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Clinical presentation, treatment, and genetic and histopathological analysis of juvenile cataracts and secondary glaucoma in a rhesus macaque (*Macaca mulatta*)

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Abstract

This report describes the clinical and histological findings, genetic study, and treatment in a 1.3-year-old rhesus macaque with bilateral cataracts and unilateral secondary glaucoma. Intravitreal injection of gentamicin decreased the intraocular pressure from 56 to <2 mm Hg. A putative genetic cause of the cataracts was not identified.

Keywords

non-human primate; intravitreal gentamicin; chronic glaucoma

Introduction

In humans, congenital and juvenile cataracts can have genetic origin or can be associated with infectious diseases, metabolic disorders or trauma.[1, 2] Nonhuman primates (NHPs) are critical in the study of ocular diseases in humans due to their similar ocular development and morphology,[3] however, spontaneous congenital or juvenile cataracts in NHPs are rare,

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with only a few cases reported.[4–8] In rhesus macaques (*Macaca mulatta*), the incidence of cataracts increases with age,[9] but secondary glaucoma from lens-induced uveitis has not been described in this species, and it is rarely reported in other NHP.[5]

Intravitreal injection of gentamicin at high dose induces a pharmacologic destruction of the ciliary body and reduction of intraocular pressure (IOP). This procedure has been used as a long-term treatment in end-stage glaucoma in dogs,[10] but its efficacy in NHPs has not been evaluated.

This case report describes the clinical, histologic, genetic findings and treatment of a 1.3-year-old female rhesus macaque with bilateral cataracts and unilateral secondary glaucoma.

Case report

A 1.3-year-old captive-born female rhesus macaque was sedated with an intramuscular injection of ketamine hydrochloride (25 mg/kg) and dexmedetomidine (0.025 mg/kg) and an ophthalmic examination was performed, including color photography (Rebel T3 EOS, Canon), rebound tonometry (TonoVet, Icare Oy), ultrasound pachymetry (Pachette 4, DGH Technology Inc) slit lamp examination (SL-17, Kowa Optics), anterior segment tomography (Pentacam, Oculus, Optikgeräte GmbH) and A-scan ultrasound biometry (PacScan 300A+, Sonomed Escalon).

Hypermature cataracts and mild diffuse corneal edema were observed in both eyes (OU). There was increased central corneal thickness (600 μm right eye, OD, and 529 μm left eye, OS) when compared with the average corneal thickness of 11 rhesus macaques from the same colony between 0.9 to 1.8 years of age (470 ± 27 μm). The IOP was 12 (OD) and 40 (OS) mm Hg. Additionally, buphthalmos with a shallow anterior chamber, anterior bowing of the iris (iris bombe) due to accumulation of aqueous humor in the posterior chamber from extensive posterior synechiae, and blood vessel proliferation on the iris surface (rubeosis iridis) were found OS (Figure 1). Axial globe length confirmed a difference in size between the two globes at 18.1 mm OD and 22.3 mm OS. The cataracts prevented visualization of the fundus by ophthalmoscopy OU. The macaque was diagnosed with hypermature cataracts OU, lens-induced uveitis OS, and secondary glaucoma OS.

One week following initial examination, the affected macaque was sedated using the aforementioned protocol and an intravitreal gentamicin injection was performed OS. Pre-injection IOP was 56 mm Hg OS. The globe was sterilely prepped, and an eyelid speculum was placed. A sterile caliper was used to create a small indentation in the sclera to mark the injection site 2.5 mm from the superotemporal limbus. A 25-gauge syringe with 1/2-inch needle was used to remove 0.5 ml of vitreous. Then, 0.15 ml of gentamicin (100 mg/ml) and 0.25 ml of dexamethasone (4 mg/ml) was injected with a 25-gauge, 1/2-inch needle at the marked site. Three weeks after the procedure, IOP was markedly reduced (<2 mmHg). Anterior segment examination revealed 1+ aqueous cell (6–25 cells in field)[11] and 2+ aqueous flare (moderate amount of protein visible to the naked eye using a focused beam of white light),[11] but was otherwise unchanged from the previous exam.

