

# An Eye on Movement Disorders

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**ABSTRACT:** Eye disorders spanning a range of ocular tissue are common in patients with movement disorders. Highlighting these ocular manifestations will benefit patients and may even aid in diagnosis. In this educational review we outline the anatomy and function of the ocular tissues with a focus on the tissues most affected in movement disorders. We review the movement disorders associated with ocular pathology and where possible explore the underlying cellular basis thought to be driving the pathology and provide a brief overview of ophthalmic investigations available to the neurologist. This review does not cover intracranial primary visual pathways, higher visual function, or the ocular motor system.

The relationship between movement disorders and the eye is long established, mostly driven by the widely recognized ocular motor manifestations that typify certain movement disorders, for example, vertical gaze palsy and slow saccades in progressive supranuclear palsy. What is perhaps not so well recognized are the other non-ocular motor associations the eye has with various movement disorders. It is this spectrum of disorders which will be the focus of this review. Highlighting these non-motor ocular manifestations allows neurologists to be cognizant of ocular manifestations which will benefit patients and may aid in diagnosis.

In this educational review we outline the anatomy and function of the ocular tissues with a focus on the tissues most affected in movement disorders. In turn, we review the movement disorders associated with ocular pathology and where possible explore the underlying cellular basis thought to be driving the pathology. Lastly, we provide a brief overview of ophthalmic investigations available to the neurologist. For purposes of brevity and focus, we are restricting the review to the lids, globe, and optic nerve. We do not cover intracranial primary visual pathways, higher visual function, or ocular motor system. A review of these aspects with respect to Parkinson's disease can be found elsewhere.<sup>1</sup> Nor do we cover conditions largely confined to the pediatric population. Rare disorders with only scant case reports of ocular involvement will not be reviewed in depth but rather listed in Fig. 1 through 4 and structured by ocular tissue involved.

## Search Strategy

We searched articles published in English using Pubmed without restriction on dates. We used a combination of medical subject headings (MeSH): Ophthalmol and/or “movement disorders” and/or retina and/or “optic atrophy” and/or “eye” and/or “eyelid disorders” and/or “retinitis pigmentosa” and/or “cherry red spot” and/or “Parkinson's disease” and/or “progressive supranuclear palsy” and/or “multiple system atrophy” and/or “corticobasal” and/or “Wilson's disease” and/or “spinocerebellar ataxia” and/or “dementia with Lewy body” and/or “brain iron accumulation” and/or “hereditary spastic paraplegia” and/or “leukodystrophy\*<sup>\*</sup>”. We also included additional references from review articles.

## Anatomy and Structure of the Eye

The human eye is a two-piece structure fused in the middle and comprising anterior and posterior segments which are then split into three layers: the outer most layer—the fibrous tunic which contains the cornea and the sclera, the middle layer—the vascular tunic or uvea which contains the choroid, ciliary body and iris, and the innermost layer which contains the retina, which comprises 10 layers.<sup>2</sup> Fig. 1 through 4 details the movement disorders associated with pathology in each of these sections of the eye

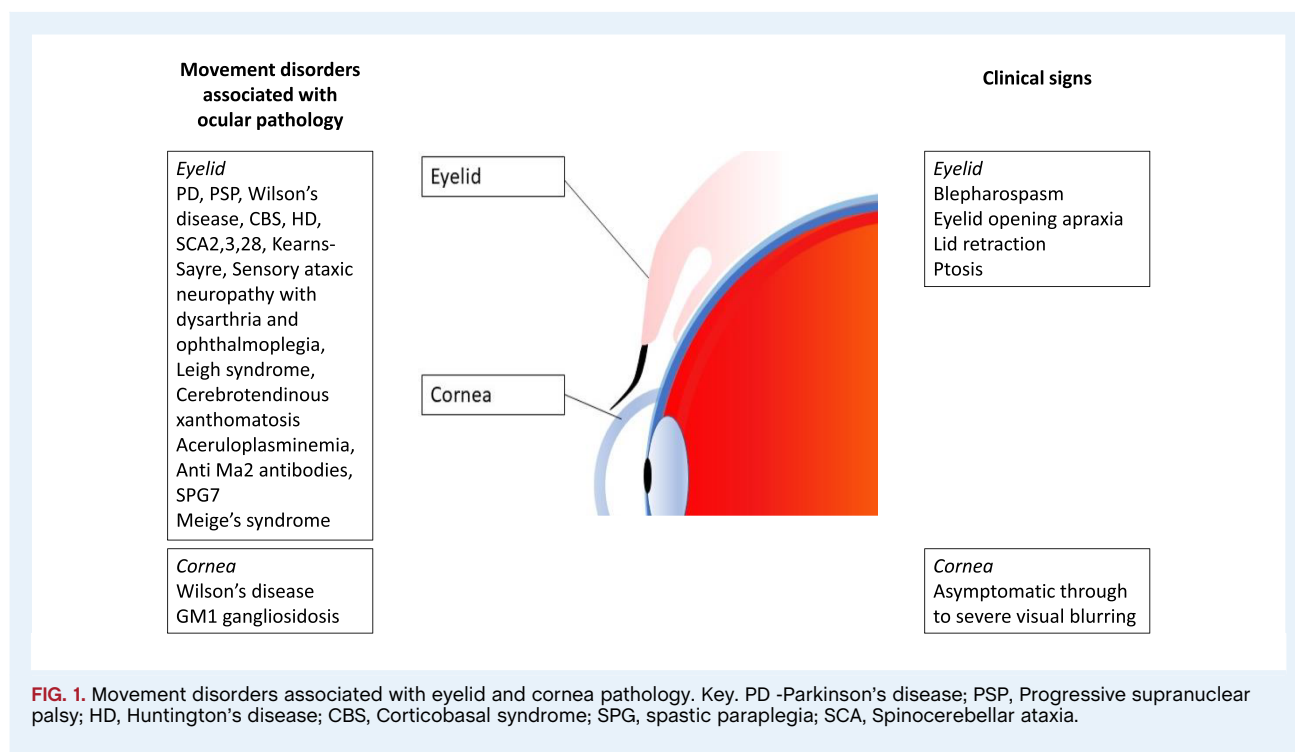
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along with the clinical manifestations which can be expected. The more detailed structure and anatomy of components of the eye associated with movement disorders are outlined below.

