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The Ultrastructure of the Lens Capsule Abnormalities in Alport's Syndrome

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Abstract: The ultrastructure of lens capsule abnormalities in Alport's syndrome is reported. An anterior lens capsule from a 29-year-old patient with lenticonus who was affected by Alport's syndrome was obtained at the time of surgery. The histopathologic findings showed the thickness of the anterior lens capsule was decreased and there were many vertical capsular dehiscences localized at the inner part of the lens capsule. Almost every dehiscence was limited to the inner two thirds of the capsule. One should be cautious in attempting intraocular lens implantation into the lens capsule of patients with Alport's syndrome, because the lens capsule may be fragile in this disease. **Jpn J Ophthalmol 1998;42:401–405** © 1998 Japanese Ophthalmological Society

Key Words: Alport's syndrome, anterior lenticonus, intraocular lens implantation, type IV collagen.

Introduction

Alport's syndrome is a hereditary nephritis often accompanied by hearing impairment. This disease is primarily X-chromosome–linked, but autosomal forms have also been described. It is generally accepted that abnormalities in the type IV collagen molecule may play a causative role in the development of this syndrome. In recent years, many studies involving biochemistry and molecular biology have greatly improved our understanding of this disease. In some instances, the gene locus of gene mutation has already been identified. Because a diversity in modes of inheritance and clinical findings has been described, this syndrome is currently considered as a group of similar hereditary diseases.

Although anterior lenticonus is the most commonly reported ocular abnormality in Alport's syndrome, little is known about the histopathologic changes in this disorder. As for the histologic findings of lenticonus, Brownell and Wolter[1] have demonstrated the thinning of the lens capsule by means of a light microscope. Electron microscopic study has demonstrated the marked thinning and vertical dehiscence of the anterior lens capsule in Alport's syndrome.[2]

Here, we describe the detailed histopathologic and ultrastructural findings in the lens capsule obtained from an Alport's syndrome patient at the time of surgery.

Case Report

A 29-year-old man came to our clinic on January 31, 1994, with the complaint of decreased vision in his left eye. At the age of 18, he had developed irreversible renal failure, and eventually he required hemodialysis. His mother and elder sister were diagnosed as having Alport's syndrome, but they were not available for ophthalmic examination.

Gross examination did not show any abnormal findings. Slit-lamp examination disclosed there was lenticonus accompanied by a subcapsular faint opacity in his left eye (Figure 1); no abnormalities were observed in the right eye. Other ocular findings were normal. Spectacle corrected visual acuity was 20/25 in the right eye and 20/40 in the left.

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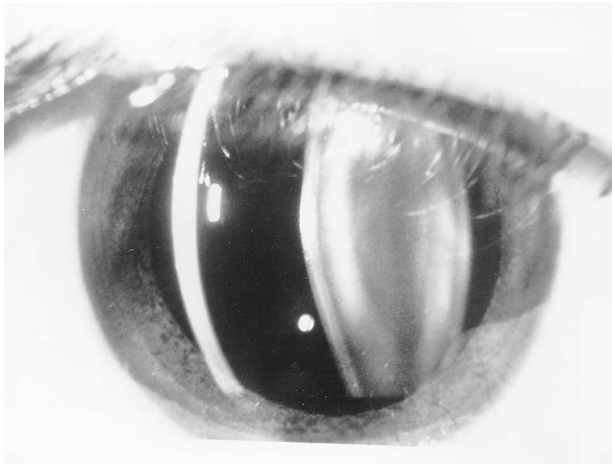

Figure 1. Slit-lamp photograph shows anterior lenticonus and anterior subcapsular faint opacity.

In July 1994, an uncomplicated phacoemulsification with a continuous circular capsulorrhexis and intraocular lens implantation was performed in his left eye. Three months after surgery, best corrected visual acuity was 20/20, and no postoperative complication was observed in this patient's left eye. We studied the histologic findings in the anterior lens capsule obtained at the time of surgery.

The anterior lens capsule was immersed in 2.5% glutaraldehyde/phosphate buffer (pH7.4) and postfixed in 1% OsO_4 in the same buffer. Dehydration in increasing concentrations of ethanol, and embedding in Epon using standard procedures followed. For light microscopic observation, 1 μm sections were stained with toluidine blue (Figure 2). Then, ultrathin sections for electron microscopy were stained with uranyl acetate and citrate. Specimens were observed by a H-7100 transmission electron microscope (Hitachi; Tokyo) (Figures 3–5).

The anterior lens capsule was about 10 μm in thickness. The thinning was found not only in the central part of the anterior capsule, but also in the peripheral part (Figure 2). There were many vertical dehiscences that varied from 1.0–8.0 μm in depth, and from 200–500 nm in width. The dehiscences were particularly prominent in the central part of the anterior capsule but they were also observed in the peripheral region. Almost every dehiscence ran vertically, but some ran horizontally. All dehiscence contained fibrillar material and vacuoles. The dehiscences emanated from the inner side of the lens capsule and were located in the inner two thirds of the capsule (Figures 3–5). Electron micrography of the anterior lens epithelium showed some pathologic changes. The lens epithelium was highly irregular, and there were extensive extracellular lacunae between the lateral margins of adjacent cells (Figures 3, 4). In some cells, lucent intracellular cisternae existed and mitochondria were increased in number.

