Case Report

Keratoconus in a Cynomolgus Monkey

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Abstract: In a seven-year-old male cynomolgus monkey, erythema of the upper eyelid and forehead and corneal opacity, edema and conical protrusion in the eye were observed. At necropsy, ophthalmological and serological examinations revealed binocular corneal opacity and conical protrusion and a high IgE level, respectively. Thinning of the epithelium and stroma of the cornea were noted histopathologically. At the center of the corneal epithelium, the number of epithelial cells was reduced, their cytoplasm was poorer and the basal cells were flatter than at the periphery. Bowman’s membrane was folded with partial loss or breakage. Collagen fibers were compacted or disarranged, and the keratocytes were increased in the stroma, with focal pyknosis or loss of the endothelium and folding of Descemet’s membrane. Electron microscopical examination revealed atrophy of the corneal epithelial basal cells. This is the first report of a case of keratoconus in a cynomolgus monkey. (J Toxicol Pathol 2010; 23: 53–58)

Key words: keratoconus, high serum IgE, atopy-like mechanism, cynomolgus monkey

Keratoconus is a non-inflammatory disease that is characterized by conical protrusion from the center of the cornea. It is a progressive disease that occurs in relatively young people (around 15 to 35 years of age). When the degree of protuberance is slight, vision can be corrected with contact lenses; however, when the protuberance becomes pronounced, there is no treatment available other than corneal transplantation. In the general population, an incidence of approximately one person in 2,000 has been reported1–3. The pathogenesis of keratoconus has not yet been elucidated, but various etiologies such as hereditary and other factors have been considered4–12, 28, 29. As well as these, habitual rubbing of the eyes is thought to be a major factor9–12. Keratoconus has been reported in the mouse13, 14, dog15 and rhesus monkey16, but not in the cynomolgus monkey. This is the first report of a cynomolgus monkey with keratoconus, in which serological, ophthalmological, histopathological and electron microscopical findings are discussed in detail.

The animal studied was a seven-year-old, naive male cynomolgus monkey (Macaca fascicularis) imported from China (Wing Freight Agent Co., Ltd., Beijing, PR China) and used for breeding. All procedures involving the animal were approved by the Animal Care and Use Committee of Shin Nippon Biomedical Laboratories, Ltd. and performed in accordance with standards published by the National Research Council, USA (Guide for the Care and Use of Laboratory Animals, NIH OACU), and the National Institutes of Health Policy on Human Care and Use of Laboratory Animals, USA. The animal room was maintained within a temperature range of 23 to 29°C and a humidity range of 35 to 75%, with 15 air changes/hour and artificial illumination for 12 hrs/day (06:00 to 18:00). The animal was housed in an individual stainless steel cage (Taiyo Stainless Co., Ltd., Kagoshima, Japan) and provided with approximately 108 g of solid food (Teklad Global Certified 25% Protein Primate Diet, Harlan Sprague Dawley Inc., Madison, WI, USA) daily at approximately 15:00. Water, certified to meet the water quality standards required by the Japanese Waterworks Law, was available ad libitum from an automatic supply system (Edstrom Industries, Inc., Waterford, WI, USA). Ophthalmological and pupillary light reflex examinations were performed using a penlight once a month for 4 months. Corneal thickness was measured once at Month 0 (Month 0 was the month in which the first observation was performed). After instillation of a mydriatic (Mydrin-P, Santen Pharmaceutical Co., Ltd., Osaka, Japan), the anterior ocular segment and optic media were examined using a portable slit lamp (SL-15, Kowa Company, Ltd., Tokyo, Japan), and the ocular fundi was examined with an indirect ophthalmoscope (10-α Small Pupil, Neitz Instruments Co., Ltd., Tokyo, Japan, and 20D, NIKON, Waterford, WI, USA). The animal room was maintained within a temperature range of 23 to 29°C and a humidity range of 35 to 75%, with 15 air changes/hour and artificial illumination for 12 hrs/day (06:00 to 18:00). The animal was housed in an individual stainless steel cage (Taiyo Stainless Co., Ltd., Kagoshima, Japan) and provided with approximately 108 g of solid food (Teklad Global Certified 25% Protein Primate Diet, Harlan Sprague Dawley Inc., Madison, WI, USA) daily at approximately 15:00. 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The thickness of the right cornea was measured using Optical Coherence Tomography (RTVue-100, Optovue, Inc., Meridianville, AL, USA). The thickness of the left cornea was not measured because corneal edema was severe. At necropsy, the animal was weighed and then anesthetized by an intravenous injection of sodium pentobarbital (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) solution (64.8 mg/mL, 0.4 mL/kg) into the cephalic vein of the forearm. After blood sampling, serum IgG, IgA and IgM were quantified by turbidimetric immunoassay using an immunoglobulin kit (Nitto Boseki Co., Ltd., Tokyo, Japan), serum IgD was quantified by latex agglutination immunoassay using an immunoglobulin kit (Nitto Boseki Co., Ltd.) and nonspecific IgE was quantified by chemiluminescent immunoassay using an immunoglobulin kit (Siemens Healthcare Diagnostics K.K., Tokyo, Japan) because it has been documented that IgE is related to the pathogenesis of keratoconus in humans10. The eyes from the animal were fixed in a mixture of 3% glutaraldehyde and 2.5% formalin, trimmed, embedded in paraffin, sectioned and stained with hematoxylin and eosin (HE), Berlin blue and Toluidine blue stains. For electron microscopical examination, freshly prepared corneal tissues from both eyes were fixed in 2.5% paraformaldehyde and 3% glutaraldehyde and were post-fixed in 1% osmium tetroxide. The fixed tissues were further processed for transmission electron microscopy (TEM).

