The eye in neurological disease

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The intimate relationship between the eye and nervous system is reflected in pathology, when ophthalmic problems may be the first manifestation of underlying, often serious, neurological disease (Acheson and Riordan-Eva, 1999; Sadler, 2000). Ocular and neurological disorders may exist together as part of a more generalized systemic condition. This review will highlight the major features of neuro-ophthalmological disease and provide a basic understanding of such disorders for all physicians.

HISTORY AND EXAMINATION

A patient's visual symptoms may be isolated or associated with neurological findings, highlighting the importance of a full ophthalmic, neurological and general medical history.

Assessment of visual acuity, field, colour vision, brightness and pupillary response gives an indication of optic nerve function (Kline and Bajandas, 2001). Visual acuity is typically measured using a Snellen acuity chart. Improvement in vision may be further achieved with a pinhole, which can correct refractive errors of up to 4 dioptres.

Visual field testing with simple confrontation techniques can readily be applied at the bedside. In contrast, formal bowl perimetry techniques such as manual Goldmann perimetry or automated Humphrey visual field analysis allows quantitative, standardized and sensitive assessment of the visual field.

Colour vision can be assessed by pseudo-isochromatic Ishihara plates, although it may suffice to test for red desaturation by presenting a red target to each eye and comparing the relative depth of colour perception from both eyes. Brightness sensation can be tested in a similar fashion by using a pen torch and assessing for comparative dimness between both eyes.

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Assessment of the pupils includes the direct, consensual and accommodative response, as well the swinging-flashlight test, which assesses the presence of a relative afferent pupillary defect (RAPD). When light is shone into the normal eye, both pupils constrict, but when it is swung to the eye with the RAPD – e.g. with optic neuritis – both pupils dilate. This test is particularly useful in the presence of asymmetric optic nerve lesions.

The full range of extraocular eye movement is examined, including the cover test, saccades, pursuit and presence of nystagmus. Fatiguability should be elicited if myasthenia is suspected and examination completed by a directed general neurological assessment.

INVESTIGATIONS

Specialized investigations include fundus fluorescein angiography and clinical electrophysiology, i.e. visual evoked potentials, electroretinography and electro-oculography. This may be supplemented by Doppler ultrasound (for carotid artery stenosis), computed tomography, magnetic resonance imaging and cerebral angiography.

NEURO-OPHTHALMIC DISEASE

The range of neuro-ophthalmic disease is diverse, but the scope of this article only allows discussion of the commoner examples of such disorders.

Demyelinating disease

Typical retrobulbar optic neuritis is a primary demyelinating process which is often isolated, but may be associated with multiple sclerosis (Foroozan et al, 2002). It presents with pain on eye movement, reduced visual acuity and decreased colour vision, usually with some recovery by 6 weeks. As the inflammation is typically behind the lamina cribrosa, the optic nerve and fundus initially appear normal, although optic atrophy can be seen later (*Figure 1*). Internuclear ophthalmoplegia may be present and is caused by demyelination of the medial longitudinal fasciculus that connects the third and contralateral sixth cranial nerve nuclei (*Figure 2*). On contralateral gaze, the patient is unable to adduct the affected eye and shows ataxic nystagmus of the contralateral eye in abduction, with convergence being preserved.

Although typical optic neuritis is usually isolated, up to 60% of patients with an initial attack show periventricular demyelinating plaques on magnetic resonance imaging (MRI), associated with an increased chance of developing clinically definite multiple sclerosis (Optic

Figure 1. Optic atrophy secondary to previous optic nerve demyelination (retrobulbar neuritis), showing pale atrophic optic disc.

