Twenty-three Cases of Primary Cornea Guttata

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Purpose: To evaluate the clinical aspects of patients with primary cornea guttata and the specular microscopical findings/morphology in their corneal endothelial cells.

Methods: Twenty-three patients consulting Kanazawa Medical University Hospital or related hospitals in Ishikawa or Fukui prefectures and diagnosed with primary cornea guttata by slit-lamp examination underwent an analysis of their clinical features and corneal endothelial cells.

Results: Most cases were middle-aged to elderly women. None of them complained of visual impairment due to cornea guttata. The 46 eyes of these cases were included in this study. Specular microscopical findings revealed that the size and density of dark areas varied, with asymmetry noted in some cases. The parameters of the endothelial cells comprising mean cell area, the proportion of hexagonal cells, and the coefficient of variation, were almost within normal limits except for 1 eye of a 79-year-old man who was speculated to be at an early stage of Fuchs endothelial corneal dystrophy. Three cases had undergone cataract surgery, but did not show significant changes in endothelial morphology before and after surgery. In a statistical study on endothelial cell morphology, cell parameters except for minimal cell area correlated significantly with age. Although the density and size of dark areas correlated with each other, neither correlated with any of the cell parameters.

Conclusion: Cornea guttata does not lead to visual impairment or abnormalities in corneal endothelial cell parameters except for a small number of cases that must be considered to be at an early stage of Fuchs dystrophy. **Jpn J Ophthalmol 2001;45:93–98** © 2001 Japanese Ophthalmological Society

Key Words: Bullous keratopathy, cataract surgery, cornea guttata, Fuchs corneal endothelial dystrophy, specular microscope.

Introduction

Cornea guttata is observed as a Descemet's membrane with a beaten-metal-appearance, which presents in the pupillary area and extends circumferentially, with its density increasing with age. On specular microscopical examination, these guttae are observed as dark areas with central bright spots. Pathologically, they are abnormal excrescences of basement membrane and fibrillar collagens produced by dystrophic corneal endothelial cells. Cornea guttata is classified into secondary cornea guttata due to inflammation or surgical damage in the anterior segment of the eye, and the primary type that appears with aging without inflammatory or surgical history. Primary cornea guttata may be an early stage of Fuchs endothelial dystrophy, causing loss of endothelial cells and bullous keratopathy in the late stage of the disease. Hereditary transmission is autosomal dominant in Fuchs dystrophy[1] and also in some cases of cornea guttata.[2]

The incidence of cornea guttata is lower in Japan than in the United States[3–6] and reports on Fuchs dystrophy in Japan are also less frequent.[7] This difference in incidence is thought to be mainly attributable to racial differences. Cases in which guttata is recognized to indicate a risk of progression to Fuchs dystrophy, and endothelial cell analysis are important in distinguishing between these two conditions.

The clinical picture and specular microscopical findings of primary cornea guttata were investigated in this study to clarify the characteristics of the disease. In some cases undergoing cataract surgery, the

corneas before and after surgery were examined to investigate the change in the corneal endothelial cells.

Materials and Methods

During the 7-year period between 1991 and 1997, the authors found 46 eyes with primary cornea guttata in 23 cases in Kanazawa Medical University Hospital and related hospitals. These hospitals are situated in Ishikawa and Fukui prefectures, which are located in the center of Honshu and face the Japan Sea. The patients were examined by slit-lamp microscopy as a routine ophthalmological procedure, and with the distinct findings of beaten-metal appearance and dark spots in the posterior surface of the cornea, the guttae were identified (Figure 1). The diagnosis of cornea guttata was confirmed by its characteristic specular microscopical findings (Figure 2). Patients with any history of ocular inflammation or surgical procedures were excluded from this study, except for two cases with primary angle closure glaucoma (case 3, case 13) who had previously undergone laser iridotomy. A family history of corneal diseases and the problems prompting their visits as well as their ocular findings were also studied.

