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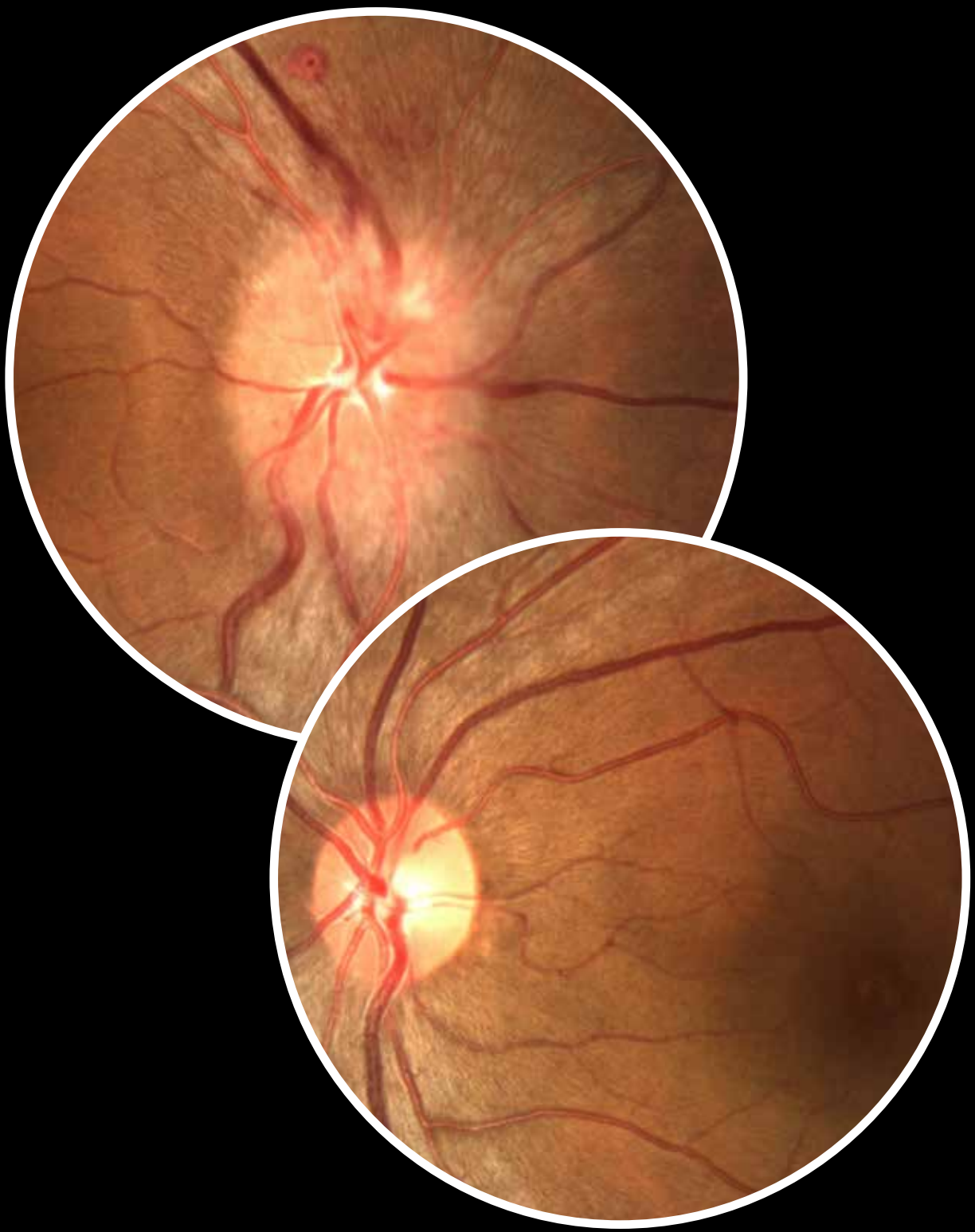
INAUGURAL ISSUE



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Editorial
A Promising Breakthrough in Neuro-Ophthalmology

Welcome to the inaugural issue of the Indian Journal of Neuro-Ophthalmology. This publication is a significant achievement in the journey of Indian Neuro-Ophthalmology Society of India . It aims to serve as a specialized forum for sharing advanced research, clinical practices, and innovations.

Our inaugural issue sets the stage for publication of outstanding, peer-reviewed papers that encompass a diverse array of subjects, including, but not restricted to:

- Clinical research refers to unpublished investigations that offer novel perspectives on the identification, therapy, and control of neuro-ocular disorders.
- Case Reports: Elaborate examinations of intricate and demanding instances that provide crucial educational opportunities.
- Review articles are detailed evaluations that provide a concise summary of existing knowledge and suggest areas for further research.
- Notes on technical aspects: Novel diagnostic and treatment approaches that improve clinical practice.

As we begin this thrilling expedition, we are aware of the obstacles and possibilities that await us. Advancements in medical technology and research methods are rapidly advancing, offering unparalleled possibilities for discoveries in neuro-ophthalmology. We want to remain at forefront of these advancements to offer our readers the most pertinent and influential information.

We cordially invite you to assist us in this undertaking. Regardless of matter whether you are a researcher, physician, or student, your suggestions are crucial for the success of this journal. Collectively, we have the ability to achieve a platform through which we can contribute in enhancing the knowledge about neuro-ocular diseases, over time leading to improved patient care.

To conclude, we deeply appreciate the support and commitment of our editorial board, reviewers, writers, and readers. We anticipate your valuable contributions and we anticipate the lively debates that will inevitably arise from the contents of this publication. Salutations to the Indian Journal of Neuro-Ophthalmology - a pioneering publication in the domain of neuro-ophthalmology.

Kind regards,

Rashmin Gandhi
Editor in Chief

From the ***Secretary's Desk***

A new and exciting chapter in the journey of neuro-ophthalmology in Indian begins as the first issue of the Indian Journal of Neuro-Ophthalmology (IJNO) is being launched. A lot of hard work has gone in the making of this issue and I wish to commend Dr Rashmin Gandhi, the Editor in Chief and Dr Swati Phuljhele, the Editor and Dr Digvijay Singh, the Associate Editor along with the highly reputed and outstanding Editorial Board.

This journal will provide an ideal platform dedicated for discussion on all issues related to neuro-Ophthalmological disorders. The purpose of IJNO is to create and extend an interest in neuro-ophthalmology among practicing ophthalmologists, residents and fellows. The journal aims to offer a wide range of content to its readers; varying from basic examination skills and investigation to advances in technologies and novel treatment approaches. Interesting cases will help to understand decision making and planning in a case with neuro-ophthalmological issues.

The inaugural issue features opinion from leading experts on the topics of optic neuritis, gene therapy and steroids in NAION. The issue also features excellent review articles on neuro-ophthalmology manifestations of COVID and hereditary optic neuropathy. All in all, a very exciting collection of articles that is sure to enrich the knowledge and understanding of all our readers.

I wish that the journal continues to grow and evolve, and provides a stage for deliberation among researchers, clinicians, and students who are passionate about advancing the understanding and treatment of neuro-ophthalmic disorders.

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Neuro-ophthalmic Complications in Covid-19- Past and Future Implications

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ABSTRACT

Initially believed to be a respiratory disease, COVID-19, however evolved as a multisystem disease with the ability to affect gastro-intestinal, cardiovascular, urinary, haematopoietic, musculoskeletal and central nervous systems. Neurological manifestations in acute as well as recovery phase of COVID-19 are abundant. Neuro-ophthalmic features constituted an important part of neurological involvement in COVID-19. This article elaborates various neuro-ophthalmic manifestations seen in association with SARS-CoV-2 infection. In most cases a temporal correlation supports the cause and effect relationship of this viral infection with the disease. However, a direct causal link could not be established. Nonetheless, as the pandemic evolved, the spectrum of these manifestations continued to diversify thereby making SARS-CoV-2 an important differential in neuro-ophthalmic diseases. Some people who had been infected with the virus experience long-term effects, known as Long COVID or Post-COVID Conditions (PCC). Although pandemic is over, we will likely co-exist with the virus for many years to come and should therefore be aware of the effects of COVID-19 and its long term implications.

INTRODUCTION

Ocular manifestations are a known occurrence in COVID-19 and in rare instances have been the presenting feature of the disease. Neurological manifestations in acute as well as recovery phase of COVID-19 are abundant.

Neuro-ophthalmic features constitute an important part of neurological involvement. Vaccine-related neurological complications also surfaced after the vaccination drive. Long term effects of the infection are also described in the form of Long COVID or Post-COVID Conditions (PCC). Here, we provide a comprehensive review of the available literature on various neuro-ophthalmological manifestations associated with COVID-19 and its future implications.

UNDERLYING MECHANISMS

The exact mechanism of action of the virus has not been completely elucidated. The binding of the viral spike (S) protein to ACE-2 receptor facilitates cell entry. Cleavage caused by cathepsin (transmembrane protease serine 2) or furin induces

endocytosis and translocation of SARS-CoV-2 into endosomes, or a direct viral envelope fusion occurs with host cell membrane.

The neuronal tissue invasion can occur through - (1) transynaptic route from the infected neurons; (2) via olfactory nerve as the olfactory bulb remains unprotected by dura matter; (3) via vascular endothelium, or white cells traversing the blood–brain barrier.

