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CLINICAL INVESTIGATION

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Ocular and systemic features of Peters' anomaly

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Abstract *Background:* To clarify the relationship between associated systemic anomalies and ocular manifestations in patients with Peters' anomaly, a retrospective study was conducted. *Methods:* We classified 37 patients with Peters' anomaly into two groups, one with (+) and one without (–) systemic anomalies. *Results:* The systemic anomaly (+) group consisted of 13 patients, eight males and five females, with mean age of 2.3 months. Peters' anomaly was bilateral in sux cases and unilateral in seven. Corneolenticular adhesion was observed in 11 cases. Associated ocular anomalies were seen in 12 cases, and developmental glaucoma was present in eight cases. The systemic anomaly (–) group comprised 24 patients, 13 males and 11 females, with mean age of 28.3 months. Peters' anomaly was bilateral in 11 cases and unilateral in 13. Corneolenticular adhesion was observed in five cases. The associated ocular anomalies were observed in 10 cases, and developmental glaucoma was accompanied in six cases. The incidences of cases with corneolenticular adhesion, those with other ocular anomalies, and those with glaucoma were significantly higher in the systemic anomaly (+) group than in the systemic anomaly (–) group. *Conclusions:* Peters' anomaly accompanying corneolenticular adhesion and/or other ocular anomalies should be evaluated for the presence of systemic anomalies.

Introduction

In 1906, Peters [19] first reported on patients with central corneal opacity and ring-shaped iridocorneal adhesion caused by the absence of the corneal Descemet's membrane. Later, similar conditions were named Peters' anomaly. Embryologically, Peters' anomaly is categorized as mesenchymal dysgenesis of the ocular anterior segment, a spectrum of developmental disorders that includes congenital glaucoma, posterior embryotoxon, Axenfeld-Rieger syndrome, and sclerocornea [2, 3, 24].

Peters' anomaly is usually seen as an isolated ocular defect, but the disease can accompany systemic anomalies [9, 10, 15, 21, 23]. The ability to detect associated systemic anomalies in their early stages is clinically significant, because early treatment for those anomalies is essential to normal development.

To clarify the relationship between associated systemic anomalies and ocular findings of Peters' anomaly, we retrospectively reviewed the clinical findings in 37 patients with Peters' anomaly encountered at our hospital during the past 18 years.

Patients and methods

In this study, patients who were considered by slit-lamp examinations to have congenital central corneal opacity due to the absence of the corneal endothelium, Descemet's membrane, and posterior stroma were diagnosed as having Peters' anomaly. We reviewed the data on 37 cases of Peters' anomaly that were encountered at Nagoya City University Hospital between January 1982 and December 1999. Ocular examinations were conducted, including visual acuity (if possible), intraocular pressure, slit-lamp examination, gonioscopy, fundus examination, and axial length measurement by ultrasonography. The following data were documented:

age at first examination, sex, pregnancy history, systemic conditions, chromosomal analysis, and family history. On being diagnosed as having Peters' anomaly, the patients were referred to a pediatrician for examination to detect associated systemic anomalies. In addition, we examined as many of the patients' relatives as possible.

We classified the 37 patients into two groups based on the presence (+) or absence (–) of associated systemic congenital anomalies. We compared ocular findings and backgrounds between the two groups.

For statistical analysis, Welch's *t*-test and chi-square test were used. A level of $P<0.05$ was accepted as statistically significant.

Results

Systemic anomaly (+) group

The systemic anomaly (+) group consisted of 13 patients, eight males and five females, ranging in age at first examination from 1 day to 7 months, mean 2.2 ± 2.4 (±SD) months. The follow-up period ranged from 1 month to 14 years, mean 4.6 ± 3.2 years. Peters' anomaly was bilateral in six cases and unilateral in seven cases. Corneolenticular adhesion was observed in 11 cases (85%) (Figs. 1–3). Associated ocular anomalies and their incidences in this group are shown in Table 1. They were observed in 12 cases (92%). These anomalies included microphthalmos in six cases, anterior staphyloma in six (Figs. 1, 2), posterior embryotoxon in five (Fig. 3), sclerocornea (peripheral sclerocornea) in four, typical iris coloboma in one, and aniridia in one. Eleven eyes (58%) of eight patients (62%) developed glaucoma. In this study, patients whose eyes had an abnormally indistinct sclerocorneal border were diagnosed as having peripheral sclerocornea (Fig. 4).

