

Lipemia Retinalis in Acquired Immunodeficiency Syndrome Treated With Protease Inhibitors

Report of a Case. A 39-year-old man with human immunodeficiency virus infection developed cytomegalovirus retinitis in the right eye in 1995, necessitating treatment with foscarnet sodium. His CD4 cell count was $0.01 \times 10^9/L$ ($10/\mu L$). His medications included zidovudine, lamivudine, trimethoprim-sulfamethoxazole, rifabutin, and acyclovir. Indinavir sulfate was added to his drug regimen in 1996. He had no history of diabetes mellitus, hypertension, or coronary artery disease. Findings from an examination in September 1996 revealed a macula-off retinal detachment in the right eye secondary to inactive cytomegalovirus retinitis. He underwent an uncomplicated right vitrectomy and silicone oil insertion in February 1997. The retina was attached postoperatively with atrophic macular changes resulting in poor vision. Retinal blood vessels were normal bilaterally. Because of a slowly climbing viral load to 162 000 copies per

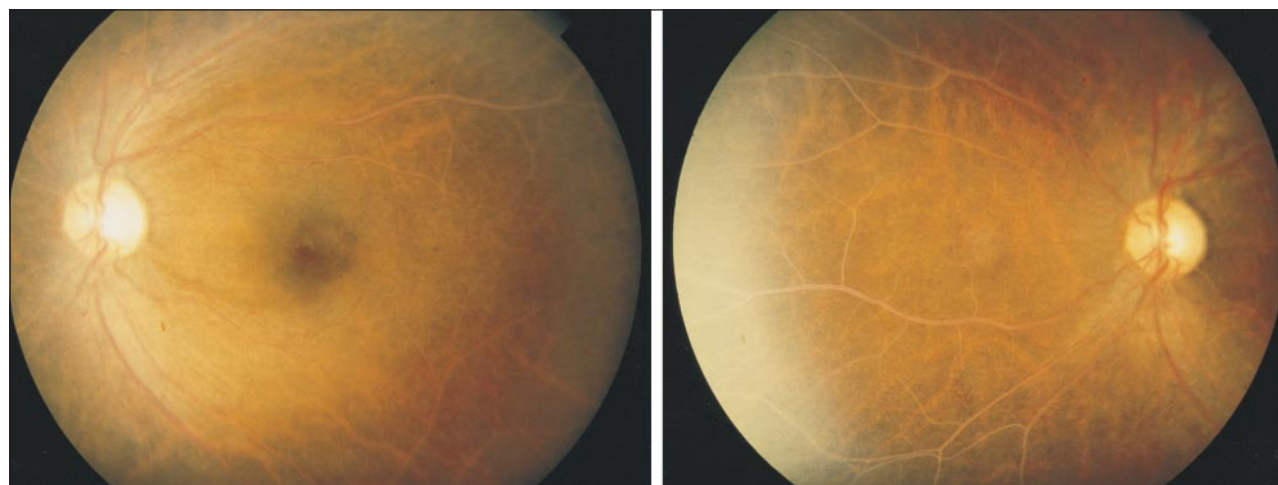
milliliter, the patient's antiviral therapy was changed in December 1997 to zalcitabine, ritonavir, saquinavir mesylate, and delavirdine mesylate.

In March 1998, the patient's best-corrected visual acuity was stable at counting fingers at 1 foot OD and 20/30 OS. Findings from a fundus examination of the left eye demonstrated whitish vessels most marked in the periphery but extending to the posterior pole (**Figure**). A view to the posterior segment of the right eye was not possible because of a silicone oil-induced cataract. Plasma cholesterol levels were 16.54 mmol/L (640 mg/dL) (reference <5.2 mmol/L [<200 mg/dL]), and triglyceride levels were 52.88 mmol/L (4684 mg/dL) (reference <1.52 mmol/L [135 mg/dL]). A diagnosis of grade II lipemia retinalis¹ was made.