ACE-2 receptor expression has also been demonstrated in arterial and venous endothelium. Also, SARS-CoV-2 infection is known to cause cytokine storm with the elevation of pro-inflammatory cytokines. So, endothelial damage and hypercoagulability due to activated coagulation cascade result in thrombo-inflammation, micro thrombi deposition and microvascular dysfunction.

Autoantibody production related to dysregulated immune response may induce the occurrence of certain diseases like optic neuritis, Miller Fisher syndrome and myasthenia gravis. This occurs due to molecular mimicry in which viral antigens induce an immune response against the self-proteins.

Lastly, hypoxia in cases of SARS-CoV-2 pneumonia can cause neural swelling, cerebral edema, and progressive cerebral injury.

CLINICAL FEATURES:

Optic nerve disorders

a. Optic neuritis- Viral illnesses are known to predispose to para or post-infectious demyelinating syndromes. Exposure to viral antigens acts as an inciting factor leading to upregulated host immune response and autoantibody production. Typical or atypical optic neuritis has been seen either as a presenting feature or in the recovery phase of COVID-19 (Figure 1). Most patients have reported good visual recovery with conventional treatment. But it is essential to rule out other infectious or inflammatory causes of optic neuritis.

   There are several reports of antibody positive atypical optic neuritis. There are also reports of anti-AQP4 Ab-positive transverse myelitis following COVID-19 infection. Atypical optic neuritis negative for both MOG and anti-AQP4 antibody has also been reported.

b. Disc oedema – Disc oedema may occur either as a manifestation of an optic nerve disorder like central retinal vein occlusion (CRVO) or due to raised

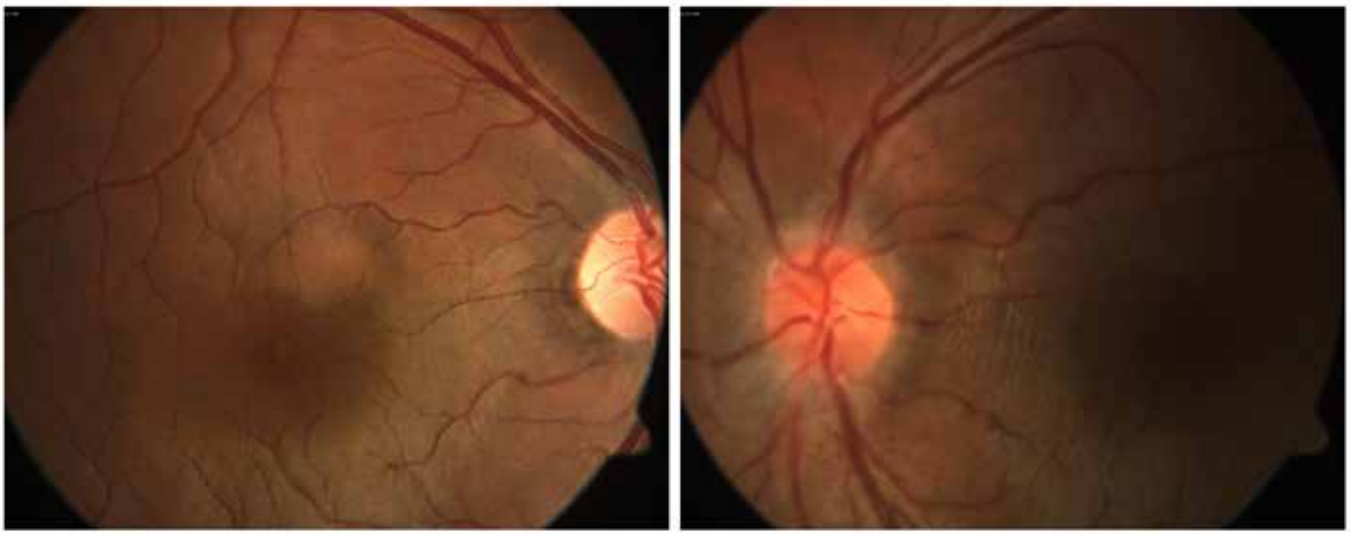

Figure 1- Fundus photograph showing right sided optic neuritis noted in a female patient in early thirties two weeks after COVID-19 infection (a&b). CEMRI suggestive of right optic nerve enhancement on axial (c) and coronal sections (d). The patient was tested positive for MOG antibody and responded well to steroids.

Figure 2- Fundus photograph showing papillodema (a&b) in a young female patient a month after being tested positive for SARS-CoV-2. She presented with complains of blurring of vision and diplopia. Enlargement of the blind spot was noted on visual fields. Neuroimaging revealed tortuous optic nerves with prominent optic nerve sheath (c) and opening CSF pressures were 270 mm of H20 suggestive of IIH.

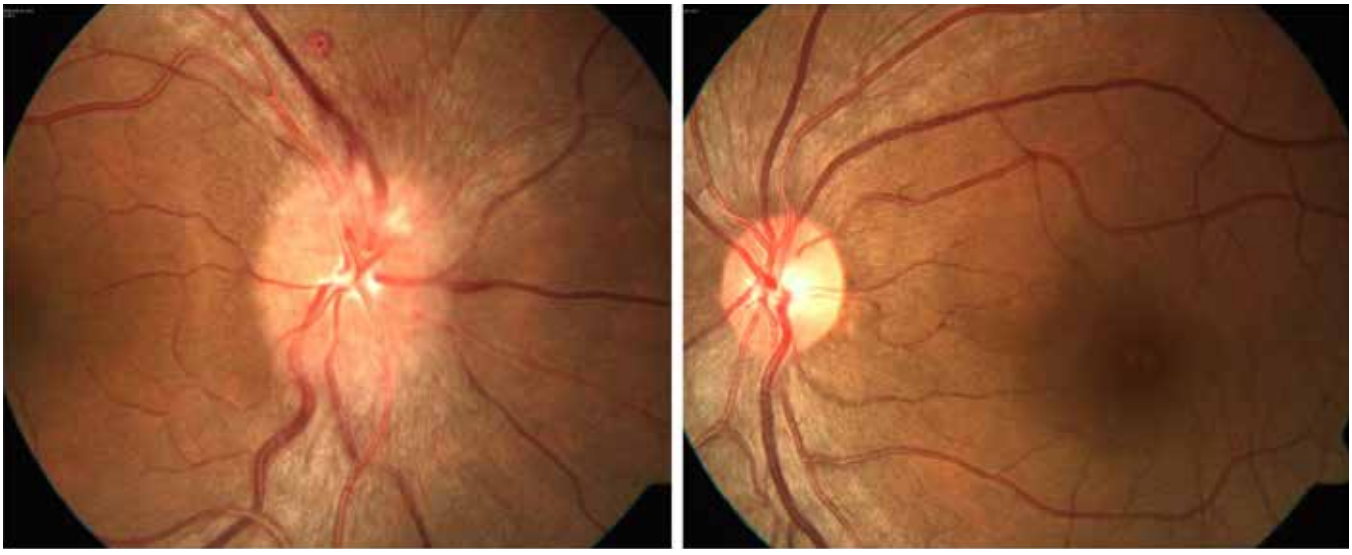

Figure 3- Fundus photograph showing right sided pale disc oedema suggestive of non-arteritic ischemic optic neuropathy noted in a female patient in early fifties with well controlled diabetes and had recently recovered from mild SARS-CoV-2 infection.

intracranial pressure (ICP) causing papilledema. Papilledema has also been reported following cerebral venous sinus thrombosis (CVST), or as a part of the multisystem inflammatory syndrome in children (MIS-C). (Figure 2).

c. Ischemic optic neuropathy- Endothelial dysfunction, hypercoaguability and hypoxemia following COVID-19 may predispose to non-arteritic ischemic optic neuropathy (NAION) (Figure 3). Recently peripapillary vascular perfusion abnormalities have also been documented in patients recovering from COVID-19. Occurrence of bilateral NAION, leading to bilateral irreversible vision loss following prolonged prone positioning advised for COVID-19 related acute respiratory distress syndrome (ARDS) has been reported. Prone positioning causes rise in IOP, reduction in ocular perfusion and alters the

ocular hemodynamics. So, a routine ophthalmic screening must be considered in prone positioned patients.

Posterior reversible encephalopathy syndrome (PRES)-

There are several reports of PRES occurring in elderly patients in the setting of severe COVID-19 infection requiring intensive care unit (ICU) care. Acute rise or fluctuation of blood pressure was noted in almost all cases. They mostly presented with new onset seizure and many had neuro-ophthalmic manifestations like visual field defects, cortical blindness, palinopsia and other visual hallucinations. Complete recovery of visual symptoms usually occurred. Endothelial injury either by viral entry or by increase in inflammatory markers are the key mechanisms causing PRES.

Cranial neuropathy-

There are several reports of cranial nerve palsy either isolated, or as a part of other disease like Miller Fisher syndrome in context of COVID-19. Abducent nerve palsy is most commonly reported.

The rapid onset of symptoms after COVID-19, unusual neuroimaging findings and improvement that paralleled recovery from COVID-19, suggest an association between the two. Ipsilateral trigeminal and lower motor neuron type of facial nerve involvement and Bell's palsy has also been reported.

