Case Report

A Case of Primary Congenital Glaucoma in Fischer344 Rat

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Abstract: A 15-week-old, male Fischer344 rat clinically had bilateral buphthalmos. Grossly, both globes were enlarged showing protrusion of the cornea with an increase in anterior chamber depth. Histologically, similar findings were observed in both globes. The cornea and sclera were slightly thinned. The iris was displaced forward, resulting in sealing of filtration angle. The root of the iris was partly connected with the corneal endothelium, in which the Descemet's membrane was lost. The trabecular meshwork was hypoplastic and covered completely with the deformed iris tissue. Neither inflammatory reaction nor fibrosis was detected in the affected angle and anterior uvea. The ciliary body was hypoplastic and dysplastic. The retina, particularly the inner layers, was atrophic and degenerative. The optic disc was deeply cupped and the optic nerve fibers were degenerated. These findings led us to diagnose the present case as primary congenital glaucoma in the rat. (*J Toxicol Pathol* 2000; 13: 119~121)

Key words: Congenital, Ocular disease, Glaucoma, Histopathology, Rat

Glaucoma is one of the most important ocular diseases in humans¹ and animals² and is essentially classified as primary or secondary glaucoma^{1,2}. Primary glaucoma may result from defective development of the iridocorneal angle, termed goniodysgenesis³. Secondary glaucoma can result from blockage of the filtration angle by fibrin, hemorrhage, or a variety of particulate matter⁴. On the other hand, congenital glaucoma is used to describe glaucoma that is seen at birth

or shortly thereafter and results from goniodysgenesis or other structural abnormalities of the eye³. Congenital glaucoma has been described in dogs³, cats⁵, and rabbits⁶. In rats, however, glaucoma has rarely been reported^{7,8}. The Fischer344 (F344) is a major strain of rats and has been used in a variety of toxicity and carcinogenicity tests. In the present paper, we describe the pathomorphological changes of primary congenital glaucoma in an F344 rat.

Thirty-six male and 36 female F344/DuCrj rats were purchased from Charles River Japan, Inc. (Kanagawa, Japan) at 6 weeks of age. They were housed in stainless steel wire-mesh cages in a barrier-sustained room controlled at $23 \pm 2^\circ$ C, $55 \pm 20\%$ relative humidity, and a 13-hr light/11-hr dark cycle. The animals had free access to a standard laboratory diet for rats (CRF-1, Charles River Japan, Inc.) and tap water. They were cared for and were treated humanely at

Fig. 1. Both eyes externally show buphthalmos with a deep anterior chamber. Note a marked deep anterior chamber in the right eye (arrow).

Fig. 2. At the anterior chamber angle, the iris is displaced forward and the ciliary body is hypoplastic. No noticeable changes are seen in the lens. HE, $\times 36$.

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Fig. 3. The filtration angle is sealed with the root of the iris without any inflammatory infiltration or fibrosis. Note vestigial ciliary processes in the hypoplastic ciliary body. HE, $\times 120$.

Fig. 4. The Descemet's membrane is missing in the peripheral portion of the cornea (arrowheads) that adheres to the root of the displaced iris. PAS, $\times 480$.

the Yamanouchi Pharmaceutical Co., Ltd. in accordance with the *Guidelines for Animal Experimentation*, published by the Japanese Association for Laboratory Animal Science⁹. During the acclimation period, a male rat aged 14 weeks exhibited enlargement of both eyes, i.e. bilateral buphthalmos. The rat was euthanized by ether inhalation and subjected to a complete necropsy at 15 weeks of age.

Grossly, both globes of the rat were enlarged and showed protrusion of the cornea with a deep anterior chamber (Fig. 1). The optic nerves at the posterior portion of the globes were atrophic. No opacity was found in the cornea and lens. The globes were fixed in a combined fixative of 1.5% glutaraldehyde and 2.5% formalin, embedded in paraffin, sectioned serially, and stained with hematoxylin and eosin (HE). Selected sections were stained by the Azan, periodic acid-Schiff (PAS), and Watanabe's silver impregnation methods.

Histologically, both globes showed similar findings. The cornea and sclera were slightly thinned and the anterior chamber increased in depth. The corneal stroma was slightly edematous. The iris was displaced forward, sealing the filtration angle (Figs. 2 and 3). The root of the iris was

Fig. 5. The inner layers of the retina, particularly the nerve fiber, ganglion cell, inner plexiform, and inner nuclear layers, are markedly atrophic. The outer plexiform layer is also atrophic. The outer nuclear layer, layer of rods and cones, and pigment epithelial layer shows no noticeable changes. A slit between the layer of rods and cones and the pigment epithelial layer is an artifact. HE, $\times 240$.