Four months before necropsy (Month 0), no abnormalities had been observed in general condition, body weight or food intake, except for erythema of the upper eyelid and forehead, corneal opacity, edema and conical protrusion of the eyes (Figs. 1b–d). The erythema of the upper eyelid and forehead and corneal edema disappeared by the time of necropsy, but corneal opacity and conical protrusion were continuously observed in both eyes.

The ophthalmological findings for the present case are summarized in Table 1. From the time they were first noted, corneal opacity and conical protrusion continued to be observed in both eyes until the time of necropsy. In the left eye, edema was observed at Months 0 and 1, but disappeared thereafter. The thickness of the right cornea was measured at all sites in the cornea. The corneal thickness was thinnest at the center, but increased gradually toward the periphery. Pupillary light reflex and intraocular pressure were normal (Table 2).

The serum IgE level was high in this monkey, but the serum IgG, IgA, IgM and IgD levels were not significantly different from those in a normal animal (Table 3). Histopathological examination showed that the cornea became centripetally thinner from the periphery toward the center (Fig. 2a). At the center of the corneal epithelium, the number of epithelial cells was reduced, their cytoplasm was poorer and the basal cells were flatter than those at the periphery. The Bowman’s membrane was folded with partial loss or breakage (Fig. 2c). Focal pyknosis or focal pyknosis or loss of the endothelium and folding of the Descemet’s membrane were also observed (Fig. 2e). All these findings in the left eye were more severe than those in the right eye. Iron deposits were observed in the choroid of the left eye. Though various changes were noted in the cornea and choroid, no leukocytic infiltration was observed. Furthermore, no abnormal changes were noted in the iris, lens, ciliary body, retina or upper eyelid in the histopathological examination.

Electron microscopical examination revealed a reduced number of cytoplasmic organelles and irregularity of the nuclear membrane, which were also noted in the light microscopical findings (Fig. 3).

