Ophthalmic manifestations of tetrasomy 18p

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PURPOSE: To characterize ophthalmic findings in patients with tetrasomy 18p, a rare chromosomal anomaly that has been previously associated with strabismus.

METHODS: All subjects underwent a complete eye examination to screen for ocular pathology.

RESULTS: A total of 25 subjects (13 female) were examined after they were diagnosed with tetrasomy 18p. The average age of subjects was 8.2 years (range, 13 months to 22 years). Of the 25 subjects, 18 (72% of examined subjects, 42% of the cohort) showed evidence of strabismus; 16 had esotropia (8 uncategorized, 5 infantile, and 3 accommodative), 1 had esophoria, and 1 was diagnosed with intermittent exotropia.

CONCLUSIONS: The coincidence of esotropia with tetrasomy 18p indicates the need to routinely screen these patients for strabismus at the time of diagnosis. (J AAPOS 2011;15:268-271)

Tetrasomy 18p is a rare chromosomal anomaly that is thought to occur in approximately 1 in 140,000 live births.1 The first description of the associated syndrome was published by Froland and colleagues2 in 1963. The cytogenetic sine qua non of this condition is the presence of a supernumerary isochromosome (a chromosome with 2 identical arms) of 18p and consequently a total of 4 copies of the short arm of chromosome 18 (Figure 1). Because the short arm of chromosome 18 harbors approximately 60 known genes, the genesis of the associated tetrasomy 18p syndrome is complex. Individuals with this condition are usually ascertained through a routine chromosome analysis as a part of an evaluation for developmental delay.

Most of the current literature on tetrasomy 18p consists of isolated case reports and small case series. The manifestations of the syndrome are well defined in infants, and cardinal features include developmental delay, microcephaly, muscle tone abnormalities, low-set ears, high arched palate, and various genitourinary anomalies.3 In contrast with Edwards syndrome (trisomy 18), patients with tetrasomy 18p generally do not have major congenital cardiopulmonary defects that require intervention, and long-term survival seems to be the rule. A variety of ophthalmic findings have also been reported, including epicanthal folds, short palpebral fissures, strabismus, and hypertelorism.3-11 This is the first comprehensive description of ophthalmic findings in a large series of patients with tetrasomy 18p.

Subjects and Methods

The ophthalmologic evaluation was performed as a component of a comprehensive evaluation of individuals with tetrasomy 18p through the Chromosome 18 Clinical Research Center at the University of Texas Health Science Center at San Antonio; the results of the comprehensive study have been previously published.12 This protocol was overseen by the Institutional Review Board of the University of Texas Health Science Center, San Antonio. Informed consent from subjects or their legal guardians was obtained.

Inclusion in the study required that the subjects have been diagnosed with tetrasomy 18p by standard cytogenetic analysis, which detects changes in chromosome number and in gross chromosome morphology. Fluorescence in situ hybridization was performed for all cases to confirm the clinical diagnosis. To define the abnormal chromosome content at the molecular level, the DNA from all subjects was analyzed with the use of microarray comparative genomic hybridization. Eye examinations included, where possible, a focused history, assessment of best-corrected visual acuity and ocular motility, dilated fundus examination, and cycloplegic refraction, depending on the subject’s abilities. Magnetic resonance imaging of the brain was performed as a component of the comprehensive systemic evaluation.

Results

Of the 43 subjects recruited as part of the comprehensive protocol, a total of 25 subjects (13 females; 52%) were evaluated by the ophthalmology service; not all patients in the comprehensive protocol were evaluated by the
ophthalmology service as the result of logistical and scheduling issues. The results are summarized in Table 1 (see also e-Supplement 1, available at jaapos.org). (Subject numbers in the table and text correspond to the subject numbers from the comprehensive tetrasomy 18p manuscript.)

The average subject age was 8.2 years (range, 13 months to 22 years). Two subjects (8 and 32) were diagnosed with variants of tetrasomy 18p. Subject 8 was confirmed to be mosaic for tetrasomy 18p, as originally identified in the karyotype from blood. Subject 32 was diagnosed with a variant isochromosome 18p, which included a duplication of a small part of the proximal long arm from the centromere to 18,536,308 million bases (Mb) (18q11.2). This created a region that was trisomic in addition to the entire short arms that were present in four copies. These patients were excluded from our statistical analysis, although the authors have included their clinical information because it reflects the genotypic and phenotypic variability that is observed with the tetrasomy 18p spectrum of chromosomal anomalies.

