Two instances of ischemic optic neuropathy associated with preeclampsia have been reported.[4,5] However, in contrast to our case, both of these events began before delivery and involved bilateral disc edema and vision loss. Our case appears to be unique in that the symptoms appeared after delivery and the vision loss and disc edema were unilateral. The disc swelling in this case was sectoral and the visual field loss was altitudinal, characteristic of a typical presentation of NAION.

The pathophysiology of preeclampsia is believed to originate from the placenta. Cytotrophoblast cells in the embryo enter the uterine wall and invade the maternal uterine spinal arteries. These cells change from an epithelial phenotype to an endothelial phenotype. This vascular remodeling seems to be disrupted in preeclampsia, resulting in the production of high levels of antiangiogenic factors that enter the maternal circulation; these antiangiogenic factors disrupt the maternal endothelium, resulting in hypertension.[6] The exact pathophysiology for NAION in preeclampsia remains elusive, but it is suggested that the uncontrolled hypertension leads to vasoconstriction or ischemia in the posterior ciliary artery circulation.

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1. Sharma R, Desai S. Postpartum hemorrhage producing acute ischemic optic neuropathy. *Asia Oceania J Obstet Gynaecol*. 1993;19(3):249-251.
2. Gupta M, Puri P, Rennie IG. Anterior ischemic optic neuropathy after emergency caesarean section under epidural anesthesia. *Acta Anaesthesiol Scand*. 2002;46(6):751-752.
3. Digre KB. Neuro-ophthalmology and pregnancy: what does a neuro-ophthalmologist need to know? *J Neuroophthalmol*. 2011;31(4):381-387.
4. Beck RW, Gamel JW, Willcourt RJ, Berman G. Acute ischemic optic neuropathy in severe preeclampsia. *Am J Ophthalmol*. 1980;90(3):342-346.
5. Koskela E, Soinne L, Valanne L, Setäälää K. Pregnancy associated ischaemic optic neuropathy. *Neuroophthalmology*. 2011;35(4):202-206. doi:10.3109/01658107.2011.593676.
6. Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. *Physiology (Bethesda)*. 2009;24(4):147-158.

COMMENTS AND OPINIONS

Recurrence of Retinopathy of Prematurity Following Bevacizumab Monotherapy: Is It Only the Tip of the Iceberg?

In 2011, a landmark article was published that could change the way retinopathy of prematurity (ROP) is treated.[1] The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) trial concluded that intravitreal injection of bevacizumab, 0.625 mg in 0.025 mL, had a beneficial effect compared with laser photocoagulation for zone 1, stage 3+ ROP.[1] However, their end point for recurrence of disease was only 54 weeks' postmenstrual age (PMA). Previously, Moshfeghi and Berrocal[2] estimated that 47.7% of recurrences would have occurred after the 54 weeks' PMA reported in the BEAT-ROP study as the primary end point for treatment success. In this journal, Hu et al[3] described their clinical experience with recurrence of ROP following intravitreal injection of bevacizumab, adding further evidence that 54 weeks' PMA is not a sufficient end point for observation.

Hu and colleagues reported 17 eyes of 9 patients who had recurrence of ROP requiring treatment on average 14.4 weeks after bevacizumab injection (range, 4-35 weeks). Notably, 5 eyes that progressed to having retinal detachment (RD) did so at a median age of 55 weeks' PMA (range, 49-69 weeks). They mentioned the shortfalls of their study as retrospective, uncontrolled, and small in number. Also, the period in which their patients were seen in relation to recent publications on bevacizumab was not described, and patients were seen and managed by different ophthalmologists without prior examination by authors of the study in some cases. Thus, this retrospective study raises concerns about nonstandardized use of a new treatment modality. Most importantly, 2 patients had repeated intravitreal injections of bevacizumab within a relatively short period. One patient (patient 3) had 6 doses of bevacizumab, 0.625 mg (total, 3.75 mg), in a 7-week period, and another patient (patient 9) had 5 doses in the same period (total, 3.125 mg). Sato et al[4] showed that a total dose injection of only 0.5 mg of bevacizumab causes a 6-fold reduction in serum vascular endothelial growth factor 2 weeks after injection in neonates. There are no data for repeated injections, but by implication, patients 3 and 9 in the article by Hu and colleagues were likely to have been subjected to even lower serum vascular endothelial growth factor levels. Systemic adverse effects remain the biggest concern among ROP experts in both the short and long term.[5-7] We therefore welcome the recommendation that recurrences of ROP should be treated with laser, not just because of a reduced RD rate[3] but also for protecting the patient from systemic complications.

We are in uncharted waters with regard to patterns of recurrence following bevacizumab treatment. Hu and colleagues defined recurrence as "arrest of anterior progression of retinal vasculature associated with a new demarcation line, ridge, or extraretinal fibrovascular proliferation (EFP) or leakage on fluorescein angiography, with or without recurrence of plus disease."[3] Recurrence did not require EFP. They also observed anatomical recurrence as anterior and/or posterior. This is different from the definitions in the BEAT-ROP study.[1] There is a need for the larger ROP community to standardize the definition and re-treatment criteria for recurrence after bevacizumab injection. In the study by Hu and colleagues, both recurrence criteria and treatment were at the discretion of the treating ophthalmologist. Again, questions can be raised regarding some patients with the information provided in the article. For example, patient 9 was born at 32 weeks' PMA, weighed 1843 g at birth, and reportedly developed aggressive posterior ROP in zone 1 with atypical stage 3 and plus disease at 35 weeks.[3] Ag-

gressive posterior ROP is usually considered to occur in the tiniest and most premature babies[8]; in our combined experience, we have not seen such a scenario in a developed country and we find the case surprising. It is unusual for such a case to even be eligible for screening, let alone to have such severe disease warranting treatment 3 weeks after birth (the first screening examination is normally 4 weeks after birth).[9] Again, without further information and independent verification, it is difficult to draw conclusions from this case as the figures attributed to the case (unlabeled as to the PMA they represent) do not match the severity described.[3]

