• Review Article •

Ocular manifestations in autism spectrum disorder

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Abstract

● Autism spectrum disorder (ASD) represents a neurodevelopmental disorder that has been the focus of numerous studies on the central nervous system (CNS). The embryological origin of the brain and retina is shared, with the axons of retinal ganglion cells (RGC) developing into the optic nerves that enter the brain through the dorsal lateral geniculate nucleus (LGN) of the thalamus, LGN, and other visual cortices. Given the evidence that individuals with ASD exhibit impairments in the visual mechanisms, including deficits in emotional face recognition, and difficulty in maintaining gaze control as well as eye contact, some studies have documented retinal alterations in individuals with ASD. These have been identified through ophthalmic assessments, including optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), and electroretinography (ERG). With the improvements in ASD animal models, it is possible to obtain a better understanding of vision dysfunction in ASD by analyzing the molecular mechanisms of retinal function and structure abnormalities. This review aims to provide a summary of the recent research on ocular alterations in ASD patients and animal models, intending to contribute to further investigation of the eye-brain connection and communication.

● **KEYWORDS:** autism spectrum disorder; retina; retinofugal; optical coherence tomography

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INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder. The prevalence of ASD has increased to 2%-3% in the general population[1]. The deficits in social interaction as well as stereotyped behaviors and restricted interests mainly characterized it. Currently, ASD is diagnosed mainly based on behavioral criteria, which is a complicated and time-consuming process[2]. However, many prospective studies have revealed that behavioral symptoms of ASD cannot be observed until the second year of life, which makes it hard for high-risk infants to get early behavioral treatments. Thus, there is an urgent need to discover reliable markers for the early diagnosis of ASD.

Embryonic and functional connections exist between retina and brain, as the neural retina is an important part of the central nervous system (CNS), and arises from the diencephalon. The anterior neuroectoderm of the telencephalic/diencephalic boundary forms the eye-field during gastrulation. Then, the eye-field becomes optic vesicle under the action of cytokines, including Rax/Rx, Pax6, Lhx2, Six3, Tll, Tbx3 and Six6. In the end, the optic vesicle gives rise to neural retina, retina pigmented epithelium (RPE)[3]. Moreover, the visual signal initiates from the retina, passes the dLGN, and enters the primary visual cortex (V1) then divided either as the ventral and the dorsal visual pathways finally arrive at the secondary visual cortices, which plays an important role in visual formation, learning, mood, and voluntary movement. Thus, as the extension of the CNS, functional and structural abnormalities of retina may reflect some CNS diseases.

Many researchers have tried to find hallmarks of CNS diseases in the eyes, they used optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), and electroretinography (ERG) to explore abnormalities of retinal structure, retinal vasculature and retinal electrical signal transduction in patients with CNS diseases, including Alzheimer's disease (AD)[4-5], Parkinson's disease (PD)[6-8], multiple sclerosis (MS)[9-10] and even posterior cortical atrophy (PCA)[11]. The advancement of eye tracking technology may make it possible to become a brand-new diagnostic tool and be incorporated into the study of retinal changes of CNS diseases, as eye tracking can be used to detect the pupillary light reflex (PLR) and changes of gaze location of patients.

Besides, abnormal visual behaviors can also be observed in ASD patients, like difficulty maintaining eye contact, disorders of emotional face recognition and disrupted circadian rhythm, some scholars believe that the retina of children with ASD is also abnormal and this abnormality may participate in the formation of autism-like behaviors. Recently, in-depth research of intrinsically photosensitive retinal ganglion cells (ipRGCs), neural loops that retinal signals may control recognition, depression and circadian rhythm have been discovered, which can provide cutting-edge perspectives about the formation of autism-like behaviors.

