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Refractive Errors and Strabismus in Children With Tuberous Sclerosis: A Controlled Study

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Abstract

Purpose—To evaluate the prevalence of refractive errors and strabismus in children with tuberous sclerosis and in control subjects.

Methods—Twenty-three children with tuberous sclerosis and 151 control subjects were evaluated. All children underwent cycloplegic autorefraction or retinoscopy, slit-lamp biomicroscopy, and dilated fundus examination. Ocular alignment was assessed by the Hirschberg, Krimsky, or prism cover test.

Results—The total prevalence of hypermetropia and amblyopia was significantly higher in patients with tuberous sclerosis ($p = .035$) than in the control subjects ($p = .002$).

Conclusion—A high prevalence of hypermetropia seems to be an additional feature of tuberous sclerosis. Early screening for this amblyogenic factor is indicated in patients with tuberous sclerosis.

INTRODUCTION

Tuberous sclerosis (TSC) is a rare genetic disease characterized by benign tumors in the brain and other vital organs, such as the kidneys, heart, eyes, lungs, and skin. It commonly affects the central nervous system.¹ Other common symptoms include seizures, intellectual disability, behavior problems, and skin abnormalities.¹ Patients with TSC have no known predilection for refractive errors.

Intellectual disability is frequent in patients with TSC. Individuals with intellectual disability may have difficulty reporting their visual problems and, when they are not treated, these problems may lead to amblyopia. This study was performed to evaluate the prevalence of refractive errors and strabismus in children with TSC and control subjects of similar age and socioeconomic background.

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PATIENTS AND METHODS

The study sample included the 23 recorded consecutive patients with TSC who were treated in the pediatric neurology department of Diskapi Children's Hospital applying for routine annual examination. The study group included patients who had TSC with or without ocular complaints. The control subjects consisted of 151 children of average intelligence who were consecutively seen at the child psychiatry outpatient clinic. The control subjects were also formally assessed. All had intelligence quotient (IQ) scores higher than 80, without any known neurologic or medical disorders primarily related to ocular functioning. The study subjects and control subjects were of similar age and socioeconomic background. The study subjects also underwent standardized formal IQ tests in the child psychiatry department that included the Stanford-Binet Intelligence Scale or the Wechsler Intelligence Scale for Children, Revised, as appropriate to the child's developmental level. The study was approved by the institutional ethics board, and all participating families gave oral informed consent.

All of the children underwent cycloplegic autorefraction (with cyclopentolate) or retinoscopy, slit-lamp biomicroscopy, and detailed dilated fundus examination. Ocular movements were evaluated and ocular alignment was assessed by Hirschberg, Krimsky, or prism cover test. Visual acuity testing with a Snellen chart and intraocular pressure measurement were performed in cooperating children. Myopia was defined as spherical equivalent refraction of at least -0.50 diopters (D), hyperopia as spherical equivalent refraction of at least $+4.00$ D, astigmatism as cylinder power of at least 1.00 D, and anisometropia as spherical equivalent difference of at least 2.00 D between the two eyes of the same child.² The prevalence of refractive errors and strabismus was compared between the TSC and control groups.

The chi-square test was used to compare categorical variables; analysis of variance was used to compare continuous variables. A *P* value of less than .05 was considered significant. The SPSS 13.0 statistical program was used for all analysis (SPSS, Inc., Chicago, IL).

RESULTS

The study group consisted of 23 children (8 boys and 15 girls; mean $\pm$ standard deviation 10.6 ± 2.7 years; age range: 3 to 16 years) and the control group consisted of 151 children (109 boys and 42 girls; mean $\pm$ standard deviation 8.9 ± 2.4 years; age range: 3 to 15 years). Although the age distribution was similar ($F = 1.8$, $P = .14$), there was a significant difference in gender between the groups (chi-square = 12.7, $P = .001$).

All of the children in the control group had IQ scores higher than 80, whereas 91.3% of patients with TSC (21 of 23) had intellectual disability. Of patients with TSC, 60.9% (14 of 23) had mild intellectual disability (IQ: 50 to 69), 26.0% (6 of 23) had moderate intellectual disability (IQ: 35 to 49), and 4.3% (1 of 23) had severe intellectual disability (IQ < 35). Only two children with TSC (8.7%) had IQ scores higher than 80.

Of patients with TSC, 78.2% had ocular findings (18 of 23) compared with 42.4% (64 of 151) of control subjects. The total prevalence of any ocular finding (strabismus, congenital

cataract, or retinal findings, such as tilted disc hypertensive retinopathy) or refractive error was significantly higher in patients with TSC (chi-square = 12.9, $P = .001$).

The prevalence of hypermetropia was 13.0% (3 of 23) in the TSC group and 2.0% (3 of 151) in the control group, which was significantly higher in patients with TSC (chi-square = 6.9, $P = .035$).

