Ophthalmic Manifestations of Smith-Magenis Syndrome

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Purpose: The Smith-Magenis syndrome (SMS) is a multiple-anomaly, mental retardation syndrome associated with deletions of a contiguous region of chromosome 17p11.2. Prior reports have described ophthalmic anomalies with SMS, including telecanthus, ptosis, strabismus, myopia, iris anomalies, cataracts, optic nerve hypoplasia, and retinal detachment. This report defines the ophthalmic spectrum in 28 individuals with SMS subjected to a multidisciplinary clinical and molecular survey.

Methods: Individuals with deletion of chromosome 17p11.2 detected by high-resolution cytogenetic analysis underwent complete ophthalmologic evaluation comprised of ophthalmic history, visual acuity, cycloplegic refraction, motility, and biomicroscopic and ophthalmoscopic examination.

Results: Among the 28 subjects, ranging in age from 0.8 to 29.3 years, the most frequent ocular findings were iris anomalies (68%), microcornea (50%), myopia (42%), and strabismus (32%). Bilateral microphthalmos with uveal and retinal coloboma was observed in one individual. No subject had cataract or retinal detachment.

Conclusions: This is the largest single-center series of subjects with SMS that includes ophthalmic evaluation. As in prior reports, iris anomalies and strabismus were observed, but microcornea had not been noted previously. The absolute refractive error was hypermetropic in half of these subjects. Cataract, ptosis, and retinal pathology, including detachment, were not observed in any subject. All individuals with SMS should be evaluated by an ophthalmologist, with special attention to strabismus, microcornea, iris anomalies, and refractive errors. *Ophthalmology 1996;103:1084–1091*

The Smith-Magenis syndrome (SMS) is a multiple-anomaly, mental retardation syndrome that is associated with similar deletions of a contiguous region in chromosome 17 band p11.2.[1–3] The clinical phenotype includes dysmorphic facial features (brachycephaly, prominent forehead, synophrys, epicanthal folds, broad nasal bridge, ear anomalies, and prognathism), brachydactyly, self-injurious behaviors (head banging, wrist biting, onychotillomania, and polyembolokoilamania[1]), auto-amplexation (self-hugging) stereotypy, speech delay, sleep disturbances, mental and developmental retardation, and clinical signs of peripheral neuropathy[1–4] (unpublished data, Smith ACM, et al; presented as an abstract at the American Society of Human Genetics Meeting, 1982). Ophthalmic anomalies previously reported among individuals with SMS include ptosis, telecanthus, strabismus, myopia, iris abnormalities (colobomas, "Brushfield spots"), bilateral cataracts, optic nerve hypoplasia, and retinal detachment[4–11] (unpublished data, Stallard R, et al; presented as an abstract at the American Society of Human Genetics Meeting, 1984). However, these reports were written mostly by dysmorphologists or geneticists, and both the diligence of the ocular examinations and the details of their de-

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scriptions vary widely. Since 1989, one of us (RAL) has participated in a multidisciplinary clinical and molecular survey of 28 patients with SMS and del17p11.2 by experienced dysmorphologists and clinical and molecular geneticists (FG, JRL) to define the ophthalmic spectrum of this phenotype.[2]

Materials and Methods

Individuals with a deletion of chromosome 17p11.2, detected by high-resolution cytogenetic analysis, underwent complete ophthalmologic examination as part of a detailed multidisciplinary survey within the General Clinical Research Center for Children at Texas Children's Hospital, Houston.[2] Subjects were solicited from regional hospitals and from clinical geneticists and cytogeneticists throughout the United States. No subject was referred to this survey specifically for the evaluation or management of any ophthalmic symptom or finding. The ophthalmologic evaluation included an assessment of prior ophthalmic history, measurement of facial dimensions, optimal visual acuity, cycloplegic refraction, motility, biomicroscopic examination, and indirect and, where feasible, binocular direct ophthalmoscopic examination.

Results

Twenty-eight subjects, 19 females and 9 males, ranged in age at examination from 0.8 to 29.3 years (mean ± standard deviation, 8.5 ± 6.6 years; median, 6.7 years) (Table 1). The most frequent ocular findings were iris anomalies (68%), microcornea (50%), myopia (42%), and strabismus (32%). One individual (case 761) had peripapillary myelinated nerve fibers in one eye noted on retinal examination. One patient (case 1076) had slightly dysplastic optic nerves in both eyes. Another patient (case 701) had bilateral microphthalmos with both iris and uveoretinal coloboma.