Accompanying systemic anomalies are listed in Table 2. They included six cases of retarded growth, five each of cleft lip and/or palate and conotruncal anomalies of the heart, two each of ear anomalies, central nervous system anomalies, and urogenital anomalies, and one each of laryngomalacia, facial anomalies, and macroglossia. In four patients, some systemic anomalies were newly detected when they were referred to the pediatrician after our examination and diagnosis of Peters' anomaly.

Surgical treatment was undertaken in five cases of cleft lip and/or palate, two cases of urogenital anomalies, and one case each of ear anomalies and laryngomalacia.

Table 1 Associated ocular anomalies in both groups

Ocular anomaly	Systemic anomaly (+) group		Systemic anomaly (–) group	
	Number of cases	Number of eyes	Number of cases	Number of eyes
Microphthalmos	6 (46%)	9 (47%)	9 (38%)	14 (40%)
Anterior staphyloma	6 (46%)	7 (37%)	3 (13%)	4 (11%)
Posterior embryotoxon	5 (38%)	5 (26%)	2 (8%)	3 (9%)
Sclerocornea	4 (31%)	5 (26%)	2 (8%)	3 (9%)
Typical iris coloboma	1 (8%)	1 (5%)	1 (4%)	1 (3%)
Aniridia	1 (8%)	1 (5%)	0	0
Persistent hyperplastic primary vitreous	0	0	2 (8%)	2 (6%)

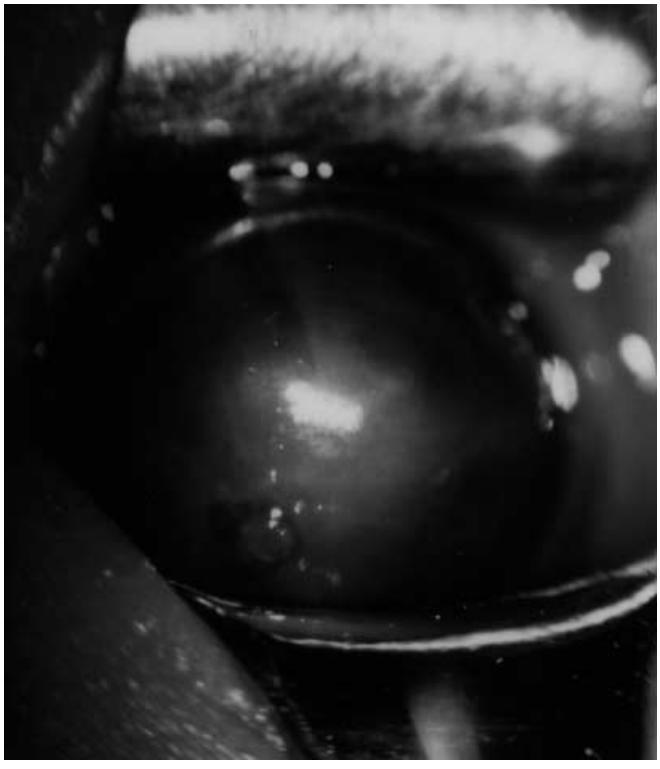

Fig. 1 Peters' anomaly with corneolenticular adhesion and anterior staphyloma in the left eye. The cornea is noticeably protruded and densely opaque overall. These findings correspond to anterior staphyloma

