Ophthalmologic disorders and risk factors in children with autism spectrum disorder

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PURPOSE To report the results of our review of all children with autism spectrum disorder (ASD) who underwent complete pediatric ophthalmologic examination at our institution over a 10-year period.

METHODS The medical records of all children (0-17 years of age) with a diagnosis of ASD seen at University of California, Davis, over a 10-year period were reviewed retrospectively. Demographic data, birth history, genetic testing results, neuropsychiatric comorbidities, and ophthalmologic findings were extracted from the record. Multiple logistic regression was used to identify risk factors for ophthalmologic disorders.

RESULTS A total of 2,555 children with ASD were seen at the university over the study period, of whom 380 (15%) were evaluated in the ophthalmology clinic. Eye examination revealed an ophthalmic diagnosis in 71% of children, of which the most common were significant refractive error (42%), strabismus (32%), and amblyopia (19%). Optic neuropathy occurred in 14 children (4%). Cerebral palsy was a significant risk factor for refractive error (OR = 3.22; $P = 0.016$), strabismus (OR = 3.59; $P = 0.012$), amblyopia (OR = 3.49; $P = 0.0097$), and optic neuropathy (OR = 14.0; $P = 0.0009$).

CONCLUSIONS Ophthalmic disorders were found in 71% of children with ASD evaluated at our university-based ophthalmology clinic. The rates of significant refractive error, strabismus, amblyopia, and optic neuropathy exceeded those of the general pediatric population. ASD and cerebral palsy may have additive risk for these disorders. (J AAPOS 2019;23:337.e1-6)

Autism spectrum disorder (ASD) affects an estimated 1.68% of children in the United States and is increasing in prevalence.[1] In the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V), the diagnostic criteria for ASD include "persistent deficits in social communication and social interaction across multiple contexts."[2] Certain visual characteristics are used in the diagnosis and study of ASD. For example, abnormalities of eye contact are considered a sign of impaired social communication, and eye tracking studies, which assess the timing and location of eye gaze to social and nonsocial visual stimuli, are commonly used to assess visual attention in ASD.[2,3] However, few studies of children with ASD address ophthalmic comorbidities, which could potentially affect both eye contact and eye tracking.[4-6]

The existing data suggest that children with ASD have an increased rate of ophthalmologic disorders (range, 15%-52%), particularly refractive errors, strabismus, and amblyopia.[4-8] However, prior studies are limited by nonstandard methods of visual assessment (eg, photoscreening and autorefraction rather than pediatric ophthalmologic examination with cycloplegic refraction) and provide limited data on genetic and neuropsychiatric comorbidities.[4-8] Furthermore, these studies may underestimate rates of ophthalmologic disorders, because many children with ASD are nonverbal or have communication deficits,[2] making it difficult for them to report visual symptoms and comply with traditional vision screening, thus preventing them from being referred appropriately to pediatric ophthalmology. The purpose of this study was to report the results of our retrospective review of all children with ASD who underwent complete pediatric ophthalmologic examination at our institution over a 10-year period, resulting in the largest sample size to date on this topic. Additionally, we aimed to report genetic and neuropsychiatric comorbidities and to identify risk factors for ophthalmologic disorders in this population.

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Subjects and Methods

This study was approved by the University of California, Davis, Institutional Review Board and adhered to the tenets of the Declaration of Helsinki and the US Health Insurance Portability and Accountability Act of 1996. The medical records of all children (<18 years of age) seen at University of California, Davis, from 2007, when the electronic record was adopted at our institution, to 2017 with a diagnosis of ASD were reviewed retrospectively. ASD diagnosis was based on International Classification of Diseases (ICD) codes (ICD-9 code 299 and ICD-10 code F84.0). Patients were included if they had undergone complete pediatric ophthalmologic examination at our institution. Patients were excluded if neuropsychological testing revealed a diagnosis other than ASD.

