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Congenital Cavitary Optic Disc Anomaly and Axenfeld's Anomaly in Wolf-Hirschhorn Syndrome: A Case Report and Review of the Literature

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Abstract

Background—Wolf-Hirschhorn syndrome is a rare genetic syndrome caused by a heterozygous deletion on chromosome 4p16.3 and is characterized by a "Greek warrior helmet" facies, hypotonia, developmental delay, seizures, structural central nervous system defects, intrauterine growth restriction, sketelal anomalies, cardiac defects, abnormal tooth development, and hearing loss. A variety of ocular manifestations may occur in up to 40% of patients.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Materials/methods—We report the genetic testing results, systemic findings, and complete ophthalmlologic examination findings in a patient with Wolf-Hirschhorn syndrome, including external photography, RetCam3 (Clarity Medical Systems, Pleasonton, CA) goniography and fundus photography. We also review the literature on ocular manifestations of Wolf-Hirschhorn syndrome.

Results—Microarray analysis revealed an unbalanced translocation between 4p16.3-15.3 and Xp22.33-p22.2. Systemic findings included “Greek warrior helmet” facies, hypotonia, cleft palate, neonatal tooth eruption, talipes equinovarus, bilateral clinodactyly, clitoromegaly, partial agenesis of the corpus callosum, bilateral renal hypoplasia, and two atrial septal defects. Ocular findings included normal intraocular pressures and corneal diameters, large-angle exotropia, downward slanting of the palpebral fissures, absent eyelid creases, upper and lower eyelid retraction with shortage of the anterior eyelid lamellae, euryblepharon, lagophthalmos with poor Bell’s reflex and exposure keratopathy, hypertelorism, Axenfeld’s anomaly, megalopapillae, and cavitary optic disc anomaly.

Conclusions—We describe the ocular phenotype of a patient with Wolf-Hirschhorn syndrome, including the rare descriptions and photographs of Axenfeld’s anomaly, megalopapilla, and cavitary optic disc anomaly in this condition.

Keywords

Wolf-Hirschhorn syndrome; cavitary optic disc anomaly; megalopapilla; Axenfeld anomaly

Introduction

Wolf-Hirschhorn syndrome is a genetic syndrome characterized by a deletion of chromosome 4p16.3. We describe the ocular phenotype of an affected patient, including the rare descriptions and photographs of Axenfeld’s anomaly, megalopapilla, and cavitary optic disc anomaly in this condition.

Materials and Methods

A complete ophthalmological examination of both eyes, including anterior segment examination, goniography, and dilated fundus examination was performed. Goniography was performed using a RetCam3 (Clarity Medical Systems, Pleasanton, CA). To obtain iridocorneal images, a viscous coupling agent was applied onto the ocular surface and the RetCam3 lens was then placed near the limbus and directed towards the opposite iridocorneal angle.

Results

The ophthalmology service at the University of Illinois at Chicago evaluated dysmorphic features in a 3-day-old female baby born to a 32-year-old mother and 34-year-old father. The child was delivered via Caesarean section at 36 weeks and 6 days estimated gestational age and weighed 1398 grams. Her intrauterine course was complicated by intrauterine growth restriction and prenatal ultrasounds suggestive of cardiac defects. Maternal TORCH titers were negative. The family history was noncontributory.

Systemic examination revealed findings consistent with Wolf-Hirschhorn syndrome, including a “Greek warrior helmet” facies consisting of a high forehead, prominent glabella, hypertelorism, “beaked” nose, micrognathia, short philtrum, and mouth with downturned corners.[1] In addition, the patient was noted to have hypotonia, a broad anterior fontanelle, low-set ears, cleft palate, neonatal tooth eruption, inverted nipples, talipes equinovarus (“clubfoot”), bilateral clinodactyly, clitoromegaly, sacral dimple, and mild anterior displacement of the anus. Magnetic resonance imaging of the brain, renal ultrasonography, and echocardiography demonstrated partial agenesis of the corpus callosum, bilateral renal hypoplasia, and two atrial septal defects.

Ophthalmological examination on the third day of life revealed bilateral reaction to light with normal pupillary reflexes. She had a large-angle, constant exotropia measuring approximately 45 prism diopters. Initial intraocular pressures (IOP) were 11 mmHg OD and 10 mmHg OS and multiple subsequent IOP measurements remained consistently in the low teens. Horizontal corneal diameters were 10mm OU. Axial lengths measured by A-scan ultrasonography were 16.69 mm OD and 17.01 mm OS.

