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Woon, WH, Greig, D, Savage, MD et al. (4 more authors) (2015) Asymmetric vitreomacular traction and symmetrical full thickness macular hole formation. Graefe's Archive for Clinical and Experimental Ophthalmology, 253 (11). pp. 1851-1857. ISSN 0721-832X

https://doi.org/10.1007/s00417-014-2884-z

This is an author-prepared, peer-reviewed version of an article published in
Graefe's Archive for Clinical and Experimental Ophthalmology **253** 1851-1857 (2015)
The final publication is available at Springer via http://dx.doi.org/10.1007/s00417-014-2884-z

Asymmetric vitreomacular traction and symmetrical full thickness macular hole formation

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The study was approved by the Research and Development department of St. James' Hospital, Leeds (R&D number: OP13/10828) and adhered to the tenets of the Declaration of Helsinki.

Abstract

Background: FTMH is often associated with vitreomacular traction and this can be asymmetric with vitreomacular traction on one side of the hole but not the other. In cross section, the elevated retinal rim around a developed FTMH is seen as a drawbridge elevation, and this drawbridge elevation may be used as a measure of morphological change. Examination of the drawbridge elevation of the retinal rim in FTMH with asymmetric vitreomacular traction may help to clarify the role of vitreomacular traction in the development of FTMH.

Method: Cases of FTMH were identified with an initial OCT scan showing vitreomacular traction on one side of the hole only, and who had a follow up OCT scan showing progression of the hole. A tangent to the retinal surface at a distance of 700 microns from the axis of the hole was used as a marker of the drawbridge elevation of the retinal rim around the macular hole. Comparisons of the drawbridge elevation and change in drawbridge elevation between the sides with and without initial vitreomacular traction were made.

Results: There was no significant difference between the drawbridge elevation, or change in drawbridge elevation, on the side of the hole with initial vitreomacular traction compared to the side without initial traction.

Conclusion: There is some intrinsic mechanism within the retina to link the morphological changes on the two sides of a FTMH. A bistable hypothesis of FTMH formation and closure is postulated to explain this linkage.

Key words: full thickness macular hole, pathogenesis, bistable, vitreomacular traction

Introduction:

It is commonly held that the main cause of full thickness macular hole (FTMH) is vitreomacular traction associated with perifoveal detachment of the vitreous [1-3]. However, there are difficulties with this hypothesis of FTMH pathogenesis, and this includes the following:

1. A FTMH is due largely to dehiscence of tissue rather than loss of tissue and this would require tangential separation of tissue [4]. However, vitreomacular traction is thought to produce largely antero-posterior traction rather than tangential traction [3,5,6].

2. FTMH can enlarge following the separation of the vitreous from the fovea [7,8] and this must be due to some mechanism other than vitreomacular traction.

3. FTMH can develop in eyes where there is no possibility of vitreomacular traction [6]. This includes eyes that have had a vitrectomy and eyes that have previously been documented to develop a full posterior vitreous detachment. The remarkable feature is not that there is another mechanism that can produce a defect of the retina but that FTMH associated with a wide range of conditions have a similar morphology and similar response to surgery.

Stage III FTMH often have an elevated retinal rim around the hole and this is seen as a drawbridge elevation of the inner retina on OCT scans of the retina, Fig.1 [9]. If the drawbridge elevation is due to vitreomacular traction then it would be expected that FTMH with asymmetric vitreomacular traction would develop in an asymmetrical way. Examining developing FTMH in which vitreomacular traction is present on one side of the macular hole but not the other may clarify the role of vitreomacular traction. We have examined such holes to determine whether the presence of vitreomacular traction produces greater drawbridge elevation of the attached retina compared to the side without vitreomacular traction.

Material and methods:

This is a retrospective study of FTMH that were observed to progress with asymmetric vitreomacular traction. Cases were identified from theatre records of patients who have had surgery for FTMH. Consecutive cases were identified that met the following inclusion criteria:

1. An initial OCT scan passing through the central fovea that shows vitreomacular attachments present on one side of the fovea only.

2. A follow up OCT scan through the same plane as the initial scan which shows progression of the FTMH compared to the initial scan. FTMH in which the initial vitreomacular attachment had become separate in the follow up OCT scan were included.