Pediatric ophthalmologic evaluation included the following: assessment of best-corrected visual acuity by visual behavior (fix and follow or central-steady-maintained fixation of visual targets) or optotype acuity (Allen or Lea symbols, HOTV, or Snellen), based on age and developmental level; pupils; intraocular pressure by palpation or iCare tonometer (iCare Finland Oy, Vantaa, Finland); fixation preference; ductions and versions; ocular alignment assessed by Krismky or alternate cover with prism testing, based on patient cooperation; confrontational visual fields, if possible; cycloplegic refraction after instillation of cyclopentolate 1% drops; anterior segment examination; and dilated fundus examination. We extracted the following data from patients' records: age at first visit to the eye clinic; follow-up duration; sex; birth history; results of genetic testing, if available; neurologic and psychiatric comorbidities; and ophthalmic diagnoses. Birth history included weeks of gestation (prematurity was defined as ≤36 weeks), known exposure to intrauterine drugs (alcohol, tobacco, or illicit drugs), and known intrauterine infection with a teratogenic pathogen. Patients were considered to have a genetic syndrome if genetic testing results were positive for a pathogenic mutation and the patient's phenotype matched the syndrome. Patients with a genetic abnormality not known to cause a genetic syndrome were considered to have a variant of unknown significance. All patients who had genetic testing underwent genetic counseling and evaluation with a genetics specialist.

Autism spectrum disorder and other psychiatric diagnoses were made based on DSM criteria. From 2007 to 2013, DSM-IV was used; DSM-V was used after its adoption in 2013. The main difference in diagnostic criteria is that autistic disorder, Asperger disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS) were separate diagnoses in DSM-IV, but are all considered part of ASD in DSM-V.[2,9] Patients diagnosed with Asperger disorder or PDD-NOS based on DSM-IV were considered to have ASD in this study. The majority (74%) of patients in this study underwent extensive neuropsychological testing with a licensed clinical psychologist at our university's neurodevelopmental institute, MIND (Medical Investigation of Neurodevelopmental Disorders), including gold-standard ASD diagnosis with the ADOS-2 (Autism Diagnostic Observation Schedule, second edition) instrument and IQ testing. An IQ of <70 was diagnostic of intellectual disability. Patients seen at the MIND institute all underwent genetic testing. The remainder underwent neuropsychological testing outside of our institute to confirm diagnosis, but details of the testing were not available for review.

Table 1. Demographics, birth history, genetics, and neuropsychiatric comorbidities of children with autism spectrum disorder who underwent pediatric ophthalmologic evaluation (N = 380)

Patient characteristic	Results
Demographics	
Mean age at first visit (range)	5.5 years (2 months to 16 years)
Mean follow-up (range)	22 months (0-10 years)
Male, no. (%)	291 (77)
Birth history, no. (%)	
Premature (<36 weeks)	71 (19)
Known intrauterine drug exposure	21 (5.5)
Known intrauterine infection	2 (0.5)
Genetics, no. (%)	
Known genetic syndrome	47 (12)
Down syndrome	12 (4.2)
Neurofibromatosis-1	5 (1.3)
Tuberous sclerosis	5 (1.3)
VUS	14 (3.7)
Neuro-psychiatric comorbidities, no. (%)	
ADHD	125 (33)
Intellectual disability	60 (16)
Seizure disorder	47 (13)
Anxiety	42 (11)
Cerebral palsy	22 (5.8)
Tourette syndrome	16 (4.2)
Depression	7 (1.8)
OCD	6 (1.6)

ADHD, attention deficit and hyperactivity disorder; *OCD*, obsessive compulsive disorder; *VUS*, variant of unknown significance.

Refractive errors were considered significant if they met the 2017 American Academy of Ophthalmology (AAO) Preferred Practice Pattern guidelines for spectacle prescription.[10] Unilateral amblyopia was diagnosed based on an interocular visual acuity difference of at least 2 lines with the presence of one or more amblyogenic risk factors (anisometropia, strabismus, or media opacity causing visual axis obstruction). In nonverbal children, consistent fixation preference in the presence of an amblyogenic risk factor was considered diagnostic of unilateral amblyopia. Bilateral amblyopia was diagnosed when best-corrected visual acuity was subnormal in each eye (worse than 20/50 in children <48 months of age, and worse than 20/40 in older children), with bilateral evidence of visual axis obstruction or ametropia (hyperopia ≥4.00 D spherical equivalent, myopia ≥ −6.00 spherical equivalent, or astigmatism ≥2.50 D). Strabismus was defined as a manifest tropia at distance or near, or a dissociated vertical or horizontal deviation that manifested spontaneously under binocular conditions.