Fig. 6. The optic nerve head shows cupping of its surface. Slits between the layer of rods and cones and the pigment epithelial layer are artifacts. HE, $\times 48$.

connected with the corneal endothelium in the limbal portion, and at that part the Descemet's membrane was missing, as demonstrated by the PAS method (Fig. 4). In normal rat eyes, the Descemet's membrane sited into the limbal portion (data not shown). The trabecular meshwork was hypoplastic and covered completely with the posterior epithelium of the deformed iris. Neither inflammatory reaction nor degenerative change was detected in the filtration angle and uvea. In addition, no fibrosis was observed in the portion by the methods of Azan and silver impregnation. Ciliary processes of the ciliary body poorly developed and became deformed, showing a hypoplastic or dysplastic state (Fig. 3). The retina was atrophic and degenerative in the whole areas. Particularly the nerve fiber, ganglion cell, inner plexiform, and inner nuclear layers were barely identifiable (Fig. 5). The retinal ganglion cells markedly decreased in number and became pyknotic and shrunken. In some portions of the

retina, only the layers of outer nuclear, rods and cones, and pigment epithelium were recognizable. There was a rosette in the peripheral portion of the retina. In the posterior pole of the globe, the optic disc showed cupping of its surface (Fig. 6). The optic nerve was atrophic, in which nerve fibers decreased in number and were degenerative, accompanied with gliosis and fibrosis. Fibrosis of the optic nerve was confirmed by the methods of Azan and silver impregnation. No abnormalities were observed in other ocular tissues.

In the present case, the buphthalmic globes possessed a deep anterior chamber, sealed filtration angles with the forward-displacing iris, degeneration of the retinal inner layers, and optic disc cupping. In the course of glaucoma, the nerve fiber and ganglion cell layers of the retina become degenerative and may be completely absent in advanced stages², and the intraocular hypertension causes depression of the optic disc into the characteristic cup shape, called optic disc cupping³. These histologic changes in glaucoma coincided with those in the present case. It has been described that optic disc cupping may occur in a relatively short time if the increase in pressure is considerable⁴. In addition, cupping of the optic nerve head secondary to glaucoma develops more rapidly in infant eyes than in adult eyes¹.

Displacement of the iris, missing of the Descemet's membrane on the peripheral portion of the cornea, and rosette formation of the retina observed in the present case seemed to have occurred congenitally, because no inflammatory reactions were observed in these areas. Congenital angle malformations including displacement of the iris are encompassed in goniodysgenesis¹⁰, and such malformations predispose to the development of glaucoma⁴. It has been described that goniodysgenesis occurs bilaterally². Hence histologic changes in the filtration angle of the present case seem to be similar to those described in goniodysgenesis. Goniodysgenesis and noninflammatory peripheral anterior synechia have been the most consistent lesions in primary congenital glaucoma¹¹. It has also been described that buphthalmos is one of the secondary ocular effects of congenital glaucoma in young eye¹. Glaucomas in three weanling Wistar rats accompanied with lens luxation, were considered to be congenital glaucoma⁸. However, there were no descriptions on histological changes of the filtration angle and uvea in these cases, although the rats showed keratitis and marked degeneration in the ganglion cell, inner plexiform, and inner nuclear layers⁸. On the other hand, glaucomas in Sprague-Dawley rats have been suggested to occur secondarily to tumors in the ciliary bodies or infections of the anterior segment of the eyes⁸. In these cases, mechanical interference of the drainage of aqueous humour caused by the conjunctivitis, keratitis, iridocyclitis and consequent synechias, and tumors of the ciliary body would be responsible to secondary glaucoma⁸. It has been described that congenital

glaucoma in the WAG rats was due to the presence of a persistent pupillary membrane obliterating the angle filtration and thus interfering with the drainage of aqueous humour away from the eye⁷. The present study was the first to elucidate that glaucoma in the rat would occur in association with goniodysgenesis.

Based on the results described by previous workers and our observations, the present case was diagnosed as primary congenital glaucoma in the rat, though intraocular pressure was not measured. The development of congenital glaucoma depends not only on the severity of the angle anomalies but on the capacity of the ciliary body to produce aqueous humour¹¹. However, the true causes of congenital glaucoma are not as yet known¹. In a colony of WAG inbred rats, a persistent pupillary membrane associated with the cause of congenital glaucoma was presumed to be inherited⁷. Genetic involvement in the present glaucoma remains to be determined.

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