

# Clinical and imaging clues to the diagnosis and follow-up of ptosis and ophthalmoparesis

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## Abstract

Ophthalmoparesis and ptosis can be caused by a wide range of rare or more prevalent diseases, several of which can be successfully treated. In this review, we provide clues to aid in the diagnosis of these diseases, based on the clinical symptoms, the involvement pattern and imaging features of extra-ocular muscles (EOM). Dysfunction of EOM including the levator palpebrae can be due to muscle weakness, anatomical restrictions or pathology affecting the innervation. A comprehensive literature review was performed to find clinical and imaging clues for the diagnosis and follow-up of ptosis and ophthalmoparesis. We used five patterns as a framework for differential diagnostic reasoning and for pattern recognition in symptomatology, EOM involvement and imaging results of individual patients. The five patterns were characterized by the presence of combination of ptosis, ophthalmoparesis, diplopia, pain, proptosis, nystagmus, extra-orbital symptoms, symmetry or fluctuations in symptoms. Each pattern was linked to anatomical locations and either hereditary or acquired diseases. Hereditary muscle diseases often lead to ophthalmoparesis without diplopia as a predominant feature, while in acquired eye muscle diseases ophthalmoparesis is often asymmetrical and can be accompanied by proptosis and pain. Fluctuation is a hallmark of an acquired synaptic disease like myasthenia gravis. Nystagmus is indicative of a central nervous system lesion. Second, specific EOM involvement patterns can also provide valuable diagnostic clues. In hereditary muscle diseases like chronic progressive external ophthalmoplegia (CPEO) and oculo-pharyngeal muscular dystrophy (OPMD) the superior rectus is often involved. In neuropathic disease, the pattern of involvement of the EOM can be linked to specific cranial nerves. In myasthenia gravis this pattern is variable within patients over time. Lastly, orbital imaging can aid in the diagnosis. Fat replacement of the EOM is commonly observed in hereditary myopathic diseases, such as CPEO. In contrast, inflammation and volume increases are often observed in acquired muscle diseases such as Graves' orbitopathy. In diseases with ophthalmoparesis and ptosis specific patterns of clinical symptoms, the EOM involvement pattern and orbital imaging provide valuable information for diagnosis and could prove valuable in the follow-up of disease progression and the understanding of disease pathophysiology.

**Keywords** Ophthalmoparesis; Ptosis; Extra-ocular muscles; Imaging; Neuromuscular disease; Involvement pattern

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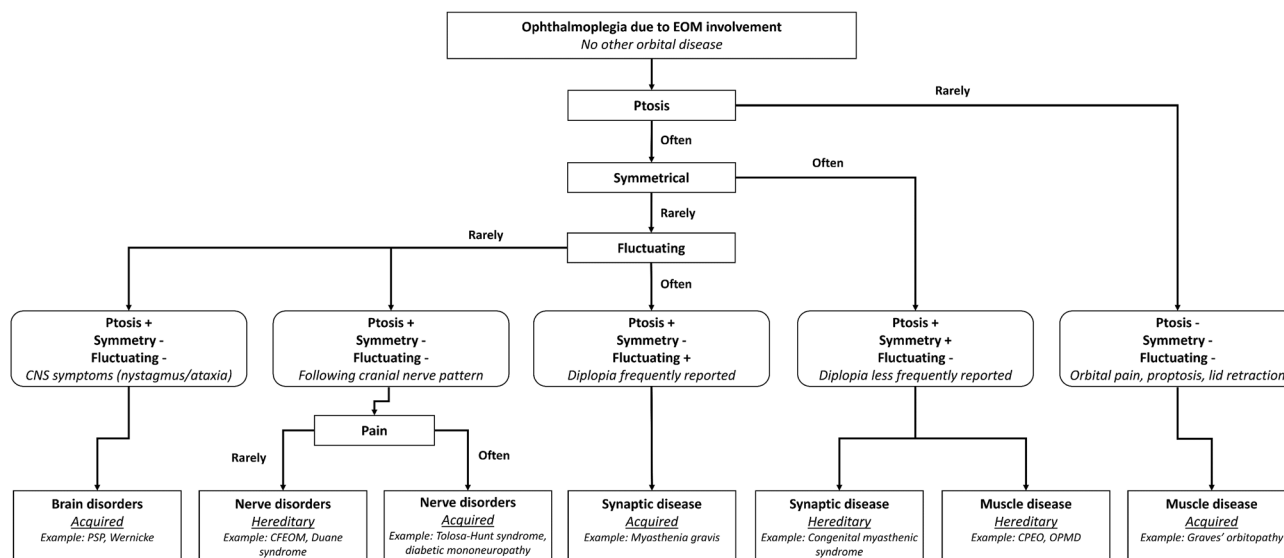
## Introduction

Ophthalmoparesis is dysfunction of the extra-ocular muscles (EOM), usually caused by muscle weakness, anatomical restrictions or pathology affecting their innervation. Three pairs of antagonizing EOMs move the eye in all directions: horizontally (medial rectus [MR] and lateral rectus [LR]) and vertically (superior rectus [SR], inferior rectus [IR], superior oblique [SO] and inferior oblique [IO]). Ptosis refers to the drooping of the upper eyelid and can be a disabling or disfiguring symptom. Ptosis is often caused by weakness of the levator palpebrae superioris (LPS) muscle, which is responsible for elevating the upper eyelid, with help from the superior tarsal muscle (Muller’s muscle). Eye lid retraction, often accompanied by bulging of the eye called proptosis, is generally caused by an increased orbital volume. In this review, we aimed to explore whether the symptomatology, the involvement pattern of EOM, and imaging can aid in diagnosis, follow-up and understanding of diseases with ophthalmoparesis and ptosis.

Causes of ophthalmoparesis and ptosis can be broadly divided into diseases affecting four anatomical locations: brain, nerve, synapse or muscle. These diseases can be either acquired or hereditary. Examples of *brain diseases* that present with ophthalmoparesis are Wernicke’s encephalopathy and progressive supranuclear palsy. *Nerve dysfunction*, as seen in congenital fibrosis of the extra-ocular muscles (CFEOM)<sup>1</sup> or acquired nerve disorders, like Miller–Fisher syndrome<sup>2</sup> or Tolosa–Hunt syndrome,<sup>3</sup> can cause ophthalmoparesis and ptosis following the innervation pattern of the affected cranial nerves. The group of *synaptic diseases* include congenital myasthenic syndromes<sup>4</sup> and acquired synaptic disease such

as myasthenia gravis, which is caused by auto-antibodies against neuromuscular junction-proteins.<sup>5</sup> Finally, the group of *muscle diseases* comprises disorders that directly affect the EOM. In acquired muscle disease, ophthalmoparesis and ptosis are often due to inflammation or enlargement of the EOM, orbital fat or other orbital structures. An example of acquired muscle disease is Graves’ orbitopathy, in which thyroid stimulating hormone receptor-antibodies cause orbital inflammation.<sup>6</sup> Examples of hereditary muscle diseases that present with ophthalmoparesis are chronic progressive external ophthalmoplegia (CPEO),<sup>7</sup> caused by mitochondrial dysfunction and oculo-pharyngeal muscular dystrophy (OPMD), with pharyngeal and ocular muscle weakness caused by a mutation in the *PABPN1* gene.<sup>8</sup>