In humans, keratoconus is a progressive non-inflammatory disorder of the cornea with the central curvature of the cornea exceeding the normal range as its cardinal sign, and it can be typically linked with characteristic histopathological findings in the cornea, such
as epithelial and stromal thinning, iron deposition in the epithelial basement membrane and breakage of the Bowman’s membrane. In the present case, as histopathological findings in the eye, thinning of the epithelium and stroma of the cornea, focal loss or breakage of the Bowman’s membrane, compaction or disarrangement of the stromal collagen fiber and increases in keratocytes were observed in both eyes, with no leukocytic infiltration. These changes correspond to the above-stated histopathological findings associated with human keratoconus. It has been reported that acute breakage of the Descemet’s membrane in keratoconus results in inflow of the aqueous humor to the corneal stroma, subsequently inducing acute corneal edema and corneal opacity, and that these disorders are ameliorated with regeneration of the Descemet’s membrane within a few months. However, in this case, the corneal edema and protuberance were observed by ophthalmological examination to have occurred at an early stage, and breakage of the Bowman’s membrane and the subsequent changes in the stroma and endothelium were observed by histopathological examination to have occurred at a late stage. Though the reasons for these changes were not clear, it was considered greatly possible that the disease resulted in such histopathological and clinical findings.

Table 1. Ophthalmological Findings for the Eyes of the Present Case and Normal Eyes of Monkeys

| Observation point | Normal monkey (n=8)† | Present case |
|------------------|----------------------|--------------|
| Left eye         |                      |              |
| Conical protrusion | P                    | P            |
| Corneal opacity  | ±                    | +            |
| Corneal edema    | 3+                   | –            |
| Right eye        |                      |              |
| Conical protrusion | P                    | P            |
| Corneal opacity  | ±                    | +            |
| Corneal edema    | 3+                   | –            |

*: within a radius of 5 mm in the center of the cornea. **: mean thickness within a radius of 2 to 5 mm or 5 to 6 mm in the center of the cornea. NE: Not examined. †: This animal was a seven-year-old, naïve male cynomolgus monkey (Macaca fascicularis) imported from China (Wing Freight Agent Co., Ltd., Beijing, PR China) and used for breeding.

Table 2. Ophthalmological and Pupillary Light Reflex Examinations of the Eyes of the Present Case and Normal Eyes of Monkeys

| Pupillary light reflex | Intraocular pressure (mmHg) (mean ± SD) | Corneal thickness (μm) |
|-----------------------|----------------------------------------|------------------------|
|                       | Normal 18.11 ± 3.14                   | Thickest*              |
|                       | Normal 19.44 ± 3.48                   | Thinnest*              |
|                       | Normal 19.11 ± 3.14                   | Within 2 mm*           |
|                       | Normal 19.44 ± 3.48                   | 2 to 5 mm**            |
|                       | Normal 19.11 ± 3.14                   | 5 to 6 mm**            |

*: within a radius of 5 mm in the center of the cornea. **: mean thickness within a radius of 2 to 5 mm or 5 to 6 mm in the center of the cornea. NE: Not examined. †: These animals were five- to seven-year-old, naïve male cynomolgus monkey (Macaca fascicularis) imported from China (Wing Freight Agent Co., Ltd., Beijing, PR China) and used for breeding.

Table 3. Serum Immunoglobulin Levels in the Cynomolgus Monkeys

|                  | Present case | Normal† |
|------------------|--------------|---------|
| IgG (mg/L)       | 13810        | 11950   |
| IgA (mg/L)       | 2330         | 2150    |
| IgM (mg/L)       | 1630         | 550     |
| IgD (mg/L)       | <6           | <6      |
| IgE (kIU/L)      | 38           | <5      |

†: This animal was a seven-year-old, naïve male cynomolgus monkey (Macaca fascicularis) imported from China (Wing Freight Agent Co., Ltd., Beijing, PR China) and used for breeding.
Fig. 2.
In the ophthalmological examination, corneal edema was observed in the left eye at a degree that was more severe than that in the right eye. Histopathological changes were more severe in the left eye than in the right. It has been reported that keratoconus in humans is generally binocular and rarely monocular, and the progress from onset can differ between the left and right eyes. The results in the present case were consistent with these clinical findings.

The pathogenesis of keratoconus has not yet been elucidated, but it is thought to be associated with hereditary factors and some disorders such as atopic disease, mitral valve prolapse syndrome and Down’s syndrome. According to experimental investigation of inheritance, there are families in which it occurs at a much higher incidence, an estimated 6 to 19%. The responsible gene has not yet been identified; however, most research has shown it is consistent with autosomal dominant inheritance. There is a high prevalence among cases of Down’s syndrome, but the pathogenesis is not clear. It was not clear whether the keratoconus was associated with hereditary factors in the present case because familial history could not be investigated.