He was admitted to the hospital in May 1998 with acute pancreatitis, likely related to his hypertriglyceridemia. In July 1998, administration of ritonavir and saquinavir was discontinued because of concerns regarding pancreatitis. Findings from follow-up retinal examination revealed normal-appearing retinal vessels with no evidence of lipemia retinalis. Visual acuity was 20/25 OS. Total cho-

lesterol levels were 11.37 mmol/L (440 mg/dL) and triglyceride levels were 27.25 mmol/L (2414 mg/dL). His visual acuity and findings from fundus examination of the left eye have remained normal.

Comment. Lipemia retinalis is a rare condition occurring in the setting of markedly elevated levels of serum triglycerides. It occurs in people of all ages and in cases of primary and secondary hyperlipidemia. Changes seen in this condition include a milky white discoloration of the retinal vessels, beginning at the periphery but progressing to involve the posterior pole as the level of serum triglycerides rises. The fundus may also appear salmon colored owing to the effect of triglycerides in the chorioidal circulation. This fundus appearance is thought to be related to the scatter of light caused by the triglyceride-laden chylomicrons. The fundus appearance is transient and resolves quickly with the treatment of the underlying hyperlipidemia. In general, plasma triglyceride levels must be at least 28.22 mmol/L (2500 mg/dL) for lipemia retinalis to occur.² There is no associated change in retinal perfusion, and patients maintain normal visual acuity.



Posterior pole (left) and nasal retina (right). Lipemia retinalis is seen in a patient with hyperlipidemia secondary to protease inhibitor therapy for acquired immunodeficiency syndrome.

Hyperlipidemia has been known to occur in people with acquired immunodeficiency syndrome (AIDS) by 2 different mechanisms. The first is thought to involve an alteration in intermediary metabolism by the release of cytokines as a result of the immune response triggered by systemic infection. More recently, reports have emerged in the literature of severe lipid abnormalities occurring with the use of protease inhibitors.³ These lipid abnormalities can occasionally be associated with severe premature cardiovascular disease. Cholesterol and triglyceride levels can rise to as high as 25 mmol/L (967 mg/dL) and 61.7 mmol/L (5465 mg/dL), respectively. It has been hypothesized that people with AIDS develop hyperlipidemia because the region in which protease inhibitors bind to the human immunodeficiency virus-1 protease shares structural similarity to proteins that regulate lipid metabolism.⁴

This is the first report to our knowledge of an association between lipemia retinalis and hyperlipidemia related to human immunodeficiency virus infection. With the decreasing morbidity and mortality of people with AIDS since the advent of highly active antiretroviral therapy, people with AIDS are living longer and are manifesting more complications of antiretroviral therapy. Although lipemia retinalis is a transient retinal finding and does not seem to directly cause any permanent retinal disease, it is important to recognize it as a sign of profound lipid abnormality in people with AIDS, potentially causing premature cardiovascular disease and pancreatitis. Referral to an internist for reassessment of their antiretroviral therapy, commencement of lipid-lowering therapy, and assessment of cardiac risk factors would be advisable.

Kenneth T. Eng, MD
Eugene S. Liu, MD
Michael S. Silverman, MD, FRCPC
Alan R. Berger, MD, FRCSC
Toronto, Ontario

Corresponding author: Alan R. Berger, MD, FRCSC, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Suite M1-202A, Toronto, Ontario, Canada M4N 3M5.

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Retinal Toxic Effects Associated With Intravitreal Fomivirsen

Fomivirsen sodium is a new oligonucleotide drug that acts as an antisense compound to inhibit viral protein translation. It is given as an intravitreal injection weekly for 3 weeks and then every 3 weeks for maintenance.¹ We report on retinal toxic effects associated with fomivirsen.