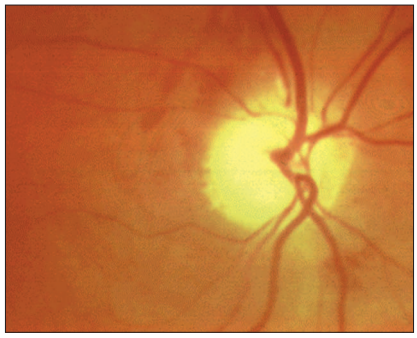
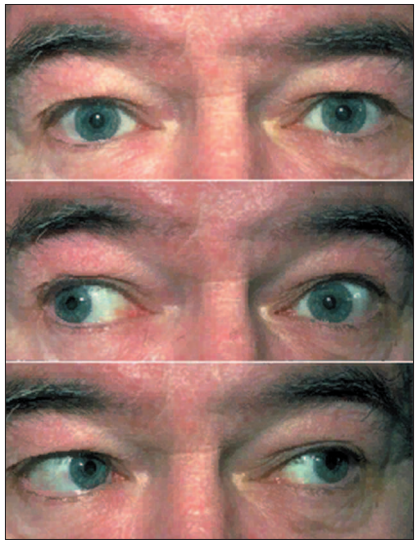


Figure 2. Left internuclear ophthalmoplegia in demyelinating disease, showing failure of adduction of the left eye on right gaze, accompanied by ataxic nystagmus of the right eye in abduction.



Neuritis Study Group, 1997). Treatment with intravenous methylprednisolone has shown no long-term visual or systemic benefit, but the potential efficacy of systemic interferon-βla appears promising (Beck, 1995; Controlled High Risk Avonex Multiple Sclerosis Prevention Study Group, 2001).

In contrast, features of atypical optic neuritis include an acutely swollen disc, absence of pain and failure of resolution within 6 weeks. The aetiology includes infectious postviral causes, autoimmune disorders such as systemic vasculitis, granulomatous optic neuropathy and paranasal sinus disease. Extensive peripheral demyelination is characteristic of Miller–Fisher syndrome, the bulbar variant of Guillain–Barré syndrome. This leads to ataxia, arreflexia and total ophthalmoplegia with loss of extraocular movements, diminished pupillary response and ptosis.

Neoplastic disease

Neoplastic disease may be primary or metastatic, the clinical manifestation depending on the anatomical location of the lesion. It can lead to papilloedema (optic disc swelling secondary to raised intracranial pressure; Acheson, 2000). Other causes include benign intracranial hypertension, cerebral arteriovenous malformation, intracranial haemorrhage, infection and thrombosis. Both discs are swollen and hyperaemic with blurring of the disc margin, usually accompanied by obscuration of disc blood vessels. Hard exudates, retinal folds, haemorrhages and cotton wool spots are seen in established papilloedema, while a 'champagne cork' appearance is seen in longstanding disease (*Figure 3*). Accelerated systemic hypertension must be excluded, as this can also cause bilaterally swollen discs with headache and neurological symptoms.

Optic nerve disease: Primary neoplasia of the optic nerve includes optic nerve glioma and meningioma. Both may present with proptosis, impaired optic nerve function and a centrocaecal scotoma, initially with a swollen disc but later optic atrophy (*Figure 4*).

Chiasmal disease: Pituitary tumours (adenomas) are associated with chiasmal involvement through suprasellar extension, initially causing a bitemporal superior quadrantanopia followed by a hemianopia (*Figure 5*). The optic nerve or tract may also be involved, depending on the anatomical relationship between the chiasm and the pituitary fossa. Endocrine manifestations are usual, either as a result of generalized pituitary failure or oversecretion by hormone-secreting adenomas, e.g. acromegaly.

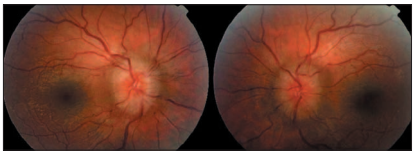


Figure 3. Bilaterally swollen optic discs in longstanding papilloedema, with a 'champagne cork' appearance.

Retro-chiasmal disease: Retrochiasmal pathology is characterized by homonymous hemianopia, with increased congruity with lesions closer to the occipital cortex (Jacobson, 1997) (*Figure 6*). Although the commonest cause is cerebrovascular disease, intracranial tumours may also be responsible; other causes include aneurysms, trauma, arteriovenous malformations, infection, demyelination and rarely neurodegenerative disorders. With extensive lesions other cortical signs may be present, while involvement of the extrastriate (secondary) visual cortex leads to defects in object recognition, colour vision and reading.