The dam, maternal granddam, and two maternal aunts of the affected macaque were examined and had normal ocular exams and IOPs (10–18 mm Hg). Whole genome shotgun sequencing was performed on the affected macaque, the four relatives examined, and seven unexamined relatives, as previously described.[12] Sequencing reads from the affected macaque were aligned to the rhesus Mmul_8.0.1 reference genome assembly using BWA-MEM.[13] The GATK pipeline[14] was used to identify single nucleotide variants and insertions/deletions, which are annotated with Effect Predictor.[15] Variants with high allele frequency (>10%) within the colony were excluded. Remaining variants mapped to known congenital cataract genes were further examined by lifting the rhesus positions over to the orthologous human position (GRCh37) and were annotated and predicted with ANNOVAR[16] and dbNSFP suite.[17] Three variants in the genes *CRYBB2*, *EPHA2*, and *VIM* were identified in the affected macaque (Table 1). Segregation analysis of these three candidate variants with phenotype indicates that these variants do not segregate with the phenotype, therefore unlikely to be causal mutations of the cataracts in this case (Figure 1).

Six weeks after the initial exam, the affected macaque was euthanized for reasons unrelated to her eyes. Histopathological examination confirmed hypermature cataracts with lens capsule wrinkling and rupture OU and leakage of lens material OS (Figure 1). Additionally, inflammation associated with leakage of lens material (phacoclastic uveitis), a collapsed ciliary cleft, a thin layer of granulation tissue over the iris (pre-iridal fibrovascular membrane), iris bombe, severe inner and outer retinal atrophy with focal retinal detachment and mild vitreous hemorrhage were observed OS (Figure 1).

Discussion

Although uncommon, congenital and juvenile cataracts have been reported in NHPs.[4–8] In our presented case, the cataracts were classified as juvenile cataracts based on the age of the primate at the time of diagnosis. No visual impairment was detected before of the exam, however, this primate was housed outdoor, where vision impairment can go unnoticed in very young individuals. This case also supports the use of intravitreal gentamicin to treat uncontrolled, end-stage glaucoma in NHPs. Although retinal changes associated with acute gentamicin toxicity have been described in NHPs,[18, 19] it was impossible to determine if the histologic changes to the retina were due to chronic glaucoma or were a consequence of the intravitreal gentamicin in the current case. Similarly, the hemorrhage in the vitreous could be secondary to the retinal detachment observed or a sequela of the intravitreal injection, as it is a commonly observed complication in dogs.[10] The development of anterior uveitis following the intravitreal gentamicin injection is expected and is the most common sequelae observed in dogs.[20] The dose of gentamicin employed in this study was below the toxic dose for aminoglycosides reported in macaques.[21]

A combined genetic and ocular screening of the relatives excluded three potential candidate gene variants as putative cause of the cataracts. Further screening of other variants did not yield any other highly confident candidate variant. In the absence of other cases in the colony, environmental, toxicological, or infectious causes are less likely to play a role in the pathogenesis of these cataracts.

In conclusion, this report describes the clinical and histological findings of a unique case of bilateral cataracts in a juvenile rhesus macaque that developed unilateral secondary glaucoma. Intravitreal injection of gentamicin in the glaucomatous eye was successful in treating the elevated IOP. A causative genetic factor for the cataracts could not be identified in this rhesus.

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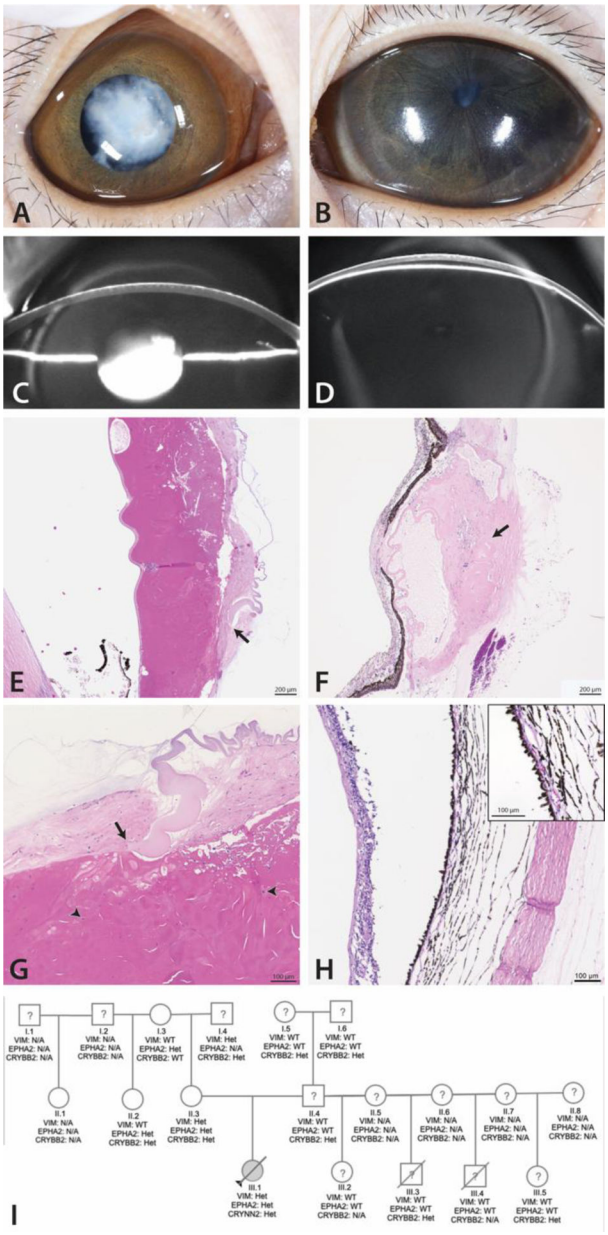