Report of a Case. A 41-year-old man with human immunodeficiency virus infection was seen with zone 2 cytomegalovirus (CMV) retinitis in his right eye on July 15, 1998. He had been enrolled in a phase III drug trial for fomivirsen sodium at a dose of 330 µg for treatment in his left eye. He was receiving 3000 mg a day of oral ganciclovir sodium to treat systemic CMV viremia (not part of study protocol). He was enrolled in the study, per protocol, at a dose of 165 µg for treatment in his right eye. The first injection was given on July 22, 1998, and was repeated on July 29 and August 5. All injections were without complication.



Figure 1. Right eye. Cotton-wool spots are seen near the fovea 4 weeks after the first dose of fomivirsen.

His visual acuity remained between 20/25 and 20/30 OD during this period.

At follow-up on August 19, 1998, nyctalopia and decreased visual acuity (20/50 OD) was noted. There was a midperipheral pigment epithelial change and cotton-wool spots around the perifoveal capillary network (**Figure 1** and **Figure 2**). A visual field examination revealed a dense midperipheral ring scotoma (**Figure 3**). During the subsequent months, his visual acuity was stable at roughly 20/40 OD until it fell to 20/200 OD on September 30. The midperipheral area was scarred. A ganciclovir implant was placed in his right eye on October 29. Between discontinuation of treatment with fomivirsen in the right eye and placement of the implant, he was treated with a foscarnet sodium intravitreal injection at a dose of 2400 µg every 2 weeks. The CMV retinitis was well controlled, and visual acuity returned to 20/30 OD. Nyctalopia persists along with visual field changes and pigment scarring. The cotton-wool spots had resolved on follow-up in January 1999. An electroretinogram was attempted to evaluate if the toxic effects were rod specific. The patient was unable to cooperate adequately.

The left eye was treated with a 330-µg dose of fomivirsen sodium per study protocol. He experienced only mild aqueous cell, which was treated successfully with topical steroids. Findings from a visual field examination performed on the left eye showed a relative scotoma corresponding to a localized temporal CMV-related retinal detachment, which had been walled off with laser photocoagulation.

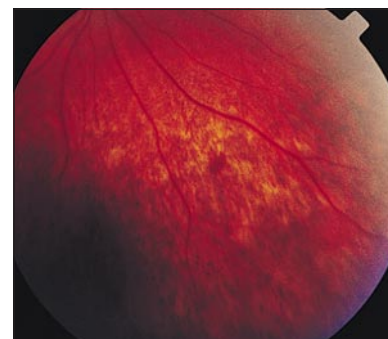


Figure 2. Retinal pigment epithelial disruption was seen circumferentially in the mid periphery.

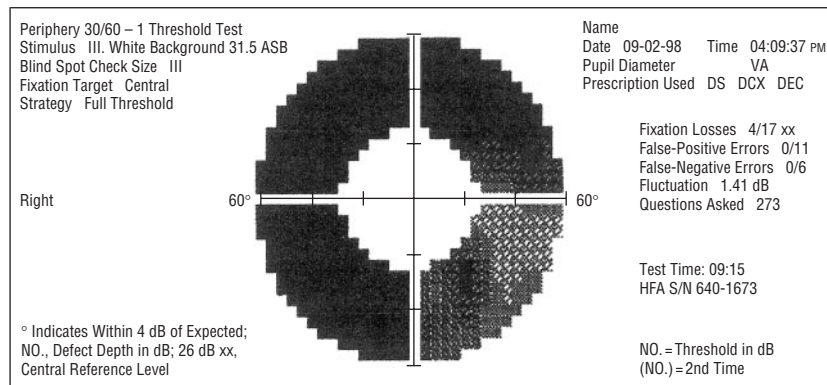


Figure 3. Visual field examination findings of the right eye show a dense midperipheral scotoma.

Comment. Antisense drugs work by inhibiting the translation of viral messenger RNA. The antisense oligonucleotide compound joins with viral messenger RNA as viral messenger RNA is released from the cell nucleus. Consequently, viral-specific proteins are not produced by infected cells.