Nineteen individuals had iris anomalies; nine had more than one iris anomaly. Seven subjects had no definable iris collarette, seven (14 eyes) had nasal corectopia, and six had stromal dysplasia with radial striations or wispy strands of anterior stroma. Peripheral displacement of the pupillary collarette beyond the mid-radial dimension was observed in four subjects. Innumerable fine mammillations that were the same color as the rest of the iris stroma were seen in two subjects. White, elevated nodules in the peripheral iris, historically termed *Wölfflin-Krückmann spots,* were observed in four individuals (Fig 1).[12,13] All subjects had normally reactive pupils to light without afferent defects (Table 1).

Although all corneas were structurally normal and approximately circular, horizontal corneal diameters ranged from 10.0 to 12.0 mm (as measured by comparison with a millimeter ruler). The mean horizontal corneal diameter was 10.6 ± 0.5 mm. Fourteen subjects (50%) had symmetric corneas that measured less than 11 mm (age range, 0.8–13 years). Neither the individual's age nor refractive error predicted the horizontal corneal diameter. Eight of the 14 subjects with small corneas also had iris anomalies. Two individuals with horizontal corneal diameters of 11 mm or greater also had posterior embryotoxon temporally in each eye.

Cycloplegic refractions were completed on 26 of 28 subjects. (Two subjects were evaluated at the bedside where formal refraction could not be performed.) Twelve subjects (46%), with a mean age of 6.2 years, were hypermetropic. The mean spherical equivalent among all examined eyes was −0.70 ± 2.95 diopters (D) in the right eye and −0.59 ± 2.80 D in the left. Only two subjects, ages 6.9 and 15.2 years, had myopia greater than −5.00 D. The average cylinder power measured 1.41 D in the right eye and 1.58 D in the left. Eight individuals had astigmatism equal to or greater than 1.25 D (range, 1.25–4.50 D). The axes of the cylinder ranged from 35° to 180° (average, 101° in the right eye and 105° in the left).

Subjects in this series were relatively myopic, 3.57 D more myopic (no significant difference between eyes), when compared with their age-adjusted spherical equivalent.[14] All 26 subjects who had a refraction were more than 0.5 D more myopic than their age-adjusted spherical equivalent.[14] None had any retinal associations of high myopia such as lacquer cracks; posterior staphyloma; disciform scars; Fuchs spots; lattice degeneration; or retinal breaks, dialyses, or detachment.

Nine subjects (32%) had strabismus. Eight subjects (5 with esodeviations, 2 with exodeviations, and 1 with right hypertropia) had a manifest deviation at the time of examination. One individual had had strabismus surgery to correct esotropia and manifested a consecutive exotropia. Another subject (case 656) had surgery to correct an esodeviation and had no observable deviation at the time of our examination. No distinctive "A" or "V" pattern, oblique dysfunction, apparent accommodative component, or manifest or latent nystagmus was identified in any subject. Among all subjects with strabismus, no retinal or foveal anomalies discriminated the deviating eye from the nondeviating eye.

Subjects with SMS have typical dysmorphic facies with a prominent forehead, broad nasal bridge, and brachycephaly (Fig 2). The intermedial canthal, interpupillary, and interlateral canthal distances were recorded in 17 individuals, ranging in age from 0.8 to 29.3 years (data not shown). The intermedial canthal distance varied from the 3rd centile to the 80th centile, the interpupillary distance from the 3rd centile to the 70th centile, the interlateral canthal distance from the 10th centile to the 85th centile. The average measurement for all three dimensions was near the 50th centile; 50% for intermedial canthal distance, 56% for interpupillary distance, and 45% for interlateral canthal distance. Although no subject exceeded the 90th centile for any dimension, seven had intermedial canthal distances at or near the 75th centile. Seven had interpupillary distances at or near the 75th centile. Parental facial dimensions were not measured for comparison, because in all instances only one parent was available during the evaluation.