Figure 4. Advanced left optic nerve meningioma, showing gross proptosis from a tumour which had been present for several years.

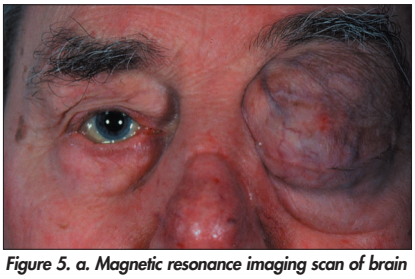
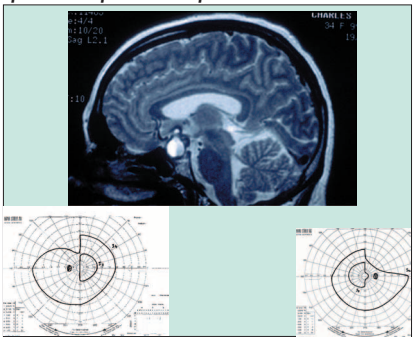


Figure 5. a. Magnetic resonance imaging scan of brain demonstrates a large pituitary adenoma. b. Goldmann visual fields show a typical bitemporal superior quadrantanopia which respects the vertical midline.



Non-Hodgkin's lymphoma of the CNS is a rare condition typically found in elderly patients, which can be preceded by ocular involvement (intraocular large cell lymphoma) (Akpek et al, 1999). It usually masquerades as a persistent vitritis, unresponsive to corticosteroid in early disease, although in later stages multifocal yellowish subretinal pigment epithelial infiltrates may be seen (*Figure 7*). Diagnosis is confirmed by vitreous biopsy, with neuroimaging often showing multiple discrete intracranial nodules, diffuse meningeal or periventricular lesions. Treatment by radiation therapy may be combined with chemotherapy if CNS disease is present.

Vascular malformations

Intracranial aneurysms and arteriovenous malformations can behave like space-occupying lesions and cause deficits in a similar way to tumours, but can also rupture and bleed into the subarachnoid space (*Figure 8*) (Biousse et al, 1998), i.e. a posterior intercommuni-

Figure 6. Goldmann visual fields show an incongruous right homonymous hemianopia secondary to an optic tract lesion. With more posterior lesions the congruity of the hemianopia increases, so that field defects in occipital lobe lesions are identical for both eyes.

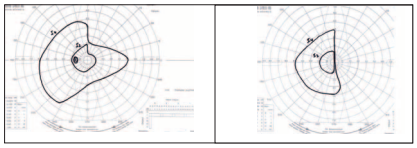
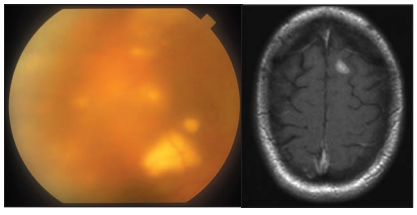


Figure 7. Non-Hodgkin's lymphoma of the CNS (intraocular large cell lymphoma). a. Fundus photograph shows multifocal yellowish subretinal pigment epithelial infiltrates, the hazy view is the result of marked vitritis. b. Magnetic resonance image of the brain shows a discrete intracranial tumour nodule.



cating artery aneurysm may cause a pupil-involving third nerve palsy. Ptosis is present and the eye faces 'down and out' because of the unopposed action of lateral rectus (sixth cranial nerve) and superior oblique (fourth cranial nerve) muscles (*Figure 9a*). Compressive lesions involve the pupil and cause mydriasis because of compression of the pupillary fibres, since they lie on the external surface of the third nerve. In contrast, non-compressive lesions caused by microvascular disease do not initially involve the pupil. A pupil-involving third nerve palsy should be urgently investigated to exclude a compressive space-occupying lesion.

