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Authors

Kim, Soohyun
Thomasy, Sara M
Ramsey, David
et al.

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Whorl pattern keratopathies in veterinary and human patients

Soo Hyun Kim¹ | Sara M. Thomas¹ | David Ramsey² | Min Zhao^{3,4} | Mark J. Mannis³ | Christopher J. Murphy^{1,3}

¹School of Veterinary Medicine, Department of Surgical and Radiological Sciences, University of California Davis, Davis, CA, USA

²The Animal Ophthalmology Center, Williamston, MI, USA

³Department of Ophthalmology & Vision Science, School of Medicine, University of California Davis, Davis, CA, USA

⁴Department of Dermatology, School of Medicine, University of California Davis, Davis, CA, USA

Correspondence

C. J. Murphy

Email: cjmurphy@ucdavis.edu

Abstract

The course travelled by corneal epithelial cells from their stem cell niche at the limbus toward the vertex of the cornea is normally not evident due to their transparency, but in certain conditions, the epithelial cells can be rendered visible to the clinician. In such cases, the pathway taken by epithelial cells can manifest as a whorl pattern described using a variety of terms including hurricane keratitis/keratopathy, vortex keratopathy, whorl keratopathy, cornea verticillata, and at times, named after causative agents as exemplified by amiodarone keratopathy. Here, we briefly discuss the terminology used and the spectrum of conditions that can result in keratopathies with whorl patterns in human patients. We review the manifestations of such patterns in veterinary patients and discuss the state of understanding of the underlying forces that create the whorl distribution of epithelial cells on the ocular surface.

KEYWORDS

cornea verticillata, corneal epithelium, hurricane keratopathy, pigmentation, vortex keratopathy, whorl pattern

1 | INTRODUCTION

The exact path taken by corneal epithelial cells is not clinically observed during normal epithelial turnover due to their transparency. However, corneal epithelial cells may be rendered visible by intrinsic alterations in cellular transparency during periods of high migration and turnover, as well as by the deposition of substances such as pigment, iron, proteins, and glycogen in a variety of clinical conditions. A whorl pattern of the corneal surface was initially described in 1910.¹ A variety of terms have been used to describe clinically apparent whorl patterns in the corneas of human patients including hurricane keratopathy,² vortex keratopathy,³ whorl keratopathy,⁴ and cornea verticillata (*from L verticillate; forming whorls*).⁵ This brief report was prepared to review concisely the terminology and spectrum of whorl patterns seen in human patients; to bring to the reader's attention the single online report of a veterinary (canine) patient with a keratopathy possessing a whorl pattern (reported as a hurricane keratopathy); to provide

additional exemplars in veterinary patients manifesting this epithelial pattern; to raise awareness of the underlying forces thought to be responsible for manifestation of this unique pattern; and to stimulate discussion and further investigation in the community of comparative ophthalmologists.

1.1 | Whorl pattern keratopathies in human patients

1.1.1 | Terminology

Whorl originates from Middle English (variant of *whirl*) and denotes anything that whirls or appears to whirl like the whorl of a spindle.⁶ The use of this descriptor has consensus across the literature to describe a spatial pattern of the superficial cornea clinically observable under a number of conditions. A variety of additional terms have been employed inconsistently and often interchangeably across the literature (and encyclopedic/dictionary sources) to

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describe clinically observable whorl patterns in the cornea. Some authors assign specific attributes to distinguish between specific terms, and others use terms more promiscuously. Although harmonized by their general clinical appearance, the ascribed names, in some cases, simply refer to synonymous descriptive terms, while others reflect known associated underlying causes. Hurricane keratitis/keratopathy, vortex keratopathy, whorl keratopathy, and cornea verticillata are terms whose origins lie in the appearance of the ocular surface (and in some cases, such as hurricane keratopathy made more obvious after application of fluorescein) while the terms amiodarone and chloroquine keratopathy implicate specific drugs as the underlying cause of the deposits seen distributed among the epithelial cells, commonly though not always in a whorl pattern.