Treatment with fomivirsen sodium was studied in patients with peripheral CMV retinitis receiving a dose of 165 µg and in patients with sight-threatening disease receiving a dose of 330 µg.² Time to progression with the 165 µg dose was 10 weeks and 13 weeks with the higher dose. There is an 18.5% incidence of a transient rise in intraocular pressure associated with injection of the drug (0.05 mL for the 330-µg dose and 0.025 mL for the 165-µg dose). This is transient and was not treated in this case. Mild intraocular inflammation occurs in 15% of cases. This is treatable with topical steroids.

Preparation for injection involves removing the drug with a filtered needle. It is possible that impurities in the constitution of the drug may have led to the reaction in our patient. It is unclear whether there is a direct effect of fomivirsen on the retinal pigment epithelium or rod cells. We believe that the observed retinal changes may not be dose related as the patient was receiving the higher dose in his fellow eye with no signs of toxic effects. The resulting damage to the retina or retinal pigment epithelium leads to severe, irreversible visual field changes and nyctalopia. Because cotton-wool spots are well known to occur in conjunction with human immunodeficiency virus reti-

nopathy, it is unclear whether the perifoveal cotton-wool spots seen in this case were related to fomivirsen.

Haris I. Amin, MD
 Rockford, Ill
 Everett Ai, MD
 H. Richard McDonald, MD
 Robert N. Johnson, MD
 San Francisco, Calif

Corresponding author: Haris I. Amin, MD, Northern Illinois Retina, 4855 E State St, Rockford, IL 61108 (e-mail: retinaguy@earthlink.net).

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Reversible Atorvastatin-Associated External Ophthalmoplegia, Anti-acetylcholine Receptor Antibodies, and Ataxia

Atorvastatin is a commonly prescribed medication used in the treatment of hypercholesterolemia. We report a case of reversible external ophthalmoplegia associated with atorvastatin.

Report of a Case. A 60-year-old woman experienced painless horizontal diplopia, vertigo, blurry vision, and paresthesias of both upper extremities for 1 week. Her medical history was significant only for hypercholesterolemia, which had been treated for 2½ months with atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-

CoA) reductase inhibitor, 10 mg daily. The patient denied dysphonia, dysphagia, and muscle weakness elsewhere in her body. There was no family history of ophthalmoplegia.

Results of a general physical examination were normal. Neurological abnormalities included generalized hyperreflexia, finger-nose ataxia, and gait ataxia. Visual acuity was 20/20 OU and the pupils were normally reactive without an afferent pupillary defect. The intraocular pressure was normal in both eyes. The ocular media were clear and the fundi were normal. There was ptosis of the right and left upper eyelids. The interpalpebral fissure was 5 mm in the right eye and 4 mm in the left eye. The levator function was 8 mm in each eye. There was no weakness of the orbicularis oculi muscles. Results of an ocular motility examination revealed upgaze limitation of -3 for the left eye and -2 for the right eye. There was neither fatigability on prolonged upgaze nor an eyelid twitch sign. On gaze to the right and left she exhibited no abduction and limited adduction of -2. Downgaze was normal. Convergence and doll's-eye movements were normal. There was no convergence retraction nystagmus.

Magnetic resonance imaging results of the orbits, head, and neck were unremarkable. Results of laboratory studies, including hematology, chemistry, and endocrine panels, were normal. Results of cerebrospinal fluid studies were normal. Tensilon testing performed on 3 occasions was negative. Results of nerve conduction studies and electromyography with repetitive stimulation were normal. Anti-acetylcholine receptor (anti-AchR) antibodies on 2 occasions were 10 times (0.22 nmol/L and 0.25 nmol/L) the upper limit of the normal range (0.00-0.02 nmol/L).