Data were recorded using Microsoft Excel (Redmond, WA); statistical analyses were conducted using Medcalc (Ostend, Belgium). Multiple logistic regression was performed to assess the effect of potential risk factors on the development of the most common ophthalmic diagnoses. Risk factors included in the model were age, sex, prematurity, known intrauterine drug

Table 2. Types and percentages of refractive errors, amblyopia, and strabismus in children with autism spectrum disorder (N = 380)

Ophthalmologic diagnosis	No. affected (%)
Any ophthalmologic diagnosis	271 (71)
Significant refractive error	159 (42)
Myopia	50/159 (31)
Hyperopia	62/159 (39)
Astigmatism	59/159 (37)
Anisometropia	34/159 (21)
Amblyopia	72 (19)
Anisometropic	23/72 (32)
Strabismic	31/72 (43)
Combined strabismic/anisometropic	8/72 (11)
Bilateral ametropic	6/72 (8)
Deprivation	4/72 (6)
Strabismus	121 (32)
ET	60/121 (50)
Accommodative ET	25/60 (42)
Partially accommodative ET	13/60 (22)
Intermittent ET	7/60 (12)
Congenital ET	5/60 (8.3)
Abducens nerve palsy	4/60 (6.7)
Sensory ET	2/60 (3.3)
Acquired comitant ET	1/60 (1.7)
Duane syndrome	1/60 (1.7)
Nystagmus blocking syndrome	1/60 (1.7)
XT	54/121 (45)
Intermittent XT	41/54 (76)
Convergence insufficiency	5/54 (9.2)
Constant XT	3/54 (5.6)
Sensory XT	3/54 (5.6)
Congenital XT	1/54 (1.9)
Duane syndrome	1/54 (1.9)
Vertical deviation	7/121 (5)
Superior oblique palsy	5/7 (71)
DVD	2/7 (29)

DVD, dissociated vertical deviation; *ET,* esotropia; *XT,* exotropia.

Table 3. Types and numbers of patients with ophthalmologic disorders other than refractive error, amblyopia, and strabismus in children with autism spectrum disorder (N = 380)

Ophthalmologic diagnosis	No. affected (%)
Retinopathy of prematurity	14 (3.7)
Optic neuropathy	14 (3.7)
Optic atrophy secondary to hydrocephalus	5 (36)
Congenital optic nerve anomaly (optic nerve hypoplasia, morning glory syndrome, optic nerve coloboma)	4 (29)
Papilledema secondary to idiopathic intracranial hypertension	2 (14)
Optic pathway glioma secondary to neurofibromatosis type 1	2 (14)
Leukemic optic nerve infiltration	1 (7)
Congenital ptosis	12 (3.2)
Congenital nasolacrimal duct obstruction	9 (2.4)
Blepharitis/chalazia	8 (2.1)
Allergic conjunctivitis	5 (1.3)
Orbicularis oculi tic	5 (1.3)
Pseudo-strabismus	5 (1.3)
Corneal abrasion	4 (1.1)
Congenital cataract	3 (0.79)
Infantile nystagmus syndrome	3 (0.79)
Oculocutaneous albinism	3 (0.79)
Acute anterior uveitis	2 (0.53)
Congenital color blindness	2 (0.53)
Congenital glaucoma	2 (0.53)
Retinal astrocytoma	2 (0.53)
Aniridia	1 (0.26)
Iris coloboma	1 (0.26)
Juvenile myasthenia gravis	1 (0.26)
Moebius syndrome	1 (0.26)
Neurotrophic cornea	1 (0.26)
Peters anomaly	1 (0.26)
Retinoblastoma	1 (0.26)
Self-inflicted gunshot wound (after enucleation)	1 (0.26)
Stickler syndrome	1 (0.26)
Vernal keratoconjunctivitis	1 (0.26)

exposure, known genetic syndrome, genetic variant of unknown significance, and neuropsychiatric comorbidities that occurred in >5% of our sample. A P value of <0.05 was considered significant.

