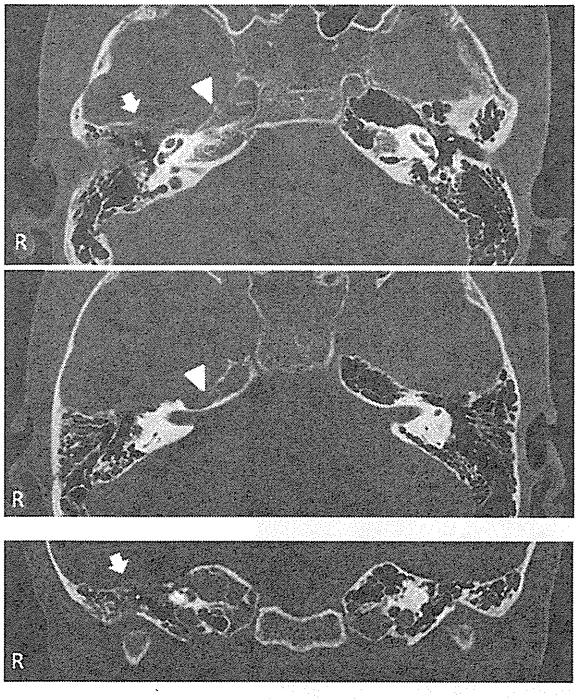


Fig. 1. Non-contrast CT of the temporal bone, axial image (a, b) and coronal image (c). Thinner skull base and partially lytic lesion in the right mastoid air cell (arrow) and petrous apex (arrow head). Note fluid in the mastoid air cells and at the apex of the petrous temporal bone. The middle ear cavity was clear.

Neurological examination revealed weak closure of the right eye and hyposensitivity of the right cheek.

Radiological findings: Axial noncontrast computed tomography (CT) imaging of the temporal bone showed a lytic lesion in the right mastoid region, petrous apex (Fig. 1). There was fluid in the anterior part of mastoid air cells and apex of the right petrous temporal bone. The middle ear cavity was clear. Axial T1 and T2-weighted magnetic resonance imaging (MRI) of the temporal bone revealed mass at the apex of the petrous part of the right temporal bone and fluid accumulation at anterior part of right mastoid air cells (Fig. 2a and b). Fat-suppressed T1 weighted MR combined with Gadolinium (Gd) enhanced image revealed cystic mass at the petrous apex compress and invade anterior clivus (Fig. 2c and d). In addition, the right trigeminal nerve was thinner than the left nerve. RI cisternography with In-111 showed asymmetric uptake at right pharynx and cervical neck region (Fig. 3a), and T2 weighted MRI showed fluid accumulated along right cervical lymphoid tissue (Fig. 3b), suggested CSF leakage from cranial base through cervical tissue. SPECT/T2- weighted MR image revealed focal uptake (Fig. 4), confirmed CSF leakage through the root of the zygoma from a medial source.

Lumbar puncture revealed a high opening pressure of 60 cmH_2O (normal: 5–15 cmH_2O). There was no growth on CSF culture, and cytology only demonstrated a few monocytes and lymphoid cells.

There were no abnormalities shown by routine laboratory 3 tests. These findings suggested a differential diagnosis of apical petrositis or a malignant tumor, including leukemia, Ewing sarcoma, Langerhans histiocytosis, or rhabdomyosarcoma of the temporal bone.

Biopsy; Surgical biopsy of the osteolytic lesion in the temporal bone was attempted. When the skin was incised, a large volume of clear fluid flowed out from the soft tissues lateral to the periosteum and petrous apex. Analysis of this fluid showed glucose positive and white blood cells (neutrophil cells). CSF culture was negative.

After elevation of a periosteal flap, mastoidectomy was attempted, but the mastoid process was found to be soft and fractured easily due to osteolysis. There was brisk flow of CSF from the mastoid region. No soft tissue lesion was found. The osteolytic temporal bone fragments were taken for pathological examination.

There was no inflammation and/or granulation tissue in the temporal bone biopsy specimen (Fig. 5). Immunopathological examination showed channels lined with endothelium that was positive for D2-40 antibody, suggesting invasion of the bone by lymph vessels with consequent decalcification and destruction.

After further review and discussion, the clinical, radiological, and pathological findings were concluded to be consistent with a diagnosis of Gorham–Stout syndrome. Lymphangiomatosis of the petrous temporal apex had presumably led to lymphatic communication with the CSF spaces, while lymphangiomatosis resulted in temporal bone fracture.

Surgical treatment; Persistent CSF leakage in a child is associated with a risk of meningitis, repair of CSF leakage and biopsy of the osteolytic lesion at the petrous apex were performed by extradural middle fossa approach. When exploring the middle fossa, a large volume of clear fluid came out from the petrous apex. A small piece of osteolytic petrous bone was taken for biopsy. The dura on the superior wall of Meckel's cavity showed partial dehiscence which exposed the trigeminal nerve at that site and allowed CSF leakage. These tegmental defects were covered with superficial temporal fascia and periosteum flap, and sealed with fibrin glue.

Medical treatment; To protect further invasion of lymphangioma, medical treatment with interferon-alpha 2b (Intron-A) was started at a dose of 2 million units/m^2 every second day for 2 months. Propranolol was also administered on a continuing basis. One year after surgery, symptoms such as headache or tinnitus have not recurred and her hearing has improved. MRI and CT suggest that there were no remarkable changes of the temporal bone after surgery, while RI cisternography has shown no CSF leakage. The opening pressure is still high on lumbar puncture, but has decreased to 26 cmH_2O. Papilledema was diminished within 4 months as her intracranial pressure decreased. The serum VEGF level was 277 pg/ml (normal: 50 pg/ml) before treatment and subsequently decreased to 161 pg/ml. MCP-1 and G-CSF levels are also elevated.