Results of serial neuro-ophthalmologic examinations remained unchanged until the ninth day, when atorvastatin therapy was discontinued. Neurological improvement began within 2 days. At 10 weeks from the discontinuation of atorvastatin therapy, the patient had complete resolution of the gait instability, par-

esthesias, ptosis, and diplopia in primary gaze. Extraocular motility was remarkably improved, with trace abduction limitation remaining in the extremes of gaze in both eyes. The anti-AchR antibody level at this time was within the normal range.

Comment. This patient had an illness characterized by external ophthalmoplegia and elevated anti-AchR antibodies, both of which resolved. We suggest that the association of atorvastatin with this neuro-ophthalmic disorder is causal rather than coincidental for the following reasons: (1) the strong temporal relationships of the initiation of atorvastatin treatment with the onset of symptoms and with its discontinuation with the resolution of symptoms; (2) the normalization of the anti-AchR level after discontinuation of the medicine; and (3) the description of ataxia in the literature as an adverse effect of fluvastatin in experimental animals; ataxia was a feature of our case.¹ In addition, the manufacturers of HMG-CoA reductase inhibitors, including lovastatin, simvastatin, and fluvastatin, report "impairment of extraocular movement" as an adverse effect in their product monographs; however, we are not aware of published literature that documents this association.

Illnesses known to be associated with a false-positive anti-AchR level (autoimmune liver disease, lung carcinoma, amyotrophic lateral sclerosis, and Lambert-Eaton syndrome) and other explanations for ophthalmoplegia (brainstem, subarachnoid space, cavernous sinus, superior orbital fissure, and orbit lesions) were all excluded by the medical history, physical examination, imaging, and cerebrospinal fluid studies.

Although some features of this patient's external ophthalmoplegia were similar to myasthenia and there was a reversible elevation in the anti-AchR antibody level, the negative tensilon test and negative repetitive stimulation test on electromyography argue against a myasthenialike drug reaction.

This is the first reported human case of external ophthalmoplegia, upper extremity paresthesias,

and generalized hyperreflexia associated with anti-AchR antibody elevation secondary to atorvastatin, which reversed after the cessation of the drug treatment. Other drugs associated with anti-AchR antibodies are known to cause reversible ophthalmoplegia. D-Penicillamine may bind to AchR, causing antigenic alteration with the induction of autoantibody formation, or it may act through prostaglandin E₁ to block the AchR binding sites.^{1,2} The association with elevated anti-AchR antibodies suggests that there is a systemic immune reaction, such as those seen with other HMG-CoA reductase inhibitors,³ or that there is antigenic alteration of the AchR which in turn results in the antibody formation.

The similarity of this patient's symptoms to those of a chronic external ophthalmoplegia suggests the possibility of mitochondrial dysfunction. In recent literature, evidence linking HMG-CoA reductase inhibitors to mitochondrial dysfunction has been documented.⁴ This finding supports the importance of further investigation in such patients and the consideration of muscle biopsy and/or serum studies for measurement of the lactate-pyruvate ratio.^{5,6}

In this case of atorvastatin-associated external ophthalmoplegia, the mechanism is unknown. Because HMG-CoA reductase inhibitors are widely and increasingly prescribed, it is important that they be considered as a possible cause for unexplained external ophthalmoplegia.

Gerald J. Negvesky, MD
Martin P. Kolsky, MD
Robert Laurenco, MD
Thomas H. Yau, MD
Washington, DC

Corresponding author: Martin P. Kolsky, MD, Physician's Office Building, Suite 321, 106 Irving St NW, Washington, DC 20010.

