Autosomal-Dominant Inheritance
of Isolated Comitant Exotropia

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Abstract

Family studies suggest that there is a strong genetic component to the etiology of comitant strabismus. Seven cases of a family in three consecutive generations found to have isolated comitant exotropia. This pattern of inheritance is highly suggestive of an autosomal-dominant mode with complete penetrance which is an unreported finding in this entity.

Keywords: Isolated Comitant Exotropia, Strabismus, Inheritance, Squint

Introduction

Strabismus (squint) is the misalignment of both eyes which is classified largely into paralytic and non-paralytic (comitant) types. Comitant strabismus is characterized by angle of deviation (magnitude of ocular misalignment) that remains the same in all directions of gaze, and with fixation with either eye. Comitant strabismus is one of the most common problems in pediatric ophthalmology, affecting 3 to 5% of children.1 Epidemiologic studies on twins have revealed the hereditary background for comitant strabismus.2-7 Heredity plays a significant role in comitant exodeviations, but the genetics of the disorder is probably multi factorial. A positive family history is often elicited. If one sibling from a multiple birth is affected, the chance of exotropia is increased by 17 folds. No such association is found for siblings from separate births.8

Although the role of heredity in comitant exotropia has been established, but no specific inheritance pattern has been found for comitant exotropia.

Case Report

A 45-year old man with three of his children referred to our clinic due to squint. Complete ophthalmic examination was performed including best corrected visual acuity (BCVA), cycloplegic refraction (CR), eye motility examination, prism cover testing (for measurement of eye deviation in nine cardinal positions and near versus far), slit lamp examination and fundoscopy. They all found to have comitant exotropia with alternating fixation. The diagnosis of isolated comitant exotropia was based on results of prism cover testing and ductions, in addition to the absence of other ocular or systemic diseases. We subsequently performed a complete ophthalmic examination on all available family members to determine the inheritance pattern.
Results
Six cases of family including three out of four siblings, the father, one out of two paternal aunts, and one out of four paternal uncles were all found to have isolated comitant exotropia. The paternal grandfather was not alive but we discovered from old photograph that he had constant exotropia and history of squint similar to other family members (Figure 1). Four out of seven patients were female (57%). There was no limitation of motion in any of nine cardinal positions. The exotropia had no pattern and the near versus far deviations were the same in all patients. BCVA was $20/20$ in all cases. Complete ophthalmic examination was done and there was no significant refractive error (>1 diopter) or other ocular abnormality. Also, there was no associated systemic disease. The pedigree of the family and photographs from affected members are presented in figure 1 and a summary of patients' data is presented in table 1. The data related to prior generations was doubtful and inconclusive.

Figure 1. The comitant exotropia in three consecutive generations that was highly suggestive for autosomal-dominant pattern with full penetrance (A) with corresponding photographs (B), top corresponds for 1, middle for 2, and bottom for 3 in the pedigree.
Table 1. Summary of patients’ data

<table>
<thead>
<tr>
<th>Family member</th>
<th>Age</th>
<th>BCVA</th>
<th>CR</th>
<th>Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grandfather*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Father</td>
<td>45 years</td>
<td>OD: 20/20</td>
<td>OS: -0.50 D</td>
<td>Near: 45 PD</td>
</tr>
<tr>
<td>Son</td>
<td>9 years</td>
<td>OD: 20/20</td>
<td>OS: 0.00 D</td>
<td>Near: 35 PD</td>
</tr>
<tr>
<td>Daughter</td>
<td>12 years</td>
<td>OD: 20/20</td>
<td>OS: 0.00 D</td>
<td>Near: 30 PD</td>
</tr>
<tr>
<td>Daughter</td>
<td>8 years</td>
<td>OD: 20/20</td>
<td>OS: +0.25 D</td>
<td>Near: 20 PD</td>
</tr>
<tr>
<td>Uncle</td>
<td>38 years</td>
<td>OD: 20/20</td>
<td>OS: -1.00 D</td>
<td>Near: 40 PD</td>
</tr>
<tr>
<td>Aunt</td>
<td>27 years</td>
<td>OD: 20/20</td>
<td>OS: 0.00 D</td>
<td>Near: 20 PD</td>
</tr>
</tbody>
</table>

BCVA: Best corrected visual acuity; CR: Cycloplegic refraction in spherical equivalent; D: Dioptr; OD: Right eye; OS: Left eye; PD: Prism diopters

* The grandfather was not alive at the time of study and there was no documented data about his ophthalmic examination.

Discussion

The familial nature of isolated or nonsyndromic strabismus has been recognized in the medical literature since Hippocrates. Cantalino and Von Noorden in 1969 reported that there may be a hereditary component to microtropia, the minor form of strabismus. Richter (1967) found lower risk in first degree relatives of a proband with divergent strabismus than with convergent strabismus. When 2 first-degree relatives were affected, the risk was about 1 in 4 and 1 in 2 for the two forms; respectively. Data compiled from multiple studies indicated that 73% of monozygotic twin pairs and 35% of dizygotic twin pairs were concordant for strabismus. Ocular alignment relies on complex sensory and motor pathways in the retina, thalamus, visual cortex, and brain stem. Also, it depends on the proper development and functioning of the extraocular muscles and orbit, suggesting that a multiplicity of components and perhaps gene loci are involved in the development of the disorder.

Family studies suggest that there is a strong genetic component to the etiology of comitant strabismus, with approximately 30% of probands with strabismus having a family member or close relative with strabismus. In a large family with nonsyndromic strabismus, Parikh et al (2003) found linkage of a presumptive strabismus susceptibility locus to chromosome 7p22.1 under a model of recessive inheritance. In 6 other multiplex families, linkage to 7p was not observed, consistent with genetic heterogeneity.

Conclusive evidence of autosomal-dominant inheritance requires demonstration of the disease in at least three successive generations. Transmission of the disorder from male to male with both sexes showing the typical disease in equal proportions must also occur. In autosomal-dominant inheritance with complete penetrance, affected persons transmit the trait to 50% of their offspring on average; and unaffected persons do not transmit the trait to their children.

In our presentation the disease presented in three successive generations; the female/male ratio was 1.33; the average of the offspring involvement in two generations was 50%; and it also fill other criteria mentioned above; so the inheritance pattern of case series in this presentation is autosomal-dominant with complete penetrance.

Although genetic predisposition is now established as an important risk factor for comitant exotropia but autosomal-dominant pattern with complete penetrance is one of the unreported findings in isolated comitant exotropia. We are unaware of the previous reports of this finding and could not find any reference to it in a computerized search utilizing PubMed and OMIM (Online Mendelian Inheritance in Men).
Conclusion

In conclusion, the occurrence of genetic transmission by an autosomal-dominant mode should be considered in patients with comitant exotropia.

References