谷明子、佐藤美保、堀田喜裕・口腔粘膜からの慢性進行性外眼筋麻痺の遺伝子診断の試み・第65回日本臨床眼科学会・2011年・東京

H. 知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得

細野克博、堀田喜裕・EYS遺伝子の変異を検出するためのプライマー、プローブ、マイクロアレイ、及び、これらを備える検出キット、並びに網膜色素変性症原因遺伝子変異の検査方法、網膜色素変性症への遺伝的感受性の検査方法・特願2010-294236・2010

2. 実用新案登録

なし。

3. その他

第115回日本眼科学会総会学術展示優秀賞受賞　細野克博、大石健太郎、山口良考、工藤純、清水信義、堀田喜裕、蓑島伸生　(視細胞特異的プロモーターとSV40LargeT抗原によるマウス培養細胞株の樹立）2011年

厚生科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

小眼球症例の眼窩内の外眼筋評価に関する研究

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研究要旨：眼球とともに眼窩内に存在する外眼筋の炎症病変の評価には，MRI 撮像方法の一つである short TI inversion recovery (STIR) 法による信号強度計測が有用である．そして，外眼筋病変と比較するため，本撮像法による正常被検者の外眼筋信号強度計測とともに，基準組織である大脳白質の信号強度も計測し，大脳白質で信号強度を正規化した（外眼筋信号強度）/（大脳白質信号強度）比を求めた．まず，外眼筋と大脳白質の信号強度計測での再現性は，測定値の変動係数が 5%未満であることから，良好なことが確認された．そして，正常者ではいずれの外眼筋でも白質との信号強度比は 2.0 未満であるため，少なくとも 2.0 以上の信号強度比は外眼筋炎症の存在を示唆する指標になると考えられた．

A．研究目的

小眼球症例では，視力障害だけでなく斜視や眼球陥凹などの障害も合併することが多い．このため，眼窩内組織として眼球の評価のみならず外眼筋の評価も重要である．そして，MRIはCTと異なり，様々な撮像方法が開発されているため外眼筋の形態の評価のみならず炎症・浮腫の評価も可能である．外眼筋の形態評価にはスピンエコー法が有用であり，一方炎症の評価には脂肪抑制画像法であるshort TI inversion recovery (STIR) 法が有用である．特にSTIR法ではMRI画像上での信号強度計測により，炎症の程度の定量化も可能である．本研究では正常外眼筋の信号強度計測を行い，外眼筋炎症の有無や程度を判断する基準値を検討した．

B．研究方法

被検者は斜視，眼球運動障害を有さない正常被検者13名（13眼）とし，外眼筋信号強度計測を行った．

1．MRI装置と撮像条件

MRI装置は3.0テスラ超伝導MRI装置であるPHILIPS社製Achieva 3.0T QUASAR DUALを用いた．STIRの眼窩冠状断撮像を行い，具体的な撮像条件はfield of view : 120mm，マトリックス数 : 256×312，加算回数 : 2回，スライス厚 : 2.5mmとした．

2．外眼筋の信号強度計測法

計測筋は上・下・内・外直筋と上斜筋とした．MRI装置の付属ソフトで，得られた眼窩冠状断画像上の測定筋をカーソルで囲み，その平均信号強度計測を求めた．なお，各被検者の信号強度を正規化するために，各被検者の同一スライスでの大脳白質を基準組織として，(外眼筋信号強度) / (大脳白質信号強度）比を算出した．

3．信号強度計測の再現性

そして，信号強度計測の再現性を評価するため，6名の各正常被検者ごとに，同一画像で信号強度計測を5回繰り返して行った．そして，その平均と標準偏差を求め，標準偏差を平均で除した比である変動係数を求め，その値から再現性を評価した．

（倫理面への配慮）

正常被検者は，体内金属が存在しないこと，妊娠の可能性の無いことを確認し，MRI検査内容を説明して同意の得られた者に実施した．また，被検者のデータから個人の特定ができないよう配慮した．

C．研究結果

各組織信号強度の変動係数の平均は上直筋で2.9%，下直筋で2.3%，内直筋で2.1%，外直筋で2.3%，上斜筋で2.2%，大脳白質で1.2%と，大脳白質の変動係数が最も低かった．また，各被検者の最大の変動係数は上直筋，内直筋，外直筋で4.6%，下直筋で4.2%，上斜筋で3.7%，大脳白質で2.6%と，いずれも5%未満であった．

各外眼筋の平均信号強度比とその標準偏差は，上直筋で1.07±0.27，下直筋で1.38±0.27，外直筋で1.32±0.18，内直筋で1.46±0.25，上斜筋で1.29±0.25であった．また，各筋の平均信号強度比と2倍の標準偏差の和の最大は，内直筋の1.96であった．さらに，各筋の信号強度比の分布は上直筋で0.59から1.53，下直筋で1.01から1.91，外直筋で1.04から1.59，内直筋で1.12から1.94，上斜筋で0.91から1.81で，正常ではいずれの外眼筋も信号強度比が2.0を超えることはなかった．

D．考察

まず，外眼筋および大脳白質の信号強度計測で

の再現性に関しては，いずれの計測組織の変動係数も最大でも5%未満であるため，計測での良好な再現性が確保されていると考えられた．特に，大脳白質の信号強度計測では，いずれの外眼筋と比較しても変動係数が小さく，信号強度の正規化のための基準組織としても適していると考えられた．

つぎに，各外眼筋の大脳白質との平均信号強度比はいずれも1.5未満であり，その平均と2倍の標準偏差は2.0未満であった．さらに，各計測値での最大値も2.0未満と，いずれも信号強度比が2.0を超える計測筋は認められなかった．この結果から，信号強度比が少なくとも2.0以上の場合，外眼筋に何らかの炎症と浮腫が存在する指標になると考えられた．