Endothelial cell parameters were analyzed using a specular microscope (CSP-580; Konan Medical, Nishinomiya) in the areas adjacent to the dark areas where the contours of the cells were defined clearly. More than 10 photographs around the optical axis were taken, and endothelial cell parameters were de-
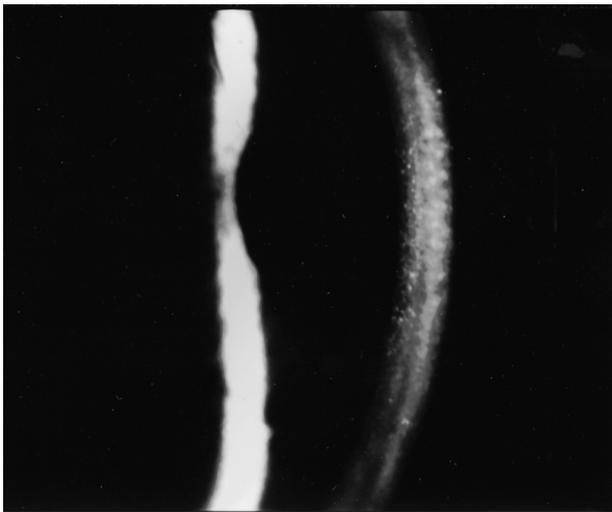

Figure 2. Specular image of case 1. Dark areas with distinct boundaries are observed between corneal endothelial cells. Bar = 100 μm.

termined by an analysis system (Konan), analyzing about 100 cells in each patient. The analyzed parameters were cell densities, mean cell areas, maximum and minimum cell areas, coefficient of variation, the proportion of hexagonal cells, as well as the differences in the right and left eyes in size and density of the dark areas. In only one case (case 10), noncontact specular microscopy (NonconRobo; Konan Medical) was used.

In 3 cases (cases 11, 12, and 14), endothelial parameters before and after cataract surgery were compared with those of 16 eyes in 10 cases without cornea guttata. The endothelial examination was performed before and within 3 months (mean 46 ± 38 days) after the surgery. Surgical procedures in all cases were phacoemulsification with foldable intraocular lens implantation through a small limbal incision.

Statistical significance in the relationship between endothelial cell parameters and guttae was evaluated with Spearman rank correlation and one-way analysis of variance.

Results

The cases are listed in Table 1. Most cases were middle-aged or elderly women, and the mean age of all cases was 61 ± 18 years. Four male adult patients and 2 young patients whose ages were 19 and 23 years old were also seen. No case had a positive family history for ocular diseases except for case 19, who was the mother of case 18 and was discovered incidentally when she accompanied her daughter to our clinic. The daughter had suffered from stromal keratitis in her right eye several years before, and visited our hospital for regular examination. Cornea guttata was detected in both her eyes and in the eyes of her mother.

The reasons for their visits for ophthalmological examination were as follows: cataract in 5 cases, 1 of whom had primary angle closure glaucoma (PACG), PACG in 1 case, primary open angle glaucoma (POAG) in 1 case, prescription for glasses in 2 cases,

Figure 1. Slit lamp image of case 1. Beaten-metal appearance of Descemet's membrane is observed with slit-lamp microscope in eyes of case 1 with primary cornea guttata.

Table 1. Patient Characteristics

Case No.	Sex	Age (y)	Primary Reason for Visit*	Dark Area Size†	Dark Area Density‡
1	F	60	Conjunctivitis	L-S	2
2	F	43	Myopia	L-S	3
3	F	72	PACG*	M-S	2
4	F	63	Conjunctivitis	L-S	R1 L2
5	F	74	Floating spots	M-S	1
6	F	59	Trichiasis	S	1
7	F	45	POAG*	M-S	3
8	F	23	Pointed out at practice	M-S	1
9	F	60	Conjunctivitis	M-S	1
10	M	82	CRAO*	L-S	R2 L1
11	M	83	Cataract	S	1
12	F	83	Cataract	M-S	R2 L1
13	F	81	Cataract/PACG*	M-S	R1 L2
14	M	79	Cataract	M-S	3
15	F	49	Cataract	M-S	3
16	F	45	SS*	M-S	2
17	F	69	Hemianopsia	M-S	1
18	F	19	Keratitis	M-S	2
19	F	42	Mother of case 18	L-S	3
20	F	67	Conjunctivitis	L-S	3
21	M	64	SS*	S	1
22	F	70	SS*/BRAO*	S	1
23	F	50	Presbyopia	M-S	1

