Early Vitrectomy Effective for Norrie Disease

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Objective: To review our experience with Norrie disease to determine if early vitrectomy abrogates the natural history of this rare disease; namely, bilateral no light perception visual acuity and phthisis bulbi.

Methods: We retrospectively reviewed the medical records of all patients seen in our tertiary care pediatric retinal clinical practice from 1988 through 2008 with a potential diagnosis of Norrie disease. Inclusion required not only clinical findings consistent with Norrie disease but also genetics and/or a family history consistent with Norrie disease.

Results: Medical record review revealed 14 boys with clinically diagnosed Norrie disease and either Norrie disease gene (NDP) mutations noted on genetic testing (13 patients) and/or a clear family history consistent with Norrie disease (4 patients). All 14 boys with definite Norrie disease had vitrectomy with or without lensectomy in at least 1 eye prior to 12 months of age. Of the 14 boys with definite Norrie disease, 7 maintained at least light perception visual acuity in 1 eye and 3 had no light perception visual acuity bilaterally; visual acuity data were not available for 4 patients. Only 2 of 24 (8%) eyes became phthisical.

Conclusions: Historically, no treatment has been offered to mitigate the dismal natural history of Norrie disease. We recommend consideration of early vitrectomy in Norrie disease.


Norrie Disease is a rare, X-linked, recessive disorder, the clinical manifestations of which have been extensively characterized by Warburg.1-6 Ocular manifestations are invariably severe; approximately one-third of patients develop hearing loss and two-thirds have mental retardation. Boys with Norrie disease are blind (no light perception [NLP]) from birth or shortly thereafter (most cases by 3 months of age) secondary to severely dysplastic retinae. Findings in infancy include leukocoria, iris atrophy, retrolental fibroplasia, vitreous hemorrhage, dysplastic retinae with a gray or grayish-yellow pseudoglioma appearance, retinal folds, and retinal detachments (often hemorrhagic). These eyes subsequently develop cataracts and opaque corneas and become phthisical within the first decade of life. Historically, no treatment has been offered.

METHODS

Institutional review board (William Beaumont Hospital) approval was granted for this retrospective study. We reviewed the medical records of all patients seen in our tertiary care pediatric retinal clinical practice from 1988 through 2008 with a potential diagnosis of Norrie disease. Patient lists were generated using International Classification of Diseases, Ninth Revision (ICD-9) codes 7438 (Norrie disease; anomaly of eye other specified), 74358 (persistent fetal vasculature; tortuous retinal vessels congenital), and 74351 (persistent hyperplastic primary vitreous; vitreous opacities congenital). These searches yielded 15, 227, and 101 patients, respectively. Clinical diagnosis of Norrie disease required the presence of bilateral dysplastic retinae. Children with clinical findings suggestive of Norrie disease but neither a family history consistent with the X-linked recessive inheritance of Norrie disease nor a Norrie disease gene (NDP; OMIM 300658) mutation noted on genetic testing were classified as having bilateral persistent fetal vasculature syndrome (PFVS), not Norrie disease.

RESULTS

Medical record review revealed 14 boys with clinically diagnosed Norrie disease with NDP mutations noted on genetic testing (Table) and/or a family history of Norrie disease. All 14 boys had bilateral dysplastic retinae notable for abnormal and limited vasculature. Some had a characteristic pseudoglioma that we have characterized as having a “pumpkin” appearance (Figure 1) with an avascular peripheral retina. Frequently noted concomitant findings included persistent stalk...
tissue extending from the dysplastic retina to the lens
(noted surgically in all cases), retinal detachment, sub-
retinal hemorrhage, and retrolental fibroplasia, often dense
and thus yielding no posterior view, and often associ-
ated with total retinal detachment with large amounts of
subretinal blood.

One additional boy had clinically suspected Norrie dis-
ease but a negative family history and an indeterminate ge-
netic test that was suspicious for an exon 2 deletion in the
NDP gene secondary to an inability to amplify exon 2. He
was therefore classified as having bilateral PFVS. One boy
with clinical findings consistent with Norrie disease had a
half brother (same mother) with a history of bilateral PFVS,
but had indeterminate genetic testing and therefore was clas-
sified as having bilateral PFVS. An additional 12 patients
(4 girls, 8 boys) had clinical findings consistent with Nor-
rie disease but negative family history and genetic testing
and therefore were diagnosed as having bilateral PFVS. Two