Table 1. Smith-Magenis Syndrome

Case No.	Age (yrs)/Sex	se-RE	sediff-R	se-LE	sediff-LE	Irides	k-RE	k-LE	Alignment
200	10.3/M	NR		NR		Corectopia	10.3	10.3	RHT
280	2.8/F	0.00	−3.13	0.00	−3.13	Normal	11.5	11.5	Ortho
479	3.3/M	1.13	−2.18	1.25	−2.05	Normal	Normal	Normal	ET
484	2.3/F	1.25	−1.69	1.25	−1.69	Normal	Normal	Normal	ET
536	6.5/M	0.25	−3.67	0.00	−3.92	Normal	10.5	10.5	Ortho
540	15.2/M	−7.00	−8.82	−6.00	−7.82	Iris dysplasia, Wölfflin-Krückmann spots	Normal	Normal	Ortho
541	3.6/F	0.50	−2.88	0.63	−2.76	Mammillations	11	11	Ortho
616	5.4/F	0.75	−3.08	0.75	−3.08	Normal	10.5	10.5	Ortho
624	4.3/F	1.88	−1.69	1.88	−1.69	Displaced collarette	10.5	10.5	Ortho
641	7.2/F	−1.88	−5.69	−1.25	−5.06	Normal	Normal	Normal	Ortho
649	2.9/M	1.00	−1.86	1.00	−1.86	Wölfflin-Krückmann spots	11	11.0	Ortho
656	7.3/M	−1.25	−5.08	−0.75	−4.58	Normal	10.5	10.5	Ortho
664	13/F	−4.00	−6.48	−4.13	−6.61	No collarette, iris dysplasia	10.5	10.5	ET
674	12.1/F	0.25	−2.26	0.25	−2.26	Wölfflin-Krückmann spots, nasal corectopia	11	11.0	Ortho
699	4.1/F	NR		NR		Corectopia, no collarette, iris dysplasia	Normal	Normal	Ortho
701	16.7/M	0.38	−1.34	0.00	−1.71	No collarette, coloboma	10	10.0	Ortho
720	2.2/F	−1.50	−4.39	−2.00	−4.89	No collarette, iris dysplasia	11	11.0	Ortho
725	9.8/F	1.38	−2.19	1.50	−2.06	Normal	10	10.0	XT
761	22.1/F	−1.63	−2.5	−1.25	−2.13	No collarette, iris dysplasia, nasal corectopia	11.5	11.5	Ortho
843	6.3/F	−0.50	−4.38	−0.50	−4.38	Displaced collarette	10.5	10.5	E(T)
852	10.1/F	−0.25	−3.37	0.25	−2.87	Displaced collarette	10	10.0	Ortho
895	4.4/M	2.50	−1.14	2.50	−1.14	Posterior embryotoxon, iris dysplasia, no collarette	Normal	Normal	Ortho
898	10.4/F	2.88	−0.32	2.63	−0.57	Mammillations, no collarette, nasal corectopia, posterior embryotoxon	Normal	Normal	Ortho
911	14.8/F	1.00	−1.14	1.50	−0.64	Corectopia	10.5	10.5	Ortho
913	2.8/F	−3.88	−6.99	−4.00	−7.12	Corectopia	10	10.0	X(T)
924	29.3/M	−2.25	−2.86	−2.38	−2.99	Wölfflin-Krückmann spots	Normal	Normal	Ortho
931	6.9/F	−10.38	−14.13	−9.75	−13.5	Normal	10.5	10.5	ET
1076	0.8/F	1.25	−1.21	1.25	−1.21	Displaced collarette	10	10.0	Ortho
Average	8.5	−0.70	−3.63	−0.59	−3.53		10.6	10.6	
Median	6.9						10.5	10.5	
SD	6.6	2.90	2.90	2.75	2.75		0.5	0.5	

se-RE = spherical equivalent in diopters-right eye; se-LE = spherical equivalent in diopters-left eye; k-RE = cornea-right eye; k-LE = cornea-left eye; NR = not recorded; RHT = right hypertropia; ET = esotropia; XT = exotropia; E(T) = intermittent esotropia; X(T) = intermittent exotropia; ET = esotropia; SD = standard deviation.