3. Discussion

The presentation of Gorham–Stout syndrome is variable and depends on the site of involvement. No other cases have been reported with CSF leakage secondary to elevation of intracranial pressure.

Making a correct diagnosis Gorham–Stout syndrome is challenging because sometimes no granulation tumor but osteolytic crest was found around affected site.

Histopathologically, Gorham–Stout syndrome is characterized by lymphovascular proliferation or fibroconnective tissue. We decalcified the osteolytic bone tissue for staining with D2-40 antibody, which is specific for the epithelium of lymphatics. Usually, lymph vessels do not penetrate the temporal bone, so this finding indicated that osteolysis was caused by proliferation of lymphatics. CT findings are useful to accurately assess the extent of bone destruction, while T2-weighted MRI can reveal the extent of abnormal lymphovascular proliferation. Contrast lymphangiography can be useful to delineate the exact site of leakage and provide information for definitive ligation. However, it is not useful for head and neck lesions because there is no lymph flow distal to the skull base.

One of life-threatening complications of Gorham–Stout syndrome is meningitis secondary to CSF leakage. Our patient had headache, nausea, and tinnitus due to increased intracranial pressure and CSF leakage. The raised intracranial pressure indicates

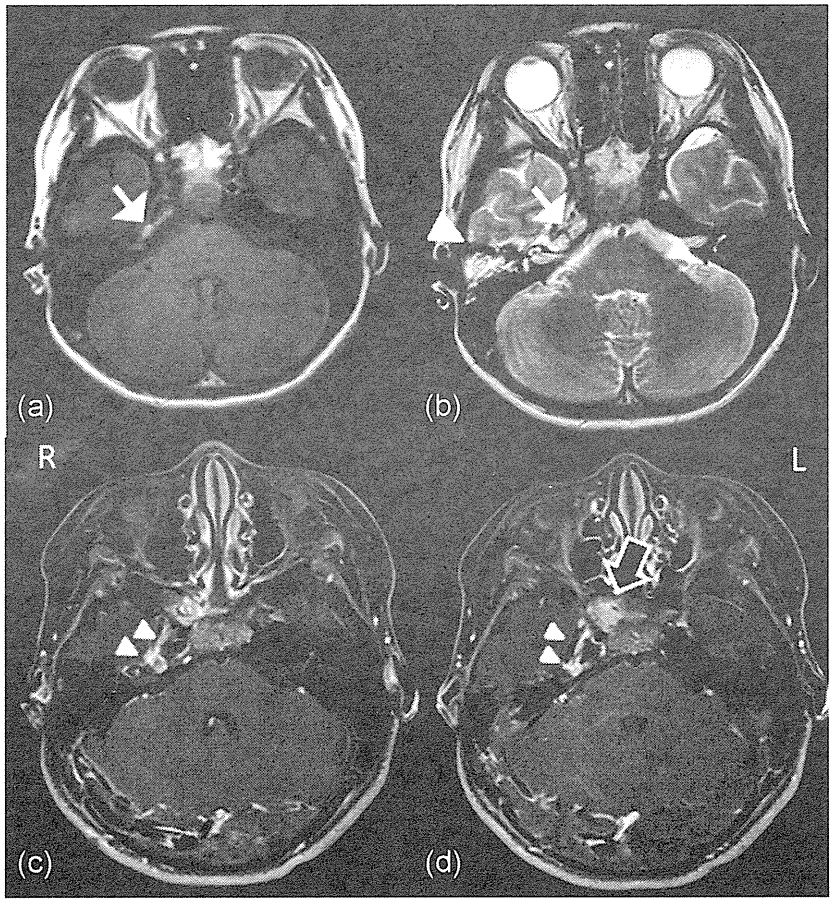


Fig. 2. Axial image of cranial T1 and T2 – weighted MRI T1 (a) and T2 (b) – weighted MR image revealed mass at the petous apex (arrow) and did not compress inner ear tract. Fluid accumulation at anterior part of right mastoid air cells (arrow head). Fat-suppressed T1 weighted MR combined with Gadolinium (Gd) enhanced image revealed cystic mass (double arrow head) (c,d). Cystic mass compress and invade anterior clivus (black arrow).

that lymph was flowing into the CSF secondary to lymphangiomatosis of the cranial base. In previous reports of Gorham–Stout syndrome with CSF leak, intracranial hypotension was observed, while our patient had intracranial hypertension [1–3]. We speculate this is due to greater amount of influx of lymph into the CSF space than CSF leakage in our case.

Surgical treatment is effective, although it does not prevent progression of the disease and grafts may also be involved by lymphangioma. Some authors have reported that chylothorax worsens after biopsy of a lesion because the damage to lymphatics causes more leakage. Therefore, osteolytic lesions should be removed carefully and minimally.

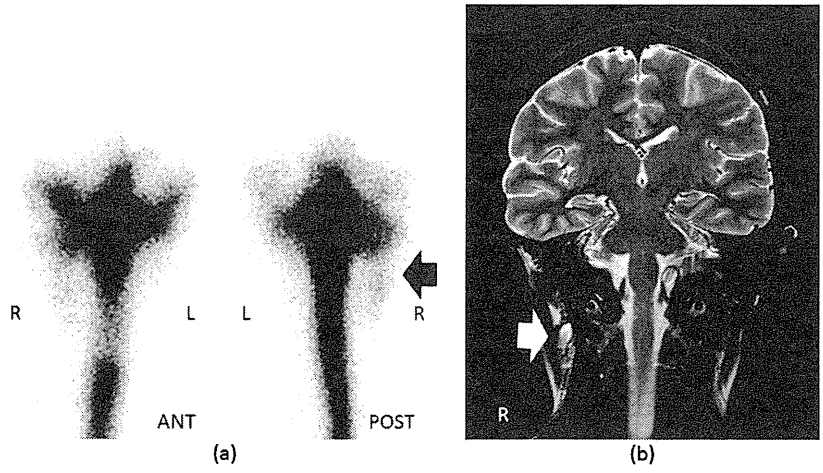


Fig. 3. (a) RI cisternography: radionuclide cisternography was performed 2.5 h after intrathecal injection of In-113. It revealed asymmetric uptake at right pharynx and cervical neck region (black arrow). (b)T2 – WI MRI: Fluid accumulated along right cervical lymphoid tissue (white arrow) suggested CSF leakage from cranial base through cervical tissue.

