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REVIEW

Recent Advances in Visual Dysfunction and Ocular Biomarkers in Neurological Disorders

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Abstract: The visual system is an integral part of the central nervous system, and visual symptoms often serve as an early manifestation of underlying neurological pathologies. This review synthesizes recent findings on visual dysfunction in various neurodevelopmental and neurodegenerative diseases. These reports emphasize that ophthalmological symptoms are increasingly recognized as part of a broader spectrum of neurological conditions, enhancing their clinical relevance for differential diagnosis and symptom management. Non-invasive, high-resolution ocular imaging techniques can identify retinal pathologies at the subcellular level. Additionally, the non-invasive visual functional assay, electroretinography, can further corroborate findings of retinal pathology. Distinct retinal changes are detectable in the early stages of progressive neurodegenerative diseases, such as Parkinson's disease, and are strongly correlated with cognitive decline in conditions like Huntington's disease, Alzheimer's disease, and Joubert syndrome. These findings highlight the clinical potential of retinal imaging for risk assessment, diagnosis, and monitoring the progression of diseases with insidious onset. Furthermore, this review emphasizes the retina's accessibility as a key component in investigating the underlying pathophysiology of neurological conditions. Additional clinical and basic science research is needed to better understand the distinct and potentially interconnected contributions of the brain and retina to specific visual symptoms. Investigating suitable preclinical mouse models will be vital for developing and refining novel ocular diagnostic markers, which are important for symptom management and the advancement of therapeutic strategies.

Keywords: visual symptom, retinal pathology, non-invasive ocular diagnosis, Alzheimer's, Parkinson's

Introduction

The visual system, which includes the retina, visual pathway, visual cortex, and visual-associated cortex, is a crucial part of the central nervous system (CNS).[1] Visual dysfunctions are increasingly identified as early indicators of neurological diseases, often preceding or occurring alongside neurological symptoms with insidious onset.[2] The retina is the only part of the CNS that can be imaged using non-invasive techniques with (sub)cellular resolution.[2] These tools are invaluable for assessing not only primary eye diseases but also visual impairments in a wide range of neurological disorders. Ocular diagnostic tests include fundoscopy, which captures en-face images of the retina; Optical Coherence Tomography (OCT), which provides cross-sectional images to measure structural changes and retinal thickness; Optical Coherence Tomography Angiography (OCTA), which visualizes retinal and choroidal vessels and their blood flow; Electroretinogram (ERG), which measures the retina's electrical responses to light; and Visual Evoked Potentials (VEP), which assess electrical activity in the visual cortex in response to stimuli.[3] Advances in eye-tracking technology enable high-resolution measurement of eye movements. Eye movement tests, such as Anti-saccade, Visually Guided Saccade (VGS), and Memory Guided Saccade (MGS), evaluate brain function and visual pathways, assessing cognitive functions, responses to stimuli, and memory-related visual processing.[4]

Although many publications cover the widely recognized ocular manifestations in systemic neurological diseases[5] or have described recent findings,[6,7] this review is the first to critically synthesize recent findings, evidence, and peer-reviewed literature published in 2023 focusing on visual dysfunction across various neurodevelopmental and neurodegenerative

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diseases. It underscores the increasing recognition of ophthalmological techniques as vital tools for detecting CNS dysfunction. Additionally, the review highlights the need for further research into the underlying mechanisms of both visual and neurological pathologies, as well as their molecular interconnections. With the rapid advancement of non-invasive ocular diagnostic tools and the multimodal imaging data integration by Artificial Intelligence (AI),[8–10] there is significant potential for early diagnosis, monitoring disease progression, improving patient care, and optimizing therapeutic outcomes. These innovations are set to play a key role in the future direction of neurological medicine.

Methods

To investigate recent findings on visual impairments in primary neurological disorders, we performed a systematic review of PubMed. We filtered results for papers published in 2023 that met specific eligibility criteria.

The inclusion criteria required that papers focus on a diagnosed neurological or neurodegenerative disease in humans with ophthalmological effects. These effects had to be presented as symptomatic manifestations and/or observed through non-invasive diagnostic techniques examining posterior eye conditions, including Anti-saccade, VGS, MGS, magnetic resonance imaging (MRI), fundoscopy, OCT, OCTA, ERG, VEP, or ocular ultrasound. Eligible studies needed to report either observable visual symptoms or measurable optic changes as a consequence of the primary neurological condition (Table 1). We included papers that presented original research or case reports.

Papers were excluded if they used animal models or reported ophthalmological effects unrelated to neurological pathophysiology, including but not limited to metabolic, infectious, gastrointestinal, vascular, or endocrine causes. We excluded any studies on primary ophthalmological diseases, such as retinitis pigmentosa (RP), macular degeneration, or microvascular eye diseases. Studies related to anterior eye conditions, visual memory, rapid eye movement disorders, emotional perception, visual-motor integration, and circadian rhythm disturbances were also excluded, as these do not represent physical symptoms or are not diagnosed with the imaging methods we considered. Additionally, conference abstracts, literature reviews, and meta-analyses were excluded.

The search was conducted in PubMed using the following algorithm:

((neurodegenerative OR neurological) disease) AND ((visual OR vision OR optic OR ocular) AND (dysfunction OR impairment))

After applying a filter for papers published in 2023, the search returned 703 articles. Citations were imported into Covidence for title and abstract screening. Two reviewers independently screened the articles for eligibility, using a standardized approach to resolve differences by consensus. Papers were excluded if they did not include a primary neurological disorder or lacked a visual symptom. After title and abstract screening, 164 papers remained for full-text review. A total of 53 papers were included in the final extraction, with no visual manifestations as the primary reason for being excluded. PRISMA flowchart shows final results (Figure 1).[11] The findings from all relevant studies are summarized and discussed in this review.

Table 1 Eligibility Inclusion Criteria According to the PICOTS Framework

Population	Humans with a primary neurological disorder and ophthalmological effect
Intervention	With or without treatment
Comparison	Healthy controls
Outcome	Physical visual manifestation, visual symptoms, or changes detected by non-invasive imaging (eg, eye movement tests, MRI, fundoscopy, OCT, OCTA, ERG, VEP, and ocular ultrasound).
Timing	Papers published in 2023
Setting	Any setting

Abbreviations: PICOTS, population, intervention, comparison, outcome, time, setting; OCT, Optical Coherence Tomography; OCTA, Optical Coherence Tomography Angiography; ERG, Electroretinography; VEP, Visual Evoked Potential.