To facilitate diagnostic reasoning, we used five main clinical patterns of symptoms that correspond to specific anatomical locations and disease characteristics pointing towards a hereditary or acquired cause of the disease (Figure 1). We used these five patterns as a starting point for pattern recognition in symptomatology, EOM involvement and imaging results of individual patients. They do not provide a stringent classification because the patterns are not completely mutually exclusive and exceptions do occur. Per pattern, we describe the severity of ptosis and ophthalmoparesis, the presence of diplopia, the symmetry, the presence of fluctuations and accompanying symptoms like pain and CNS symptoms. Per disease, we describe the involvement pattern of individual EOM. Lastly, for imaging, we describe identification of causes of ophthalmoparesis and ptosis by identifying primary tumours, metastasis, infection or inflammation and changes due to dysinnervation. In addition, we describe how imaging can identify the involved EOM in specific diseases and help



**Figure 1** Five patterns characterized by the presence of combination of ptosis, ophthalmoparesis, diplopia, pain, proptosis, nystagmus, extra-orbital symptoms, symmetry or fluctuations in symptoms. Each pattern was linked to anatomical locations and either hereditary or acquired diseases, as a starting point for clinical evaluation rather than providing a stringent, mutually exclusive classification.

understand the pathophysiology of ophthalmoparesis and ptosis in specific diseases. Disorders of brain and nerve and orbital diseases causing secondary muscle dysfunction (e.g., tumours and infections) are beyond the scope of this paper, but are for a large part reviewed in a recent paper.<sup>9</sup>

## Five patterns of clinical presentation of ophthalmoparesis and ptosis

Diseases with ophthalmoparesis or ptosis can be classified using different patterns of signs and symptoms (*Figure 1* and *Table 1*). Diplopia is a patient-reported symptom, while ophthalmoparesis can be assessed with physical examination and quantified using orthoptic measures like ductions as measured with a synoptophore, Hess chart or with the Goldmann perimeter.<sup>53</sup> We defined ptosis as a decreased distance between the borders of the eyelids due to drooping of the upper eyelid. Several reports provide criteria for ptosis using defined physical landmarks like the border of the eyelids and express their distance in millimetres.<sup>9</sup> This implies that the upper eyelid is lower than its normal anatomical position, typically 1–2 mm below the superior corneoscleral limbus.<sup>54</sup> Similarly, proptosis on magnetic resonance imaging (MRI) or computed tomography (CT) is defined as a distance >23 mm from the anterior surface of the globe to the interzygomatic line<sup>55</sup> or an asymmetry >2 mm as measured with an exophthalmometer.<sup>56</sup> These strict definitions are not consistently used in the literature that we collected on the many different diseases. Therefore, we accepted the definition that was used in the selected papers.

Diplopia is less frequently seen in hereditary neuromuscular disease with ophthalmoparesis (e.g. in at least half of CPEO patients<sup>15</sup>), probably due to its slow progression, symmetrical involvement and facultative suppression.<sup>7</sup> Ptosis generally occurs symmetrically in these disorders. The co-occurrence of ptosis and ophthalmoparesis is commonly seen in hereditary neuromuscular disease and in synaptic disease, whereas ptosis is rarely present in acquired myopathic disease, commonly associated with pain, proptosis and/or swelling of eyelids and conjunctiva due to EOM enlargement and inflammation.

In the first pattern, constant ophthalmoparesis with diplopia is present with or without ptosis, and accompanied by central nervous system (CNS)-abnormalities such as upper gaze paralysis, nystagmus or other neurological extra-ocular manifestations. This pattern is characteristic of acquired brain disease, in which diplopia and ophthalmoparesis co-occur with evident CNS abnormalities and the presence of nystagmus. The presence of nystagmus is evident in internuclear ophthalmoparesis caused by multiple sclerosis (MS) or stroke: when one eye adducts, nystagmus of the contralateral eye is observed. Examples of CNS abnormalities

accompanying the ocular symptoms are parkinsonism, dementia and swallowing problems (or dysphagia) in progressive supranuclear palsy and the triad of ataxia, ocular symptoms and an altered mental state in Wernicke encephalopathy. Moreover, nystagmus is also commonly present in Wernicke encephalopathy.

The second pattern consists of constant ophthalmoplegia or ptosis, and is often asymmetrical or painful. This pattern points towards nerve disorders, either acquired or hereditary. A patient with this pattern typically has constant painless ophthalmoplegia or ptosis that can be attributed to the innervation pattern of a specific cranial nerve. For example in CFEOM, the muscles that lack cranial nerve innervation become fibrotic. In CFEOM type I there is agenesis of the superior division of N. III<sup>1,10</sup> and in CFEOM type II, there is agenesis of the entire N III and N IV.<sup>1,11</sup> In other congenital ptosis syndromes, atrophy of the EOM are often secondary to abnormal innervation and development: in Duane syndrome the N. VI is absent and the LR is innervated by a branch of the N. III, Marcus-Gunn syndrome is caused by an anomalous connection of motor fibres from the N. V to the n III and blepharophimosis syndrome (BPES) with narrowing of the eyelids.<sup>9,13</sup> In acquired nerve diseases, the symptomatology is often asymmetrical because the nerve is affected unilaterally, for example, in Horner syndrome, where only the superior tarsal muscle is affected, or diabetic mononeuropathy (often N. III<sup>31</sup>). If the cause is within the cavernous sinus (e.g. Tolosa–Hunt syndrome), multiple ipsilateral cranial nerves can be affected (N. III in 80% of cases, N. VI in 70% of cases and N. IV in 30% of cases<sup>3</sup>). An exception to this pattern is Miller–Fisher syndrome, which often has a symmetrical bilateral involvement of several cranial nerves.

In the third pattern, patients present with fluctuating ophthalmoparesis with diplopia and asymmetrical ptosis, which is indicative of an *acquired synaptic disease* like myasthenia gravis.<sup>57</sup> In this pattern, muscle weakness fluctuates over larger periods of time and within one day, with symptoms becoming worse during the day and improving after a period of rest. In myasthenia gravis, the EOM are involved in about 80% of patients, but other muscles are often involved like the bulbar, neck and limb muscles.<sup>58</sup>

The fourth pattern is characterized by constant ophthalmoparesis with diplopia, but ptosis is not usual. These symptoms are most commonly asymmetrical and painful, but again without clear fluctuation. This is typical for *acquired muscle disease*. This pattern most often points to inflammatory disease: Graves' orbitopathy, IgG-4 related orbital disease (IgG4-ROD), idiopathic orbital inflammation and idiopathic orbital myositis.<sup>42,45,46,59,60</sup> Patients experience asymmetrical retrobulbar pain with accompanying ophthalmoparesis and sometimes proptosis. The differential diagnosis of painful ophthalmoparesis included the inflammatory diseases mentioned, but is very wide. It also includes vascular diseases such as aneurysms and dissections,