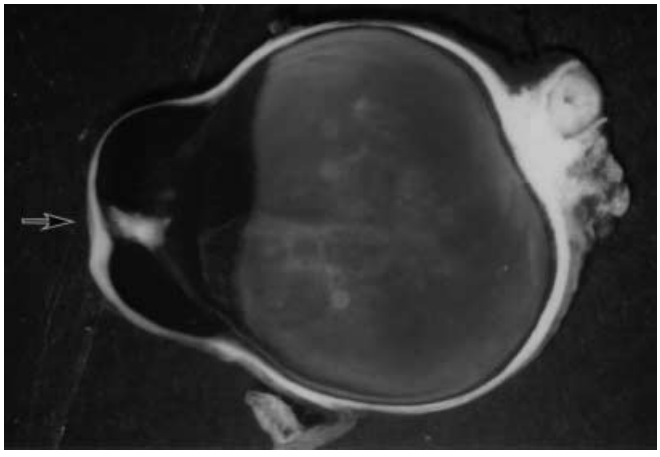

Fig. 2 A photograph of the section of the eyeball described in Fig. 1. The degenerative lens adheres to the central cornea by the lens stalk (*arrow*)

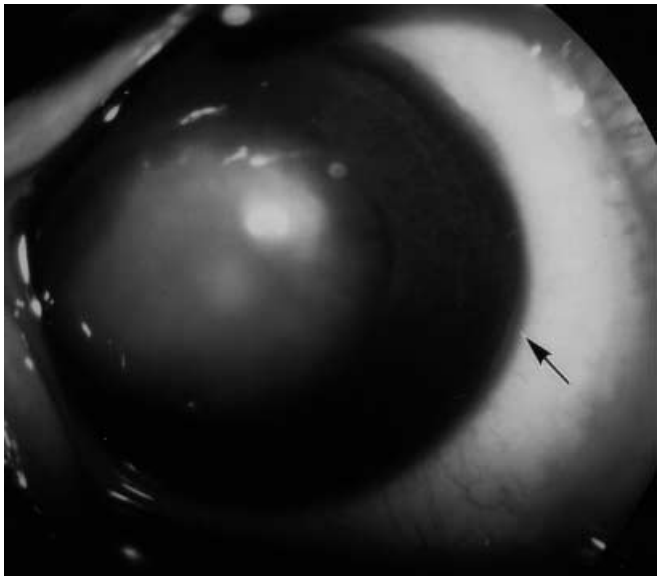

Fig. 3 Peters' anomaly with corneolenticular adhesion and posterior embryotoxon in the left eye. Central corneal opacity is evident, and corneolenticular adhesion is seen in the center of the corneal opacity. Prominent Schwalbe's line corresponding to posterior embryotoxon is observed along the temporal limbus (*arrow*)

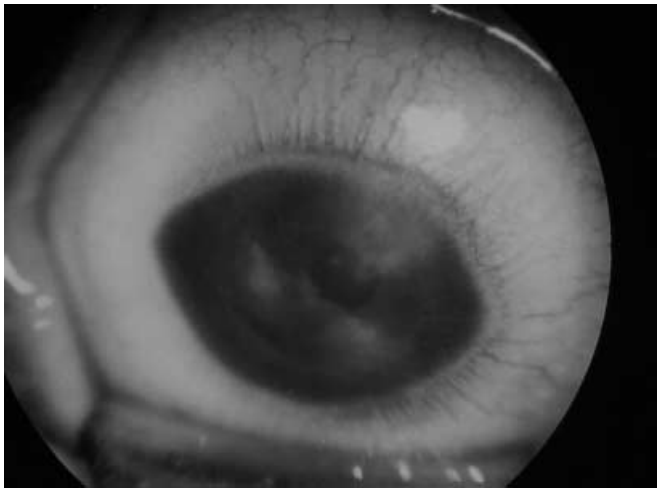

Fig. 4 Peters' anomaly with peripheral sclerocornea in the right eye. Mild central corneal opacity is observed with several iridocorneal adhesions. The upper sclerocorneal border is indistinct, corresponding to peripheral sclerocornea

In all cases, serological tests for TORCH embryopathy were negative. No teratogens were identified in any pregnancies. Chromosomal analysis was performed in 12 of 13 patients, and all patients examined showed normal karyotypes.

In one family, the elder sister of the affected patient suffered from congenital glaucoma with mild peripheral sclerocornea.