At the same time, we also conducted a histologic examination of similar ocular sections from patients without Alport's syndrome at cataract surgery. In sections obtained by the same procedures of fixation, embedding, and sectioning, we did not observe any dehiscences; epithelial cells were cuboidal-shaped and their lateral borders were closely joined (Figure 6). Therefore, it is difficult to consider that the dehiscences observed in this Alport's patient were arti-

Figure 2. Photomicrograph of anterior lens capsule stained with toluidine blue; multiple dehiscences emanate from epithelial cell surface.

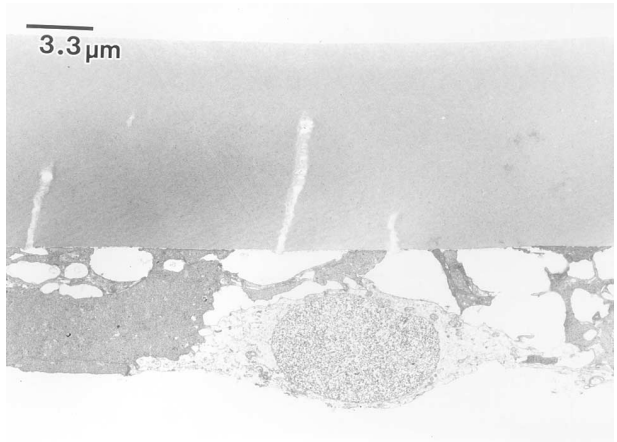

Figure 3. Transmission electron micrograph of anterior lens capsule. Dehiscences run vertically, never perforate capsule, and are located in inner two thirds of capsule.

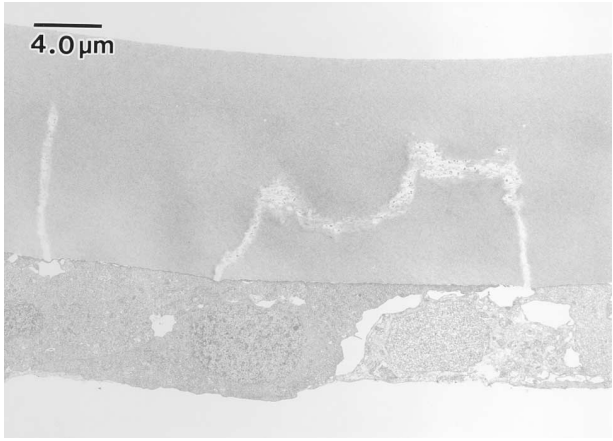

Figure 4. Transmission electron micrograph of anterior lens capsule. Horizontal dehiscence associated with fibrillar material is visible on this specimen.

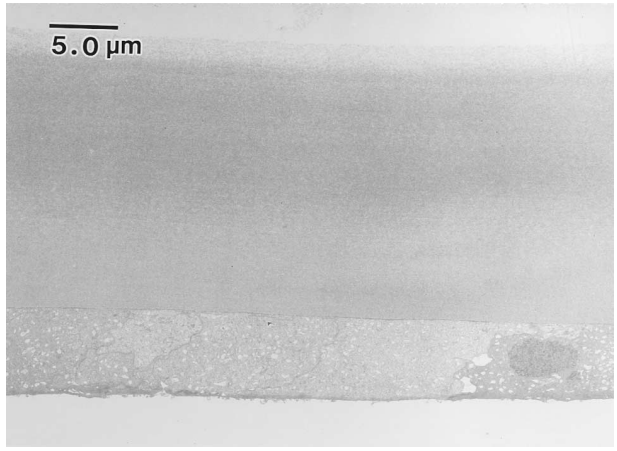

Figure 6. Control section obtained at cataract surgery in patient without Alport's syndrome.

facts due to procedures in the preparation of the sections.

Discussion

In 1927, Alport[3] reported a familial disorder characterized by progressive nephritis associated with nerve deafness. This syndrome causes recurrent hematuria with progression to renal failure; men are more frequently and severely affected than women. It is often accompanied by sensorineural hearing loss and ocular abnormalities. Some previous studies described that lenticonus was present in about half the cases.[4,5] The other ocular changes, arcus juveniles, posterior polymorphous dystrophy, cataract, iris atrophy, and so forth have also been reported.[5] Although anterior lenticonus is the most frequently described finding, only one electron microscopic study, as far as we are aware, has been performed on the lenticonus. Streeten and colleagues[2] reported ultrastructural findings in the anterior lens capsule from a 30-year-old Alport patient. Their observations included marked thinning of the anterior lens capsule and many dehiscences. These results agreed well with the findings from our ultrastructural observations: namely, (1) almost every dehiscence ran vertically; (2) the dehiscences were located in the inner two thirds of the anterior capsule; (3) the dehiscences contained fibrillar material and vacuoles.