### Table. Clinical Data for 14 Boys With Definite Norrie Disease

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Family History</th>
<th>Surgery (Age at Time of Surgery)</th>
<th>Total Duration of Follow-up, mo</th>
<th>Final Visual Acuity (Age, mo)</th>
<th>Phthisis</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>LSV OD (3.5 mo); Lens/Vit OS (3.5 mo);</td>
<td>33</td>
<td>20/200 Teller acuity OD,</td>
<td>Prephthisis OS</td>
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<tr>
<td></td>
<td></td>
<td>repeat Vit OS (10 mo &amp; 15 mo)</td>
<td></td>
<td>±LP OS (36)</td>
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<tr>
<td>2</td>
<td>None</td>
<td>Lens/Vit OU (6 mo); repeat Vit OS (15 mo)</td>
<td>47</td>
<td>NLP OU (53)</td>
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<td>3</td>
<td>None</td>
<td>Vit OS (3 mo); outside surgeon; Lens/Vit OD (8 mo)</td>
<td>61</td>
<td>NLP OU (64)</td>
<td>Prephthisis OS</td>
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<tr>
<td>4</td>
<td>None</td>
<td>LSV OS (4.5 mo); Lens/Vit OD (4.5 mo)</td>
<td>29</td>
<td>LP OS, NLP OD (33)</td>
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<td>5</td>
<td>None</td>
<td>Lens/Vit OD (3 mo); outside surgeon;</td>
<td>69</td>
<td>LP OS, NLP OD (74)</td>
<td>Prephthisis OS</td>
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<tr>
<td></td>
<td></td>
<td>Lens/Vit OS (5 mo); repeat Lens/Vit OD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5 mo); repeat Vit OS (14 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>Vit OS (4 mo), OD (5 mo); repeat Vit with</td>
<td>Follow-up elsewhere</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lens OS (6 mo), all outside surgeon</td>
<td></td>
<td>. . .</td>
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<tr>
<td>7</td>
<td>Older brother with ND (patient 8)</td>
<td>LSV OD (1 wk); Lens/Vit OS (1 wk);</td>
<td>78</td>
<td>LP OD, NLP OS (78)</td>
<td>Phthisis bulbi OS</td>
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<td></td>
<td>Vit OS (2 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Younger brother with ND (patient 7)</td>
<td>Vit OU (1 mo), outside surgeon; repeat</td>
<td>90</td>
<td>NLP OD, LP OS (117)</td>
<td>Phthisis bulbi OD</td>
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<td>Vit OS (27 mo)</td>
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<td></td>
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<tr>
<td>9</td>
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<td>Lens/Vit OU (3 mo)</td>
<td>Follow-up elsewhere</td>
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<td>Lens/Vit OU (1.5 mo)</td>
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<td>LP OD, 20/400 Teller acuity OS (4.5); at least LP OU (11.5)</td>
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<td>11</td>
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<td>Lens/Vit OD (11.5 mo), OS (14 mo)</td>
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<td>NLP OD, CF 2 ft OS (212)</td>
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<td>12</td>
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<td>Lens/Vit OS (1 mo), OD (1.5 mo)</td>
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<td>. . .</td>
<td>No</td>
</tr>
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<td>Younger brother with ND (patient 12)</td>
<td>Lens/Vit OU (1 mo)</td>
<td>12</td>
<td>±LP</td>
<td>Prephthisis OD</td>
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<tr>
<td>14</td>
<td>None</td>
<td>Lens/Vit OU (3 mo)</td>
<td>12</td>
<td>NLP OU (15)</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: CF, counting fingers; ellipses, unknown; Lens, lensectomy; Lens/Vit, lensectomy and vitrectomy; LP, light perception; LSV, lens-sparing vitrectomy; ND, Norrie disease; NLP, no light perception; OD, right eye; OS, left eye; OU, both eyes; Vit, vitrectomy.

*Defined as bilateral dysplastic retinae and NDP mutation on genetic testing and/or family history of Norrie disease.

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**Figure 1.** Pumpkin lesions in Norrie disease. Severely dysplastic retinae in Norrie disease may have this pseudoglioma appearance. A, A Retcam photograph shows the preoperative appearance in the left eye of patient 4 (Table). Notice the vascularized dysplastic retinal mass located posteriorly with associated subretinal hemorrhage and lipid. A stalk of tissue extended from this mass to the posterior lens surface. The retina peripheral to the pumpkin lesion was avascular. The right eye had dense retrolental fibroplasia. B, A Retcam photograph shows the preoperative appearance in the right eye of patient 1. Compared with the left image, there is less subretinal lipid/blood. Also note, at the base of the pumpkin there are some retinal blood vessels seen posteriorly.
such patients also were noted to have a pumpkin appearance to their dysplastic retinas (Figure 2). Eight additional patients (6 boys, 2 girls) had no genetic testing data in their medical records. The 22 patients with ocular findings consistent with Norrie disease but classified as having bilateral PFVS also had vitrectomy in at least 1 eye if there was evidence of at least light perception (LP) preoperatively. There were 5 additional patients (3 male, 2 female) with clinical characteristics consistent with Norrie disease without a family history or positive genetic testing, and thus classified as having bilateral PFVS, who did not have vitrectomy surgery at any point, for various reasons. eg, NLP visual acuity or being an adult patient. Four patients (3 girls, 1 boy) had clinical findings consistent with Norrie disease but genetic analysis was still pending so they were not included in the Norrie disease cohort.