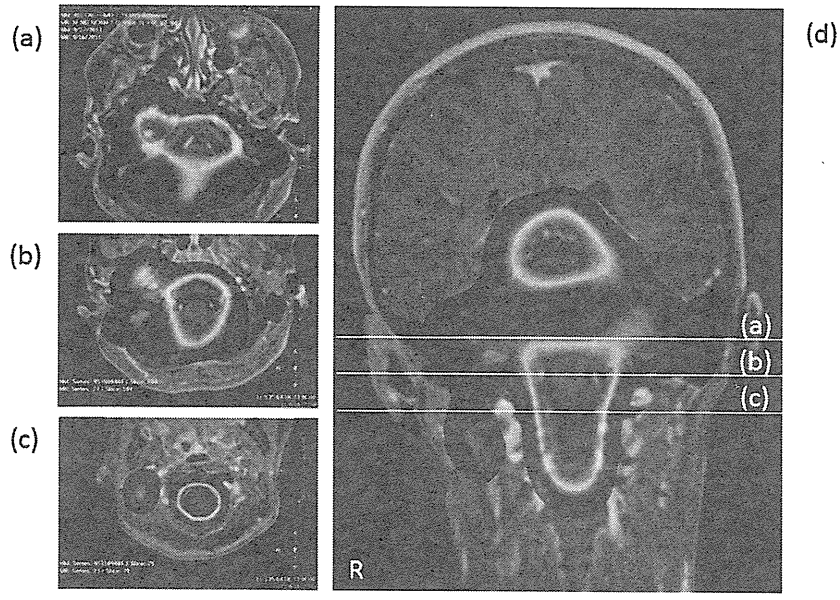


Fig. 4. SPECT/T2-weighted MRI (SPECT 2.5 h). Focal uptake at right petrous apex (a), para-pharynx (b) and peripheral cervical lymphnode (c,d) was identified, suggested CSF leakage.

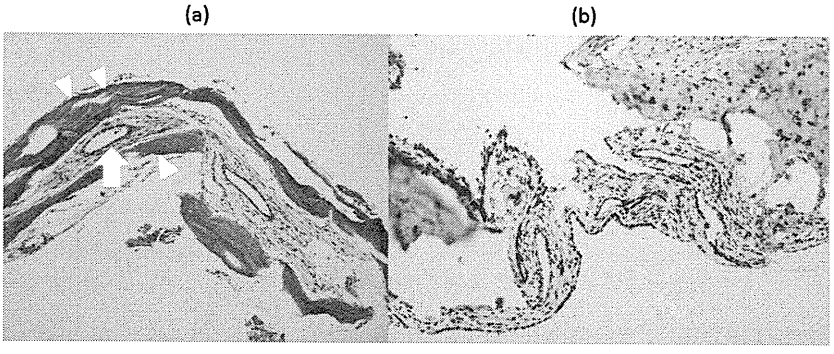


Fig. 5. Immunopathological findings of temporal bone. (a) Proliferative vascular lumens penetrate into the temporal bone without any inflammation. (b) Immunopathological examination showed positive for the lymphatic marker D2-40.

The etiology of lymphangiomatosis is still unknown. Increased levels of inflammatory cytokines, especially interleukin-6, TNF-alpha, and VEGF, suggest that osteoclast activity may increase [4] or that VEGF may promote pathological lymphangiogenesis [5,6]. Anti-IL6 receptor antibody and anti-VEGF antibodies such as bivacizumab decrease angiogenic activity, while bisphosphonates decrease osteoclast activity and bone resorption, thus stabilizing the disease. The mechanism of interferon has not been fully elucidated, but it might downregulate VEGF expression [7]. Propranolol is thought to reduce VEGF expression and induce apoptosis of capillary endothelial cells as its mechanisms of antiantiogenetic activity [8]. Dupond reported that the serum level of VEGF is closely correlated with disease activity [6]. In our case, the VEGF level and intracranial pressure both decreased gradually during treatment, revealing the effects of interferon combined with propranolol.

4. Conclusion

We reported a rare case of Gorham–Stout syndrome affecting the apex of the petrous temporal bone. Our patient had headache, nausea, mild hearing loss and tinnitus due to elevation of the intracranial pressure, followed by CSF leakage. Surgical repair of CSF leakage should be performed by obliteration, since damage to the lymph vessels leads to persistent leakage of lymph. The combination of interferon and propranolol can be helpful for decreasing intracranial pressure, and serum VEGF level would be a good marker for following lymphangiomatosis activity. However, further study is required to determine the optimum management of this disease in infants and children.

Financial disclosure

None

Conflicts of interest

None

Acknowledgement

We would like to thank Dr. Jun Abe for special advise in biochemical analysis.

References

[1] S.L. Cushing, G. Ishak, J.A. Perkins, J.T. Rubinstein, Gorham–Stout syndrome of the petrous apex causing chronic cerebrospinal fluid leak, Otol. Neurotol. 31 (2010) 789–792.

[2] C. Hernandez-Marques, A. Serrano Gonzalez, F. Cordobes Ortega, J. Alvarez-Coca, S. Sirvent Cerda, F. Carceller Lechon, et al., Gorham–Stout disease and cerebrospinal fluid otorrhea, Pediatr. Neurosurg. 47 (2011) 299–302.

[3] G.K. Nazarian, S.S. Gebarski, J.K. Niparko, Cranial lymphangiomatosis causing CSF otorrhea and recurrent meningitis: CT features, J. Comput. Assist. Tomogr. 14 (1990) 121–123.

