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Histopathological Study of a Case with Glaucoma Due to Sturge-Weber Syndrome

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Purpose: To investigate the cause of the secondary glaucoma in a case of Sturge-Weber syndrome by histopathology.

Case: A 10-year-old boy with Sturge-Weber syndrome and glaucoma in the right eye was studied. Trabeculectomy was performed because of uncontrolled intraocular pressure, and the trabeculectomy specimen was examined histologically by both light and electron microscopy.

Results: Histological examination of the trabeculectomy specimen showed that the ciliary muscle was dislocated anteriorly, and the Schlemm canal was not present. The spaces in the juxtacanalicular connective tissue (JCT) were replaced by vascular structures and connective tissue. There were two kinds of vascular structures: in one, the endothelium was surrounded by pericytes; and in the other, the endothelium was not surrounded by pericytes.

Conclusions: Developmental abnormalities of the Schlemm canal and the JCT may have caused the glaucoma. These observations suggest that the developmental abnormalities of both the mesoderm and the neural crest might be involved in the pathogenesis of the glaucoma in cases of Sturge-Weber syndrome. **Jpn J Ophthalmol 2003;47:151–157**

Key Words: Glaucoma, histopathology, juxtacanalicular connective tissue, the Schlemm canal, Sturge-Weber syndrome.

Introduction

Glaucoma develops in as many as 30% of patients with Sturge-Weber syndrome.[1] Increases in the episcleral venous pressure[2,3] and developmental anomalies in the anterior chamber angle[4] have been reported as the main causal factors of the glaucoma associated with Sturge-Weber syndrome. However, the etiology of the condition remains unclear.

We report the histological findings of specimens obtained from a patient with glaucoma associated with Sturge-Weber syndrome who underwent trabeculectomy, and we discuss the embryological aspects of this condition.

Case Report

The patient was a 10-year-old boy who was first examined on January 12, 1996. His family history was unremarkable. The patient had been followed by another hospital since the diagnosis of Sturge-Weber syndrome was made at birth.

At 4 months of age, his intraocular pressure (IOP) was 27 mm Hg in the right eye and 19 mm Hg in the left eye. The IOP in the right eye remained between 10 and 25 mm Hg thereafter. When the patient was 7 years old, he underwent trabeculotomy at a university hospital outside Tokyo because the IOP in the right eye had increased to about 30 mm Hg. Thereafter, his family moved to Tokyo, and he was referred to the Department of Ophthalmology of the Japanese Red Cross Medical Center.

On his first visit, his visual acuity was 0.1 (0.5) in the right eye and 0.6 (1.2) in the left eye. No abnormalities were noted in the anterior segment or optic

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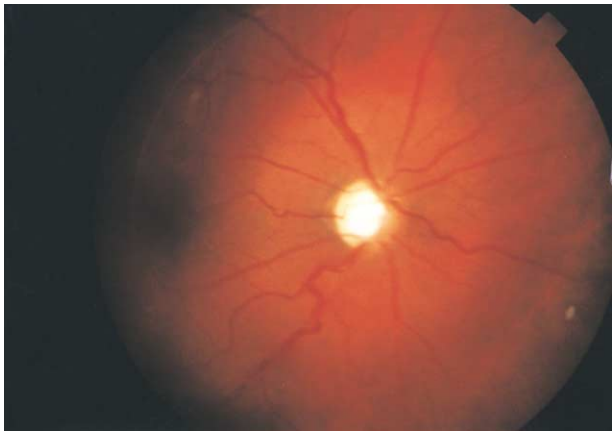

Figure 1. Fundus photograph of the right eye of a 10-year-old boy with Sturge-Weber syndrome. Glaucomatous disc cupping with a cup-to-disc ratio of 0.7 can be noted.