Cranial polyneuropathy (V, VII, and IX cranial nerves) has been seen as a presenting feature in COVID-19. Guillane Barre syndrome (GBS) with facial paresis or diplegia, Miller Fisher syndrome (with anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, albuminocytologic dissociation and positive testing for GD1b-IgG antibodies) and polyneuritis cranialis (ageusia, bilateral abducens palsy, areflexia and albuminocytologic dissociation) are other notable associations of COVID-19 occurring due to aberrant immune response.

Neuromuscular junction disorder

There is increasing evidence that COVID-19 not only exacerbates but also triggers the development of new myasthenia gravis (MG). There are reports of newly diagnosed MG within days to weeks after the infection. The cases were positive for AchR antibody or muscle-specific tyrosine kinase (MuSK) antibody and responded well to various forms of management like pyridostigmine, steroids, IVIGs, or PLEX.

Nystgamus and other eye movement disorders

Intermittent horizontal nystagmus, bilateral acquired pendular nystagmus and opsoclonus with limb myoclonus have been reported following COVID-19. This may need medical management, although spontaneous recovery is known to occur in some cases.

Vascular occlusion

Venous and arterial thrombotic events have been reported in > 30% of COVID-19 patients, with venous involvement being the commonest (27%). As they occur due to endothelial susceptibility to SARS-CoV-2 damage along with exacerbated pro-inflammatory cytokine response, **elevated D-dimer and fibrinogen levels** are often associated.

a. Cortical Visual Impairment/Stroke

SARS-CoV-2 has been implicated with greater incidence of stroke (1-5%) than other corona and seasonal viruses. Old age, hypertension, diabetes, hyperlipidemia, atrial fibrillation and congestive heart failure along with elevated inflammatory markers are the predisposing factors. There is greater risk of multi-system involvement, death and disability in such patients. Stroke is also being increasingly reported in otherwise healthy young COVID-19 positive individuals with almost 7-fold increase in incidence reported during the pandemic. As hypercoagulability, endotheliopathy and immune mediated responses are causative, there is consensus to start early anticoagulation therapy. Outcomes are usually poor.

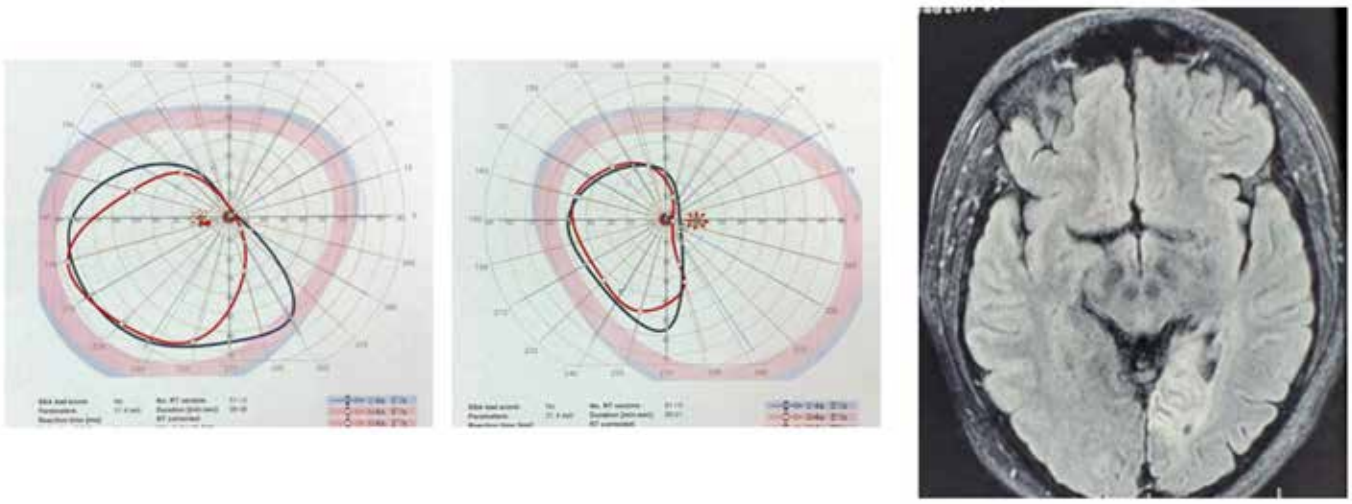

Figure 4- Visual fields of otherwise healthy male patient in his late fifties showing right homonymous hemianopia (a&b). The patient presented with the complains of right field defect 2-weeks following recovery from COVID-19 infection requiring hospitalization. MRI brain revealed left sided occipital lobe infarct (c).

Stroke can present with neuro-ophthalmic features like vision loss and visual field defects (Figure 4) depending on the site of CNS involvement. It is noteworthy that bulk of patients with CVA had COVID-19 related ARDS.

b. Central retinal artery occlusion (CRAO) or ocular stroke is a blinding ocular emergency. There are handful reports linking COVID-19 with CRAO. Hypertension is the most common risk factor. Neuroimaging may be unremarkable or may have some underlying cause like internal carotid artery obstruction causing secondary CRAO.

c. Central retinal vein occlusion (CRVO) may occur in elderly as well as young healthy individuals in association with elevated inflammatory markers. Usually, good visual recovery is achieved with management. Papillophlebitis and impending CRVO are other notable associations.

d. Cerbral venous sinus thrombosis (CVST)- Early evidence suggest higher-than-expected frequency of cerebral venous thrombosis among hospitalized COVID-19 patients.

Pupillary defects

Anisocoria following Adie's tonic pupil is the most common pupillary anomaly reported with COVID-19. Pupillary involvement may be related to viral neurotropism. Alternately, most cases occurring in the recovery phase of COVID-19 infection suggest an immune-mediated mechanism.

Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C can rarely be complicated by disc oedema and abducent nerve palsy due to elevated ICP. This is related to infectious or inflammatory meningitis or the alteration of CSF dynamics akin to the pseudo tumour syndrome. The children usually present with shock syndrome and markedly elevated SARS-CoV-2 antibody. Other causes of raised ICP should be ruled out. Mostly good recovery is noted spontaneously or with treatment with acetazolamide or steroids.

Table 1: Table showing the various neuro-ophthalmological manifestations of COVID-19

Type of involvement	Type of involvement	Associated signs and symptoms
Optic nerve disorders	1) Optic neuritis a. Typical b. Atypical (± Anti-MOG Ab/Anti-AQP4 Ab positive) c. As a part of acute disseminated encephalomyelitis (ADEM) 2) Disc edema/Papilledema 3) Ischemic optic neuropathy	• Unilateral or bilateral visual impairment. • Relative afferent papillary defect (RAPD) unless both eyes affected • Dyschromatopsia • Visual field defects- central, centrocecal, altitudinal, arcuate, general sensitivity reduction. • Fundus- Normal appearing fundus, disc edema, papilledema
Vascular occlusion	1) Central retinal artery occlusion (CRAO) 2) Central retinal vein occlusion (CRVO), Papillophlebitis	• Visual impairment • Visual field defects as per involvement • Fundus: cherry red spot with retinal whitening, intra-retinal haemorrhages
CNS/Occipital Cortex involvement	1) Posterior reversible encephalopathy syndrome (PRES): Non-enhancing, T2-weighted (T2)/fluid-attenuated inversion recovery (FLAIR) hyperintensities in the occipital cortex 2) Cortical Visual Impairment/Stroke 3) Cerbral venous sinus thrombosis (CVST)	• Visual hallucinations and palinopsia • Visual field defect: Homonymous hemianopia, enlargement of blind spot • Fundus: Normal appearing fundus/papilledema
Cranial nerve involvement	1) VIth nerve palsy (most common) 2) IIIrd nerve palsy 3) IVth nerve palsy 4) Bells palsy (VIIth nerve) 5) Cranial polyneuropathy 6) Associated with clinical syndrome: a) Guillane Barre syndrome (GBS) b) Miller Fisher syndrome	• Diplopia • Ptosis • Anisocoria • Paralytic squint • Features of facial palsy • Paraesthesia and numbness of face • Reduced corneal sensations
Neuromuscular junction disorder	1) Myasthenia gravis	• Ptosis • Diplopia • Paralytic squint
Pupillary defects	1) Adie's tonic pupil 2) Adie-Holmes syndrome	• Anisocoria • Absence of deep tendon reflexes
Nystgamus and other eye movement disorders	1) Intermittent horizontal nystagmus 2) Bilateral acquired pendular nystagmus 3) Opsoclonus with limb myoclonus	
Others	1) Multisystem Inflammatory Syndrome in Children (MIS-C) 2) Internuclear ophthalmoparesis 3) Idiopathic Intracranial Hypertension (IIH)	

COVID-19 VACCINE RELATED COMPLICATIONS

According to reports published in the VAERS database, COVID-19 vaccines had several local and systemic neurological complications that occur in different people appearing within one day to 1 month after injection.

In addition to mild effects like weakness, numbness, headache, dizziness, transient reduction in visual acuity and transient visual field defects are also reported post-vaccination.

There are reports of CRVO and acute abducent nerve palsy following *mRNA SARS-CoV-2* vaccine.

Autoimmune disorders like MG exacerbation have been triggered by vaccination.

LONG COVID

Long COVID (sometimes referred to as 'post-acute sequelae of COVID-19') is a multisystemic condition comprising of symptoms that follow a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection mostly seen in non-hospitalized patients with a mild acute illness (as this population represents the majority of overall COVID-19 cases).