Discussion

Contiguous gene syndromes are characterized by a constellation of variable features that affect several organ systems and whose defects are not apparently linked by function.[15] Numerous contiguous gene syndromes have ocular and facial manifestations: Prader-Willi syndrome, del15q11; DiGeorge and velocardiofacial syndrome, del22q11; Langer-Gideon syndrome, del8q24; Miller-Dieker syndrome, del17p13; retinoblastoma/mental retardation, del13q14; Wilms tumor, aniridia, genitourinary tract malformations, and mental retardation, del11p13; and the Beckwith-Wiedemann syndrome, dup11p15.[15] The variation in presentation among individuals with similar deletions may depend on the extent of the chromosomal segment deleted (or duplicated) or may result from either haploinsufficiency and loss of critical normal genetic functions or the unmasking of recessive mutant

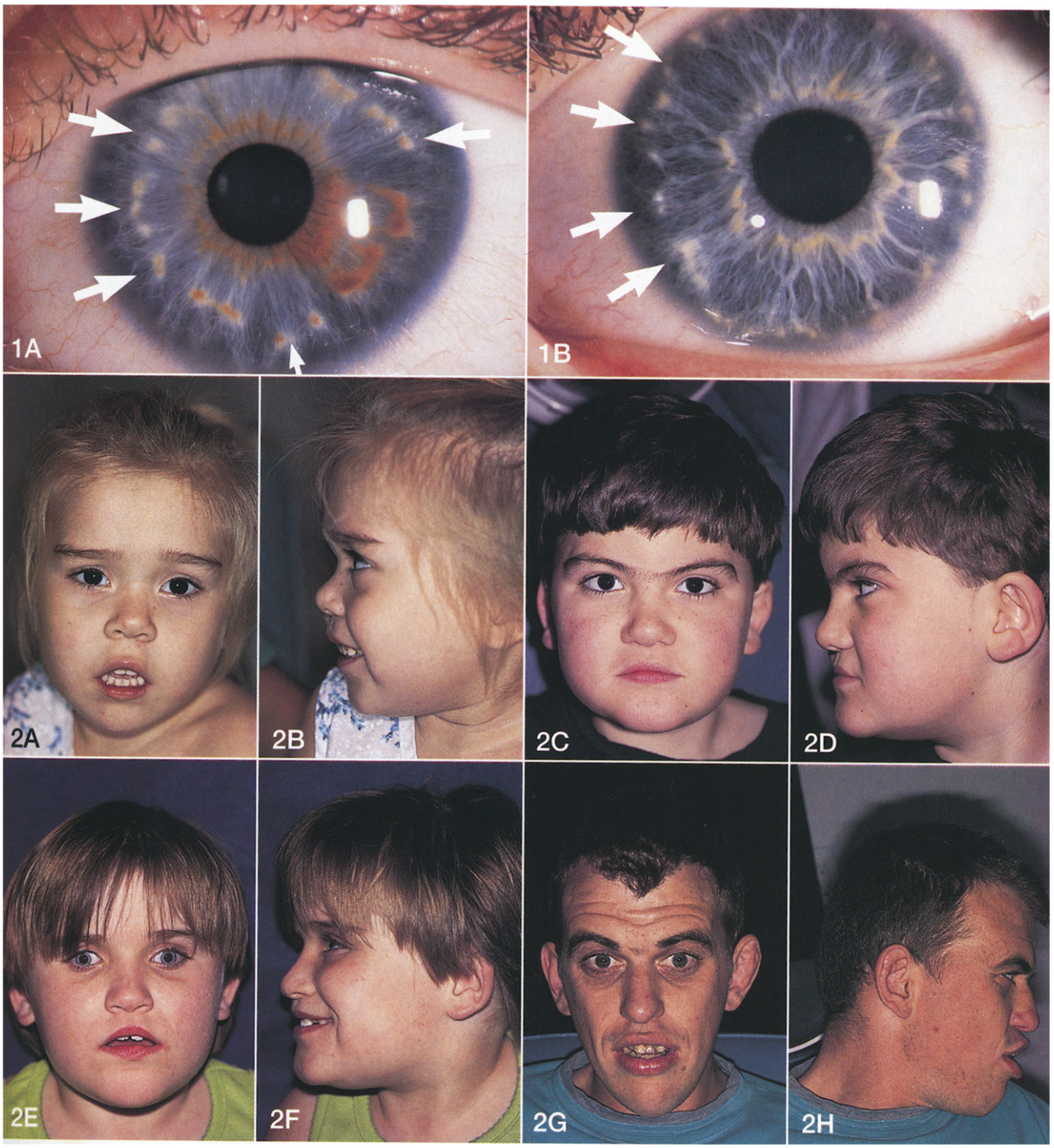

Figure 1. Iris anomalies in Smith-Magenis syndrome. **A,** left iris of a 12-year-old girl (case 674); **B,** right iris of a 15-year-old boy (case 540). Notice slight nasal corectopia, poorly defined or absent collarette, altered anterior stromal texture, and prominent Wölfflin-Krückmann spots (arrows).

Figure 2. Spectrum of craniofacial dysmorphism in Smith-Magenis syndrome. **A** and **B,** a 3.5-year-old girl (case 541); **C** and **D,** a 7-year-old boy (case 656); **E** and **F,** a 9-year-old girl (case 725); **G** and **H,** a 29-year-old man (case 924). Some common features, more distinct in older individuals, include brachycephaly, broad and flat facies, mid-facial hypoplasia, synophrys, strabismus, down-turned upper lip, prognathism, and malformed and/or malpositioned helices.[2]

alleles that remain on the intact chromosomal homologue after the deletion.[3]

Since first reported in 1982, many ophthalmologic abnormalities, including telecanthus, ptosis, strabismus, iris abnormalities, cataracts, optic nerve hypoplasia, and myopia, have been observed in individuals with SMS (Table 2) (unpublished data: Smith ACM, et al; presented as an abstract at the American Society of Human Genetics