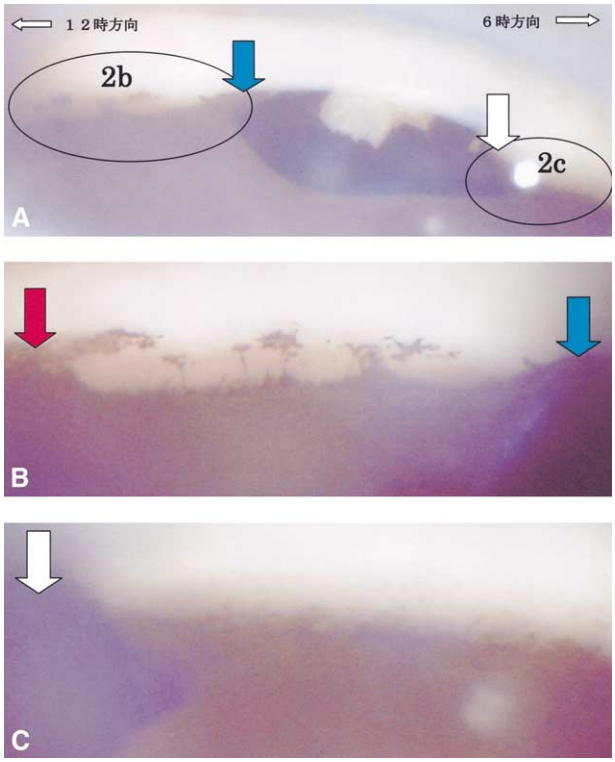

Figure 2. The anterior chamber angle after trabeculectomy (March 26, 2001). (**A**) The surgical site of trabeculectomy is shown in the middle of the picture between the blue arrow and the white arrow. (**B**) High magnification of the area adjacent (in the 12 o'clock direction) to the surgical scar shown in (**A**). Blue arrows indicate the same area in (**A**) and (**B**). The red arrow indicates the site at which the peripheral anterior synechia developed after the previous trabeculotomy. There is no surgical scar or ciliary body band between the red and blue arrows although a number of tall iris processes are noted. (**C**) High magnification of the area adjacent (in the 6 o'clock direction) to the surgical scar shown in (**A**). Ciliary body band is not present although a large number of short iris processes are present.

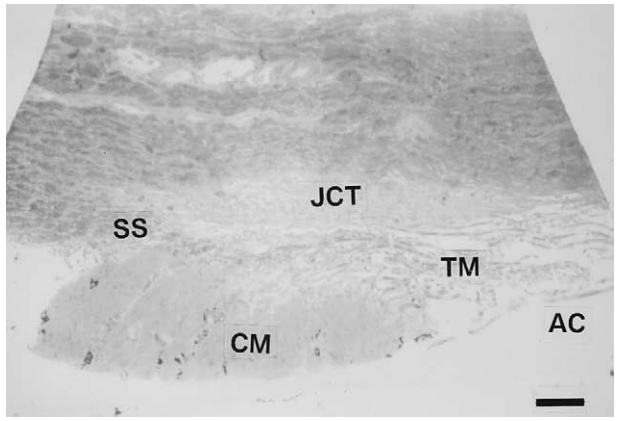

Figure 3. Light microscopic photograph of the anterior chamber angle obtained during trabeculectomy. The ciliary muscle (CM) is located markedly anterior to its normal position and attached to almost the middle of the presumed Schlemm canal area. A large number of canalicular structures are seen in the deep portion of the sclera. SS: scleral spur, AC: anterior chamber, TM: trabecular meshwork, JCT: juxtacanalicular connective tissue. Toluidine blue staining. Bar = 100 μm.

media. The corneal diameter was 12 × 12 mm in the right eye and 11 × 11 mm in the left eye. The IOP was 24 mm Hg in the right eye and 14 mm Hg in the left eye. Hemangiomas were noted in the territory of the first and second trigeminal branches on the right side of his face.

Funduscopy of the right eye showed optic disc cupping with a cup-to-disc ratio of 0.7 (Figure 1), lattice degeneration, and an extended hemangioma in the peripheral area of the choroid. The left eye exhibited neither optic disc cupping nor abnormalities in the retina and choroid.

A peripheral anterior synechia was noted in the anterior chamber angle between 10 and 2 o'clock of the right eye at the site of the previous trabeculotomy (Figure 2B). There was no trace of an incision in the trabecular meshwork inferior to the area of the synechia (Figures 2B and 2C). The ciliary body band was not found in the anterior chamber angle around the site of the trabeculectomy (Figure 2A), but many tall and short iris processes were observed that were not a direct effect of the previous trabeculotomy (Figures 2B and 2C).