## Eyelid

The eyelids are folds of skin housing the levator palpebrae and orbicularis oculi muscles, along with extensive connective tissue, which helps to regulate light to the underlying eye and protect the eye. Together with the lacrimal system and tear film these serve to produce and spread tears over the eyeball. All blinks (corneal reflex, spontaneous blinks, and reflexive blinks to stimuli approaching the eye) have a closing phase in which the levator (innervated by cranial nerve III) is inhibited, and orbicularis (innervated by cranial nerve VII) is activated and an opening phase in which the levator is reactivated, and the orbicularis activity ceases. Blink rate is thought to be under dopaminergic control, as evidenced by its variation in neurological and psychiatric disorders that involve disrupted dopamine pathways.<sup>3</sup> Further, blink rates increase in Parkinson's disease with dopamine replacement<sup>3,4</sup> and deep brain stimulation<sup>5</sup> suggesting a direct association.

## Cornea

The cornea is a transparent avascular connective tissue that acts primarily as an infectious barrier but assists with refraction. It comprises five layers: two cellular and three interface.<sup>6</sup> The cornea is one of the most densely innervated tissues in the body. The nerve supply is derived from the nasociliary branch of the

ophthalmic division of the trigeminal nerve (V1) which enters the stroma in thick trunks and passes the Bowman's membrane to form a rich plexus.<sup>6</sup> The cornea also contains autonomic sympathetic fibers<sup>7</sup> but these appear to be very sparse and of unclear clinical significance.<sup>8</sup> The cornea itself is avascular but relies on tiny vessels on its outermost edge to provide the necessary blood components to remain healthy.<sup>6</sup>

## Lens

The main function of the lens is to fine-tune the focusing of light onto the retina. The lens is composed of a single cell type and 60% of its mass comprises proteins, mainly type IV collagen, laminin, entactin, perlecan, type XVIII collagen, heparin sulfate proteoglycan, and fibronectin.<sup>9</sup> The lens fibers are generated from the outside (the lens epithelium) and migrate toward the center. Therefore, the nucleus of the lens is made up of the oldest fibers.<sup>10</sup> The lens is susceptible to damage resulting in cataracts and presbyopia through the inability of non-nucleated fiber cells to turn over coupled with inadequate reducing enzyme activity. Causes include normal aging, environmental factors, and oxidative stressors. (Fig. 2).<sup>9</sup>

## Retina

The retina is the light sensitive layer of tissue inner most in the eye. It is organized such that light must first travel through unmyelinated nerve fibers and the cell bodies of the retina (Ganglion cell, Amacrine cell, Horizontal cell, Bipolar cell) before striking the light sensitive photoreceptors. Such

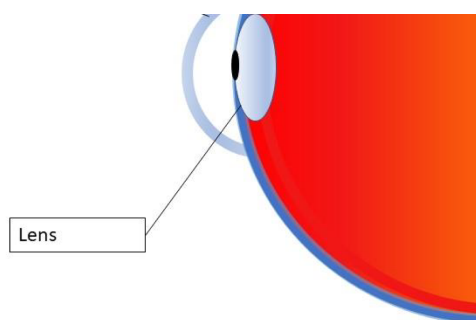
### Movement disorders associated with ocular pathology

#### Lens

Parkinson's disease,  
Wilson's disease,  
4H leukodystrophy,  
GM1 gangliosidosis,  
Cerebrotendinous-  
xanthomatosis,  
Marinesco-Sjogren  
syndrome,  
MELAS  
HSP (SPG9, SPG25,  
and SPG46),  
X-Linked  
adrenoleukodystrophy

### Clinical signs

#### Cataracts



**FIG. 2.** Movement disorders associated with lens pathology. 4H, hypomyelination with hypogonadotropic hypogonadism leukodystrophy; MELAS, mitochondrial encephalopathy lactic acidosis and stroke like episodes; SPG, spastic paraplegia; HSP, hereditary spastic paraplegia.

organization prevents back scatter of light and image degradation. Retinal tissue is organized with the photoreceptors—rods and cones—abutting the retinal pigment epithelium and neural signaling occurs both vertically (back of the eye toward the front) and horizontally.<sup>11</sup> Vertical transmission takes place predominantly from photoreceptor to bipolar cell to retinal ganglion cell. The principal neurotransmitter of the vertical system is glutamate, acting on both excitatory ionotropic and inhibitory metabotropic glutamate receptors. Horizontal neurotransmission occurs in the outer and plexiform layer between the photoreceptors and bipolar cells and in the inner plexiform layer between bipolar cells and the retinal cell ganglion; together with electrical gap junctions, these connections are mediated primarily by the inhibitory transmitters, GABA and glycine. Dopaminergic neurons also play a part in vertical and horizontal signaling in both the outer and inner layers at multiple levels<sup>12</sup> acting as a clinical messenger for light adaptation and promoting flow of information through the cones and away from the rods. Indeed, drugs which affect GABA (vigabatrin) and Dopamine (levodopa) can affect these retinal systems. Visual field constriction from disruption of amacrine and bipolar cells with vigabatrin has been well described,<sup>13</sup> and improvement in contrast sensitivity with levodopa also described.<sup>14</sup>

## The Optic Nerve Head

The optic nerve head or optic disc is the beginning of the optic nerve. It is the location where the axons of the retinal ganglion cells pass through the connective tissue of the lamina cribrosa beams.<sup>15</sup> Astrocytes are the predominant cell type in the optic nerve head.<sup>15</sup> Blood supply is mostly derived from the short posterior ciliary arteries as well as some supply from the pial arteries.<sup>16</sup>

## Specific Disorders of Ocular Structures

### Blepharospasm and Apraxia of Eyelid Opening

Blepharospasm, the spontaneous, erratic, and strong contractions of the orbital, preseptal, and pretarsal segments of the orbicularis oculi<sup>17</sup> is a focal dystonia, involving co-contraction of both agonist and antagonistic muscles. It may initially present with an increased blink rate<sup>18</sup> and it is postulated blepharospasm is due to overactivity of reflex blinking, especially in response to light<sup>19</sup> Apraxia of (eye)lid opening is the inability to open the eyes due to disrupted supranuclear control of the levator palpebrae and orbicularis oculi muscles. A characteristic sign of eyelid opening apraxia is overaction of frontalis muscle attempting to open the eyes. The neural basis of both blepharospasm<sup>17</sup> and eyelid opening apraxia are poorly understood. The anterior cingulate and supplemental motor areas have both been implicated in positron emission tomography (PET) studies.<sup>20,21</sup>

