Dissociated vertical divergence (DVD) remains one of the most controversial ocular motor disturbances. It is characterized by the slow ascent of either eye followed, after a variable period of time, by a slow descent back to its neutral position. Although it is generally associated with infantile esotropia, it can also accompany other forms of binocular misalignment that develop in early infancy.

Alfred Bielschowsky, M.D., defined the essential role of luminance disparity in DVD in 1931. The importance of fixation was demonstrated in 1944 by Adolph Posner, M.D. “It remains unknown yet today, however, whether a binocular luminance disparity can trigger DVD in the absence of a pre-existing binocular fixational stimulus,” says Michael C. Brodsky, M.D., an ophthalmologist at Mayo Clinic’s campus in Rochester, Minnesota. “This issue is crucial to understanding the pathophysiology of DVD,” says Dr. Brodsky. “To address it, our research team performed video-oculographic eye movement recordings in subjects with DVD while independently controlling for luminance and fixational disparity in the two eyes.” Study results were published in *Investigative Ophthalmology & Visual Science* in 2015.

**Fixation Is the Primary Driver of Dissociated Vertical Divergence**

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**6 subjects, 6 controls, 4 conditions tested**

Dr. Brodsky’s team measured vertical eye position in six subjects with DVD (ages 11-47 years, five females, one male) and six controls (ages 16-40 years, five females, one male) using video-oculography under conditions of change in fixation and luminance. Diagnosis of DVD was based on these clinical criteria: a clinical history of infantile strabismus and the finding of a hyperdeviation of each eye when covered on alternate cover testing in primary position. Exclusion criteria included inability to perform the eye movement recording protocol (age younger than 8 years), a refractive error greater than 3 diopters (unless corrected with contact lenses) or a history of vertical muscle surgery.

Simultaneous horizontal, torsional and vertical eye movements were recorded using the SensoMotoric infrared video-oculographic system, a measurement system for acquisition of eye movements based on noninvasive video image processing technology using head-mounted infrared video cameras.

The testing protocol for all subjects involved four specific conditions, performed in consecutive order, in succession, and at less than one-minute intervals:

1. Alternate occlusion without fixation (monocular darkening)
2. Alternate increased luminance without fixation (monocular flashlight)
3. Alternate occlusion with fixation in darkness (crossbar)
4. Alternate occlusion with fixation (room light)

Control subjects showed no vertical divergence under any testing conditions, but in subjects with DVD:

- In monocular darkening, when fixation was precluded with a translucent filter and bright light was shined into one eye to produce a marked binocular luminance disparity, some subjects had a small induced vertical divergence causing the illuminated eye to be lower than
Patients Report Better Vision-Related Quality of Life After Endothelial Keratoplasty

The management advantages of DSEK over PK from the surgeon’s perspective are well-known,” says Sanjay V. Patel, M.D., an ophthalmologist at Mayo Clinic’s campus in Rochester, Minnesota, “but little is known about the impact of EK on patient-reported outcomes.” Results of a study by Dr. Patel and a research team at Mayo Clinic to assess vision-related quality of life in Fuchs’ dystrophy and changes in vision-related quality of life after three types of keratoplasty — PK, DLEK and DSEK — were published in Ophthalmology in 2014.

**Consecutive studies**

Fuchs’ dystrophy is a slowly progressive disease that typically affects both eyes symmetrically, resulting in impaired visual function with decreased visual acuity and increased disability glare. Patients who required their first keratoplasty in either eye because of decreased vision caused by Fuchs’ dystrophy were recruited from the Mayo Clinic cornea service. Of 63 subjects, 12 (12 eyes) received PK, 11 (11 eyes) received DLEK, and 40 (40 eyes) received DSEK. All subjects were enrolled in two consecutive prospective studies.

In the first study, subjects were randomized to PK or DLEK between 2004 and 2006 and examined prospectively through three years after surgery. Entrance best-corrected visual acuity was 20/40 (Snellen equivalent) or worse, and only subjects with a recipient diagnosis of Fuchs’ dystrophy were included. In the second study,
subjects with Fuchs’ dystrophy were prospectively examined through three years after DSEK. Enrollment occurred between 2006 and 2009, and there was no entrance visual acuity criterion.

Corneal surgeons performed PK with a recipient diameter of 7.5 or 7.75 mm (mean, 7.55 mm), with the donor secured to the host using a double-running suture technique. DLEK was performed through a 9- to 10-mm scleral tunnel incision initiated at a depth of 350 mm. DSEK was performed through a 5- to 6-mm temporal scleral tunnel incision and inserted in the donor by using a folding technique. For phakic eyes, cataract extraction and intraocular lens insertion were performed simultaneously.