1.1.2 | Hurricane keratopathy/keratitis

Mackman et al⁷ employed the term hurricane keratitis to describe a whorl pattern observed on the corneal surface in post-penetrating keratoplasty patients that became more apparent upon application of topical fluorescein. In a review of the literature, while most reports imply fluorescein retention as an integral element in use of the term hurricane keratopathy/keratitis,^{8,9} others do not.¹⁰ In this regard, hurricane keratitis/keratopathy is most commonly employed to describe the whorl pattern observed associated with conditions that promote high epithelial turnover. We note that the term vortex keratopathy is employed by some sources synonymously with hurricane keratopathy (eg, https://link.springer.com/content/pdf/10.1007%2F978-3-642-35951-4_957-1.pdf). The clear trend in the literature, however, is to limit the term “hurricane keratopathy” to cases in which improved visualization of the whorl pattern occurs subsequent to application of topical fluorescein (indicating a deficiency in interepithelial cohesion during a period of high epithelial migration). This is commonly the case post-transplantation.^{2,9} This pattern has been reported in early postoperative corneal transplants which, when stained with fluorescein, form a characteristic spiral pattern in the central portion of the graft, often extending to the periphery of the transplant⁷ (Figure 1). This is reported to develop in more than 70% of patients who have had corneal graft surgery, and the distribution of the hurricane pattern is clockwise in 89.2% of eyes.⁸ Initially, the toxic effects of topical corticosteroid and/or its preservative on the corneal epithelium were suspected as a reason for development of the hurricane pattern.⁷ Authors proposed that the grafted epithelium was sensitive to the effects of corticosteroids, as the pattern developed only in the donor button, and patterns were not observed in postcataract corneas that were also exposed to topical steroids. Another report proposed

that the hurricane pattern was related to the graft sutures.³ Centripetal migration of cells could be seen in apparent streaming or palisading of cells around sutures, and these sutures created irregular contours that interrupted the continuous central flow of epithelial cells. Moreover, the hurricane pattern disappeared after suture removal. This hurricane pattern is also recognized in patients who wear rigid gas-permeable contact lenses associated with increased epithelial turnover.⁸ We suggest that the specialty of veterinary ophthalmology follows the trend in the physician-based literature to limit the use of the term hurricane keratopathy to cases in which the whorl pattern is accentuated following the application of topical fluorescein. This has value as its use intrinsically suggests increased epithelial turnover and may inform diagnostic and therapeutic approaches.

1.1.3 | Vortex keratopathy, whorl keratopathy, and cornea verticillata

As simply descriptors of spatial patterns, these terms are used more promiscuously and often used interchangeably. Broadly, these terms are most often used to describe whorl patterns of the corneal surface clinically observable by slit lamp examination that are not accentuated by application of topical fluorescein and are most often made visible due to deposits within the epithelium and/or superficial stroma.¹¹ We note, however, that the term vortex

FIGURE 1 Hurricane keratopathy made evident after fluorescein staining of the grafted cornea in a human eye. /Note. Adapted from “<http://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/Hurricane-keratopathy/>.” These images by EyeRounds.org. The University of Iowa are licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License

keratopathy is occasionally employed interchangeably with hurricane keratopathy (ie, employed in cases wherein the whorl pattern is made more evident after the application of fluorescein). Cornea verticillata is a descriptive term and can have numerous underlying causes including drugs, heritable metabolic disorders (eg, Fabry disease), and dysproteinemias such as multiple myeloma.¹¹ It is characterized by corneal deposits in the epithelium and Bowman's layer forming a fine opaque golden-brown whorl pattern.⁵ Although not consistently used to distinguish between the two, in reviewing the broad literature, cornea verticillata is more commonly employed even in cases where curvilinear whorl patterns are observed that do not achieve a degree of spiraling as to evoke imagery of a vortex. We suggest that the terms vortex keratopathy and cornea verticillata be employed in veterinary ophthalmology solely in cases, which a whorl pattern is observed and is not clearly accentuated by the application of topical fluorescein. This would imply that in such cases, the pattern is manifested due to deposits in the epithelium and subepithelial layer or is attributable to altered translucency of the epithelial cells due to increased epithelial turnover. In such case, however, it is not associated with the compromise of intercellular adhesion.

1.1.4 | Drug associated keratopathies (eg, amiodarone, chloroquine, tamoxifen, name the drug keratopathy) with whorl patterns

These terms denote a specific underlying causation of the observed pattern. Exposure to drugs, most commonly chloroquine¹² and amiodarone,¹³ is well recognized as being associated with the formation of a whorl pattern. We note, however, that a wide array of additional drugs have been associated with deposits in the cornea, and while vortex/whorl patterns can occur with a number of these, similar to amiodarone and chloroquine, the formation of whorl pattern is not a requisite attribute of the condition.¹⁴ The biomicroscopic findings are characterized by symmetrical and typically bilateral yellow-brown corneal epithelial deposits that commonly appear in a whorl pattern from a line below the pupil and swirl outward, generally sparing the limbus. Amiodarone is concentrated in tears, and exacerbation of the associated keratopathy has been associated with contact lens wear, potentially secondary to trapping of tears and the formation of lipid-bearing intralysosomal inclusions in the corneal epithelial basal layer.¹³