Results

We identified 2,555 children diagnosed with ASD at our university between 2007 and 2017. Of these, 380 (15%) underwent pediatric ophthalmologic evaluation. The demographic data, birth history, genetic findings, and neurologic and psychiatric comorbidities of these 380 patients are provided in Table 1. The mean age at first ophthalmology visit was 5.5 years, and patients were followed for an average of 22 months. Of the 380, 291 subjects (77%) were male, and 71 (19%) were premature. This is consistent with the known male predominance of ASD; prevalence of ASD in males is 3-4 times that of females.[1] A genetic syndrome was diagnosed in 47 cases (12%), and genetic testing identified a variant of unknown significance in 14 (3.7%). The most common neuropsychiatric comorbidity was ADHD, in 125 children (33%), and 60 children (16%) had an intellectual disability. Cerebral palsy (CP) was diagnosed in 22 children (5.8%).

The ophthalmologic findings of the 380 children with ASD are given in Tables 2 and 3. Table 2 details the subtypes and percentages of children with refractive errors, amblyopia, and strabismus; Table 3, the percentages of patients with other ophthalmic diagnoses. Overall, 271 children (71%) were diagnosed with an ophthalmologic disorder. Significant refractive errors were found in 159 children (42%). Myopia, hyperopia, and astigmatism were each diagnosed in 31%-39% of children, whereas anisometropia was found in 21% of cases. Amblyopia occurred in 72 children (19%) and was at least partially refractive in 51% of cases (pure anisometropic, 32%; bilateral ametropic, 8%; combined strabismic-anisometropic, 11%). Strabismus contributed to amblyopia in 54% of children (pure strabismic, 43%; combined strabismic-anisometropic, 11%), and 4 patients (6%) had deprivational amblyopia due to congenital cataracts (3) or Peters anomaly (1).

Besides refractive error, amblyopia, and strabismus, the most common ophthalmologic diagnoses were retinopathy

Table 4. Odds ratios for risk factors for refractive error, amblyopia, and strabismus in children with autism spectrum disorder, by multiple logistic regression

Risk factor	Odds ratios (95% confidence interval)			
	Significant refractive error[a] (n = 159)	Amblyopia (n = 72)	Strabismus (n = 121)	Optic neuropathy (n = 14)
Age, by year	1.16 (1.08-1.24); $P < 0.0001$	0.95 (0.88-1.03)	0.95 (0.88-1.01)	1.18 (0.98-1.42)
Female	0.92 (0.53-1.57)	0.80 (0.41-1.53)	1.16 (0.67-2.01)	0.45 (0.08-2.64)
Premature	0.90 (0.49-1.65)	1.10 (0.55-2.19)	1.82 (1.0-3.35) $P = 0.05$	0.85 (0.18-3.98)
Known intrauterine drug exposure	1.13 (0.42-3.03)	0.78 (0.23-2.72)	1.16 (0.43-3.14)	N/A
Known genetic syndrome	0.72 (0.36-1.45)	1.74 (0.83-3.63)	1.51 (0.76-2.97)	1.09 (0.21-5.73)
Genetic variant of unknown significance	1.83 (0.59-5.62)	0.68 (0.14-3.23)	1.16 (0.37-3.69)	N/A
ADHD	0.63 (0.37-1.07)	1.13 (0.61-2.07)	0.47 (0.26-0.84); $P = 0.012$	0.67 (0.14-3.11)
Anxiety	1.15 (0.53-2.49)	1.14 (0.46-2.81)	1.03 (0.43-2.47)	1.10 (0.10-11.6)
Cerebral palsy	3.22 (1.24-8.35); $P = 0.016$	3.49 (1.35-9.01); $P = 0.0097$	3.59 (1.33-9.70); $P = 0.012$	14.0 (2.95-66.5); $P = 0.0009$
Intellectual disability	0.87 (0.46-1.63)	0.70 (0.33-1.52)	1.83 (0.99-3.37)	4.82 (1.20-19.4) $P = 0.027$
Seizure disorder	0.63 (0.31-1.27)	1.03 (0.47-2.26)	0.96 (0.47-1.95)	3.59 (1.0-13.5); $P = 0.05$