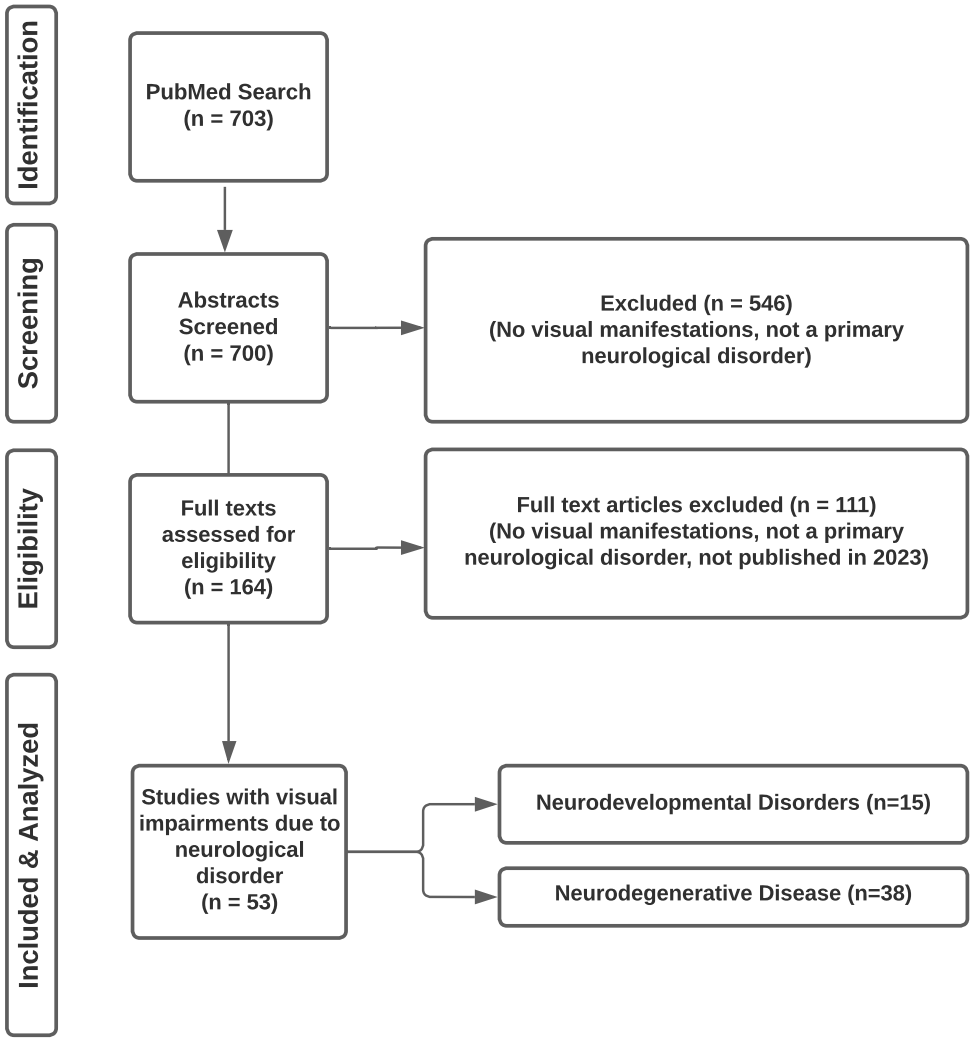

Figure 1 PRISMA flowchart for the systematic review.

Results

A total of 53 studies reviewing 32 distinct diseases were categorized into two major groups: 13 neurodevelopmental (Table 2) and 19 neurodegenerative diseases (Table 3) although some neurodevelopmental disorders exhibit neurodegenerative features. Visual symptoms, along with occasional hearing loss, are associated with several common clinical manifestations including seizures, ataxia, and deficits in motor and cognitive function. Several neurodevelopmental

Table 2 Tabular Overview of Current (2023) Research on the Visual Manifestations of Neurodevelopmental Diseases

Primary Disease	Author	Study Design	Study Population	Visual Dysfunction
ATP1A3-Related Disorders	Huang et al[12]	Retrospective cohort study	11 children with ATP1A3-related disorders	Bilateral optic atrophy
Biotinidase Deficiency	Biswas et al[13]	Retrospective case series	14 patients with biotinidase deficiency	Vision loss, optic atrophy

(*Continued*)

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Table 2 (Continued).

Primary Disease	Author	Study Design	Study Population	Visual Dysfunction
Boucher-Neuhauser Syndrome (BNHS)	Peretz et al[14]	Case report	Young male patient	Optic atrophy, rod-cone dystrophy, photophobia
Canavan Disease	Irilouzadian et al[15]	Case report	14-month-old female	Optic atrophy
Developmental and Epileptic Encephalopathy (DEE)	Vetro et al[16]	Cohort study	17 individuals with DEE	Nystagmus, cortical visual impairment
Genetic Forms of Epilepsy	Abdulkareem et al[17]	Case series	Five consanguineous Pakistani families, each with individuals affected by epilepsy	Nystagmus, optic atrophy
GNAO-1 Related Encephalopathies	Gambardella et al[18]	Cohort study	Seven children with GNAO1 deficiency	Reduced visual acuity, reduced visual field
Hypomyelination with Atrophy of Basal Ganglia and Cerebellum (H-ABC) in the UFM1 gene	Ivanov et al[19]	Case series	Nine children with UFM1-linked H-ABC	Nystagmus, absence of visual fixation or pursuit
Idiopathic Intracranial Hypertension (IIH)	Bozdoğan et al[20]	Cohort study	25 patients with IHH, 22 control individuals	Visual impairments with optic nerve sheath diameter as proxy
Joubert Syndrome	Morelli et al[21]	Retrospective cross-sectional analysis	59 children with Joubert syndrome	Refractive errors, retinal pigmentation, retinal or optic nerve colobomas
Kinesin Family Member 1A Gene (KIF1A)	Paprocka et al[22]	Cohort study	9 Polish patients with pathogenic *KIF1A* variants	Strabismus, astigmatism, myopia, optic nerve atrophy
Mitochondrial Disorder	Ardissone et al[23]	Cohort study	150 patients	Ocular involvement, vision loss, ocular motility alterations
	Howard et al[24]	Case report	9-year-old boy	Reduced visual acuity, reduced color vision, optic atrophy
	Wang et al[25]	Case report	33-year-old male	Blurred vision, ophthalmoplegia, macular retina thinning
Shashi-Pena Syndrome (SHAPNS)	Yuan et al[26]	Case report	21-day-old neonate	Bilateral retinal paving-stone-like white lesions on fundoscopy

diseases are also characterized by microcephaly, macrocephaly, developmental delay, and additional non-neural manifestations. Most neurological diseases involve genetic factors, either due to specific genetic mutations or genetic susceptibility. Aging is the most prominent risk factor for the development of complex neurodegenerative diseases.