Clinical Course

The IOP of the right eye remained at 24–26 mm Hg even after the instillation of 0.5% timolol maleate, 0.1% dipivefrin hydrochloride, and 1% pilocarpine hydrochloride. The visual field was determined with the Goldmann perimeter and was classified as Aulhorn stage II.

On July 24, 1996, a trabeculectomy was performed with intraoperative topical application of mitomycin

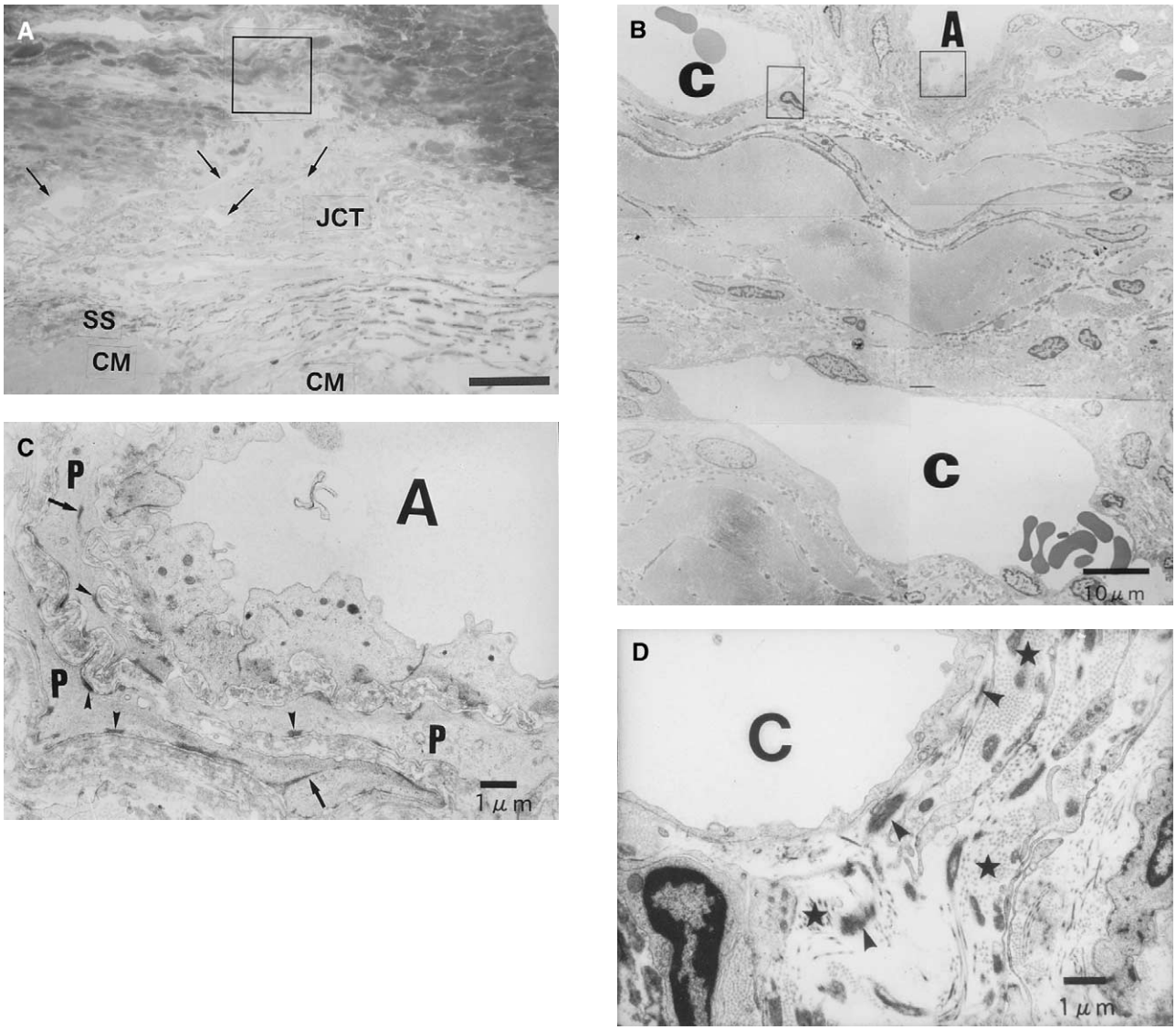

Figure 4. (**A**) Light microscopic photograph of the specimen obtained during trabeculectomy. Spaces in the uveal meshwork connected to the ciliary muscle (CM) are well developed. Although the scleral spur (SS) is well formed, the corneoscleral meshwork connected to the SS is hardly visible. Instead, a structure similar to the juxtacanalicular connective tissue (JCT) is connected to SS. The Schlemm canal is not observed. The JCT is also seen in the areas corresponding to the Schlemm canal. Canalicular structures (arrows) are also noted. Toluidine blue staining. Bar = 100 μm. (**B**) Transmission electron microscopy photograph of the area surrounded