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Case Report

Anterior segment dysmorphogenesis of the eye and glaucoma in MG-W gerbils

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Abstract: Unilaterally swollen eyes were histopathologically characterized in four MG-W gerbils. The primary lesions resided in the anterior segment of the eye where neural crest cells play a critical role in embryonic development. They included indistinct filtration angle, unformed canal of Schlemm, hypoplastic iris, and ciliary body. The findings noted in the retina, optic nerve, optic tract, and lateral geniculate nucleus were consistent with the lesions induced following the persistent elevation of intraocular pressure as a result of insufficient drainage of aqueous humor. Thus, the present cases observed in the eyes of MG-W gerbils exemplified the anterior segment dysmorphogenesis associated with inadequate neural crest migration or differentiation, leading to subsequent glaucoma. (DOI: 10.1293/tox.2020-0090; J Toxicol Pathol 2021; 34: 245–249)

Key words: MG-W gerbil, eye, anterior segment dysmorphogenesis, glaucoma

MG-W gerbils are inbred species of experimental animals established in Japan. They were produced from Mongolian gerbils (*Meriones unguiculatus*) that are frequently utilized for their biological features in studies investigating infectious diseases, cancer biology, auditory range, genetic studies, etc[1]. However, the profiles of spontaneously occurring lesions, including ocular pathology, are not yet fully known. This communication describes the characterization of histopathological findings of spontaneous ocular lesions of anterior segment dysmorphogenesis and glaucoma found in four MG-W inbred gerbils.

A total of 686 neonates delivered from four pairs of MG-W gerbils were weaned from January 2012 to March 2013 at the National Institute of Health Sciences. Among them, unilateral swelling of the eyes was clinically identified in four males and one female aged 6–23 weeks, of which one each was subjected to ophthalmological and histopathological examinations together with age-matched controls at 6, 8, 19, and 23 weeks of age. The results of the ophthalmological examinations have been reported[2]; thus, this report describes the detailed histopathological findings. All the gerbils were euthanized by exsanguination under anesthesia with isoflurane (Pfizer, Tokyo, Japan). The eyes and brains were sampled, fixed in a combination fixative of 3% glutaraldehyde and 2.5% phosphate-buffered formalin, and 10% phosphate-buffered formalin, respectively, processed into paraffin-embedded sections, and stained with hematoxylin and eosin (HE) in a standard manner. Representative sections were also examined with special staining with Klüver-Barrera (KB) and Masson trichrome (MT), as well as immunohistochemical staining with anti-glial fibrillary acidic protein rabbit polyclonal antibody (GFAP, Dako IR524, Tokyo, Japan) and anti-ionized calcium binding adapter protein 1 rabbit polyclonal antibody (Iba 1, Wako, Tokyo, Japan). All these pathological procedures were designed in full compliance with pertinent public laws and guidelines, as well as the institutional standard of Code of Conduct in Animal Experiment, BoZo Research Center, Inc., to meet the principles of animal welfare and approved by the Institutional Animal Ethics Committee at Tsukuba Research Institute, BoZo Research Center Inc., Japan.

The eyes were swollen in two left- and one right-side eyes of the male, and one right-side of the female MG-W gerbils at the ages of 8, 23, 19, and 6 weeks, respectively. The histopathological findings were consistent among all the swollen eyes. The contour of the eyeball became oval, with an expanded intraocular space (Fig. 1). The filtration angle was indistinct, leaving a scarce remnant of the trabecular meshwork, and the canal of Schlemm was not formed. The iris and ciliary body were not well developed, and syn-

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echia was present to the cornea that was partially thin. The sclera was also thinned around the entire circumference (Fig. 2). The lens lost its biconvex structure and turned to be an irregularly shaped mass filled with amorphous and eosinophilic substances (Fig. 1-B and Fig. 2-B). The numbers of neurons in the ganglion cell layers of the retinas were remarkably reduced, while those in the inner and outer nuclear layers were slightly reduced (Fig. 3-1), resulting in diminished optic nerve diameters. The GFAP immunohistochemistry revealed the distributions of networks of activated Müller cells in the retina (Fig. 3-2). The optic papilla was substantially excavated and replaced in large parts by fibrous tissue (Fig. 4). The relevant optic tract and lateral geniculate nucleus were also diminished in area (Fig. 5-1). Activated astroglia and microglia were revealed by GFAP and Iba 1 immunohistochemistry, respectively (Fig. 5-2).