E．結論

MRIでは外眼筋の形態評価のみならず，その炎症評価も可能であり，その炎症評価法としてSTIR法が有用で，大脳白質を基準組織として信号強度比による定量評価も可能であった．また，その信号強度計測には良好な再現性が確認された．

F．健康危険情報

該当する危険なし

G．研究発表

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H．知的財産権の出願・登録状況

（予定を含む。）

1．特許取得

なし．

2．実用新案登録

なし．

3．その他

なし．

厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

安全な小眼球症の白内障手術治療の開発に関する研究

研究分担者　黒坂　大次郎　岩手医科大学眼科学講座　教授

研究要旨：小眼球症への白内障手術の問題点などを調べる目的で、2000 年以降に報告された小眼球例の白内障手術における術前合併症、術式、術後合併症、視力予後につき調べた。対象となったのは 7 論文であり、ほぼ全例で浅前房または閉塞隅角緑内障を合併し、術中・後合併症を 1～４割に認めていた。術後の視力回復は 6～7 割で、3～2 割は改善が得られていなかった。多くの例で白内障手術により、前房が深くなり眼圧のコントロールが良好となったが、一部には悪性緑内障などの重篤な障害を来していた。以上の点から、極端に浅前房になる前に、閉塞隅角緑内障を予防する観点から比較的早期での白内障手術を今後検討する必要があると思われた。

A. 研究目的

我々の検討では、小眼球症での白内障手術では、通常白内障手術に比べ、小児、閉塞隅角緑内障、脈絡膜欠損(コロボーマ)を伴った症例が多く、チン小帯の脆弱例など問題点が多かった。そこで、国内外の文献をもとに、現在の小眼球症に対する白内障手術の実態を調べることを目的とした。

B. 研究方法

医学中央雑誌または Pubmed において、それぞれ小眼球症と白内障手術、nanophthalmos and cataract surgery を検索語として 2000 年以降の文献を調べた。このうち、日本語、英語の文献で、小眼球症に対する白内障手術成績が記述されていた 7 論文 1～7）につき、術前合併症、術式、術中・後合併症、視力予後につき調べた。

C. 研究成果

7 論文の結果を表 1 に示す。記載があるもののほぼ全例で浅前房または閉塞隅角緑内障を合併しており、術中・後合併症を 1～４割に認めていた。術後の視力回復は 6～7 割で、3～2 割は改善が得られなかった。多く例で白内障手術により、前房が深くなり眼圧のコントロールが良好となったが、一部には悪性緑内障などの重篤な障害を来していた。

	例数 年齢	術前合併症	術式	術中・後合併症	視力予後
[illegible]ら	9例13眼 64歳			CCC不完全23% IOL嚢外固定15% 一過性角膜浮腫46% フィブリン析出15%	改善77% 不変23%
[illegible]ら	1例1眼 79歳	浅前房 高眼圧	ECCE	駆逐性脈絡膜出血	
[illegible]ら	1例1眼 52歳	浅前房 ACG	PEA+IOL +GSL	なし	不変
[illegible]ら	2例4眼 50.5歳	浅前房100%	PEA+IOL	なし	不変
Faucherら	4例6眼 58歳	浅前房100% ACG100%	PEA+IOL 83% PEA+IOL+AV17%	17%悪性緑内障	
Wuら	8例12眼 59歳	ACG100%	PEA+IOL58% PEA+IOL+瞳孔拡大17% ECCE+IOL+瞳孔拡大8% PEA+IOL+AV+瞳孔拡大8% PEA+IOL+T8%	術後炎症8% IOL支持部破損8% 緑内障進行8% 脈絡膜出血8%	改善58% 不変25%
Nihalaniら	84眼	小瞳孔40% 緑内障33% PE7%	PEA+IOL	手術操作困難70% ぶどう膜損傷14% デスメ膜剥離6% 後嚢破損2% 術後早期角膜浮腫75% 術後炎症23%	

表1 小眼球症に対する白内障手術結果

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D. 考按

水晶体は、生涯にわたり成長を続け徐々に大きくなる組織であるが、虹彩・角膜などの前眼部は、幼少期以降には大きくならない。このため、小眼球症では、壮年期以降水晶体に対し前眼部が相対的に小さくなり、浅前房やそれに伴う閉塞隅角緑内障を発症しやすくなると考えられる。

白内障手術にあっては、この浅前房が、前嚢切開、超音波操作を困難にすると思われる。現在は、Viscoadaptive 製剤のような高分子の粘弾性物質が開発され、前房形成は以前より行いやすくはなるのもの、白内障手術操作が前房内操作であることを考えると、浅前房は白内障手術にとって大きな壁と思える。

一方、角膜内皮細胞数は、角膜が小さいと相対的に多くなり、浅前房で角膜に対する侵襲は通常よりも多いとは思われるが、水泡性角膜症のような術後合併症の報告はなかった。また、一部に悪性緑内障のような重篤な障害を生じるものの、多くの例で白内障術後には、前房が深くなり閉塞機転が改善されていた。

以上の点を考慮すると、極端に浅前房になる前に、閉塞隅角緑内障を予防する観点から今後検討する必要がある必要があると思われた。

E. 結論

小眼球症における白内障手術では、合併する浅前房により手術操作が困難であることが多く、約 1〜4 割に何らかの術中・後合併症を認め、視力回復は 7 割程度に留まっていた。

F. 健康危険情報

該当する危険なし

G. 研究発表

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H. 知的財産権の出願・登録状況

なし

研究成果の刊行に関する一覧表

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著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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CLINICAL INVESTIGATION

Survey of microphthalmia in Japan

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Abstract
Purpose To report the current status of patients with microphthalmia based on a cross-sectional survey of patient hospital visits.
Methods A questionnaire was sent to the departments of ophthalmology in 1,151 major Japanese hospitals to survey the following: the number of patients with microphthalmia who visited the outpatient clinics between January 2008 and December 2009; gender; age; family history; associated ocular anomalies; complications and systemic diseases; surgical treatment; vision and management. A retrospective quantitative registry of 1,254 microphthalmic eyes (851 patients) from 454 hospitals (39.4%) was compiled.
Results Of the patients for whom data were available, 50% ranged in age from 0 to 9 years. The major ocular findings were nanophthalmos, coloboma, and vitreoretinal malformations. Ocular complications frequently developed, including cataracts, glaucoma, and retinal detachment. Surgery was performed in 21.4% of all cases, and systemic diseases were present in 31% of all cases. The vision associated with microphthalmia exceeded 0.1 in about 30% of the eyes. Glasses and low vision aids were used by 21.6% of patients.
Conclusions Patients with microphthalmia often have ocular and systemic anomalies. Early assessment and preservation of vision and long-term complication management are needed.