by the box in (**A**). Two kinds of canalicular structures (**A**, **C**) are noted in the area corresponding to the collector channels. (**C**) High magnification of area A surrounded by the box in (**B**). The basement membrane is located lateral to endothelial cells. Pericytes (P) with dense plaque (arrows) attachment and plaque (arrowheads) formation can be seen lateral to the basement membrane. (**D**) High magnification of area C surrounded by the box in (**B**). The basement membrane is not clearly observed under the endothelial cells. Elastic fibers (arrowheads) and collagen fibers (stars) are seen in the peripheral area.

C. After creating a triangular scleral flap measuring 4 × 4 mm at the 9 o'clock position, the trabecular meshwork was resected in an area measuring 1.5 mm wide and 2.0 mm long.

Postoperative Findings

Mild uveal effusion developed in the peripheral area of the fundus 7 days following surgery as a postoperative complication. This condition persisted for

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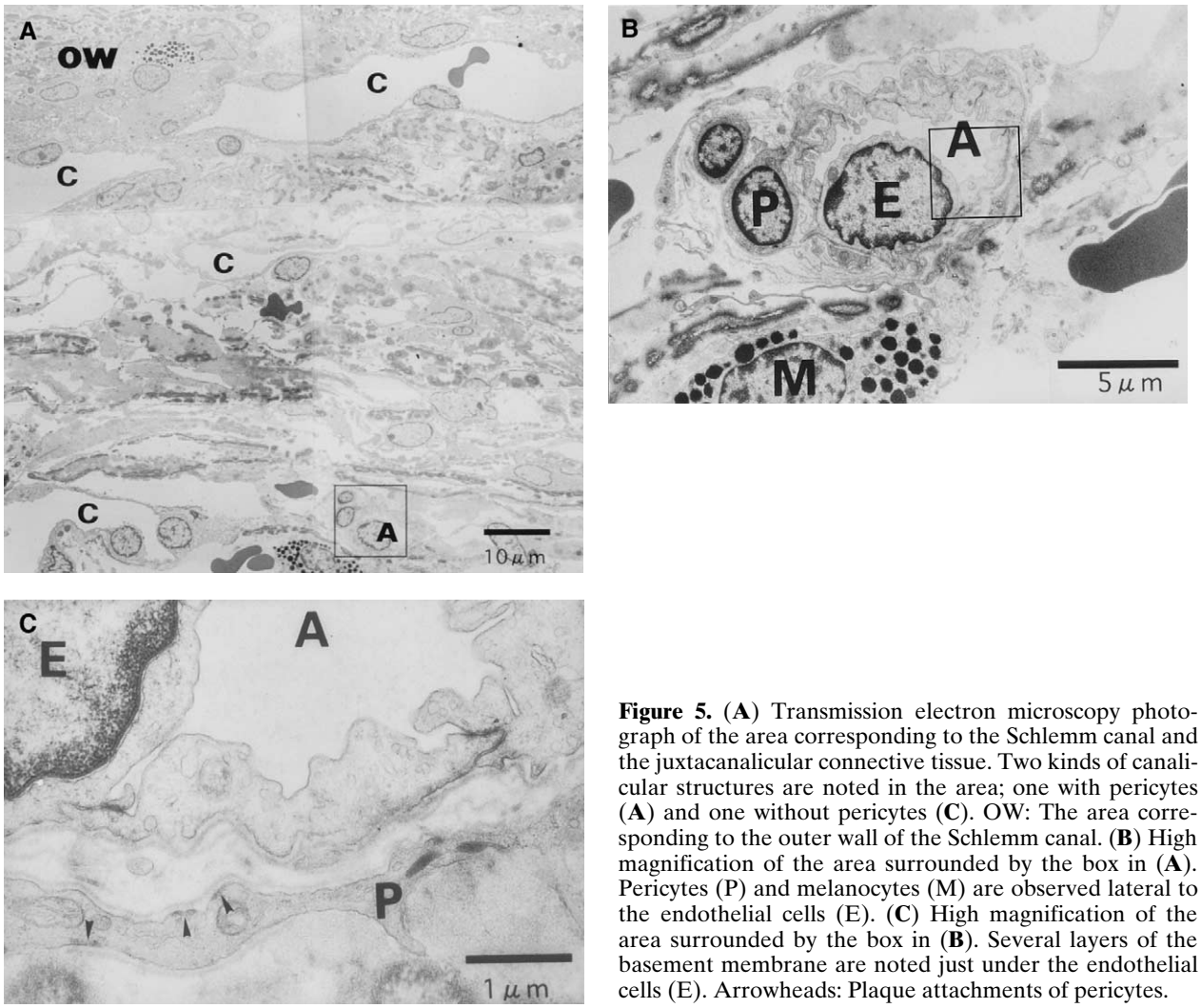