The external ophthalmological examination revealed bilateral downward slanting of the palpebral fissures, bilateral absent eyelid creases, bilateral upper and lower eyelid retraction with shortage of the anterior eyelid lamellae, bilateral euryblepharon, bilateral lagophthalmos with poor Bell’s reflex, and hypertelorism (Figure 1). Anterior segment examination revealed normal-appearing though temporally displaced puncti, meibomian glands, and conjunctiva bilaterally. There appeared to be a thin band of probable circumferential corneal scleralization bilaterally (Figure 2). The corneal epithelium had inferior punctate epithelial erosions bilaterally, consistent with exposure keratopathy from her lagophthalmos. The anterior chamber depth, iris, and lens were unremarkable in both eyes with the exception of a Mittendorf dot OS.

An externally visible posterior embryotoxon was present circumferentially in both eyes (Figure 2). Using RetCam3 goniography, both eyes were found to have prominent iris processes in all visualized portions of each iridocorneal angle (Figure 2). The combination of posterior embryotoxon and prominent iris processes is termed Axenfeld’s anomaly, a rarely described finding in Wolf-Hirschhorn syndrome.

The fundus examination revealed dysplastic optic nerves with enlarged disc diameters, or megalopapillae (Figure 3). The cups were deeply excavated and circumferentially enlarged with narrow neuroretinal rims (cup-to-disc ratio approximately 0.9 OU). The central retinal vessels were not apparent ophthalmoscopically and retinal vessels appeared to enter and leave from the disc periphery.

Microarray analysis using a comparative genomic hybridization and single nucleotide polymorphism (SNP) array revealed an unbalanced translocation between 4p16.3-15.3 (involving the deletion of 20.55 Mb and 387 genes) and Xp22.33-p22.2 (involving the duplication of 16.07 Mb and 186 genes). Several important deleted genes that are hypothesized to be integral to the pathogenesis of Wolf-Hirschhorn syndrome were involved, including WHSC1, NELFA (WHSC2), and LETM1.[2] Chromosomal loci that have reported

associations with Axenfeld-Rieger syndrome or related anterior segment dysgenesis phenotypes were not affected. The constellation of clinical findings and the genetic analysis confirmed the diagnosis of Wolf-Hirschhorn syndrome.

The patient's exposure keratopathy was treated with frequent ocular lubrication. Ultimately, she underwent bilateral eyelid reconstructive surgery with full-thickness post-auricular skin grafts to repair her eyelid retraction and lagophthalmos. Despite the glaucomatous-appearing enlargement and excavation of the optic nerve cup, there were no other signs to suggest the presence of glaucoma in either eye; therefore, IOPs were regularly measured in follow-up examinations and no IOP-lowering intervention was required.

Discussion

Wolf-Hirschhorn syndrome is characterized by a heterozygous gene deletion on chromosome 4p16.3, often as a result of a *de novo* deletion or an unbalanced translocation.[3] It affects an estimated 1/50,000 to 1/20,000 births and has a 2:1 female predilection.[1] In a review of 87 cases of Wolf-Hirschhorn syndrome, the following non-ophthalmic features were noted: "Greek warrior helmet" facies (100%), hypotonia (nearly 100%), developmental delay (100%), seizures (93%), structural central nervous system defects (80%), intrauterine growth restriction (80%), skeletal anomalies (60%), cardiac defects (50%), abnormal tooth development (50%), and hearing loss (40%).[1] In the same study, various ocular manifestations were present in 40% of patients.

Prior studies have demonstrated a range of ocular manifestations in Wolf-Hirschhorn syndrome, including hypertelorism, downslanting palpebral fissures, upper lid coloboma, epicanthal folds, shallow orbits, nasolacrimal drainage system obstruction, ptosis, eyelid hypoplasia, exodeviation, rotary nystagmus, microphthalmos, microcornea, peripheral corneal scleralization, Peters' anomaly, foveal hypoplasia, glaucoma, and colobomas of the choroid, retina, optic nerve, eyelid, or iris.[4–8] This case features the rare description and first photodocumentation of Axenfeld anomaly in Wolf-Hirschhorn syndrome. Few cases of prominent iris processes, posterior embryotoxon, or Rieger anomaly have separately been reported previously in Wolf-Hirschhorn syndrome, suggesting the role of affected genes in anterior segment development.[8,9]