[4] R.D. Devlin, H.G. Bone III, G.D. Roodman, Interleukin-6: a potential mediator of the massive osteolysis in patients with Gorham–Stout disease, J. Clin. Endocrinol. Metab. 81 (1996) 1893–1897.

[5] R. Venkatramani, N.S. Ma, P. Pitukcheewanont, M.H. Malogolowkin, L. Mascarenhas, Gorham's disease and diffuse lymphangiomatosis in children and adolescents, Pediatr. Blood Cancer 56 (2011) 667–670.

[6] J.L. Dupond, L. Bermont, M. Runge, M. de Billy, Plasma VEGF determination in disseminated lymphangiomatosis-Gorham–Stout syndrome: a marker of activity? A case report with a 5-year follow-up, Bone 46 (2010) 873–876.

[7] B. Cano, S. Insa, C. Cifrian, H. Cortina, M. Hernandez, Radiologic findings in Gorham–Stout syndrome, Radiologia 48 (2006) 33–36.

[8] M. Ozeki, T. Fukao, N. Kondo, Propranolol for intractable diffuse lymphangiomatosis, N. Engl. J. Med. 364 (2011) 1380–1382.

Original Investigation | CLINICAL SCIENCES

Visual Outcomes After Early Vitreous Surgery for Aggressive Posterior Retinopathy of Prematurity

Noriyuki Azuma, MD, PhD; Makiko Ito, MD; Tadashi Yokoi, MD, PhD; Yuri Nakayama, MD; Sachiko Nishina, MD, PhD

IMPORTANCE Aggressive posterior retinopathy of prematurity (AP-ROP) rapidly progresses to retinal detachment despite application of photocoagulation. Early vitreous surgery might achieve prompt regression of neovascular activity and a high incidence of retinal reattachment.

OBJECTIVE To evaluate visual outcomes in eyes with AP-ROP after early vitreous surgery.

DESIGN Retrospective nonrandomized study of patients who underwent early vitreous surgery with lensectomy when retinal detachment developed despite photocoagulation. Aphakic correction with spectacles or contact lenses and the use of orthoptics were continued postoperatively. The best-corrected visual acuity (VA) was measured in eyes with a total retinal reattachment using the preferential looking technique in patients ranging in age from 8 months to no more than 3 years and a VA chart with Landolt rings or pictures for older children. The VA findings were converted to Snellen lines.

SETTING Institutional ophthalmology practice.

PARTICIPANTS Of the 103 eyes (57 patients) that underwent early vitreous surgery for AP-ROP, the VA was measured in 58 (32 patients) at a corrected age ranging from 8 months to 4 years.

INTERVENTIONS Early vitreous surgery and VA measurement using the preferential looking technique and a VA chart.

MAIN OUTCOMES AND MEASURES Postoperative VA, ROP stage, extent of fibrovascular tissue (FT) growth, and laterality of the eyes that underwent surgery.

RESULTS The VAs ranged from 20/2000 to 20/40. The VA may not be related to the preoperative ROP stage 4A or 4B but may depend on the preoperative extent of FT growth. In 39 of 58 eyes (67.2%), the FT had not reached the vitreous base preoperatively, and foveal formation occurred postoperatively with nearly age-appropriate VA (range, 20/250 to 20/40). In 17 of 58 eyes (29.3%), the FT had reached the vitreous base, and no fovea formed (VA range, 20/2000 to 20/250). Two of 58 eyes (3.4%) had deprivation amblyopia with a VA worse than 20/1600. The difference in VA between both eyes of patients who underwent bilateral vitreous surgery depended on ROP progression; patients who underwent a unilateral procedure in which the fellow eyes with ROP stabilized after photocoagulation tended to have poor vision because of deprivation amblyopia.

CONCLUSIONS AND RELEVANCE Early vitreous surgery may be beneficial for AP-ROP and should be performed before the FT reaches the vitreous base to facilitate foveal formation and good VA outcomes. The roles of photocoagulation, vitreous surgery, and anti-vascular endothelial growth factor therapy in the treatment of AP-ROP should be investigated in randomized trials regarding efficacy, safety, convenience, and cost.

Author Affiliation: Department of Ophthalmology and Laboratory of Cell Biology, National Center for Child Health and Development, Tokyo, Japan.

Corresponding Author: Noriyuki Azuma, MD, PhD, Department of Ophthalmology and Laboratory of Cell Biology, National Center for Child Health and Development, 2-10-1, Okura, Seatagaya-ku, Tokyo 157-8535, Japan (azuma-n@ncchd.go.jp).

JAMA Ophthalmol. 2013;131(10):1309-1313. doi:10.1001/jamaophthalmol.2013.4148
Published online August 29, 2013.

With the improving survival of very small premature infants owing to progress in neonatal intensive care, the incidence of aggressive posterior retinopathy of prematurity (AP-ROP), an unusual and severe form of ROP, is increasing and threatening vision.[1] Retinal photocoagulation, which stabilizes classic ROP, often fails to stop progression to retinal detachment in AP-ROP.[1] Previous vitreous surgery performed to treat retinal detachment has obtained poor visual outcomes ranging from light perception to ambulatory vision despite successful retinal reattachment.[2]

One study[3] has proposed that patients undergo early vitreous surgery for AP-ROP, which has resulted in prompt regression of neovascular activity and a high incidence of retinal reattachment. We report here the visual outcomes after early vitreous surgery for AP-ROP.