RETINAL STRUCTURAL CHANGES IN ASD PATIENTS

OCT and OCTA are common ophthalmic examinations, which can quickly acquire images of retina structure and even retinal blood flow without damages, with the following image segmentation, as well as analysis, we can measure the thickness of separate retinal layers, size of specific functional area and retinal blood flow perfusion. Thus, OCT and OCTA are ideal tools for finding hallmarks of CNS diseases in the eyes. Many researchers have used OCT and OCTA to find fundus imaging markers, hoping to achieve early diagnosis of ASD. Emberti Gialloreti *et al*[12] were the first to study the fundus abnormalities using OCT. They recruited 11 patients who were diagnosed with high functioning autism spectrum disorder (HFA), and 13 asperger syndrome (AS) patients, and showed significantly reduced average nasal retinal nerve fiber layer (RNFL) thickness compared with the typical development (TD) group. They correlate this reduced thickness to verbal-IQ/performance-IQ. Similar conclusion was reached by Bozkurt *et al*[13]. In their program included 40 ASD children with normal IQ, significant RNFL thinning was discovered in the temporal, temporal superior, nasal superior, temporal inferior quadrant and global retina in the ASD group, however, the RNFL thickness does not correlate with the severity of ASD and no significant differences in macular thickness and volume. Nonetheless, Friedel *et al*[14] reported reduced thickness in macular and the outer nuclear layer (ONL) in their research, and strong negative correlation were found between this thickness and ASD severity measured by the Social Responsiveness Scale–Second Edition (SRS-2). In contrast to results mentioned above, García-Medina *et al*[15] presented greater foveal thickness at whole retina, inner retina, inner plexiform layer (IPL) and inner nuclear layer (INL), and macular thickness at whole retina and inner retina were significantly higher than that of controls. Inferior, nasal inferior and temporal inferior sectors of peripapillary retinal nerve fiber layer (pRNFL) were also thicker in the ASD group. Then, OCTA was used to investigate ocular blood flow perfusion, they perceived a significant higher perfusion density, which suggest more area covered by vascularization at the peripapillary inferior quadrant of optic nerve head (ONH) and reduced flux index in this region, which means fewer red blood cells pass through this area per unit time[16]. The reason why these scientists have different results is still unknown. We speculated it may be because ASD is a multifactorial disorder, maternal immune activation (using valproic acid or thalidomide during pregnancy), inflammation and mutations in synaptic associated protein genes can cause ASD[17]. However, scientists just recruit ASD patients and simply divide them into different subgroups according to symptoms, like HFA, ASD patients with normal IQ, which result in patients caused by different factors were divided into the same group and finally disturb the experimental results. For example, retina may become thicker at some steps during in inflammation, and mutations in synaptic function-related genes makes retina much thinner[18]. The following researches may need to form subgroups stratified by the causes, instead of symptoms, which helps to find more accurately the retina changes of ASDs. In our recent research included 58 HFA children, we segmented retina into 11 layers using deep learning method IPN-V2, and discovered more potential characters of ASD: the thickness of the ellipsoid zone (EZ) was highly increased in ASD patients as well as reduced large-caliber arteriovenous of the inner retina.Specially, these irregularities manifested in the left eye[19]. Another recent published work from our team specially separated the optic disc area for research, which find a descrease in the thickness in the INL and ganglion cell layer (GCL) around the disc area[20].

Few attentions were paid to fundus images of ASD patients. Lai *et al*[21] analyzed fundus images of ASD patients, suggesting more nipping, hemorrhage, exudates and larger optic disc, cup diameter in ASD patients (Table 1).