As such, the primary lesions most likely reside in the anterior segment of the eye, including the filtration angle, canal of Schlemm, iris, and ciliary body. The incomplete development of the filtration angle and canal of Schlemm, together with the formation of anterior synechia, could result in insufficient aqueous drainage and subsequent increased intraocular pressure (IOP), leading to a series of progressive neuronal alterations characterized by the degeneration of the retinal ganglion cells and cupping in the optic papillary[3]. Besides mechanical stress on the axon caused by remodeling of the lamina cribrosa, disruption of retrograde axonal transport of neurotrophin from the lateral geniculate nuclei precedes somal apoptosis of retinal ganglion cells[4, 5]. Müller cells are activated in association with retinal diseases[6]. Thus, the distinct network of Müller cells found in the affected retina likely represented evidence that the retina had developed and undergone acquired damage. Increased IOP reduces the density and number of neurons in the lateral geniculate nucleus as well as the size of the nucleus itself as a consequence of decreased neuronal activity within the retino-geniculo-cortical pathway[7]. Neuronal degeneration was well suggested within the affected lateral geniculate nucleus by the finding that the nucleus was atrophic and contained numerous activated both astroglia and microglia.

The findings observed in the anterior segment of the swollen eyes were of interest. The anterior segment of the eye is formed by four embryonic lineages: the surface ectoderm, neuroectoderm, mesenchymal cells derived from the

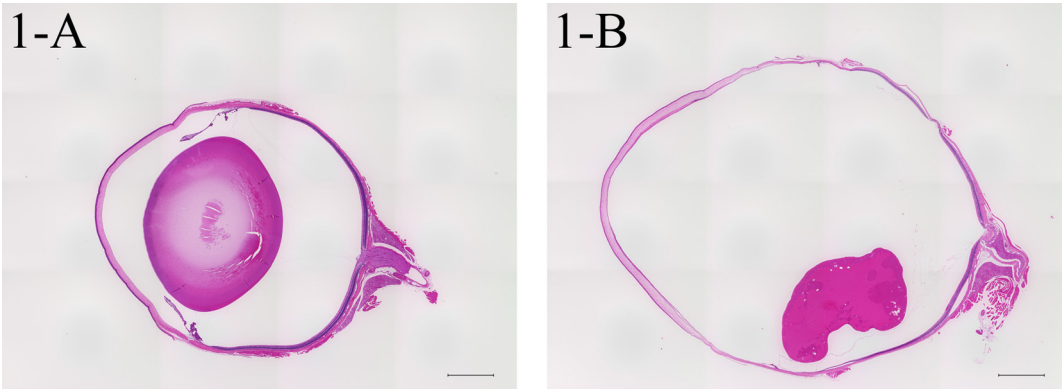

Fig. 1. A male MG-W gerbil, 23 weeks of age (HE, bar=1,000 μm). 1-A: Normal. 1-B: The contour is elongated expanding the intraocular space. The lens is distorted and latero-posteriorly dislocated. HE, hematoxylin and eosin.

