



Ophthalmologic Manifestations in Autism Spectrum Disorder

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Abstract

Objectives: The purpose of this study was to describe the ophthalmologic manifestations found in patients with autism spectrum disorder (ASD) and to assess their prevalence in the different types of ASD.

Materials and Methods: This prospective observational study included 344 patients with ASD seen over a period of 8.5 years. They were classified into four subgroups (autism, Asperger syndrome, pervasive developmental disorders not otherwise specified [PDD-NOS], and other). Data obtained from ophthalmological examinations were compared between the groups. Statistical analysis was performed with chi-square, Kruskal-Wallis, and Mann-Whitney tests.

Results: Refractive defects were detected in 48.4% of the patients, with the most prevalent being hyperopia and astigmatism. There was a higher prevalence of myopia in Asperger syndrome. Evaluation of extraocular motility revealed the presence of strabismus in 15.4% of patients, with a statistically significantly higher prevalence in autism and the "other" disorders group. The most frequent type of strabismus was exotropia. Convergence was found to be normal in 43.6% of the patients. Nystagmus was observed in only 0.9% of patients. In the binocular sensory tests performed, patients with Asperger syndrome had significantly better results compared to the other groups. Optic nerve abnormalities were found in 4% of patients, with significantly higher prevalence in the "other" disorders group.

Conclusion: Ophthalmologic manifestations occur more frequently in patients with ASD than in the general child population. Of these, the most frequent are refractive defects and ocular motility disorder. Therefore, we consider it necessary to perform an ophthalmological evaluation in patients with ASDs.

Keywords: Autism spectrum disorder, refractive errors, strabismus, amblyopia, optic nerve hypoplasia

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Introduction

Autism spectrum disorder (ASD) refers to a range of neurodevelopmental conditions characterized by a certain degree of social, communication, and language impairment and the presence of restricted, stereotyped, and repetitive patterns of behavior, interests, and activities. ASD encompasses autism, Asperger's syndrome, Rett's syndrome, Heller's syndrome, fragile X syndrome, and other less common disorders that are included in the pervasive developmental disorders not otherwise specified (PDD-NOS). ASD manifests during childhood and tends to persist into adolescence and adulthood. In most cases, the condition becomes apparent during the first 5 years of life.

Twenty-five years ago, the incidence of ASD was estimated as 1:2,500, whereas the reported current prevalence ranges from 1:250 to 1:88, which supports the notion that the prevalence of ASD appears to be increasing globally. The current reported prevalence of ASD portrays the high impact that this condition has in a community at the social and clinical level.¹ There are many possible explanations for this apparent increase, including improved awareness, expansion of diagnostic criteria, better diagnostic tools, and improved and rigorous reporting.

Numerous studies have associated the communication and social interaction deficiencies in ASD patients with visual processing capacity.^{1,2,3,4,5,6,7,8} The prevalence of ophthalmologic disorders was found to be more frequent among these patients than in the general pediatric population.^{9,10,11} The most frequent eye disorders identified in ASD patients are strabismus, nystagmus, and refractive errors or amblyopia. Optic nerve hypoplasia or retinal alterations evidenced in the electroretinogram have also been described.^{1,12,13,14,15,16}

The purpose of this study was to describe the ophthalmologic manifestations found in these patients and assess their prevalence in the different types of ASD, since these manifestations may contribute to the communication and social interaction deficiencies in ASD patients. Our aim is to raise awareness of the need to protocolize early ophthalmologic evaluation in ASD patients.

Materials and Methods

Patient Cohort

The study included 344 patients who were referred to the ophthalmology department of our hospital by the AMITEA (from Spanish: Integral Medical Attention to Patients with Autism Spectrum Disorder) Program during a period of time spanning from the end of 2009 until March 2018.

Of the 344 patients, 28 (8.1%) were consistent with Asperger's syndrome, 219 (63.7%) with autism, 76 (22.1%) presented PDD-NOS, and 21 (6.1%) had other diagnoses (Rett's syndrome, fragile X syndrome, Angelman syndrome, Lennox-Gastaut syndrome, and Klinefelter syndrome). Patients were diagnosed according to the criteria of the AMITEA Program.