Methods

From July 1, 2004, through December 31, 2011, 103 eyes of 57 patients (31 girls and 26 boys) with AP-ROP underwent early vitreous surgery with lensectomy. Diagnosis of AP-ROP was based on the protocol of the International Classification of Retinopathy of Prematurity,[4] including prominent plus disease and a posteriorly located flat network of neovascularization at the deceptively featureless junction between the vascularized and nonvascularized retina. In all eyes, dense laser photocoagulation had been applied previously at our clinic or elsewhere; however, this treatment failed to stop progression of ROP. When fibrovascular tissue (FT) continued to proliferate or recurred after transient regression and progressed circumferentially for 6 or more continuous clock hours with a tractional retinal detachment that developed simultaneously (stage 4), the same surgeon (N.A.) performed early vitreous surgery as a secondary treatment. The surgical procedure has been described previously.[3] The refractive error of aphakia was corrected postoperatively with spectacles or contact lenses, and continuous occlusion therapy was provided in cases in which a unilateral procedure was performed.

Postoperative foveal formation was evaluated by fundus photography and fluorescein angiography using a retinal camera (RetCam; Massie Research Laboratories, Inc)[5] in all eyes. We examined the visual outcomes after vitreous surgery in eyes that achieved total retinal reattachment. Patients who were mentally challenged were excluded. The best-corrected visual acuity (VA) was measured with the preferential looking technique at a distance of 50 cm using a commercially available inspection apparatus (Awaya-Mohindra-type apparatus; Nitten Pharmaceutical Co, Ltd)[6] in patients ranging in age from 8 months to younger than 3 years; a VA chart with Landolt rings or pictures at 5 m was used for older children. The VA findings were converted to Snellen lines. We also determined the normal curve of VA development. One eye each of 81 healthy children (40 girls and 41 boys; age range, 2 months to 3 years) who had no bilateral abnormalities detected by ocular examination and who had good visual function was evaluated by the preferential looking technique[7]; and 72 eyes of 72 healthy children (37 girls and 35 boys; age range, 3-6 years) were evaluated using a VA chart.

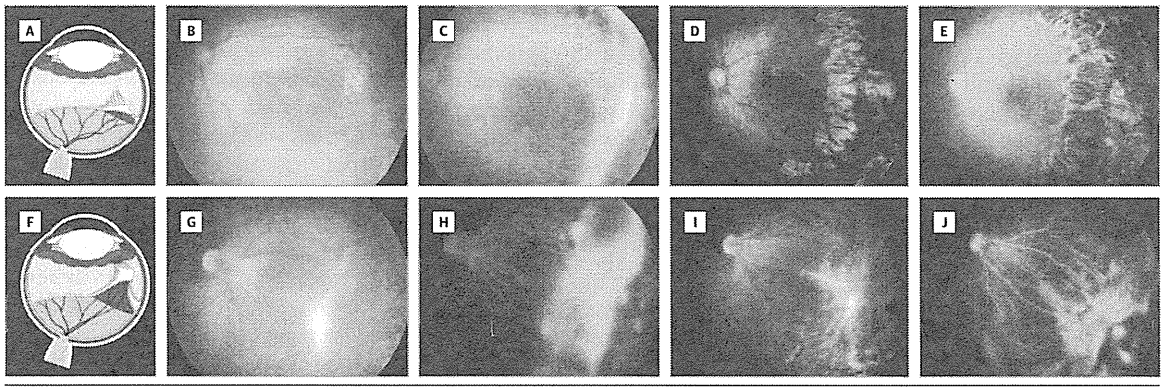
Results

Gestational age at birth ranged from 22 to 30 (mean, 24) weeks. Birth weight ranged from 268 to 1676 (mean, 706) g, and the postmenstrual ages at vitreous surgery ranged from 34 to 44 (mean, 37) weeks. Because capillary hypoperfusion is present in the entire retina with AP-ROP, preoperative photocoagulation applied up to the vascularized retina may be the key to good surgical outcomes.[8,9] In 89 eyes with adequate photocoagulation, total retinal reattachment was achieved in 81 (91.0%) and partial reattachment in 8 (9.0%); the fovea was well formed in 63 (70.8%). In contrast, among 14 eyes treated with inadequate photocoagulation, total retinal reattachment was achieved in 2 (14.3%), partial reattachment in 5 (35.7%), and no reattachment owing to FT regrowth in 7 (50.0%). The fovea was unformed in all 14 eyes with inadequate photocoagulation. In the eyes in which retinal reattachment was achieved, formation of the fovea depended on the absence (**Figure 1**A-E) or the presence of retinal dragging by residual FT (Figure 1F-J).

The postoperative VAs were measured in 64 eyes of 35 patients (19 girls and 16 boys; 58 eyes underwent simultaneous bilateral surgery and 6 eyes, unilateral surgery) at corrected ages ranging from 8 months to 4 years. We compared the VA in these patients with the visual development curve obtained from the controls. To compare the anatomic and functional outcomes, 2 eyes with bilateral corneal opacity due to congenital anterior segment dysgenesis and 4 eyes with bilateral small corneas and postoperative glaucoma (VA of worse than 20/200 in each eye) were excluded. Thus, 58 eyes of 32 patients (bilateral surgery, 52 eyes; unilateral surgery, 6 eyes) underwent analysis. Preoperative development of ROP reached stage 4A in 42 eyes and stage 4B in 16 eyes. All 41 eyes in which the FT preoperatively had not reached the posterior lens surface or the vitreous base achieved foveal formation postoperatively; the remaining 17 eyes in which the FT already reached the posterior lens surface or the vitreous base had no fovea. The postoperative VAs ranged from 20/2000 to 20/40. Forty eyes (69.0%) obtained VAs of 20/250 or better (**Figure 2**).