The study was approved by the Research and Development department of St. James' Hospital, Leeds (R&D number: OP13/10828) and adhered to the tenets of the Declaration of Helsinki.

Patients had had horizontal raster OCT scans using a Heidelberg OCT spectralis, spectral domain OCT scanner. The OCT scans passing through the central fovea were used. Tiff files of the OCT scans with the same horizontal and vertical scale were downloaded. The drawbridge elevation of the retina was used as a measure of the overall morphological change of one side of a macular hole. This measure was used in preference to the height of the macular hole due to the difficulties in using height when a hole has not formed or when there is an attached operculum with local distortion of the retina. A tangent to the inner retinal surface at a distance of 700 microns from the axis of the hole was taken to represent the drawbridge elevation of the retina. The tangent at this fixed distance from the axis of the hole was arbitrarily chosen, as it seemed to accurately reflect the drawbridge elevation in stage III FTMH. The drawbridge angle is defined as the angle between the tangent and a line parallel to the base of the hole (Fig.1). The nomenclature is that the angle on the side with initial vitreous traction is the drawbridge angle VMT (even if the vitreomacular attachments have separated in the follow up OCT scan) whilst the opposite angle is the drawbridge angle on the side without initial vitreomacular traction (Fig.1). Measurements were made using Serif drawplus version 3, and Universal Desktop ruler v3.6.3481. The convention is that tangents tipping into the base of the fovea have a negative angle and tangents tipping away from the base of the fovea have a positive angle. The following three analyses were made to assess the effect of vitreomacular traction on the morphology of a macular hole:

1. Comparison between the initial drawbridge angle VMT and initial drawbridge angle opposite in the initial OCT scan.

2. Comparison between the final drawbridge angle VMT and final drawbridge angle opposite in the follow up OCT scan.

3. Comparison between the change in drawbridge angle VMT and the change in drawbridge angle opposite that occurs between the initial and follow up OCT scans.

To rule out the possibility that the asymmetric vitreomacular traction is isolated to the single central OCT scan, adjacent scans in the same raster were examined to estimate the extent of the vitreomacular attachments around the fovea.

Statistical analysis was performed using GenStat 10th edition.

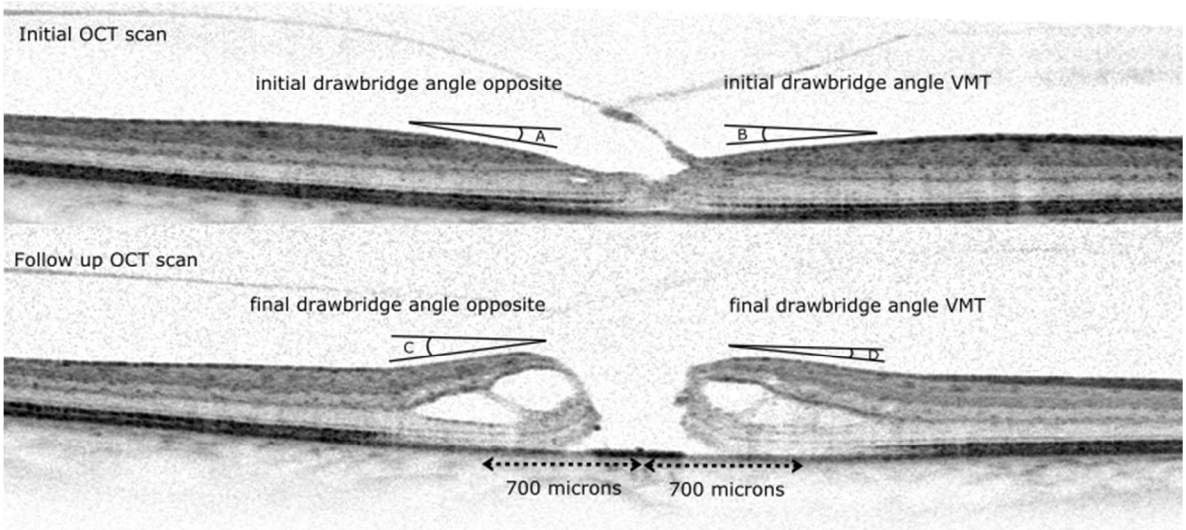

Fig 1. The inner retina becomes elevated in the FTMH in a "drawbridge manner". The angle between a tangent to the inner retinal surface and a line parallel to the base of the hole provides a measure of the drawbridge angle. Change in drawbridge angle opposite = A + C, change in drawbridge angle VMT = B + C.

