Case Report

Optic Nerve Aplasia: Case Report and Literature Review

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Abstract

Purpose: To report three cases of optic nerve aplasia (ONA).
Case Report: Herein three subjects with ONA are described, two subjects had unilateral involvement. In one of these cases, the fellow eye had an associated persistent hyperplastic primary vitreous (PHPV). The third patient had bilateral ONA with multiple intracranial anomalies. Previous reports are reviewed and reported findings are summarized. Orbital and brain magnetic resonance imaging (MRI) were normal in two of our cases and loss of corpus callosum in the third case. Narrow optic nerve was observed on the right side and normal appearance in other two patients.
Conclusion: The diagnosis of optic nerve abnormalities in children requires a thorough ophthalmic examination and proper ancillary testing. Although MRI is valuable in the diagnosis of associated central nervous system anomalies, the optic nerve may appear in normal size and course on MRI images and thus one may not be able to diagnose ONA in eyes with opaque media.

Keywords: Central Nervous System Anomaly; Optic Nerve Anomaly; Optic Nerve Aplasia

J Ophthalmic Vis Res 2015; 10 (2): 187-192.

INTRODUCTION

Optic nerve aplasia (ONA) is a rare developmental anomaly characterized by congenital absence of the optic nerve, retinal blood vessels and retinal ganglion cells, without any gender or racial predilection.[1-3] ONA may be an isolated finding or associated with other congenital ocular and non-ocular abnormalities. It is characterized by no light perception (NLP) vision together with a relative afferent pupillary defect (RAPD). It seems that ONA falls within a malformation complex which is fundamentally distinct from optic nerve hypoplasia, as evidenced by its tendency to occur unilaterally and its frequent association with microphthalmos and other malformations which are confined to the involved eye.[3,4]

Unilateral ONA is generally associated with otherwise normal brain development, while bilateral ONA is usually accompanied by other central nervous system (CNS) abnormalities.[4]

Herein, we report three cases of ONA who were referred to Farabi Eye Hospital, Tehran, Iran, and describe their associated findings. Previous reports on ONA have also been summarized.

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Received: 03-05-2013 Accepted: 30-06-2014

Access this article online

Quick Response Code:

Website: www.jovr.org

DOI: 10.4103/2008-322X.163779

How to cite this article: Ghassemi F, Bazvand F, Hosseini SS, Karkhaneh R, Ebrahimiadib N, Shekarchi B. Optic nerve aplasia: Case report and literature review. J Ophthalmic Vis Res 2015;10:187-92.

CASE REPORTS

Case 1

An 18-month-old boy born from non-consanguinous parents, who was full-term at birth and had uncomplicated delivery and a normal neonatal period, presented with bilateral ptosis (margin reflex distance = 1 mm) together with congenital right esotropia and hypertropia [Figure 1].

Family history was negative for ocular abnormalities. The patient had NLP in the right eye but a normal response to light was present in the left eye. Cycloplegic refraction was −13.00 sphere and +1.5–0.75 × 70, in the right and left eyes respectively. Slit lamp examination showed microcornea (9.0 mm × 7.5 mm) and a persistent pupillary membrane; fundus examination revealed absence of the right optic nerve head and central retinal vessels, and a large chorioretinal coloboma with rudimentary retinal vessels originating from the choroid at the margin of the coloboma with localized hemorrhage in the retina [Figure 1]. Intraocular pressures were normal in both eyes. No pathologic findings were documented in the fellow eye. There was no associated systemic disease. Orbital and brain MRI was normal, and a narrow optic nerve was observed on the right side [Figure 1]. Fluorescein angiography (FA) showed bilateral choroidal flush, and hypofluorescent presumed optic disc and macula. Electroretinogram (ERG) was flat in the same eye.