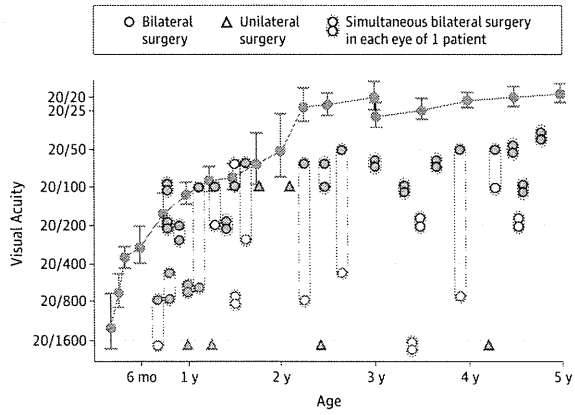
The VA outcomes may be unrelated to the preoperative stages of ROP: the VAs in the 42 eyes with ROP stage 4A ranged from 20/2000 to 20/40, and those in the 16 eyes with ROP stage 4B ranged from 20/2000 to 20/65. The difference in the VAs between both eyes of each patient may depend on the preoperative extent of the FT growth. Thirty-seven of the 52 eyes (71.2%) that underwent bilateral surgery when the FT had not reached the posterior lens surface or vitreous base achieved foveal formation and had VAs ranging from 20/250 to 20/40, which was nearly age appropriate (Figure 1A-E and Figure 2). In contrast, the 15 eyes (28.8%) in which the FT reached the posterior lens surface or vitreous base failed to achieve foveal formation and had VAs ranging from 20/2000 to 20/250 (Figure 1F-J and Figure 2). The fovea was absent in 15 eyes: in 11 (73%) because of progression of retinal dragging by contraction of the excessive FT and in 4 (27%) because of malformation of an immature retina despite preservation of the presumed foveal region.

Figure 1. Preoperative and Postoperative Fundus Images of Aggressive Posterior Retinopathy of Prematurity (AP-ROP)



Early vitreous surgery was performed in the left eyes of patients 1 (top row) and 2 (bottom row) with different fibrovascular tissue (FT) growth. A and F, Preoperative drawings. B and G, Preoperative photographs. C and H, Preoperative fluorescein angiograms (FA). D and I, Postoperative photographs. E and J, Postoperative FA. The gestational age of patient 1 was 25 weeks, with a birth weight of 798 g; of patient 2, 26 weeks and 897 g, respectively. Preoperative images in patient 1 show minimal FT present in the photocoagulation scars; in patient 2, FT has grown extensively toward the vitreous base, under which a regional traction retinal detachment has developed. In both patients, vascular activity in the FT shown by fluorescein dye leakage has stabilized after vitrectomy. Patient 1 shows a reattached retina without retinal dragging and with the fovea; patient 2, retinal reattachment with retinal dragging resulting from contraction of residual FT and without the fovea.

Figure 2. Final Postoperative Visual Outcomes



The gray line with standard deviations (vertical bars) indicates normal visual development (visual acuity [VA]) in patients examined using the preferential looking technique from ages 0 to 3 years and using a Landolt ring chart or pictures from 3 to 5 years. Filled shapes indicate the preoperative findings of retinopathy of prematurity (ROP), stage 4A; open circles and triangles, ROP stage 4B; red, fibrovascular tissue (FT) that has not reached the posterior lens surface or vitreous base (Figure 1A); and blue, FT that is attached to the posterior lens surface or vitreous base (Figure 1F). The faint ovals pairing eyes indicate that both eyes are from the same patient. The 4 triangles at the VA level below 20/1600 indicate the worse eyes; their fellow eyes do not have a retinal detachment after successful photocoagulation. Of these 4, the 2 younger patients had retinal dragging, and the 2 older patients had deprivation amblyopia. The 2 triangles at the 20/100 VA level indicate the better eyes, the fellow eyes of which progressed to total retinal detachment (stage 5).

Six eyes underwent unilateral vitreous surgery. Two eyes with good anatomic outcomes obtained good VA at 20/100; the fellow eyes had ROP and developed a total retinal detachment (stage 5). In contrast, 4 eyes had poor VA (worse than 20/1600) despite successful retinal reattachment, postoperative aphakic correction with a contact lens, and continuous occlusion therapy. The fellow eyes achieved ROP stabilization after photocoagulation, foveal formation, and good VA. Two eyes had retinal dragging as a result of worsening ROP, and the other 2 eyes with a nearly normal fovea may have developed deprivation amblyopia.

Discussion

The results of this study indicate that early vitreous surgery may provide benefits for patients with AP-ROP. The disease can stabilize in some eyes treated with only dense photocoagulation; however, when FT continues to grow and a retinal detachment develops, ROP no longer regresses spontaneously. Thus, vitreous surgery is necessary as a secondary treatment.[3,10] Postoperatively, the retina reattached completely in 83 of the 103 eyes (80.6%), and the fovea formed in 63 eyes (61.2%); these results were much better (ie, 91.0% and 70.8%, respectively) when adequate photocoagulation was applied preoperatively. Of the eyes with a total retinal reattachment, postoperative VAs ranged from 20/250 to 20/40 in 68.9%, and those patients could be expected to be mainstreamed into public school systems. The VA outcomes obtained in our patients are fairly good compared with those obtained after lens-sparing vitrectomy for classic ROP[11] despite the poor conditions for visual development, including retinal prematurity in association with a very early birth and postoperative aphakia. Although our study is limited by its uncontrolled retrospective case series design, it is one of the few analyses, to our knowledge, that have examined the functional outcomes of AP-ROP management after surgical procedures performed by a single surgeon.

The VA outcomes are related principally to foveal formation, which starts prenatally and continues postnatally.[12] The fovea was well formed in 71.2% of the eyes in which the VA was

examined but not in the remaining 28.8% because of retinal dragging or malformation of an immature retina. Whether the foveal region is preoperatively involved in a retinal detachment (ROP stage 4B) or not (ROP stage 4A) may not be related to foveal formation and VA outcomes when the retina is promptly reattached postoperatively. Because AP-ROP rapidly progresses to severe retinal dragging and retinal detachment, prompt surgery performed when FT begins to grow and does not reach the posterior lens surface or the vitreous base[3] is expected to facilitate foveal formation and good VA outcomes.