### Cataracts

Cataracts are the loss of lens transparency due to opacification (e.g. Fig 2.). They are broadly grouped into age related cataracts, pediatric cataracts and cataracts secondary to other causes. Age related cataracts are divided into three locations: nuclear, cortical and posterior subcapsular. Oxidative stress primarily occurs in the metabolically active peripheral epithelial cells, the cells then migrate toward the center where compression and eventually opacification results.<sup>22</sup> Pediatric cataracts can be infantile or

congenital with up to one third being inherited. Another third is usually part of a multisystem or metabolic syndrome.<sup>10</sup>

## Retinitis Pigmentosa

Retinitis pigmentosa (RP) describes retinal changes which include bone-spicule pigmentary clumping, vascular attenuation, and optic nerve pallor (eg, Fig. 5).<sup>23</sup> These changes lead to a progressive loss of rod photoreceptors, initially presenting with nyctalopia (“night-blindness”) followed by a secondary cone photoreceptor degeneration resulting in decreased central visual acuity. RP is caused by a heterogeneous collection of inherited disorders.<sup>24</sup> The underlying pathophysiology of RP is poorly understood but retinal vasoconstriction and neuro-retinal remodeling seem to be implicated.<sup>23</sup>

There are several genetic conditions which feature both RP and movement disorders (Fig. 3) and whilst uncommon, the finding of RP is helpful in narrowing down the differential diagnosis.

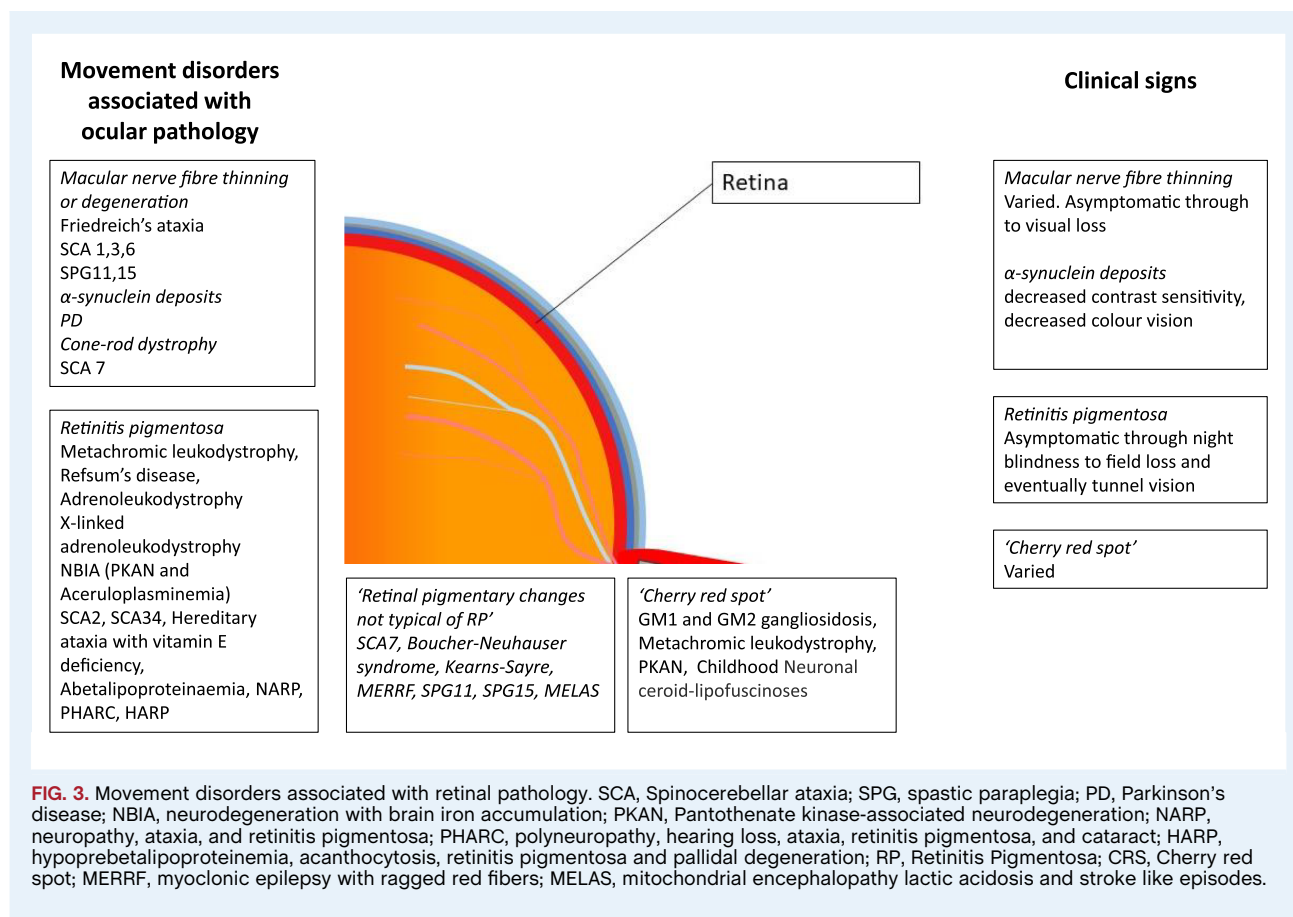
## The “cherry red spot”

The cherry red spot (CRS) is a fundoscopic sign and result of thickening and loss of transparency in the perifoveal aspect of posterior pole of the retina (eg, Fig. 5).<sup>25</sup> Unlike other parts

of the retina, the fovea has almost no ganglion cells and in normal situations appears as an intense spot of color (usually red but does vary with ethnicity). In storage diseases (eg, the gangliosidoses) material can build up in the ganglion cells surrounding the fovea (sparing the fovea due to a lack of ganglion cells) leading to opacification giving the appearance of a “cherry red spot”. A perifoveal white patch may be more appropriate terminology as it reflects the underlying disease process and, depending on the ethnicity of the patient, the fovea may not appear red at all.<sup>26</sup> Several storage disorders are associated with both CRS and movement disorders (Fig. 3).