Table 2 Associated systemic anomalies in the systemic anomaly (+) group

Systemic anomaly	Number of cases
Retarded growth	6 (46%)
Cleft lip/palate	5 (38%)
Conotruncal anomalies of the heart	5 (38%)
Ear anomalies	2 (15%)
Central nervous system anomalies	2 (15%)
Urogenital anomalies	2 (15%)
Facial anomalies	1 (8%)
Laryngomalacia	1 (8%)
Macroglossia	1 (8%)

Systemic anomaly (–) group

The systemic anomaly (–) group comprised 24 patients, 13 males and 11 females, ranging in age at first examination from 3 days to 55 years, mean 28.3 ± 134.6 months. The follow-up period ranged from 1 month to 15 years, mean 5.2 ± 4.9 years. Peters' anomaly was bilateral in 11 cases and unilateral in 13 cases. Corneolenticular adhesion was observed in only five cases (21%). Associated ocular anomalies and their incidences in this group are listed in Table 1. They were observed in 10 patients (42%). These anomalies included nine cases of microphthalmos, three cases of anterior staphyloma, two cases each of posterior embryotoxon, sclerocornea (peripheral sclerocornea) (Fig. 4), and persistent hyperplastic primary vitreous, and one case of typical iris coloboma. Ten eyes (29%) of 6 patients (25%) developed glaucoma.

In all cases, serological tests for TORCH embryopathy were negative. No teratogens were identified in any pregnancies. Chromosomal analysis was performed in 21 of 24 patients, and all showed normal karyotypes.

Four cases involved siblings, two each from two families. In each family, normal parents had two affected children.

Ocular and systemic findings of each case are listed in Table 3.

Comparison between the two groups

There was no significant difference between the two groups in sex (chi-square test), laterality (chi-square test), or age (Welch's *t*-test). However, the incidence of cases with corneolenticular adhesion was significantly higher in the systemic anomaly (+) group than in the systemic anomaly (–) group (chi-square test, P=0.0007). The incidence of patients with other ocular anomalies was also significantly higher in the systemic anomaly (+) group than in the systemic anomaly (–) group (chi-square test, P=0.0082). In addition, the incidence of cases accompanied by glaucoma was significantly higher

Table 3 Clinical findings in 37 patients with Peters' anomaly (*B* bilateral, *L* left, *R* right; *PHPV* persistent hyperplastic primary vitreous, *COFS* cerebro-oculo-facio-skeletal)

Patient no.	Age	Sex	Laterality	Corneol enticular adhesion	Anterior staphyloma	Glaucoma	Associated ocular malformations	Associated systemic anomaly	Others
1	1 month	Male	L	(L+)	(L+)	(–)	L: PHPV, microphthalmos	(–)	L: Enucleation
2	2 weeks	Male	B	(L+)	(–)	(B+)	R: Posterior embryotoxon, microphthalmos	Micropenis	L: Keratoplasty; B: lens extraction
3	2 weeks	Male	B	(R+)	(–)	(B+)	R: Posterior embryotoxon	Low-set ears	B: Trabeculectomy; brother of no. 1
4	1 month	Male	R	(–)	(–)	(–)	(–)	(–)	
5	55 years	Female	L	(–)	(–)	(–)	(–)	(–)	
6	11 months	Female	B	(–)	(–)	(–)	(–)	(–)	
7	7 months	Female	R	(–)	(–)	(–)	(–)	Double ureters	R: Keratoplasty
8	1 month	Male	L	(–)	(–)	(–)	(–)	(–)	
9	2 weeks	Female	R	(–)	(–)	(–)	R: Persistent pupillary membrane, microphthalmos	(–)	
10	1 week	Male	L	(–)	(–)	(–)	L: Microphthalmos	(–)	
11	1 week	Male	B	(R+)	(–)	(–)	L: Iris coloboma; B: microphthalmos	(–)	
12	5 months	Male	L	(L+)	(L+)	(L+)	L: Sclerocornea, iris coloboma, microphthalmos	Retarded growth, heart anomalies	L: Cyclocryo-cautery, enucleation
13	3 days	Female	L	(L+)	(L+)	(L+)	L: Sclerocornea, microphthalmos	Microcephalia, facial anomalies, heart anomalies, retarded growth, cleft palate, craw fingers (COFS syndrome)	
14	3 months	Male	L	(L+)	(L+)	(–)	L: Sclerocornea	Heart anomalies, cleft lip and palate, retarded growth, ear anomalies	
15	3 weeks	Male	L	(–)	(L+)	(L+)	L: Sclerocornea, PHPV, micro-phthalmos	(–)	L: Cyclocryo-cautery, enucleation
16	1 month	Male	B	(B+)	(–)	(B+)	B: Sclerocornea, microphthalmos	(–)	
17	1 month	Female	B	(L+)	(B+)	(B+)	B: Microphthalmos	(–)	
18	3 months	Male	B	(R+)	(–)	(–)	B: Sclerocornea; R: Posterior embryotoxon microphthalmos	Laryngomalacia	
19	1 week	Male	B	(–)	(–)	(B+)	B: Microphthalmos	(–)	
20	1 week	Female	B	(–)	(–)	(–)	B: Iris hypoplasia	(–)	Sister of no. 19
21	3 months	Female	B	(B+)	(B+)	(L+)	B: Microphthalmos	Arachnoid cyst, retarded growth	
22	1 day	Female	B	(B+)	(L+)	(L+)	B: Microphthalmos	Cleft palate, retarded growth	
23	1 week	Female	B	(B+)	(–)	(B+)	B: Microphthalmos, posterior embryotoxon	(–)	B: Trabeculectomy; sister: B congenital glaucoma

