Lens Holder Artifact Simulating Glaucomatous Defect in Automated Perimetry

Most automated perimetry artifacts are associated with diffuse abnormalities in the visual field. Occasionally, isolated quadrant defects can be seen.1 We recently encountered a case in which an apparent nerve fiber bundle defect was caused by improper positioning of the lens holder.

Report of a Case. A 36-year-old man was seen in the neuro-ophthalmology clinic with a complaint of a subacute decrease of visual acuity in his right eye of approximately 1 month's duration. He denied any associated eye pain and had no history suggestive of demyelinating disease or similar episodes.

Neuro-ophthalmologic examination demonstrated visual acuity of 20/50 OD and 20/20 OS. There was a mild dyschromatopsia in the right eye and a 0.3-log unit, relative, afferent pupillary defect in the right eye. Automated perimetry (Humphrey Visual Field Analyzer, Program 24-2, Allergan Inc, San Leandro, Calif) showed a mild cecocentral depression in the right eye. The left visual field had a dense scotoma that looked like an arcuate defect emanating inferiorly from the blind spot and disappearing at the vertical midline (Figure 1). A dense scotoma that appeared to be a nasal step was also

Figure 1. Humphrey visual field (24-2) program of subject's asymptomatic left eye. Gray scale and probability plots suggest inferior arcuate defect and inferior nasal step; however, inspection of individual threshold values shows that points in the scotoma were not seen (threshold of 0 dB), while those adjacent to the scotoma had normal values for threshold.

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present. The patient denied any visual symptoms in the left eye and the nerve fiber layer and optic disc showed no abnormalities.

Careful ophthalmic examination of the Humphrey 24-2 visual field of the left eye demonstrated that the involved points were not seen, even with the brightest target, and all adjacent points had a normal threshold. A diagnosis of optic neuritis in the right eye was made, and he was treated conservatively. In the absence of visual symptoms in the left eye, this field was thought to be artifactual, and no further workup was performed.

He returned for follow-up treatment 6 weeks later with marked visual acuity improvement in the right eye and no change in the left. Visual acuity had improved to 20/20 OD and remained 20/15 OS. The dyschromatopsia and pupillary abnormalities had disappeared. A second automated perimetry (Humphrey 24-2) showed a mild, residual, cecocentral depression in the right eye. The left eye’s visual field showed no abnormalities (Figure 2).

Comment. Refractive errors during automated perimetry are corrected by placing a trial lens in a lens holder and centering it in front of the patient’s eye. In our case, the dense nature of the scotoma, combined with the lack of symptoms and spontaneous resolution in the left eye on repeated testing suggested an artifact of testing. Placing the lens holder just right of center instead of centering it would produce a scotoma from the left edge of the lens holder emanating from the blind spot. To test this hypothesis, I attempted to create a similar defect by positioning the lens holder to connect to his own blind spot. A similar inferior arcuate scotoma was produced (Figure 3). A nasal step was not present, but trigonometric calculations show that placing the lens holder 40 mm from the nodal point of the eye would place the right edge of the lens holder at the 27° nasal horizontal when the left edge was at the blind spot. The lens holder can be moved closer to or away from the eye and could easily have been at this distance during our patient’s field.

While it is plausible that an asymptomatic demyelinating optic neuropathy could have caused this visual field, we believe it is unlikely. The patient’s lack of complaints and symptoms, the rapid and complete resolution of the defect, and the depth of the scotoma with no abnormalities at the adjacent points, all argue against a true optic neuropathy. In addition, the defect extends vertically from the blind spot and stops at the vertical midline, unlike the more typical rounded anatomy of a nerve fiber bundle defect. Ophthalmologists should be aware of the importance of center-
I describe a 1-year-old child with blue-gray irides with minimal brown pigment who developed increased iris pigmentation after 5 months of treatment with latanoprost.

Report of a Case. A 13-month-old boy initially was seen on September 25, 1997. The child at birth had a port-wine stain covering the right side of the forehead, eyelids, cheek, left eyebrow, upper eyelid, and part of the right arm and right side of the trunk. These lesions had undergone several dermatologic laser treatments. A magnetic resonance imaging scan showed no intracranial vascular abnormalities. The child had been evaluated for the possibility of glaucoma, and the available hospital medical records showed a maximum intraocular pressure (recorded during general anesthesia for the laser treatments) of 22 mm Hg OD and 19 mm Hg OS. A diagnosis of glaucoma was not made, although a documented myopic shift from −3.5 diopters (D) to −5.5 OD occurred within 1 month (+0.75 D OS).