The appearance of the optic nerves in this patient is unusual, and characterized by a large disc diameter (megalopapillae), deep excavation, circumferential enlargement of the cup-to-disc ratio with neuroretinal rim narrowing, and seemingly absent central retinal vessels with vessels located at the edge of the optic discs. The distribution and appearance of the retinal vessels suggest a rarely described "vacant disc" appearance. The vacant disc has been previously described as a normal-sized disc with absent central retinal vessels and an exclusively cilioretinal vascular supply, and may be associated with renal abnormalities (papillorenal syndrome). [10] While this patient had bilateral renal hypoplasia and optic nerves reminiscent of the vacant disc, megalopapilla is not considered to be a feature of the vacant disc. In other cases of Wolf-Hirschhorn syndrome, the appearance of the optic nerve has been variably described as megalopapilla, optic nerve coloboma, morning glory disc anomaly, dysplastic, and glaucomatous.[4,5] We hypothesize that the optic nerve findings in

some prior reports of Wolf-Hirschhorn syndrome may be referring to the same or a similar phenotypic manifestation with differing terminology. For this reason, we have chosen to use a broader term, congenital cavitary optic disc anomaly,[11] to describe the optic nerve appearance because it encompasses features that resemble optic pit, optic nerve coloboma, megalopapilla, vacant disc, and morning glory disc anomaly. The photographs depicted here represent, to our knowledge, the first published photodocumentation of this optic disc appearance in Wolf-Hirschhorn syndrome. We anticipate that these photographs may serve as reference photographs for other patients with Wolf-Hirschhorn syndrome and similar congenital optic nerve findings and may allow for standardized terminology.

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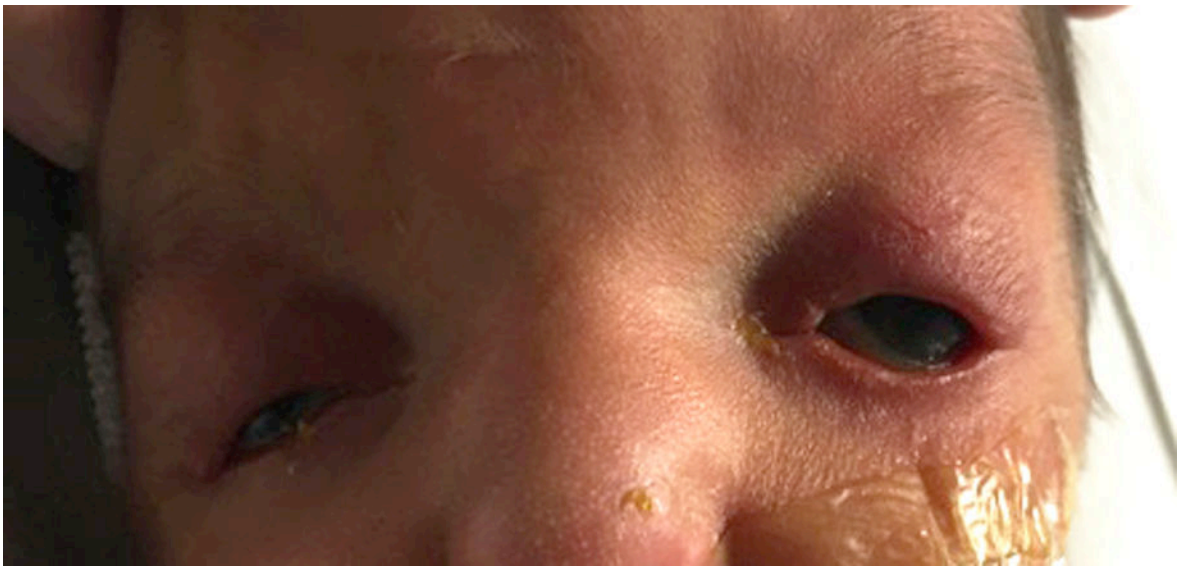

Figure 1.
External photograph showing bilateral downward slanting palpebral fissures, hypertelorism, bilateral lateral upper eyelid colobomas, bilateral congenital blepharoptosis, and bilateral absent eyelid creases.