*PACG: primary angle closure glaucoma, POAG: primary open angle glaucoma, CRAO: central retinal artery occlusion, SS: Sjögren's syndrome, BRAO: branch occlusion of central retinal artery.

†L: large, M: medium, S: small.

‡1: grade 1, 2: grade 2, 3: grade 3, R: right eye, L: left eye.

central artery occlusion in 1 case, conjunctivitis in 4 cases, work-up for Sjögren's syndrome in 3 cases, one of whom also had branch occlusion of central retinal artery, and floating spots, hemianopsia, work-up for keratitis, and trichiasis, in 1 case each. Two cases were discovered accidentally, 1 of them was the mother of case 19 described above, and the other a female medical student who was taking bedside study in ophthalmology.

On specular microscopy, the size and density of the dark areas varied in individual cases. The size of the dark areas was denoted as "small" when the area measured up to 2 or 3 endothelial cells, as "medium" when it was about 7-cell-sized, and as "large" when it was more extensive consisting of an aggregation of smaller areas. The density of the dark areas was divided into 3 grades: grade 1: sparse with the total size of the dark areas amounting to less than 1/3 in the picture; grade 2: the total size of the dark areas occupying up to 2/3; and grade 3: the total size of the dark areas exceeding 2/3 (Figure 3).

Regarding the size of the dark areas, a mixed type of small and medium areas was most frequently observed (13 cases), followed by a mixed type with all three sizes (6 cases), and only small areas in 4 cases. Regarding the density of the dark areas, grade 1 was observed in 9 cases, grade 2 in 4 cases, and grade 3 in 6 cases. In 4 cases, the density differed in each eye, being grade 1 in one and grade 2 in the other.

In cell parameters, the mean cell area was 372 ± 132 μm^2, mean cell density $2895 \pm 616/mm^2$, maximum cell area 664 ± 366 μm^2, minimum cell area 193 ± 132 μm^2, coefficient of variation 0.26 ± 0.09, and proportion of hexagonal cells $66.0 \pm 11.3\%$. All values approximated previously described normal limits.[8,9] Cell density of each case did not show a correlation with either the size or density of the dark areas. In Figure 4, the data in this study were plotted as compared to the data of Ohara et al[9] on normal Japanese controls. Three parameters showed good values except for the mean cell area of the 80-year-old group. In case 10, the cell area in his right eye was $1,097$ μm^2 (cell density: $912/mm^2$), although the corneas were clear and the cell density in his left eye was almost normal ($2,309/mm^2$).

Statistical analysis was performed on the data from all subjects (group A), and also on group B, in which patients were excluded who had diseases that may damage corneal endothelial cells; namely, PACG, POAG, keratitis, and trichiasis. The size and density of dark areas correlated in both groups ($r = 0.515$ in group A, $r = 0.536$ in group B, $P < .001$ in groups A and B). All cell parameters except for minimum cell area in both groups correlated with age (r: 0.48–0.62, $P < .001$), but no parameters correlated with the size or density of dark areas.