Clinical Parameters

In all cases, the following descriptive parameters were analyzed: age, sex, presence of verbal language, presence of

mental retardation, and the degree of collaboration (on a scale of 0 to 3 based on the number of tests answered and extent of cooperation in subjective tests).

Subjective tests requiring the patient's collaboration were adapted to their age and IQ level ("retarded," "non-retarded," or "non-evaluated"), which as provided by the AMITEA Program in the patients' clinical records. These tests included monocular visual acuity tests (LEA test, Pigassou optotypes, Snellen E, letters, numbers); ocular motility assessment with cover test and prism cover test; evaluation of ductions, versions, convergence, and presence or absence of nystagmus; and assessment of binocular sensory function using the Lang, TNO, and Worth tests.

Objective tests were also carried out, including cycloplegic refraction by retinoscopy and a pediatric autorefractor and table-top autorefractor, funduscopy examination, and slit-lamp anterior segment examination. Pathological refractive error was defined as more than +2 diopters of hyperopia, more than -0.50 diopters of myopia, and more than +/-0.75 diopters of astigmatism.

Treatment was administered on a patient-by-patient basis.

Statistical Analysis

Statistical analysis was performed with SPSS software (version 24.0 for Windows; IBM Corp, Armonk, NY, USA), including descriptive parameters, frequency and correlation of qualitative variables using chi-square, Kruskal-Wallis, and Mann-Whitney tests.

Statistical significance was accepted at $p < 0.05$.

Results

The patient cohort was predominantly male, with 257 male patients (74.7%) versus 87 female patients (25.3%). The mean age at first ophthalmologic consultation was 10.9 ± 8.1 years (mean \pm standard deviation). When analyzed by group, the mean age was 10.8 ± 8.9 years in the autism group, 12.5 ± 7.4 years in the Asperger group, 8.2 ± 5.2 years in the PDD-NOS group, and 12.2 ± 7.2 years in the other disorders group. Age at first ophthalmologic consultation was significantly higher in the Asperger syndrome group compared to the autism group ($p < 0.003$).

Of the 344 patients, 202 (58.7%) were able to verbally communicate, while 142 (41.3%) were unable to communicate through speech. However, in 11 patients from the latter group, it was still possible to evaluate visual acuity by means of pictograms.

Intellectual deficit was observed in 231 patients (67.2%), while 74 patients (21.5%) presented a normal IQ. Thirty-nine patients (11.3%) had not been evaluated. In the Asperger syndrome group, the incidence of associated intellectual deficit was statistically significantly lower than in the other three patient groups ($p < 0.001$).

The degree of collaboration was assessed as null or poor (0-1) in 155 patients (45.1%), intermediate (2) in 55 patients (16.0%) who responded actively to most of the tests requested,

and very good (3) in 134 patients (39.0%). A statistically significant difference in the degree of collaboration and verbal communication was observed between patients with Asperger syndrome and autism, with the latter group displaying poorer collaboration and more limited verbal communication skills ($p < 0.001$).

Visual acuity could be determined for 385 of the 688 eyes analyzed (56.0%), with a slightly higher proportion of right eyes (as a rule, the first to be examined) than left eyes (56.4% vs. 55.5%). Visual acuity was 0.7 or better in 169 right eyes (49.1%) and 167 left eyes (48.6%) and was 0.3 or worse in 8 right eyes (2.3%) and 7 left eyes (2.0%). We observed significantly better visual acuity in the Asperger syndrome group compared to the autism and other disorders groups ($p < 0.001$) (Figure 1).

Total refractive error observed by retinoscopy and autorefractors was determined in 659 eyes (95.8%), of which 340 (51.6%) were emmetropic. The rest of eyes were classified as having astigmatism (130 eyes, 19.7%), myopia (54 eyes, 8.2%), or hyperopia (135 eyes, 20.5%). Refractive error could not be determined in 29 eyes (4.2%) because of poor collaboration.

Regarding the variation in refractive defects according to age, we observed that in children up to 6.5 years of age, there was a higher percentage of hyperopia (29.9%), followed by astigmatism (15.3%). Between 7 and 8 years, most patients were hyperopic (22.9%) or astigmatic (20%). Between 8 and 12 years, most patients presented astigmatism (21.3%), followed by hyperopia (13.1%). Between 12 and 15 years, astigmatism was most common (27.6%), followed by myopia (17.2%).