Table 3 (continued)

Patient no.	Age	Sex	Laterality	Corneol enticular adhesion	Anterior staphyloma	Glaucoma	Associated ocular malformations	Associated systemic anomaly	Others
24	6 days	Male	L	(L+)	(L+)	(L+)	L: Posterior embryotoxon	Cleft palate, heart anomalies	L: Cyclocryocautery, enucleation
25	5 weeks	Female	R	(–)	(–)	(R+)	(–)	(–)	
26	3 months	Male	R	(R+)	(–)	(–)	R: Posterior embryotoxon	Cleft palate	
27	3 weeks	Male	L	(–)	(–)	(–)	(–)	(–)	
28	5 months	Female	R	(–)	(–)	(–)	R: Posterior embryotoxon	Retarded growth, heart anomalies	
29	1 month	Male	R	(–)	(–)	(–)	(–)	(–)	
30	3 days	Male	R	(–)	(–)	(–)	(–)	(–)	
31	2 weeks	Male	B	(–)	(–)	(–)	(–)	(–)	
32	1 month	Male	B	(–)	(–)	(–)	(–)	(–)	
33	3 weeks	Female	B	(–)	(–)	(–)	(–)	(–)	
34	2 weeks	Female	B	(–)	(–)	(–)	(–)	(–)	
35	2 weeks	Female	R	(–)	(–)	(–)	(–)	(–)	
36	1 week	Female	L	(–)	(–)	(–)	(–)	(–)	
37	1 week	Male	B	(L+)	(L+)	(B+)	B: Aniridia	Macroglossia	L: Enucleation; R: trabeculotomy

in the systemic anomaly (+) group than in the systemic anomaly (–) group (chi-square test, P=0.0287)

Considerable variation in the location and severity of corneal opacity was encountered in both groups. However, the location or severity of corneal opacity did not correlate with the presence of associated systemic anomalies.

Discussion

First, we evaluated the associated systemic anomalies observed in the systemic anomaly (+) group according to their embryonic origin. Craniofacial bones, cartilage, and connective tissues [4, 25] and the conotruncus of the heart [11, 12] are of neural crest origin, suggesting that cleft lip and/or palate, ear anomalies, laryngomalacia, macroglossia, and heart anomalies may have their origin in from the maldevelopment of neural crest cells. In addition, the adenohypophysis of the pituitary gland is derived from neural crest cells [4, 25], therefore, the most frequently associated anomaly, retarded growth detected in six (16%) of 37 cases, might be due to inadequate secretion of growth hormone from the adenohypophysis. Heon et al. [10] also reported that 15% of the patients with Peters' anomaly presented retarded growth.

As described above, all associated systemic anomalies appeared to arise from maldevelopment of the neural crest cells.