FUNCTIONAL CHANGES DISCOVERED BY ERG IN ASD RETINA

ERG is a visual electrophysiologic examination for retinal neurons, revealing abnormal retinal function. Numerous scholars believe that ASD is a kind of synaptic developmental disorder and it may also appear on retina, thus ERG could be an important tool to diagnose this neuropsychiatric disorder[22]. Constable *et al*[23] studied 11 ASD patients using full-field ERG, and found decayed light-adapted (LA) b-wave, implying the disfuction occurs after phototransduction, like impaired bipolar cell function or disrupted synaptic transmission between photoreceptors and bipolar cells[24-25]. The same author then enlarged the sample size to 90 in his next study, he reported reduced a-wave which indicates disfunction of photoreceptors, meanwhile, down-regulated b-wave amplitudes at high flash strengths and the slower b-wave peak times[26]. His results are consistent with the widespread idea that ASD is a kind of

Table 1 Previous researches on retinal structural changes in ASD patients

Study	Subjects	Age, y, mean±SD	Male/female	Total IQ, mean±SD	Results (ASD *vs* HC)
Emberti Gialloreti *et al*[12]	11 HFA	25.9±5.8	10/1	66.2±8.5	Nasal RNFL thickness ↓ in ASD group (HFA and AS)
	13 AS	21.2±5.5	10/3	98.4±21.0	
	24 HC	23.9±4.9	20/4	N/P	
Bozkurt *et al*[13]	40 ASD	9.4±1.6	36/4	8.6±10.2	Temporal, temporal superior, nasal superior, temporal inferior quadrant and global RNFL thickness ↓; No differences in macular thickness and volume
	40 HC	9.4±1.6	36/4	104.3±11.2	
Friedel *et al*[14]	34 ASD	35±10	21/13	111±16	Macular and ONL thickness ↓
	31 HC	35±10	19/12	107±11	
García-Medina *et al*[15]	27 ASD	13.70±3.03	23/4	N/A	Foveal thickness at total retina, total inner retina, inner plexiform and inner nuclear layers ↑; macular thickness at total retina and total inner retina. Inferior, nasal inferior ↑; temporal inferior sectors of pRNFL ↑
	27 HC	13.70±3.03	23/4	N/A	
García-Medina *et al*[16]	13 HFA	16.62±2.99	10/3	N/A	Peripapillary inferior quadrant ONH perfusion density ↑; ONH flux index ↓; No differences in FAZ parameters
	14 HC	16.86±4.06	10/4	N/A	
Li *et al*[19]	58 HFA	6-13	51/7	N/A	EZ thickness ↑; large-caliber arteriovenous↓in inner retina
	53 HC	6-13	48/5	N/A	
Wang *et al*[20]	47 HFA	9.57±1.83	41/6	98.3±22.9	INL and GCL thickness↓ around disc area
	47 HC	9.89±1.70	41/6	N/A	

HFA: High-functioning autism; AS: Asperger syndrome; HC: Healthy controls; N/P: Not performed; RNFL: Retinal nerve fiber layer; pRNFL: Peripapillary retinal nerve fiber layer; N/A: Not available; ONH: Optic nerve head; FAZ: Foveal avascular zone; ONL: Outer nuclear layer; EZ: Ellipsoid zone; INL: Inner nuclear layer; ASD: Autism spectrum disorder; GCL: Ganglion cell layer.

synaptic developmental disorder. Lee *et al*[27] recruited another special patient group, attention deficit hyperactivity disorder (ADHD), a common comorbidity of ASD. They discovered a rise of b-wave amplitudes as well as early spike arrival times of b-wave and the photopic negative response (PhNR), while the b-wave amplitudes of ASD group were much lower than the control group, which means ERG could not only help diagnose ASD, but also provide a new differential diagnosis tool between ASD and ADHD. PhNR is a negative wave after b-wave, which is associated with the activation of the retinal ganglion cell (RGC). This result suggested signal transmission could be interrupted when RGC axons converge into the optic nerve. However, Friedel *et al*[14] had different views, no significant differences were found in their study, which included 32 ASD adults. Manjur *et al*[28] tried to use machine learning to further analyze the time and the spectral domain of ERG of ASD patients. They claimed the classification accuracy of their machine learning model was 86%, with 98% sensitivity. Another group of researchers, Siper *et al*[29] studied a special kind of ASDs, Phelan-McDermid Syndrome (PMS), with the deficiency of functional *SHANK3* gene. They found decayed amplitudes in P60-N75 and N75-P100 in PMS patients at 5-year-old male, 9-year-old female and 11 to 12-year-old patients, suggesting disrupted signal transmission in visual pathway after lateral geniculate nucleus (LGN). ERG results have been highly affected by the subtype and severity of ASD, and as retinal tertiary neurons are a single unit, any single changes could affect the signal transmission in the next level, which may explain the opposite conclusions made by different researchers (Table 2).