Neurodevelopmental Disorder

ATP1A3-Related Disorders

ATP1A3-related disorders refer to a group of neurological conditions caused by autosomal dominant mutations in the ATP1A3 gene and are characterized by a range of symptoms, including hemiplegia, cerebellar ataxia, seizures, and early-onset dystonia-parkinsonism.[65] A retrospective cohort study of 11 pediatric patients with this disorder reported that one patient (9%) developed severe bilateral optic atrophy after the onset of other neurological symptoms, and the condition persisted without recovery.[12]

Table 3 Tabular Overview of Current (2023) Research on the Visual Manifestations of Neurodegenerative Diseases

Primary Disease	Author	Study Design	Study Population	Visual Dysfunction
Alzheimer's Disease (AD)	López-Cuenca et al[27]	Cohort	105 with family history of AD and 39 without	Inner retina thinning
	Ma et al[28]	Cohort	43 AD patients, 62 mild cognitive impairment patients, 34 healthy controls	Reduced blood perfusion and vessel density in retina
	Marquié et al[29]	Cohort	144 individuals with mild cognitive impairment	Macular vessel density
	Mathew et al[30]	Cross-sectional	75 participants (cognitively normal, subjective cognitive decline, mild cognitive impairment, AD)	RNFL thinning
Amyotrophic Lateral Sclerosis (ALS)	Zaino et al[31]	Cohort	12 spinal and 6 bulbar ALS patients	Longer visually guided saccades
	Youn et al[32]	Cohort	53 patients with ALS	Square-wave jerk, saccadic pursuits
Charcot-Marie-Tooth Disease (CMT)	Cipriani et al[33]	Cohort	15 families with CMT	Optic atrophy
Creutzfeldt-Jakob Disease (CJD)	Rajalingam et al[34]	Case Study	Five patients with CJD	Ocular dysmetria, visual hallucinations
	Hisata et al[35]	Case Study	72-year-old female with the Heidenhain variant of sCJD	Photophobia, blurred vision, diplopia, homonymous hemianopia, loss of visual acuity
Dementia with Lewy Bodies (DLB)	Gharbi et al[36]	Cohort	268 patients with DLB	Visual hallucinations
	Schumacher et al[37]	Cohort	Cohort 1: 48 DLB, 46 AD, 38 mild cognitive impairment with Lewy Bodies, 35 mild cognitive impairment due to AD, 71 healthy controls Cohort 2: 34 DLB, 34 AD, 35 healthy controls	Visual hallucinations
	TingSKS et al[38]	Cohort	Prodromal 111 DLB patients, 501 Alzheimer's disease patients	Visual hallucinations
Essential Tremor (ET)	Rekik et al[39]	Cross-sectional	62 patients with ET, 66 controls	Abnormal saccadic movements
Fragile-X Associated Tremor/Ataxia Syndrome (FXTAS)	Fielding-Gebhardt et al[40]	Case-Control	22 premutation carriers and 32 age-matched controls	Prolonged anti-saccadic latency
Gaucher's Disease (GD)	Tullo et al[41]	Cohort	22 patients with GD	Abnormal saccadic movements
	Venkatachari et al[42]	Cohort	45 children with GD	Gaze palsy, abnormal saccades
Huntington's Disease (HD)	Murueta-Goyena et al[43]	Cross-sectional	36 hD subjects, 36 matched controls.	RNFL thinning

(*Continued*)

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Table 3 (Continued).

Primary Disease	Author	Study Design	Study Population	Visual Dysfunction
Lafora Disease	Sun et al[44]	Case Study	Proband with Lafora Disease	Progressive visual impairment
Leukodystrophies	Benzoni et al[45]	Cohort	18 adult-onset patients with vanishing white matter leukodystrophy	Visual disturbance, RNFL thinning, macula thinning
	Dong et al[46]	Cohort	13 pediatric patients with genetic white matter disorders	Visual impairments
	Li et al[47]	Cohort	16 patients with 8 pathogenic variants	Reduced visual acuity, optic nerve atrophy
Neuronal ceroid lipofuscinoses (NCLs)	Cameron et al[48]	Case Series	10 patients from six families with protracted CLN3 disease	Visual loss
	Purzycka-Olewiecka et al[49]	Case Series	Four children with CLN3	Low visual acuity
	Refeat et al[50]	Cohort	37 patients with NCL	Vision loss
	Sakti et al[51]	Cohort	5 CLN3 patients	Macular degeneration
Multiple Sclerosis	FranksCJr et al[52]	Case Study	26-year-old black male	Progressive visual impairment, horizontal nystagmus
	Young et al[53]	Cross-sectional	5478 participants with multiple sclerosis	Visual disturbance
	ZainalAbidin et al[54]	Case Study	29-year-old female	Decreased visual acuity, nystagmus, adduction deficits
Neuronal intranuclear inclusion disease (NIID)	Sone et al[55]	Case Series	4 NIID patients	Macular atrophy, loss of visual acuity, retinal thinning
Parkinson's Disease	Diez-Cirarda et al[56]	Cohort	47 Parkinson's patients and 27 controls	Decreased contrast sensitivity, thickening of the photoreceptor layer
	Tester et al[57]	Cross-sectional	92 persons with Parkinson's	Cataracts, vision loss
	Lucas-Jiménez et al[58]	Cohort	62 patients with synucleinopathies (6 E46K-SNCA mutation carriers, 8 dementia with Lewy bodies, and 48 PD) and 37 controls	Low-contrast visual acuity, photopic contrast sensitivity
Pontocerebellar Hypoplasia Type 8 (PCH8)	He et al[59]	Case Study	6-year-old patient with heterozygous variants of CHMP1A	Delayed visual tracking, inability to fixate
Progressive Supranuclear Palsy (PSP)	Naito et al[60]	Case-Control	26 patients with PSP and 26 healthy controls	Impaired visual fixation suppression
	Nunomura et al[61]	Case Study	63-year-old female with PSP	Saccadic ping-pong gaze, square wave jerks

(*Continued*)

Table 3 (Continued).

Primary Disease	Author	Study Design	Study Population	Visual Dysfunction
Spinocerebellar Ataxia (SCA)	Inomata-Terada et al[62]	Cross-sectional	20 SCA patients and 19 controls	Impaired VGS latency
	Ouchi et al[63]	Case Study	42-year-old male with spinocerebellar ataxia type 7 (SCA7)	Progressive visual loss, macular degeneration, optic atrophy
Wolfram Syndrome (WS)	Carvalho et al[64]	Case Study	23-year-old male with WS	Optic atrophy

Abbreviations: RNFL, Retinal Nerve Fiber Layer; VGS, Visually Guided Saccades.