Case 2

The patient was a 6-month-old boy, the first child of non-consanguinous parents, referred to our center because of low vision. He was the result of normal pregnancy and had an uneventful neonatal period. The anterior segment was unremarkable and fundus examination showed no optic nerve head with an unvascularized retina in the left eye [Figure 2]. Examination of the right eye revealed diffuse corneal opacity, flat anterior chamber and a fibrovascular strand on B-scan echography, compatible with persistent hyperplastic primary vitreous (PHPV). FA showed choroidal flush and a hypofluorescent presumed optic disc and macular area. ERG responses were flat in both eyes.

Case 3

The patient was a 9-month-old boy referred with wandering eyes. Anterior segment and vitreous examination of the right eye were unremakable. Fundus examination revealed optic nerves aplasia in both eyes with no retinal vessels [Figure 3]. MRI showed agenesis of the corpus callosum together with lesions in the thalamus and chiasm. Orbital MRI revealed normal appearing ONs in the orbit attached to the globe on both sides. The ERG was flat in both eyes. His sister had a history of blindness due to bilateral retinal nonattachment.

DISCUSSION

Optic nerve aplasia is a non-hereditary malformation of the optic nerve of controversial etiology. Alqahtani reviewed 27 cases of ONA reported from 1977 to 1998.[2,3,5,6-11] In the current review, previous reports have been updated [Table 1].[12-20] According to Scheie and Adler before 1976, there were six true cases of ONA.[21]

Thus far, 38 cases of ONA have been reported in the literature of which 30 (81.6%) cases were

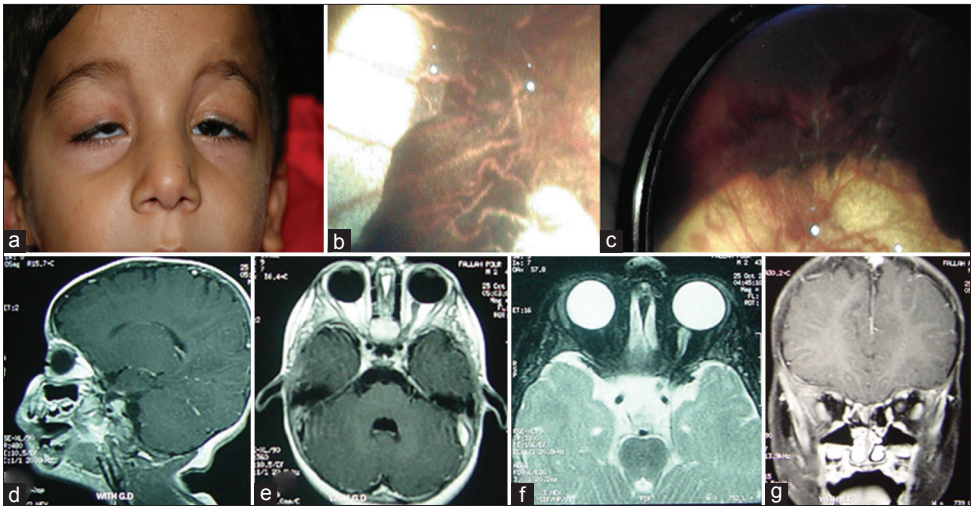

Figure 1. Case 1 – (a) bilateral ptosis, microphthalmia and strabismus in the right eye; (b) fundus photograph of the right eye shows a large chorioretinal coloboma and no retinal vessels and optic nerve head; (c) the superotemporal border of coloboma in the same eye shows a vascular tuft originating from the choroidal vessels. The left eye had normal fundus. (d-g) MRI shows a narrow stalk representing the presumed right optic nerve in the orbit but no other central nervous system anomaly is present. MRI, magnetic resonance imaging

