DMEK Best Practices Session 3 – Guttae

Fuchs' endothelial dystrophy (FED) remains the leading indication for DMEK, characterized by collagen excrescences on the Descemet membrane known as *guttae*. Identifying these structures in both patient eyes and donor tissue is crucial for optimal clinical outcomes. How do guttae impact vision? What do they look like in donor corneas? And can they reappear after transplantation?

FED and guttae in patients: diagnostics and decision-making for DMEK

The cornea

- The cornea should remain transparent. A dysfunctional cornea is cloudy and edematous.
- While from the anterior chamber side the cells have a beautiful hexagonal morphology, there is a complex structure underneath. The deeper into the Descemet's the more complicated and interdigitated the cells are.
- Endothelial cell density is the highest when we are born, with the cells clustered in the center. The first decrease comes when the eye grows (6000 cells/mm^2 then stretch over the entire cornea), the second after cataract surgery.
- The decompensation threshold of the cornea is around 500 cells/mm^2.

The Descemet membrane and the origin of guttae

- The Descemet membrane is a structure that thickens your whole life. You are born with a very thin Descemet Foetal Anterior Banded Layerwith deposition of DM on top of it year after year in regular neat layers.
- As for peeling donor tissue, preferably start with older donors. The younger the donor, the thinner the Banded Layer and the depositions on it, it is likely to tear.
- Descemetorhexis is easier to perform in an older patient due to the neat layer of depositions
- Guttae, mushroom-like protrusions poking through the endothelium, are of the very similar material as the rest of the Descemet, coming from endothelial cells that are no longer regularly depositing.

What is in the guttae?

- Because they are so related to Extra cellular matrix (ECM)guttae contain a lot of ECM proteins, type 1 and type 8 collagen, fibronectin and agrin. But they are not exactly the same as normal Descemet.
- Some studies have identified specific proteins that are present in guttae but not in healthy Descemet membranes.

Imaging of guttae

- Central guttae are classical for FED. Using specular microscopy can yield a wide variety of cell countings from the same cornea.
- Optimal would be a pan-corneal specular but it is not (yet) available.
- Confocal microscopy gives high quality images but the machine is not produced anymore.
- Scheimpflug tomography/pentacam will not image the cells but shows an idea of the function and what the cells do. Recommended article for its practicality:

Sun SY, Wacker K, Baratz KH, Patel SV. Determining Subclinical Edema in Fuchs Endothelial Corneal Dystrophy: Revised Classification using Scheimpflug Tomography for Preoperative Assessment. *Ophthalmology. 2019;2:195-204*.

- Three important features in this article help to decide how much of the problem is coming from the cornea and how much from the cataract:
  1. Displacement of thinnest part of the cornea
  2. Loss of parallel isopachs, lines of similar pachymetry joined together; normal corneas should have very similar central isopachs
  3. Focal area of posterior surface depression, the cornea is swelling a bit downwards (towards anterior chamber)

Current treatment options for corneal endothelial dysfunction

- Endothelial Keratoplasty: you need a donor.
- Cell Therapy: available from Japan, but you will need to remove the guttae.
- In vivo Regeneration: Descemet Stripping Only etc.: guttae still have to be removed and healing takes longer. But: guttae are coming back with time since they are made by the same endothelial cells.

How to remove the guttae?

- Descemetorhexis works incredibly well.
- Not recommended: Using YAG to remove the guttae. It worked to disrupt the back of the guttae but with serious damage to the posterior stroma.

Eye rubbing

Eye rubbing can result in completely inverting the cornea, and hitting the anterior structures is part of the problem in some cases. To all patients with IOL or other lenses: forbidden to rub the cornea, not only for Keratoconus patients.

Take home messages

- Guttae are like icebergs, you just see the tip.
- Guttae are an aberrant arrangement of the ECM, the cells do not know any more how to behave properly.
- It is unclear how new cell therapies will react, since the guttae must be removed to create space for new cells.
- Guttae removal is possible. There is a difference in European or Asian eyes. Guttae run deep in European eyes, may be different in Asian eyes.

Discussion

Guttae-like deposition in retina
Similar aberrant depositions between hexagonal cells poke up in retinal tissue. The drusen in Macular Degeneration share many risk factors like genetic predisposing factors, oxidative stress and age. They might represent outcomes of the same type of disease process.