1.2 | Keratopathies having a Whorl Pattern in Veterinary Patients

Only a single online report (http://vetweb.com.br/ver_ar_tigo.php?id=167) with an associated abstract¹⁵ describing a

keratopathy with a whorl pattern in a canine patient could be found in the veterinary literature. In this report, the term "hurricane keratopathy" was employed, and the finding developed in an 11-year-old Shih Tzu 4 weeks subsequent to healing of a superficial corneal ulcer. The whorl pattern was accentuated after the topical application of fluorescein. This patient was initially presented with photophobia and tearing with the clinical signs improving a few weeks after cessation of topical corticosteroids and initiating treatment with topical artificial tears. To the authors' knowledge, the only other report of whorl pattern (and also using the term "hurricane keratopathy") in a veterinary patient is limited to the presentation of a photograph by D Ramsey at the 2011 ACVO annual meeting (and available for viewing through the ACVO website (<http://www.acvo.org/new/diplomates/ce/2011PhotoCompWinners.shtml>)). The photograph is provided in Figure 2 along with salient case details. In both of these cases, the development of the whorl-patterned keratopathy was associated with a decreased translucency of corneal epithelial cells without evidence of a disruption of epithelial integrity and without frank evidence of deposits or pigment. After reviewing the literature, we suggest that the term "hurricane keratopathy" be limited in use to those cases in which the whorl pattern is accentuated by the application of fluorescein. Using this as a requisite attribute, the online case report would be appropriately termed a hurricane keratopathy whereas the patient presented in Figure 2 would best be described as having a vortex

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FIGURE 2 Canine patient exhibiting vortex keratopathy in a clockwise direction. (image initially published online at <http://www.acvo.org/new/diplomates/ce/2011PhotoCompWinners.shtml>). Right eye of 5-year-old neutered male Lhasa Apso. Adjacent to an oval-shaped and of fibrosis after delayed healing of corneal ulcer (arrow), a faint white, lightly opaque vortex pattern was detected in the corneal epithelium by slit lamp biomicroscopic examination. The vortex pattern was lacy in appearance and was oriented in a clockwise direction. There were no cellular infiltrates evident, and fluorescein sodium dye was not retained

keratopathy. We note that while amiodarone keratopathy was reported in 1 of 6 dogs after treatment, a whorl pattern was not manifested.¹⁶ As the authors of that report correctly point out, there are a range of findings possible with amiodarone keratopathy in human patients with many amiodarone-associated deposits seen clinically that do not assume a whorl pattern.

In veterinary patients, the authors have not observed and could not locate a report of a keratopathy with a whorl pattern that was accentuated by the topical application of fluorescein. The authors have observed that migration of melanotic corneal epithelial cells is the most common scenario in veterinary patients, wherein corneal epithelial cells are rendered clinically evident and become distributed across the ocular surface in a whorl or vortex pattern. We note that a prodromal finding of altered translucency of the corneal epithelial cells in the affected region may be observed ahead of the appearance of pigment-containing cells. Frank epithelial defects may or may not be antecedent to their development. Similarly, a history of prior corneal vascularization is variable. Corneal epithelial melanosis occurs frequently in several canine corneal diseases including keratoconjunctivitis sicca, chronic exposure keratopathy, and pigmentary keratopathy. A whorl or vortex patterned distribution of the pigmented corneal epithelial cells, when present, primarily forms in a clockwise

pattern. Figure 3 depicts the typical appearance of corneal pigmentation arranged in a vortex pattern. We propose the use of the term “pigmentary vortex keratopathy” as an appropriate descriptor in such patients. We also suggest that use of the term be employed only in cases where the pigment observed is limited to the epithelium and subepithelial region. This has utility, since these most superficial accumulations of melanin are more likely to diminish upon addressing of underlying conditions. Use of the term also implies engagement of the biophysical forces discussed below that are thought to underlie manifestation of this distinct spatial distribution.

1.3 | Biophysical forces and the development of whorl/vortex patterns

Here, the terms whorl and vortex are used interchangeably. The central whorl formation during the corneal epithelial cell migration has been shown by visualizing LacZ labeled corneal epithelial cells in mice.¹⁷ Rhee and coauthors documented that corneal epithelial cells and subepithelial collagen spatial patterns both demonstrated a clockwise hurricane pattern at the central cornea.¹⁸ A vortex pattern in the superficial cornea is manifested not only by the epithelium but also by the corneal sub-basal nerve plexus. Patel and McGhee¹⁹ reported the two-dimensional

FIGURE 3 Pigmentary vortex keratopathy in dogs. A whorl patterned distribution of faint white corneal epithelial opacity with pigmentation in both clockwise and counterclockwise directions is present in the central cornea. A, Right eye of 9-year-old spayed female Shih Tzu, (B) Left eye of 14-year-old neutered male Miniature Poodle, (C) Right eye of 4-year-old neutered male Shih Tzu, (D) Right eye of 12-year-old spayed female Shih Tzu. Note that in this image, the whirling pigment pattern follows a counterclockwise path along most of its course