Biotinidase Deficiency

Biotinidase deficiency is a metabolic disorder caused by autosomal recessive mutations in the BTD gene, leading to low levels of free biotin.[66] It is characterized by symptoms such as seizures, hypotonia, hearing loss, and vision loss.[66] In a retrospective case series of 14 patients with biotinidase deficiency, one of seven (14%) patients under 3 months of age; three out of four (75%) patients between aged 5–14 years; and one out of three (33%) patients aged 18–24 years experienced vision loss. MRI imaging revealed optic chiasm involvement in four of these 14 patients (29%).[13] Early diagnosis of biotinidase deficiency is crucial, as many of its symptoms are reversible with biotin supplementation when treated early, whereas delayed treatment can result in permanent optic atrophy.

Boucher-Neuhauser Syndrome (BNHS)

BNHS, caused by autosomal recessive mutations in the PNPLA6 gene, is characterized by early-onset chorioretinal dystrophy, cerebellar ataxia, and hypogonadotropic hypogonadism.[67] A recent case report describes a patient with a novel pathogenic mutation in the HK1 gene.[14] Interestingly, this patient, initially diagnosed with rod-cone dystrophy, became legally blind by age 23 and later developed cerebellar atrophy and mild parkinsonism, features commonly seen in BNHS.

Canavan Disease (CD)

CD is a genetically inherited leukodystrophy caused by autosomal recessive mutations in the ASPA gene, leading to the accumulation of N-acetylaspartate due to a deficiency in the aspartoacylase enzyme.[68] Patients with CD typically present with macrocephaly, hypotonia, and vision loss.[68] A case report describes a 14-month-old CD patient, who presented with intractable seizures and hypotonia and was confirmed to be blind based on VEP exam.[15]

Developmental and Epileptic Encephalopathy (DEE)

Over 90 genes have been identified as potential causes of DEE.[16] In a cohort study involving 17 individuals with DEE, linked to TMEM63B gene variants, 11 patients (65%) exhibited early-onset nystagmus and cortical visual impairments concurrently with the onset of epilepsy within the first year of life.[16]

Genetic Forms of Epilepsy

Novel pathological variants in the CARS and ARSA genes were identified in five consanguineous Pakistani families, all of whom presented with differential visual manifestations.[17] Among the four tested patients, two (50%) had nystagmus—one carrying an ARSA mutation and the other carrying a CARS2 mutation. Additionally, one patient with the ARSA mutation also exhibited optic atrophy.[17]

GNAO-1 Related Encephalopathies

GNAO1-Related Encephalopathies are caused by autosomal dominant mutations in the GNAO1 gene.[18] These conditions are characterized by epilepsy, movement disorders, and impaired cognitive function. A study presents the first visual

function assessment of young children with GNAO1 deficiency, made possible by using an adapted protocol for this age group with severe epileptic and movement anomalies.[18] The study found that all patients (7/7) aged 2–8 years exhibited difficulties tracking complex actions. Additionally, none of the patients had stereopsis, and they all showed reduced contrast sensitivity and visual acuity. Nearly all patients (5/6) also had a reduced visual field. These findings underscore the importance of considering visual impairments in young children with GNAO1-related encephalopathies for appropriate management strategies.

Hypomyelination with Atrophy of Basal Ganglia and Cerebellum (H-ABC)

H-ABC is characterized by neurodevelopmental delays and deficits in motor, speech, and sensory functions, caused by mutations in the TUBB4A and UFM1 genes.[19] Nine children carrying UFM1 mutations exhibited impaired vision, including nystagmus and absent visual fixation or pursuit, starting at birth or within the first few months.[19]

Idiopathic Intracranial Hypertension (IIH)

Patients with IIH often experience impaired vision, headaches, and tinnitus due to elevated intracranial pressure (ICP), typically resulting from dysregulated cerebrospinal fluid (CSF) accumulation.[69] A definitive diagnosis of IIH is made by measuring ICP via lumbar puncture. A study involving 25 IIH patients demonstrated that lumbar puncture concomitantly reduced CSF volume, ICP, and optic nerve sheath diameter (ONSD), as measured by optic ultrasonography. This finding suggests that ONSD measurement could be a promising non-invasive tool for both diagnosing and monitoring IIH.[20]

Joubert Syndrome

Joubert syndrome, a type of ciliopathy caused by mutations in over 40 genes, is clinically diagnosed by the molar tooth sign on MRI.[70] Although the specific manifestations vary depending on the gene involved, visual impairments are often among the earliest symptoms, preceding the onset of cerebellar symptoms such as ataxia, dysmetria, and developmental delay.[70] A retrospective cross-sectional study involving 59 children with Joubert syndrome, carrying mutations in the AHI1, CC2D2A, CEP290, CPLANE1, or RPGRIP1L genes, is among the first to investigate retinal pathology beyond the known oculomotor impairments associated with cerebellar dysfunction in this disease. Half of the children exhibited signs of retinal dystrophy, such as reduced ERG responses and altered VEP, even in the absence of visible funduscopic abnormalities. Notably, a significant association between retinal dystrophy and intellectual disability was found in these patients ($p=0.047$).[21]

KIF1A-Related Disorders

KIF1A-related disorders, caused by mutations in the KIF1A gene, refer to a group of heterogeneous disorders with variable impairments in motor, cognitive, and visual functions.[71] A report identified three novel pathogenic KIF1A variants in 5 patients who exhibited non-uniform visual manifestations, including an 11-year-old male with strabismus, astigmatism, and hypermetropia; a 6-year-old female with +4.0 D bilateral hyperopia by age 2; a 3-year-old male with cortical visual disturbance; and a 2-year-7-month-old male with optic nerve atrophy.[22]

Mitochondrial Disorders

Mitochondrial disorders, caused by numerous variants that alter mitochondrial DNA or nuclear DNA affecting mitochondrial function, lead to a range of symptoms depending on the specific disorder.[72] A retrospective study of 150 Italian patients with mitochondrial disorders found that ocular motility abnormalities were present in patients with Leigh syndrome (51.8%) and in those with Progressive External Ophthalmoplegia plus (7.3%). This high rate of ocular involvement in these two diseases has not been previously reported.[23] In a case report, a 9-year-old Leigh syndrome patient, who first presented with reduced vision at age 5, was found to subsequently develop severe bilateral visual acuity reduction, color vision deficiency, and bilateral optic atrophy.[24] Another case study reported a 33-year-old man diagnosed with mitochondrial neurogastrointestinal encephalopathy, based on clinical presentations and the presence of a pathogenic variant in the TYMP gene. In addition to the optic neuropathy typically associated with MNGIE, this patient also exhibited inner retinal ganglion cell complex thinning and an electronegative ERG. This study is the first to link inner retinal anatomical and functional impairment to MNGIE.[25]