The difference in the VA outcomes in the fellow eyes of the patients who underwent simultaneous bilateral surgery may depend on the preoperative progression of the FT and the postoperative foveal formation. Refractive correction for aphakia using spectacles or contact lenses also helped to facilitate good visual development, although the lens was removed. The eyes that underwent unilateral surgery, the fellow eye of which was blind because of ROP progression, also achieved a good VA. In contrast, in cases of unilateral vitrectomy and/or lensectomy with a functioning fellow eye, the VA outcomes were disappointing despite good anatomic outcomes. When the fellow eye achieves a good VA after successful ROP stabilization by photocoagulation, deprivation amblyopia may develop despite aphakic correction and continuous occlusion therapy. Lens preservation is important to prevent deprivation amblyopia and promote visual development[13,14]; thus, amblyopia is predictable after unilateral surgery with lens removal, which can only contribute to prevention of blindness.

Good anatomic results after lens-sparing vitrectomy for AP-ROP have been reported[15,16] in cases in which the surgery was performed before or just after development of a retinal detachment, which was earlier than in our study. We cannot easily predict whether FT that circumferentially extends less than 1 quadrant will regress or progress after photocoagulation. Furthermore, FT often expands vertically and circumferentially at about 1 week after transient resolution of and sudden recurrence of plus disease.[3,17] However, our experience with lens-sparing vitrectomy to treat AP-ROP in which FT progressed circumferentially for more than 2 continuous quadrants did not stop the progression of retinal detachments compared with the group in which lensectomy was performed.[3] Vitrectomy removes the vitreous gel along which the FT grows; however, when vitrectomy is performed to spare the lens, highly active FT regrows along the residual vitreous gel in the periphery, resulting in progression of the retinal detachment. Fundus angiography showed capillary hypoperfusion throughout the nonvascularized and vascularized retina with AP-ROP; this hypoperfusion is usually restricted to the nonvascularized retinas with classic ROP, indicating release of vascular endothelial growth factor (VEGF) from the wide ischemic area of capillary hypoperfusion, which was insufficiently suppressed by wide dense application of photocoagulation.[8,9] Thus, vitrectomy associated with lens removal facilitates total removal of the vitreous gel and washout of VEGF from the eye. The indication for and timing of surgery and the choice between a lens-sparing procedure or lens removal may be determined by further analysis of FT behavior and changes in VEGF concentrations in the vitreous cavity.

Intravitreal injection of anti-VEGF drugs, primarily bevacizumab (Avastin), which stabilizes neovascular formation, is thought to be useful for treating ROP.[18-20] However, the efficacy of the drug as therapy for AP-ROP is not well established. Monotherapy administered to avoid photocoagulation in the treatment of ROP[18] may not stabilize severe ROP involving the entire retina that is hypoperfused in the presence of a large amount of VEGF. Relatively good outcomes after anti-VEGF therapy combined with other surgical interventions have been reported recently, such as salvage therapy that prevents progression of retinal detachments after application of photocoagulation[19] and an adjunctive therapy to achieve a dilatory effort before planned vitreous surgery,[20] for which some problems remain to be addressed. Contraction of FT, an adverse drug effect that promotes retinal dragging and detachment,[21] is critical when the FT is extensive. Because a large amount of VEGF may be released during a long period in eyes with AP-ROP, a transient effect of the drug may later result in unpredictable recurrence of the retinal detachment.[22] Serum evaluation has shown that intravitreally injected bevacizumab can migrate from the eye into the systemic circulation and reduce the serum level of VEGF in infants with ROP.[23] This adverse effect might disrupt organ development, including that of the central nervous system, in extremely small premature babies with AP-ROP. Thus, the roles of photocoagulation, vitreous surgery, and anti-VEGF therapy in the treatment of AP-ROP should be further investigated in randomized trials regarding efficacy, safety, convenience, and cost. However, a combination of photocoagulation and early vitreous surgery may be a good option for managing this difficult problem at the present time.

ARTICLE INFORMATION

Submitted for Publication: September 23, 2012; final revision received February 15, 2013; accepted February 20, 2013.

Published Online: August 29, 2013. doi:10.1001/jamaophthalmol.2013.4148.

Author Contributions: Dr Azuma had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Azuma. *Acquisition of data:* All authors. *Analysis and interpretation of data:* Azuma, Yokoi, Nakayama. *Drafting of the manuscript:* Azuma, Ito, Nishina. *Critical revision of the manuscript for important intellectual content:* Azuma, Yokoi, Nakayama. *Statistical analysis:* Yokoi. *Obtained funding:* Azuma. *Administrative, technical, and material support:* Azuma, Yokoi, Nakayama, Nishina. *Study supervision:* Azuma.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grants for the study of sensory disorders from the Ministry of Health, Labor and Welfare and from the National Center for Child Health and Development.

REFERENCES

1. Hiraoka M, Watanabe T, Kawakami T, et al. Retinopathy of prematurity in extremely low birth weight infants: a Tokyo multicenter study [in Japanese]. *Nihon Ganka Gakkai Zasshi*. 2004;108(10):600-605.

2. Trese MT, Droste PJ. Long-term postoperative results of a consecutive series of stages 4 and 5 retinopathy of prematurity. *Ophthalmology*. 1998;105(6):992-997.

3. Azuma N, Ishikawa K, Hama Y, Hiraoka M, Suzuki Y, Nishina S. Early vitreous surgery for aggressive

posterior retinopathy of prematurity. *Am J Ophthalmol*. 2006;142(4):636-643.

4. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol*. 2005;123(7):991-999.

5. Nishina S, Yokoi T, Yokoi T, Kobayashi Y, Hiraoka M, Azuma N. Effect of early vitreous surgery for aggressive posterior retinopathy of prematurity detected by fundus fluorescein angiography. *Ophthalmology*. 2009;116(12):2442-2447.

6. Gwiazda J, Wolfe JM, Brill S, Mohindra I, Held R. Quick assessment of preferential looking acuity in infants. *Am J Optom Physiol Opt*. 1980;57(7):420-427.