Table 2. Literature Summary

	Smith et al,[4] 1986	Stallard 1984	Patil and Bartley,[5] 1984	Stratton et al,[6] 1986	Hamill et al,[7] 1988	de Almeida, et al,[8] 1989	de Rijk-van Andel et al,[9] 1991	Moncla et al,[10] 1991	Finucane et al,[11] 1993
No. of subjects	9	2	1	6	1	1	3	3	10
Age	3 mos to 65 yrs	26 and 51 mos	4 yrs		3 yrs	3 yrs	1.5–59 yrs	3 and 8 days, 30 mos	6 to 50 yrs
Findings									
Strabismus	1 with ET, 1 with XT	1	1	1	1	1	1 with ET	2	10
Ptosis	1								
Hypertelorism	3						1		
"Apparent telecanthus"	1					1			
Epicanthus								3	
"Brushfield spots"	2			2	1				
Iris coloboma				1					
Cataracts						1 (both eyes)			4
Iris abnormalities									7
Pupillary asymmetry	1								
Myopia			1				1		8
Amblyopia	1								1
Optic nerve hypoplasia	1								
Retinal detachment									4
Note			Findings in 1 patient		Findings in 1 patient	Findings in 1 patient	Findings in 1 patient		

ET = esotropia; XT = exotropia.

Meeting, 1982; and Stallard R, et al; presented as an abstract at the American Society of Human Genetics Meeting, 1984).[4–10] The largest series reported to date from a single center included ten patients.[11] In that report, Finucane et al[11] observed myopia (−1.75 to −22.0 D) and retinal detachment in three (4 eyes) of ten subjects and thus concluded that subjects with SMS were at high risk for both myopia and retinal detachment. However, these ten subjects with SMS were selected from a survey of 547 residents of a long-term care facility for the mentally handicapped who were first screened for refractive errors. Those with refractive myopia of 3.00 D or greater underwent chromosomal analyses (presented as a poster at the American Academy of Ophthalmology Annual Meeting, Atlanta, October/November 1995). This criterion of prior selection precludes any conclusions about the association between myopia and SMS. Self-injurious behavior may be more prevalent in an institutionalized population and might place these myopic individuals at risk for retinal detachment.