Shashi-Pena Syndrome (SHAPNS)

SHAPNS, caused by autosomal dominant mutations of the ASXL2 gene, is characterized by distinct facial features with additional neurological disorders including macrocephaly, seizure, and hypotonia.[73] A case report detailed the molecular and clinical diagnoses of a 21-day-old patient, carrying ASXL2 gene truncation, manifested previously undescribed bilateral retinal paving-stone-like white lesions under fundoscopy.[26]

Neurodegenerative Disease

Alzheimer's Disease (AD)

AD is the most common progressive neurodegenerative disorder and the leading cause of dementia.[74] The histopathological hallmarks of AD—amyloid beta (Aβ) aggregates and hyperphosphorylated Tau (pTau) tangles—have been used as CSF biomarkers, while amyloid plaques can also be visualized through positron emission tomography imaging.[74] However, these tests are invasive and costly. Retinal functional and structural changes in AD have gained increasing attention as potential non-invasive, more accessible and scalable approach for diagnosing high-risk AD individuals. A study of 75 participants (28 cognitively normal, 26 with subjective cognitive decline, 17 with mild cognitive impairment (MCI), and 4 with AD) found that reduced retinal nerve fiber layer (RNFL) thickness was linked to smaller volumes in several brain regions (eg, hippocampus, amygdala, temporal and occipital lobes) and worse cognitive scores.[30] In a study examining the preclinical stage of AD, ophthalmological examinations of 144 healthy individuals —105 with a family history of AD and 39 without, some carrying and some not carrying the high-risk APOE ε4 allele— found that the high-risk group had increased visual acuity but showed a trend toward thinning of the inner retina. The authors suggest that higher visual acuity in preclinical AD may be linked to Aβ deposition, which induces hyperexcitability of retinal cells. As the disease progresses, visual acuity is expected to decline, as observed in other studies.[27]

A study of 43 AD patients, 62 individuals with MCI, and 34 healthy controls found that both AD and MCI groups had reduced vessel density and blood perfusion density in retinal superficial capillary plexus ($p<0.05$). This reduction was significantly correlated with lower scores in cognitive, visuospatial, and executive functions ($p<0.05$), but not with CSF biomarkers such as Aβ and p-Tau.[28] Another study of 144 MCI patients categorized by CSF biomarkers exhibited unchanged macular vascular density.[29]

Amyotrophic Lateral Sclerosis (ALS)

ALS, primarily recognized as a motor neuron disease, can also affect non-motor regions of the brain that regulate oculomotor function.[75] A study involving 18 ALS patients and 13 controls found that two ALS subtypes—spinal variant and bulbar variant—exhibited distinct saccadic profiles. This study not only supports the diagnostic value of eye movement analysis in ALS but also indicates the involvement of different neural networks associated with each ALS subtype.[31] Additionally, a prospective observational study of 53 patients with various types of motor neuron diseases found that 64.2% had ocular dysfunction, including square-wave jerks in 37.7% and saccadic pursuit impairments in 30.2%. These ocular abnormalities were significantly associated with the disease stage.[32]

Charcot-Marie-Tooth Disease (CMT)

CMT disease encompasses a group of relatively common neurological disorders caused by mutations in at least 100 different genes, typically affecting motor neurons, sensory neurons, and vision.[33] A recent study identified a new autosomal recessive variant of the *MYO9B* gene in a cohort of CMT type 2 patients with optic atrophy. This discovery prompted further investigation, leading to the identification of compound heterozygous *MYO9B* mutations in patients with isolated optic atrophy.[33]

Creutzfeldt-Jakob Disease (CJD)

CJD is a fatal prion disease associated with rapidly progressive dementia and often presents with visual symptoms.[76] A case series of five Tasmania CJD patients found four with visual hallucinations, one with ocular dysmetria and saccadic pursuits.[34] In another case, a 72-year-old woman with Heidenhain variant CJD progressed from photophobia and blurred vision to severe visual deterioration.[35] This patient also experienced left homonymous hemianopia and

restricted downward movement of the left eye, while the pupillary light reflex was intact with a normal fundoscopy.[35] The Heidenhain variant is notably associated with early visual symptoms, including blurred vision, as seen in these cases.

Dementia with Lewy Bodies (DLB)

DLB, the second most common neurodegenerative dementia associated with parkinsonism, is a type of synucleinopathy characterized by phosphorylated α-synuclein aggregates and Lewy bodies (LBs) as pathological hallmarks.[77] Among 268 DLB patients stratified by symptom onset, visual hallucinations were the most common in the mixed-onset group ($p=0.025$).[36] Another study found visual hallucinations in 11% of prodromal DLB patients, significantly higher than in AD (OR 11.98, $p<0.0001$).[38] Additionally, increased free water fraction in the pedunculopontine nucleus-thalamus pathway was associated with hallucinations in DLB patients, although the association was not reproducible in a second cohort ($p=0.017/p=0.18$).[37] These findings suggest that visual hallucinations in DLB may relate to specific brain pathways.

Essential Tremor (ET)

ET describes a group of very common, cerebellar dysfunction diseases characterized by intention tremor, mild gait ataxia, and eye movement disorder.[78] A cross-sectional study of 62 ET patients and 66 controls found 46.7% of ET patients (vs 20% in controls) had significant eye movement issues, including prolonged saccadic latency (38.7%, $p=0.033$), altered smooth pursuit (38.7%, $p=0.033$), anti-saccadic errors (16%, $p=0.034$), and square-wave jerks (11.5%, $p=0.024$).[39] The study also identified a distinctive ET phenotype with anti-saccadic errors and subcortical cognitive decline, even without overt cerebellar signs.

