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Ocular findings associated with chromosome 22q11.2 duplication

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We describe the ocular features of the chromosome 22q11.2 duplication syndrome and provide ophthalmologic examination recommendations for affected patients. The medical records of 19 children with chromosome 22q11.2 duplication who had undergone complete ophthalmological examination, including dilated fundus examination and cycloplegic refraction, were studied retrospectively. Over half of the children with 22q11.2 duplication syndrome were found to have visually significant ocular abnormalities, including 6 with strabismus, 2 with moderately high astigmatism requiring glasses, 1 with unilateral congenital cataract requiring surgery, 1 with optic disk drusen, 1 with bilateral megalocornea with normal eye pressures, 1 with nystagmus that resolved spontaneously, and 1 with delayed visual maturation. Because of the high incidence of conditions that could affect visual development, we recommend that children with 22q11.2 duplication syndrome have a complete ophthalmological examination on diagnosis and regular vision screenings by their primary care physician thereafter.

The chromosome 22q11.2 region is susceptible to nonallelic homologous recombination events.[1] Resultant disorders include the 22q11.2 deletion syndrome (22q11.2DS), which encompasses the entities formerly known as DiGeorge syndrome and velocardiofacial syndrome. Over 90% of 22q11.2DS patients have the same-sized 3 million base deletion, which results in haploinsufficiency of approximately 50 genes.[1] The 22q11.2DS is characterized by a typical facial appearance, submucousal cleft palate, and cardiovascular malformations as well as immune and endocrine conditions. Most patients have learning disabilities; some have major psychiatric illness. 22q11.2DS was recently reported to occur in 1/992 unselected pregnancies.[2]

Interchromosomal, nonallelic homologous rearrangements lead to a 22q11.2 deletion or reciprocal duplication in germ cells. Because this mechanism may lead to a duplication of the

same 22q11.2 region that is deleted, it is not surprising that individuals would eventually be found that carry 22q11.2 duplication. The first family with reciprocal 22q11.2 duplication was identified by interphase FISH testing.[3] Additional affected individuals have been identified.[4] The main clinical findings include mild but different craniofacial anomalies from 22q11.2Del, similar types of congenital heart disease, and cognitive deficits—all occurring with variable expressivity.[3-6] In contrast to individuals that carry the typical 3 Mb deletion, patients with duplication exhibit reduced penetrance and frequently inheritance. With widespread usage of clinical microarray comparative genome hybridization testing, 22q11.2 duplications are increasingly being identified in subjects with idiopathic developmental delay or other medical findings. The 22q11.2 duplication syndrome (22q11.2DupS) affects similar structures as for 22q11.2DS, although it is unknown whether identical genes are involved in its pathogenesis. It too is common, having been identified in 1 out of 850 unselected pregnancies, making it a potentially important condition for ophthalmic health care providers.[4] Because 22q11DS has visually significant associated ocular abnormalities, this study sought to describe the ophthalmological findings of children with 22q11.2DupS, hypothesizing that children with this duplication would also have visually significant findings potentially requiring management by an ophthalmologist.[7,8]

Subjects and Methods

The study was approved by the Institutional Review Board of the Children's Hospital of Philadelphia. Study data were handled in compliance with the US Health Insurance Portability and Accountability Act of 1996. The medical records of children with 22q11.2DupS seen at the Children's Hospital of Philadelphia between 2006 and 2015 were retrospectively reviewed.

Eligible children had a diagnosis of the 22q11.2DupS confirmed by chromosomal

microarray, obtained because of autism, cardiac defects, or clinical suspicion. They were referred for ophthalmological evaluation by the 22q and You Center at the Children's Hospital of Philadelphia for an eye examination based solely on the genetic diagnosis. All children were evaluated by a pediatric ophthalmologist to assess visual function; ocular motility and alignment; pupillary, anterior segment, and posterior segment examinations, which included indirect ophthalmoscopic dilated fundus examination; and cycloplegic refraction with retinoscopy or subjective refraction after cycloplegia with cyclopentolate 1% and tropicamide 1% eyedrops.

Results

A total of 19 children (12 boys) with 22q11.2DupS were included. Mean age at initial examination was 7.3 years (range, 1 to 16 years). Twelve (63%) children had ocular abnormalities (Table 1). Six (32%) children had strabismus, including 1 each with bilateral inferior oblique overaction, infantile esotropia, and an alternating nonaccommodative esotropia, all requiring surgery. One child had accommodative esotropia, treated with glasses; and 2 children with alternating intermittent exotropias, not requiring surgery. Two children had moderately high astigmatism (> +1.50 D), requiring spectacle correction. Five children had hyperopia of >2 D, 2 of whom were treated with glasses, and 1 child was treated with glasses for myopia. Finally, there was 1 child with each of the following findings: unilateral congenital cataract requiring surgery, pseudopapilloedema due to optic disk drusen, bilateral megalocornea with normal intraocular pressures, nystagmus that resolved without intervention; and delayed visual maturation. Seven children (37%) had a normal eye examination, of which 2 (11%) had prominent epicanthal folds that gave the appearance of a visually nonsignificant pseudostrabismus.

Discussion

In this series of 22q11.DupS, the largest reported to date, we found that over half of children have visually significant ocular abnormalities. For example, one-third of the children had strabismus, compared with only 2%-3% of the general population. One observed finding not previously reported in association with 22q11.2DupS was nystagmus, which occurs in 0.35% of the general population. Most of the children with 22q11.2DupS had small refractive errors not requiring glasses. However, 2 patients had a significant amount of astigmatism, consistent with the prevalence of 15.1% for American children 7-15 years of age.

Previous studies of ophthalmological findings in 22q11.2DupS patients reported a high prevalence of some features that we did not commonly observe, such as prominent epicanthal folds (42%), ptosis (25%), and down-slanting palpebral fissures.[9] A report of 2 patients with 22q11.2DupS was noted an association with the congenital cranial dysinnervation disorders of Marcus Gunn jaw-winking ptosis and Duane retraction syndrome as well as primary infantile glaucoma and retinal vascular tortuousity.[10] Of note, retinal vascular tortuosity is present in half of patients with 22q11.2DS and it is much higher than in the general population. Perhaps our cohort of patients had less externally apparent ocular pathology than these prior reports, because the children in our study were referred for a baseline eye examination as opposed to having been referred to an eye hospital for management of noted ocular pathology.

Based on our and previously reported study findings, we recommend that children with 22q11.2DupS have a complete ophthalmological examination on diagnosis and thereafter regular vision screenings by their primary care physicians in order to identify conditions that might affect visual development. Conversely, knowledge of these ocular findings, together with developmental, neuromuscular, and other systemic findings, might alert treating physicians to consider the possibility of 22q11.2DupS as an underlying unifying diagnosis and referral for

genetic testing and systemic management.

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Table 1. Ocular findings in 19 children with 22q11.2 duplication syndrome

Ocular abnormality	No. patients (%)
Strabismus	6 (32)
Bilateral IO overaction	1 (5)
Infantile ET	1 (5)
Nonaccommodative ET	1 (5)
Accommodative ET	1 (5)
Intermittent XT	2 (11)
Strabismus surgery	3 (16)
Nystagmus	1 (5)
Congenital cataract	1 (5)
Optic disk drusen	1 (5)
Megalocornea	1 (5)
Astigmatism ≥1.50 D	2 (11)
Any ocular abnormality	12 (63)

D, diopter; *ET*, esotropia; *IO*, inferior oblique; *XT*, exotropia.