In the DMEK decision making process: focus mostly on the function of the cornea or on the patients' visual quality?
How much of the patient's problems comes from the cornea and how much from the internal lens?
- Patients under the age of 56: only do DMEK.

- Patients over 56, just do the cataract surgery and see what happens. The Patel paper gives answers: if you note the mentioned features of subclinical edema in your patient's cornea the cataract surgery alone is probably not enough.
Sun SY, Wacker K, Baratz KH, Patel SV. Determining Subclinical Edema in Fuchs Endothelial Corneal Dystrophy: Revised Classification using Scheimpflug Tomography for Preoperative Assessment. *Ophthalmology. 2019;2:195-204*.

Is the difference of guttae embedding shown in the images in old compared to young age due to stroma nature or to the guttae itself?
Young FED patients have really different depositions than old patients, not the classical type of FED. Young patients have a lot of aberrant material diffusely spread over the entire cornea.It is a different genetic inheritance pattern. Very centrally in classical older patients, whereas in younger patients it might be limbus to limbus, a clear center and a ragged zone in the periphery with loads of guttae. New (cell) therapies include that the guttae need to be removed. Guttectomy might be a technique we need to refine in the future.

The appearance of guttae in donor tissue and ongoing research in eye banking

Guttae in the eye bank

- The presence of guttae in donor corneal tissue is a reason for rejection of donor tissue.
- No real consensus between eye banks.
- In some pictures it is hard to determine if we are looking at guttae or at artefacts.
- In the eye bank we use Light Microscopy (LM) to evaluate the endothelium.
- FED is a contraindication for donating eye tissue so we do not see donor tissue with guttae in the eye bank.
- Literature about guttae in corneas in living patients (with confocal, slitlamp, OCT, specular microscope) is readily available, but not about guttae in donor corneas with LM from eye banks.
- Guttae are a focal thickening of the Descemet Membrane which causes a distortion in the endothelial mosaic. This distortion causes abnormal cell morphology and cell death in donor corneas.

Our research

- Healthy corneas have a good distribution of the endothelial cells on the DM. To study guttae we looked at the appearance of guttae in the eye bank and at the structure of guttae with H&E staining.
- We compared proven FED patients' post-mortem corneas with donor corneas from the eye bank.
- We examined the corneas diagnosed with Fuchs with LM and H&E staining and saw that the guttae lighted up as white to green spots under the LM and with H&E staining we saw protrusions.
- We also see in FED patient's corneas that the guttae are changing the shape of the cells around them (LM). With H&E staining we see endothelial cells being pushed away by the guttae, which causes them to distort and perhaps to die.

Guttae appear as

- transparent to dark greenish spots which tend to lighten up (LM)
- small to large 'bumps' (LM and H&E)
- areas without normal endothelial cells around them (LM and H&E).

Difficulties

- In the eye bank it is hard to distinguish between guttae and artefacts in LM
  - when do we reject the cornea?
  - what is the effect on the patient outcome?

Discussion

What is the protocol in the eye bank with guttae?

Guttae are not often seen in the eye bank. If in doubt, we first ask a colleague to have a second look, and we don't take the risk if we are not sure. The issue is, are we rejecting the tissue because there are guttae or do we see something else?

If you see the Hassall-Henle bodies at the periphery, do you doubt?
No, because they are on the periphery and we doublecheck. We are alarmed when the Hassall-Henle bodies are in the center. When they are in the periphery they will be left out after trephination and the morphology of the endothelial cells will still be normal .

Recurrence of guttae post-DMEK and the effect of pre-and post-DMEK guttae on clinical outcomes

What happens after DMEK when you see guttae in the graft? What is the impact the guttae have on the clinical outcomes?

What is the effect of preoperative guttae on DMEK outcomes?