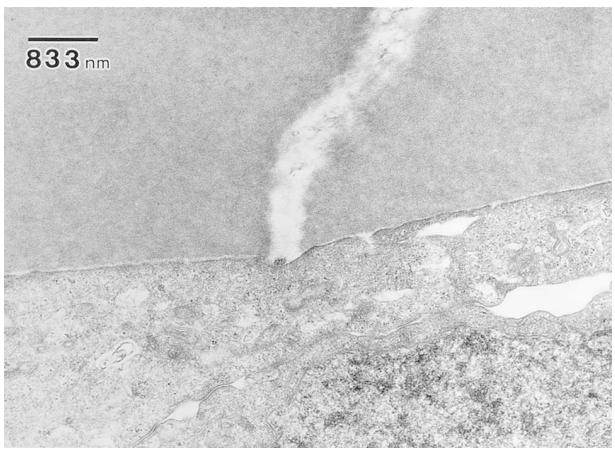

Figure 5. High magnification electron micrograph of anterior lens capsule. Dehiscences contain fibrillar material and vacuoles.

Although the pathogenesis of Alport's syndrome is not precisely understood, it has recently become apparent that abnormalities in the type IV collagen molecule, which is a major structural component of basement membrane, lead to the development of this syndrome. Basement membrane is composed of type IV collagen, laminin, and various heparan sulfate proteoglycans. Type IV collagen is thought to be the major structural element. This molecule was initially believed to be a heterotrimer containing two α 1 (IV) chains and one α 2 chain.[6] Recently evidence for the existence of four additional different chains, α 3, α 4, α 5, and α 6, have been reported.[7–13] Each chain contains three distinct domains: a carboxyl nontriple-helical (NC-1) domain, a triple helical (COL1) domain, and an amino terminal (7S) domain.[14]

Previous studies demonstrated that type IV collagen molecules, unlike the fiber-forming collagens, form a polymeric structure. Yurchenko and Ruben[14,15]

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proposed that type IV collagen molecules self-assemble into a polygonal network held together prominently by side-by-side interactions as well as the end-domain interactions. This hypothesis was supported by Barnard and colleagues,[16] who reported the three-dimensional organization of the collagen skeleton in the mammalian lens capsule, using the techniques of rapid freezing, deep-etch, and rotary replication.

In 1982, McCoy and colleagues[17] demonstrated, employing an indirect immunofluorescence technique, that human antiglomerular basement membrane (GBM) sera from patients with Goodpasture syndrome reacted with normal GBM, but failed to react with GBM of the patients with Alport's syndrome. In later studies, the Goodpasture antigen has been proposed to be the α 3(IV) NC-1 domain that is absent in the patient with Alport's syndrome.[18,19] Additionally, a point mutation in the type IV collagen α 5 chain gene has been identified in Alport's syndrome; accordingly the X-linked form is thought to be caused by mutations in the α 5(IV) chain gene (COL4A5).[20]

The shape of the lens depends on the elasticity of its capsule.[21] The anterior lens curvature is more convex centrally during accommodation. Thus, the anterior capsule of the lens plays the main role in accommodation; at the same time, it is always exposed to dynamic stress from the ciliary muscle.

In the basement membrane, type IV collagen forms a mesh structure with the NC-1 domain as hinges. In patients with Alport's syndrome, because of an abnormality in NC-1 domains, as in a frame structure without hinges, it becomes difficult to maintain the cubic structure. The basement membrane becomes thin and fragile and undergoes the mechanical stress associated with accommodation. Gradually, dehiscences are produced and anterior lenticonus results.

In the present case, it should be emphasized that the dehiscences never extended into the lens capsule and were limited to the inner two-thirds of the capsule. In composition and structure, the lens capsule is usually considered to consist of uniform tissues. However, based on the above findings, it is presumed that there are differences in the composition and structure between the inner layer and the outer layer of the lens capsule. Our histologic examination in this study suggests that the primary abnormalities in Alport's syndrome are limited to the inner layer of the lens capsule.

Ljubimov and colleagues[22] showed type IV collagen heterogeneity in the corneal Descemet's membrane; its stromal side was composed of the α 1(IV) and α 2(IV) chains; whereas, the α 3(IV)–α 5(IV) chains were present on the endothelial side. These findings have never been reported in the lens capsule.

Employing autoradiography, Young and Ocumpau[23] demonstrated that the lens capsule was a product of the subjacent cells and that new capsular material was deposited on the inner surface of the lens capsule. With regard to such a heterogeneity of the lens capsule, further investigation will be necessary, including determining whether or not there is any qualitative difference in the subchain of type IV collagen produced by the lens epithelial cells in the generative or developmental process.

On the basis of our findings, the lens epithelial abnormality coexisted with a lens capsule disorder. This could indicate that the lens epithelium might be also involved in this disease.

In patients with Alport's syndrome, because of decreased visual acuity or the complication of cataract, it could be that lensectomy and implantation of an intraocular lens (IOL) may be indicated, making it very likely that the lens capsule will become even more fragile. During surgery, attention must be paid to the procedures of capsulotomy and lensectomy. In the above patient, the IOL was fixed within the capsule, and neither during nor after the operation were any complications observed. In cataract patients with Alport's syndrome, as an alternative method, a ciliary sulcus fixation of the IOL may be performed.

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