## Optic Atrophy

Optic atrophy is the result of any disease process affecting the optic nerve. It is characterized clinically by a pale optic disc on fundoscopy and by retinal nerve fiber layer (RNFL) thinning on optic coherence tomography (OCT) and develops 2 to 3 months after the insult. The optic nerve being a central nervous system structure, has limited ability for self-repair. Degeneration of the optic nerve itself and its vascular supply form the basis of optic atrophy. Disorders leading to optic atrophy are varied. These include compressive, vascular, inflammatory, infectious, metabolic, toxic, genetic/congenital, and neoplasia.





# Movement Disorders Associated with Ocular Pathology

## The Parkinsonian Disorders

### Eyelid

Decreased blink rate, and less commonly blepharospasm and eyelid opening apraxia are well recognized in Parkinson's disease (PD)<sup>27–30</sup> but are more associated with progressive supranuclear palsy (PSP). Additionally, lid retraction is almost universal in PSP<sup>19</sup> but not a feature of the other parkinsonian disorders. A decreased blink rate can cause dry eyes which is a major cause of reduction in visual quality.

Blink rates should ideally be assessed on a per minute basis over a 5-minute period.<sup>31</sup> In patients with PD, a mean blink rate in 1 minute (8.5 blinks) was significantly less than controls (12.4), but significantly more than patients with PSP (1.9).<sup>31</sup>

In one study of PD, blepharospasm was present in 13% of patients but in none of the controls<sup>27</sup> although these were all in patients with severe disease on dopamine replacement. Corneal irritation can mimic blepharospasm and must be considered prior to other therapies such as botulinum toxin.

Whilst more characteristic of PSP, apraxia of eyelid opening can be seen in up to 7% of patients with PD,<sup>27</sup> again only in patients with advanced disease on dopamine replacement.

Both blepharospasm<sup>32</sup> and apraxia of eyelid opening<sup>33</sup> have been reported in corticobasal syndrome (CBS). However, due to the difficulty in diagnosing this condition and the widespread overlapping features it shares with PSP, caution should be undertaken in the interpretation of these case reports. Indeed, the autopsy findings of a patient with apraxia of eyelid opening who was diagnosed with CBS were more in keeping with PSP.<sup>34</sup>

Both blepharospasm and apraxia of eyelid opening have been reported to be improved or aggravated by dopaminergic medication depending on the underlying parkinsonian disorder.<sup>35–37</sup>

### Lens

Small cohort studies show cataracts are over-represented in patients with PD<sup>38</sup> and tend to be located in nuclear and posterior subcapsular lens.<sup>39</sup> The physiology underlying this finding is unclear but may be associated with alpha-synuclein deposition in the lens<sup>40,41</sup> which co-localize with alpha crystallins,<sup>42</sup> a protein which prevents protein accumulation and cataract formation.<sup>38</sup>

### Pupil

Pupillary response is driven by iris dilator and sphincter muscles under control by ambient light and the autonomic nervous system. PD has been associated with significantly larger pupils, anisocoria and longer constriction times in light adaptation.<sup>27,43</sup> These likely reflect autonomic dysfunction associated with PD rather than a direct association with the dopaminergic system.

Abnormal pupillary responses occur in approximately 30% of patients with Multiple System Atrophy (MSA) likely reflecting autonomic dysfunction with the following abnormalities found: dark anisocoria—whether due to abnormal miosis or mydriasis being uncertain, reduced light reflex, and reduced near reflex.<sup>44</sup>

### Retina

Retinal dysfunction is associated with several Parkinsonian conditions. Patients with Parkinson's disease experience a range of visual dysfunction at the retinal level including problems with visual acuity, decreased contrast sensitivity, decreased color vision, and decreased motion sensitivity, all of which can lead to functional impairment. Small absolute decreases in visual acuity, independent of cognitive impairment, have been documented in patients with PD.<sup>45</sup> Such changes have been proposed to contribute to visual hallucinations. Although the decreased acuity in PD is not overt enough to cause Charles Bonnet syndrome, it may contribute by priming de-afferentation of the visual cortex.<sup>46</sup> Decreased contrast sensitivity is well documented in PD, mostly at low contrast<sup>47</sup> and with temporal variation<sup>12,47</sup> which may improve with levodopa.<sup>12</sup> How much of this is at the level of the retina is unclear as there may be some element of a cortically driven process.<sup>48</sup> Decreased contrast sensitivity has been implicated in falls, reading difficulties, driving difficulties, and activities of daily living in elderly patients without PD<sup>49–51</sup> and likely has the same implications in patients with PD. Furthermore, like impaired visual acuity, it may contribute to visual hallucinations.<sup>52</sup> Patients with PD also have trouble with color vision<sup>53</sup> and color discrimination<sup>54</sup> perhaps driven by impairments to parvocellular, koniocellular, and magnocellular pathways, in patterns quite different from other age-related conditions.<sup>55</sup> Motion perception is also affected in PD<sup>56</sup> but teasing out what is retinally driven and what is cortically driven is difficult with recent work suggesting motion perception abnormalities are more likely cortically derived.<sup>57</sup>

Phosphorylated  $\alpha$ -synuclein accumulates in the retina in parallel with that in the brain in patients with PD and DLB as well as in pre-clinical states making the retina an attractive potential non-invasive biomarker of early PD should in-vivo retinal  $\alpha$ -synuclein imaging become widely available.<sup>58</sup> These aggregates are dispersed within the amacrine cells (the principal synthesizer of retinal dopamine) at the border of the inner nuclear layer and in the retinal ganglion cell layer and particularly in the inner plexiform layer.<sup>59,60</sup> In addition to  $\alpha$ -synuclein accumulation, the amacrine cell numbers are decreased in PD patients by up to 58% in different retinal regions.<sup>61</sup>

### Optic Nerve Head

Retinal nerve fiber layer (RNFL) thinning of the optic nerve has been documented in PD<sup>62,63</sup> with a preferential loss of temporal fibers.<sup>64</sup> However, there are several other factors including age, race, and optic disc area which must be considered when interpreting these findings.<sup>65</sup> Patients with PSP also have reduced RNFL thickness in the inferior nasal and inferior temporal areas

compared with controls. However, the retinal changes do not correlate with disease severity or duration.<sup>66</sup> Similarly, RNFL thinning and optic atrophy are documented in MSA,<sup>67,68</sup> predominantly nasally but not associated with any visual field defect.<sup>69</sup> These findings can be determined relatively easily with optical coherence tomography (OCT) which is becoming a popular tool in neuro-ophthalmology.<sup>70</sup> (Fig. 5).