This study also demonstrates the problems relating to unknown follow-up protocol for patients with ROP after bevacizumab injection.[3] It is not reported whether the high proportion of RDs was due to loss to follow-up and hence preventable in some cases. For example, patient 2 was described as having stage 4A RD in the right eye at 50 weeks' PMA, progressing to stage 5 RD at 54 weeks' PMA. The patient's left eye was reported as having stage 5 RD at 55 weeks' PMA without any indication of what happened in this eye during the preceding 5 weeks while the fellow eye was being observed. It is difficult to deduce the speed and pattern of complications with the information available. The authors could not comment on whether the RDs were rhegmatogenous or tractional. Stage 5 RDs (3 patients) were categorized as anterior recurrence of ROP even though in the table of results the diagnosis was made at presentation.[3] However, if injections were carried out at 2.5 mm behind the limbus as described in the BEAT-ROP study,[1] a rhegmatogenous cause may be the culprit as this distance lies in full-thickness retina in a neonate.[10] Nevertheless, it is appropriate to conclude that with bevacizumab, regular long-term observation is vital to identify potentially preventable RDs. How often follow-up should be performed is not known, and loss to follow-up is of greater concern than laser-treated eyes, which on average have a more predictable course within 12 weeks.[2] The study demonstrates the need for long-term follow-up requiring skilled ophthalmological observation and emphasizes that while bevacizumab injection treatment may be less time-consuming than laser as initial therapy, it has significant long-term follow-up issues. This has implications in terms of workforce commitment for ophthalmologists and the necessity to ensure that the patients are brought for outpatient assessment.

Despite the shortfalls of the study by Hu and colleagues, the study demonstrates that late recurrence after bevacizumab injection is a major cause for concern. Recurrence with resulting RD has a very poor prognosis; therefore, missed recurrence can severely affect the child's vision. The authors conclude that "only with complete vascularization to the ora serrata and no active disease can treatment [with bevacizumab] be considered successful."[3] Parents should be alerted of the need for prolonged regular follow-up visits and the potential need for a general anesthetic for indented examination of the peripheral retina and possibly a fluorescein angiogram in some of the older children (≥50 weeks' PMA). Further standardized and controlled studies with longer follow-up are required so that the late recurrence of ROP can be assessed, and they should also aim to establish a safe end point for ROP screening examinations following bevacizumab monotherapy.

Finally, it is important to note that laser photocoagulation for ROP does not have the problem of recurrence. There may be a failure to adequately respond to laser, but once ROP has regressed it does not recur weeks to months later.[11] The concluding paragraph of the Early Treatment of ROP (ETROP) randomized trial states, "Even with the addition of early [laser] treatment for selected eyes with prethreshold ROP, some eyes will still progress to an unfavorable visual and/or structural outcome. Thus, additional research is needed to identify better methods for the prevention and treatment of severe ROP."[11] Hence, no treatment is perfect for ROP at present and the search must continue for better outcomes. Bevacizumab may not be the ideal treatment if the problems of recurrence and suboptimal local and systemic long-term safety profiles prove to be only the tip of the iceberg.

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1. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med*. 2011;364(7):603-615.
2. Moshfeghi DM, Berrocal AM. Retinopathy of prematurity in the time of bevacizumab: incorporating the BEAT-ROP results into clinical practice. *Ophthalmology*. 2011;118(7):1227-1228.
3. Hu J, Blair MP, Shapiro MJ, Lichtenstein SJ, Galasso JM, Kapur R. Reactivation of retinopathy of prematurity after bevacizumab injection. *Arch Ophthalmol*. 2012;130(8):1000-1006.
4. Sato T, Wada K, Arahori H, et al. Serum concentrations of bevacizumab (Avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. *Am J Ophthalmol*. 2012;153(2):327-333, e1.
5. Gilbert CE, Zin A, Darlow B. Bevacizumab for retinopathy of prematurity. *N Engl J Med*. 2011;364(24):2359-2360, author reply 2361-2362.
6. Gole GA, Camuglia JE, Ells AL. Bevacizumab for retinopathy of prematurity. *N Engl J Med*. 2011;364(24):2360-2361, author reply 2362.
7. Lim LS, Cheung CM, Mitchell P, Wong TY. Emerging evidence concerning systemic safety of anti-VEGF agents: should ophthalmologists be concerned? *Am J Ophthalmol*. 2011;152(3):329-331.
8. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol*. 2005;123(7):991-999.
9. Section on Ophthalmology, American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity [published corrections appear in *Pediatrics*. 2006; 117(4):1468 and *Pediatrics*. 2006;118(3):1324]. *Pediatrics*. 2006;117(2): 572-576.
10. Hairston RJ, Maguire AM, Vitale S, Green WR. Morphometric analysis of pars plana development in humans. *Retina*. 1997;17(2):135-138.
11. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity randomized trial. *Arch Ophthalmol*. 2003;121(12):1684-1694.