**Table 1** Differential diagnosis ophthalmoparesis and/or ptosis.

Hereditary disorders	Ptosis	Ophthalmoparesis	Diplopia	Asymmetry	Pain	Fluctuating	Most frequently involved EOM*	Other symptoms
Nerve CFEOM <sup>1</sup>	Yes	Yes	No	No	No	No	LPS, SR (depends on affected nerves) <sup>1,10-12</sup>	No
Duane syndrome <sup>9,13</sup>	Yes	Yes	No	No	No	No	LPS, LR, MR (aberrant innervation)	No
Blepharophimosis syndrome (BPES) <sup>9,13</sup>	Yes	No	No	No	No	No	LPS	Horizontal narrowing of the eyelids, epicanthus inversus, lacrimal duct abnormalities Upper eye lid retraction when chewing or laughing.
Marcus-Gunn syndrome <sup>9,13</sup>	Yes	No	No	No	No	No	LPS	Other muscles
<b>Synapse</b> Presynaptic congenital myasthenic syndromes <sup>14</sup> ; Congenital Lambert–Eaton-like, choline acetyltransferase deficiency, reduced quantal release, paucity of synaptic vesicles and reduced quantal release	Yes	Rare	No	No	No	No		
Synaptic congenital myasthenic syndromes <sup>14</sup> : Endplate AChE deficiency, CMS with LAMB2 mutation	Yes	Yes	No	No	No	No	LPS, LR, SR, IO <sup>4</sup>	Other muscles
Post-synaptic congenital myasthenic syndromes <sup>14</sup> : Slow channel syndrome, AChR deficiency, fast channel syndrome, Rapsyn deficiency, plectin deficiency, Dok-7 myasthenia	Yes	Yes	Rare	No	No	No	LPS, LR, SR, IO <sup>4</sup>	Other muscles
<b>Muscle</b> Progressive external ophthalmoplegia <sup>7</sup> Pompe disease <sup>5</sup> OPMD <sup>5</sup> Myotonic dystrophy Type 1 <sup>18,19</sup> Centronuclear myopathy <sup>22,23</sup>	Yes	Yes	Half patients <sup>15</sup> No Rare <sup>17</sup> No No	No	No	No	LPS, SR <sup>7</sup> LPS <sup>16</sup> LPS, SR, LR <sup>8</sup> LPS (cases of LR and MR). <sup>21</sup> LPS, SR, LR <sup>22,23</sup>	Other muscles and organs (heart) Other muscles Pharyngeal and leg muscles Other muscles Other muscles

Acquired disorders	Ptosis	Ophthalmoparesis	Diplopia	Asymmetry	Pain	Fluctuating	Most frequently involved EOM*	Other symptoms
<i>Brain</i>								
Progressive supranuclear palsy	No	Yes	No	No	No	No	SR, IO, IR, SO <sup>24</sup>	Parkinsonism, balance, dementia, bulbar symptoms
Internuclear ophthalmoparesis (MS/stroke)	No	Yes	Yes	No	No	No	MR	Other CNS symptoms and nystagmus
Wernicke encephalopathy	Rare	Yes	Yes	No	No	No	LR <sup>25</sup>	Encephalopathy and ataxia. Predominantly nystagmus.
Brain stem tumour <sup>26</sup>	Yes	Yes	Yes	Yes	No	No	Location dependent.	Other cranial nerves and lateralized CNS symptoms
<i>Nerve</i>								
Miller-Fisher syndrome <sup>27</sup>	Yes	Yes	Yes	No	No	No	LR > LPS, SR, IR, MR <sup>27</sup>	Vestibular and facial
Recurrent painful ophthalmoplegic neuropathy	Yes	Yes	Yes	Yes	Yes	No	LPS, SR, IR, MR, IO (N. III) <sup>28</sup>	Attacks of headache
Horner syndrome	Yes	No	No	Yes	No	No	No EOM (superior tarsal muscle) <sup>29</sup>	Anhidrosis and myosis
Tolosa-Hunt syndrome <sup>30</sup>	Yes	Yes	Yes	Yes	Yes	No	LPS, SR, IR, MR, IO (N. III) or LR (N. VI) <sup>3</sup>	No
Diabetic mononeuropathy <sup>31</sup>	Rare	Yes	Yes	Yes	No	No	LPS, SR, IR, MR, IO (N. III) or LR (N. VI) <sup>31</sup>	Transient palsy. Presence of diabetes.
<i>Synapse</i>								
Autoimmune LEMS <sup>14,32,33</sup>	Yes	Rare <sup>34</sup>	Yes	Yes	No	Yes	LPS <sup>32</sup>	Other muscles and autonomic
Autoimmune myasthenia gravis <sup>14</sup>	Yes	Yes	Yes	Yes	No	Yes	LPS, IO, SR > LR, MR <sup>35-37</sup>	Other muscles (bulbar, neck)
Botulism <sup>38,39</sup>	Yes	Yes	Yes	No	No	No	LPS <sup>39</sup>	Other muscles
Acetylcholinesterase intoxication <sup>40</sup>	Yes	Yes	Yes	No	No	No	Unknown	Other muscles
<i>Muscle</i>								
Orbital lymphoma	Rare	Yes	Yes	Yes	Rare	No	Location dependent. <sup>41</sup>	Depends on localization
Idiopathic Orbital myositis <sup>42</sup>	Rare	Yes	Yes	Yes	Yes	No	LR, SR, MR, IR <sup>43,44</sup>	Chemosis, Proptosis. Involvement of lacrimal gland and orbital fat.
IgG4-related disease of the orbit <sup>45,46</sup>	Rare	Yes	Yes	Yes	Yes	No	LR <sup>47</sup> > IR, SR <sup>43,48</sup>	Proptosis. Involvement of lacrimal gland, orbital fat and nerves.
Thyroid orbitopathy/Graves' disease <sup>49,50</sup>	No	Yes	Yes	Yes	Yes	No	IR, MR, SR <sup>43,44</sup>	Eyelid retraction, proptosis and thyroid involvement.
Systemic auto-inflammatory diseases <sup>45,51</sup>	No	Rare	Rare	Yes	Yes	No	-	Involvement of other organs
Rare presentation of amyloidosis <sup>52</sup>	No	Rare	Rare	Yes	Rare	No	LR, MR <sup>52</sup>	Other organs

*Note:* Symptomatology is described as the presence of ptosis, ophthalmoparesis, diplopia, asymmetrical symptoms, pain, fluctuating symptoms and the presence of other non-ocular symptoms. The frequently involved extra-ocular muscle (EOM) are mentioned for each disease (\* a more specific description of the EOM involvement pattern can be found in Table S1). The neuromuscular diseases are categorized in acquired and hereditary, and then clustered by the localization of the pathology. Abbreviations: IO, inferior oblique muscle; IR, inferior rectus muscle; LPS, levator palpebrae superior; LR, lateral rectus muscle; MR, medial rectus muscle; OPMD, oculo-pharyngeal muscular dystrophy; SO, superior oblique muscle; SR, superior rectus muscle.

neoplastic diseases such as lymphoma and metastases, infectious diseases including tuberculosis and extended bacterial infections and other inflammatory diseases like Tolosa–Hunt syndrome (for a wider differential see Montagnese et al and Gladstone et al.).<sup>42,61</sup> Rarely, systemic auto-inflammatory diseases may present with a painful ophthalmoplegia, including amyloidosis,<sup>52</sup> systemic lupus erythematosus,<sup>62,63</sup> sarcoidosis<sup>64</sup> and Crohn's disease.<sup>51,65,66</sup> Therefore, a systemic diagnostic evaluation in inflammatory orbital diseases is important, as a systemic disease should be thoroughly excluded before labelling the disease idiopathic.<sup>67</sup> In these diseases ptosis is rarely observed or masked by proptosis; however, due to bulging of one eye and contralateral lid retraction, the presence of ptosis is sometimes reported. This is referred to as pseudoptosis.