## The Leukodystrophies

### Eyelid

Blepharospasm, although rare, has been described in cerebrotendinous xanthomatosis.<sup>71</sup>

### Cornea

Corneal clouding may affect just over 20% of patients with adult onset GM1 gangliosidosis.<sup>72</sup>

### Lens

4H (hypomyelination, hypodontia, hypogonadotropic hypogonadism) leukodystrophy caused by mutations in *POLR3A* or *POLR3B* and associated with tremor, dysmetria, ataxia or dystonia, can rarely cause cataracts but is limited to five cases in the literature.<sup>73,74</sup> A small single center review suggests 10% of patients with GM1 gangliosidosis can develop cataracts<sup>72</sup> as can patients with X linked adrenoleukodystrophy.<sup>75</sup> Patients with Cerebrotendinous xanthomatosis almost universally develop cataracts, often in the first decade of life.<sup>76</sup> Cataracts can be the presenting symptom of this disease.<sup>77,78</sup> Up to 30% of patients with Refsum's disease have cataracts.<sup>79</sup>

### Retina

RP is seen universally in Refsum's disease and nearly always is present prior to diagnosis.<sup>80</sup> RP is a feature of most cases of neonatal adrenoleukodystrophy, although said to appear more as leopard spots rather than classical RP.<sup>81</sup> Retinal changes are not seen in adult-onset forms. GM1 and GM2 gangliosidosis both result in ganglioside accumulation to an abnormal degree within the cytoplasm of retinal ganglion cells resulting in the CRS. This is seen in around 50% of patients with GM1 type 1 and the majority of GM2 type 1 patients except for late onset GM2 in which the CRS is rarely present.<sup>82</sup>

### Optic Nerve Head

Three percent of adult patients with adrenomyeloneuropathy have pale discs on clinical examination<sup>83</sup> which may be driven by demyelination.<sup>84</sup> Optic atrophy is recognized in the older patients with 4H leukodystrophy and Metachromatic leukodystrophy, but its true incidence is unclear as it was not specifically looked for in the largest case series available.<sup>73</sup> In patients with 4H leukodystrophy, optic atrophy is confined to a few case

reports from the 1950s through 60s.<sup>85</sup> Lastly, a pale optic disc is a feature in just under half of patients with Cerebrotendinous xanthomatosis.<sup>75</sup>

## Neurodegeneration with Brain Iron Accumulation Disorders (NBIA)

The NBIA's are a rare, inherited, clinically and genetically heterogeneous group of disorders with age-independent brain iron store accumulation as their unifying feature.<sup>86</sup> Whether the iron accumulation is pathological or an epiphenomenon remains unresolved. The exact prevalence of this condition is unknown but likely falls into the ultra-rare (<1/1,000,000) category.<sup>87</sup> Mutations in the pantothenate kinase gene are responsible for 35%–50% of NBIA cases and are termed Pantothenate Kinase-associated Neurodegeneration (PKAN).<sup>86</sup> Patients with PKAN can have a typical or atypical presentation. Typical cases are more severe and earlier onset, whereas atypical presentations more often have speech, cognitive, and psychiatric disturbances.<sup>88</sup> Phospho-Lipase-Associated Neurodegeneration (PLAN) is the second most common NBIA subtype accounting for approximately 20% of cases.<sup>86</sup> Beta-propeller protein associated neurodegeneration (BPAN) accounts for 7% of NBIA's, whilst rarer subtypes; Fatty acid hydroxylase associated neurodegeneration (FAHN), Kufor-Rakeb disease, Hereditary ferritinopathy, Aceruloplasminemia, Coxsy protein-associated neurodegeneration (COPAN), and Woodhouse Sakati syndrome make up the rest.<sup>87</sup>

### Eyelid

There has been one case report of blepharospasm in Aceruloplasminemia.<sup>89</sup>

### Retina

Retinal degeneration is the most frequent ocular finding in classical NBIA type 1 (classical PKAN) present in 20% to 68%.<sup>88,90</sup> Retinitis pigmentosa was documented in only 40% of patients with genetically confirmed PKAN but 70% of patients had an abnormal electroretinography (ERG) suggesting some degree of cone-rod retinal dysfunction.<sup>91</sup> One study suggests all patients with genetically confirmed atypical NBIA type 1 have a retinopathy as evidenced by an abnormal ERG despite nearly all having a normal appearing fundus and normal acuities.<sup>92</sup> Retinal degeneration is also common in Aceruloplasminemia, occurring in 64% of patients.<sup>89</sup>

### Optic Nerve Head

Optic neuropathy has been documented in the classical variant NBIA type 1, although infrequent, and seen in less than 4% of patients.<sup>88,90</sup> In contrast optic atrophy is a frequent finding in

PLAN,<sup>93</sup> is present in all patients with MPAN,<sup>94</sup> and all patients with advanced FAHN.<sup>95</sup>

## The Ataxias

### Eyelid

Apraxia of eyelid opening has been associated with SCA2 and SCA3,<sup>96,97</sup> eyelid retraction is characteristic in SCA3<sup>70</sup> and ptosis is seen in SCA28<sup>98</sup> which may be driven by mitochondrial mutations.<sup>99</sup>

### Conjunctiva

Conjunctival telangiectasia is present in nearly all cases of Ataxia Telangiectasia and a useful diagnostic feature but rarely has symptomatic impact.<sup>100</sup>

### Lens

Juvenile, but not necessarily congenital, cataracts are a typical feature of Marinesco-Sjogren syndrome.<sup>101</sup>

### Retina

OCT indicates that patients with Friedreich's ataxia have a thinner peripapillary retinal nerve fiber layer, decreased ganglion cell complex, and decreased outer macular ring volume when compared to healthy controls which worsens with disease progression.<sup>102</sup> Together with optic atrophy (outlined below) this can manifest with profound visual loss, field deficits, or be asymptomatic.<sup>103</sup> Many of the SCA's have retinal pathology. Cone-Rod dystrophy is characteristic of SCA7, and visual symptoms (decreased acuity) may predate motor symptoms. Examination reveals early loss of normal foveal reflex, followed by retinal pigmentary epithelium changes with retinal atrophy in the fovea.<sup>104</sup> How expanded triplet repeats cause degeneration of the retina is not understood but may be mediated by RNA-mediated toxicity.<sup>104</sup> Outside of SCA7, macular thinning assessed by optic coherence tomography is evident in patients with SCA1, SCA3, and SCA6 but not SCA2.<sup>105</sup>