In four previously reported series,[4,6,7,11] one or more subjects had iris anomalies. These series describe "Brushfield-like" spots, pupillary asymmetry, and heterochromic irides (Table 2). In our subjects, 68% (19/28) had anomalous irides. However, the iris nodules observed in 14% (4/28) of our subjects with SMS are better described as Wölfflin-Krückmann spots. Wölfflin,[12] Krückmann,[13] and Donaldson[16] independently described iris nodules in healthy subjects that appear similar to Brushfield spots but are less well defined, more peripherally located, and typically fewer in number. Brushfield spots, seen only in individuals with Down syndrome, are white or lightly colored, elevated areas located most often on the anterior surface of the midperiphery of the iris and are seen most readily on lightly colored irides, but they may occur on dark irides as well.[17]

In addition to Wölfflin-Krückmann spots, we observed iris stromal mammillations, absent or peripherally displaced collarette(s), nasal corectopia, and coarse stromal dysplasia (Table 1). The mention of "pupillary asymmetry" by Smith et al[4] actually might be corectopia. The iris abnormalities that we observed may have been present in the subjects in previous reports, but without the benefit of slit-lamp biomicroscopy, they would have been difficult to detect and to discriminate from normal iris structures.

Small corneas in subjects with SMS have not been documented previously. In newborn children, the horizontal corneal diameter is approximately 10 mm.[18] By 2 years of age, the adult horizontal corneal diameter reaches 11.75 mm. All our subjects except one (0.8 years) were 2.2 years of age or older and should have attained adult corneal dimensions. We found that 50% (14/28 subjects) had corneas that measured 10.5 mm or less. No subject had unilateral microcornea. The two subjects (cases 540 and 641) who apparently had the smaller deletions did not manifest microcornea.[2,19,20]

Microcornea can be either an isolated finding usually transmitted as an autosomal dominant and rarely an autosomal recessive trait or associated with glaucoma, cat-