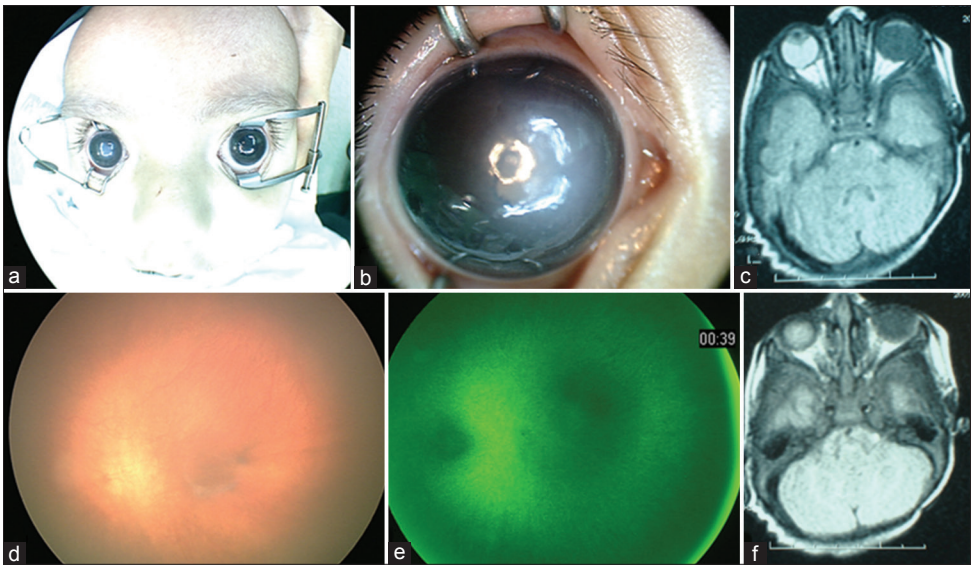

Figure 2. Case 2 – (a and b) corneal opacity, pupillary synechiae and cataract precluding fundus examination in right eye; (c) MRI shows no optic nerve thinness or absence in the orbit of both eyes; (d) fundus photograph (retcam image) of the left eye shows an absence of optic nerve head and retinal vessels; (e) fluorescein angiography confirms findings described in D. The presumed optic nerve head area and macula revealed hypofluorescence.The long ciliary nerve is extended more posteriorly; (f) another section of the axial MRI shows nearly normal optic nerve course and diameter on both sides. MRI, magnetic resonance imaging

Table 1. Updated review of literature on ONA

Author	Date of report	Number of cases	Laterality	Other congenital anomalies	Diagnosis	Clinical features
Weiter et al	1977	13	Unilateral	Absent	Aplasia	Absent disc, vessels, ganglion cells
Hotchkiss and Green	1979	3	Unilateral 1 absent 2 present	Aplasia Aplasia	Aplasia	Absent disc, vessels, ganglion cells
Ginsberg	1980	1	Unilateral	Present	Aplasia	Absent disc, vessels, ganglion cells
Margo	1992	1	Unilateral	Absent	Aplasia	Absent disc, vessels, ganglion cells, normal papillary reflex
Blanco	1992	1	Unilateral	Absent	Aplasia	Absent disc, vessels
Howard	1993	1	Unilateral	Absent	Aplasia	Absent disc, vessels
Recapero	1994	1	Unilateral	Absent	Aplasia	Absent disc, vessels
Lee	1996	2	1 unilateral 1 bilateral	Absent	Aplasia	Absent disc, vessels, absent optic nerve on CT
Chat	2002	1	Unilateral	Absent	Aplasia	Absent disc, vessels, ganglion cells, nerve fiber layers
Mosin	2004	1	Bilateral	Absent	Aplasia	
Brodsky	2004	1	Bilateral	Absent	Aplasia	Absent disc, vessels, CNS anomalies
Sanjari	2006	1	Bilateral	Absent	Aplasia	Absent of CNS anomalies
Graafe	2007	1	Unilateral	Absent	Aplasia	Present retinal dysplasia and retrolental retinal detachment
Alqahtani	2008	1	Unilateral	Present	Aplasia	Absent disc, vessels, ganglion cells
Caputo	2009	1	Unilateral	Absent	Aplasia	absent disc, vessels
Aziz	2009	1	Unilateral	Present	Aplasia	Bilateral iris coloboma, chorioretinal coloboma
Floyd	2010	1	Unilateral	Absent	Aplasia	Present glaucoma
Meire	2011	3	2 bilateral 1 unilateral	Absent	Aplasia	Absent disc, vessels
Ghassemi	2012	3	2unilateral 1 bilateral	2 absent 1 present	Aplasia	Absent disc, vessels, coloboma PHPV, absent disc, vessels Absent disc, vessels