Keywords Microphthalmos · Epidemiology · Survey · Intractable disease

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Introduction

Microphthalmos is defined as the arrested development of all global dimensions and is often is associated with other ocular and systemic anomalies [1]. Chromosomal disorders, genetic syndromes, and environmental factors, such as maternal infection and exposure to X-rays or drugs, are reported as causes [2]. However, in most cases the precise pathogenesis is unknown although some causative genes (*SOX2* and *PAX6*) have been identified [2–4].

Previous studies conducted in the UK report that the prevalence rates of microphthalmia, anophthalmia, and typical coloboma are 10–19 per 100,000 births [4–7]. Microphthalmia is rare, and only a few disease, genetic, and epidemiologic studies and a few reports on the practical patient status have been published. The condition generally causes substantial visual impairment, but standard management and treatments have not been established.

We conducted a cross-sectional national survey to investigate the current status of patients with microphthalmia, focusing especially on ocular associations,

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complications, surgery, and vision examinations performed by ophthalmologists.

Materials and methods

A questionnaire was sent to the departments of ophthalmology in 1,151 major hospitals nationwide, all of which are authorized by the Japanese Ophthalmological Society as training institutions for physicians specializing in ophthalmology, to survey the number of patients with microphthalmia who visited their outpatient clinics between January 2008 and December 2009. Patients referred to other hospitals during this period were excluded.

The diagnostic criterion for pure microphthalmos is the presence of an eye with two-thirds the normal ocular volume, i.e., 0.87 below the normal axial length [1]. The Japanese criteria were established by Majima [8], based on the average axial length for each age group of Japanese patients. The clinical definition can be determined by a substantial size difference between the two eyes. Axial lengths of <21 mm in adults and <19 mm in 1-year-old children, i.e., two standard deviations below normal, are used. Corneal diameters of <10 mm in adults and <9 mm in infants are used for a simple diagnosis [9]. In our survey, either Majima's criteria for pure microphthalmos or the clinical definition for complicated microphthalmos was applied.

The questionnaire asked for either the numbers of patients or the number of eyes and was divided into two sheets. The first sheet comprised questions on the number of cases, the number of cases operated on, whether the condition was unilateral or bilateral, gender, age, family history; the second sheet consisted of questions about the number of associated ocular anomalies and complications, surgical treatment, associated systemic diseases, vision and management with glasses, low vision aid, and the use of a prosthetic shell.

A retrospective quantitative registry of microphthalmia was compiled from the responses from 454 hospitals (39.4%). The data from 1,254 microphthalmic eyes of 851 cases in total were collected from the first sheet, but as some hospitals did not complete the second sheet, only data from 1,069 eyes of 722 cases were collected from the second sheet. Of the data collected for these 1,069 eyes, data on the vision of 56 eyes (5.2%) were incomplete. Thus, data from 1,013 eyes were analyzed for vision.

We surveyed the number of patients managed in Japanese hospitals and analyzed the associated ocular anomalies and complications, surgical treatment, systemic diseases, vision and ophthalmic management.

Results

Of the 851 cases [396 (46.5%) male, 455 (53.5%) female] of microphthalmia reported on the first sheet, 444 (52%) were unilateral and 405 (48%) were bilateral (for two cases no information on unilateralism or bilateralism was reported). In terms of age distribution, 50% of the patients were 0–9 years and 16% were 10–19 years; between ages 20 and 79 years, the prevalence remained relatively constant, ranging between 4.3 and 6.8% (Fig. 1). Family histories were positive in 61 cases (7.2%), of which 25 cases (41%) of autosomal dominant inheritance, three cases of X-linked recessive inheritance, and one case of autosomal recessive inheritance were identified; the other 32 cases were undetermined.

The data from the 1,069 microphthalmic eyes of 722 cases retrieved from the second sheet were compiled and analyzed for associated ocular anomalies and complications, surgical treatment, associated systemic diseases, and management with glasses, low vision aids, and prosthetic shells. The ocular abnormalities and complications associated with microphthalmia are shown in Fig. 2. The identified ocular findings were nanophthalmos, coloboma (choroid, retina, lens, iris), vitreoretinal malformation (retinal dysplasia, retinal fold, persistent fetal vasculature, etc.), anophthalmos/extreme microphthalmos, anterior segment dysgenesis (Peters' anomaly, aniridia), and optic

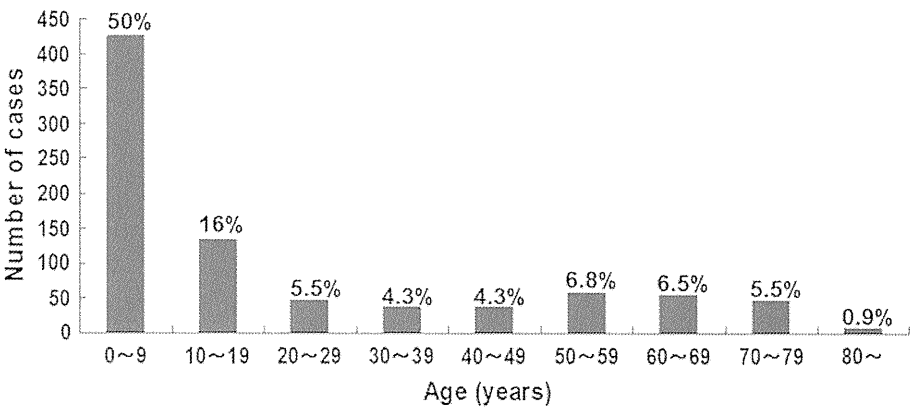

Fig. 1 Ages of patients with microphthalmia managed in the surveyed hospitals. The rate is given for each age group ($N = 851$ cases)