Calculating the prevalence of refractive defects in the different ASD groups showed that the rate of emmetropia was 51.0% in the autism group, 57.1% in the Asperger syndrome group, 52.7% in the PDD-NOS group, and 36.8% in the other disorders group. The prevalence of astigmatism was 20.5% in the autism group, 17.9% in the Asperger syndrome group, 20.3% in the PDD-NOS group, and 21.1% in the group of other disorders. Hyperopia tended to be more common in autism (19.5%), PDD-NOS (21.6%), and other disorders (42.1%)

than in Asperger syndrome (7.14%), whereas myopia was more common in Asperger syndrome (17.9%) than autism (9.1%) and PDD-NOS (5.4%). However, these trends were not statistically significant.

Assessment of extraocular motility revealed strabismus in 53 patients (15.4%), of which 32 (9.3%) exhibited exotropia, 19 (5.5%) esotropia, 1 (0.3%) exophoria, and 1 (0.3%) vertical strabismus. It was not possible to determine the presence or absence of extraocular muscle dysfunction in 4 patients (1.2%).

Strabismus was present in 16.4% of patients with autism, compared to 3.6% of patients with Asperger syndrome. Exotropia was the most common type of strabismus in autism, PDD-NOS, and other disorders, while esotropia was most common in the Asperger group. The incidence of strabismus was significantly lower in the Asperger and PDD-NOS groups in comparison to the group of other disorders ($p < 0.007$).

Convergence could not be determined in 105 cases (30.5%) due to the difficulty caused by inherent sight fixation, which was more prevalent in patients in the autism and other disorders groups. Among the patients who could be examined, convergence was found to be normal in 150 (43.6% of the total), of which 92 patients belonged to the autism group, 37 to the PDD-NOS group, 15 to the Asperger syndrome group, and 6 to the other disorders group. There were 89 cases of convergence deficit (25.9%), of which 52 patients belonged to the autism group, 21 to the PDD-NOS group, 12 to the Asperger syndrome group, and 4 to other disorders. No statistically significant differences in convergence deficit were observed amongst the ASD groups.

Nystagmus was observed in only 3 patients (0.9%), of whom 2 were autistic and 1 was included in the other disorders group. Nystagmus was not detected in the remaining 341 patients either because the patient did not cooperate or because they did not present it.

Among the binocular sensory tests performed, the Worth test was successfully performed on 135 patients (39.2%), of which only 3 suppressed the vision of one eye and 132 fused the vision of both eyes. The Lang test was successfully performed in

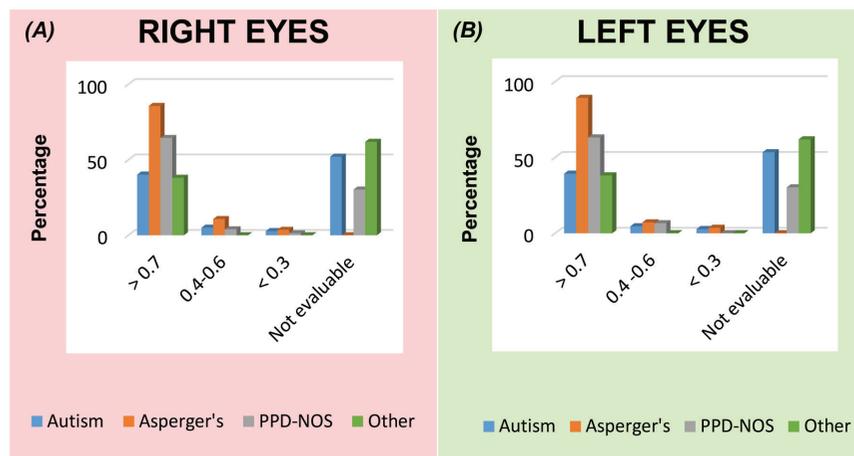


Figure 1. Visual acuity in right eyes (A) and left eyes (B) in different autism spectrum disorder groups. PPD-NOS: Pervasive developmental disorders not otherwise specified

342 patients (99.4%), of whom 126 patients showed stereopsis (36.6%). However, the TNO test revealed only 56 patients (16.3%) with stereopsis. In these three sensory tests, the Asperger syndrome group had significantly better results in comparison to the other ASD groups ($p < 0.001$) (Figure 2).