The Center for Disease Control (CDC) has formulated "post-Covid conditions" to describe health issues that persist more than four weeks after being infected with COVID-19. These include (i) Long Covid (which consists of a wide range of symptoms that can last weeks to months) or persistent post-Covid syndrome (PPCS) (ii) Multiorgan effects of COVID-19 and (iii) Effects of COVID-19 treatment/hospitalization.

The typical clinical symptoms of "long covid" are tiredness, dyspnea, autonomic dysfunction, headache, persistent loss of smell or taste, depression, low-grade fevers, palpitations, dizziness, muscle and joint pains that may last for years or a lifetime. In addition they are also at increased risk of stroke, cognitive disorders, peripheral neuropathy, epilepsy/seizure disorders, extrapyramidal and movement disorders, mental health disorders, musculoskeletal disorders, hearing or vision abnormalities, and other disorders including Guillain–Barré syndrome and encephalitis.

Several hypotheses for its pathogenesis have been suggested, including persistent circulation of SARS-CoV-2 in plasma; immune dysregulation with or without reactivation of underlying pathogens including herpesviruses; autoimmunity and cross-reactive antibody responses from molecular mimicry and microvascular endothelial dysfunction/ endothelitis leading to clots.

Overall, emerging evidence has shown that the long-term effects of COVID-19 can lead to various ocular problems and underline the importance of regular follow ups of these patients after recovery.

Some groups are particularly susceptible, including (i) people who have experienced severe COVID-19 illness necessitating hospitalisation or intensive care, (ii) people who have underlying health conditions, such as diabetes, asthma, autoimmune diseases, or obesity, people who did not get a COVID-19 vaccine, (iii) people who experiences multisystem inflammatory syndrome (MIS) during or after COVID-19. Other factors that may be important include female sex, older age, immune response to initial infection and the SARS-CoV-2 variant that caused the initial infection.

Current studies suggest that covid-19 vaccines might have protective and therapeutic effects on long covid.

CONCLUSION

This review article provides a roadmap on the current literature linking COVID-19 with various neuro-ophthalmic manifestations. Although the causal link may seem reasonable in most cases, it cannot be asserted with absolute certainty. We will likely co-exist with the virus for many years to come, so long COVID will remain a global challenge to health care system and economy. To effectively deal with long COVID, it is important to raise public awareness of its risk factors and conduct research on proper management options.

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An Update on Hereditary Optic Neuropathies - Clinical Features, Current and Upcoming Therapeutic Approaches

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INTRODUCTION

Optic atrophy is characterized by the degeneration of the optic nerve, encompassing a spectrum of structural and functional alterations within the optic nerve head ultimately leading to the discernible loss of retinal ganglion cells. It also includes shrinkage of the optic nerve, often due to demyelination and axonal loss, as well as pallor of the optic disc. The axons constituting the optic nerve are notably characterized by extensive myelination, which functions, akin to white matter tracts, distinguishing the optic nerve from the typical architecture of a peripheral nerve and contributing to its behavior as a white matter structure. Notably, these glial cells express a plethora of inhibitory factors for axonal regeneration, thereby imparting a significant impediment to regenerative processes within the optic nerve's intricate network of 1.2 million fibers.

VIN DITTCH MD is a mnemonic for the risk factors for the development of optic atrophy. The following conditions are denoted by this mnemonic: V: Vascular; I: Inflammatory and infectious; N: Neoplastic or compressive; D: Primary demyelinating illness or idiopathic optic neuritis. T(2): Toxic and traumatic; C: Congenital; H: Hereditary; M: Metabolic and endocrine; D: Degenerative.

Hereditary optic neuropathies (HON) are a set of illnesses in which the origin of optic nerve impairment appears to be heritable. Clinical heterogeneity, both within and between families with the same illness, frequently complicates diagnosis and categorization. Classification has traditionally depended on the observation of comparable traits and patterns of transmission, but genetic analysis now allows the diagnosis of hereditary ocular neuropathies in the absence of family history or the context of unique clinical presentations. As a result, the clinical phenotypes of each illness are more diverse, making it simpler to identify rare instances.

Inherited optic neuropathies are characterized by symmetric, bilateral, central vision loss. Many of these illnesses impact the papillomacular nerve fibre bundle, resulting in central or cecocentral scotomas. The precise location of the disease along the ganglion cell and its axon, as well as the pathophysiologic processes behind optic nerve damage, are poorly understood. Optic

nerve injury is frequently permanent and gradual in many disorders. Significant nerve damage has already occurred when optic atrophy is evident.

When identifying hereditary optic neuropathies, it is critical to rule out primary retinal degenerations, which might present as primary optic neuropathies due to the common finding of optic disc pallor. Retinal observations can be mild, especially in cone dystrophies, where optic nerve pallor is a common early symptom. Even if the retina is not visibly aberrant, the potential of a primary retinal process should be explored in individuals with temporal optic atrophy. These disorders should be distinguished from primary optic neuropathies by the presence of retinal artery attenuation and more importantly, aberrant electroretinography.

The pattern of transmission is used to classify hereditary optic neuropathies. The three most prevalent inheritance patterns are autosomal dominant, autosomal recessive, and maternal (mitochondrial). The former two are a result of the involvement of nuclear genes while the latter is due to the involvement of the mitochondrial genome. Distinct genetic abnormalities can result in the same or similar phenotypes—some of which are inherited in the same way, while others are not. Alternatively, the same genetic alteration may result in many clinical manifestations, however, the inheritance pattern remains consistent. To make matters worse, single instances are frequently assumed or shown to be caused by inherited genetic abnormalities, rendering the pattern of familial transmission ineffective as a categorization help.

Optic nerve dysfunction is frequently the only sign of the illness in some inherited optic neuropathies. Various neurologic and systemic disorders are often reported in others. Furthermore, multisystem degenerations, which are hereditary disorders with predominantly neurologic or systemic signs, can involve optic atrophy.

As additional genetic mutations are uncovered, our understanding of the phenotypes of these illnesses, as well as our categorization, will most certainly evolve. Genetic counseling will benefit from a more precise characterization of the underlying genetic disorders. Furthermore, identifying the gene defect, elucidating the gene product and its normal function, and clarifying the abnormality caused by the mutation should improve our understanding of the pathophysiologic mechanisms underlying optic nerve dysfunction and pave the way for the development of targeted therapies.

Leber's Hereditary Optic Neuropathy (LHON) and Dominant Optic Atrophy (DOA) are the two most prevalent non-syndromic hereditary optic neuropathies, accounting for the majority of HONs encountered in clinical practice and causing persistent vision impairment in children and young adults.

Other monosymptomatic ocular neuropathies are exceedingly infrequent when compared to LHON and DOA. Congenital recessive optic atrophy, apparent sex-linked optic atrophy, and perhaps autosomal recessive chiasmal optic neuropathy are among them.

Certain neurologic or systemic symptoms are frequently associated in pedigrees with hereditary optic neuropathies. The examples include autosomal dominant optic atrophy and deafness; autosomal dominant optic atrophy with hearing loss and ataxia; hereditary optic atrophy with hearing loss and polyneuropathy; autosomal recessive optic atrophy with hearing loss, spastic quadriplegia, mental deterioration, and death (opticocochleodentate degeneration); opticoacoustic nerve atrophy with dementia; diabetes insipidus, diabetes Wolfram's syndrome, and Behr's syndrome. A detailed description of the various isolated and systemic HON with their ocular and systemic manifestations and genes is given in table.

Inherited disorders with mostly neurologic or systemic indications, such as multisystem degenerations, might include optic atrophy as a subsequent and inconsistent result. This group includes inherited ataxias, hereditary polyneuropathies, hereditary spastic paraplegias, hereditary muscular dystrophies, storage diseases, other infantile brain degenerations, and mitochondrial illnesses other than LHON.

CLINICAL ENTITIES

Leber's hereditary optic neuropathy

Leber's Hereditary Optic Neuropathy (LHON) often presents with visual loss in one eye, followed by the fellow eye experiencing similar symptoms. The second eye is typically affected within 1 year of disease onset, with a median interval of 6 to 8 weeks. Bilateral simultaneous onset occurs in 25% of LHON cases, whereas long-term unilateral visual loss is rare. During the acute stage of LHON, patients exhibit optic nerve head hyperemia, telangiectatic peripapillary vessels, increased retinal vasculature tortuosity, and edematous retinal nerve fiber layer (RNFL) due to axoplasmic stasis. Optic disc pallor becomes apparent around 6 weeks, and non-glaucomatous cupping of the optic nerve head may develop in chronic cases.

The visual prognosis for LHON is generally poor, with severe visual deterioration and most patients experiencing visual acuity less than 20/200. Spontaneous visual recovery can occur, especially within the first year, but the probability varies across genetic mutations. Pupillary reflex and circadian rhythms are well-preserved in LHON due to the relative sparing of melanopsin-expressing retinal ganglion cells. A link has also been found between Optic nerve lesion length and visual function of a patient in LHON's pre-chronic phase, wherein in lesion length with T2-STIR hyperintensities have been proposed to function as a biomarker for visual disability in LHON.