Results:

OCT scans of 161 cases of macular holes that were operated on over a 43 month period were examined. Most macular holes had only one OCT scan prior to the operation. 17 cases were identified which showed progression on serial OCT scans prior to surgery and had evidence of vitreomacular traction. Of these 17 cases, 9 cases had vitreomacular attachment on both sides of the fovea in the central horizontal OCT scan, and 8 had vitreomacular attachments on one side of the fovea only. Thus, eight cases of FTMH meeting the inclusion criteria were identified. Seven patients were female and one male. The mean age was 62.4 years (range: 56 – 69). There was no past ocular history of note excepting that two patients had a FTMH in the fellow eye. The interval between the OCT scans was between 10 and 53 days for cases 1-7, and 790 days for case 8. OCT scans of all eight cases are shown in figure 2. In all cases, there is distortion of the retina at points of vitreomacular attachments to show that vitreomacular traction forces are acting at these points. The OCT scans appear to be fairly symmetrical with approximately equal drawbridge angles on the two sides of the macular hole excepting the initial scan of case 4 and the initial and follow up scans of case 8. In three cases (cases 2, 3, and 4), the vitreomacular attachments have separated in the follow up OCT scan.

The estimated extent of the vitreomacular attachments around the fovea for each of the eight cases is shown in figure 3. The numbering in figures 2 and 3 correspond to the same cases. It can be seen that the absence of vitreomacular attachments on one side of the hole occurs not just in the central OCT scan but extends around most of the ipsilateral side of the fovea in all cases.

Summary statistics of drawbridge angles (DBA) are shown in table 1, and box plots of the data are shown in figure 4. Paired t-test analysis found no significant difference between the drawbridge angles VMT and the drawbridge angles opposite in the initial OCT scans ($p = 0.88$) or the follow up OCT scans ($p = 0.94$). In addition, there is no significant difference between the change in drawbridge angle VMT and the change in drawbridge angle opposite ($p = 0.81$).