FIGURE 4 Corneal sub-basal nerve architecture. A, Whole mounts of entire corneal innervation of mouse cornea. B, The detailed structures of corneal nerves in the central area showing the clockwise vortex pattern. Images kindly provided by Drs. Jincheng He and Haydee E.P. Bazan; Neuroscience Center of Excellence and Department of Ophthalmology, Louisiana State University Health, School of Medicine

architecture of the corneal sub-basal nerve plexus in the living human eye using in vivo confocal microscopy. The whorl-like corneal nerve architectures at the central cornea are also reported in rodents (Figure 4).²⁰ Nerve fibers arranged in a whorl pattern are observed in sub-basal bundles and superficial free endings. Pax6, an essential transcription factor for ocular development, has been implicated in the whorl distribution²¹ and in the thyl-yellow fluorescent protein (YFP) mouse.²² These observations suggest that the migration of corneal epithelial cells and epithelial nerves is affected by similar forces that determine their spatial distribution.

Currently, there is a lack of consensus as to the driving force(s) responsible for the vortex pattern. The number and variety of conditions in which a vortex pattern develops, however, indicate that it is not a specific disease process but rather represents a phenomenon that occurs during the

migration of corneal epithelial cells in a variety of circumstances.²³ Implicating regional factors as being central to the creation of a vortex pattern is the finding of similar spatial patterns for both corneal epithelial cells and the sub-basal nerve complex. As noted previously, a shared factor for many clinical presentations of hurricane keratopathies in humans, though admittedly not documented in all cases, is an increased rate of corneal epithelial cell turnover.⁸ It is noteworthy that when the stimulus for increased epithelial turnover is removed, the hurricane pattern typically disappears.

Multiple theories have been proposed as to why the vortex pattern manifests predominantly in a clockwise pattern.^{2,7,24} One theory suggests that the specific distribution of the corneal epithelium is the effect of the electromagnetic field generated by the electrical potential of the eye. The eye has its own electrical field and behaves like a

FIGURE 5 Electromagnetic distribution of the eye, producing a clockwise whorl pattern. A, Current distribution. A, apex of cornea; L, limbus; S, sclera. B, Magnetic field distribution. Notice that the magnetic flux density (force of the magnetic field) is clockwise. C, Concentric distribution of the combined electromagnetic fields. D, The torsional effect of the combined electromagnetic fields on the centripetal radial migration of epithelial cells to produce a clockwise whorl pattern. Adapted from "cornea epithelial cell migration in humans: 'hurricane and blizzard keratopathy'. Dua et al, 1993, Eye 7, 53-58. Copyright 1993 by the Nature Publishing Group. Adapted with permission (license number: 411185028641)

dipole, oriented along its anteroposterior axis with a potential difference of 6 mV.² The presence of electric fields in the eye generates a current, which ultimately leads to the generation of an electromagnetic field that distributes the current in concentric circles and in a clockwise magnetic flux (Figure 5). Therefore, when corneal epithelial cells migrate from the limbus to the vertex of the cornea, they encounter these electromagnetic fields and receive a torsional effect to their movement, producing a clockwise whorled pattern.

Cells respond to electrical current with changes in their morphology and behavior.²⁵ Specifically, epithelial cells display galvanotaxis, moving in response to weak electrical fields.²⁶ Corneal epithelial cells respond to the electromagnetic fields as evidenced by the movement of cultured corneal epithelial cells in response to electric fields with migration toward the cathode²⁷ and magnetic fields with a clockwise whorl pattern forming in response to magnetic fields in subconfluent human corneal epithelial cells cultured in vitro.²³ Moreover, corneal epithelial cells encounter precisely ordered fiber arrays on the nanoscale in tandem with an endogenous electric field that cooperate to control cell axis alignment.²⁸

It needs to be acknowledged that the clockwise pattern does not develop in 100% of patients manifesting a vortex pattern (Figure 3D) suggesting that generation of the vortex pattern may result from multiple inputs and/or there is individual variability in the vector attributes of weak electromagnetic fields.

2 | SUMMARY

The terminology used to describe keratopathies that manifest in a whorl pattern is complex and is not employed consistently across the literature. Keratopathies with a whorl pattern occur under a variety of conditions. Hurricane keratopathies with a whorl pattern accentuated by topical fluorescein appear in an environment of increased corneal epithelial cell turnover with weak electromagnetic fields influencing the creation of the whorl pattern. In veterinary ophthalmology, vortex patterns are most commonly observed with the migration of pigmented epithelial cells (with the term pigmentary vortex keratopathy suggested to denote such cases), and, in rare cases, veterinary patients can manifest a vortex keratopathy in the absence of pigment.

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