Approximately 1.2 million axons from retinal ganglion cells (RGCs) traverse the retinal nerve fiber layer, converging at the optic nerve head and passing through the lamina cribrosa to form the optic nerve. These axons require substantial energy and mitochondrial concentration to transmit visual information to the brain. RGCs generate adenosine triphosphate (ATP) through oxidative phosphorylation in mitochondria, involving complexes I, II, and III. Pathogenic variants in these complexes lead to reduced ATP synthesis and increased reactive oxidative species production. The vulnerability particularly of RGCs to energy failure, potentially stems from their narrow axons, especially in the P-type RGCs located in the papillo-macular bundle; as well as the lack of myelination they have, which is essential for retinal transparency and light penetration. Mitochondrial DNA (mtDNA) variations are known to be about 100 times higher than nuclear DNA, due to the mtDNA's naked double-ring structure, limited repair mechanisms, and local environmental factors, with oxidative radicals playing a role in inducement.

The primary LHON mutations are missense mutations within Complex I, constituting approximately 95% of LHON cases, and are characterized by three main mtDNA mutations located at positions *m.11778G > A, m.3460 G > A*, and *m.14484T > C* within the *MT-ND4*, *MT-ND1,* and *MT-ND6* genes, respectively. The remaining 10% of LHON cases involve eleven other mutations found in the *MT-ND1* gene (m.3635G > A, m.3700G > A, m.3733G > A, and m.4171C > A), the MT-ND4L gene (m.10663T > C), and the MT-ND6 gene (*m.14459G > A, m.14482C > A, m.14482C > G, m.14495A > G, m.14502T > C,* and *m.14568C > T*). Notably, the *m.14484T>C (MTND6*) mutation has a higher likelihood (37-58%) of partial visual improvement compared to the *m.11778G>A (MTND4*) mutation (4-25%), yet MTND4 happens to be the most common mutation in these cases.

Interestingly, not all LHON carriers experience blindness, and it's unusual for blindness to occur after the age of 50. There's a significant gender difference in the risk of visual loss, with approximately 50% of male carriers becoming blind compared to only 10% of female carriers. This incomplete penetrance and gender disparity may be influenced by secondary mitochondrial and nuclear genetic factors, along with a possible protective effect of estrogen.

A second category of LHON is autosomal recessive LHON (arLHON). The clinical manifestation of arLHON mirrors that of the conventional LHON caused by mitochondrial DNA mutations (mtLHON). This similarity is evident in the acute phase characterized by sudden and profound vision loss, the presence of

telangiectatic and tortuous vessels surrounding the optic nerve, and swelling of the retinal nerve fiber layer. However, arLHON does present a distinctive genetic landscape compared to its counterpart.

arLHON has been confirmed via sequencing, showing biallelic variants in the following genes: *DNAJC30, NDUFA12, NDUFS2* and *MCAT*. While the latter three genes were found in individual families, the *DNAJC30* variant was particularly frequent, appearing in 88 families. The variants in this gene have included two missense and one 1-codon deletion, a recurrent nonsense mutation, and a substitution thought to be the founder substitution (*p.Tyr51Cys*), as it was present in 82 of the 88 reported families. It is thought to have originated in Russia, subsequently spreading to central Europe.

The exact manner in which these mutations affect Complex I has been explored to some extent, proving that arLHON is also majorly due to the dysfunction within Complex I subunits in the inner membrane. *NDUFS2,* is a gene encoding NADH-ubiquinone oxidoreductase Fe-S protein 2, patients with arLHON-causing missense changes showed a mild reduction in protein abundance and complex I assembly, without affecting overall enzymatic activity. Expressing mutant alleles in Y. lipolytica revealed one variant as a hypomorphic mutation and the other causing complete absence of the complex. *DNAJC30* mutations altered chaperone activity, reducing the complex I subunit turnover and slightly increasing CI activity. The functional impact of *NDUFA12* mutations remains uncharacterized, but the delayed assembly of Complex I, or its reduced stability is expected; while *MCAT* mutations are predicted to impact mitochondrial fatty acid synthesis. These findings underscore that arLHON involves mitochondrial DNA-encoded inner membrane CI subunit dysfunction, similar to maternal LHON disease.

In arLHON cases, the identification of biallelic nuclear mutations holds significant implications for genetic counseling. Unlike mtLHON, where the transmission of the mtDNA pathogenic variant is 100% from a carrier mother, arLHON follows an autosomal recessive inheritance pattern. This means that both parents, regardless of gender, can contribute pathogenic alleles to their offspring, impacting the probability of disease development (Lenaers et al., 2023b).

The risk of an individual developing arLHON is influenced primarily by the genetic connections between the parents. When parents carrying one or two arLHON alleles are genetically unrelated, the risk tends to approach zero. However, consanguinity and endogamy elevate the likelihood of bi-allelism for mutated arLHON alleles, consequently increasing the risk of the disease. Importantly, similar to mtLHON, arLHON exhibits incomplete penetrance particularly observed with the *DNAJC30* mutation, though this phenomenon has not been confirmed to be exclusively belonging to this mutation.

Dominant optic atrophy

Dominant Optic Atrophy (DOA), also known as Kjer's optic neuropathy, is a relatively rare condition, with an estimated prevalence of 1 in 25,000. It is considered the most common inherited optic neuropathy. Approximately 60–70% of DOA cases are attributed to mutations in the optic atrophy 1 gene (*OPA1*), a nuclear gene responsible for encoding a transmembrane dynamin-related GTPase protein crucial for mitochondrial dynamics. DOA is distinguished by the progressive degeneration of retinal ganglion cells (RGCs), leading to ascending atrophy of the optic nerve (ON) and subsequent disruptions in color vision accompanied by a decrease in visual acuity. The clinical manifestations of DOA encompass several discernible features integral to the understanding of the condition. A primary clinical facet of DOA is the gradual and relentless loss of vision, emanating from the degenerative processes affecting the RGCs.

OPA1-DOA follows an autosomal dominant inheritance pattern, and its phenotypic expression can vary widely, even within the same family, reflecting incomplete penetrance. The *OPA1* gene, located on chromosome 3q28, consists of 31 exons. Alternative splicing of exons 4, 4b, and 5b results in eight different mRNA

variants coding for distinct isoforms expressed across human tissues. The *OPA1*-dedicated database lists a total of 864 *OPA1* variants, with over 70% considered pathogenic. Two-thirds of these variants are situated in the dynamin and GTPase protein domains. The majority of *OPA1* mutations are substitutions (64%) or deletions (27%), with fewer occurrences of duplications (5%), insertions (1.4%), and in/del (0.9%) mutations. Although mutations are often family-specific, some exhibit recurrence.

In approximately 50% of cases, pathogenic mutations introduce a premature stop codon, leading to the truncation of the open reading frame. This truncation results in mRNA decay and the subsequent loss of function of the mutant allele, establishing haploinsufficiency as the primary pathological mechanism in these instances. Pathogenic mutations in *OPA1* result in the fragmentation of the mitochondrial network, loss of mitochondrial membrane potential, disorganization of cristae structure, and compromised mitochondrial fusion. The susceptibility of retinal ganglion cells to mitochondrial dysfunction in DOA is intertwined with the distinctive anatomical characteristics of the optic nerve, notably the presence of an unmyelinated segment in the retinal nerve fibre; which is what causes the RGCs to be more susceptible to the disease.

Hereditary Optic Neuropathies	Subtypes	Ocular manifestations	Associated systemic manifestations	Genes Involved
LHON	mtLHON	optic nerve head hyperemia, telangiectatic peripapillary vessels, increased retinal vasculature tortuosity, and edematous retinal nerve fiber layer, Optic disc pallor, non-glaucomatous cupping of the optic nerve head at ~15 years age followed by second eye affection within 1 year of disease onset	-	*MT-ND4, MT-ND1, MT-ND6, MT-ND4L* **(Shamsnajafabadi et al., 2023)**
	arLHON	sudden and profound vision loss, presence of telangiectatic and tortuous vessels surrounding the optic nerve, swelling of the retinal nerve fiber layer	-	*DNAJC30, NDUFA12, NDUFS2*, *MCAT* **(Lenaers et al., 2023c)**

ADOA	Kjer type	progressive degeneration of retinal ganglion cells, ascending atrophy of the optic nerve disruptions in color vision, decrease in visual acuity	-	*OPA1* **(Delettre et al., 2000)**
	Behr's syndrome	early-onset optic atrophy	contractures, lower limbs, Achilles tendon contractures, Hamstring contractures, Adductor longus contractures, Delayed motor development progressive Spasticity, progressive Ataxia, Impaired gait, Pyramidal signs, Hyperreflexia, Extensor plantar responses, Dysmetria, Tremor, Mental retardation, Posterior column sensory loss, Cerebellar atrophy	*OPA1* **(Bonneau et al., 2014; Carelli et al., 2015)**
	optic atrophy 8	Optic atrophy, Central scotoma, Visual loss, Diffuse reduction in retinal nerve fiber layer, Abnormal pattern visual evoked potentials	Affected auditory system, Mitral valve prolapse, Mitral valve insufficiency, Subsarcolemmal accumulation of mitochondria	*OPA8*(Carelli, Schimpf, et al., 2011)
	optic atrophy 4/5	optic nerve pallor, decreased visual acuity, color vision defects, impaired VEP, and normal ERG	-	*OPA4* **(Delettre et al., 2000),** *OPA5* **(Barbet et al., 2005; Gerber, Charif, et al., 2017)**
X-Linked OA	Optic atrophy 2	Early onset optic atrophy	Mental retardation, Hyperactive knee jerks, Absent ankle jerks, Extensor plantar reflexes, Dysarthria, Tremor, Dysdiadochokinesis, Abnormal tandem gait	*OPA2* locus Xp11.4-p11.21 **(Katz et al., 2006; Völker-Dieben et al., 1974)**