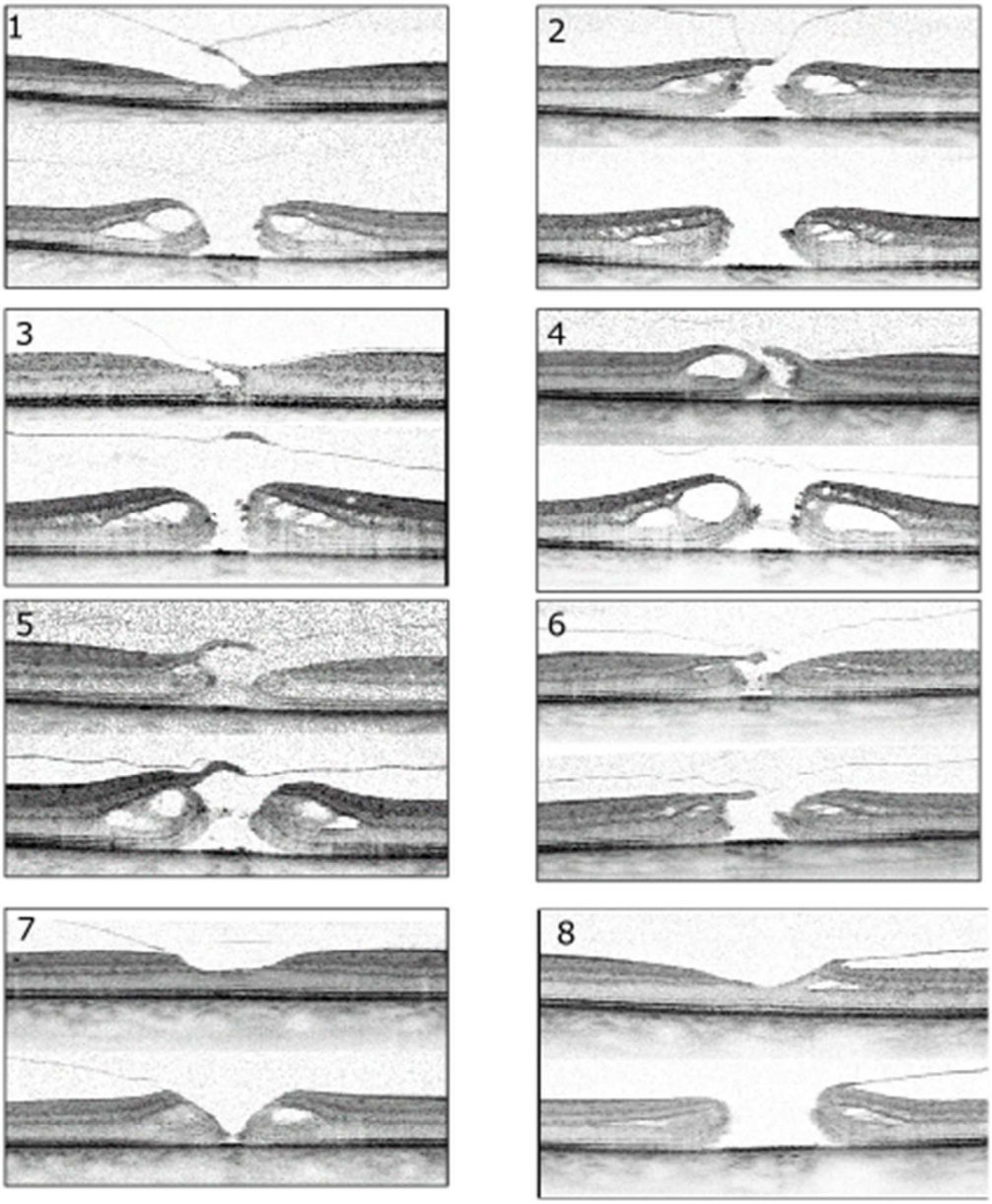

Fig 2. Initial and follow up OCT scans of the eight cases.

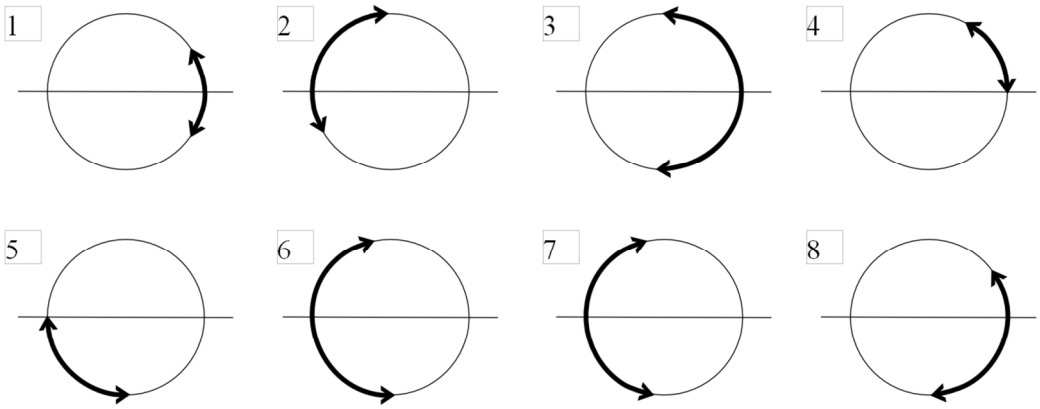

Fig 3. The extent of the vitreomacular attachments around the fovea is shown for each of the eight cases. The double arrowed curve represents the arc of a circle around the fovea where vitreomacular traction is present.

	Initial DBA VMT	Initial DBA opposite	Final DBA VMT	Final DBA opposite	Change DBA VMT	Change DBA opposite
Number	8	8	8	8	8	8
Mean	-2.7	-3.5	7.3	7.5	10.0	10.6
Range	-7.0 – 7.5	-9.5 – 12.0	1.8 – 13.8	1.7 – 14.1	-2.7 – 16.7	-0.9 – 22.7
Paired t - test	p = 0.88		p = 0.94		p = 0.81	

Table.1. Summary statistics for drawbridge angles (DBA). Paired t-test uses the null hypothesis of no difference between the compared quantities. Angles are in degrees