The majority of subjects (18/23; 78.2%) demonstrated some evidence of strabismus (Figure 2). Esotropia was most common (16/23; 69.5%). The precise classification of esotropia could not be determined in 3 of the 16 subjects (50%) on the basis of examination and history; 5 (31.3%) demonstrated infantile esotropia, and 3 (19%) accommodative esotropia. Nine of the 23 subjects had esodeviations >15°; 1 subject demonstrated an esophoria, and 1 subject was found to have an intermittent exotropia (Figure 3). Dissociated vertical deviation was observed in 4 of the 23 subjects (17.4%). Seven subjects had undergone previous strabismus surgery.

Only 2 subjects (9%) were diagnosed with amblyopia. Subject 41 had a history of unilateral nasolacrimal duct obstruction that failed to resolve with 2 attempts of probing and irrigation. Subject 42 showed 2 clock hours of supero-temporal iris atrophy in both eyes. Torticollis of nonocular origin was diagnosed in 1 subject. Only 4 subjects (17%) were found to have a normal eye examination for their age. Of note, there were no abnormalities of the lens or retina observed in any subject.

Refractive errors were common, with 1 subjects (4%) displaying high hyperopia (>+5.00 D) in at least one eye and 2 (9%) subjects presenting with high myopia (>−5.00D). Many of the subjects in the study had lower degrees of hyperopia in at least 1 eye.

Magnetic resonance imaging of the brain was performed on 8 of the 25 subjects (32%). The remaining patients were either not sufficiently sedated for the examination according to the approved chloral hydrate protocol or the family declined the examination. Four subjects (8, 26, 30, and 38) demonstrated no abnormality. Subject 3 showed mild dilation of the left lateral ventricle. Subject 42 showed a possible delay in myelination of white matter within the forceps major (posterior white matter tracts connecting the occipital lobes via the splenium of the corpus callosum). Subject 44 showed the presence of a cerebrospinal fluid shunt but otherwise had a structurally normal brain. Subject 2 was noted to have a small corpus callosum and a relative increase in extra-axial fluid spaces, which is suggestive of atrophy or hypoplasia.

**Table 1. Subject data**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Number of subjects, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strabismus</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Uncategorized ET</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Infantile ET</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Accomodative ET</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Esophoria</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>Intermittent XT</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>DVD</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>2 (9)</td>
</tr>
<tr>
<td>NLDO</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Iris atrophy</td>
<td>1 (4)</td>
</tr>
<tr>
<td>High hyperopia (&gt; +5.00)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Moderate hyperopia (+0.25 to +5.00)</td>
<td>16 (70)</td>
</tr>
<tr>
<td>High myopia (&gt; −5.00)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Moderate myopia (−0.25 to −5.00)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>10 (43)</td>
</tr>
<tr>
<td>Normal eye examination</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

*D, dissociated vertical deviation; ET, esotropia; NLDO, nasolacrimal duct obstruction; XT, esotropia.*

**Discussion**

Most of the subjects in the present study demonstrated some form of clinically significant ophthalmic pathology. In light of this and the generally good long-term prognosis for survival, the authors recommend that all patients with tetrasomy 18p undergo a screening examination by an ophthalmologist skilled in the diagnosis and management of strabismus at the time of diagnosis. Because of the developmental disabilities frequently encountered in this population, optimizing visual function is important to ensure that these patients achieve their full social and developmental potential. Although amblyopia was relatively uncommon in this series, it remains a potential comorbidity for this cohort, given the frequency of strabismus.

Other chromosomal anomalies, such as Down syndrome and chromosome 22q11.2 deletion (DiGeorge/velocardiofacial spectrum disorders), are also known to carry a risk of...
strabismus (20% with Down syndrome and 18% with DiGeorge/velocardiofacial spectrum disorders), but the proportion of patients with esotropia appears to be much higher with tetrasomy 18p, ranging from 46% (19/41) to 83% (19/23) based on our results.13,14 There are likely genes on 18p whose products are dosage sensitive. This means that a change in gene copy number alters the amount of gene product, thereby changing the stoichiometry of a molecular interaction or the dynamics of a rate limiting step.15 This could result in structural or functional neurological anomalies at a cellular level that interfere with the development of stereopsis, accommodation, and fusional mechanisms. Further investigation is necessary to more fully elucidate the correlation between tetrasomy 18p and esotropic strabismus.

Literature Search

MEDLINE was searched via OVID (1963 to the present) using the following terms: tetrasomy, 18p, and isochromosome 18p. Additional papers of interest were identified through examination of the references retrieved from this search. The Online Mendelian Inheritance in Man (OMIM) was also searched: there is currently no OMIM number for this condition.

Acknowledgments

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References


First Person

“My new patient questionnaire includes a section asking where the child attends day care, pre-K, and/or school. The very next question asks “Grade in school,” to which one parent wrote “C+”!

—Steven E. Rubin, MD