CT, computed tomography; CNS, central nervous system; PHPV, persistent hyperplastic primary vitreous; ONA, optic nerve aplasia

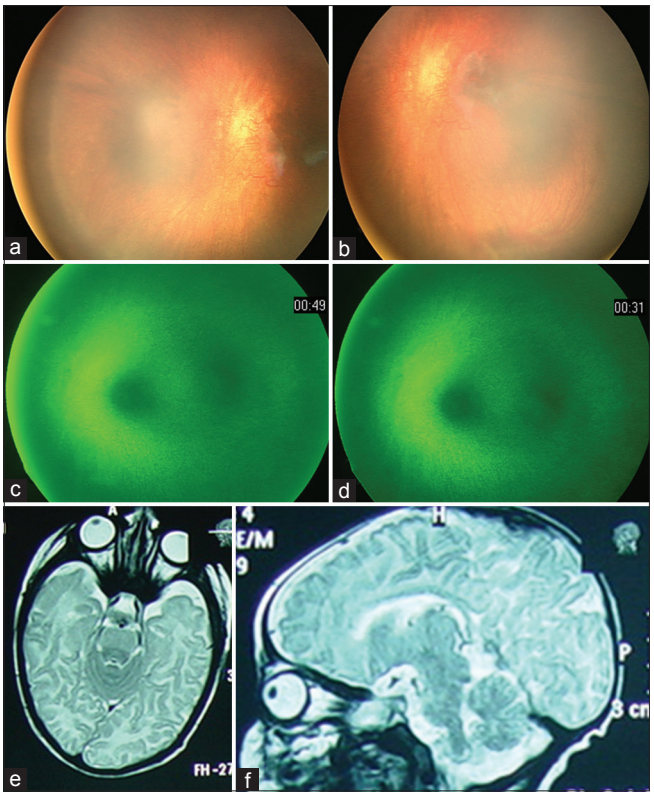

Figure 3. Case 3 – (a and b) fundus photograph of the right and left eyes, respectively. The long ciliary nerve is extended more posteriorly; (c and d) fluorescein angiography of both eyes shows no patent retinal vessels but active fluorescence at the choroid level. The optic nerve area and macular areas have hypofluorescence making the differentiation between these two areas difficult; (e and f) MRI on both sides shows normal appearance of the optic nerve inside the orbits. MRI, magnetic resonance imaging

unilateral [Table 1]. The incidence of ONA could be underestimated because it has never been studied in microphthalmic eyes. Fundus examination is not possible in some severely microphthalmic eyes with an opaque cornea as in our second case with media opacity and cataract. This illustrates that ONA may remain under-diagnosed in severely microphthalmic eyes or those with severe media opacities precluding fundus examination. MRI in microphthalmos is recommended to exclude ONA;[22] however, considering the experience in our cases, normal size and course of the ONs do not guarantee the presence of the optic nerve head in fundus.

Signs and Symptoms

Vision is no light perception (NLP) with no direct or consensual pupillary response to light and a positive RAPD. Reported anterior segment abnormalities with ONA included anterior segment dysgenesis, microphthalmos, cataract, sclerocornea, microcornea, hypoplasia of the corneal stroma, corneal edema independent to intraocular pressure or due to glaucoma, microphakia, persistent tunica vasculosa lentis and iris anomalies (hypoplasia, coloboma or aniridia) and absence of the pars plicata.[5-7,12,14,16,22-24] Our first case had peripheral coloboma with ectopic rudimentary vascularization of nearby retina from the border the coloboma.