OP, autosomal recessive	Optic atrophy 6	Optic atrophy, Photophobia, Dyschromatopsia with red-green confusion, Visual acuity for distant vision ranges from 1/10 to 2/10	-	*OPA6* **(Barbet et al., 2003)**
Optic atrophy with or without auditory neuropathy	Optic atrophy 7	Reduced visual acuity, Optic atrophy, Temporal optic nerve pallor, Central scotoma, Visual field constriction, Dyschromatopsia, Thinning of retinal nerve fiber layer seen on optical coherence tomography, Horizontal nystagmus, Strabismus	Cardiomyopathy, Sensory-motor axonal neuropathy, sensorineural Hearing loss	*OPA7* (**Hanein et al., 2009; Kloth et al., 2019)**
Autosomal dominant optic atrophy and cataract	Optic atrophy 3 with cataract	Optic atrophy, Decreased visual acuity, Cataract	Mild Tremor, Extrapyramidal signs	*OPA3* **(Chevrollier et al., 2008; Reynier et al., 2004)**
Diabetes insipidus, diabetes mellitus, optic atrophy, deafness (DIDMOAD) / Wolfram syndrome		Optic atrophy, Pigmentary retinopathy, Ptosis, Nystagmus	Growth retardation, low-frequency sensorineural hearing loss, impaired glucose regulation, cardiomyopathy, Testicular atrophy, Hydronephrosis, Hydroureter, Neurogenic bladder, Limited mobility of proximal interphalangeal joint, Mental retardation, Seizures, Ataxia, Tremor, Dysphagia, Dysarthria, Stroke-like episodes, Psychiatric disorders, Brain atrophy	*WFS1* **(Cano et al., 2007)**

Deafness-dystonia-optic neuronopathy syndrome (DDON) Or Mohr- Tranebjaerg syndrome		slowly progressive decreased visual acuity from optic atrophy beginning about age 20 years	prelingual or postlingual sensorineural hearing impairment, slowly progressive dystonia or ataxia, dementia, paranoia, progressive auditory neuropathy, focal dystonia	*TIMM8A* (x-linked) **(Tranebjærg et al., 2000, 2001)**
Autosomal dominant cerebellar ataxia, deafness and narcolepsy			Ataxia, hearing loss, narcolepsy, cataplexy, dementia, sensory neuropathy, cataracts, lymphedema, incontinence, depression, psychosis	*DNMT1* **(Winkelmann et al., 2012)**
Charcot-marie-tooth disease, type 6a		Optic atrophy, Pale optic disks, Subacute deterioration of visual acuity, Color vision defects, Central scotoma, Abnormal visual-evoked potentials, Recovery of visual acuity occurs in 60% of patients, Cogwheel ocular pursuit, Dysmetric saccades	Mild Hearing loss, Tinnitus, Anosmia, Vocal cord paresis, Scoliosis, Pes cavus, multiple Peripheral nervous system defects	*MFN2* **(Voo et al., 2003)**

CURRENT TREATMENTS AND CLINICAL STUDIES

LHON

Genetic Treatments

Using mitochondrial targeting sequences (MTSs) integrated into adeno-associated virus capsids (AAV), mitochondrial proteins, or mRNA, researchers have been able to cross the hurdle of being unable to get nucleic acids through the hydrophobic mitochondrial double membranes. One approach that utilizes a refined version of this is allotopic gene transfer, which allows for the relocation of the mitochondrial genes, into the nucleus. The polypeptide that is expressed is then moved to the mitochondria itself. This is the only technique thus far to make it to clinical trials.

Large scale studies have taken place to treat the mutation occurring in the MTND4 gene, with 4 stages: REVERSE [NCT02652780], RESCUE [NCT02652767 (both of which were phase 3 clinical trials)], RESTORE [NCT03406104 (which was a long term follow up on the patients from the previous two trials)], and REFLECT [NCT03293524 (an ongoing clinical trial)].

The REVERSE and RESCUE trials represent pivotal phase 3 clinical investigations evaluating the efficacy of rAAV2/2-ND4, aka lenadogene nolparvovec, (GS010) in treating Leber's Hereditary Optic Neuropathy (LHON) associated with the *m.11778G>A* mtDNA mutation. In the REVERSE trial, patients with a mean baseline BCVA of 1.61 logMAR demonstrated significant improvements in visual acuity following

treatment with rAAV2/2-ND4, with a bilateral recovery occurring around 12 weeks post-treatment. Conversely, the RESCUE trial, conducted with patients in the early stages of LHON, showed comparable BCVA evolution between rAAV2/2-ND4–treated and sham-treated eyes, with bilateral recovery taking place over an average of 24 weeks post-treatment. Notably, the difference in mean BCVA between the two trials became statistically significant from week 63.5 after disease onset, suggesting that, counterintuitively, earlier treatment in RESCUE did not yield superior visual outcomes at 96 weeks compared to later-stage treatment in REVERSE.

REFLECT began in 2018 and has been designed to assess whether lenadogene nolparvovec can improve both the functional and structural outcomes of the retina in subjects with LHON, with a specific focus on those who are ≥ 15 years old at onset, who have experienced vision loss ≤ 365 days at enrolment. The results of the clinical trial are expected to arrive in June of 2024.

An open-label dose escalation study (NCT02161380) at the University of Miami aimed to establish the safety of low and medium doses of scAAV2(Y444,500,730F)-P1ND4v2 viral vector for treating LHON patients with the G11778A mutation. The initial phase I study involved intravitreal injections in one eye of five participants with vision loss. A subsequent phase involved 14 participants with chronic bilateral visual loss (>12 months), acute bilateral visual loss (<12 months), or unilateral visual loss. After 12 months, the injected eyes showed an average improvement of 0.24 logMAR, more significant than fellow eyes. Uveitis, a vector-related adverse event, occurred in 29%, with a higher incidence in higher-dose eyes. Some improvements in best-corrected visual acuity (BCVA) were observed in treated and fellow eyes, but all study eyes in the unilateral visual loss group (Group 3) lost ≥15 letters within the first year. The study suggests limited and dose-independent treatment efficacy, emphasizing the potential influence of disease stage and the need for a control group for a more comprehensive assessment of treatment effects.

A preclinical vector, rAAV2-ND4, underwent an investigator-led clinical trial (NCT01267422) in China, involving nine patients with Leber's Hereditary Optic Neuropathy (LHON). Intravitreal injection of the vector in one eye showed no adverse events during the 9-month follow-up. Six patients exhibited a significant improvement in visual acuity (VA) by at least 0.3 logMAR, with enlarged visual fields (VF) and stable retinal nerve fiber layer (RNFL). Long-term results over three years confirmed the safety and demonstrated improvements in BCVA, VF, and visual evoked potential (VEP) in treated eyes. Subsequent phase II and III clinical trials (NCT03153293) confirmed the positive outcomes of intravitreal rAAV2-ND4 treatment, with higher baseline values associated with better VA outcomes. VF defect severity appeared independent of age, progressing within 6 months and stabilizing after 9 months, leading to decreased inter-eye differences as the disease progressed.

Antioxidant Treatment

Clinical studies have shown the potential utility of ubiquinone analogs in the management of conditions such as DOA and LHON. Ubiquinone plays a crucial role in the mitochondrial respiratory chain by shuttling electrons from complexes I and II to complexes III. Combination therapies involving CoQ10 and other nutritional supplements not only improved plasma lactate concentrations but also showed positive effects on body composition, ankle dorsiflexion strength, and oxidative stress in LHON patients. However, despite CoQ10's historical use in mitochondrial disorders, a Cochrane review found no objective evidence of significant benefit in LHON. The limited efficacy of CoQ10 in LHON may be attributed to its lipophilic nature, impeding delivery to mitochondria following oral administration. Idebenone, a synthetic analog of CoQ10, emerged as a prominent antioxidant drug for LHON treatment. Studies indicate that cell lines from LHON patients treated with ubiquinone demonstrate increased ATP production, reduced reactive oxygen species (ROS) levels, and prevention of retinal ganglion cell (RGC) deterioration in a mouse model of LHON,

potentially mitigating oxidative cellular damage and lipid peroxidation.

While a multi-center study, RHODOS, involving 85 LHON patients did not meet its primary endpoint, secondary endpoints revealed positive trends in final visual acuities in the idebenone-treated group. Subgroup analyses suggested that patients with discordant visual acuity between the eyes at enrollment were more likely to benefit, emphasizing the potential advantage of earlier introduction of idebenone. Follow-up studies supported the notion that earlier treatment within one year after visual loss yielded the greatest benefit. However, Idebenone also has its drawbacks. **Varricchio et al.,** found that the efficacy of idebenone in rescuing cells in the rotenone ex vivo model suggested that the beneficial effects of idebenone hinge upon the expression of cytosolic enzyme NAD(P)H: quinone acceptor oxidoreductase (NQO1). Their study corroborates the NQO1-dependent activity of idebenone and introduces a novel finding: the cytotoxicity of idebenone is closely linked to the cellular expression of NQO1.