The fundus could not be examined in 11 patients (3.2%). In those who underwent fundus examination by indirect

ophthalmoscopy, a normal fundus was observed in 318 patients (92.4%) and findings of pallor and/or optic nerve atrophy were seen in only 15 patients (4.4%). The incidence of alterations in the optic nerve was higher in the other disorders group compared to the rest of the ASD groups ($p < 0.006$).

No treatment was prescribed to 271 patients (78.8%) either because they had no or negligible ophthalmologic defects, or because a full diagnosis and treatment prescription was not possible due to incomplete or inconclusive (lack of collaboration) ophthalmologic examination. From the study cohort, only 73 patients (21.2%) required treatment. The most common treatment options were eyeglass prescription for refractive errors, monocular occlusion, and injection of intramuscular botulinum toxin for strabismus control.

Discussion

The incidence of ASD has increased from an estimated 1:2,500 a quarter century ago to a reported prevalence of 1:250 to 1:88 today. At present, there are approximately 450,000 children with ASD in our region.¹⁷ Some of the possible explanations for this increase in prevalence are greater awareness of these disorders, improvement and expansion of the diagnostic criteria, better diagnostic tools, and more rigorous clinical reporting.¹

These disorders present diagnostic challenges because of the peculiarities of these patients.¹¹ In some patients in our cohort, we could not perform certain examinations due to the complete absence of collaboration.

The patient cohort presented in this study is one of the largest and most specific in terms of characterizing ophthalmologic defects in ASD. Importantly, our study focused exclusively on ASD, whereas many of the published studies consider patients with general intellectual disability. This includes not only patients with ASD, but also patients with other conditions characterized by developmental delay (e.g., Moebius syndrome, Charge syndrome, Down syndrome). In all these articles, different ophthalmologic manifestations were analyzed and strabismus, nystagmus, and refractive errors or amblyopia were found to be the most common conditions. Optic nerve hypoplasia or retinal alterations evidenced in electroretinogram have also been described.^{1,12,13,14,15,16}

The main limitation of our study is that we did not include an age-matched control group in order to compare the prevalence of ophthalmologic defects amongst ASD and the general population, as this program included only children with a diagnosis of PPD.

In our study, the most prevalent alteration of extraocular motility was exotropia, and the most common refractive errors were astigmatism and hyperopia. In a retrospective study published in 2013, Ikeda et al.¹⁶ present results similar to ours. They reported that 21% of patients had strabismus and 29% had refractive errors. However, in their study they determined that accommodative esotropia was most common among those who had strabismus, unlike in our study.