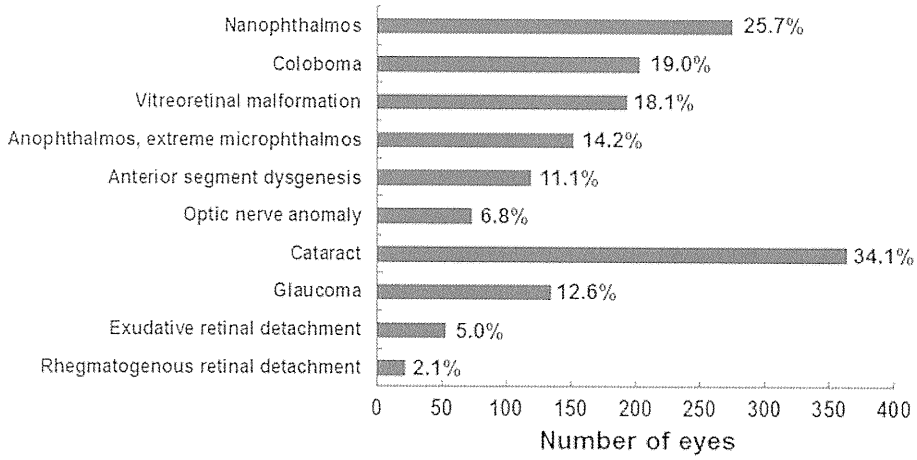

Fig. 2 Ocular abnormalities and complications associated with microphthalmia. The rate of each associated anomaly or complication is given ($N = 1{,}069$ eyes)

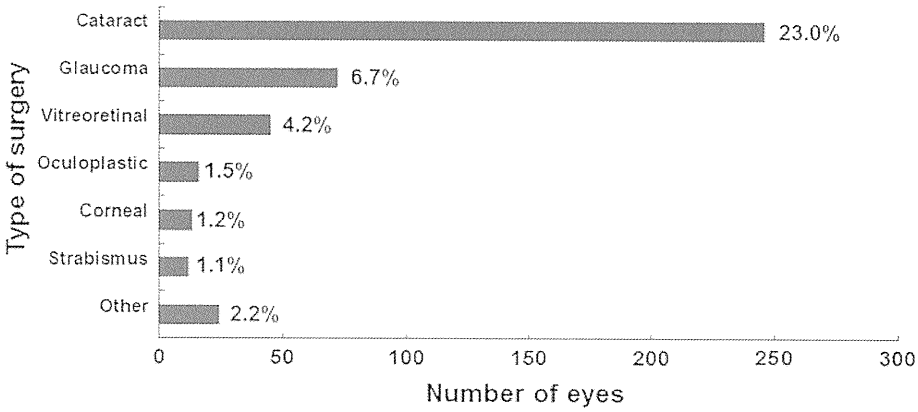

Fig. 3 Surgical treatments for ocular complications in microphthalmia. The rate of each surgical procedure is given ($N = 1{,}069$ eyes)

nerve anomaly (disc anomaly, optic nerve hypoplasia). The most frequent ocular complications were cataracts in 34.1%, followed by glaucoma and exudative or rhegmatogenous retinal detachment.

Surgery had been performed in 182 (21.4%) of the 851 cases; the surgical procedures for ocular complications are shown in Fig. 3. The procedures performed the most often were cataract extraction in 246 eyes (23.0%) of 1,069 eyes, followed by glaucoma surgery and vitreoretinal surgery.

Systemic diseases were present in 224 patients (31%) of 722 cases of microphthalmia, with 92 cases (12.7%) of developmental cerebral anomalies and mental deficiency, 68 cases (9.4%) of multiple anomalies and genetic syndromes, 26 cases (3.6%) of chromosomal disorders, and 38 cases (5.3%) of others.

The distribution of vision in microphthalmia is shown in Fig. 4. The data from 1,013 microphthalmic eyes were analyzed for vision. The visual acuity (VA) in microphthalmos was <0.02 in 348 eyes (34.4%), <0.1 but not <0.02 in 116 eyes (11.4%), <0.3 but not <0.1 in 93 eyes (9.2%), not <0.3 in 157 eyes (15.5%), unmeasurable with poor visual performance in 241 eyes (23.8%), and good visual performance in 58 eyes (5.7%).

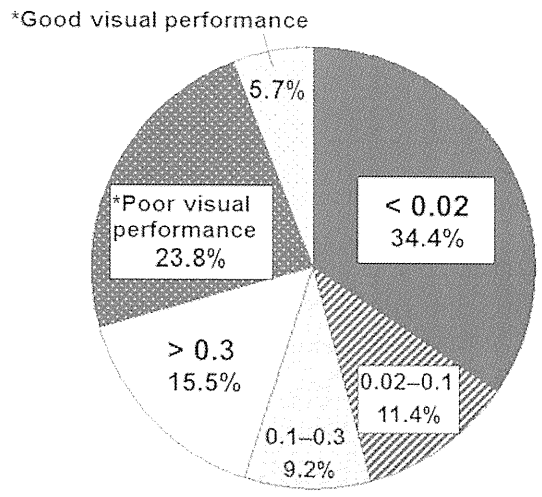

Fig. 4 Visual acuity (VA) in microphthalmos. *Asterisk* VA not measured due to young age or mental retardation. The rate of each VA group is given ($N = 1{,}013$ eyes)

Glasses and low vision aids were used in 156 cases (21.6%) of 722 cases, while prosthetic shells were applied in 211 eyes (19.7%) of 1,069 eyes.