Figure 5. (**A**) Transmission electron microscopy photograph of the area corresponding to the Schlemm canal and the juxtacanalicular connective tissue. Two kinds of canalicular structures are noted in the area; one with pericytes (**A**) and one without pericytes (**C**). OW: The area corresponding to the outer wall of the Schlemm canal. (**B**) High magnification of the area surrounded by the box in (**A**). Pericytes (P) and melanocytes (M) are observed lateral to the endothelial cells (E). (**C**) High magnification of the area surrounded by the box in (**B**). Several layers of the basement membrane are noted just under the endothelial cells (E). Arrowheads: Plaque attachments of pericytes.

about 2 weeks and gradually resolved. The IOP of the right eye remained at 14–16 mm Hg for 12 months after the surgery. However, it increased to 21–24 mm Hg 18 months after the surgery, which required the instillation of 1% pilocarpine hydrochloride, and timolol maleate was also later used.

At present, 3.5 years after surgery, the visual acuity is 0.1 (0.5) in the right eye and 0.6 (1.2) in the left eye. The visual field of the left eye is normal and the optic disc has no abnormal findings. The IOP of the left eye remains at 18–20 mm Hg.

Pathological Findings

The surgical specimen obtained during the trabeculectomy measured 1.5 × 2.0 mm and was fixed in 1% glutaraldehyde/2.5% formalin and embedded in epoxy resin. Two-micron–thick sections were cut and stained with toluidine blue for light microscopic examination. Ultra-thin sections were also cut and stained with uranyl acetate/lead citrate for transmission electron microscopy (TEM).

Under the light microscope, the Schlemm canal was not clearly identified, making it difficult to differentiate the area corresponding to the Schlemm canal from the juxtacanalicular connective tissue (JCT). The ciliary muscle was located markedly anterior to its normal position and was attached near the middle of the presumed Schlemm canal area (Figure 3). On careful observation of serial sections, there were no abnormalities in the trabecular structure of the uveal meshwork connected to the ciliary muscle. Although the scleral spur was well formed, the corneoscleral meshwork was so thin that it ap-

peared similar to the JCT in most areas (Figure 4A). The spaces in the JCT were insignificant and were occupied by canalicular structures and connective tissue. Canalicular structures were also noted in the areas corresponding to the Schlemm canal and collector channels (Figure 4A).

TEM revealed two kinds of canalicular structures in the areas corresponding to the collector channels, the Schlemm canal and the JCT (Figure 4B). Under high magnification, one type of canalicular structure possessed a basement membrane and pericytes with dense plaques and attachment plaques located lateral to endothelial cells (Figures 4C, 5B and 5C). This construction was also found in the trabecular meshwork at the boundary of the corneoscleral and uvea meshwork (Figure 5A).