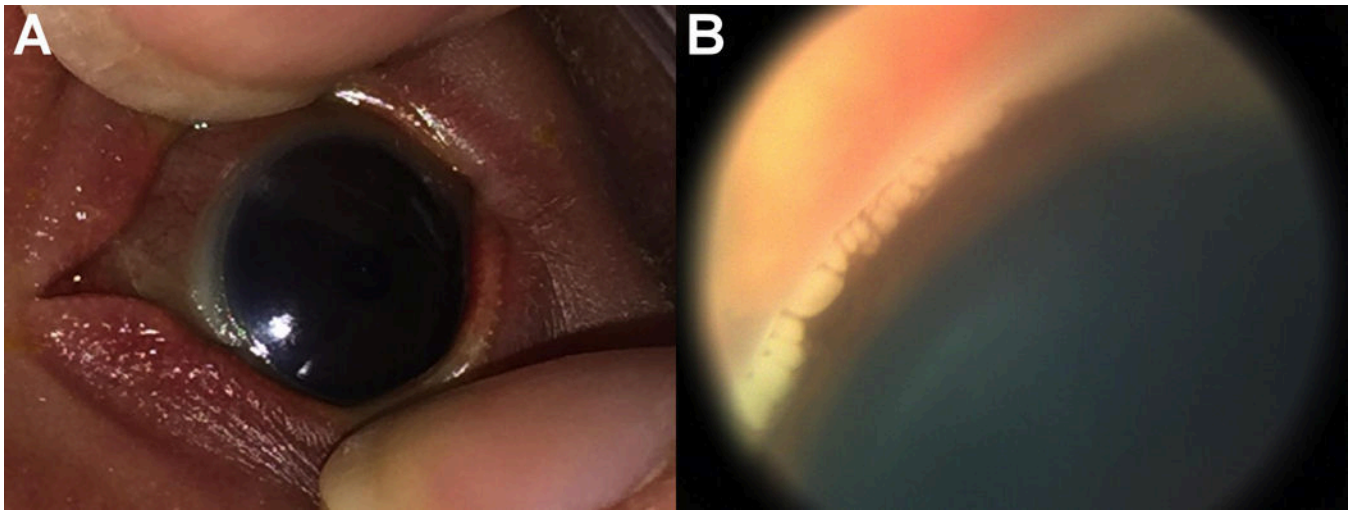

Figure 2.

External photograph (A) showing an externally visible, circumferential posterior embryotoxon. This finding was present bilaterally. RetCam-assisted examination of the iridocorneal angle (B) revealed prominent iris processes that extended across the iridocorneal angle to an anteriorly displaced Schwalbe line (posterior embryotoxon). This finding was present in all visualized quadrants of both eyes.

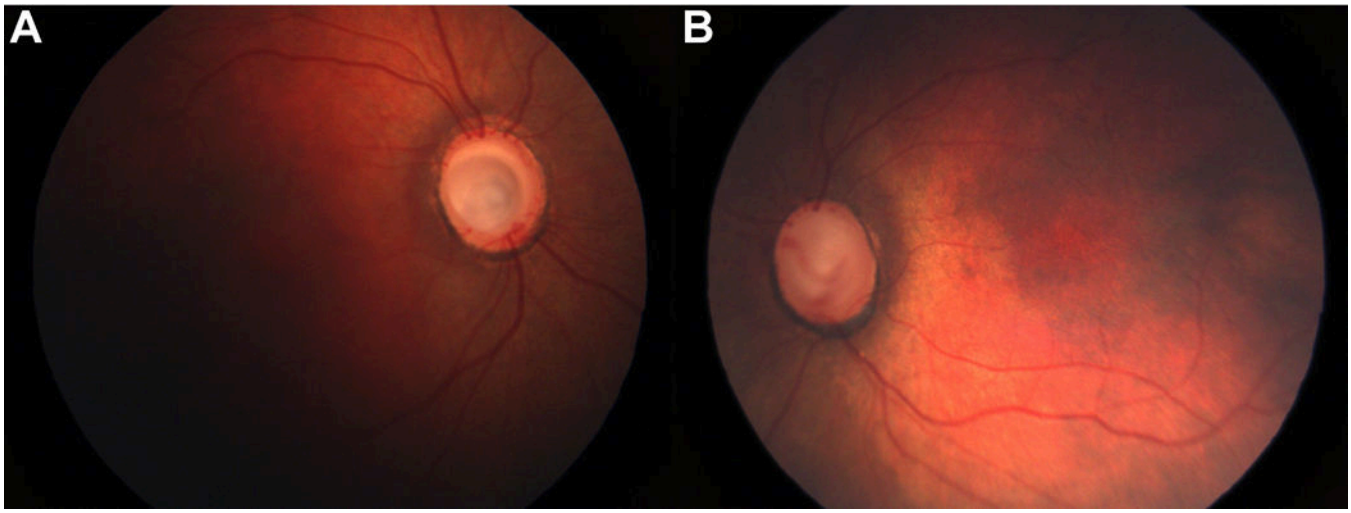

Figure 3.
Fundus photographs of the right (A) and left (B) eyes revealing bilateral megalopapilla and congenital cavitary optic disc anomaly.