Fragile-X Associated Tremor/Ataxia Syndrome (FXTAS)

FXTAS, characterized by action tremors, gait ataxia, and cognitive impairments, primarily affects older adult carriers of the FMR1 gene premutation, which consists of 55–200 CGG repeats.[79] Due to its X-linked inheritance pattern, most studies have focused on males. A study of oculomotor behavior in female-dominant subjects (16 out of 21 carriers, 21 out of 32 controls) found that carriers exhibited prolonged antisaccade latencies compared to controls. A strong correlation between reduced saccade accuracy and increased antisaccade latency was observed, which was associated with neuromotor impairments in carriers, both when considering both genders and females separately. These findings suggest that oculomotor measures could serve as potential biomarkers for FXTAS in both genders.[40]

Gaucher's Disease (GD)

GD, one of the most common lysosomal storage disorders, is caused by mutations in the GBA1 gene, leading to glucocerebrosidase deficiency and the accumulation of glucosylceramide.[80] GD typically manifests with early-onset seizures and progressive declines in motor and cognitive functions. A study involving 45 Indian pediatric patients with GD (aged 2.5–15 years) found that cognitive impairment was the most common feature (31/45, 86.7%), followed by gaze palsy (27/45). Additionally, 12 out of 32 testers exhibited abnormal saccades.[42] In another study of 22 GD patients, abnormal saccadic movements were found in all GD3 subtype patients (3/3, 100%) and in one GD1 subtype patient (1/19, 5%).[41] A significantly higher rate of saccadic impairment was observed in homozygous patients compared to heterozygous patients (3/3, 100% vs 0/19, 0%; $p<0.001$). These findings support the notion that impaired saccades are a hallmark of neuronopathic GD and may be useful for early diagnosis of the disease.

Huntington's Disease (HD)

HD, caused by CAG repeat expansions in the huntingtin gene, is an autosomal dominant neurodegenerative disorder that primarily affects the striatum and leads to motor and cognitive impairments.[81] A study comparing 36 hD patients with 36 controls found that the manifested patients had significantly thinner RNFL near the optic nerve head in the temple region ($p=0.011$).[43] This study also showed that the macular inner nuclear layer thickness was consistently and significantly associated with cognitive performance in manifest HD patients, suggesting this retinal pathology is a potential biomarker for monitoring cognitive function in HD. Additionally, this report reveals that the external limiting membrane–Bruch's membrane complex, which includes the photoreceptor inner and outer segments and the retinal pigment epithelium, is also significantly thinner in HD patients. This is the first study to evaluate the thickness of the outermost retinal layer in

HD patients, and the results align with prior observations of outer retinal degeneration in various preclinical HD mouse models.

Lafora Disease

Lafora disease, caused by autosomal recessive mutations in the EPM2A and EPM2B genes, is characterized by early-onset seizures, ataxia, and visual impairment, followed by a rapid decline in cognitive and motor function.[82] The pathological hallmark of Lafora disease is the deposition of polyglucosan bodies (Lafora bodies). A case report and genetic study described two affected siblings with a novel EPM2A mutation. Both presented with poor visual acuity at the time of diagnosis at age 15, lost all light perception within 4 years, and died at age 24.[44]

Leukodystrophies

Leukodystrophies, a group of white matter disorders caused by mutations in over 60 genes, result in myelin damage and are characterized by declines in motor, speech, visual, and cognitive functions.[83] A whole-exome sequencing study of 16 patients with leukodystrophy identified 8 potentially pathogenic variants in the AARS2, ABCD1, CSF1R, and GALC genes, three of which were novel. One patient carrying a CSF1R variant presented with reduced visual acuity and optic nerve atrophy.[47] The authors proposed that axonal degeneration of retinal ganglion cells, probably due to dysregulated myelination of the optic nerve, represents the primary ocular pathology, independent of white matter abnormalities.

A retrospective study of 13 pediatric patients with white matter disorders found that four (30.8%) with ABCD1 mutations showed visual impairment, often associated with occipital lobe involvement on MRI.[46] In a cohort of 18 patients with adult-onset vanishing white matter leukodystrophy, 6 out of 7 tested patients exhibited an attenuated ERG b-wave with a normal a-wave. One patient presented with visual disturbances, and two others had thinning of the ganglion cell-inner plexiform layer in the macula, as well as RNFL thinning in both the macula and temporal sector.[45] The authors concluded that the common retinal alterations observed in adult-onset leukodystrophy warrant further investigation as potential surrogate biomarkers of disease progression.

Neuronal Ceroid Lipofuscinoses (NCL)

NCL, also known as Batten disease, is a type of lysosomal storage disorder with 14 clinical subtypes (CLN1–CLN14).[84] Common features of NCL include early-onset seizures, vision loss, and subsequent motor and cognitive function decline.[84] The pathological hallmark of NCL is the accumulation of lipofuscin due to a lysosomal waste clearance dysfunction. Studies showed four[49] and ten[48] CLN3 mutation-carrying children exhibited abnormal ERG, retinal degeneration, and optic atrophy as the initial symptoms, with onset occurring between 4 and 9 years of age. Another study of five CLN3 patients, with a median age of 6.2 years, revealed electronegative ERG, disrupted ellipsoid zone on OCT, bull's-eye maculopathy on fundoscopy, and a hyperautofluorescent ring surrounding the central hypoautofluorescent area on fundus autofluorescence imaging.[51] A separate study involving 37 NCL patients, stratified by CLN subtype, found that vision loss was the most common symptom, reported in 21 out of 24 (87.5%) patients.[50]

Multiple Sclerosis (MS)

MS is an autoimmune disease characterized by demyelination of several types of nerve fibers, including the optic nerves, causing optic neuritis.[85] A case report described a 29-year-old patient with MS, who had previously been diagnosed with Wall-Eyed Bilateral Internuclear Ophthalmoplegia (WEBINO). The patient presented with binocular diplopia, alternating exotropia, bilateral adduction deficits, nystagmus, and impaired convergence.[54] Another case report detailed a 26-year-old man who presented with rapidly progressive vision impairment in one eye, with horizontal nystagmus developing 1–2 years after MS diagnosis.[52] A UK study of 5,478 MS patients found 80% reported visual issues, which were more common with longer disease duration.[53] A follow-up showed that relapsing-remitting MS patients were more sensitive to visual changes, highlighting the need for early ophthalmologic assessment.

Neuronal Intranuclear Inclusion Disease (NIID)

NIID, caused by expanded GGC repeats in the NOTCH2NLC gene, is generally characterized by motor and cognitive symptoms.[86] The neuropathological hallmark of NIID is the deposition of ubiquitin-containing nuclear

inclusions. In postmortem tissue from four genetically confirmed NIID patients, similar inclusions were observed in several brain regions as well as throughout the retinas.[55] Among these four patients, two (cases 1 and 2) had significantly reduced retinal thickness and ERG abnormalities without any fundus anomalies, while the other two (cases 3 and 4) exhibited both fundus and ERG anomalies, and severe photoreceptor degeneration. Case 3 had been diagnosed with RP 15 years prior to the diagnosis of NIID. This report, consistent with previous studies, highlights that visual dysfunction can be an early sign of NIID, despite clinical heterogeneity. It also supports, for the first time, the pathological contribution of NOTCH2NLC GGC expansion-caused intranuclear inclusions in retinal disorders.