Vatiquinone (EPI-743) is a quinone molecule derived from the hydrolysis of vitamin E. Initially developed for treating Leigh syndrome, it has undergone scrutiny in various clinical trials for inherited mitochondrial diseases and neurodegenerative disorders, including Friedreich ataxia, garnering Orphan Drug Designation and Fast Track Designation from the FDA. With the ability to traverse the blood–brain barrier, vatiquinone demonstrates notable potency, being 1000-to 10,000-fold more effective than CoQ10 or idebenone in safeguarding mitochondrial patient fibroblasts under oxidative stress conditions. Notably, EPI-743 has been assessed in a small open-label clinical trial involving five patients, with genetically confirmed LHON, who had lost their vision to an acute degree, reporting moderate improvement in visual function. However, it's crucial to acknowledge the limitations of this trial, as it was relatively small, open-label and lacked randomization or control. Thus, further rigorous research is warranted to validate the efficacy and safety of EPI-743 in mitochondrial disorders.

Stem Cell Therapy

The Stem Cell Ophthalmology Treatment Study (SCOTS, NCT 01920867) and its follow-up study (SCOTS 2, NCT 03011541) represent non-randomized, open-label efficacy trials focused on the treatment of retinal and optic nerve diseases through ganglion cell replacement. Mesenchymal stem cells, derived from the posterior iliac crest bone marrow, were administered via various delivery routes, including retrobulbar, subtenon, intravitreal, intraocular, subretinal, and intravenous injections. The reported results demonstrated statistically significant improvements or stabilizations in vision for the majority of patients. Specifically, based on the outcomes of six patients with Leber's hereditary optic neuropathy (LHON), 83.3% exhibited improved vision in both eyes within 24 months.

This improvement is attributed to the transformation of bone marrow mesenchymal stem cells into developed ganglion cells, coupled with the transfer of mitochondria and lysosomes to damaged cells. The study's findings suggest a potential therapeutic avenue for retinal and optic nerve diseases through the replacement of ganglion cells using mesenchymal stem cells, highlighting the promising outcomes observed in patients, particularly those with LHON.

It should be noted, however, that due to the immediate discharge of patients to local follow-ups, the claims of vision improvement in the trial remain unverifiable according to. In their review, they cautioned against considering the trial with seriousness in scientific debates.

Dominant Optic Atrophy

To date, there has yet to be a treatment established for DOA, that is FDA approved. Despite the knowledge of disease pathogenesis and genetic basis, it is only recently that any treatments have begun to be tailored to the disease.

The treatment that has advanced the farthest thus far is a branch of the Stem Cell Ophthalmology

Treatment Study (SCOTS), with id NCT03011541. Bone marrow-derived stem cells (BMSCs) have been explored as a treatment avenue for diseases such as Retinitis Pigmentosa and even LHON. BMSCs have been seen to differentiate into neuron-like cells, all the while releasing neuroprotective compounds, such as NGF, safeguarding RGCs, and assisting with RGC integration into the preexisting neural networks, re-establishing neural connections. An advantageous aspect of autologous BMSC treatment is its exemption from the need for immunosuppression, the absence of teratoma formation risk, and the absence of ethical or moral concerns. When applied to DOA by **Weiss & Levy,** observed 5 out of 6 significantly improving their visual acuity by 33.3%, with no adverse effects. The MSCs were proposed to address the mitochondrial dysfunction of DOA by transferring their mitochondria to the target cells. There was, however, clearing of the cells seen in the patient whose visual acuity did not improve significantly, at a two-month postoperative visit after being treated with these BMCS in an intravitreal manner. It was noted that the early departure of BMSCs may result in diminished therapeutic effects and limited improvements, potentially leading to minimal decreases in vision in the treated eye.

EXPLORATORY TREATMENTS LHON

Ongoing Clinical Trial

The objective of the clinical study sponsored by Neuropath Therapeutics Inc, is to assess the safety, tolerability, and preliminary efficacy of NFS-02 in treating Leber's Hereditary Optic Neuropathy (LHON) caused by a mitochondrial *ND1* gene mutation. The study, NCT05820152, began in 2023, and its primary endpoint is set in 2024. The participants must exhibit reduced visual acuity due to LHON associated with ND1 mutation, with a confirmed G3460A mutation in a CLIA-certified laboratory, and a duration of reduced visual acuity lasting between 6 months and 10 years, for the study to be considered a complete success. As up until now all of the gene therapeutics have targeted the ND4 gene, having a treatment exploring other mutations is likely to give patients with rarer a greater chance of improvement.

Ketogenic Treatment for LHON

A study conducted by investigated the efficacy of ketogenic treatment in Leber hereditary optic neuropathy (LHON). The research demonstrated a noteworthy reduction in the percentage of the m.13094 T > C heteroplasmic mutation within cybrid cell lines. Moreover, this intervention exhibited an increase in mitochondrial DNA levels associated with the m.11778G > A mitochondrial genotype. These findings suggest the potential therapeutic utility of a ketogenic diet in addressing LHON.

Mitochondrial Biogenesis in LHON Carriers Comparative analyses of fibroblasts from individuals affected by Leber's hereditary optic neuropathy (LHON), carriers, and controls, under various metabolic demands, indicate that carriers exhibit the highest mitochondrial biogenesis activation capacity. This suggests that the heightened mitochondrial biogenesis in carriers may mitigate some pathogenic effects of mitochondrial DNA mutations. Theoretical exploration of pharmaceutical activation of mitochondrial biogenesis as a preventive measure for carriers is currently underway.

Estrogens and Their Potential Protective Role underscores the potential protective value of estrogens and their interactions with retinal ganglion cells (RGCs). Specifically, estrogens binding to receptors in RGCs were observed to mitigate apoptosis in LHON cybrid cells carrying the ND4 mutation (Wu et al., 2018).

Regenerative Medicine for LHON

The ambit of regenerative medicine in LHON seeks to address cell damage, with a primary challenge lying in the regeneration of the optic nerve. In cases of LHON, the utilization of iPSC-derived RGCs demonstrated a substantial decrease in apoptosis levels within cybrid-corrected RGCs. The realization of this goal necessitates the precise localization of cells within the retina and subsequent extension of their axons to the lateral

geniculate body, with approximately half traversing the optic chiasm in the process.

DOA

w3PUFAs

Despite advancements in understanding *OPA1* functions and related cellular pathways, effective treatments for ADOA remain elusive. An invitro model was described in a study carried out by **Kalogerou et al**. exploring the potential therapeutic effects of omega-3 polyunsaturated fatty acids (ω3-PUFAs) in Opa1enu/+ mice, a mouse model of ADOA. Oral administration of ω3-PUFAs restored RGC and optic nerve axon densities to levels comparable to untreated wild-type mice. The treatment demonstrated a tendency for RGC axonal preservation in 12-month-old Opa1enu/+ mice, suggesting a potential therapeutic avenue. Additionally, ω3-PUFA treatment suppressed astrocyte activation in the retinas of wild-type mice, while a non-significant decrease was observed in Opa1enu/+ mice. Microglia in ω3-PUFA-treated mice exhibited a ramified and quiescent morphology compared to untreated mice, indicating a potential modulatory effect on immune responses. Overall, these findings propose ω3-PUFAs as a promising therapeutic approach for ADOA, warranting further investigation into their efficacy and mechanisms of action.

Splice site correction

The novel *OPA1: c.1065+5G>A* mutation affects the consensus splice donor site of exon 10 and causes exon 10 skipping during splicing. This single base pair exchange most likely prevents the recognition of the mutated splice donor site by U1, an essential splice factor required to initiate the splicing process. As a consequence, exon 9 of *OPA1* is directly fused to exon 11, resulting in a transcript with an 81 nt in-frame deletion predicted to be translated into an *OPA1* protein lacking 27 amino acids. It was found that *OPA1* protein levels were reduced by approximately 50%. Since exon 10 encodes an essential part of the highly conserved GTPase domain of *OPA1*, it is suggested that the shortened protein is most likely non-functional and/or unstable and degraded rapidly. This supports previous observations that *OPA1* mutations cluster within the GTPase domain and that haploinsufficiency represents the major pathomechanism leading to DOA.

The study conducted by **Jüschke et al**, utilized engineered U1 splice factors to treat the *OPA1* defects. These factors, designed to target specific locations in *OPA1* exon 10 or intron 10, effectively reduced mutated transcripts while increasing normal *OPA1* transcripts. Engineered U1 factors offer advantages over gene augmentation, being small and easily applicable via viral vectors with limited capacity. Engineered U1 factors, binding near mutated splice donor sites or intronic sites, successfully recruited the splicing machinery. Notably, an engineered U1 located in the intronic proximity of the mutation showed superior effectiveness, showing the potential for overcoming haploinsufficiency.

CONCLUSION

Hereditary optic neuropathies, as described in this review, comprise a group of disorders in which the cause of optic nerve dysfunction could be heritable, based on family history or genetic analysis. In some hereditary optic neuropathies, optic nerve dysfunction remains isolated. In others, various neurological and systemic abnormalities co-occur with the ocular abnormalities. The most common hereditary optic neuropathies are autosomal dominant optic atrophy (Kjer's disease) and mitochondrial Leber's hereditary optic neuropathy. In this review we have described the clinical phenotypes of these and other inherited disorders with optic nerve involvement. Current treatment techniques focus on symptomatic management rather than offering a definite cure. Gene therapy, stem cell research, and targeted molecular interventions, on the other hand, provide potential paths for the creation of more specialized and effective medicines. These new medicines seek to address the underlying genetic abnormalities, intending to perhaps slow or reverse the course of hereditary ocular atrophy. There is currently no commonly acknowledged therapy for HOAs while continuing animal and clinical studies of oral medicines and gene insertion provide new hope. While continuing research attempts to untangle the

nuances of this issue, the changing landscape of tailored medicine offers tremendous promise in providing hope to individuals suffering from hereditary optic atrophy, potentially improving their visual health's future.