Lastly, the fifth pattern consists of ophthalmoparesis and ptosis, but without diplopia as a predominant feature. The pattern of symptoms indicates a *hereditary muscle disease*. OPMD and CPEO are hereditary muscle diseases that are directly associated with ophthalmoparesis and ptosis.<sup>7,8,11,14,68</sup> In general, diplopia is less frequently reported in these diseases.<sup>7</sup> In addition, there is no clear asymmetry, pain or fluctuation. The lack of diplopia in the presence of clear ophthalmoparesis points towards a hereditary muscle disease, because the brain can adapt to the slowly developing ophthalmoparesis, a phenomenon called facultative suppression. However, throughout their disease at least half of for example CPEO patients do experience diplopia at some time in the disease course.<sup>15</sup> In centronuclear myopathy<sup>22</sup> and myotonic dystrophy Type 1,<sup>18–20</sup> ptosis and ophthalmoparesis occur regularly. In later stages of Pompe's disease, ptosis<sup>16</sup> may occur. In many other hereditary muscle diseases, including Duchenne muscular dystrophy,<sup>69</sup> the eye muscles are remarkably spared. Congenital myasthenic syndrome, although a synaptic disease, also presents with ophthalmoplegia, often without diplopia, and symmetrical ptosis. The postsynaptic types of congenital myasthenic syndrome (slow channel syndrome, AChR deficiency, fast channel syndrome, Rapsyn deficiency, and Plectin deficiency) present more frequently with ocular symptoms than synaptic and presynaptic congenital myasthenic syndromes.<sup>14</sup> For clinical reasoning, it is important to note that some congenital myasthenic syndromes can have an onset in early or even late adulthood, especially congenital myasthenic syndrome associated with rapsyn,<sup>70</sup> agrin, plectin, ALG14 and *GMPPB* gene mutations.<sup>71</sup>

## Imaging of extra-ocular muscles

Magnetic Resonance Imaging is the primary tool for the assessment of ophthalmoparesis. It provides detailed information on orbital soft tissues, cranial nerves and the posterior cranial fossa. Besides anatomic sequences (T1 weighted

[T1w] and T2 weighted [T2w] images) functional sequences such as diffusion weighted imaging (DWI), reflecting the Brownian motion of water molecules and thereby sensitivity to tissue architecture. Also contrast-enhanced perfusion may be added to characterize lesions.<sup>43,72</sup> CT scans also demonstrate orbital pathology, in particular of bony origin. In MRI, there is a difference between quantitative and qualitative scans.<sup>73</sup> Quantitative scans allow for the numeric measurements of T1 and T2 (multi-echo spin-echo) relaxation times and for example chemical shift-based water–fat separation scans allow for the quantification of fat fractions in tissue. Qualitative anatomical sequences can be used to identify a focal mass or changes in volume and cross-sectional area of the EOM, reflecting EOM enlargement due to hypertrophy or inflammation or atrophy. Changes in signal intensities on qualitative T1w, T2w or DWI images, and enhancement and contrast scans can all indicate different types of tissue alterations. For instance, oedema and/or inflammation will cause an increase in the T2 relaxation time of water, and thereby signal intensity increase on T2w images, which can be observed on fat-suppressed images. Fat replacement, that is, the replacement of muscle tissue with fat, will be hyperintense on both T1w and T2w images<sup>74</sup> due to the shorter T1 relaxation and longer T2 relaxation time of fat. On fat-suppressed images, this will be shown as signal loss.<sup>73</sup> Fibrotic tissue has a very short T1 and T2 relaxation time, and hence is hardly visible on T1w and T2w images. The location and number of involved EOM may be suggestive of a specific disease (e.g., in IgG4 related orbitopathy usually bilateral involvement with a predilection for the lateral rectus muscle<sup>47</sup> is seen, while IOM is typically unilateral and mostly affects the medial rectus muscle). Supportive findings such as involvement of the lacrimal glands, increased orbital fat and vascular engorgement aid in the differential diagnosis but fall outside the scope of this paper.

For all diseases, we included MRI and CT studies in this review in which the EOM were studied or mentioned. Such studies were not available for all mentioned diseases; No MRI or CT studies describing the EOM were reported in Pompe's disease, in OPMD, Lambert–Eaton myasthenic syndrome (LEMS) and congenital myasthenic syndromes. For some diseases, we found only a small number of case reports; one case report describing a patient with myotonic dystrophy, in which no changes in the EOM were reported<sup>20</sup> and a small number of case reports of EOM involvement for systemic auto-inflammatory disease.<sup>51,62,63,65,66</sup> (Table 2).

## MRI and volume of the extra-ocular muscles

In acquired muscle disease of the orbit, EOM enlargement in different extent with or without tendon involvement is a

**Table 2** Reported imaging findings in the extra-ocular muscles for orbital disease with ophthalmoparesis and ptosis interpreted as histopathological changes: fat increases, inflammation, enlargement and atrophy.