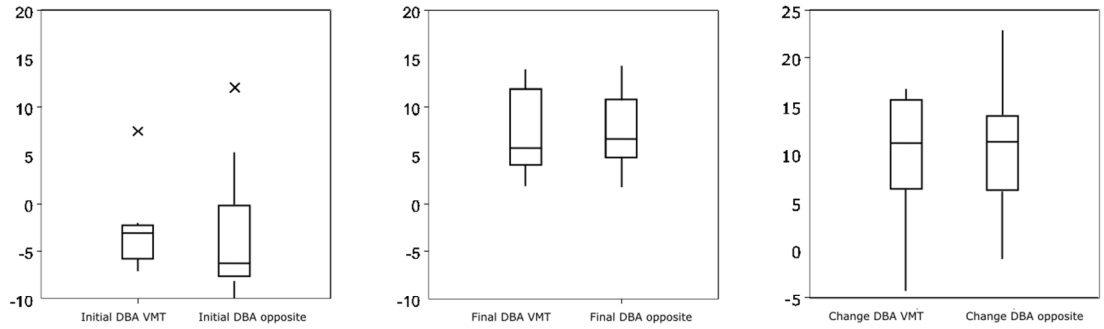

Fig 4. Box plots comparing initial drawbridge angles (DBA), final DBAs, and change DBAs. Angles are in degrees

Discussion:

This study found that on average the drawbridge angle on opposites sides of a FTMH with asymmetric vitreomacular traction is approximately equal and remained so as the hole progressed. The study is limited by the small size of the sample and it is possible that there is a true difference between drawbridge angle VMT and drawbridge angle opposite that would be detected by a larger study. However, the data would suggest that any difference is not large and that the symmetry of a FTMH is preserved despite asymmetric vitreomacular traction. Indeed, the study found that the average increase in drawbridge angle was greater on the side without vitreomacular traction than on the side with traction. This would suggest that the drawbridge elevation of the retina cannot be attributed solely to vitreomacular traction and that there is some other mechanism to account for the symmetry of FTMH. Previous authors have noted the problems of basing a hypothesis of FTMH formation on vitreomacular traction when there is vitreomacular attachment at a single point, and felt that this is evidence for a glial cell proliferation theory of FTMH formation [6]. However, glial cell proliferation would have to be remarkably symmetric to consistently produce the symmetry and uniformity of FTMH. In comparison, lamellar macular holes due to epiretinal membrane formation can be irregular in shape [10].

We have postulated a bistable hypothesis of FTMH formation and closure that would explain the symmetrical development of FTMH. The layer of inner retinal complex around the fovea, comprising the nerve fibre layer, the ganglion cell layer and the inner plexiform layer, follows

the shape of the foveal depression [11] and has the shape of a shallow disc cone (Fig.5). This area of the inner retinal complex will be referred to as the disc cone of inner retinal complex (DCIRC). A structure of this shape with appropriate elasticity would be expected to be bistable and could be flipped inside out and back again like an umbrella [12]. Intermediate positions, with the disc cone flat or with only one side flipped, would be unstable although they could be held in these unstable positions by external forces such as vitreomacular traction or epiretinal membrane. The intermediate positions would also occur as the fovea passes from one stable configuration to another.

Our bistable hypothesis of FTMH formation and closure has three elements (Fig. 5):

1. Bistability of the DCIRC: The hypothesis postulates that the DCIRC is a bistable structure and it can be flipped inside out like an umbrella. It is stable when in the configuration of the normal fovea and when it has been flipped inside out into the shape seen in a developed (stage III) FTMH. The flipping of the DCIRC would require a triggering force and this could be provided by a variety of conditions such as vitreomacular traction, epiretinal membrane, or trauma.

2. Linkage of the movement of the DCIRC to the outer retina by Muller cells: The movement of the outer retinal complex (outer nuclear layer and the photoreceptor inner and outer segments) is linked to the movement of the DCIRC by the Muller glial cells that pass between these layers. At the fovea, the Muller cells are arranged in an axially symmetric pattern [13], and they pass centrifugally and obliquely through the retina from the outer retinal complex to the inner retinal complex [14, 15]. When the DCIRC is moved in an antero-posterior direction, tension is produced in the Muller cells and this is transmitted to the outer retina along the line of the Muller cell. Each Muller cell thus produces an oblique force with an antero-posterior and a centrifugal component on the outer retina.