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Familial Occurrence of Ablepharon Macrostomia Syndrome: Eyelid Structure and Surgical Considerations

Ablepharon macrostomia syndrome (AMS) is a rare congenital disorder. To our knowledge, only 4 cases have been reported since the original description of this syndrome by McCarthy and West¹ in 1977.²⁻⁵ The syndrome is characterized by redundant skin, low-set ears, macrostomia, ambiguous genitalia, and severe eyelid malformation.¹⁻⁵ Although the designation *ablepharon* literally means absence of eyelids, some patients have been described as having inadequate³ or shortened² eyelids. Several techniques have been used to reconstruct the eyelids in patients with AMS, including rotational and bridge flaps.^{2,3}

Four years ago we had the opportunity to operate on one patient with AMS.⁴ At that time we suggested that the eyelid condition in AMS should not be considered a true example of ablepharia because key anatomical structures were clearly present in the malformed upper eyelids.⁴ The relative normality of the posterior lamella allowed us to make an excellent reconstruction using free skin grafts only.⁴

In this article we report for the first time to our knowledge a familial AMS recurrence. Intraoperative photographic documentation of this case confirms that AMS is not a true ablepharia. Long-term surgical results from our first case demonstrate that free skin grafts placed over the Müller muscle layer provide adequate and long-standing corneal protection with excellent eyelid position and motility.

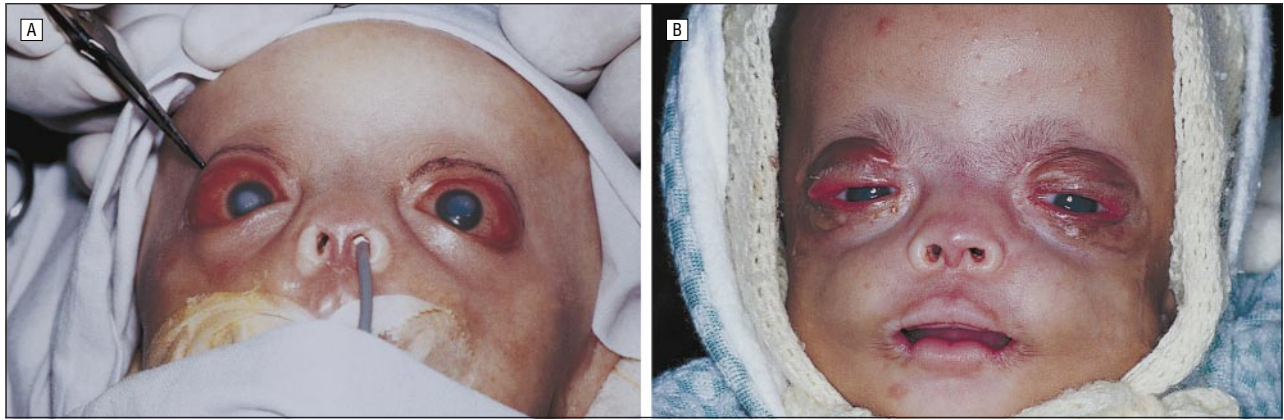


Figure 1. A, Ablepharon macrostomia syndrome with bilateral corneal ulcers on the patient's third day of life. B, Placement of the upper eyelid incision and final result, one week after surgery. The corneas are not clouded.