ABNORMAL PLR IN ASD PATIENTS

ASD is also known as a disorder of CNS, multiple nuclei were involved. PLR is a kind of pupil constriction guided by suprachiasmatic nucleus (SCN) and other nuclei[30]. Several researches have confirmed abnormal PLR in ASD patients[31-32]. Scientists tried to use eye tracker for further quantifying the PLR process according to this theory. Daluwatte *et al*[31] reported a longer PLR latency as well as reduced relative constriction amplitude in the ASD group. They also found that the PLR latency shortened with age in the control group, however, this age-related change was not discovered in ASD children. Contrary to their finding, Nyström *et al*[33] showed more sensitive PLR in infants with an older sibling with autism, which means PLR in high-risk infants is stronger and faster. In their subsequent follow-up study, they found high-risk infants who were diagnosed with ASD have larger relative constriction compared with those who were not. The magnitude of PLR is associated with symptom severity. We noticed that Nyström *et al*[33] excluded pupil activities after flash stimulation until 1s to avoid blinks caused by flashlight, which may affect the result of this research. This might explain why Nyström *et al*[33] and Daluwatte *et al*[31] had different conclusions. In addition, the children have poor cooperation, like excessive eyeball rotation or eyelid closure for a long time could be another factor affecting research[33]. The following research may need to optimize entry criteria of ASD children and reduce error caused by poor cooperation.

RETINA IMPAIRMENTS IN ASD ANIMAL MODELS

To date, numerous protocols can be used to create ASD animal models, including intraperitoneal administration of

Table 2 Visual electrophysiology results of ASD patients

Study	Subjects	Age,y, mean±SD	Sex: male/ female	IQ, mean±SD	Methods	Results
Constable *et al*[23]	11 HFA	37.2±12.2	10/1	116±10	fERG	B-wave amplitude↓ at LA
	15 HC (DA)	36.9±13.2	11/4	N/A		
	14 HC (LA)	35.3±12.9	11/3	N/A		
Constable *et al*[26]	90 ASD	13.0±4.2	130/47 eyes	98.9±16.5	LA-fERG	A-wave and b-wave amplitude↓; B-wave peak time↑
	87 HC	13.8±4.8	82/97 eyes	N/A		
Lee *et al*[27]	57 ASD	13.7±4.8	43/14	99.6±18.9	LA-fERG	B-wave amplitude ↓ in ASDs; B-wave amplitude ↑; PhNR amplitude at 72 ms ↑ in ADHDs
	15 ADHD	15.3±3.5	8/7	92.9±14.2		
	59 HC	13.3±4.6	31/28	N/A		
Friedel *et al*[14]	32 ASD	34±11	19/13	111±16	LA-fERG	No differences in LA-fERG
	31 HC	35±11	19/12	107±11		
Siper *et al*[29]	31 PMS	6.57±2.68	13/18	48.79±13.88	VEP	P60-N75 and N75-P100 amplitudes↓
	79 iASD	6.72±2.58	70/9	89.99±25.69		
	20 PMS sibs	7.20±2.31	5/15	107.94±16.00		
	45 HC	6.69±2.67	25/20	113.21±18.37		

HFA: High-functioning autism; HC: Healthy controls; DA: Dark-adapted; LA:Light-adapted; N/A: Not available; fERG: Full-field ERG; ADHD: Attention-deficit/hyperactivity disorder; VEP: Visual evoked potentials; iASD: Idiopathic autism spectrum disorder; PMS sibs: Unaffected siblings of children with Phelan-McDermid Syndrome.