The effect of cataract surgery on endothelial cells was evaluated, comparing the change of cell area with controls and cell area before surgery, but no significant differences were noted.
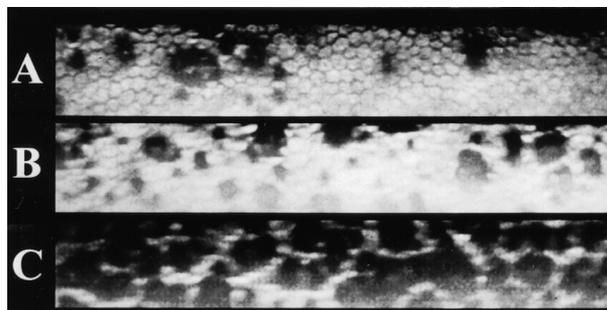

Figure 3. Density of dark areas. (**A**) Sparse (grade 1), (**B**) moderate (grade 2), (**C**) dense (grade 3).
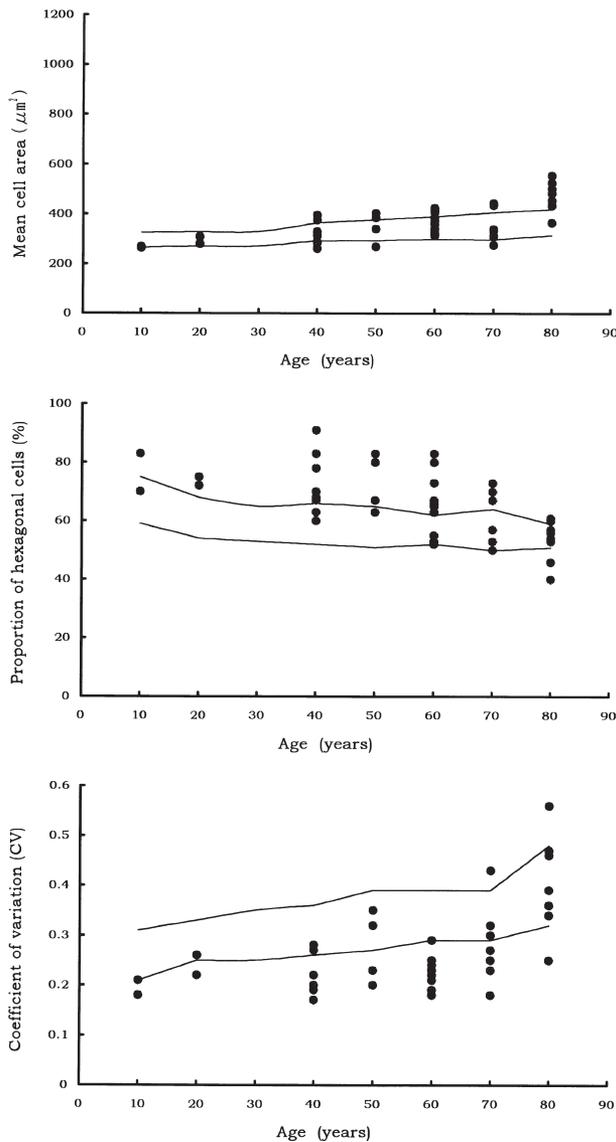
Figure 4. Endothelial morphology of cornea guttata. Mean cell area (top), incidence of hexagonal cells (middle), and coefficient of variation (bottom) of 46 eyes are plotted in order of age. Two lines show normal range reported by Ohara et al[8] and listed in same graph for sake of comparison with our data. Cell area in 80-year-old group is much larger in our group than range shown by Ohara et al. In incidence of hexagonal cells and coefficient of variation, a slight tendency to deteriorate is observed after age 70.

Discussion

Cornea guttata is a term first used by Vogt in 1921 to describe multiple drop-like excrescences on the posterior surface of the cornea.[10] The incidence of primary cornea guttata increases with age. Guttae appear first in the central cornea and gradually spread peripherally and become more numerous.[6]

Endothelial cell loss in cases over 70 years of age,[11] decrease of corneal barrier function and increase of corneal thickness were reported.[12] In our cases, although there was no tendency for dark areas to increase with age, cell density decreased in patients over 80 years old, and other parameters, the incidence of hexagonal cells and the coefficient of variation, also deteriorated somewhat. The decrease in endothelial cells with age must be emphasized when there is the existence of cornea guttata.