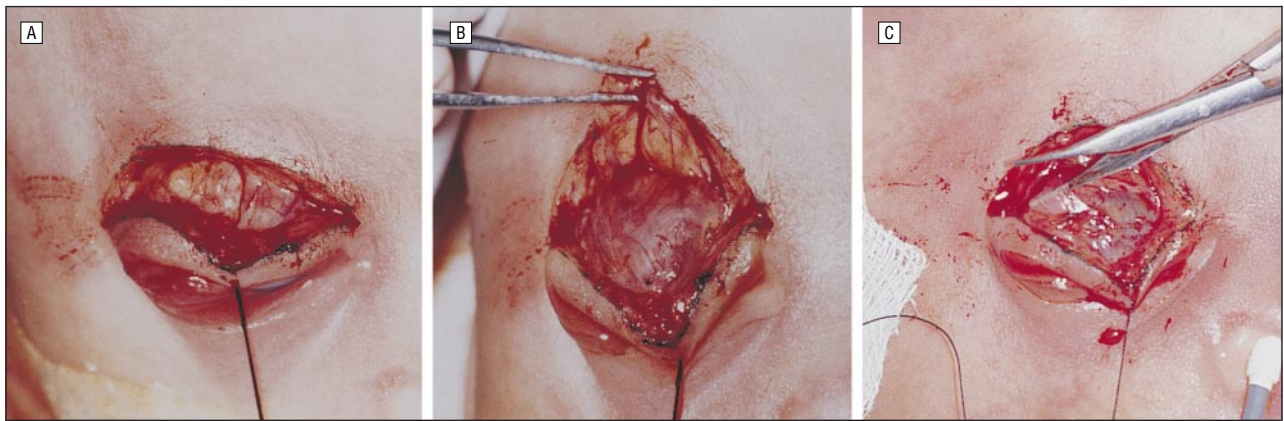


Figure 2. A, After opening the skin and the orbicularis muscle layer, the septum is easily exposed. B, Preaponeurotic fat and levator aponeurosis. C, Excision of the levator aponeurosis.

Report of a Case. The patient, a girl, was born at term by cesarean delivery to a 22-year-old mother and non-consanguineous 26-year-old father. At birth several anomalies were noted: severely shortened upper and lower eyelids without eyelashes, bilateral exposure keratopathy and chemosis, hypertelorism, flattened malar eminences, macrostomia (fishlike mouth), malformed and low-set ears, a nose with bilateral alar deformity, dry and redundant skin, absence of lanugo, female genitalia with vagina near the anus, and an omphalocele that was surgically corrected at birth. The infant was the third child of a family whose first child was born with AMS.⁴ A second child born 2 years earlier was healthy. When we examined the patient on her third day of life, both corneas were clouded by central ulcers.

Surgical Repair. *Upper Eyelid.* Surgery started with a skin incision placed between the eyelid margin

and the lower border of the eyebrows (**Figure 1**, A). After opening the orbicularis oculi muscle layer, the septum was easily identified (**Figure 2**, A). The septum was then incised, allowing the preaponeurotic fat to prolapse. The fat was excised and the levator aponeurosis exposed (Figure 2, B). The tarsal plate was not identifiable. The aponeurosis, which had a normal appearance, was removed from the margin up to the superior orbital rim level (Figure 2, C). The Whitnall ligament was not developed. After these steps, the eyelid margin could be moved down without any tension. The Müller muscle layer also had a normal appearance, including the presence of a supratarsal vascular arcade near the margin. A full skin graft was taken from the supraclavicular fossa and sutured to the wound directly over the Müller muscle. Mattress sutures were passed laterally from the conjunctival side and tied over a bolster on top of the

graft, reducing upper fornix prolapse.

This procedure is exactly the same as the one we used to reconstruct the upper eyelids of our first patient with AMS. **Figure 3** shows that after a 4-year follow-up period, the upper eyelids are still in good position, contour is smooth, and corneal protection is excellent.

Lower Eyelid. Instead of a full-thickness skin graft, we decided to lengthen the lower eyelids with local flaps. An infraciliary horizontal skin approach was used to open the orbicularis muscle layer. The tarsal plates were absent. A white tissue beneath the orbicularis oculi muscle was identified as a fibrous expansion of the capsule-palpebral fascia. Careful incision of this tissue revealed a more vascularized muscle layer. The defect created was more important laterally than medially. Vertical flaps from the zygomatic region were then rotated to allow support for the lateral canthus