valproic acid (VPA) or poly(I:C) during the mid-pregnancy and single gene knock-out (Shank3, Fmr1 *etc.*)[34]. Besides CNS abnormalities, abnormal visual behaviors can also be observed in ASD patients, like difficulty maintaining eye contact, disorders of emotional face recognition and disrupted circadian rhythm. It is reasonable to speculate that an unusual retina structure and function may participate in the formation of ASD symptoms. James *et al*[35] reported hyperconnected neural networks in the optic tectum (OT, usually referred to as the superior colliculus in mammals), increased excitatory and inhibitory synaptic drive on tadpoles exposed to VPA. Rossignol *et al*[36] observed lower a-wave and b-wave amplitudes by ERG in the retina of ASD mouse (Fmr1 KO). They discovered the downregulated Syt1a (a protein located at presynaptic membrane) and PSD95 (a protein located at postsynaptic membrane) and the upregulated mGluR5 in Fmr1 KO mice, which is consistent with results reported in CNS[37]. Golgi stain on retina revealed more immature synapses on amacrine cells. In addition, rhodopsin, a kind of photosensitive G-protein-coupled receptor on out segments of photoreceptors, was lower expressed than the control group. Electron microscopy revealed that the regular linear structure of photoreceptor outer segments disappeared in ASD mice[36]. Guimarães-Souza *et al*[38] did similar work on ASD mice induced by VPA. They also found decayed a-wave amplitude, though not statistically significant, there was a downward trend of b-wave amplitude. This may be because they used drug-induced ASD instead of single gene knockout, fewer synapses were impaired compared to knocking out the synaptic function-related genes. Likewise, they also found downregulated Syt1a and upregulated mGluR5 in retina slices. Furthermore, they reported reduced GABA in the retina, as gamma-aminobutyric acid (GABA) is mainly present in retinal amacrine cells[39], combining the results mentioned above that immature synapses arise on amacrine cells, we can hypothesize that amacrine cell may play an important role in the formation of ASD. It has been reported that contrast sensitivity is related to *PDZK1* gene[40] and abnormal contrast sensitivity is another common phenotype of ASD. Xie *et al*[41] found reduced b-wave amplitude on PDZK1-ko zebrafish, yet no synaptic abnormalities were reported. Zhang *et al*[42] studied another autism-associated gene *Engrailed-2*. They identified lower a-wave and b-wave amplitudes, along with reduced calbindin$^+$ horizontal cells, while the number of calbindin$^+$ amacrine cells was higher than the controls. Rhodopsin of photoreceptors and bipolar cells were both reduced. According to these researches above, we summarized most of these animals have abnormal ERG findings, including downregulated a-wave and b-wave, which remind us impaired photoreceptor functions and disturbed synaptic transmission between photoreceptors and bipolar cells. These results can partly interpret eye phenotypes on ASD patients. However, still no effective ocular interventions could be achieved on ASD, and we cannot determine to what extent these retinal abnormalities affect functions of the brain, which finally form ASD.

IPRGCS PARTICIPATE IN ASD FORMATION

ipRGC is another photosensitive cell in the retina[43], different from traditional visual pathway, its axons reach nuclei like SCN, supraoptic nucleus (SON), participating in controlling PLR, circannual rhythms and other behaviors[44]. Recently,

