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.
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 macular area. ERG responses were flat in both eyes.

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 unremarkable. 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...
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   | 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   | Absent disc, vessels                                                             |
| 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 unilaterial | 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 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
Optic Nerve Aplasia; Ghassemi et al

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 dysgenensis, microphthalmos, cataract, sclerocornea, microcornea, hypoplasia of the corneal stroma, corneal edema independent to intraocular pressure or due to glaucoma, microphakia, persistent tunica vasculosa lenti 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.[7,12,33]

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[31] 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 colobomases, advocated an anomalous invagination

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
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.\[15\]

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.

**REFERENCES**

1. Little LE, Whitmore PV, Wells TW Jr. Aplasia of the optic nerve. J Pediatr Ophthalmol 1976;13:84-88.
2. Weiter JJ, McLean IW, Zimmerman LE. Aplasia of the optic nerve and disk. Am J Ophthalmol 1977;83:569-576.
3. Hotchkiss ML, Green WR. Optic nerve aplasia and hypoplasia. J Pediatr Ophthalmol Strabismus 1979;16:225-240.
4. Brodsky MC, Baker RS, Hamed LM. Congenital optic disc anomalies. In: Pediatric Neuro-Ophthalmology. New York: Springer-Verlag New York Inc.; 1996. p. 42-75.
5. Alqahtani J. Optic nerve aplasia: A case report and literature review. J Pediatr Neurosci 2008;3:150-153.
6. Ginsberg J, Bove KE, Cuesta MG. Aplasia of the optic nerve with aniridia. Ann Ophthalmol 1980;12:433-439.
7. Margo CE, Hamed LM, Fang E, Dawson WW. Optic nerve aplasia. Arch Ophthalmol 1992;110:1610-1613.
8. Blanco R, Salvador F, Galan A, Gil-Gibernau JJ. Aplasia of the optic nerve: Report of three cases. J Pediatr Ophthalmol Strabismus 1992;29:228-231.
9. Howard MA, Thompson JT, Howard RO. Aplasia of the optic nerve. Trans Am Ophthalmol Soc 1993;91:267-276.
10. Recupero SM, Lepore GF, Plateroti R, Abdolrahimzadeh S. Optic nerve aplasia associated with macular ‘atypical coloboma’. Acta Ophthalmol (Copenh) 1994;72:678-770.
11. Lee BL, Bateman JB, Schwartz SD. Posterior segment neovascularization associated with optic nerve aplasia. Am J Ophthalmol 1996;122:131-133.
12. Meire F, Delpierre I, Brachet C, Roulez F, Van Nechel C, Depasse F, et al. Nonsyndromic bilateral and unilateral optic nerve aplasia: First familial occurrence and potential implication of CYP26A1 and CYP26C1 genes. Mol Vis 2011;17:2072-2079.
13. Caputo R, Sodi A, Menchini U. Unilateral optic nerve aplasia associated with rudimentary retinal vasculature. Int Ophthalmol 2009;29:517-519.
14. Brodsky MC, Arendes SP, Fowlkes JL, Sundin OH. Optic nerve aplasia in an infant with congenital hypopituitarism and posterior pituitary ectopia. Arch Ophthalmol 2004;122:125-126.
15. Sanjari MS, Ghasemi Falavarjani K, Parvaresh MM, Kharazi HH, Kashkooli MB. Aplasia of the optic nerve and chiasm, and tracts in an otherwise healthy infant. Br J Ophthalmol 2006;90:513-514.
16. Floyd MS, Kwon YH, Shah S, Benson C, Longmuir SQ. Unilateral congenital glaucoma in a child with optic nerve aplasia. J AAPOS 2011;15:200-202.
17. Chat L, Hertz-Pannier L, Roche O, Boddart N, Baraton J, Brunelle F. Value of MRI in the diagnosis of unilateral optic nerve aplasia: A case report. J Radiol 2002;83(12 Pt 1):1853-1855.
18. Mosin IM, Vasil’eva O, Pykov MI, Shuleshko OV, Sheinov NG. Isolated aplasia of the optic nerve. Vestn Ophthalmol 2004;120:47-51.
19. de Graaf P, van der Valk P, Moll AC, Imhof SM, Schouten-van Meeteren AY, Castelijns JA. Retinal dysplasia mimicking intracocular tumor: MR imaging findings with histopathologic correlation. AJNR Am J Neuroradiol 2007;28:1731-1733.
20. Aziz HA, Sisk RA, Berrocal AM, Murray TG. Optic nerve aplasia in Aicardi syndrome. J Pediatr Ophthalmol Strabismus 2010;47:e3-e4.
21. Scheie HG, Adler FH. Aplasia of the optic nerve. Arch Ophthalmol 1941;26:61-70.
22. Meire FM. Optic nerve hypoplasia. Ophthalmolology 1998;105:4-5.
23. Taylor D. Optic nerve axons: Life and death before birth. Eye (Lond) 2005;19:499-527.
24. Margo CE, Hamed LM, Fang E, Dawson WW. Optic nerve aplasia. Arch Ophthalmol 1992;110:1610-1613.
25. Pieramici DJ, Gonzalez C, Raja SC. Choroidal neovascularization associated with aplasia of the optic nerve. Am J Ophthalmol 2001;132:439-440.
26. Hackenbruch Y, Meerhoff E, Besio R, Cardoso H. Familial bilateral optic nerve hypoplasia. *Am J Ophthalmol* 1975;79:314-20.