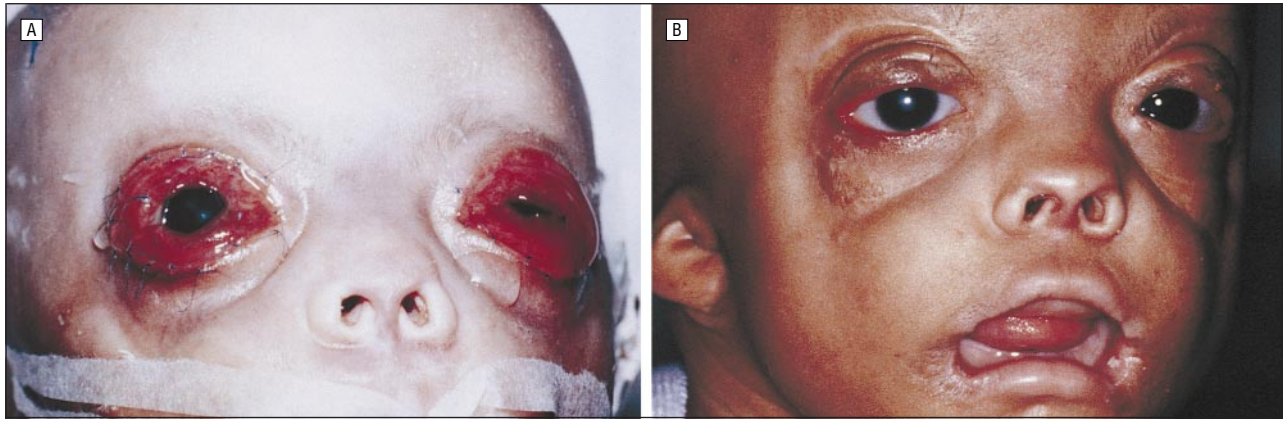


Figure 3. A, *Ablepharon macrostomia syndrome.* B, *Four years after surgery.*

area and correct the lower eyelid retraction.

Comment. The main goal when performing surgery on patients with AMS is to reduce the area of the palpebral fissure and thus provide adequate corneal protection. If a real ablepharia existed in AMS, eyelid repair would be complex; that is not the case. The eyelids in patients with AMS are abnormal, but most key anatomical structures are present, including skin, orbicularis oculi muscle, septum, preaponeurotic fat, levator aponeurosis, the Müller muscle, and conjunctiva. Only the more anterior structures (skin, orbicularis oculi muscle, septum, and levator aponeurosis) are vertically shortened, raising the eyelid margin close to the eyebrows. The posterior lamella (conjunctiva and Müller muscle) is not shortened and therefore prolapses.

The goal of the eyelid repair is to lengthen all layers that are located anterior to the Müller muscle. The procedure allows us to take advantage of the relative normality of the posterior eyelid

lamella. Septum incision and levator aponeurosis recession are essential steps for achieving a good final position. For the 2 patients on which we have operated, the Müller muscle layer provided excellent blood support to the free skin grafts (Figure 1, B and Figure 2, B). Patients with AMS have loose, redundant skin, and grafts can be taken from different sites. In the upper eyelids, the free skin grafts allowed for good eyelid position and motility. In both patients contour was smooth, with excellent corneal protection. In the less mobile lower eyelids, the main goal is to correct the lateral retraction. Local flaps probably offer a more stable result than free skin grafts.

In conclusion, patients with AMS should be described as having an extreme form of vertical eyelid shortening rather than ablepharia. A thorough understanding of the eyelid anatomy in patients with AMS is important because this syndrome represents one of the most dramatic examples of an eyelid surgical emergency in neonates. Upper eyelid repair is not as complicated

as the clinical picture might suggest, but it cannot be delayed.

Antonio A. V. Cruz, MD, PhD
 Carmo A. Souza, MD
 Victor E. F. Ferraz, MD
 Carlos A. C. Monteiro, MD
 Fabiana A. Martins, MD
 São Paulo, Brazil

Corresponding author: Antonio A. V. Cruz, Departamento de Oftalmologia, Hospital das Clínicas-Campus, Faculdade de Medicina de Ribeirão Preto-USP, Ribeirão Preto, São Paulo 14048-900, Brazil (e-mail: aavecruz@fmrp.usp.br).

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