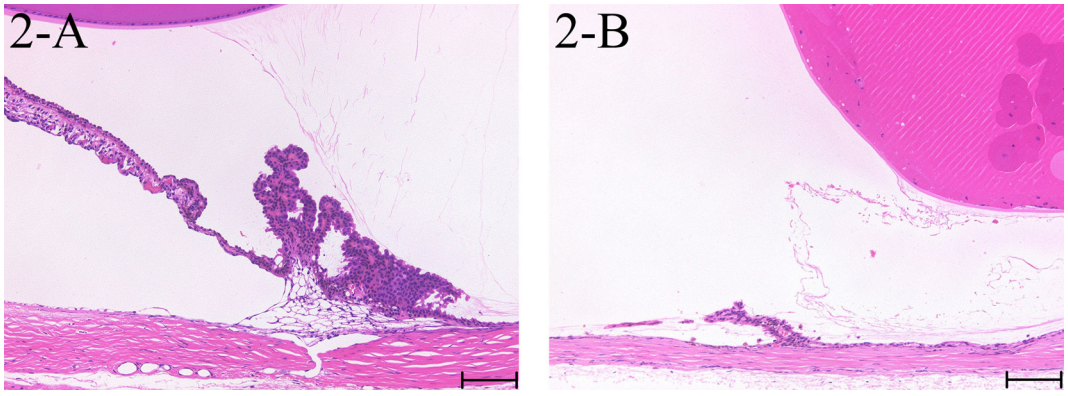

Fig. 2. Middle-power view of Fig. 1 (HE, bar=100 μm). 2-A: Normal. 2-B: The filtration angle, iris, and ciliary body are hypoplastic, and canal of Schlemm is aplastic. The cornea and sclera are thin. HE, hematoxylin and eosin.

neural crest, and cranial paraxial mesoderm[8]. Neural crest cells contribute to the development of the corneal endothelium and stroma, sclera, iris stroma, ciliary muscle, process, zonule and body, trabecular meshwork, canal of Schlemm, and pericytes of the ocular blood vasculature[9–11]. Anterior segment mesenchymal dysgenesis in humans encompasses a group of developmental disorders of the eye caused by abnormal neural crest cell migration and differentiation[12], and is frequently associated with iris hypoplasia, synechia, enlarged corneal diameter, ectopia lentis, and abnormal development of the trabecular meshwork and canal of Schlemm, with subsequent glaucoma[9, 12, 13]. The lens undergoes morphological alterations with posterior dislocation[14]. The findings in the anterior segment were localized in the tissues where neural crest cells play a critical role in embryonic development. This finding strongly suggests that the