Ophthalmic examination showed an alert child with mild right hemifacial hypertrophy. A port-wine stain covered the face as described. Vision was poor fixation and following in the right eye and good fixation and following in the left eye, with definite objection to occlusion in the left eye. A penlight examination showed mild buphthalmos in the right eye without corneal clouding or Haab striae; there was no conjunctival or episcleral vascular engorgement or telangiectasia and both irides were identically blue-gray without a darker pupillary ruff, but with small flecks of brown pigment centrally. The fundus examination showed a circumscribed choroidal hemangioma occupying the inferior macula in the right eye without the classic “tomato catsup” appearance of a diffuse choroidal hemangioma. The cup-disc ratio was 0.05 OD (a very tiny declivity around the retinal vessels) and 0 OS The cup-disc ratio showed no intracranial vascular abnormalities.

An ophthalmic examination under anesthesia 1 week later, with intraocular pressure checked by Tonopen (Mentor Ophthalmic Instruments, Norwell, Mass) immedi

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**Increased Iris Pigment in a Child Due to Latanoprost**

Latanoprost is an analog of the prostaglandin dinoprostone tromethamine (PGF2-α) that is effective in treating glaucoma in adults, but increased iris pigmentation has been reported as a novel side effect. Iris specimens removed at surgery revealed increased intracellular melanin accumulation, rather than increased numbers of melanocytes. Patients with patches of brown iris on a blue-gray, green, or yellow background appear most susceptible, and no adult patient with light blue or blue-gray irides has been described with increased iris pigmentation. In the Latanoprost Study Group, only 1 patient with blue-gray eyes and slightly brown pigment has shown a color change (N = 76).

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**Figure 3.** An attempt to reproduce the left eye’s field defect by positioning the left edge of the lens holder in the blind spot. The inferior arcuate defect is nearly identical to that shown in Figure 1. A nasal step could be created by moving the lens holder away from the patient’s eye.

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**Probability Symbols**

- $P<0.05$
- $P<0.02$
- $P<0.01$
- $P<0.001$
- $P<0.0001$

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ately after mask inhalation induction showed multiple readings of 25 to 26 mm Hg OD and 16 to 19 mm Hg OS. Intraocular pressure was rechecked 20 minutes later and was 20 to 21 mm Hg OD and 15 mm Hg OS. A diagnosis of infantile glaucoma OD in association with Sturge-Weber syndrome was made. Treatment was started with 0.5% timolol maleate (Timoptic XE) once daily. Intraocular pressure was checked 3 weeks later with oral sedation done at the office, and was 23 to 25 mm Hg OD and 19 mm Hg OS. Timolol therapy was discontinued and on October 30, 1997, therapy with 0.003% latanoprost every night was started. The family was informed that this was an off-label use with unknown, long-term, side effects, especially about increased iris pigmentation. Latanoprost successfully lowered intraocular pressure from 17 to 22 mm Hg as documented on office examinations with the patient sedated, and the myopic shift stopped. No change in iris pigmentation was noted until April 16, 1998, when the child’s mother stated that she had seen darkening of the right iris during the past several weeks. Because of the excellent therapeutic response, simple medication schedule, and lack of systemic side effects, the family wished to continue treatment with latanoprost and expressed no reservations over a possible further increase in iris anisochromia. The child’s condition was reevaluated May 16, 1998, and the mother reported that the right iris had not darkened further (Figure).

Comment. Infantile and juvenile glaucomas vary in origin and are frustrating to treat. Although no commercially available glaucoma medication is approved for use in pediatric patients, physicians and families are often willing to try off-label use in an effort to avoid glaucoma surgery. Latanoprost has been of particular interest since the free-acid form enters the circulation after transconjunctival absorption and does not cross the blood-brain barrier,2 thus lowering the likelihood of central nervous system side effects, a particular problem with children. Combined with the novel mechanism of action (increased uveoscleral outflow), this has led physicians to try the drug in recalcitrant cases of pediatric glaucoma.

Enyedi et al described 45 eyes in 38 patients with uncontrolled intraocular pressure treated with latanoprost in combination with other medications. Patient age varied from 7 to 179 months (mean age, 78 months); follow-up was from 1 to 10 months (mean age, 4.5 months). Four patients had Sturge-Weber syndrome, 2 of whom were considered to have a clinical response. The 45 eyes were observed for a total of 206 patient-months while receiving latanoprost, and no iris color changes were noted. The distribution of baseline iris color was not given. The authors reported no serious systemic side effects, no cystoid macular edema, and no uveitis.