Disease	Volume changes on anatomical sequences	T2 weighted (T2w) imaging with fat suppression	T1 weighted imaging (T1w)/T2 weighted (T2w) imaging without fat suppression/chemical shift-based water–fat separation (Dixon)	Other findings
Acquired disease				
Idiopathic orbital myositis	EOM enlargement with tendon involvement. <sup>42,43</sup>	Increased signal on T2w imaging of the affected EOM. <sup>59,75,76</sup>		Surrounding T2 increases due to cellulitis. <sup>75</sup>
IgG4-related disease of the orbit	EOM enlargement with tendon sparing (fusiform enlargement), mostly LR. <sup>47</sup>	Decreased signal on T2w imaging of the affected EOM. <sup>75</sup>		Lacrimal gland and infra-orbital nerve enlargement. <sup>47</sup>
Thyroid orbitopathy/Graves' orbitopathy	Fusiform enlargement of all EOM, often with tendon sparing, most pronounced in IR, MR and SR. <sup>6,77</sup>	Increased signal in the acute inflammatory phase <sup>6,79</sup>	T1 hyperintense signal, mainly in chronic patients. <sup>6,24,80,81</sup>	Optic nerve enlargement. <sup>42</sup> Increased orbital fat volume. Enlarged lacrimal glands. Vascular engorgement.
Systemic auto-inflammatory diseases	Increases in volume most pronounced in active stage; volume decreases in chronic but may still be enlarged. <sup>78</sup>			
	Sarcoidosis: Bilateral EOM enlargement. <sup>72,82</sup>	T2w hypointensity or hyperintensity of affected EOM. <sup>51,65,66</sup>		Sarcoidosis: enlarged lacrimal gland, thickening and enhancement optic nerve
	Crohn's disease: Enlargement of the SR and LPS. <sup>65</sup> Enlargement of the LR. <sup>51</sup> Enlargement of the IR. <sup>66</sup>			
	Often with tendon involvement.			
Amyloidosis	Enlargement of the LR muscle with tendon sparing in amyloidosis. <sup>52</sup>	No hyperintensity on T2w-STIR. <sup>52</sup>		An area without contrast enhancement, as compared with the rest of the EOM, is observed. <sup>52</sup>
Orbital lymphoma	Muscle enlargement or focal mass. <sup>83</sup>	Focal hyperintense or isointense (as compared with the EOM) mass. <sup>83,84</sup>	Focal hypointense or isointense (as compared with the EOM) mass. <sup>83</sup>	Diffusion restriction: low ADC value. <sup>11,49</sup>
Synaptic disease				
Autoimmune LEMS	Not reported.	Not reported.	Not reported.	
Autoimmune myasthenia gravis	Decreases in volume in chronically untreated/treatment resistant patients <sup>85–87</sup> and in muscle-specific tyrosine kinase (MUSK) positive patients. <sup>88</sup>	No hyperintensity on T2w scan in 20 myasthenia gravis patients. <sup>90</sup>	Increases in fat fraction in the EOM in myasthenia gravis on Dixon scans. <sup>89</sup>	Central hypo-intensity on T2w scans with fat suppression. <sup>90</sup>
	No changes or small increases in volume in chronically treated and recent myasthenia gravis patients. <sup>81,89</sup>			
Congenital myasthenic syndrome	Not reported.	Not reported.	Not reported.	
Hereditary disease				
Chronic progressive external ophthalmoplegia (CPEO)	Decrease in volume in all EOM, most pronounced in SR/LPS. <sup>81</sup>	Two patients with STIR hyperintensities. <sup>80</sup>	T1 hyperintense signal that is hypointense on STIR. <sup>80,81</sup>	(Continues)

Table 2 (continued)

Disease	Volume changes on anatomical sequences	T1 weighted imaging (T1w)/T2 weighted (T2w) imaging with fat suppression/chemical shift-based water-fat separation (Dixon)	Other findings
	Atrophy/swelling	Fat increase	
	Decrease in cross-sectional area in all EOMS (43%). <sup>80</sup>	Prolonged (global) T2 relaxation time. <sup>80</sup>	
Pompe disease	Not reported.	Not reported.	Not reported.
OPMD	Not reported.	Not reported.	Not reported.
Myotonic dystrophy	Case report: No changes in EOM. <sup>20</sup>	Case report: No changes in EOM. <sup>20</sup>	
CFEOM	Severe atrophy of LPS and SR in CFEOM type 1. <sup>91</sup> Atrophy of all EOM, especially also SO and LR is relatively spared in CFEOM type 2. <sup>11,12</sup>	Bright signal regions and longitudinal fissures in LR and MR in CFEOM type 2 on T1w imaging. <sup>91</sup>	Absence of superior division of N. III in CFEOM type 1. <sup>10,91</sup> Absence of N. III and N. IV in CFEOM type 2. <sup>11</sup>
Congenital ptosis syndromes (e.g., Duane syndrome and BPES)	Atrophy/hypoplasia of the SO in Duane syndrome. <sup>92</sup> Atrophy of the LPS in BPES. <sup>93</sup>	Increases in T2 showing fatty patches in the LPS. <sup>93</sup>	Aberrant innervation of LR by branch of N. III and absence of N. VI in Duane syndrome. <sup>94</sup>

Note: The neuromuscular diseases are categorized in acquired, synaptic and hereditary.

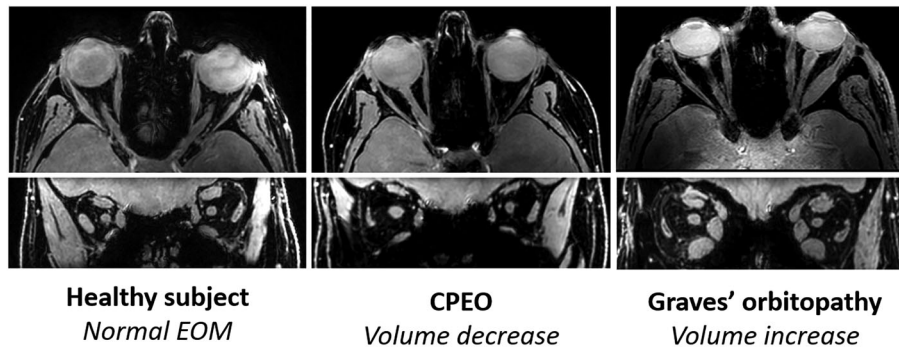
Abbreviation: CFEOM, congenital fibrosis of the extra-ocular muscles; EOM, extra-ocular muscles; LPS, levator palpebrae superioris; OPMD, oculo-pharyngeal muscular dystrophy

## MRI and inflammation

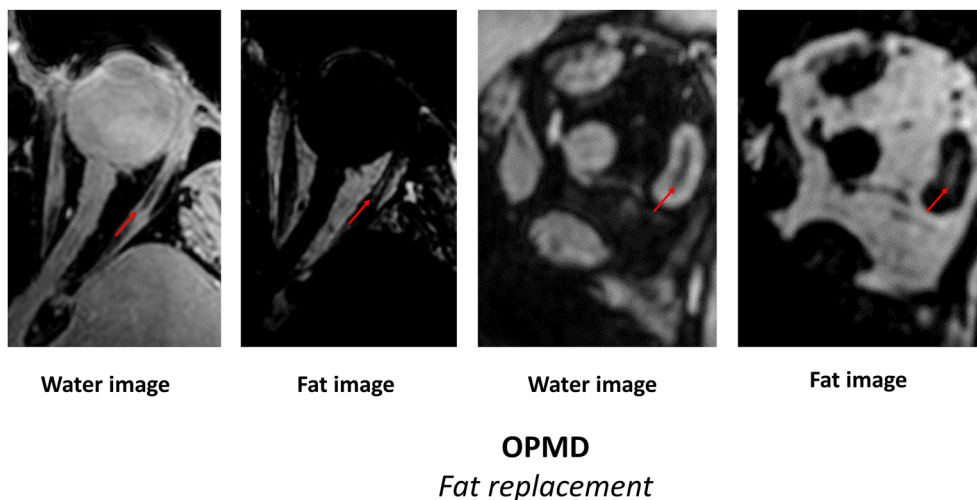
When inflammation of orbital fat or muscle is the cause of ophthalmoparesis and ptosis, the inflammatory process is often shown as hyperintense on T2w MRI images due to the presence of oedema. The EOMs have an increased signal on T2w imaging with fat suppression in idiopathic orbital myositis,<sup>59,75,76</sup> in active Graves' orbitopathy<sup>6,79</sup> and in systemic auto-inflammatory diseases like Crohn's disease, sarcoidosis and systemic lupus erythematosus.<sup>51,65,66,96</sup>