Discussion

This is the first national survey that reports the epidemiologic aspects and current status of patients with microphthalmia in Japan. It is also the largest survey conducted by ophthalmologists of patients with microphthalmia who present at a hospital. The results based on cross-sectional surveys of patients' hospital visits may be considerably biased and may not be comparable with those of previous epidemiologic studies in other countries. However, the results of this survey showing the precise ocular associations, complications, types of surgeries, and vision, may be useful for future ocular management and investigation.

Approximately one-half of the patients in this survey who presented to a hospital were children under the age of 10 years, indicating that diagnosis and treatment of microphthalmia during the period of visual development are both needed and common practice in Japan. In addition, continuous management of low vision and ocular complications is required in order to maintain proper vision throughout life. Among the responders in this study, the distribution of microphthalmia was evenly divided between men and women and between unilateral cases and bilateral cases. Previous studies also report no biased association between microphthalmia and gender; however, those on laterality are mixed, with bilateral being more common in some studies and unilateral cases being more common in others [10]. Kallen et al. [11] reported that among their patient population, >70% of microphthalmia cases were bilateral and associated with chromosomal disorders, 53–60% were either associated or not associated with other malformations, but only 27% were cases of isolated microphthalmia. Microphthalmos associated with systemic diseases, nanophthalmos, colobomatous microphthalmos, and some cases of complicated microphthalmos often develop bilaterally and need more medical management for low vision and periodic follow-up. However, the current survey indicated that unilateral cases also require ophthalmic treatment and management.

The family histories were positive in 7.2% of cases; however, most cases have not been investigated for genetic etiology. To clarify the pathogenesis of various microphthalmia and develop useful treatments, effective genetic screening should be performed.

The current patient population had varying kinds and degrees of ocular-associated anomalies; among these, posterior segment dysgenesis, including coloboma and vitreoretinal malformations, was seen frequently. Thus, early morphologic and electrophysiologic evaluation of the posterior segment may be required to assess the visual potential and indications for surgical, optical, and amblyopia treatment or for a cosmetic shell.

The rates of developing cataracts, glaucoma, and retinal detachments were extremely high among the young patients. These ocular complications were major indications for surgical intervention, although the prognoses were generally poor [12]. Patients with microphthalmia require lifelong management for early prevention and detection of these complications. A less invasive surgical procedure for microphthalmia should be developed [13–19].

Various systemic anomalies are frequently associated with microphthalmia, indicating that initial assessment and continuous management by pediatricians are essential. Although 31% of the cases in our survey were microphthalmia associated with systemic disease, analysis of a population-based birth defects registry in Hawaii from 1986 to 2001 revealed that only 5% of the 96 cases had either isolated anophthalmia or microphthalmia, whereas 25% had confirmed chromosomal abnormalities, such as trisomy 18 and 13, and others had malformation syndromes, limb and musculoskeletal system defects, and cardiac and circulatory system defects [10]. Our survey included more unilaterally isolated cases, probably because ophthalmologists conducted the survey and provided detailed descriptions of the ocular status of the patients who presented to the hospitals.

Overall useful vision and good visual performance >0.1 were obtained in about 30% of microphthalmia cases, whereas about 34% of microphthalmia patients were blind (VA <0.02). However, glasses and low vision aids were used in around 22% of the cases, while prosthetic shells were used in about 20% of eyes. The visual prognosis of microphthalmos depends largely on the difference between the two eyes. The chances of obtaining good VA are limited in cases of severe unilateral microphthalmos, where orbital growth may be retarded and facial deformity may develop. Early socket expansion and wearing of a prosthetic shell are important for cosmetic treatment in anophthalmos and extreme microphthalmos [20]. However, microphthalmos with visual potential should be assessed early and glasses prescribed to maximize the VA.

In summary, our analysis of the survey data revealed that patients with microphthalmia have various ocular and systemic anomalies and that the rates of ocular complications are high in young patients. Early assessment, preservation of vision, and long-term management of complications are needed for these patients.

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RESEARCH ARTICLE

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Ophthalmic Features of CHARGE Syndrome With CHD7 Mutations

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Coloboma and various ocular abnormalities have been described in CHARGE syndrome, although the severity of visual impairment varies from case to case. We conducted a multicenter study to clarify the ophthalmic features of patients with molecularly confirmed CHARGE syndrome. Thirty-eight eyes in 19 patients with CHARGE syndrome and confirmed CHD7 mutations treated at four centers were retrospectively studied. Colobomata affected the posterior segment of 35 eyes in 18 patients. Both retinochoroidal and optic disk colobomata were bilaterally observed in 15 patients and unilaterally observed in 3 patients. The coloboma involved the macula totally or partially in 21 eyes of 13 patients. We confirmed that bilateral large retinochoroidal colobomata represents a typical ophthalmic feature of CHARGE syndrome in patients with confirmed CHD7 mutations; however, even eyes with large colobomata can form maculas. The anatomical severity of the eye defect was graded according to the presence of colobomata, macula defect, and microphthalmos. A comparison of the severity in one eye with that in the other eye revealed a low-to-moderate degree of agreement between the two eyes, reflecting the general facial asymmetry of patients with CHARGE syndrome. The location of protein truncation and the anatomical severity of the eyes were significantly correlated. We suggested that the early diagnosis of retinal morphology and function may be beneficial to patients, since such attention may determine whether treatment for amblyopia, such as optical correction and patching, will be effective in facilitating the visual potential or whether care for poor vision will be needed.