All 14 boys with definite Norrie disease (based on clinical diagnosis and genetic mutation) had vitrectomy with transection of stalk tissue exerting traction on the detached retina, with or without lensectomy, in at least 1 eye prior to 12 months of age. Of the 14 boys with definite Norrie disease, 7 maintained at least LP visual acuity in 1 eye (follow-ups 3, 29, 33, 69, 78, 90, and 202 months) and 3 had NLP bilaterally (follow-ups 12, 47, and 61 months) (Table). Visual acuity data were not available for 4 of the 14 patients with Norrie disease. One child developed 20/200 visual acuity in his better eye after lens-sparing vitrectomy (Figure 3). Of the 7 patients with at least LP in the better eye, the median age at time of vitrectomy in the better eye was 3.5 months (range, 1 week to 14 months; mean, 4.3 months). The median age at the time of vitrectomy for the 3 patients with bilateral NLP was 4.5 months (range, 3-8 months; mean, 4.8 months). that did not have surgery. Lev et al also referred to a patient with Norrie disease who had bilateral lensectomy and vitrectomy at 1 month of age but outcome data were not reported. We have found in all of our patients with Norrie disease that there is residual stalk tissue (hyaloidal vessel remnant) connecting the posterior lens to the dysplastic retina. Intraoperatively we have noted that, as this stalk tissue is transected (preferably early in the surgery), significant traction on the retina is often released. We feel that this release of traction on the retina is likely to at least partly explain the benefit of vitrectomy for Norrie disease. Release of this traction not only allows the retina to settle posteriorly but also eliminates an anterior-posterior tether that likely restricts normal ocular development. In cases in which there is a dense retrolental plaque with total retinal detachment, we feel that meticulously peeling away this tissue from the retinal and ciliary processes not only allows the retina to gradually reattach but also decreases the likelihood of hypotony secondary to ciliary body traction. Given the natural history of the disease (NLP by 3 months of age in most cases), we perform vitrectomy as early as possible. If there is significant lens opacity obscuring our view of the fundus or significant retrolental fibroplasia intimately apposed to the lens, we often remove the lens in addition to performing a vitrectomy. Interestingly, despite the presence of large areas of avascular retina (which we do not treat with laser photocoagulation or cryotherapy), we have not noted any neovascularization in our patients. Perhaps the avascular retina is so dysgenic that it does not mount a significant vascular endothelial growth factor response.

This study has the inherent deficiencies of a noncontrolled retrospective review. Despite this, we feel that we provide convincing evidence that early vitrectomy effectively alters the natural course of Norrie disease. Warburg’s extensive study of Norrie disease only revealed rare cases with vision beyond infancy. Of 24 patients in her series, all had NLP except for 1 who could count fingers until age 12, when LP was lost, and another boy who could perceive light. In Warburg’s review of the literature, she
identified an additional 106 patients with Norrie disease. Of these, only 6 were noted to have LP or pupillary reactivity after 3 months of age. Three were from the same Greek family. One could read large print with the right eye and had LP in the left until 13 years of age, after which he was amaurotic. A 3-year-old boy had ambulatory vision in the right eye and LP in the left. Another patient from this family had LP visual acuity. Three other patients from an American family had LP. In total, only 8 of 130 (6%) patients had some vision noted after the age of 3 months. This is in stark contrast to our series of patients with Norrie disease, 70% of whom maintained at least LP visual acuity in 1 eye after vitrectomy.

In this study, we have limited our definition of Norrie disease to patients who have both the ocular phenotype of the disease (bilateral dysplastic retinae) and either a clear family history consistent with the X-linked transmission of Norrie disease or a mutation of the NDP gene noted on genetic testing. We have previously found that mutations that affect the cysteine-knot motif of the NDP gene product norrin result in severe retinal dysgenesis.10 These mutations were found to result in a pumpkin appearance to the dysplastic retina that has also been referred to as a pseudoglioma. This phenotype may not be pathognomonic of Norrie disease, though. Figure 2 shows a similar phenotype in a child that we labeled as having bilateral PFVS. Although he had ocular features consistent with Norrie disease, he had neither a family history of Norrie disease nor any abnormalities in his NDP gene revealed by genetic testing. It is possible that he and other patients that we have categorized as having bilateral PFVS have mutations in the NDP gene (eg, intron mutation that affects splicing) not revealed by current protocols for genetic testing. Another possibility is that Norrie disease and bilateral PFVS with severe posterior findings are phenotypically similar. Our surgical experience with bilateral PFVS is remarkably similar to what we have found in Norrie disease.11

There are several reasons that we feel surgery to preserve even rudimentary vision is worthwhile. Seaber et al12 found in their study involving vitrectomy for stage V retinopathy of prematurity that only form vision is required for ambulation using visual cues, not 5/200 vi-
sual acuity as previously reported. They also noted that even children with only LP objected strenuously to bilateral occlusion, suggesting that they value any residual vision. Light perception is also beneficial for the maintenance of normal circadian rhythms and sleep-wake cycles in children, which is likely important in maximizing the potential for attention and learning in children with limited vision. It has also been our anecdotal experience that NLP often results in behavioral disturbances in children (not shown). Additionally, the future holds promise for the development of technologies for vision restoration. We feel that it is safe to assume that a child with at least LP is likely to be in a better position to benefit from these technologies than a child with no ability to perceive light. Thus, based on these premises and our experience with Norrie disease, during the past 2 decades in particular, we recommend early vitrectomy for patients with Norrie disease.

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REFERENCES


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