frequent observation. In idiopathic orbital myositis, EOM volume is increased with involvement of the tendons, presenting as tendon thickening. In contrast, Graves' orbitopathy<sup>6,77</sup> and IgG4-related orbital disease<sup>47</sup> (in 96% of patients) cause EOM enlargement of on average twice the size<sup>42,78</sup> with tendon sparing, known as fusiform enlargement. This specific pattern of enlargement can therefore be useful in differential diagnostics. An example of EOM enlargement in Graves' orbitopathy can be found in *Figure 2*. In systemic diseases with EOM involvement, like Crohn's disease, sarcoidosis, systemic lupus erythematosus and amyloidosis, EOM volumes are increased as qualitatively described in several case reports.<sup>52,63–66,95</sup> In Graves' orbitopathy, EOM volume usually decreases in the inactive stage of the disease (e.g., for the SR: 1.1 cm<sup>3</sup> in chronic inactive compared with 1.3 cm<sup>3</sup> in chronic active), but is still more than double compared with healthy EOM (0.6 cm<sup>3</sup>).<sup>78</sup> EOM atrophy is a common finding in hereditary neuromuscular disease. In CPEO, the mean cross-sectional area of all EOM was 43% lower than for controls.<sup>80</sup> An example of atrophy in CPEO can be seen in *Figure 2*. The most pronounced reduction is in the SR and the LPS muscle, which is consistent with the clinical presentation with ptosis and gaze limitations in elevation.<sup>81</sup> One case report reported normal volumes of the EOM in a patient with ophthalmoparesis associated with myotonic dystrophy.<sup>21</sup> In CFEOM, many imaging studies have shown that the denervated EOM are atrophic. In CFEOM Type 1, caused by agenesis of the upper branch of the oculomotor nerve, there is atrophy of the LPS and the SR in all subjects, with an average volume reduction of 60% in the SR.<sup>91</sup> In CFEOM Type 2, with more global dysgenesis of the oculomotor nerve, the SO and LR are relatively spared, and the other EOM are severely atrophic.<sup>11,12</sup> In myasthenia gravis, an acquired synaptic disease, case reports describe qualitatively decreases in volumes in chronically untreated or treatment-resistant patients<sup>85,86</sup> and in muscle-specific tyrosine kinase (MUSK) positive myasthenia gravis patients.<sup>88</sup> However, normal volumes or slight increased volumes (0.8 ± 0.2 cm<sup>3</sup> in MG and 0.6 ± 0.2 cm<sup>3</sup> in healthy controls, all recti EOM averaged) were observed in recently diagnosed and chronic myasthenia gravis patients.<sup>81,89</sup>





**Figure 2** Magnetic resonance imaging scans of the orbit. Chemical shift-based water–fat separation (using the Dixon technique) was used and the water image is shown; on top the transverse image and on bottom the coronal image. Volume decrease, indicative of atrophy, of the extra-ocular muscle (EOM) is clearly demonstrated in chronic progressive external ophthalmoplegia and enlargement of the EOM in Graves' orbitopathy.



**Figure 3** Magnetic resonance imaging scans of the orbit. Chemical shift-based water–fat separation (using the Dixon technique) was used and the transverse water image (first), transverse fat image (second), the coronal water image (third) and the coronal fat image (fourth) are shown. This MRI scan demonstrates fat replacement of the extra-ocular muscle in a patient with oculo-pharyngeal muscular dystrophy. The fat replacement is predominantly observed in the lateral rectus muscles (red arrows).

IgG4-ROD<sup>75</sup> demonstrates relatively low signal intensity on T2w -MR images because of its increased cellularity and amount of fibrosis. In hereditary muscle and synaptic disease, however, evidence of inflammation is sparse. In two patients with CPEO, hyperintensities were observed on a T2w scan with fat suppression.<sup>80</sup> No hyperintensities were present on T2w scans in 20 myasthenia gravis patients.<sup>90</sup>

## MRI and fat replacement

In the chronic stages of Graves' orbitopathy, an increase in fat in the EOM is observed on MRI, which is the result of adipogenesis by fibroblasts and fibrocytes.<sup>44,77,97</sup> In CPEO, an increase in signal intensity on a T1w scan has been described

within EOM,<sup>81</sup> as well as a quantitative increase in T2 relaxation time,<sup>80</sup> both indicative of fat replacement in the EOM. Signal loss on fat-suppressed images confirmed the presence of fat in this study. An example of fat replacement of the EOM as quantitatively measured with chemical shift-based water–fat separation imaging (using the Dixon technique) in an OPMD patient can be seen in *Figure 3*. The fat fraction of the EOM increases to up to 10% in myasthenia gravis patients on chemical shift-based water–fat separation scans.<sup>89</sup> In addition, central hypo-intensities were observed on T2w scans with fat suppression in myasthenia gravis.<sup>90</sup> In myasthenia gravis, fat replacement appears to be less frequently reported in literature than in CPEO. In CFEOM Type II, T1w imaging shows bright signal regions and longitudinal fissures in the LR and the MR, also indicative of fat replacement.<sup>91</sup>

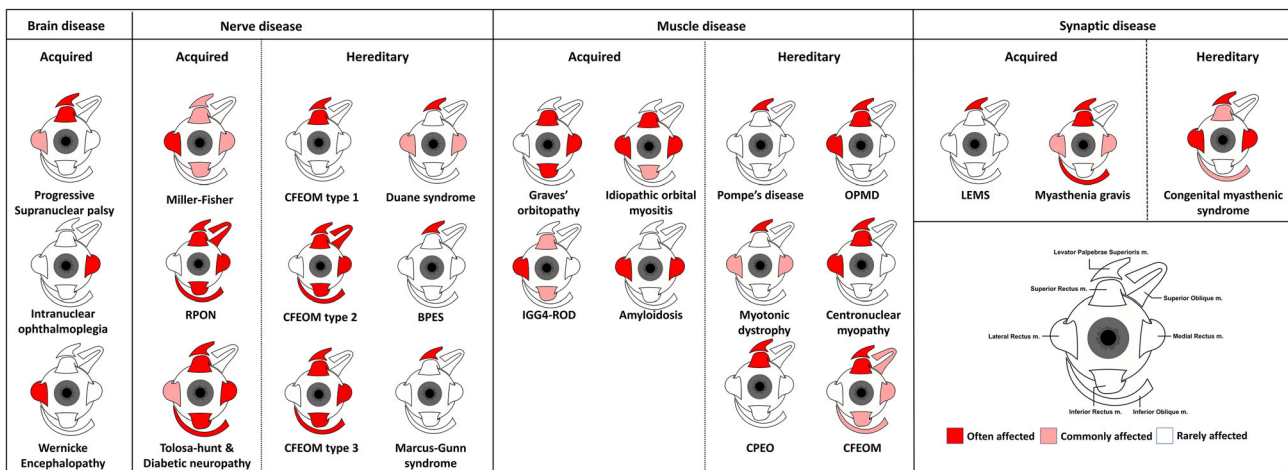
## Correlating quantitative MRI parameters with disease activity and disease severity