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A Tête-à-tête with Neuro-Ophthalmologists


Dr Clement Tan


Dr Padmaja Sudhakar


Dr Prem Subramanian


Dr Sachin Kedar


Dr Sangeeta Khanna


Dr Satoshi Kashii


Dr Syntia Nusanti


Dr. Rohit Saxena

Neuro-ophthalmology is a constantly evolving field. Our better understanding of pathogenesis and advances in diagnostics have led to a shift in how we perceive and manage conditions which were once considered idiopathic or unexplained. A perfect example of this is the discovery of Myelin Oligodendrocyte Glycoprotein (MOG) antibodies and recognition of many cases of erstwhile atypical optic neuritis as MOG optic neuritis. With better insight of disease mechanisms, role of therapies such as steroids for non-arteritic ischemic optic neuropathy have been studied scientifically and with renewed interest in the recent past. Gene therapy for hereditary optic neuropathies have moved into phase 3 human trials and qualified success has been achieved. The understanding of molecular genetics is growing at an astonishing pace and translational research has a lower lead and lag time than ever before. Therapeutics in neuro-ophthalmology are evolving and there is a need to catch up with changing paradigms. In view of this, The Indian Journal of Neuro-ophthalmology interacted with experts from across the world to get their insight on what's changing and what's changed in certain aspects of the field of neuro-ophthalmology.

Our editors, Dr Swati Phuljhele and Dr Digvijay Singh have brought together views in this article through conversations with various key opinion leaders. They are ***Dr Clement Won Teck Tan***, who is a senior consultant heading the neuro-ophthalmology service at The National University Hospital, Singapore; ***Dr Padmaja Sudhakar***, who is an assistant professor of ophthalmology and neurology at Lexington, Kentucky and is affiliated with University of Kentucky Albert B. Chandler Hospital, United Kingdom; ***Dr Prem S. Subramanian***, who is Clifford R. and Janice N. Merrill Endowed chair in ophthalmology, professor of ophthalmology, neurology, and neurosurgery and vice chair for academic affairs at Sue Anschutz-Rodgers Eye Center, University of Colorado School of

Medicine, Colorado, United States; ***Dr Sachin Kedar***, who is Cyrus H Stoner professor of ophthalmology, professor of neurology and vice-chair for education, neuro-ophthalmology division of department of ophthalmology, Emory University School of Medicine, Atlanta, Georgia, United States; ***Dr Sangeeta Khanna***, who is a clinical associate professor, ophthalmology and visual sciences, University of Michigan Kellogg Eye Center, department of ophthalmology and visual sciences, Ann Arbor, Michigan, United States; ***Dr. Satoshi Kashii***, who is professor of visual sciences and ophthalmology, faculty of health and medical sciences, Aichi Shukutoku University, Aichi, Japan and ***Dr Syntia Nusanti***, who is the head of neuro-ophthalmology division, ophthalmology department, faculty of medicine, University Of Indonesia, RSCM Kirana, Cipto Mangunkusumo Hospital, Central Jakarta, Indonesia.

Dr Rohit Saxena who is professor and head of the Strabismus and Neuro-Ophthalmology Services at Dr Rajendra Prasad Centre for Ophthalmic Sciences, All Indian Institute of Medical Sciences, New Delhi.

Excerpts of the interview are shared below.

Q1: What change have you noticed (over the last decade) in the clinical and demographic profile of optic neuritis patients that you are seeing in your practice?

Clement Tan: No. The clinical and demographic profile has largely remained the same. However, since the AQP4 and MOG antibodies were discovered and the clinical syndromes defined, we have been more aggressive with our immunosuppression, keeping patients on i/v Methylprednisolone for 5 days, pushing for plasma exchange if there's no improvement in vision, keeping them on oral steroids longer, starting steroid-sparing agents earlier.

Padmaja Sudhakar: Yes, I am now seeing a lot of MOG optic neuritis and NMOSD related optic neuritis

Prem Subramanian: Yes, Either because of better recognition or earlier referral, more patients with optic neuritis from non-demyelinating causes such as NMO and MOGAD are being seen. We also have seen more ON associated with West Nile virus infections. We are also seeing more optic neuritis in older patients (over age 60).

Sachin Kedar: I don't think so; however, many atypical presentations in the elderly and young are now being diagnosed as NMO or MOG optic neuritis given the increased awareness and availability of serological and radiological testing.

Sangeeta Khanna: We are seeing a lot more of MOG and NMO optic neuritis as distinct entities given the antibody availability.

Satoshi Kashii: We now initiate pulse steroid therapy to those with suspected optic neuritis without hesitation. Gd-E MRI is also taken immediately when the patient is suspected to have optic neuritis, as it is the earliest possible way of diagnosing AQP4 or MOG optic neuritis before we get the blood test results.

Syntia Nusanti: The incidence and trend of optic neuritis have notably changed in my practice site, Indonesia. There is an observable increase in cases of Neuromyelitis Optica Spectrum Disorder (NMOSD) over time. The clinical and demographic profile of patients has become more diverse, affecting individuals across a wide age range, from pediatrics to the elderly. Additionally, the incidence of optic neuritis due to infection has risen, with a notable increase in identified cases of syphilitic optic neuritis.

Rohit Saxena: Over the past decade, with increasing availability of serological tests and better MRI imaging, our diagnosis of the disease has improved. Earlier older patients were misdiagnosed as NAION, now there is an increasing understanding of the wide variety of presentation of optic neuritis. Therefore while there is an apparent change in the clinical profile in the cases of optic neuritis, it may be due to our better understanding of the disease. This growing awareness, improved testing and aggressiveness in investigating optic neuritis patients that has led to surge in diagnosis of NMO and MOG in general and in the elderly in particular. Also during the years of the Covid pandemic, there

were many patients that were thought to be due to the disease or the vaccination and a definite increase in the incidence was noticed.

Q2: Do you use steroids in non arteritic ischemic optic neuropathy? If so, oral or injectable?

Clement Tan: I do not use steroids as a routine.

Padmaja Sudhakar: I never use steroids for NAION.

Prem Subramanian: I don't use steroids for NAION routinely. I may use them if the patient has second eye involvement and is desperate, with the understanding that I don't expect a dramatic improvement and that the risk of side effects is not low. In such cases, oral dosing suffices.

Sachin Kedar: No. Unless patient insists or there is second eye involvement. In those cases I will use oral steroids.

Sangeeta Khanna: No. AT our centre, we don't use or advocate steroids for NAION.

Satoshi Kashii: No. I don't use oral steroids for Non Arteritic Ischemic Optic Neuropathy.

Syntia Nusanti: Yes, we use oral steroids in the following conditions:

a. NAION on the only one remaining functional eye
b. Acute phase optic neuropathy (edema of the optic nerve head or within 2 weeks of onset).

We also incorporate a multidisciplinary approach, involving internists to manage underlying risk factors such as diabetes mellitus, hypertension, and other metabolic diseases associated with optic neuritis.

Rohit Saxena: While no strong evidence exists that oral steroids improve final visual outcome, oral steroids are shown to decrease disc oedema in patients of NAION. Therefore they cannot be considered as standard therapy for even early NAION. However it can be considered in acute presentation in the absence of systemic causative features particularly diabetes.

Q3. Do you think, we will see gene therapy and stem cell therapy as a major therapeutic modality for neuro-ophthalmic conditions in the coming decade? If so which conditions?

Clement Tan: I hope we will! There are already some encouraging results from the genetic treatment for LHON though it is limited to the 11778 group. I hope target therapy will be more readily available for the other mutations soon. Perhaps as costs come down. Stem cells therapy seems to be moving forward for RPE cells. I hope they will be available for the large range of optic neuropathies for which there is no treatment at the moment.

Padmaja Sudhakar Yes I think gene therapy will become widely available for at least LHON.

Prem Subramanian: Gene therapy shows promise for LHON and possibly ADOA. These vectors also may be used to induce production of a desired drug in a local compartment, such as with an orbital depot injection of steroid but much longer acting since the drug will be expressed by the local cells/tissues.

Sachin Kedar: Yes, particularly for LHON and maybe Dominant Optic Atrophy

Sangeeta Khanna: Gene therapy for hereditary optic neuropathy-especially LHON/ stem cell therapy for optic nerve regeneration is less promising at this stage.

Satoshi Kashii: It would be great, if it turns out to be so.

Syntia Nusanti: Gene therapy holds promise as a potential therapeutic option for Leber's Hereditary Optic Neuropathy (LHON). On the other hand, stem cell therapy may prove useful in cases of optic atrophy resulting from toxic optic neuropathy or traumatic optic neuropathy.

Rohit Saxena: The early results of the gene therapy trials for LHON hold promise. But it may be too early to conclude about its practicality in routine clinical practice, particularly in Indian scenario where such a therapy may be out of reach for many patients due its cost.

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