The other canalicular structure contained endothelial cells but no pericytes. The basement membrane was absent or discontinuous (Figures 4D and 6B). Elastic fibers surrounded by abundant granular substance (sheath-like substance) were noted in the area corresponding to the JCT (Figures 6A and 6B).

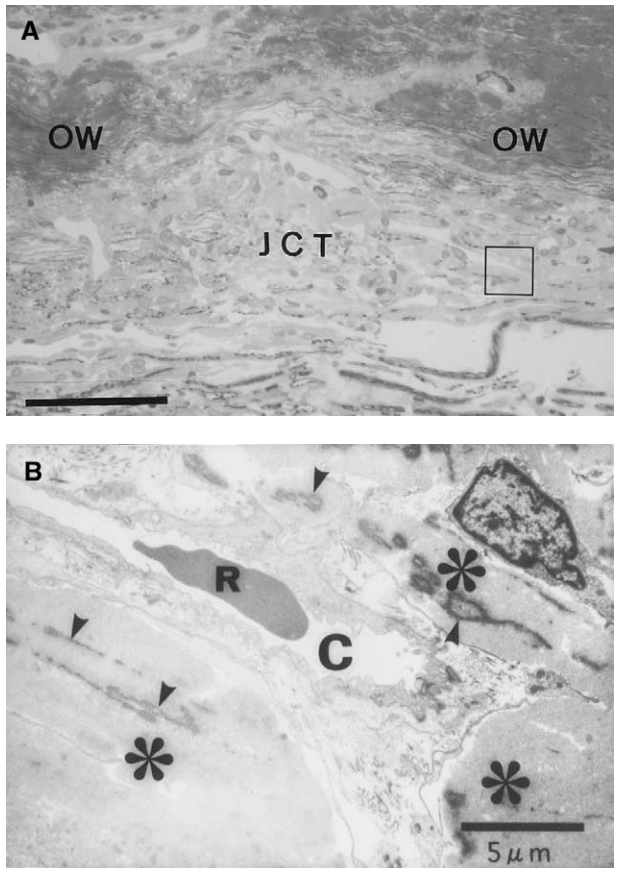

Figure 6. (**A**) Light microscopic photograph of the area corresponding to the Schlemm canal. OW: The area corresponding to the outer wall of the Schlemm canal outer wall, JCT: juxtacanalicular connective tissue. Toluidine blue staining. Bar = 100 μm. (**B**) Transmission electron microscopy photograph of the area surrounded by the box in (**A**). Red blood cells (R) and plasma components can be seen in the lumen. The basement membrane is discontinuous and there are no pericytes. Abundant elastic fibers (arrowheads) and sheath-like substances (asterisks) are observed lateral to the canal.

Discussion

Glaucoma develops in as many as 30% of patients with Sturge-Weber syndrome. Glaucoma also develops in eyes with buphthalmos before the age of 2 years in 60% of cases and before adolescence in the remaining 40%.[1] Although a number of theories have been advocated, increases in the episcleral venous pressure[2,3] and developmental anomalies in the anterior chamber angle[4] are considered to be the main causal factors for the glaucoma associated with the Sturge-Weber syndrome. It has also been reported that early-onset syndromic glaucoma had morphological features similar to those of congenital glaucoma, while late-onset syndromic glaucoma showed various signs of immaturity in the anterior chamber angle corresponding to the time of onset.[4]

A histological study of early-onset glaucoma associated with Sturge-Weber syndrome showed that abnormal collagen accumulated in the intra-trabecular spaces and increased episcleral venous pressure played important roles in increasing the IOP.[5] Abnormalities in the Schlemm canal[6–8] and episcleral hemangiomas[6] have been reported in eyes of patients with Sturge-Weber syndrome. In a previous histological case report of Sturge-Weber syndrome, the Schlemm canal was reported to be nonexistent, and the trabecular area was occupied by abundant vascular spaces and immature mesenchymal cells. However, gonioscopic abnormalities, such as goniosynechia and high attachments of the iris root, were not detected.[7] Mwinula et al[8] reported morphological abnormalities in the Schlemm canal, vascular structures in the trabecular meshwork, and abundant accumulation of extracellular matrices in the basement membrane under the inner surface of the Schlemm canal. Abnormal canalicular structures in the outflow routes in eyes of patients with the Sturge-Weber syndrome were not described in detail in previous studies.

