Endothelial Cell Changes as an Indicator for Upcoming Allograft Rejection Following Descemet Membrane Endothelial Keratoplasty

Jack Parker Jr, MD; Lamis Baydoun, MD; Claire Monnereau; Gerrit R. Melles, MD, PhD
The Netherlands Institute for Innovative Ocular Surgery (NIIOS), Melles Cornea Clinic, and the Amnitrans Eye Bank, Rotterdam, The Netherlands.

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Background

• While performing routine specular microscopy evaluations in our entire cohort of DMEK patients, we observed characteristic endothelial changes in eyes that later developed a clinically manifest allograft rejection.

• Therefore, the aim of the current study was to evaluate which early endothelial cell changes could be detected by retrospective analysis of sequential, in vivo specular microscopy images at standardized time intervals before a rejection became clinically apparent.
Experimental Design

Of 500 eyes that underwent DMEK at a tertiary referral center, 7 developed typical clinical signs of an allograft rejection.

Specular microscopy images before, during, and after the rejection episode were analyzed and compared with a case-control group of 49 asymptomatic DMEK eyes that matched baseline characteristics of the rejection group.

Endothelial cell morphology was evaluated by subjective scoring (range 1–5) in a masked fashion as well as by an objective comparison of endothelial cell density, cell size, coefficient of variation, and hexagonality in rejection vs control eyes.
Reference specular microscopy images. The images display the sequential stages used to subjectively score the endothelial cell morphology on a scale from 1 to 5: (1) quiet endothelial cell layer with a regular cell morphology and distribution, without any sign of cellular activation; (2) slightly irregular endothelial cell morphology and/or distribution, but without any sign of cellular activation; (3) mild to moderate irregular endothelial cell morphology and/or distribution, and mild to moderate appearance of cellular activation; note the increased cellular reflectivity (black arrow) with detectable cell nuclei (white arrow); (4) severe irregular endothelial cell morphology and/or distribution, and clear presence of cellular activation with enlarged cell nuclei; (5) extreme irregular endothelial cell morphology and/or distribution, and presence of highly activated cells.
Results

Before their rejection episodes, eyes that later developed an allograft rejection showed a large and statistically significant difference in subjective scoring, endothelial cell density, and hexagonality, compared to control eyes.

This indicates that despite the absence of clinical signs of rejection, specific changes in endothelial cell morphology could already be observed. These changes in endothelial cell features were visible an average of 6 months (range, 1–18 months) before detectable subjective and/or objective clinical signs of rejection.
Specular microscopy images after DMEK (rejection group).

The images show the central (Upper images) and peripheral (Lower images) donor endothelium at various time intervals after DMEK (in one eye).

The eye suffered from a rejection episode at 42 months after surgery. (Upper left and Lower left image)

At 6 months after DMEK, specular microscopy shows a normal quiescent endothelial cell layer with a regular hexagonal pattern. (Upper second left and Lower second left image)

At 24 months after DMEK, however, in the complete absence of any clinical signs of an allograft rejection, the overall cell morphology has changed: prominent cell nuclei are visible, as well as a disorganized cell mosaic. (Upper third and Lower third image)

At 42 months after DMEK, the patient requested a consultation on his own initiative for ocular discomfort and a subjective drop in visual acuity, and the eye is diagnosed with an allograft rejection. (Upper right and Lower right image)

After intensified steroid therapy, the rejection subsided clinically, but the aberrant changes in endothelial cell morphology persisted in the long term, causing progressive central corneal edema (so that further specular microscopy imaging was not possible).
Conclusion

Our study suggests that allograft rejection may not be an acute event, but rather a slow-onset immune response. Early, specific changes in endothelial cell morphology were found to “announce” an upcoming allograft rejection. If so, monitoring donor endothelium after DMEK or other forms of keratoplasty may be used to anticipate a rejection episode and/or to prevent an allograft rejection from clinically manifesting itself.
Thank you!

<table>
<thead>
<tr>
<th>Jack Parker</th>
<th><a href="mailto:jack.parker@gmail.com">jack.parker@gmail.com</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerrit Melles</td>
<td><a href="mailto:info@niios.com">info@niios.com</a></td>
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