Key words: CHARGE syndrome; *CHD7*; coloboma; ophthalmic features

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INTRODUCTION

CHARGE syndrome is a multiple malformation syndrome named from the acronym of its major features: coloboma, heart defects, atresia of the choanae, retarded growth and/or development, genital anomalies, and ear abnormalities [Pagon et al., 1981; Zentner et al., 2010]. The major ocular feature of CHARGE syndrome is coloboma, and a previous investigation by ophthalmologists revealed an incidence of up to 86%, although the severity

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of coloboma and visual impairment varied from case to case [Russell-Eggitt et al., 1990].

Recently, the gene *Chromodomain helicase DNA-binding protein-7* (*CHD7*) at chromosome 8q12.1 was identified as a causative gene of CHARGE syndrome [Vissers et al., 2004]. Up to 70% of patients clinically diagnosed as having CHARGE syndrome exhibit mutations in the *CHD7* gene [Aramaki et al., 2006a; Jongmans et al., 2006; Lalani et al., 2006]. Although the exact function of this gene product remains unknown, it may have an important effect on an early stage of ocular morphogenesis.

We conducted the present multicenter study to clarify the ophthalmic features of patients with molecularly confirmed CHARGE syndrome and to explore the role of *CHD7* in ocular development.

PATIENTS AND METHODS

Thirty-eight eyes in 19 patients clinically diagnosed as having CHARGE syndrome at the National Center for Child Health and Development, the Osaka Medical Center and Research Institute for Maternal and Child Health, the Kanagawa Children's Medical Center, or the Institute for Developmental Research, Aichi Human Service Center were retrospectively studied. All the patients had been molecularly confirmed to carry *CHD7* mutations at the Keio University School of Medicine [Aramaki et al., 2006a]. The clinical diagnosis of CHARGE syndrome was made based on the Blake criteria [Blake et al., 1998]. Molecular screening for mutations in the *CHD7* gene was conducted as reported previously [Aramaki et al., 2006b]. Ophthalmic features were examined using slit-lamp biomicroscopy and binocular indirect ophthalmoscopy. Two patients were also examined using a spectral domain optical coherence tomography (SD-OCT). The SD-OCT images were obtained with RS-3000 (NIDEK Co., Ltd., Gamagori, Japan). The best-corrected visual acuity (BCVA) was measured with a standard Japanese VA chart using Landolt rings or pictures at 5 m, then converted to Snellen VA.

The anatomical severity of the eye defect was classified as follows: Grade 1, Normal; Grade 2, colobomata with macular formation; Grade 3, colobomata including the macula; and Grade 4, colobomata, macular defect, and microphthalmos. Then, Cohen's kappa coefficient [Cohen, 1960] was used to measure the agreement of the severity in the two eyes among 19 CHD7-mutation positive patients. The potential correlation between the anatomical severity of the eyes in an individual and the amino acid position where the truncation of the *CHD7* protein occurred in the same individual was evaluated among 14 patients with protein-truncating mutations.

This study was approved by the institutional ethics committee; the patients or the parents of the patients provided informed consent prior to enrollment in the study.

RESULTS

The characteristics of the 38 eyes of the 19 patients with CHARGE syndrome carrying *CHD7* mutations are summarized in Table I. Ten patients (53%) were male and 9 (47%) were female. The age of the patients at the time of the examination ranged from 1 to 21 years (mean 7.9 ± 5.0 years). Ocular abnormalities were found in 18 patients (94.7%), bilateral abnormalities were observed in 17 patients (89.4%), and unilateral abnormalities were observed in 1 patient (5.3%). Among these 18 patients, all 35 abnormal eyes had varying severities of colobomata.

TABLE I. Characteristics of Patients of CHARGE Syndrome With CHD7 Mutations (n = 9)

Variable	Number
Gender	
Male	10 (53%)
Female	9 (47%)
Age at examination	1–21 years
Mean	7.9 ± 5.0 years
Ocular abnormalities (colobomata)	
Bilateral	17 (89.4%)
Unilateral	1 (5.3%)
None	1 (5.3%)
BCVA	
<20/400	4 (21.1%)
20/400 to <20/60	7 (36.8%)
20/60 to 20/20	6 (31.6%)
Not measured	2 (10.5%)

BCVA, best-corrected visual acuity.

The ocular features of the individual patients are summarized in Table II. Colobomata affected the posterior segment in 35/38 eyes (92.1%), retinochoroidal coloboma was present in 33 eyes (86.8%), and optic disk coloboma was present in 33 eyes (86.8%). Both retinochoroidal coloboma and optic disk coloboma were bilaterally present in 15 patients (78.9%) and unilaterally present in 3 patients (15.8%). The coloboma involved the macula totally or partially in 21 eyes (55.3%) of the 13 patients (68.4%): bilaterally in 8 patients

TABLE II. Ocular Features of the Patients (n = 19 patients, 38 eyes)

	Number of patients (%)			
Findings	Bilateral	Unilateral	Total	Number of eyes (%)
Colobomata	17 (89.5)	1 (5.3)	18 (94.7)	35 (92.1)
Retinochoroidal	15 (78.9)	3 (15.8)	18 (94.7)	33 (86.8)
Optic disk	15 (78.9)	3 (15.8)	18 (94.7)	33 (86.8)
Macula	8 (42.1)	5 (26.3)	13 (68.4)	21 (55.3)
Iris	1 (5.3)	0 (0.0)	1 (5.3)	2 (5.3)
Lens	0 (0.0)	1 (5.3)	1 (5.3)	1 (2.6)
Microphthalmos	3 (15.8)	2 (10.5)	5 (26.3)	8 (21.1)
Microcornea	3 (15.8)	1 (5.3)	4 (21.1)	7 (18.4)
Ptosis	1 (5.3)	1 (5.3)	2 (10.5)	3 (7.9)
PFV	0 (0.0)	1 (5.3)	1 (5.3)	1 (2.6)
Cataract	0 (0.0)	1 (5.3)	1 (5.3)	1 (2.6)
High myopia (>6.0 D)	2 (10.5)	1 (5.3)	3 (15.8)	5 (13.2)

PFV, persistent fetal vasculature.