Parkinson's Disease (PD)

PD, a type of synucleopathy, is the most common neurodegenerative movement disorder, characterized by dopaminergic neuronal loss that leads to motor symptoms.[87] Several nonmotor symptoms including visual impairment (eg, visual hallucinations, impaired visual acuity, reduced spatial contrast sensitivity, depth perception issues, and color vision deficits) are highly prevalent in the early stages of the disease.[88] A hierarchical cluster analysis of 37 controls and 62 patients with various forms of synucleopathies (ie, DLB, PD, carriers with E46K mutation of SNCA gene) revealed that the mild subtype presented only nonmotor symptoms such as altered visual acuity, while patients in the severe subtype exhibited both marked motor and visual impairments.[58] These findings highlight the potential value of nonmotor symptoms, such as impaired visual acuity, in subtyping different forms of synucleopathies and monitoring their associated brain pathophysiology. Comprehensive clinical and imaging analyses of 47 PD patients (12 with and 35 without visual hallucination) plus 27 controls found patients with visual hallucinations had significantly lower visual contrast sensitivity and thicker retinal photoreceptor layers on OCT compared to those without hallucinations and to controls. These observations warrant further studies validating that the visual system is a pathological basis and biomarker for visual hallucinations in PD.[56]

The awareness of visual dysfunction of PD is often overshadowed by motor symptoms and the effects of aging. A cross-sectional electronic survey assessed the prevalence of awareness regarding PD-associated visual dysfunction among 92 PD patients. Findings revealed that approximately half of the participants who recognized visual issues had a diagnosed eye condition, with cataracts being the most common, followed by intraocular disorders, ocular motor dysfunctions, and optic nerve disorders ($p<0.05$). Notably, the analysis also showed that ophthalmologic symptoms in PD are more closely associated with the disease itself rather than age-related eye conditions.[57]

Pontocerebellar Hypoplasia Type 8 (PCH8)

PCH8, caused by autosomal recessive mutations in the CHMP1A gene, is characterized by both motor and cognitive impairment.[59] Severe visual symptoms, present from infancy, are also a hallmark of this rare condition. In a case study of a 6-year-old patient, who is the eighth known case of PCH8 worldwide, exhibited severe developmental delay, an inability to track visual stimuli, and was unable to fixate on small objects until the age of two.[59]

Progressive Supranuclear Palsy (PSP)

PSP, a neurological disorder affecting movement, balance, cognition, and eye control, is characterized by the predominant accumulation of tau tangle at the brainstem, subthalamic nucleus, and basal ganglia.[60] A retrospective study of 26 PSP patients and 26 PD patients showed that all PSP patients failed to suppress caloric nystagmus ($p=0.002$), indicating poor visual fixation suppression, a phenotype that was not presented by PD patients.[60] A case report described a 63-year-old woman with gait disturbance who initially presented with "saccadic ping-pong gaze" and square-wave jerks during examination, particularly under dim light or with eyes closed. She was diagnosed with PSP 1.5 years later.[61]

Spinocerebellar Ataxia (SCA)

SCA is a group of autosomal dominant neurodegenerative disorders characterized by cerebellar atrophy, motor dysfunction, and visual impairment in some forms of SCA.[89] A case report described a Japanese patient with SCA7 who presented with cerebellar ataxia at age 34, followed by progressive vision loss at age 42, macular degeneration, and slow eye movement at age 51. Postmortem tissue examination of this patient revealed widespread neuronal degeneration and

polyQ-positive inclusions in multiple neural and visual pathways.[63] A study comparing VGS and MGS task performance in 20 patients (12 with SCA6 and 8 with SCA31) and 19 controls revealed that patients had increased saccade latency and more variable amplitude ($p<0.01$) in the VGS task, but not in the MGS task, suggesting the more prominent involvement of cerebellar dysfunction than previously recognized. SCA disease progression was also found to associate with altered saccade velocity, underscoring the potential value of saccade velocity analysis as a tool for investigating cerebellar pathophysiology during SCA progression.[62]

Wolfram Syndrome (WS)

WS, caused by the WFS1 gene mutation, is a multisystemic genetic disorder that presents both non-neurological and neurological symptoms including early-onset optic atrophy followed by ataxia, cognitive decline, dementia, and psychiatric issues.[90] WS patients often became blind by adolescence. A case report discussed a 23-year-old with WS, who presented at the ER with repeated loss of consciousness and had previously been diagnosed with optic atrophy when the patient was 8 years old.[64]

Discussion

Visual Dysfunction in Neurological Disorders

This review highlights recent advancements in recognizing the critical role of visual symptoms as early indicators of various neurological disorders, including some that were previously unrecognized. For example, a study found that ALS, traditionally thought to spare oculomotor functions, actually presented with oculomotor dysfunctions, such as impaired volitional saccades.[31,32] Children with GNAO1-related encephalopathies exhibit severe ocular pathologies, which were identified through specialized protocols designed for individuals with severe epileptic and movement disorders.[18] Another example is the high prevalence of ocular pathologies in Leigh syndrome.[23]

Atypical initial presentations—such as WEBINO in MS,[54] impaired visual fixation suppression in PSP,[60] and paving-stone-like white fundus lesions in SHAPNS[26] — demonstrate how visual symptoms and retinal pathologies can prompt more comprehensive neurological evaluations and potentially enable earlier diagnosis. A report describing two distinct subtypes of ALS identified differential anti-saccadic profiles,[31] underscoring that visual manifestations may also provide valuable insights for differential diagnosis when considered alongside molecular diagnostics, medical history, and neurological assessments.

Ocular Markers in Neurological Disorders

Abnormal eye movements and optic atrophy, resulting from impaired visual pathways and brain cortices, are visual symptoms in neurological disorders. Altered retinal structure and function, however, are increasingly observed in various neurodegenerative diseases. Diminished ERG signals and retinal degeneration, leading to retinal thinning, have been documented in patients with Joubert Syndrome,[21] leukodystrophies,[45] MNGIE,[25] NCL3,[48,49] and NIID.[55] These findings underscore the diagnostic value of retinal pathology in these conditions. They also emphasize retinal pathology is involved in at least some aspects of visual dysfunction of various neurological diseases. In this context, it is to noteworthy that rod-cone dystrophy (ie, RP) has been reported to occur years before the onset of neurological symptoms in patients with BNHS[14] and NIND.[55] Additionally, the HK1 gene, recently linked to BNHS,[14] is also associated with RP.[91]

The current clinical diagnosis of progressive neurodegenerative diseases, such as AD and PD, relies on symptoms that manifest only after significant neuronal loss, often occurring years after the initial neuronal damage.[92] This highlights the critical need for biomarkers that can facilitate early detection of neuronal functional decline and identify therapeutic windows before the clinical manifestation of the disease. A study describing altered retinal structures and visual acuity in PD patients without cognitive deficits suggests the retina's involvement in early PD.[56] Additionally, growing evidence supports associations between reduced retinal vessel density in the superficial capillary plexus and patients with AD and MCI,[28] as well as between RNFL thinning and cognitive decline in AD.[30] A strong association between RNFL thinning and cognitive decline in HD[43] and between retinal dystrophy and intellectual disability in Joubert syndrome[21] has also been found. These reports support the need for future research into the mechanistic connection between retinal anatomical changes and cognitive impairment.