It has been reported that Fleischer’s ring and Vogt’s striae are observed with keratoconus during ophthalmological examinations and that iron deposition in the epithelial basement membrane is associated with the pathogenesis of keratoconus. In the present case, iron deposition was not observed in the cornea. Iron deposition in the choroids was considered to reflect an old hemorrhage and to be unrelated to the keratoconus. Electron microscopical studies have suggested that the primary lesion in keratoconus is degeneration of the basal cells in the corneal epithelium and that this may liberate proteolytic enzymes, resulting in loss of collagen fibrils and formation of the cone. The liberation of hydrolytic enzymes from lysosomes of connective-tissue cells may be responsible for some of the destructive changes seen in connective-tissue diseases. The atrophy of the basal cells in the cornea revealed by TEM in the present case might also suggest that the basal layer of the epithelium is the primary target site of keratoconus.

The immunological mechanism is not known to participate as the primary causal factor of keratoconus; the disease is non-inflammatory, and it is difficult to see how an immunopathological process can produce changes in the cornea without inducing any inflammatory reaction. However, the clinical impression that keratoconus shows a strong tendency to coexist with atopic disorders, for reasons that remain unexplained, is confirmed by the high incidence from breakage of the Bowman’s membrane.

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**Fig. 3.** Electron microscopy of the corneal epithelium of the left eye with keratoconus. The number of the epithelial cells (E) is decreased, and the epithelial basal cells (EB) are atrophied. In the stroma (S), the collagen fibers are disordered and compacted. The Bowman’s membrane (B) is folded or has disappeared. Scale Bar=10 μm. Inset: The basal cell shows a reduced number of cytoplasmic organelles and irregularity of the nuclear membrane. Scale Bar=1 μm.

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**Fig. 2.**

a) Low magnification view of the cornea of the left eye in the present case. The corneal epithelium, stroma and endothelium are thinned. HE stain. Scale Bar=200 μm.

b) Low magnification view of the cornea of the left eye in the normal monkey. HE stain. Scale Bar=200 μm.

c) High magnification view of the corneal epithelium of the left eye in the present case. In the corneal epithelium, the number of epithelial cells decreases, the cytoplasms are poor and the basal cells are flattened. The Bowman’s membrane also disappeared. The stromal collagen fiber is disordered and compacted, and the number of keratocytes has increased. HE stain. Scale Bar=20 μm.

d) High magnification view of the corneal epithelium of the left eye in the present case. In the corneal epithelium, the number of epithelial cells decreases, the cytoplasms are poor and the basal cells are flattened. The Bowman’s membrane also disappeared. The stromal collagen fiber is disordered and compacted, and the number of keratocytes has increased. HE stain. Scale Bar=20 μm.

e) High magnification view of the corneal endothelium of the left eye in the present case. The endothelial cell has pyknosis (arrowhead) and is partially detached (arrows). HE stain. Scale Bar=20 μm.

f) High magnification view of the corneal endothelium of the left eye in the normal monkey. HE stain. Scale Bar=20 μm.

g) The cornea of the left keratoconus eye. The Bowman’s membrane is folded (arrows). Toluidine blue stain.
IgE level above 31 kIU/L. In the present case, erythema of the upper eyelid and forehead, and corneal edema might have resulted from habitual rubbing of the eyes, and the high serum IgE level (38 kIU/L) suggests a possible atopy-like mechanism in this monkey.

One case of keratoconus in a rhesus monkey has been reported; however, that report only covered specular microscopical examination of the corneal endothelium. The ophthalmological findings in the rhesus monkey were quite similar to those in the present case; however, serological, histopathological and electron microscopical examinations were not performed for the rhesus monkey.

In conclusion, the present case shows that keratoconus can occur in the cynomolgus monkey. Similar to human cases, a high serum IgE level and rubbing of the eyes may play a role in the pathogenesis of the disease. This is the first report of a case of keratoconus in a cynomolgus monkey.

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