(42.1%) and unilaterally in 5 patients (26.3%). The SD-OCT demonstrated a partially formed macula and cystic changes in the colobomatous area in 1 case (Fig. 1).

Only 2 eyes of 1 patient (5.3%) were identified as having iris colobomata, and 1 eye (2.6%) of another patient was revealed by examination under general anesthesia to have a dislocated and colobomatous lens. No cases of eyelid colobomata were seen, but congenital ptosis was present in 3 eyes (7.9%) of 2 patients who had undergone surgical treatment. All the cases of ptosis were not pseudoptosis associated with microphthalmos and/or cranial nerve palsy, but were true congenital ptosis associated with poor levator function. We evaluated the levator muscle function in each case. None of the patients had a history of acquired causes or signs of oculomotor palsy, such as paralytic strabismus and limited ocular movement.

Microphthalmos was found in 8 eyes (21.1%) of 5 patients (26.3%): bilaterally in 3 patients (15.8%) and unilaterally in 2 patients (10.5%). Microcornea was also present in 7 eyes (18.4%) of 4 patients (21.1%): bilaterally in 3 patients (15.8%) and unilaterally in 1 patient (5.3%). Persistent fetal vasculature was identified in 1 eye (2.6%). Cataracts had developed in 1 eye (2.6%), but neither glaucoma nor retinal detachment was observed in this series.

The refraction could be estimated in 23 eyes of 12 patients (63.2%). Of these eyes, 10 were myopic, 7 were emmetropic, and 6 were hypermetropic. High myopia (−6.00 diopters or more) was found in 5 eyes (13.2%) of 3 patients (15.8%).

The BCVA are shown in Table I. The measurement of VA was possible in 17 patients (89.5%) older than 3 years of age. The remaining 2 patients were infants or mentally retarded. The binocular BCVA or BCVA in the better eye was less than 20/400 in 4 patients (21.1%), less than 20/60 but no less than 20/400 in 7 patients (36.8%), and 20/60 to 20/20 in 6 patients (31.6%) with macular formation (Fig. 1). The overall prevalence of blindness and visual impairment (less than 20/60) [World Health Organization, 1992] among the 17 patients was 65%.

The agreement of anatomical severity between the 2 eyes in each of the 19 patients was evaluated using Cohen's Kappa statistics. The κ statistic of 0.41 suggested a moderate degree of agreement, per the guidelines by Landis and Koch [1977]. Because there was a moderate, if not a substantial, agreement between the severity of the 2 eyes, the severity grading of the more severely affected eye was used as the representative grade for the severity of the eyes in an individual. The correlation between the anatomical severity of the eyes in an individual and the amino acid position where the truncation of the CHD7 protein occurred in the same individual is illustrated in Figure 2. Patients with truncated protein devoid of the SANT domain tended to have severer anatomical defects of the eyes. Subcategorization of the patients according to the presence or absence of the SANT domain (4 cases with intact SANT domain and 10 other cases), and the subcategorization of the anatomical severity of the eyes in an individual (7 cases classified as Grade 1 or 2 vs. 7 cases classified as Grade 3 or 4) revealed a statistically

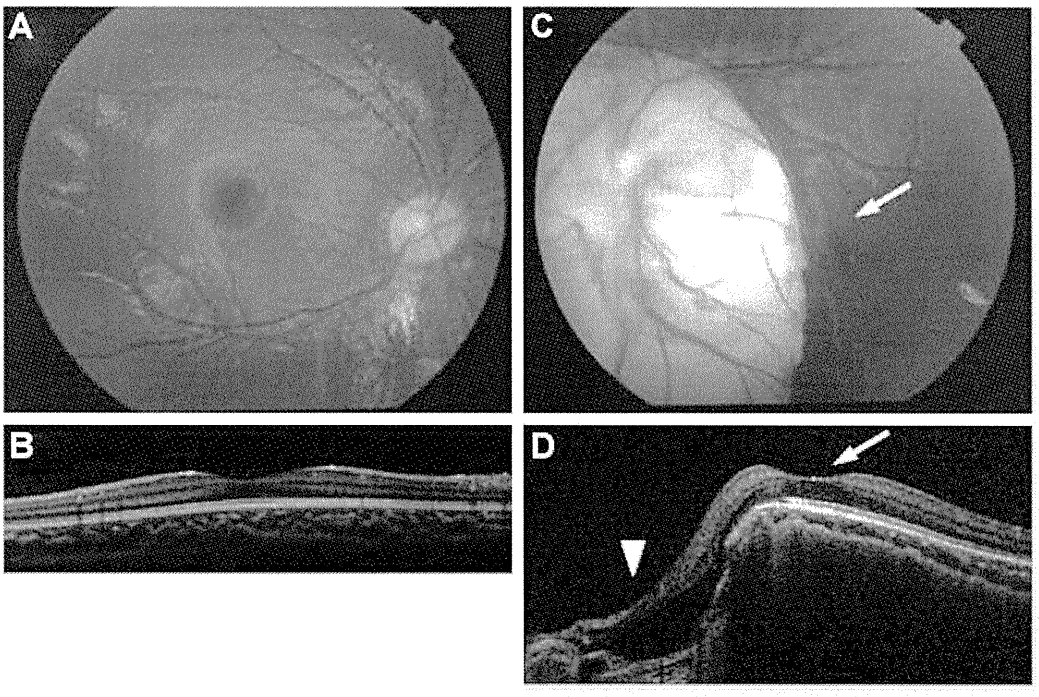

FIG. 1. Fundus photographs and spectral domain optical coherence tomography (SD-OCT) scan of the retina in the right eye (A,B) and the left eye (C,D) in a 6-year-old girl. A: Retinochoroidal colobomata inferior to the optic disk is visible in the right eye. B: The SD-OCT shows a good macular formation in the right eye, resulting in a BCVA of 20/20. C: Retinochoroidal and optic disk coloboma are seen in the left eye. The colobomata partially involved the macula (arrow). D: The SD-OCT shows a partially formed macula (arrow) and cystic changes in the colobomatous area (arrow head) in the left eye, resulting in a BCVA of 20/50 after amblyopia treatment.