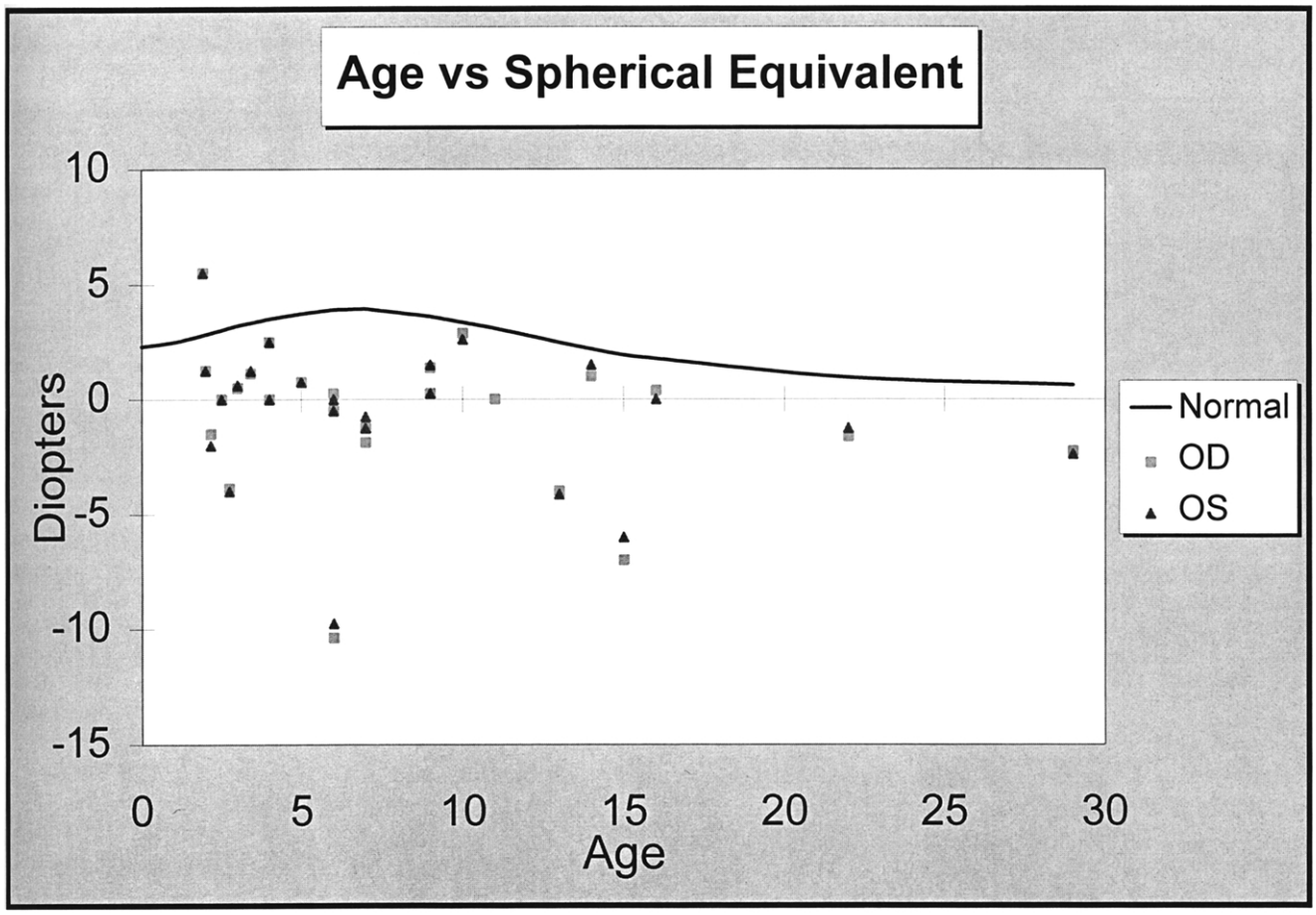

Figure 3. Spherical equivalent versus age in Smith-Magenis syndrome. The normal value was derived from age-adjusted spherical equivalents of healthy individuals.[25] The spherical equivalents of each subject with Smith-Magenis syndrome are plotted.

aracts, or microphthalmia.[18,21–24] While one individual in our series had colobomatous microphthalmos of each eye, none had lenticular opacities or glaucoma. De Almeida et al[8] described a 3-year-old boy with bilateral "cataracts." In the report of Finucane et al,[11] two individuals had unilateral "cataracts" and two had bilateral "cataracts." Both their subjects with unilateral cataract had undergone retinal detachment repair in the same eye. One individual with bilateral cataracts had bilateral retinal detachments; one eye was repaired. Another subject with bilateral cataracts was 50 years of age at the time of examination. No report details the location, distribution, and anatomic type of these lens opacities. Because the temporal relation among the cataracts, the retinal detachments, and their repair cannot be delineated from these reports, the causal association between SMS and cataracts cannot be assessed retrospectively and is not supported by any findings in our subjects.

We cannot support any inference of an association of retinal detachment with SMS from our observations of these 28 individuals. No subject in this series had high-risk characteristics for retinal detachment such as lattice degeneration, retinal tears or holes, dialyses, or unusual vitreous syneresis, and none had evidence of either rhegmatogenous or exudative retinal detachment. Similarly, and unlike the series by Finucane et al,[11] the overwhelming majority of our subjects was not institutionalized and none was selected for this series by any ophthalmic symptoms or signs.

In three prior reports, authors have noted myopia in patients with SMS.[5,9,11] Patil and Bartley[5] reported a 4-year-old girl with SMS and myopia (refraction not given) who received a diagnosis by conventional cytogenetics. de Rijk-van Andel et al[9] described an 18-month-old boy with refractive errors (spherical equivalents) of −8.5 D in the right eye and −6.5 D in the left eye. Finucane et al[11] documented that eight of ten individuals (2 did not undergo refraction) had spherical equivalents ranging from −1.75 to −22.0 D. However, their patients were selected by myopic refractive error for cytogenetic evaluation, not by independent clinical features or by the cytogenetic diagnosis of SMS.

In contrast to these several reports of high myopia in SMS, 54% (14/26) of our (refracted) subjects were hypermetropic. Because the average refractive error in healthy individuals varies with age,[14,25,26] we considered the age-adjusted refractive error and the absolute refractive error in each subject. Our subjects were relatively myopic com-

pared with the age-adjusted refractive error. However, only five subjects had more than 4 D of myopia than the age-adjusted standard (Table 1; Fig 3).