The following outcomes were determined at examinations before keratoplasty and at regular intervals through three years after keratoplasty:

- Vision-related quality of life was assessed using the 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25)
- Best spectacle-corrected and uncorrected visual acuities were measured by using the electronic Early Treatment Diabetic Retinopathy Study protocol
- Keratometric cylinder was measured by a manual keratometer
- Disability glare was measured with a straylight meter

Scores improve for all treatments

The composite score for all eyes with Fuchs’ dystrophy before keratoplasty was 72 ± 11 (n = 63) and did not differ between eyes destined for PK, DLEK or DSEK (P = 0.88). Vision-related quality-of-life composite scores improved by six months with all treatments when compared with preoperative (PK, P = 0.008; DLEK, P = 0.03; DSEK, P < 0.001), with continued improvement between six months and three years after PK (P = 0.01) and DSEK (P = 0.004). At six months, the composite score was higher after DSEK than after PK (P = 0.006). At three years, there were no differences in composite scores between the three treatments. The mean composite score for all three was 90 (P = 0.33).

“Vision-related quality of life in all patients with Fuchs’ dystrophy improved after corneal transplantation,” says Dr. Patel (Table). “Although all three keratoplasty techniques examined resulted in similar improvement over the first three postoperative years, improvement was fastest after DSEK and slowest after PK, which may be explained in part by rapid improvement in uncorrected visual acuity. Best-corrected visual acuity after DSEK frequently improves close to that of subjects with normal vision, indicating that other aspects of visual function are important for overall function.”

For more information


### Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>6 Months</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best spectacle-corrected visual acuity</td>
<td>-0.34 (0.03)</td>
<td>-0.22 (0.46)</td>
<td>-0.21 (0.10)</td>
<td>-0.20 (0.31)</td>
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<tr>
<td>Uncorrected visual acuity</td>
<td>-0.37 (0.002)</td>
<td>-0.38 (0.001)</td>
<td>-0.25 (0.11)</td>
<td>-0.36 (0.02)</td>
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<tr>
<td>Keratometric cylinder</td>
<td>-0.27 (0.06)</td>
<td>-0.03 (0.80)</td>
<td>-0.17 (0.17)</td>
<td>-0.21 (0.29)</td>
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<tr>
<td>Intraocular straylight (disability glare)</td>
<td>-0.04 (0.93)</td>
<td>-0.09 (0.56)</td>
<td>-0.29 (0.07)</td>
<td>-0.41 (0.02)</td>
</tr>
</tbody>
</table>

Regenerative Medicine Biotrust Provides Hope for Patients With Best Disease

Eleven-year-old Madison’s sight had never been great — she first wore eyeglasses at age 4, starting with a +3D prescription. Then at age 6, local doctors noted bilateral macular scarring and referred her to Mayo Clinic.

Jose S. Pulido, M.D., with the Department of Ophthalmology at Mayo Clinic’s campus in Rochester, Minnesota, evaluated Madison and diagnosed autosomal recessive bestrophinopathy, a rare recessive form of the already rare Best disease, an inherited form of macular degeneration. Best disease usually does not impair vision until later in life, which made Madison’s early onset difficult to detect. Her even rarer recessive
form of Best disease makes it just as difficult to predict her prognosis. Although she is unlikely to become completely blind, legal blindness is a real possibility and there is currently no treatment to prevent it.

**Innovative stem cell treatment**

In August 2013, Alan D. Marmorstein, Ph.D., an expert on Best disease at Mayo Clinic’s campus in Minnesota, proposed the development of an innovative stem cell treatment to help Madison. If successful, the treatment could help people with Best disease around the world.

Dr. Marmorstein has worked on Best disease since 1998, when the gene that causes the disease was discovered. He believes that bioengineered stem cells might halt the disease’s progression, or even cure it. Mayo Clinic’s Center for Regenerative Medicine has the capability to bioengineer induced pluripotent stem cells from adipose tissue and is pioneering methods to convert skin cells into stem cells for subsequent differentiation.

The center also houses the Regenerative Medicine Biotrust, which enables Dr. Marmorstein to test a number of possible treatments at once. Dr. Marmorstein has partnered with the biotrust to develop a regenerative medicine protocol focused on Best disease.

“We went from being experts in Best disease to being able to apply stem cells to Best because of the assistance of the biotrust experts,” Dr. Marmorstein says. “I can’t emphasize how critical they have been for this work. In one year, we’ve been able to accomplish what would have taken five years anywhere else.”

**RPE cell use for Madison**

The biotrust converted Madison’s skin samples into bioengineered stem cells and is now helping Dr. Marmorstein and colleagues convert those cells into functioning retinal pigment epithelial (RPE) cells — the cells affected by Best disease. The team will be able to test a number of possible treatments for Madison by working with the bioengineered cells before ever treating her. The first potential treatment will be gene therapy. The team will also use the cells to test drugs that show promise but are not approved by the Food and Drug Administration for Best disease. Both of these approaches have drawbacks: Gene therapy might lead to the unregulated expression of the protein involved in the disease, and medications always carry the risk of side effects.

Dr. Marmorstein believes the most effective solution may be to remove Madison’s damaged RPE cells and replace them with RPE cells bioengineered from her skin cells after the mutation causing the disease has been repaired. This approach could enable a permanent treatment with no potential side effects.

“Gene therapy doesn’t remove the bad protein. Finding a drug would mean Madison would be on that drug for the rest of her life,” Dr. Marmorstein says. “The best approach may well be to replace her RPE cells with new ones in which we have repaired the gene.” Information about Dr. Marmorstein’s research in the use of stem cells as a cure for bestrophinopathies was published in *Ophthalmology Update* in 2014.

**For more information**