ADHD, attention deficit and hyperactivity disorder; *N/A,* not applicable—unable to calculate odds ratio because there were no subjects with optic neuropathy with these risk factors.
[a]Refractive errors were considered significant if they met the 2017 American Academy of Ophthalmology Preferred Practice Pattern guideline criteria for spectacle prescription.

of prematurity (ROP) and optic neuropathy, which each occurred in 14 children (4%). The most common causes of optic neuropathy were optic atrophy secondary to hydrocephalus and congenital optic nerve anomaly. Congenital ptosis, congenital nasolacrimal duct obstruction, and blepharitis were also relatively common (2%-3% of children).

The results of multiple logistic regression analysis of risk factors for significant refractive error, amblyopia, strabismus, and optic neuropathy are given in Table 4. Older age was associated with increased risk of refractive error (OR = 1.16 per year of age; $P < 0.0001$). There was a borderline increased risk of strabismus in premature individuals (OR = 1.82; $P = 0.05$). CP significantly increased the risk of all four ophthalmologic disorders (OR = 3.22-14.0; $P < 0.02$). Intellectual disability and seizure disorder also increased the risk of optic neuropathy (OR = 4.82 and 3.59, resp.; $P \leq 0.05$). ADHD was associated with a decreased risk for strabismus (OR = 0.47; $P = 0.012$).

Discussion

Prior studies have similarly reported high rates of ophthalmologic disorders in children with ASD, although the percentage of affected children in this study is higher than that reported in others (71% vs 15%-52%).[4-6] This discrepancy may be related to referral bias. Our university has an institute specifically devoted to children with neurodevelopmental disabilities, which may attract a higher percentage of children with medical comorbidities. This in turn may have led to increased rates of ophthalmologic diagnoses, based on our finding that certain neurologic disorders increased the risk of ophthalmic pathology. Moreover, only 15% of children with ASD were seen in the eye clinic, and children with suspected ophthalmic disorders were probably more likely to be referred.

The rates of strabismus (32%), amblyopia (19%), and significant refractive errors (42%) in the present study far exceeds the prevalence of these disorders in the general pediatric population. Among preschool-aged children, the Baltimore Pediatric Eye Disease Study (BPEDS) and Multi-Ethnic Pediatric Eye Disease Study (MEPEDS) both reported that the prevalence of strabismus ranged from 2.1% to 3.6%.[11-13] These studies also found a general prevalence of amblyopia ranging from 0.8% to 2.6%, and a significantly greater prevalence in Hispanic children.[11-13] The BPEDS additionally reported that 5.1% of children met the criteria for spectacle correction,[14] based on the 2007 AAO Preferred Practice Pattern guidelines. Our study is not directly comparable to these large epidemiologic studies because of its retrospective nature and differences in age and possibly race (which was not evaluated in the present study). However, the magnitude of difference between the children with ASD in this study compared to the general pediatric population (approximately 10 times higher in those with ASD) suggests that there may be a true increased risk of ophthalmologic disorders in this population.

Although the overall rates of strabismus and amblyopia reported in this study are much higher than the general

pediatric population, the subtypes of these disorders are similar. Strabismus in our patients was nearly equally divided between esotropia (50%) and exotropia (45%). In the BEPDS and MEPEDS, esotropia and exotropia were fairly equal in prevalence in most groups, although esotropia was more common in non-Hispanic whites, whereas exotropia predominated in Asians.[11-13] In the present study, amblyopia was also nearly equally split between refractive (51%) and strabismic (54%) cases. Prior epidemiologic studies have reported varying ratios of refractive and strabismic amblyopia.[11-13,15] In the BPEDS and MEPEDS, refractive and strabismic causes of amblyopia were fairly equally represented[11-13]; however, population-based studies of preschool-aged children in Singapore and Australia reported higher rates of refractive (81%-85%) than strabismic (15%-19%), amblyopia.[15,16]