Compatible with prior reports, strabismus was observed in 32% of this series. All prior reports describe individuals with strabismus, although the type of deviation is not always defined (Table 2). Strabismus is found in 2% to 5% of preschool children of the general population.[27] It is unclear why subjects with SMS have a higher frequency of strabismus. It is unlikely that the mild facial and orbital dysmorphism contributes any mechanical cause as observed in craniofacial syndromes such as Apert and Crouzon syndromes.[28] The mental retardation and developmental delay in SMS might limit sensory fusion mechanisms and result in the higher prevalence of ocular misalignment. No consistent or predictable pattern of strabismus was found, although the majority seemed to have infantile esotropia.

In three previous reports, authors describe "apparent telecanthus" or hypertelorism (without measurements).[4,8,9] Although the facial dimensions of our subjects fell within the normal range for their ages, 7 of 17 persons had intermedial canthal distances and interpupillary distance above the 75th centile. This might give the appearance of telecanthus, which is not confirmed by measurement.

Smith et al[4] mentioned one subject with ptosis and another with optic nerve hypoplasia. None of our subjects had lid asymmetry or abnormalities. One subject had mild optic nerve dysplasia without functional limitations. We did note one subject with peripapillary myelinated retinal nerve fibers in one eye, which occurs in less than 1% of the general population and therefore is probably coincidental in this setting.[29]

This series of 28 subjects with SMS, confirmed by cytogenetic analysis, is the largest single-center study to include a detailed ophthalmic evaluation. As in prior reports, we observed iris anomalies and strabismus. Microcornea in subjects with SMS has not been described previously. The absolute refractive error was hypermetropic in half of individuals. Overall, however, the refractive errors are moderately myopic compared with age-adjusted standards. No subject had cataract, ptosis, or retinal pathology.

The variability of these findings in different subjects may reflect the variability of phenotypic expression of the deletions of chromosome 17p11.2.[2] This study represents a step toward phenotype/genotype correlations for the genes important for ocular development that may map within the SMS critical interval. The new recognition of subtle iris anomalies and microcornea should foment further inquiry about the appearance of ocular anomalies in smaller chromosomal deletions. Because half of our population with SMS has microcornea, and because isolated microcornea usually is transmitted as an autosomal-dominant trait, it is possible that a candidate gene for this anomaly lies within the SMS common deletion interval but outside the minimal SMS critical region defined by cases 540 and 641. As more individuals with this syndrome are recognized and assessed in detail, it should become more evident which findings truly are associated with this entity and which are incidental. We recommend that all individuals with SMS be evaluated thoroughly by an ophthalmologist, with special attention to strabismus, microcornea, iris anomalies, and refractive errors.

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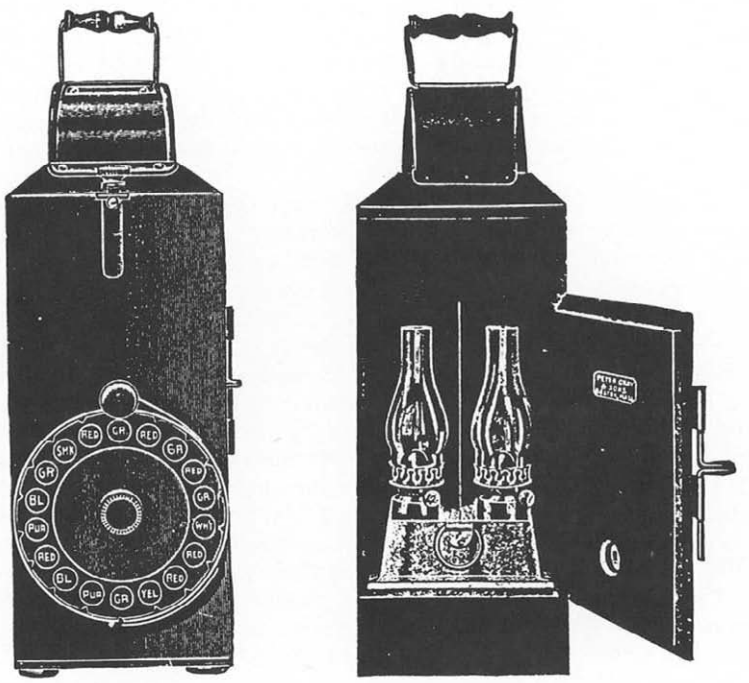

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