3. Circumferential stretching of the outer retinal complex: The Muller cells are arranged in a radially symmetric pattern like the spokes in an umbrella [13] and the tissue at the fovea is pulled in the direction of these "spokes" when the DCIRC has been flipped through. In cross section, the tissue appears to have contracted to form a hole but in three dimensions there is overall stretching of tissue as the tissue must be stretched circumferentially as it moves away from the centre of the fovea. A circular layer of outer retinal has thus been stretched into the shape of a truncated bell. If the outer retina is elastic, there will be tension within the truncated bell of outer retinal complex and this will tend to return the outer retinal complex to its normal position. However, the truncated bell of outer retinal complex can be held under tension by the bistable nature of the DCIRC. In effect the DCIRC is acting as a switch. The DCIRC in its normal configuration could be triggered to flip inside out to form a macular hole; and the DCIRC in a FTMH could be triggered to flip back to close a macular hole. Closure of a macular hole may only require a small triggering force as the movement is aided by tension within the stretched outer retinal complex.

This bistable hypothesis uses a simplified model of the mechanical properties of the fovea. Everyday bistable structures such as an umbrella flip rapidly whilst a macular hole develops very slowly in comparison. This is because the steel frame of an umbrella is stiff and can

generate large forces that are not dissipated by viscosity. In comparison the forces generated by de-stabilising the DCIRC would be small. There would be resistance from the outer retina and the movement would be damped due to the viscous behavior of the tissues. Movement of the retinal tissues to form a macular hole would thus be expected to be relatively slow but could occur as long as the force from the DCIRC is larger than the resistance from the other layers of the retina. In addition, the bistable hypothesis only applies if tissue atrophy and healing have not developed, and this may not be the case with chronic FTMH.

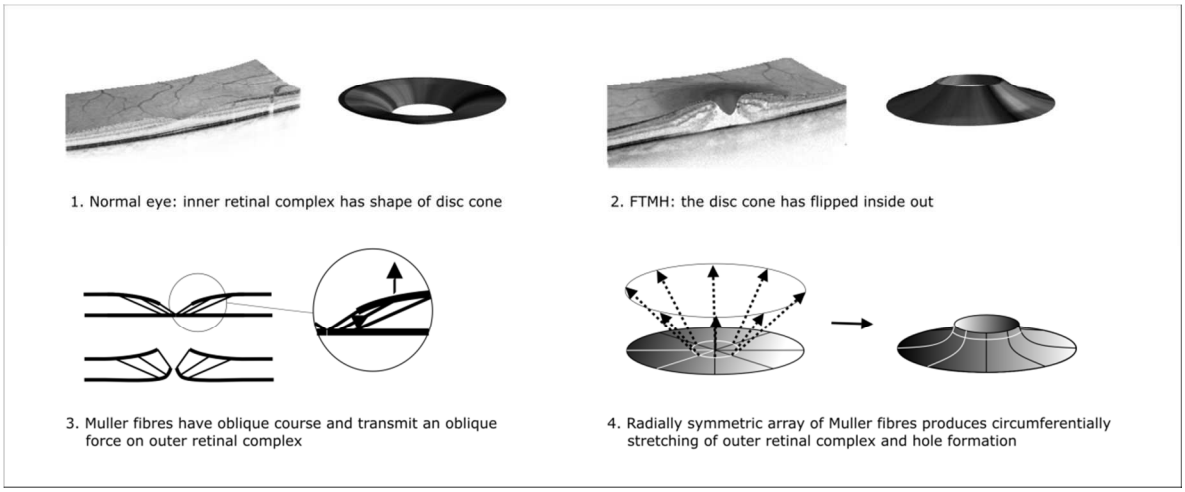

Fig 5. The bistable hypothesis of FTMH formation

The oblique path of the Muller cells used in the above description of our bistable hypothesis is a simplification of the "z-shaped" path taken by the Muller cells at the fovea, Fig. 6 [14]. Most of the centrifugal path of the Muller cells occurs in Henle's fibre layer where the Muller cells follow the long photoreceptor axons and these axons can be up to 320 microns long [15]. Straightening of the Muller cells produced by lifting of the inner retinal complex would cause the Muller fibres to separate in Henle's fibre layer and we believe that this is the mechanism of cyst formation in FTMH, and that these Muller fibres are seen as straight lines separating the cysts in OCT scans, Fig. 6.