Glaucoma, ptosis and esotropia have rarely been documented.[5-7,12,14,16,22-24] The vitreous is usually clear, but PHPV may co-exist.[5] In our second case, one eye had anterior segment dysgenesis with corneal opacity and PHPV. A life-long risk for choroidal neovascularization exists which has been well documented by Pieramici et al[25]

Pathology

Absence of ganglion cells, optic nerve fibers and retinal vessels in eyes with ONA have been described before.[5,12,13,26-31] Other reported abnormalities include the presence of retinal pigment epithelium over the area of the optic disc, remnants of the dural sheath, rudimentary retinal vessels entering the posterior pole in a chaotic manner,[2,27,32] retinal hypoplasia, rosette formation in the retina and hypoplasia of the ciliary body.[5,33] The inner layers of the retina were more markedly hypoplastic than the outer layers and the nerve fiber layer was extremely attenuated and scarcely recognizable resulting in reduced volume of the ipsilateral chiasma and optic tract without any degenerative or reactive changes in these areas.[33]

Embryology and Pathogenesis

The pathogenesis of ONA remains unknown, however a number of theories have been proposed. The optic nerve develops from the optic stalk, the original connection between the optic vesicle and the forebrain. Any problem in formation of retinal ganglion cell (RGC) axons or their guidance, exemplified by deranged Netrin and Eph/ephrin molecule formation as guidance molecules, may seriously impact the development of optic nerve.[34-40]

The choroidal vasculature appears to be normal in ONA. The absence of retinal vessels and lacunar retinal defects in the ONA suggest defective retinal development and failure of retinal angiogenesis in the 3rd–4th months of gestation may contribute to secondary degeneration of retinal ganglion cells.[34] ONA has been attributed to a malformed embryonal fissure, failure of the hyaloid system to enter the embryonal fissure, or agenesis of retinal ganglion cells.[7,32,33]

Scheie and Adler[21] suggested that ONA might be due to failure of mesodermal elements in the development of connective tissue and hyaloid vessels. On the other hand, Weiter et al[2] did not believe Scheie's idea as the dural sheath structured from these mesodermal tissue was present in the majority of eyes, consistent with findings in our cases. Other authors, explaining cases of ONA with colobomas, advocated an anomalous invagination

of the optic vesicle, which may induce misdirection of ganglion cell axons.[2,15] Because of the complicated nature of human retinas compared with the studied animals, multiple factors may be involved in the optic nerve maldevelopment or aplasia.

Genetics

The information regarding the genetic basis in ONA is limited. Mutations in PAX6 and OTX2 have been documented.[12,41] Meire et al[12] reported a form of non-syndromic ONA with autosomal-dominant pattern and incomplete penetrance due to deletion of two genes including CYP26A1 and CYP26C1, encoding retinoic acid degrading enzymes.[12]

Systemic Anomalies

Unilateral ONA is generally associated with normal brain development, while most bilateral cases have CNS derangement.[14] The CNS involvement in bilateral ONA includes congenital hypopituitarism and posterior pituitary ectopia,[14] hydranencephaly, meningoencephalocele, and septo-optic dysplasia.[14,42,43] ONA and its chorioretinal lacuna can also overlap with the autosomal-dominant microcephaly-lymphedema-chorioretinal dysplasia syndrome.[44] In the present study, comparable findings including corpus callosum agenesis with lesions in the thalamus and chiasma in bilateral case were observed, in contrast to unilateral subjects.

Some cardiovascular, gastrointestinal and vertebral anomalies have been reported with ONA.[5]

The present review showed that out of all reported ONA cases, 15. 8% were associated with other congenital anomalies. Congenital anomalies were found in 16. 2% and 14.3% of subjects with unilateral and bilateral ONA, respectively. According to these findings bilateral involvement does not seem to reflect a great risk for systemic and central nervous system anomalies.

In conclusion, the diagnosis of optic nerve abnormalities in children requires a thorough ophthalmic examination and proper ancillary testing. Neuroimaging such as MRI may be of some diagnostic value for documenting ONA and associated conditions, although normal orbital optic nerve diameter could not rule out optic nerve aplasia. A comprehensive systemic workup for ruling out the associated hypopituitarism and other systemic anomalies is indicated particularly in bilateral ONA cases.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

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