7. Katsumi O, Uemura Y, Oshima T, Yoshitake H. Development of visual acuity in infants and young children assessed with preferential looking [in Japanese]. *Jpn J Clin Ophthalmol*. 1983;37(7):965-970.

8. Yokoi T, Hiraoka M, Miyamoto M, et al. Vascular abnormalities in aggressive posterior retinopathy of prematurity detected by fluorescein angiography. *Ophthalmology*. 2009;116(7):1377-1382.

9. Yokoi T, Yokoi T, Kobayashi Y, Nishina S, Azuma N. Risk factors for recurrent fibrovascular proliferation in aggressive posterior retinopathy of prematurity after early vitreous surgery. *Am J Ophthalmol*. 2010;150(1):10.e1-15.e1. doi:10.1016/j.ajo.2010.02.005.

10. Sanghi G, Dogra MR, Katoch D, Gupta A. Aggressive posterior retinopathy of prematurity: risk factors for retinal detachment despite confluent laser photocoagulation [published online September 27, 2012]. *Am J Ophthalmol*. 2013;155(1):159-164.e2. doi:10.1016/j.ajo.2012.07.012.

11. Singh R, Reddy DM, Barkmeier AJ, Holz ER, Ram R, Carvounis PE. Long-term visual outcomes following lens-sparing vitrectomy for retinopathy of prematurity. *Br J Ophthalmol*. 2012;96(11):1395-1398.

12. Barishak YR. *Embryology of the Eye and Its Adnexa*. 2nd ed. Basel, Switzerland: Karger; 2001:105-106.

13. Taylor D, Hoyt CS. *Pediatric Ophthalmology and Strabismus*. 3rd ed. Edinburgh, Scotland: Elsevier Saunders; 2005:450-451.

14. Maguire AM, Trese MT. Lens-sparing vitreoretinal surgery in infants. *Arch Ophthalmol*. 1992;110(2):284-286.

15. Micelli Ferrari T, Furino C, Lorusso VV, et al. Three-port lens-sparing vitrectomy for aggressive posterior retinopathy of prematurity: early surgery before tractional retinal detachment appearance. *Eur J Ophthalmol*. 2007;17(5):785-789.

16. Drenser KA, Trese MT, Capone A Jr. Aggressive posterior retinopathy of prematurity. *Retina*. 2010;30(4)(suppl):S37-S40.

17. Vinekar A, Trese MT, Capone A Jr; Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) Cooperative Group. Evolution of retinal detachment in posterior retinopathy of prematurity: impact on treatment approach. *Am J Ophthalmol*. 2008;145(3):548-555.

18. 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.

19. Law JC, Recchia FM, Morrison DG, Donahue SP, Estes RL. Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. *J AAPOS*. 2010;14(1):6-10.

20. Kusaka S, Shima C, Wada K, et al. Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity: a pilot study. *Br J Ophthalmol*. 2008;92(11):1450-1455.

21. Honda S, Hirabayashi H, Tsukahara Y, Negi A. Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(7):1061-1063.

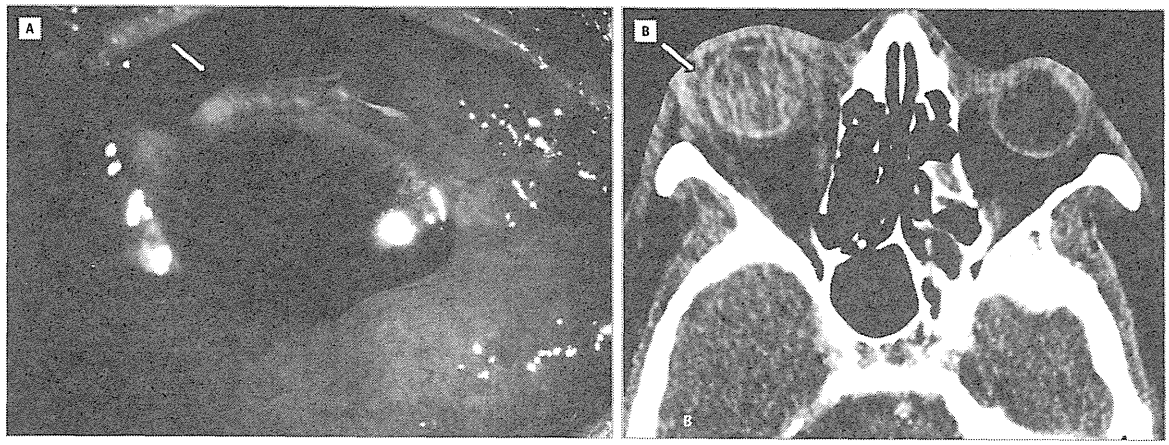
22. Hu J, Blair MP, Shapiro MJ, Lichtenstein SJ, Galasso JM, Kapur R. Reactivation of retinopathy of prematurity after bevacizumab injection. *Arch Ophthalmol*. 2012;130(8):1000-1006.

23. 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.e1-333.e1. doi:10.1016/j.ajo.2011.07.005.

OPHTHALMIC IMAGES

Intraocular and Orbital Hemorrhage in a Patient With Dengue Fever During Cataract Surgery

Jagat Ram, MS; Abiraj Kumar, MS



A 55-year-old man developed hyphema and vitreous and orbital hemorrhage during cataract surgery (A). He was later diagnosed as having dengue hemorrhagic fever with a platelet count less than 17 × 10^3/μL (to convert to ×10^9/L, multiply by 1) and positive serologic results for NS1 antigen and IgG and IgM antibodies. Computed tomography scan of the orbit showed orbital and intraocular hemorrhage (B). The platelet count at 2 months was more than 290 × 10^3/μL.

小児 CKD 患者の移行医療

東京都立小児総合医療センター腎臓内科
本田雅敬

日本小児腎不全学会雑誌　VOL. 33, 2013（2013年 7 月）別刷