Optic neuropathy occurred in 4% of children with ASD in this study. Most of these children had optic atrophy secondary to hydrocephalus or congenital optic nerve anomalies, including optic nerve hypoplasia (ONH). Prior investigators have noted an apparent high rate of ASD symptoms and diagnosis in children with ONH.[17,18] Fink and Borchert[18] used the Social Responsiveness Scale to rate autistic symptoms in 46 children with ONH and found that 46% of participants demonstrated deficiencies in reciprocal social behavior. It is noteworthy, however, that diagnosis of ASD in the context of visual impairment may be complicated (for example, lack of eye contact in such individuals should not be interpreted as a sign of ASD), and modifications to standard instruments for ASD diagnosis may be necessary to evaluate such children.[19]

Among the factors evaluated in this study, CP was associated with the highest risk of an ophthalmologic diagnosis in children with ASD. Strabismus has been reported to occur in up to 64% of children with CP.[20] Afferent visual disorders are less commonly studied in CP; however, one study found that 46% of children with CP had decreased vision in one eye, most commonly due to amblyopia (24%) and optic neuropathy (16%).[21] Additionally, 37% were diagnosed with a significant refractive error.[21] Of 23 children with both ASD and CP in this study, 14 (61%) had a significant refractive error, 12 (52%) had amblyopia, 14 (61%) had strabismus, and 5 (22%) had optic atrophy. Thus, the combination of ASD and CP may increase the risk of ophthalmologic disorders over CP alone.

Other risk factors for ophthalmologic diagnoses in children with ASD included prematurity (increased risk of strabismus), seizure disorder, and intellectual disability (the last two both increased risk of optic neuropathy). Among the general pediatric population, prematurity is associated with an increased risk of strabismus, especially those with a history of retinopathy of prematurity.[22] Seizures and intellectual disability may be associated with neuroanatomic abnormalities, which may predispose to congenital optic nerve anomalies or optic atrophy.[23,24] Based on this study, the risk factors for ophthalmic pathology in children with ASD appear similar to typically developing children.

One exception is the finding that ADHD was associated with a lower risk for strabismus (OR = 0.47; 95% CI, 0.26-0.84; $P = 0.012$). ADHD has been suggested to increase risk of some visual disorders, including convergence insufficiency.[25] The reason for the apparent decreased risk of strabismus in children with ADHD may be the diagnostic change from DSM-IV to DSM-V in 2013. In DSM-IV, ADHD could not be diagnosed simultaneously with ASD, whereas dual diagnosis is permitted in DSM-V.[2,9] Thus, ADHD was most likely underdiagnosed in this study, possibly contributing to the unexpected finding that ADHD decreased the risk of strabismus.

We did not find that a genetic diagnosis or variant of unknown significance increased the risk of ophthalmologic disorders in children with ASD. Although ASD is believed to have a strong genetic basis, the heterogeneity of this disorder precludes a simple genetic explanation.[26] The relationship between ophthalmologic disorders and ASD may have both genetic and environmental components; however, the genetic contribution will require further investigation to identify potential genetic susceptibility factors. Furthermore, 74% of patients in this study underwent genetic testing, and it is possible that some genetic diagnoses and associations were missed because of incomplete testing.

The findings of this study must be interpreted in light of its limitations. This investigation is subject to selection bias, because children with suspected ophthalmologic diagnoses were probably more likely undergo ophthalmologic evaluation. Selection bias would lead to overestimation of the rates of ophthalmic disorders in our study. Furthermore, our ASD cohort may not be entirely representative of the larger ASD population. For example, the rates of certain medical comorbidities in our cohort differed from that reported in population-based studies of ASD (intellectual disability occurred in only 16% of our patients, compared to 31%-40% in epidemiologic studies),[1,27] although the rates of other medical disorders, such as seizures and CP, were comparable.[6,27] Additionally, age and race may affect frequency and type of ophthalmologic disorders, but this study included children of varying ages and follow-up durations, and it did not assess race. Moreover, the methods of testing visual acuity varied, and the diagnosis of amblyopia may have been hindered in some instances by limited patient cooperation. Furthermore, the change in diagnostic criteria from DSM-IV to DSM-V may have introduced a lack of uniformity in the psychiatric diagnoses of the subjects. Finally, we did not specifically test for cognitive visual impairment in our patients, and a recent study of 30 children with ASD found that all had some component of cognitive visual impairment when specialized testing was performed.[28]

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