Pigmentary changes are a consistent finding in patients with SCA7,<sup>106</sup> though not typical of RP (see Fig. 5B) and not a constant feature. RP has been rarely identified in cases of SCA2<sup>107</sup> and SCA34.<sup>108</sup> RP has also been described in Hereditary ataxia with vitamin E deficiency but due to its rarity incidence is not known.<sup>109</sup> RP or atypical RP is likely a common finding in Abetalipoproteinaemia, being consistently reported in case reports and studies.<sup>109,110</sup> Lastly, Boucher-Neuhäuser Syndrome (BNS) presents with extensive atrophic changes of the retinal pigment epithelium and choriocapillaris.<sup>111</sup> The presence of chorioretinal atrophy in a patient with ataxia and hypogonadotropic hypogonadism make the PNPLA6 gene defect associated with BNS highly likely.

## Optic Nerve

SCA1, SCA2, and SCA3 are associated with optic atrophy<sup>105,112</sup> with SCA1 having significantly higher prevalence (44%) than SCA2 and SCA3 (14% and 11%, respectively).<sup>112</sup> Patients with Friedreich's ataxia have variable degrees of optic atrophy, ranging from diffuse optic pallor to near normal appearances on fundoscopy.<sup>103</sup>

## The Mitochondrial Cytopathies

### Lens

Some patients with mitochondrial encephalopathy, lactic acidosis, and stroke like episode (MELAS) can develop early posterior subcapsular cataracts,<sup>113,114</sup> though this is likely an uncommon finding as it was not reported in a large case series.<sup>115</sup>

### Retina

The retinal pigment epithelium is highly affected by mutations in the mtDNA. All patients with Kearns-Sayre develop a retinopathy with widespread defects of the retinal pigment epithelium, giving the "salt and pepper retina" appearance which is quite different from typical RP. These changes are associated with variable visual loss.<sup>113</sup> RP is seen in all patients with Neuropathy, ataxia, and retinitis pigmentosa (NARP), Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC) and Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration (HARP). Subtle retinal pigment changes have been described in one patient with myoclonic epilepsy with ragged red fibers (MERRF), but the visual loss in this patient was thought due to the concurrent optic atrophy.<sup>113</sup> Retinal pigment abnormalities are highly prevalent in MELAS (57%) but are asymptomatic and not evident on routine fundoscopy, only being appreciated with retinal photography.<sup>115</sup>

### Optic Nerve Head

All patients with Leber's optic neuropathy (LON) and some two thirds of patients with MERRF have optic atrophy.<sup>113</sup> Those with LON develop peripapillary microangiopathies early in their disease course, visible on fundoscopy, and seen in >50% of cases, many asymptomatic.<sup>113,116</sup>

## The Antineuronal Antibody Syndromes

### Eyelid

Anti-Ma2 antibodies can be associated with a PSP phenotype with eyelid opening apraxia being a prominent feature.<sup>117</sup>

## Optic Nerve Head

Autoimmune glial fibrillary acidic protein (GFAP) inflammatory disorder typically presents with optic nerve head swelling from papillitis. Occasionally these patients can develop ataxia, tremor, or undefined movement disorders as part of their syndrome.<sup>117</sup> Neuromyelitis spectrum disorders often present with a papillitis/optic neuritis<sup>118</sup> and can be referred to the movement disorder clinic with painful tonic spasms. Glycine receptor antibodies which are associated with thymoma and other various cancers may present with Stiff Person Syndrome, ataxia or myoclonus, and were identified in 6% of patients with isolated optic neuritis;<sup>119</sup> however, as far as we are aware, there have been no reported cases of the combination of both a movement disorder and optic neuritis. Collapsin response mediator protein antibody disease can mimic neuromyelitis spectrum disorder, presenting with optic neuritis and associated chorea (Fig. 4).<sup>117</sup>

## The Hereditary Spastic Paraplegias (HSP)

### Eyelid

Ptosis is seen in up to 90% of patients with compound heterozygous mutations in spastic paraplegia type 7 (SPG7).<sup>75,120</sup>

### Lens

Cataracts are a key feature of SPG9, SPG25, and SPG46.<sup>75</sup>

## Retina

Retinal degeneration is a hallmark of SPG11 but is also seen in SPG15, with the appearance of yellow flecks throughout the retinal pigment epithelium.<sup>75</sup> These tend to occur late in the disease when the neurological manifestations are advanced, although complaints about impaired visual acuity are rare.