To my knowledge, this is the first reported case in which a pediatric patient with blue-gray eyes with minimal brown pigment developed iris color change after 5 months of treatment with latanoprost. This corresponds to the time course in adults, most of whom developed increased pigment in the first 6 months of treatment.3 This child also seems to have less baseline brown pigment than published color photographs of affected adults, and lacks the darker, peripupillary ruff typically seen in blue-gray eyes that undergo color change.3,7,8 Although the exact biochemical mechanism by which latanoprost causes increased melanin accumulation in melanocytes is unclear, cessation of the drug in adults seems to stabilize iris color, suggesting that there is no pigmentedary release and no permanent metabolic up-regulation of melanocytes.9 The fact that an iris color change can be induced in a 1-year-old child with minimal brown iris pigment suggests that investigation of age-dependent variables in melanocyte metabolism may provide a clue to the biochemical pathways that are up-regulated by prostaglandin analogs.

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New Retinoblastoma Tumors in Children Undergoing Systemic Chemotherapy

Traditionally, bilateral retinoblastoma has been treated by enucleating the most involved eye and applying external beam radiotherapy to the second eye. More recently, simultaneous bilateral external beam radiotherapy has been shown to be an effective treatment for medium-sized retinoblastomas. However, external beam radiotherapy of pediatric patients with germline mutations predisposing to retinoblastoma development is associated with a 35% risk of secondary neoplasms by 30 years of age and a 90% risk of cosmetic deformity and cataracts.1,2 Therefore, although chemotherapy has been reserved for extraocular extension of retinoblastoma and systemic and central nervous system metastases in the past, there is now increasing interest in treating intraocular retinoblastoma with chemotherapy. Indeed, chemotherapy combined with focal laser therapy and cryotherapy has been shown to be a successful primary treatment for intraocular retinoblastoma.3,4 In this article we report 4 cases in which patients developed new retinoblastoma tumors while being treated with chemotherapy.

Report of Cases. Case 1. A 4-month-old boy was seen with Reese-Ellsworth stage IIIA retinoblastoma in the right eye. Systemic evaluation (including brain computed tomography with and without contrast, bone marrow aspiration, and lumbar puncture) demonstrated no evidence of metastatic tumor and the patient was treated with 9 cycles of vincristine, carboplatin, and etoposide (1 cycle every 3 weeks). The patient underwent an examination under anesthesia every 3 to 4 weeks. After the sixth cycle of chemoreductive therapy, a new tumor was found (Figure 1) and was treated with laser hyperthermia. Four months after the ninth and final cycle of chemotherapy, a new tumor was found and treated with laser hyperthermia.

Case 2. A 2-month-old boy was seen with Reese-Ellsworth stage IVB retinoblastoma in the right eye and Reese-Ellsworth stage IIIA retinoblastoma in the left eye. After computed tomography of the brain with and without contrast, bone marrow aspiration, and lumbar puncture demonstrated no metastatic disease, the patient was treated with 9 cycles of vincristine, carboplatin, and etoposide. Examinations under anesthesia were performed every 3 to 4 weeks. After the fourth cycle of chemotherapy, a new tumor was noted in the left eye and treated with laser hyperthermia. After 7 cycles of chemotherapy, a new tumor was found in the right eye and was treated with laser hyperthermia. Two and 6 months after the ninth cycle of chemotherapy, new tumors in the right eye were treated with cryotherapy. There was no new tumor activity during the next 6 months.

Comment. It is unclear whether the development of new tumors in patients being treated with chemotherapeutic agents is due to chemotherapy alone, the primary stage of the disease, or the effect of systemic chemoreductive therapy. The longer the follow-up, the greater the risk of new tumors.

Case 3. A 7-month-old girl was seen with bilateral retinoblastoma (Reese-Ellsworth stage VB in the right eye and stage VB retinoblastoma in the left eye) and, after computed tomography of the brain with and without contrast, bone marrow aspiration, and lumbar puncture demonstrated no metastatic disease, the patient was treated with 10 cycles of carboplatin, etoposide, and cyclosporine. Examinations under anesthesia were performed every 3 to 4 weeks. After 5 cycles of chemotherapy, a new retinoblastoma tumor was noted in each eye (Figure 2) and was treated with laser hyperthermia. No new tumor activity developed during the subsequent 24 months of follow-up.

Case 4. A 34-month-old girl was seen with Reese-Ellsworth stage II retinoblastoma in the right eye and stage VB retinoblastoma in the left eye. After computed tomography of the brain with and without contrast, bone marrow aspiration, and lumbar puncture demonstrated no metastatic disease, the patient underwent primary enucleation of the left eye and was treated with 9 cycles of vincristine, carboplatin, and etoposide. Examinations under anesthesia were performed every 3 to 4 weeks. After 2 cycles of chemotherapy, a new retinoblastoma tumor was noted in the right eye and treated with cryotherapy. Ongoing follow-up shows no new tumor activity.
therapy results from primary tumor resistance, selection of a resistant tumor cell line, or inadequate chemotherapeutic levels within tumor cells. Small tumors may have little intrinsic vascularity and, therefore, may not receive adequate chemotherapeutic doses. A major concern, of course, is that if chemotherapy for intraocular retinoblastoma facilitates selection of chemoresistant tumor cells, the armamentarium of treatment options for those patients who develop extraocular disease is reduced. Although cyclosporine has been associated with a reversal of chemoresistance in retinoblastoma, one of the patients in our series developed a new retinoblastoma tumor while receiving chemotherapy and cyclosporine.