Figure 1.

Clinical and histologic features of bilateral, hypermature cataracts and unilateral secondary phacoclastic uveitis and glaucoma in a 1.3-year-old female rhesus macaque and phenotype and segregation of the variants within the pedigree. Hypermature cataracts were visible with color photography in both eyes (A, B). Buphthalmos, iris bombe, and rubeosis iridis was observed OS (B). With anterior segment tomography a deep, anterior chamber and small, hyperreflective lens was found in OD (C), and a shallow anterior chamber visualized in OS (D). Histology confirmed the presence of hypermature cataracts and identified posterior lens capsule rupture in both eyes (arrow) (E, F). Surrounding the lens capsule OS, low number of macrophages, lymphocytes, and scant degenerated neutrophils were identified, consistent with phacoclastic uveitis. Additionally, OS had occasional mild lymphocytic

infiltrates in the iris and ciliary body stroma as well as posterior synechiae with formation of a segmental, pre-iridal fibrovascular membrane, and iris bombe in OS (F). The lens had swollen lens fibers with vacuoles as well as Morgagnian globules, bladder cells (arrowhead), and rupture of the lens capsule (arrow) (G). In OS, a segmental retinal detachment with retinal pigmented epithelium hypertrophy (inset) and inner and outer retinal atrophy were observed (H). The pattern of co-segregation combined with the phenotype excluded the variants examined as putative cause of the cataract in the affected rhesus (I). Circles: females. Squares: males. Cross circle/square: dead. Grey: juvenile cataract. White: examined and free of juvenile cataract. Question mark: not examined. WT: Wild type for the variant. Het: Heterozygous for the variant. N/A: inconclusive.

Table 1.

Analysis of the three variants of interest detected after whole genome sequencing the affected macaque.

Nonsynonymous mutations were detected in *CRYBB2, EPHA2,* and *VIM*, genes previously associated with inherited cataracts in humans.[2] The location of the variant in the human genome (GRCh37) as well as the variant, the type of mutation are included. After analyzing these variants in the relatives with normal ocular exams, they were excluded as the putative cause of the cataracts in this rhesus macaque. 1: SIFT_pred. 2: Polyphen2_HDIV. 3: CADD_phre. 4: REVEL score. AF: Allele frequency of the identified variant. AC: Allele count of the identified variant. AN: Total number of alleles in called genotypes.

Gene name and symbol	Gene function	Diseases associated with mutations in the gene	Identified variants (GRCh37)	Annotation of the variants	In-silico prediction of the variants	Allele frequency of the variants in 530 rhesus macaque genomes
Ephrin Type-A Receptor 2 (EPHA2)	Tyrosine-Protein Kinase Receptor, involved in developmental events.	Autosomal dominant cataract in humans.	chr1:16456826:T>C	EPHA2:NM_004431:exon15:c.A2564G:p.Q855R	1: Damaging 2: Benign 3: 25.6 4: 0.515	AF:0.002825 AC:3 AN:1060
Vimentin (VIM)	Type III intermediate filament protein involved in cell shape and cytoskeletal interactions.	Autosomal dominant cataract in humans.	chr10:17271573:G>C	VIM:NM_003380:exon2:c.G152C:p.S51T	1: Tolerated 2: Benign 3: 9.9 4: 0.119	AF:0.004444 AC:4 AN:898
Crystallin Beta B2 (CRYBB2)	Crystallin responsible for maintaining the transparency and refractive index of the lens.	Multiple types of cataracts in humans.	chr22:25627683:C>T	CRYBB2:NM_000496:exon6:c.C562T:p.R188C	1: Damaging 2: Deleterious 3: 28.1 4: 0.79	Not found