- Categorization used is the Modified Krachmer Grading: the classification of preoperative disease severity. This grading is based on how many guttae are present and whether or not these guttae are confluent or not.
- Grade 1 and 2 are mild, you do not perform DMEK in that stage, grade 3 and 4 are moderate FED corneas, grade 5 and 6 are the advanced FED corneas. (grading by slitlamp, standard or in retro-illumination mode but also specular microscopy or Scheimpflug imaging can show guttae distribution).
- NIIOS study: Vasiliauskaitė I, Kocaba V, van Dijk K, Baydoun L, Lanser C, Lee D, Jager MJ, Melles GRJ, Oellerich S. Long-term outcomes of Descemet membrane endothelial keratoplasty: Effect of surgical indication and disease severity. *Cornea 2023;42:1229-39.*
  In this study the long-term outcomes up to 10-years postoperatively of a large DMEK cohort were analyzed.
- Eyes with moderate Fuchs pre-OP had
  -better visual acuity outcomes at all follow-ups.
  -a better graft survival probability at 10 years of 94% versus 88% for the more severe Fuchs group.

-a higher Endothelial Cell Density that was significant at most follow-ups (but not at 10 years any more).
- Overall you can say that pre-OP disease severity will have an effect on the outcomes and you should consider this when looking at the best timing for a DMEK surgery.

Do these guttae come back after DMEK?

- In most cases, they don't, but there is a reported recurrence rate of isolated guttae or patches of confluent guttae in up to 25% of the grafts after PK and up to 19% of grafts after DMEK.
- At NIIOS, however, the number was way below 5% after DMEK.
- In PubMed there are currently less than 10 articles on guttae after DMEK.

How do you know that guttae will come back?

- In 2017, study conducted on "dark spots" on the endothelium after DMEK (Zygoura et al, CORNEA) and these were classified in 4 different groups. At that point it seemed, based on specular microscopy and slit-lamp findings, that these dark spots were not guttae.
- In 2024, another study (Vasanthananthan et al, CORNEA) concluded that there can be guttae after DMEK, including one case originally labeled in the 2017 study as 'superimposed spots'.
- What changed? The use of confocal microscopy instead of specular microscopy on those eyes where guttae were suspected. On those images whitish, spiky spots were seen, an indicator for the presence of guttae.
- Confocal microscopy is a better tool to clearly identify guttae than specular microscopy.
- In the article "Recurrence of corneal guttae after DMEK" by K. Vasanthananthan et al. (2024) we included 13 eyes (13 patients) with post-DMEK guttae. Six of them had bilateral DMEK, but showed recurrent guttae in one of their DMEK eyes.
- Guttae were already visible within the first post-operative month.
- All the light microscopy images of the grafts with recurrent guttae that were taken by the eye bank were checked but also in retrospect no guttae were seen in the donor tissue.
- There was an inhomogeneous distribution of the post-DMEK guttae in the cornea of the patients. Two eyes had only central guttae, others central and paracentral guttae. In about half of the eyes the guttae density was stable.
- In 2 out of 13 grafts a re-DMEK was required after 56 and 74 months. 10 eyes had clear corneas at the last available follow-up with very good BCVA of 0.9 or more.

Take home messages

- Preoperative FECD severity (guttae density) influences postoperative outcomes, the less guttae, the better the outcomes.
- Reported rates for post-DMEK guttae vary, but rates tend to be low.
- Post-DMEK guttae most likely originate from the donor, they might have been hidden in the graft, but also patient related factors (like stress factors) play a role, more research is needed.
- Presence of post-DMEK guttae should be verified by confocal microscopy.
- In most cases, post-DMEK guttae are visible within one month post-OP.
- Density, distribution and progression of post-DMEK guttae show plenty of variation.
- Overall, good and stable long-term clinical outcomes can be achieved, even with the presence of guttae.

Discussion

- For research it is good to know if they are guttae. In clinical practice it is not so relevant, the only thing you can do for the patient is follow them up. You cannot give drops to resolve the guttae since the guttae are of the same material as the endothelial cells and you would melt the whole endothelium down.
- Systematic feedback of endothelial images of the central cornea 1, 2 or 3 months post-OP might help to improve the selection process in eye banks. It is not only about the guttae but also about the clinical survival. A good relation between the surgeon and the eye bank is helpful in this regard.
- Other ways of identifying guttae:
  -There is a way with the slitlamp. It's 'old way', with a specular with high magnification. If you increase your eye piece magnification and put it up to the highest and you use one eye. You put a tangential beam on the reflection of light, one eye will be able to help you see. You will get a very nice idea of the dispersion of the guttae. There are tutorial YouTube videos on this slitlamp method.
  -A new machine from Kova, making nice pictures with specular microscopy and has a much better wide field of the endothelial. At the confocal it is difficult to reproduce the same spot.