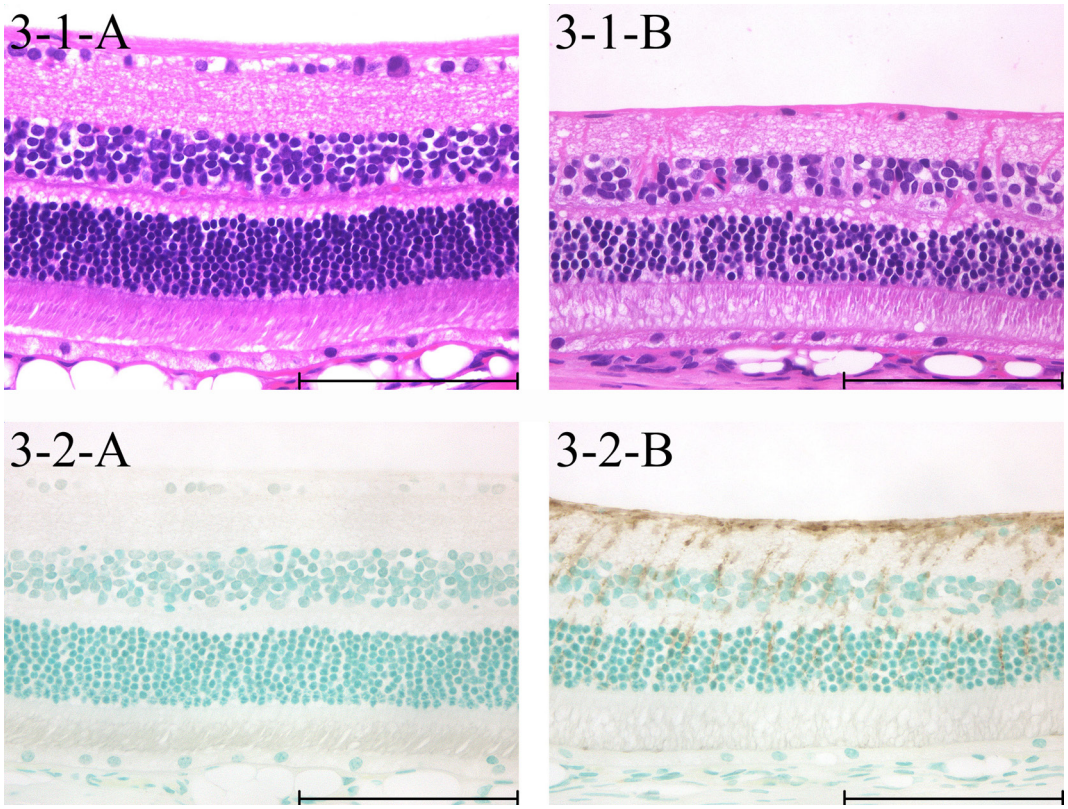

Fig. 3. High-power view of Fig. 1 (HE, bar=100 μm). 3-1-A: Normal. 3-1-B: The number of neurons in the ganglion cell layer, and inner and outer nuclear layers are reduced. High-power view of Fig. 1 (GFAP, bar=100 μm). 3-2-A: Normal. 3-2-B: GFAP-positive Müller cells form a prominent network HE, hematoxylin and eosin; GFAP, glial fibrillary acidic protein

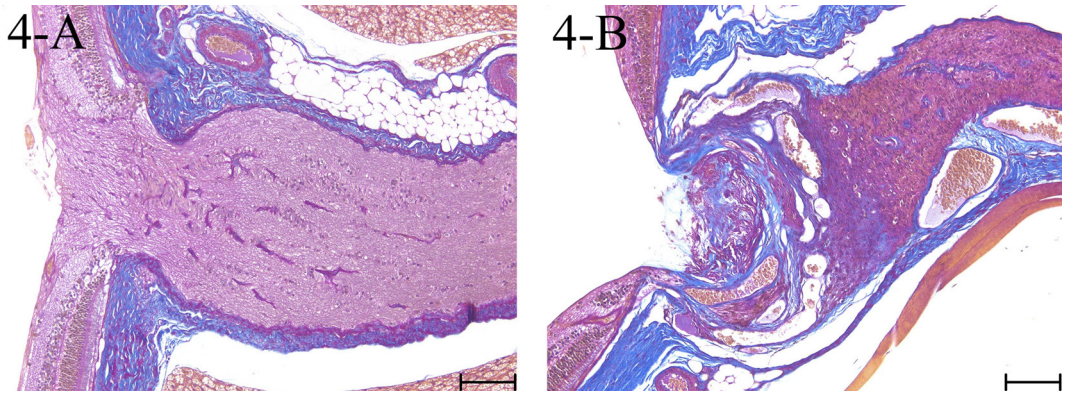

Fig. 4. A male MG-W gerbil, 23 weeks of age (MT, bar=100 μm). 4-A: Normal. 4-B: The optic papilla is substantially excavated and replaced in large part by fibrous tissue. MT, Masson trichrome.