In our case, the observations made by light microscopy suggested that the Schlemm canal was absent, and TEM revealed abundant granular sub-

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stances (sheath-like substance) surrounding the elastic fibers in the area corresponding to the Schlemm canal and the JCT. Earlier pathological studies have reported an accumulation of sheath-like substances in cases of primary open angle glaucoma,[9] and the accumulation of granular substances in cases of juvenile glaucoma.[10] Therefore, the accumulation of granular substances surrounding abundant elastic fibers in the area corresponding to the Schlemm canal and the JCT might support the hypothesis that developmental anomalies in the anterior chamber angle are associated with the Sturge-Weber syndrome.[4] However, in our case, the substances found by light microscopy in the trabecular meshwork and around the collecting channels were divided into two types after TEM; one with pericytes and the other without pericytes. We considered that the canalicular structures with pericytes were the hemangiomas, while those without pericytes were thought to develop into collector channels or the Schlemm canal. The Schlemm canal was judged to be immature because the canals without pericytes were not only narrow but also shortened to one half length or less. This is in addition to the fact that the small spaces in the JCT were thought to be immature JCT. All of these findings indicated that these canals may not function as an outflow pathway.

Embryologically, almost all mesenchymal cells in the eye, including trabecular cells, are derived from the neural crest.[1] Vascular structures are often found in the trabecular meshwork in patients with Sturge-Weber syndrome.[7,8] The presence of hemangiomas in the trabecular meshwork is a characteristic finding of Sturge-Weber syndrome and is never associated with congenital glaucoma of other origin.

How do blood vessels develop in the trabecular meshwork, which originally contained only mesodermal tissue? It was once considered that abnormalities in Sturge-Weber syndrome were of mesodermal origin because hemangiomas were often found in patients with Sturge-Weber syndrome. It was later suggested that vascular abnormalities might occur at an early embryonic stage of ectodermal differentiation.[11] Enjolras et al[12] suggested that the Sturge-Weber syndrome was caused by anomalies in the neuroectoderm and mesoectoderm at an early embryonic stage. They reported that the risk of glaucoma was high in patients with facial port-wine stain in the territory of the first trigeminal branch. To explain this phenomenon, they suggested that simultaneous anomalies occurred in the neural crest cells differentiating into skin in the territory of the first trigeminal branch, choroid, and cranial pia mater resulting in abnormal vascular systems in these areas. This hypothesis explains the histological abnormalities in our case very well.

The anterior attachment of the ciliary muscle was not a direct effect of the previous trabeculotomy because the present surgical field did not include the previous surgical site. The anterior attachment of ciliary muscle is a finding observed at the middle embryonic stage where the separation of the trabecular meshwork from the iris and ciliary body is immature.[13] We therefore suggest that the anterior attachment of ciliary muscle was caused by developmental anomalies in the anterior chamber angle. Thin corneoscleral meshwork and the nearly nonexistent space of the JCT may be caused by abnormal development of mesenchymal tissue in these areas which are thought to be derived from the neural crest.[14] The abnormality in such areas may be caused by abnormal trabecular cells, also derived from the neural crest.

The immaturity of the Schlemm canal might be explained by either of the following two hypotheses. First, the development of the Schlemm canal could be disturbed during an anomalous development of the anterior chamber angle, or the development of the Schlemm canal may be disturbed by hemangiomas during the embryonic descent process of the Schlemm canal from the episclera to the trabecular meshwork. It has been suggested that trabecular cells induced the growth of the Schlemm canal.[13] Therefore, the developmental abnormalities of the Schlemm canal may also arise after anomalous development of the trabecular cells.

It is necessary to be careful in discussing the cause of ocular hypertension based on the histological findings of a specimen obtained during trabeculectomy because the specimen was very small and limited to the aqueous outflow pathway. The episcleral venous pressure might be increased by the effect of choroidal hemangiomas. However, we considered that the disturbance of the aqueous outflow was due to the (1) abnormality (immaturity) of the Schlemm canal, and (2) the increased IOP caused by developmental anomalies in the JCT.

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