## Optic Nerve Head

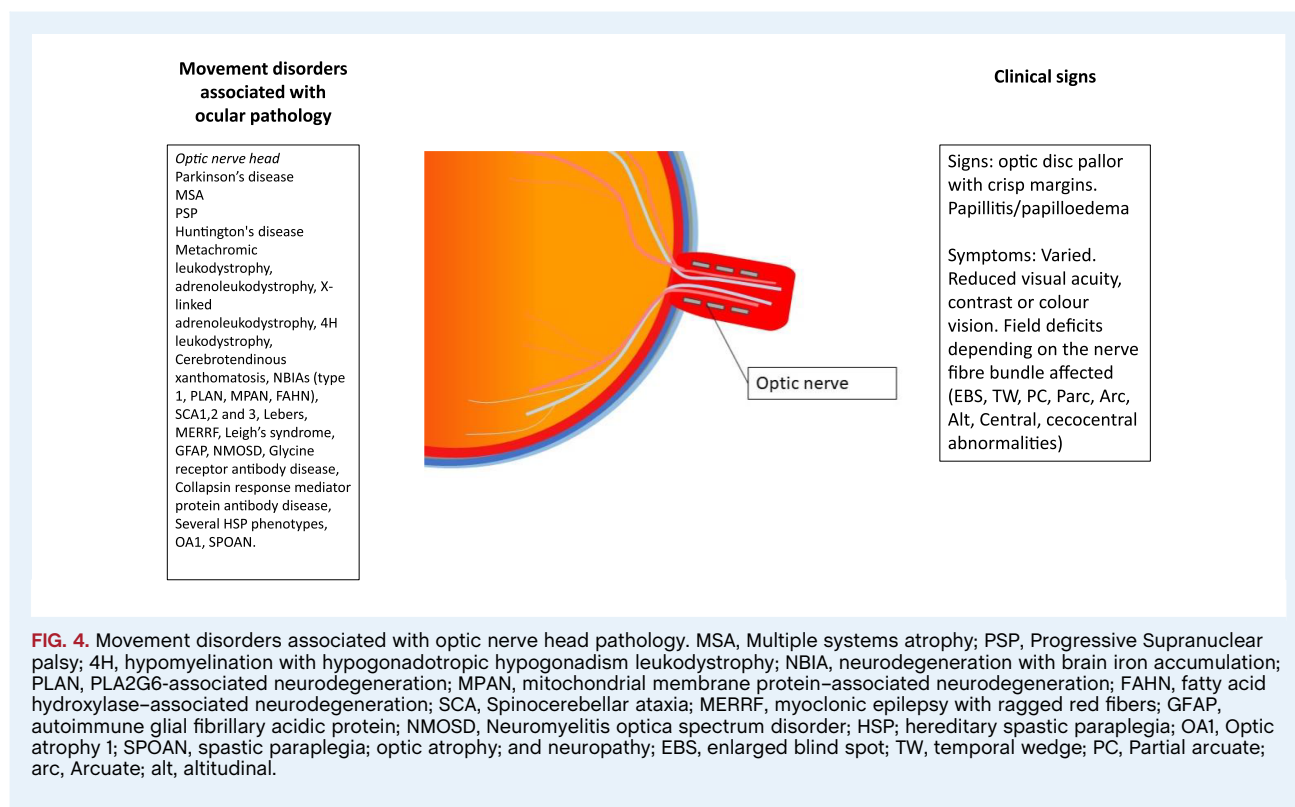
Optic atrophy is encountered in several HSPs: SPG2, SPG7, SPG16, SPG35, SPG45, SPG54, SPG55, SPG57, and SPG68. In addition to the HSPs, optic atrophy 1 and Spastic paraplegia and optic atrophy and neuropathy (SPOAN) can present with a spastic paraplegia and show pallor of the optic disc.<sup>75</sup>

## Other Specific Conditions Not Named Above

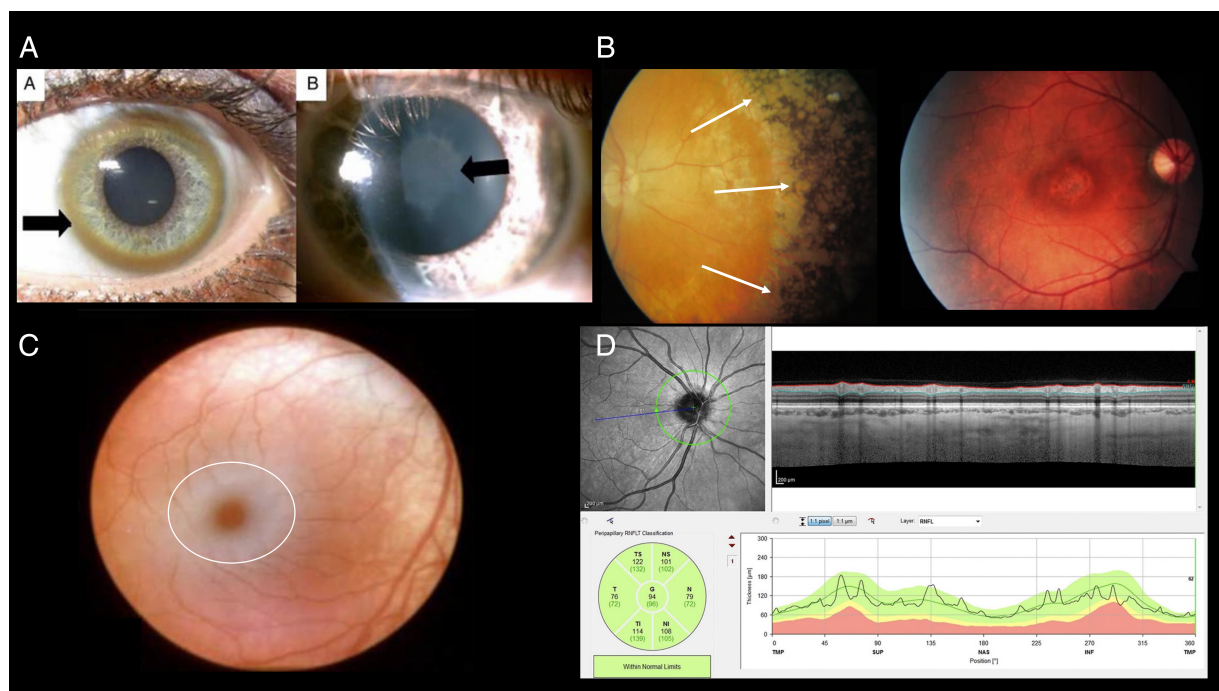
### Huntington's Disease

#### Eyelid

Huntington's disease (HD) may be accompanied by eyelid opening apraxia<sup>121</sup> whilst in contrast, an increased blink rate is seen in up to 75% of patients perhaps due to a hyperdopaminergic state with increased nigrocollicular pathway activity leading to



**FIG. 4.** Movement disorders associated with optic nerve head pathology. MSA, Multiple systems atrophy; PSP, Progressive Supranuclear palsy; 4H, hypomyelination with hypogonadotropic hypogonadism leukodystrophy; NBIA, neurodegeneration with brain iron accumulation; PLAN, PLA2G6-associated neurodegeneration; MPAN, mitochondrial membrane protein-associated neurodegeneration; FAHN, fatty acid hydroxylase-associated neurodegeneration; SCA, Spinocerebellar ataxia; MERRF, myoclonic epilepsy with ragged red fibers; GFAP, autoimmune glial fibrillary acidic protein; NMOSD, Neuromyelitis optica spectrum disorder; HSP, hereditary spastic paraplegia; OA1, Optic atrophy 1; SPOAN, spastic paraplegia; optic atrophy; and neuropathy; EBS, enlarged blind spot; TW, temporal wedge; PC, Partial arcuate; Arc, Arcuate; alt, altitudinal.