Only in a small number of the reviewed imaging studies, quantitative MRI parameters were correlated with disease activity or disease stage. In CPEO the range of eye movement was correlated with the global T2 relaxation time of the EOM, a parameter mainly reflecting fat replacement: patients with a smaller range of motion had more fat replacement.<sup>80</sup> In Graves' orbitopathy, EOM volume as measured with MRI and ultrasound is strongly correlated with disease activity. Mild and pronounced active stages of disease (stages G1 and G2) show progressively larger EOM volumes (e.g., for the SR: 1.1 cm<sup>3</sup> in chronic inactive compared with 1.3 cm<sup>3</sup> in chronic active) than normal subjects. Hereafter, volumes decrease in later stages with longstanding active disease (Stage G3) and chronic stages without active disease (Stage G4) but remain about 10% higher than in normal subjects.<sup>78</sup> In another study into the natural course of Graves' orbitopathy with a follow-up of at least 4 years, also a slight increase of orbital fat volume from 15 to 16.8 ml, a decrease in muscle volume of 1 ml (decrease of ~20% on a muscle of 4.5 ml), and visible intramuscular fat was observed.<sup>98</sup> In case reports of the EOM in myasthenia gravis patients, long untreated and chronic myasthenia gravis patients appear to have EOM atrophy and fat replacement as qualitatively described.<sup>85,86</sup> On the contrary, a slight increase in EOM volume of 0.2 cm<sup>3</sup> was observed in chronically treated and recent myasthenia gravis patients, also suggesting differences between different disease stages.<sup>81,89</sup>

## Clinical and radiological clues from the different combinations of extra-ocular muscle weakness

To accurately assess the involvement pattern of individual EOM in orbital disease, both imaging studies and orthoptic studies were reviewed (*Table S1* and *Figure 4*). For the three most commonly acquired orbital diseases the involvement pattern is well described in literature. In Graves' orbitopathy, the IR, MR and SR are most predominantly asymmetrically involved with remarkable sparing of the LR and the oblique muscles. In idiopathic orbital myositis, involvement is unilateral and the LR is not spared.<sup>43,44</sup> In IgG4-ROD the LR is most often involved bilaterally,<sup>47</sup> with the IR and SR affected subsequently.<sup>48</sup> Auto-inflammatory diseases with orbital involvement have a variety of involvement patterns, for example, as extensively described in case reports for Crohn's disease with MR and oblique muscles relatively spared.<sup>51,65,66</sup> In a case report of systemic lupus erythematosus, the MR and IR were involved,<sup>62</sup> and in another case report, the LR was solely involved.<sup>63</sup> In amyloidosis, the horizontal rectus muscles seem most predominantly affected.<sup>52</sup>

In hereditary muscle disease with orbital muscle involvement the LPS is most frequently affected. In CPEO, elevation limitation due to weakness of the SR is the second most present ocular symptom.<sup>7</sup> In OPMD, the SR is the most affected muscle, followed by the LR.<sup>8</sup> In Pompe's disease,<sup>16</sup> centronuclear myopathy<sup>22</sup> and myotonic dystrophy,<sup>18,19</sup> the LPS is often the only affected ocular muscle, but case reports have described horizontal ophthalmoparesis with weakness of the MR and LR in myotonic dystrophy<sup>20,21</sup> and elevation and abduction limitations in centronuclear myopathy.<sup>23</sup>



**Figure 4** Involvement pattern of the six extra-ocular muscles and the levator palpebrae superioris muscle for brain diseases, nerve diseases, muscle diseases and synaptic disease split into either acquired or hereditary. An example of the right eye is shown.

In synaptic disorders, the individual variation of EOM involvement is high, with ptosis being more common than ophthalmoparesis. In literature, the ocular involvement pattern in myasthenia gravis differs; however, elevation is most often found to be limited (IO > SR), followed by horizontal limitations (LR > MR).<sup>35–37</sup> In LEMS, the LPS is frequently weak, causing ptosis in up to 54% of patients. EOM weakness does not occur frequently in LEMS, but 30% of patients have ocular motility abnormalities.<sup>32</sup> The pattern of congenital myasthenia gravis is similar to autoimmune myasthenia gravis with almost no limitations in depression; however, horizontal eye movements (LR > MR) are more frequently limited than elevation.<sup>4</sup>

In disorders where nerve pathology and lack of innervation cause muscle dysfunction, the involvement pattern is confined to the innervation area of one or more cranial nerves. In CFEO the agenesis of (a branch) of the oculomotor nerve, or less common the abducens nerve, causes atrophy of the innervated muscles. Similarly, diabetic mononeuropathy also affects the oculomotor nerve and the abducens nerve.<sup>31</sup> In Tolosa–Hunt syndrome, the oculomotor nerve is affected in 80% of individuals, followed by the abducens nerve in 70% and the trochlear nerve in 30%.<sup>3</sup> In Miller–Fisher syndrome, dysfunction of the LR, due to involvement of the abducens nerve, is most commonly involved and the last to recover.<sup>27</sup> Interestingly in Miller–Fisher syndrome, the ophthalmoparesis is mostly symmetrical.<sup>27</sup>

In brain disease with ophthalmoparesis, ptosis is unusual except for brain stem pathology such as brain stem tumours. Brain stem tumours are known to mimic other diseases, for example, myasthenia gravis, and symptoms are dependent on tumour localization. In Wernicke's encephalopathy, limitations in abduction due to palsies of the LR are most common.<sup>25</sup> Progressive supranuclear palsy is a disease that can mimic dementia and Parkinson's, and ophthalmoparesis is always in the vertical direction. Internuclear ophthalmoparesis is a rare gaze abnormality characterized by impaired adduction of the affected eye, with nystagmus of the abducted contralateral eye.

## Discussion

This review combines clinical symptoms and EOM involvement pattern on imaging to provide clues for diagnosis of diseases with ophthalmoparesis and ptosis, including acquired and hereditary diseases with pathology located in the brain, nerve, synapse or muscle.

Some general conclusions can be made, based on the combination of clinical symptoms, and the involvement pattern and imaging features of the different EOMs. First, in brain disease, some specific EOM weakness patterns, often

accompanied by nystagmus, point towards a specific disease, with for example vertical gaze limitation in progressive supranuclear palsy and abduction limitation in Wernicke's encephalopathy. Second, nerve diseases follow the specific cranial nerve innervation pattern and in hereditary muscle diseases, the LPS and the SR are more frequently involved than the other EOM, and the IR is usually spared. Third, in synaptic diseases in general, the involvement pattern is highly variable per patient and over time, but the LPS and SR are most often involved, followed by the LR and MR; the IR is often spared. LEMS is an exception: Ophthalmoparesis is rare, and ptosis is more frequently observed. In acquired muscle diseases, the presence of pain and proptosis is often evident. The involvement pattern can be very specific per disease, for example, in Graves' orbitopathy the progressive involvement of the EOM generally follows a specific order: IR > MR > SR > LR > SO. In general, the LPS and the oblique muscles are spared and the IR is involved, in contrast with hereditary diseases.