While it is impossible to prove that the new tumors were not pre-existing tumors overlooked on prior examinations, all children underwent multiple examinations under anesthesia by multiple investigators before the new tumors were found; the likelihood that these tumors were previously overlooked is small. Another possibility is that the new tumors represent subretinal or vitreous seeding. However, subretinal seeding is typically associated with exudative retinal detachment and vitreous seeding is generally associated with noncohesive tumors. In the patients described in this report, new tumors developed in eyes without vitreous seeding on presentation (in case 3, new tumors were noted in both eyes, while vitreous seeding on presentation was observed in only the right eye). The clinical impression of a number of ophthalmologists experienced in examining retinoblastoma patients was that the lesions noted in this series represent new tumor foci that developed in children who were actively being treated for retinoblastoma with systemic chemotherapy.

This series emphasizes the importance of close follow-up of patients on systemic chemotherapy for the treatment of retinoblastoma, since prompt identification of new tumors permits curative focal treatment. Our small sample size does not permit the identification of clinical factors (eg, younger age at diagnosis) that may predispose a patient who is undergoing chemotherapy for retinoblastoma to new tumor development. In addition, since the duration and regimen of chemotherapy employed in our practice varies little among patients, we cannot analyze the potential prognostic implications of these variables. The National Cancer Institute (Bethesda, Md) has funded an international clinical trial to evaluate systemic chemoreductive therapy in the management of patients with large bilateral retinoblastomas. This clinical trial has the potential to determine the incidence of new tumor development and to investigate clinical factors associated with new tumor development in patients undergoing systemic chemotherapy for retinoblastoma.

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Figure 1. View of a fundus of the right eye showing mass formation caused by an allergic reaction to Toxocara cati.

Toxocara cati-Induced Ocular Toxocariasis

Toxocara canis and Toxocara cati are nematode members of the family Ascarididae and known to cause toxocariasis in dogs and cats, as well as ocular toxocariasis in humans. Toxocara canis was first successfully recovered from a human eye in 1950 and has been recognized as a major cause of ocular toxocariasis in humans. We report a case in which T cati was possibly involved in the development of ocular toxocariasis.

Report of a Case. A 38-year-old woman, with a history of keeping cats, complained of decreased visual acuity in her right eye. Corrected visual acuity was 20/200 OD. We found a yellowish, creamy lesion of two-thirds disc diameter in the inferior region of the macula. (Figure 1). Standard enzyme-linked immunosorbent assay (ELISA) using excretory–secretory products of second-stage larvae of T canis showed that antibody production was marginal. Despite this inconclusive result, we suspected ocular toxocariasis. If T cati was involved, antibody titer could be weak owing to an incomplete cross-reactivity between T canis and T cati. We conducted ELISA of the patient’s serum samples using antigens of adult T cati, adult T canis, and second-stage larvae of T canis (Figure 2).

In Figure 2, our case corresponds to patient 2, who showed an extraordinarily high antibody titer against adult T cati as compared with patients 3 and 4. Patients 3 and 4 were diagnosed as having ocular toxocariasis, shown by ELISA using T canis larvae and typical funduscopic features. The patient’s severe cats also provided evidence of ocular toxocariasis possibly caused by T cati. Though we had been unable to detect the presence of ova of
T cati in the soil of cats, an unusually high titer of antibody against T cati prompted us to initiate therapy. Visual acuity in our patient returned to 20/20 OD following corticosteroid treatment.

Comment. Clinical diagnosis of ocular toxocariasis depends on serological testing, and ELISA has both high sensitivity and high specificity. Standard ELISA tests use the antigen prepared from T canis and show a high cross-reactivity between T canis and T cati, that is by no means incomplete. In this case, standard ELISA using T canis revealed that antibody titer was marginal. When using an antigen prepared from T cati, antibody titer was exceptionally high; consequently, we reached to a clinical diagnosis of ocular toxocariasis caused by T cati. Uga et al reported that cats are in closer contact to humans than dogs, underscoring the need to consider T cati in cases of ocular toxocariasis. Ophthalmologists should always be aware that ocular toxocariasis can be caused by T cati and consider conducting serological testing using T cati as a routine examination.

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REFERENCES