**FIG. 5.** A) Keyser-Fleischer ring (A) and Sunflower cataract (B) in a patient with Wilson's disease—modified with permission from *Practical Neurology* 2015;15:385–386. B) Retinitis Pigmentosa (white arrows) in a patient with Refsum's disease in contrast to the retinopathy seen in SCA7 Modified with permission from *J Med Case Reports*. 2008;2:80 and *Eye (Lond)*. 2018 Jan;32(1):120–127. C) The Cherry Red Spot (white circle outlining the perifoveal opacification) in a patient with Tay Sachs disease. Modified with permission from *Surv Ophthalmol*. 2014 Jan-Feb; 59(1). D) Measurement of the retinal nerve fiber layer in patients with Parkinson's disease. In this patient the measurement of the RNFL is within normal limits in all quadrants. Modified with permission from *Kaohsiung J Med Sci* 2018 Mar;34 (3):166–171.

decreased inhibition of physiological blinking.<sup>19,122</sup> In one case this was the presenting feature, pre-dating other more typical symptoms by 2 years.<sup>123</sup>

## Optic Nerve Head

Optic nerve head changes have been identified in patients with Huntington's disease using OCT. Temporal thinning has been the more widely documented<sup>124,125</sup> with greater thinning in those with longer disease duration<sup>124</sup> and superior retinal thinning less commonly present.<sup>125</sup> It has been proposed that deficits in mitochondrial trafficking may be the cause of such thinning.<sup>125</sup>

## Wilson's Disease (WD)

### Eyelid

There is scant information on eyelid disorders in Wilson's disease with a sole case report of an increased blink rate.<sup>126</sup>

### Cornea

Kayser–Fleischer (KF) rings, which are asymptomatic, are present in in nearly all patients presenting with movement disorders in Wilson's disease (Fig. 5). KF rings, which result from copper

deposition in Descemet's membrane of the cornea,<sup>127</sup> typically disappear with treatment over 3–5 years and reappear with disease progression,<sup>128</sup> and so are a useful clinical sign to monitor treatment compliance. Initially they are only evident using slit lamp examination but may become visible to the naked eye as the disease progresses.

### Lens

Wilson's disease can be associated with a “sunflower” cataract, with central opacification surrounded by additional secondary opacifications arranged in ray-like structures in a pattern resembling a sunflower<sup>129</sup> (Fig. 5). Whilst said to be pathognomonic of WD it is rare (perhaps only seen in 1% of cases) and can disappear with copper chelation therapy.<sup>130</sup>

## Blepharospasm-Oromandibular Cranial Dystonia (Meige Syndrome)

### Eyelid

Blepharospasm–oromandibular cranial dystonia (Meige syndrome) as the name suggests typically presents with blepharospasm, sometimes so severe it can render the patient functionally



blind. Coexistent eyelid opening apraxia has also been described.<sup>131</sup> Neurophysiology studies show that the cranial-brainstem reflex arcs are normal whereas the blink reflex recovery curves are not, indicating a failure of the inhibitory neurons in the network controlling the lid. This abnormal excitatory drive may originate in the basal ganglia.<sup>132</sup>

## Ophthalmological Assessments

In addition to the bedside tools clinicians have at their disposal (ophthalmoscope, Snellen charts, Ishihara plates, red or white hat pins), there are several investigations which can prove fruitful. Deciding which investigations to choose, and in whom, can be difficult. Below we outline the most useful additional tests and suggestions on when to request these.

### Ophthalmological Referral for Slit Lamp Examination and Retinal Photography

Ophthalmological referral can be the most useful additional investigation in patients with movement disorders. With the enormous etiological and clinical heterogeneity seen in movement disorders, identifying pathology outside of the neurological system can be very helpful. Whilst cataracts and optic atrophy are very common in the older population, careful ophthalmological review with a slit lamp to identify features such as the cherry red spot or retinitis pigmentosa can drastically narrow down a differential diagnosis and help target further investigations. If available, we advocate for a neuro-ophthalmologist, who is more likely to be familiar with movement disorders and can better search for efferent visual system clues which are likely to increase diagnostic yield. Slit lamp examination may be the only way to identify KF rings which can be used to guide treatment adherence. Thus, ophthalmological assessment is an integral assessment in patients who have (or may have) Wilson's disease.

### Optical Coherence Tomography (OCT)

OCT is a non-invasive technique which gives cross sectional imaging of living tissue. Using near infrared spectral range light, it can penetrate a few 100 microns into retinal tissue and give high resolution structural imaging greater than that of ultrasound or MRI. With many movement disorders having overlapping clinical spectrums, the practical use of OCT is to identify (the often asymptomatic) thinning of the RNFL thereby narrowing a wide differential diagnosis. OCT may however help differentiate visual loss at a retinal rather than optic nerve level, and this feature can be helpful in individual cases.

### Electroretinogram (ERG) and Visual Evoked Responses/Potentials (VER or VEPs)

ERG and VER measure the amplitude and latency of electrical responses within the retina and retro-orbital visual pathway, respectively, with VERs being especially responsive to disorders of the optic nerves. The ERG is an excellent method for precise diagnosis and follow-up of patients with RP. Usual ERG findings include general reduction in the amplitude of five ERG responses (rod, maximum, oscillatory, cone, and flicker), with a reduction in rod responses often the first to be affected.<sup>133</sup> VERs are used to quantify the functional integrity of the optic nerve, and the subsequent afferent visual pathways to the primary and association visual cortex. Simultaneous recordings using VERs together with ERG can usefully distinguish early maculopathy from optic nerve demyelination and atrophy.<sup>134</sup>

## Conclusion

Eye disorders spanning a range of ocular tissue are common in patients with movement disorders. Retinal and optic nerve changes are reportedly the most common, reflecting the now widespread use of OCT, although many of these oftentimes subtle changes are asymptomatic. Clinicians should interrogate their patients for any visual changes they may be experiencing. Color vision, motion perception, contrast sensitivity should all be explored in movement disorders known to affect the retina. The identification of cataracts (in a younger patient), retinitis pigmentosa, or a cherry red spot points toward a defined number of disorders and can be very helpful in narrowing down a differential diagnosis and help guide investigations.

## Author Roles

- (1) Research project: A. Conception, B. Organization, C. Execution;
- (2) Manuscript: A. Writing of the first draft, B. Review and Critique.  
 DW: 1A, 1B, 1C, 2A  
 TA: 1A, 1B 2B  
 MH: 2B

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