Our hypothesis would explain the symmetry of FTMH. An asymmetric DCIRC would be unstable and a partially flipped DCIRC would tend to move into the configuration in the normal fovea or the configuration in a stage III FTMH. Thus case 4, which is initially asymmetrical, becomes symmetrical in the final OCT scan.
In addition, bistability also offers an explanation for the spontaneous closure or spontaneous enlargement of FTMH that can occur following separation of vitreomacular attachments [7,8]. This can be understood as movement of an unstable flattened inner retinal complex into either of its two stable position.

We present a hypothesis to explain the symmetry of FTMH in cases with asymmetric vitreomacular traction. This hypothesis can be extended to all FTMH and seems to explain known behavior including how small non-specific forces could trigger hole closure. If the bistability of the DCIRC can be demonstrated it would allow systematic development of treatment for this sight threatening condition. We thus believe the hypothesis should be considered and tested further and we propose to pursue mathematical modeling and micromechanical measurements of the retinal.

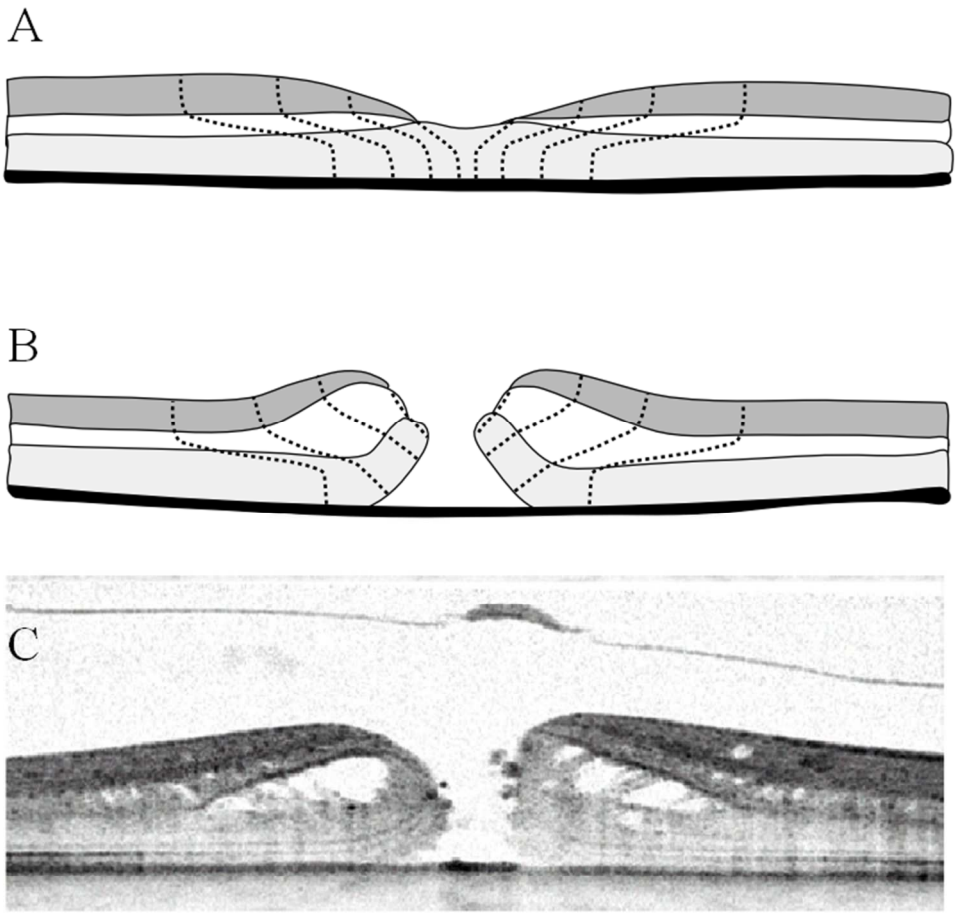

Fig 6. A: Schematic of the path of the Muller cells in the normal fovea showing the characteristic "Z-configuration". B: Schematic of postulated path of Muller cells in a Macular hole, the Muller cells have been straightened and become separate in Henle's fibre layer. C: Straight lines are seen running between the cysts in the OCT scan of case 3 and it is postulated that these are the Muller cells.

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