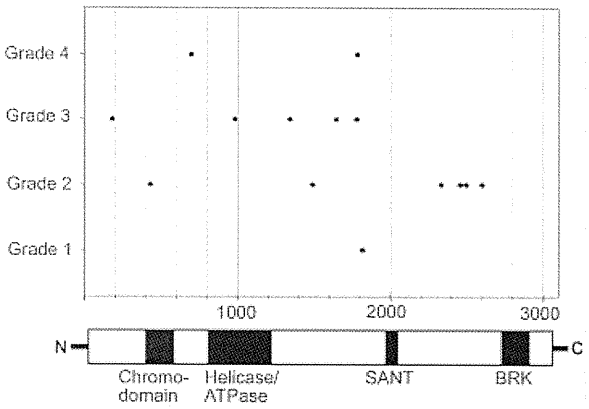

FIG. 2. The correlation between the anatomical severity of the eyes in an individual and the amino acid position where the truncation of the CHD7 protein occurred in the same individual. Horizontal axis indicates amino acid position of the CHD7 protein together with the domains of the protein. Vertical axis indicates the anatomical severity of the eye defect classified as follows: Grade 1, Normal; Grade 2, colobomata with macular formation; Grade 3, colobomata including the macula; and Grade 4, colobomata, macular defect, and microphthalmos.

significant correlation between the location of protein truncation and the anatomical severity of the eyes ($P = 0.02$, chi-squared test).

DISCUSSION

In the current series, the incidence of coloboma, the major ocular feature of CHARGE syndrome, was 94.7% (18/19), which was much higher than the previously reported incidence. Since most of the authors were ophthalmologists, the number of cases without eye defects might have been underrepresented. Hence, this high incidence should be viewed with caution. Nevertheless, attending clinical geneticists were on duty at all the participating children's hospitals, and thus the bias from such underrepresentation may be relatively small. The finding that there was one mutation-positive patient who did not have abnormal eye findings confirms that no finding in CHARGE syndrome has a 100% penetrance as is sometimes surmised.

Both retinochoroidal and optic disk coloboma occurred in 94.7% of the cases, mostly bilaterally, while the incidence of iris coloboma was only 5.3% (1/19). Coloboma also affected the macula in 68.4% of the cases. We confirmed that bilateral large retinochoroidal colobomata represent a typical ophthalmic feature of CHARGE syndrome with *CHD7* mutations.

The incidence of anomalies in the anterior segment was lower than that in the posterior segment, although microphthalmos, microcornea, PFV, and cataracts were present in some cases bilaterally or unilaterally. The presence of characteristic large retinochoroidal coloboma indicates the essential role of *CHD7* in the closure of the fetal fissure posteriorly between 5 and 6 weeks of gestation, and the malfunction of *CHD7* may have an effect so severe as to influence the entire ocular morphogenesis to some degree. Although most cases had bilateral colobomata in the posterior segment, the severity and associated features often differed between the two eyes. Other associated features in this series were ptosis in 10.5% and high myopia in 15.8%. Subtle-associated anomalies and refractive errors may have been underestimated in examinations that were not performed under general anesthesia.

The anatomical severity grading of the eye defect was evaluated in two ways: a comparison between the severity in one eye in comparison with that in the other eye and the correlation between the severity and the genotype. The low-to-moderate degree of agreement between the two eyes (i.e., left and right) reflects the general facial asymmetry in patients with CHARGE syndrome [Zentner et al., 2010]. In other words, the lack of substantial or perfect agreement between the anatomical severity of the right and the left eyes indicates a variable phenotypic effect of the same mutation. Yet, the location of protein truncation and the anatomical severity of the eyes were significantly correlated: if the chromodomain, helicase/ATP domain, and SANT domains are intact, the severity of the eyes tends to be milder. Interestingly, all four cases in which those domains were intact had less severe eye defects with intact macula. Further studies are warranted to verify this potential genotype–phenotype correlation.

The visual acuities of the eyes ranged between no light perception and 20/20, and the prevalence of blindness and visual impairment (less than 20/60) was 65% among 17 patients. A poor visual prognosis depended on the presence of a large coloboma involving the macula in the posterior segment and associated microphthalmos or microcornea, as reported previously [Russell-Eggitt et al., 1990; Hornby et al., 2000]. On the other hand, even eyes with large colobomata as a result of *CHD7* mutations were capable of forming maculas, resulting in good central visual acuity with superior visual field defects. As shown in the case illustrated in Figure 1, even a partially formed macula will enable useful vision following the adequate treatment of amblyopia as optical correction and patching during the earlier age of visual development. A recent report of a case examined using OCT revealed additional morphologic characteristics of eyes in patients with CHARGE syndrome carrying *CHD7* mutations [Holak et al., 2008]. Further investigation of retinal morphology and function using OCT and electroretinograms (ERG) may help to clarify the function of *CHD7* in ocular morphogenesis, including macular formation.

We suggested that the early diagnosis of retinal morphology and function, especially of macular lesions by way of OCT and ERG, may be beneficial to patients, since such attention may determine whether treatment for amblyopia, such as optical correction and patching, will be effective in facilitating the visual potential or whether care for poor vision will be needed. An infant's visual acuity rapidly develops during its first 2–3 years and continues up until 7–8 years of age, but plasticity decreases progressively thereafter. Thus, a better visual prognosis can be obtained with the earlier treatment of amblyopia during the critical period of visual development.