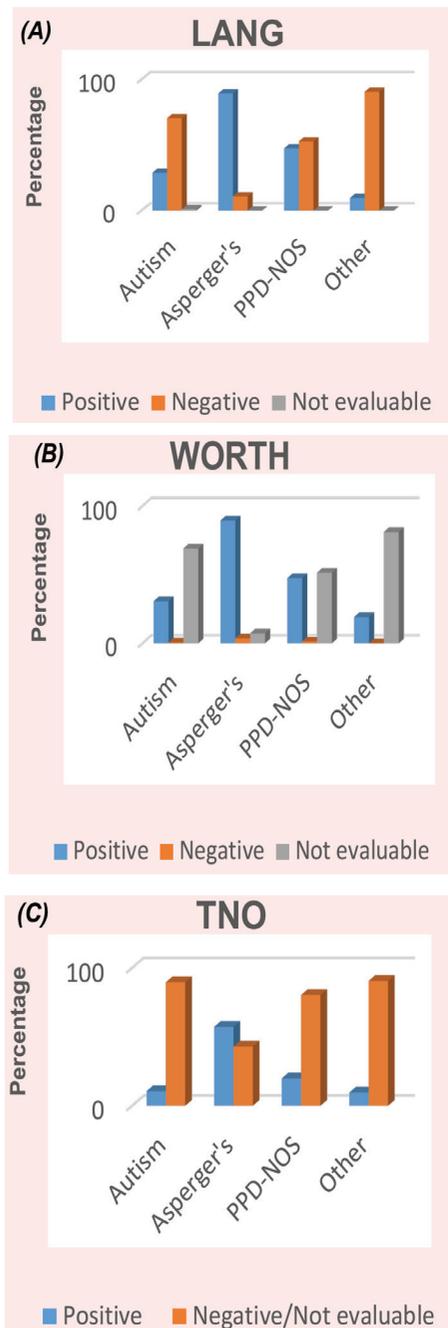


Figure 2. Binocular sensory test results in different autism spectrum disorder groups. (A) Lang test, (B) Worth test, and (C) TNO test. PPD-NOS: Pervasive developmental disorders not otherwise specified

Milne et al.¹⁸ reported in 2009 that of 51 individuals with ASD, most aspects of vision (including visual acuity) were not affected. However, they emphasized that convergence must be assessed, because they observed differences from the general population. Our data confirm their findings, as convergence was altered in 25.9% of the patients examined in our study.

Subjective examinations were more limited than objective tests in this study. Visual acuity could not be determined in 44% of the patients. Convergence could not be determined in 30.5% of the patients, and the presence of nystagmus could be assessed in only a small percentage (0.9%). Of the binocular sensory tests, results could not be obtained in 84% of patients when using the TNO test, in 1% when using the Lang test, and in 61% when using the Worth test. The poor collaboration in this respect precludes valid conclusions regarding the presence of stereopsis and amblyopia in these patients.

The response to binocular tests, especially in the TNO and Worth tests, is once again a true reflection of the varying degree of difficulty in understanding, communicating, and/or cooperating that is characteristic to patients with ASD. In this sense, it is possible that some of the examination methods should be improved to facilitate the collaboration of certain patients.

In approximately half of the children whose vision could be assessed, it was close to normal.¹ This is consistent with the refractive defects found, as we detected astigmatism in 20%, hyperopia in 20%, and myopia in 8% of the patients. Examinations in which the active participation of the patient is not required were much more positive; the fundus could not be examined in only 3% and refractive error could not be analyzed in 4% of the patients.

Regarding the development of new technologies to facilitate ophthalmological examination, it is worth noting the usefulness of tools such as the PlusoptiX photorefractometer for the screening of amblyopia risk factors in patients with ASD, as shown in the recent publications by Singman et al.¹⁹ and McCurry et al.²⁰

In recent years, electronic devices have been designed to analyze eye movements such as tracking, fixation, or saccades. These devices seem to enable the very early diagnosis of alterations in ocular motility and thus allow much earlier initiation of a treatment regimen.^{2,4,5,6,7,21} Because our study started in 2009, we did not perform such an evaluation, as patients recruited earlier could not be examined in this way.

Study Limitations

The rate of optic nerve pathology observed in our study was markedly lower than that reported in the literature.^{12,13} Papillary alteration was found in only 3%. However, we are aware that limitations in examination may lead to slight papillary pallor being overlooked.

The fact that children do not have social interaction, are not able to follow objects, and present limitations in language does not mean in any way that they cannot be examined. Ophthalmologists can learn other forms of communication to adapt to these patients' disability. In fact, from the time

recruitment started, we used pictograms that eased patient collaboration.

Conclusion

The present study illustrates the need for ophthalmological evaluation in patients with ASD, as refractive errors as well as ocular motility disorder are common.^{3,10} Therefore, we consider it necessary to implement evaluation protocols to manage these patients in a holistic way that will facilitate improvements in their quality of life and social functioning.^{1,8,11,15,22} Future studies should investigate whether the follow-up and appropriate treatment of ophthalmological manifestations might improve these patients' social interaction and communication.

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Ethics

Ethics Committee Approval: Since the study was conducted with ophthalmologists, not on patients, the permission of the ethics committee was not required.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: P.G.L., P.M., C.G., J.L.M., Concept: P.G.L., P.M., Design: P.G.L., P.M., Data Collection or Processing: P.G.L., P.M., C.G., J.L.M., Analysis or Interpretation: P.G.L., P.M., C.G., J.L.M., Literature Search: C.G., J.L.M., Writing: P.G.L., P.M., C.G., J.L.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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