Imaging studies of the EOM in hereditary and acquired neural and synaptic diseases describe atrophy and an increase in fat in the EOM, indicating that denervated EOM have a tendency towards atrophy accompanied by fat replacement of muscle fibres. In hereditary muscle diseases such as CPEO, fat replacement is also observed, which is also indicative of progressive muscle wasting.<sup>81</sup> Consequently, in myasthenia gravis, a synaptic disease, small increases in fat fraction are observed in patients with longstanding chronic or untreated disease and they show a small decrease in EOM volume,<sup>87</sup> but more recent findings rather point to a small and variable increase in muscle volume.<sup>89</sup> In acquired orbital diseases, inflammation seen as hyperintensity on T2w scans with fat suppression is observed in active stages of disease, accompanied by increases in muscle volume. In the chronic stages of Graves' orbitopathy, an increase in fat in the EOM is observed due to adipogenesis by orbital fibroblasts and fibrocytes.<sup>97</sup>

Not in all neuromuscular diseases the EOMs are affected. This could provide valuable clues in the pathophysiology of EOM involvement and in disease pathophysiology in general, since the EOM differ anatomically and physiologically from skeletal muscles. They have distinct fibre type composition,<sup>99</sup> multiple innervation,<sup>100</sup> smaller motor units,<sup>101</sup> higher levels of utrophin expression,<sup>102</sup> a distinct contraction–excitation coupling,<sup>103</sup> have an increased capability of regeneration and preferentially use glucose-based aerobic metabolic pathways.<sup>69</sup> The latter means that EOM are packed with mitochondria, explaining the predominant ocular phenotype in mitochondrial diseases such as CPEO. In other primary muscle diseases, such as Duchenne muscular dystrophy, the EOMs are remarkably spared, which has been hypothesized to be mainly due to the increased regenerative capacity of the EOM and higher levels of utrophin expression.<sup>104</sup> The LPS is relatively spared in acquired orbital disease with an

inflammatory origin and is frequently affected in hereditary neuromuscular disease. This may be explained by differences between the EOM and the LPS. The LPS carries thicker muscle fibers<sup>105</sup> and has a higher arteriole–nerve distance.<sup>106</sup>

Fat increase in the EOM does occur in OPMD, indicative that muscle damage of the EOM also causes the replacement of muscle tissue by fat in dystrophic disease with EOM involvement. Fat increase in the EOM also occurs in synaptic neuromuscular disorders. This may indicate that (relative) muscle denervation of the EOM causes the replacement of muscle tissue with fat. This phenomenon has been described previously in denervating disease with skeletal muscle involvement.<sup>107</sup> In addition, there is evidence from histological studies of the EOM in myasthenia gravis that atrophy and fat replacement occur.<sup>108</sup> In chronic stages of acquired orbital muscle disease with an inflammatory origin, such as Graves' orbitopathy, there is evidence of adipogenesis by fibroblasts in a later stage of the disease.<sup>6,44,80,81,97</sup> Therefore, because intramuscular fat increase seems to correlate with the disease stage to some extent, it may be a valuable biomarker in the follow-up of disease progression.

In neuromuscular disease with known EOM involvement, MRI of the EOM is rarely performed compared with MRI of skeletal muscles. For OPMD, Pompe disease and congenital myasthenic syndromes imaging of the EOM has not been described, and in other diseases, like myotonic dystrophy, only a few case reports have been published. There are challenges when performing orbital MRI because the eyes are prone to motion and close to air–bone–tissue interfaces causing artefacts. However, scans can be optimized for these challenges.<sup>109</sup> Scan time can be reduced, and cued blinking could be used<sup>89</sup> to prevent movement artefacts and for example spin-echo sequences are less sensitive to field inhomogeneities as compared with gradient-echo sequences.<sup>110</sup> Currently, it is recommended to include T1w sequences, T2w sequences with and without fat suppression, T1w scans with contrast and DWI.<sup>43</sup> Given the small size of the orbital structures, sequences with an in plane resolution of at least 0.8 mm and slices of 3 mm are generally sufficient to detect clinically relevant EOM swelling and atrophy in our experience, although reports show that an isotropic resolution below 0.6 mm are also clinically feasible.<sup>111</sup> These can be obtained with a brain MRI setup on 3 T. To more directly assess the EOM pathophysiology in the context of research, we recommend including scans with water–fat separation to study fat fraction increases of the EOM. T2w imaging with fat suppression is recommended to differentiate intramuscular fat from inflammation/oedema, as is commonly performed in skeletal muscle imaging studies.<sup>112</sup> Many orbital inflammatory diseases are now labelled as idiopathic, and a systemic diagnostic evaluation might be needed to identify underlying and associated disease as proposed by McNab.<sup>67</sup> We believe that imaging can play an important role in this respect.

Additionally, quantitative MRI could be a valuable addition in the follow-up of disease progression and in the correlation of MRI to disease activity and disease progression, as is known in the field of neuromuscular diseases like Duchenne and Becker muscular dystrophy. In general, for these muscle diseases, the recommended technique to quantify fat fraction is chemical shift-based water–fat separation.<sup>74</sup> The feasibility of performing such scans of the EOM has been previously shown.<sup>89</sup> To quantify inflammation, T2 relaxation time maps of the water component could be acquired as is done in skeletal muscle.<sup>73</sup> Applying these quantitative techniques to study fat replacement and T2 relaxation time changes in the EOM could prove valuable in disease with EOM involvement. Finally, EOM volume can be quantified using anatomical scans such as T1w, T2 or Dixon. Clinical diagnostic evaluation of scans is conventionally performed by comparing the cross-sectional area of the EOM, which is generally sufficient to detect EOM swelling or atrophy. In the context of research however, we believe volume to be a more robust measure than cross-sectional area because the entire EOM is included and the measurement is more independent of variations in EOM shape or position. Also, we observe a high variation in EOM volume in healthy controls (e.g., for the medial rectus  $569 \pm 129 \text{ mm}^3$ ),<sup>113</sup> therefore including a healthy control group for reference in studies is recommended. To determine the source of this variation, future studies should focus on and the influence of orbital volume, age and race on EOM volume. In conclusion, in diseases with ophthalmoparesis and ptosis specific patterns of clinical symptoms, the EOM involvement pattern and orbital imaging provide valuable information for diagnosis. Additionally, orbital imaging could prove valuable in the follow-up of disease progression and the understanding of disease pathophysiology.

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## Conflicts of interest

K. R. Keene reports involvement in myasthenia gravis research sponsored by Argenx, Alexion Pharmaceuticals and the CHDR, with all reimbursements received by Leiden University Medical Center and research support from Philips Healthcare. H. E. Kan reports research support from Philips Healthcare, trial support from ImagingDMD; no personal fees

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research. The LUMC receives royalties for MuSK antibody assays.

## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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