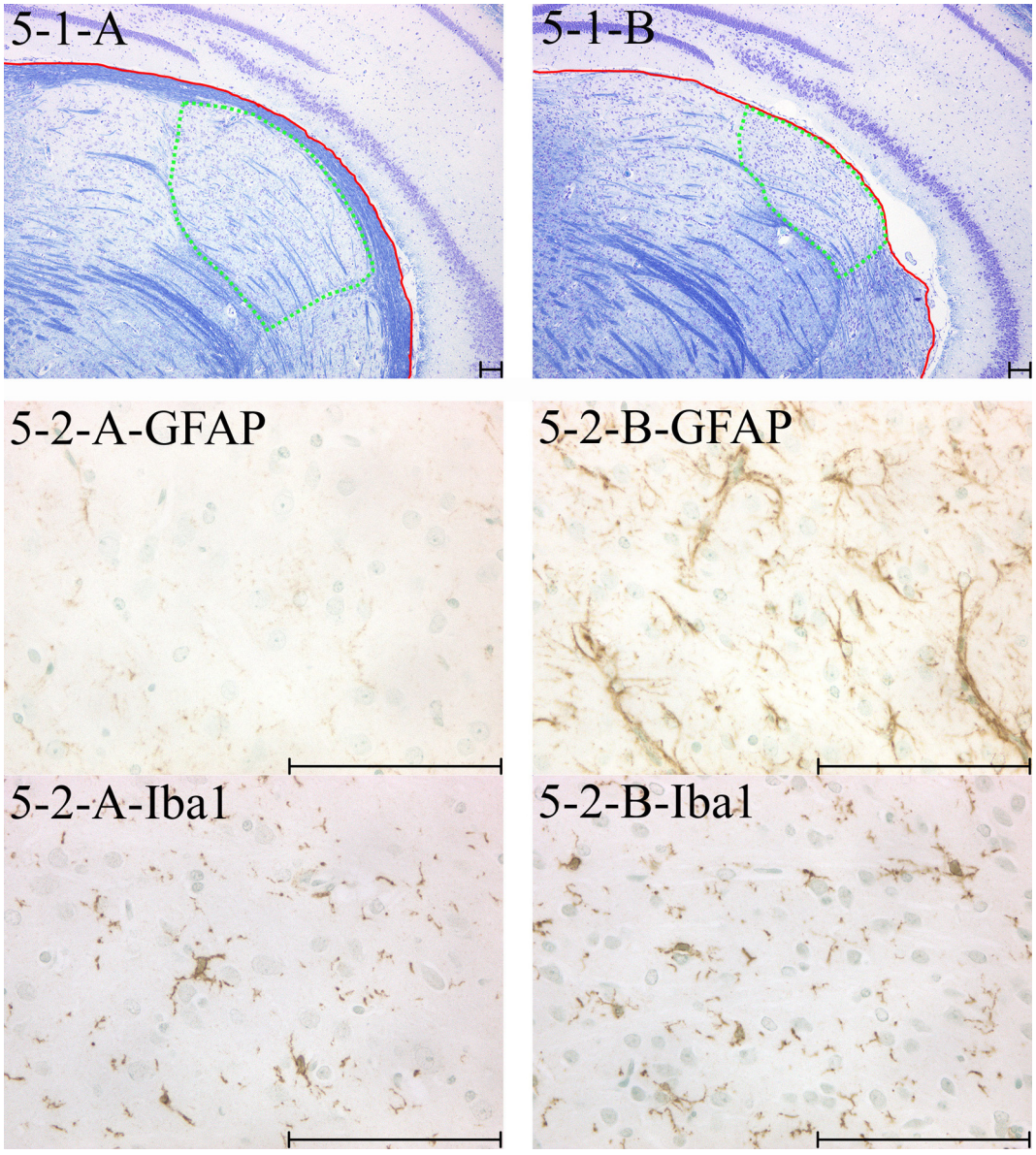

Fig. 5. A male MG-W gerbil, 23 weeks of age (KB, bar=100 μm). 5-1-A: Normal. 5-1-B: The relevant optic tract (red line) and lateral geniculate nucleus (green dotted line) are diminished in size. A male MG-W gerbil, 23 weeks of age (GFAP and Iba1, bar=100 μm). 5-2-A: Normal. 5-2-B: Both astroglia and microglia are activated in the lateral geniculate nucleus. KB, Klüver-Barrera; GFAP, glial fibrillary acidic protein; Iba1, ionized calcium-binding adapter molecule 1.

primary lesions in the present cases were consistent with anterior segment congenital anomalies associated with inadequate neural crest migration or differentiation. A number of genes are involved in anterior segment mesenchymal dysgenesis[10, 12, 13]. Genomic alteration cannot entirely be ruled out in the present cases.

The inconsistency between the congenital nature of dysmorphogenesis of the anterior segment and the acquired nature of the increased IOP may be ascribed in part to the functioning outflow of aqueous humor through the unconventional uveoscleral pathway[15].

Combined, these findings indicate the need for special attention to ocular pathology when employing MG-W gerbils for research purposes.

Disclosure of Potential Conflicts of Interest: The authors declare that there are no conflicts of interest.

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