About the incidence of cornea guttata, the present authors previously investigated corneal endothelial cells in Japanese and Singaporeans over 50 years of age.[13] The incidence in Japanese was 1.9%, which was lower than that of Singaporeans (6.7%). This result suggests that the incidence of cornea guttata differs between races and may explain why Fuchs dystrophy is rarely observed in Japanese.

Very few reports have focused on cornea guttata in Japan. Kadowaki et al[14] reported 29 cases discovered with specular microscopy performed as preoperative examinations for cataract surgery. Cases reported by Nagaki et al[3] were also discovered through preoperative examinations. Specular imaging before cataract surgery seems to present a good chance for detecting cornea guttata. In the report by Kadowaki et al,[14] mean cell density was 2,559/mm^2 with 1,000 to 2,000/mm^2 in 4 cases, with no statistical decrease in cell density found after surgery.

Fuchs dystrophy is seen commonly in women, and corneal lesions, the degree of which is sometimes asymmetrical, exist in both eyes.[15] Also in our cases of cornea guttata, women made up 82.6% of the total (19/23 cases), with asymmetry in the extent of the dark areas also noted in several cases.

In the early stage of Fuchs dystrophy, when corneal edema evincing endothelial decompensation does not exist, it is difficult to differentiate this condition from cornea guttata. Case 10, who revealed marked cell loss without corneal edema in his right eye, could be diagnosed as having an early stage of Fuchs dystrophy. However, in such a condition, corneal edema becomes prominent usually after the sixth decade of life,[16] but this case is much older and the corneal abnormality remained subclinical. A certain percentage of cases of cornea guttata will progress to Fuchs dystrophy[17] and some cases like case 10 will manifest an intermediate pattern. A study on Fuchs dystrophy in three generations in a single family revealed progression of the endothelial lesions with advancing age,[7,17] and long-term follow-up of our cases will be necessary to determine whether progression to Fuchs dystrophy occurs.

In cell parameters, it was natural that deterioration with age was observed. About the dark areas, the size and density seemed to be independent of cell parameters, which means that guttae do not reflect the endothelial cell abnormalities directly, but in the long term, the abnormalities seemed to be exposed as cell loss and occurred especially in Fuchs dystrophy.

The three cases undergoing cataract surgery did not show any marked endothelial cell loss during the 3-month period after surgery, similar to other reports.[14,18] In contrast, Bourne et al[19] reported that the rate of cell loss was almost twice as high in cases of cornea guttata as compared to normal subjects. Long-term observation is also necessary to evaluate the effect of cataract surgery on corneal endothelial cells of cornea guttata.

Endothelial dystrophy may accompany glaucoma because endothelial cells, which have degenerated and become epithelialized, grow over the trabeculum. The relationship of glaucoma and corneal endothelial dystrophy is obvious in iridocorneal endothelial syndrome and in some cases of congenital endothelial dystrophy and posterior polymorphous dystrophy.[20,21] A relationship between Fuchs dystrophy and angle closure glaucoma has been both denied and confirmed.[22,23]

After laser iridotomy, the number of endothelial cells decreases over several years,[24,25] and in the presence of cornea guttata, bullous keratopathy may easily occur.[26] In cases 3 and 13, laser iridotomy had previously been performed, and so the cornea guttata was possibly a secondary phenomenon due to photocoagulation. However, the corneal endothelial damage previously reported after laser iridotomy consisted of only cell loss without cornea guttata, and so we considered it appropriate to include these 2 cases in this study as primary cornea guttata. Endothelial cell density was slightly decreased only in the left eye of case 13.

This study clarified the clinical and corneal endothelial characteristics of cornea guttata observed in our hospitals. It will be necessary to observe the cases for a longer period to assess the endothelial morphological changes in cornea guttata occurring with age and to differentiate them from the early stage of Fuchs dystrophy.

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