Peters' anomaly is usually seen as an isolated ocular defect [10, 15, 23]. In our series, 35% of patients with the anomaly developed systemic anomalies. Therefore, Peters' anomaly deserves special attention because of the possible presence of systemic anomalies, especially in tissues derived from neural crest cells.

In 1984, van Schooneveld et al. [23] first proposed the term Peters'-Plus syndrome, comprising Peters' anomaly, face anomalies, clefting, short limb dwarfism, and retarded development. In our series, several patients presented with some of these findings; however, no cases completely fulfilled the criteria for this syndrome [9]. On the other hand, case 13 presented Peters' anomaly accompanied by microcephalia, heart anomalies, facial anomalies, retarded growth, cleft palate, claw fingers, and short neck, and was diagnosed as having cerebro-oculo-facio-skeletal syndrome [18].

This study revealed that Peters' anomaly with corneolenticular adhesion, other ocular anomalies, or glaucoma was accompanied by systemic anomalies more frequently than not. Therefore, it is conceivable that cases with Peters' anomaly accompanied by corneolenticular adhesion, other ocular anomalies, or glaucoma especially need to be evaluated for the presence of systemic anomalies. Recently, we have been referring such patients for examination by a pediatrician at their first visit.

We also evaluated associated ocular anomalies in both groups according to their embryonic origin. Posterior embryotoxon and sclerocornea have been attributed to mesenchymal dysgenesis of the anterior ocular segments resulting from the abnormal migration of neural crest cells as well as Peters' anomaly [2, 3, 24]. Because the primary vitreous is of neural crest origin [14, 20], it is conceivable that the maldevelopment of neural crest cells is responsible for persistent hyperplastic primary vitreous. Moreover, we recently demonstrated in mice [16, 17, 20], using the method of experimental teratology, that the faulty closure of the embryonic fissure corresponding to typical uveal coloboma and developmental abnormalities of the vitreous corresponding to persistent

hyperplastic primary vitreous are caused by the abnormal migration of excessive mesenchymal cells derived from the neural crest. Therefore, typical iris coloboma and persistent hyperplastic primary vitreous are considered to develop from a disorder of the neural crest cells. As described above, almost all of the associated ocular anomalies in patients with Peters' anomaly in both groups are related to the maldevelopment of the neural crest cells.

Based on these observations, patients with Peters' anomaly should be examined for the presence of both ocular and systemic anomalies that are related to the maldevelopment of neural crest cells.

Recently, an ultrasound biomicroscope has been demonstrated to be very useful for imaging architectures of the anterior chamber and the chamber angle, and measuring central and peripheral corneal thickness [1, 22]. In addition, in cases with opaque cornea, an ultrasound biomicroscope could yield morphological information on the anterior chamber and the chamber angle [7]. Therefore, it is inferred that typical ocular findings for Peters' anomaly such as corneolenticular and iridocorneal adhesions, and central corneal thinning can be clearly detected by ultrasound biomicroscopy. In this study, however, we could not examine the patients with this apparatus because it was not available in our institution.

Four (14%) of the 37 cases occurred in two families. Our investigation thus confirms that familial cases of Peters' anomaly are not uncommon in Japan. Therefore, it is essential to examine the relatives of patients with the anomaly. Peters' anomaly has been described as displaying various patterns of inheritance, e.g. an autosomal dominant and an autosomal recessive pattern [21]. In the present two families, normal parents had two affected children, one of each sex and all these five cases accompanied other ocular anomalies. Although, in these cases, we could not examine other family members, e.g., siblings of the parents, we could infer the inheritance of Peters' anomaly with other ocular anomalies as an autosomal recessive pattern.

It was demonstrated by the method of experimental teratology that taking an excessive dose of vitamin A [13], retinoic acid [5, 16] or ethanol [5, 6] could induce keratolenticular adhesion corresponding clinically to Peters' anomaly. In the series, however, we detected no environmental agents.

Recently, mutation or deletion of the PAX6 gene was demonstrated to underlie some cases of Peters' anomaly [8]. In this retrospective clinical study, we could not examine the patients in the series genetically; however, genetic investigation of both patients and their relatives is required if we are to elucidate the causes of this anomaly.

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