27. Curtis E, Margo L, Latif M, Hamed; Ervin Fang; William W. Dawson. Optic Nerve Aplasia. *Arch Ophthalmol* 1992;110:1610-1613.

28. Caputo R, Sodi A, Menchini U. Unilateral optic nerve aplasia associated with rudimental retinal vasculature. *Int Ophthalmol* 2009;29:517-9.

29. Hackenbruch Y, Meerhoff E, Besio R, Cardoso H. Familial bilateral optic nerve hypoplasia. *Am J Ophthalmol* 1975;79:314‑320.

30. Margo CE, Hamed LM, Fang E, Dawson WW. Optic nerve aplasia. *Arch Ophthalmol* 1992;110:1610-1613.

31. Caputo R, Sodi A, Menchini U. Unilateral optic nerve aplasia associated with rudimental retinal vasculature. *Int Ophthalmol* 2009;29:517-519.

32. Mann I. The Development of the Human Eye. New York: Grune and Stratton, Inc.; 1964. p. 1-221.

33. Yanoff M, Rorke LB, Allman MI. Bilateral optic system aplasia with relatively normal eye. *Arch Ophthalmol* 1977;83:569-576.

34. Jakobiec F, editor. Prenatal development of the eye and its adnexae. In: Ocular Anatomy, Embryology and Teratology. Ch. 2. Philadelphia: Harper and Row; 1982. p. 11-96.

35. Lauderdale JD, Davis NM, Kuwada JY. Axon tracts correlate with netrin-1a expression in the zebrafish embryo. *Mol Cell Neurosci* 1997;9:293-313.

36. de la Torre JR, Höpker VH, Ming GL, Poo MM, Tessier-Lavigne M, Hemmati-Brivanlou A, et al. Turning of retinal growth cones in a netrin-1 gradient mediated by the netrin receptor DCC. *Neuron* 1997;19:1211-1224.

37. Deiner MS, Kennedy TE, Fazeli A, Serafini T, Tessier-Lavigne M, Sretavan DW. Netrin-1 and DCC mediate axon guidance locally at the optic disc: Loss of function leads to optic nerve hypoplasia. *Neuron* 1997;19:575-589.

38. Höpker VH, Shewan D, Tessier-Lavigne M, Poo M, Holt C. Growth-cone attraction to netrin-1 is converted to repulsion by laminin-1. *Nature* 1999;401:69-73.

39. Mann F, Harris WA, Holt CE. New views on retinal axon development: A navigation guide. *Int J Dev Biol* 2004;48:957-964.

40. Shibuya K, Tajima M, Yamate J, Kudow S. Unilateral optic nerve aplasia in two young Slc Wistar rats. *Vet Pathol* 1989;26:518-520.

41. Azuma N, Yamaguchi Y, Handa H, Tadokoro K, Asaka A, Kawase E, et al. Mutations of the PAX6 gene detected in patients with a variety of optic-nerve malformations. *Am J Hum Genet* 2003;72:1565-1570.

42. Guercio JR, Martyn IJ. Congenital malformations of the eye and orbit. *Otolaryngol Clin North Am* 2007;40:113-140, vii.

43. Storm RL, PeBenito R. Bilateral optic nerve aplasia associated with hydranencephaly. *Ann Ophthalmol* 1984;16:988-992.

44. Casteels I, Devriendt K, Van Cleynenbreu gel H, Demaere l P, De Tavernier F, Fryns JP. Autosomal dominant microcephaly – Lymphoedema-chorioretinal dysplasia syndrome. *Br J Ophthalmol* 2001;85:499-500.