The prevalence of any additional ocular finding was significantly higher in the TSC group. Additional ocular findings, including unilateral congenital cataract, bilateral tilted disc, and hypertensive retinopathy, were noted ($n = 3$, 10.8%) in the TSC group. These conditions were not detected in any of the control subjects (chi-square = 13.6, $P = .007$).

Myopia was more common in the control group. None of the patients with TSC and 17.2% of the control subjects had myopia (chi-square = 4.7, $P = .027$).

The prevalence of astigmatism, anisometropia, and strabismus was similar in both groups. Astigmatism was found in 43.4% of patients with TSC and 25.2% of control subjects (chi-square = 3.4, $P = .08$). Anisometropia was noted in 8.7% of patients with TSC and 4.0% of control subjects (chi-square = 1.0, $P = .286$). None of the patients with TSC and 1.3% of the control subjects had strabismus (chi-square = 0.31, $P = .99$).

Visual acuity could be assessed properly in 10 of the patients with TSC. The remaining patients with TSC could not cooperate with visual acuity testing because of intellectual disability. Three of these 10 patients with TSC (30%) had amblyopia compared with 2 of the control subjects (1.3%). The prevalence of amblyopia was significantly higher in the TSC group (chi-square = 25.63, $P = .002$).

The prevalence of ocular findings and refractive errors in both groups is summarized in the table.

DISCUSSION

Tuberous sclerosis is caused by defects, or mutations, of two genes, TSC1 and TSC2.³ Mutation of one of these genes leads to TSC.³ TSC can affect any or all systems of the body, causing a variety of signs and symptoms. In addition to the benign tumors that frequently occur with TSC, other common symptoms include seizures, intellectual disability, behavior problems, and skin abnormalities.³

There are no pathognomonic clinical signs of TSC. A combination of signs, classified as major or minor, is required to establish a clinical diagnosis.⁴ Major features include facial angiofibromas or forehead plaque, nontraumatic ungual or periungual fibroma, more than three hypomelanotic nodules, shagreen patch (connective tissue nevus), cortical fiber in the brain, subependymal nodule in the brain, subependymal giant cell astrocytoma in the brain, multiple retinal nodular hamartomas, cardiac rhabdomyoma, lymphangioleiomyomatosis in the lungs, and renal angiomyolipoma. Minor features include multiple randomly distributed pits in the dental enamel, hamartomatous rectal polyps, bone cysts, cerebral white matter "migration tracts," gingival fibromas, nonrenal hamartoma, skin lesions, a retinal achromic

patch, and multiple renal cysts. A definite diagnosis of TSC is established in the presence of either two major features or one major feature plus two minor features. One major feature plus one minor feature leads to a probable diagnosis. Either one major feature or two or more minor features leads to the suspicion of TSC.^{4,5}

Astrocytic retinal hamartomas are the main ocular finding in TSC.^{4,5} Angiofibromas of the eye-lids, colobomas, hamartomas of the iris and ciliary epithelium, cataracts, retinal angiomas, persistent pupillary membranes, papilledema, band-shaped keratitis, and pigmentary retinopathy have also been reported in TSC.^{6–10}

To the authors' knowledge, this is the first study comparing the prevalence of refractive errors and strabismus in children with TSC and control subjects of similar age and socioeconomic background. The authors documented that the total prevalence of any ocular finding or refractive error and the prevalence of hypermetropia were significantly higher in patients with TSC, whereas the prevalence of astigmatism, myopia, anisometropia, strabismus, and additional ocular findings was similar. The prevalence of hypermetropia varies in different populations: 21% in children 6 to 18 years old in Poland,¹¹ 1.0% in children 13 to 16 years old in China,¹² and 12.8% in children 5 to 17 years old in the United States.¹³ The current study showed a similar overall rate of hypermetropia (15.9%) in the control group.

Rowley et al.¹⁴ evaluated the ocular manifestations of TSC and reported that 27% of eyes were myopic, 22% were hypermetropic, and 27% had astigmatism of greater than 0.75 D. In the absence of a control group, they compared their findings with the results of previous studies of similarly aged children without TSC and reported that the prevalence of refractive errors in patients with TSC was similar to that of children of similar age without TSC.

A high prevalence of hyperopia seems to be an additional feature of TSC. Early screening for this amblyogenic factor is indicated in patients with TSC.

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TABLE

Prevalence of Ocular Findings and Refractive Errors in the Study Group

Ocular Findings	TSC Group (n = 23)	Control (n = 151)	Chi-square (df = 2)	p
Strabismus	0	2 (1.3%)	0.31	.99
Hypermetropia	3 (13.0%)	24 (15.9%)	6.9	.035
Astigmatism	10 (43.5%)	38 (25.2%)	3.4	.08
Myopia	0	26 (17.2%)	4.7	.027
Anisometropia	2 (8.7%)	6 (4.0%)	1.0	.286
Additional ocular findings (cataract retinal findings)	3 (10.8%)	0	13.6	.007
Any ocular finding	18 (78.2%)	64 (42.4%)	12.9	.001

TSC = tuberous sclerosis.