Collectively, these findings stress the potential of multimodal retinal imaging and functional assessments in identifying novel markers that could be valuable for risk assessment, monitoring disease progression, and gaining insights into specific aspects of neurological symptoms, particularly in disorders with insidious onsets.

Mechanistic Insights of Retinal Dysfunction in Neurological Diseases

The retina offers several distinct advantages for researching CNS pathology, including its relatively simple structure, accessibility to imaging and functional assays for longitudinal monitoring, and potential for targeted therapeutic agent delivery. Retinal dystrophies observed in the early stages of neurodegenerative diseases suggest a common underlying mechanism between retinal and brain pathology. Supporting this, ubiquitin-rich intranuclear inclusions, similar to those found in the brains of patients with NIID, have also been observed in their retinas.[55] Additionally, both the retina and brain exhibit similar deposition of lipofuscins in patients with NCL,[93–95] β-amyloids in AD,[96–101] and LBs in PD.[102,103] Mouse models replicating these diseases also exhibited similar pathologies in brains and retinas. For example, studies involving AD transgenic mice have revealed abnormal retinal Aβ deposition.[104–106] Fluorescent Aβ plaques, marked by the binding of curcumin (a fluorochrome with high and selective affinity for Aβ), can be visualized in the retinas of both AD mouse models and AD patients using confocal scanning laser ophthalmoscopy (cSLO).[97,101] Additionally, hyperspectral imaging could be used to detect changes in the reflected light spectra caused by retinal Aβ deposition in both AD mouse models and human patients.[98,107] These advancements highlight the additional potential of ocular imaging for AD diagnosis by detecting the characteristic pathological lesions of Aβ. AI may further enhance the precision and reliability of multiple imaging modalities for AD diagnosis.[108,109] Notably, the imaging of tauopathy, which may be more directly relevant to AD pathology,[110,111] remains to be fully explored.

CSF diagnosis of α-synuclein has been recent developed for PD diagnosis,[112] despite its invasive nature. The high prevalence of early visual symptoms in PD and the presence of LBs in the retinas of PD patients and mouse models[113] have sparked interest in the development of ocular imaging for detecting retinal LBs, yet this remains an underexplored area of research. In a novel mouse model $Rod^{\Delta Vps35}$ developed by our group, LBs containing endogenous α-synuclein aggregates were found to accumulate in the retina, partially concentrated in activated retinal microglial cells, at the onset of retinal dystrophy.[88] Importantly, cSLO sensitively detected these LBs as bright autofluorescent foci in live animals, suggesting their potential as a novel ocular biomarker for the early diagnosis of PD and other synucleinopathies. Validating this approach in human patients is of paramount clinical significance, particularly for identifying an optimal time window for therapeutic interventions and clinical trials. These studies collectively demonstrate that preclinical mouse models of AD and PD are crucial not only for understanding the pathogenesis of these disorders but also for developing novel ocular diagnostic methods.

Limitations

This review has several limitations to consider. The exclusion of studies published before 2023 may have omitted valuable historical data on visual dysfunctions in primary neurological disorders, potentially narrowing the scope of insights. Additionally, variability in study methodologies and sample sizes among the included studies could limit the generalizability of the results, particularly for rare disorders often reported through case studies or small cohorts, which might not represent the broader population affected by these conditions. Furthermore, visual manifestations are rarely specific to a single disease, necessitating comprehensive diagnostic workups to determine their etiology. Case studies, while highlighting atypical presentations, may not generalize to larger populations but serve as crucial reminders of the variability in disease presentation. Atypical cases underscore the diverse clinical manifestations of neurological disorders, emphasizing the need for clinicians to maintain a high index of suspicion when evaluating visual symptoms. The potential effects of drug administration have not been considered.

Gaps and Further Developments

While this review provides a brief overview of the potential connection between visual dysfunction and neurodegenerative diseases, there are differing theories on the mechanisms that contribute to this decline. In the context of visual

dysfunction in neurological disorders, different schools of thought focus on whether ocular manifestations merely mirror central neurodegeneration or emerge through distinct pathophysiological mechanisms.[114] This debate also extends to the origins of oculomotor abnormalities in conditions traditionally considered to spare ocular pathways, such as ALS, with some studies suggesting cortical involvement while others implicate midbrain or brainstem circuits.[115] Additionally, there are controversies around whether the retina and brain share similar pathological changes in the context of AD and inquiries about the need to simultaneously explore retinal and brain structural changes to disentangle correlations between the two.[116] Among the fundamental issues, proving causality between retinal and brain pathology remains challenging, despite mounting evidence of correlations between retinal thinning and neurodegenerative disease severity.[117,118] Imaging techniques such as OCTA can produce inconsistent results due to motion artifacts and limitations in use among older patients and children,[119] and overlapping ocular phenotypes in rare neuro-ophthalmic diseases make differential diagnoses exceedingly complex.[120] Current research gaps include a lack of large-scale, longitudinal studies that would validate retinal biomarkers in conditions like PD,[121] and insufficient clarity regarding whether early inflammatory or degenerative changes in the retina reflect compensatory adaptations or harmful processes or even drug treatment.[122] Looking ahead, advanced imaging modalities and AI-driven analytics show promise for early risk assessment and disease monitoring,[123] while new translational animal models could clarify shared molecular pathways and pinpoint optimal therapeutic windows,[113] thus fostering the development of novel ocular diagnostic techniques and interventions.

Conclusion

Visual impairments, including ocular-motor, optic nerve, and retinal function deficits, often precede or accompany neurological conditions, emphasizing the need to incorporate visual assessments into clinical practice. Non-invasive ophthalmological examinations are crucial for the high-resolution, high-sensitivity detection of subtle changes in the retina and visual pathways. Advances in imaging technology, the establishment of normative data, and the integration of AI can further enhance the diagnostic value of ocular biomarkers. Longitudinal studies are essential for assessing their prognostic significance. Future research should focus on uncovering the underlying mechanisms of visual dysfunction in neurological conditions. These efforts have the potential to optimize the diagnosis, management, and treatment of both ocular and neurological symptoms across a range of disorders.

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