scientists have found it can even regulate glucose metabolism through downstream signaling[45]. The investigation of ipRGC-related neural pathway has become a major focus of current research. Previous studies have reported ipRGC-related neural pathway can also control some autism-like behaviors, such as mood and learning[46]. Hu *et al*[47] reported ipRGC-SON-PVN pathway, in this pathway, light-activated ipRGCs promote oxytocinergic neurons of SON and paraventricular nucleus of the hypothalamus (PVN) releasing oxytocin into cerebrospinal fluid (CSF), which in turn, promote synaptic development and maturation in the hippocampus and other cortex. Without this kind of ipRGC-mediated, light-promoted early cortical synaptogenesis compromised learning ability in adult mice. Another important function discovered in ipRGC is its ability to control circannual rhythms[44], as many clinical studies have reported the proportion of ASD children with circadian disruption was higher than the controls[48] and mutations of circadian clock genes may also leads to autism-like behaviors[49-51]. Thus, ipRGC may be the culprit in circadian disruption. Fernandez *et al*[52] reported ipRGCs project to PHb, which regulates mood of mice. ipRGC can also have projections to SCN, and affect learning behaviors of mice. These pathways remind us there are multiple downstream paths of ipRGC. Together they control learning, mood, and recognition behaviors. Wang *et al*[53] intervened ASD mice (*Cntnap2* KO) with long wavelength (red light) and short wavelength (blue light) dim light at night (DLaN), they found improved stereotyped behaviors in mice irradiated with red light but mice intervened by blue light showed worse social interaction as well as stereotyped behaviors. As the shorter the wavelength the stronger the ipRGCs activation, their research preliminarily demonstrates the potential of ipRGCs in improving ASD. It has been confirmed that ipRGC activation can suppress melatonin secreted by the pineal gland[54]. Since the melatonin disorder observed in ASDs mainly characterized by higher during daylight and lower at night in comparison to normal individuals[55], melatonin has been used to treat ASDs, by improving sleep disorders[56], social interaction, stereotyped behaviors[57]. Wang *et al*[58] also tried to use melatonin to treat ASD mice, they found melatonin treated mice had recovered stereotyped behaviors. Whether ipRGC takes part in the abnormol melatonin level of ASDs is still unknown, possibly because there are no suitable animal models, as the most commonly used C57BL/6 mice lack melatonin Innately.

SUMMARY AND OUTLOOK

OCT and OCTA revealed retinal structure changes and abnormal ocular blood flow perfusion in ASD patients. Those abnormal waves in ERG, along with investigations of ASD animals, suggested retinal signal transduction was disrupted, especially between photoreceptors and bipolar cells. PLR is controlled by nuclei in the brain, which makes the eye-tracker a great choice to show brain lesions.

There are still some limitations in the clinical study on ASDs: 1) The current recruiting and grouping depend mainly on symptoms like HFA, however, as a multifactorial disorder, different factors may have different pathological changes and instrumental findings, simply place these patients into the same group may affect results. 2) Poor cooperation of ASD children is another problem, we noticed most of these children cannot maintain eye gaze to 15s, which is necessary for most OCT models to finish examination. This limitation generates more artifacts in the final images and affects the subsequent results of the analysis. 3) ASD usually occurs at an early age, but the built-in software of OCT or OCTA, mainly based on the adult database, leads to inaccurate results when applying the segmentation algorithm designed for adults to children. Thus, we developed the child OCT and OCTA database, hoping to elevate the accuracy of child retina image measure[19]. The reasons mentioned above may answer why the previous researches have different results. The follow-up clinical studies may need to change grouping strategies, maybe more effective according to pathogenesis of ASD. In addition, advanced equipment may be needed, to improve patients' cooperation and minimize artifacts.

For ASD animal models, less research so far combined the retina and brain to assess the influence of abnormal retina on ASD symptoms. The following researches can try to elaborate how much does vision affects the course of the ASD based on "visual critical period" theory, which has been proved that synapses in the brain tend to be immature without visual stimuli during brain development. As a special photosensitive cell, ipRGC could be the key to illustrate retinofugal pathway. However, ipRGC investigation requires corporation of ophthalmologist and neurologist conducting vitreous cavity injection and stereotactic injection separately.

Connection and communication of eye-brain is a burgeoning and promising research field. Advanced ocular examination equipment may become auxiliary diagnostic tools for the early detection of ASD. Further investigations of ocular manifestations in ASD will provide possibilities for discovering new pathogenesis, developing early diagnosis and performing effective treatment of ASD, and finally will improve the prognosis of ASD children in the future.

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