human corneal basal epithelial cells and corneal anterior stroma.9-6 Cx43 is also expressed in chick and rat lens epithelial cells.9,10 Furthermore, it localizes between retinal Müller cells in goldfish and mud puppies, with a higher density near the outer limiting membrane,11 as well as between RPE cells in goldfish, mud puppy, and rat.11 Within mice, Cx43 has been identified in the iris, within the RPE, in the corneal epithelium and endothelium, and at the junction of ciliary body pigmented epithelium and nonpigmented epithelium.12-14

In patient 1, the in-frame deletion affects a phylogenetically fully conserved domain and is likely to be a disease-causing mutation. In these transmembrane domains, mutations occurring in polar amino acids, such as serine and glutamic acid in this case, are often associated with protein malfunction, especially compared with similar mutations in soluble proteins. Three other patients carrying mutations G22E,11 K23T,13 and A40V,1 all of which are also seen in the first transmembrane domain, had confirmed ODDD.

Our hypothesis about the origin of the iridociliary cysts in the ciliary body region is a weakness in the adhesion of the pigmented epithelium and the nonpigmented epithelium as a result of the Cx43 in-frame deletion, similar to the iridociliary cysts observed by Calera et al14 in a targeted deletion of Cx43 in mice; however, a complete characterization of all the connexins in the iris has yet to be performed. Therefore, we can only speculate that the iris splitting between its posterior pigmented epithelium and its myoepithelium is also due to the mutated Cx43, which is likely because the nonpigmented epithelium and the anterior pigmented epithelium, respectively, share the same embryological origin.15

Patient 2 was seen with bilateral dysplastic optic discs with nasally dragged and tortuous retinal vessels, as well as poorly pigmented RPE that revealed the choroidal vessels. These findings are uncommon features in ODDD. Notably, the same heterozygous missense mutation N31C>T identified in this patient was reported by Jamsheer et al3 in a patient with a different ocular phenotype (small pale optic discs). This variation in phenotype emphasizes the clinical heterogeneity of the disease even in the presence of an identical mutation, although in both phenotypes, the optic nerve is involved. Patient 1 also had evidence of retinal dysplasia with foveal hypoplasia, anomalous optic nerve heads, and linear areas of RPE, which we attribute to poor development of the RPE in the foveal region.

Both patients had smaller ocular structures (microphthalmia and microcornea in patient 1 and microcornea in patient 2), which is not surprising because these features have been previously described in patients with ODDD.3 The degree of microcornea and microphthalmia was more severe in patient 1. It is also notable that only patient 1 had iridociliary cysts, which could be a manifestation of a more severe phenotype.

The clinical significance of this study relates to the importance of the first transmembrane domain of Cx43, especially its behavior when mutated by the deletion reported herein, which could cause a particular iridociliary phenotype (as in patient 1). The ocular phenotype of ODDD is variable, with a common occurrence of glaucoma. Retinal and optic nerve dysplasia might be more prevalent than previously appreciated and may be associated with reduced vision. We recommend that special attention should be paid to the occurrence of iridociliary cysts in patients with ODDD. Their presence may exacerbate glaucoma or complicate its management.

Submitted for Publication: June 24, 2010; final revision received July 24, 2010; accepted August 2, 2010.

Correspondence: Elias I. Traboulsi, MD, Cole Eye Institute, Cleveland Clinic, Mail Code i32, 9500 Euclid Ave, Cleveland, OH 44195 (traboue@ccf.org).

Financial Disclosure: None reported.