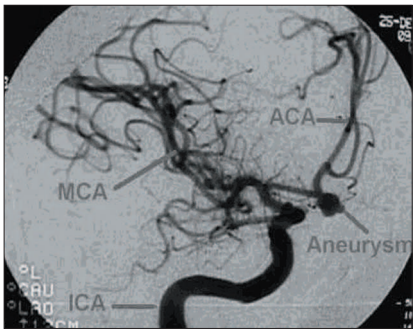
A carotid-cavernous fistula is an abnormal connection between the carotid artery and cavernous sinus, occurring either spontaneously or post-trauma. Findings include chronic conjunctival injection, pulsatile proptosis with an audible bruit and multiple cranial nerve involvement with visual loss, diplopia and sensory loss over the ophthalmic division of the trigeminal nerve.

Cavernous malformations (cavernous haemangiomas) are berry-like masses of enlarged vascular spaces in which high-flow arterial or venous vessels are absent, unlike 'true' arteriovenous malformations. When in the brainstem, they can cause supranuclear, nuclear and fascicular ocular motility abnormalities.

Cerebrovascular disease

Vascular diseases can all affect the eye and nervous system. Hypertension is linked to haemorrhagic stroke and generalized cerebrovascular disease, leading to vascular dementia (Schubert, 1998). Arteriovenous nipping and retinal arteriolar sclerosis ('copper' wiring) are found in mild hypertensive retinopathy, while more severe changes include cotton wool spots, retinal haemorrhages, hard exudates and chorioretinal atrophy; in accelerated hypertension, bilateral optic disc swelling is also present.

Figure 8. Cerebral angiogram shows an aneurysm of the posterior intercommunicating artery. ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery.



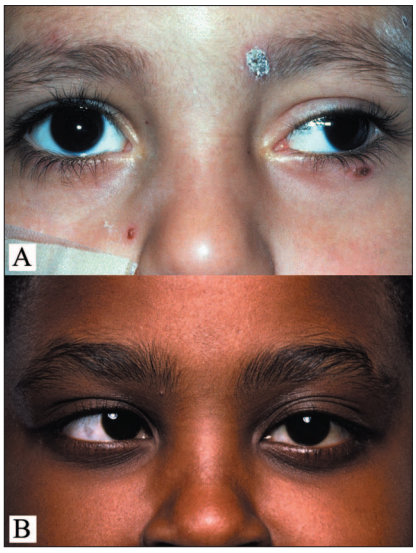


Figure 9. a. Left pupil-involving third nerve palsy with a dilated pupil, ptosis and the left eye pointing 'down and out' because of the unopposed action of the lateral rectus (sixth cranial nerve) and superior oblique (fourth cranial nerve) muscles. b. Right sixth cranial nerve palsy with a marked right paralytic esotropia as a result of loss of abduction by the lateral rectus muscle.

Both hypertension and diabetes mellitus cause microvasculopathy and are important risk factors for cranial nerve palsies. These are isolated and usually start to resolve by 6 weeks, but if this does not occur, urgent investigation is warranted to exclude a space-occupying lesion. In sixth cranial nerve palsy, paresis of the lateral rectus causes an abduction deficit turning the affected eye inwards (esotropic), more for distance than near (*Figure 9b*). In fourth cranial nerve palsy, the affected eye is hypertropic (elevated), with a compensatory head tilt away from the side of the lesion and a chin-down position (*Figure 10*). The hypertropia is maximized on tilting the head towards the side of the lesion (Bielschowsky head tilt test).

Carotid artery stenosis can affect both the eye and brain, the most obvious example being transient ischaemic attacks (Biousse, 1997). These can cause blackouts when the cerebral circulation is affected, while transient monocular blindness (amaurosis fugax) is seen when the retinal arteries are involved. A thorough cardiovascular workup is carried out in these patients, including carotid artery Doppler ultrasonography and echocardiography to exclude a source of emboli. These can lodge in the retinal arterial circulation and cause either central or branch retinal artery occlusion, while in the brain this can cause cerebral infarction (*Figure 11*).

Connective tissue disorders

Autoimmune and connective tissue disorders affect both the eye and nervous system, often with generalized systemic involvement (Borruat, 1996). Examples include sarcoidosis, Behçet's disease, polyarteritis nodosa, systemic lupus erythematosus and Tolosa–Hunt syndrome.

Giant cell arteritis (GCA) is an idiopathic granulomatous vasculitis affect-

Figure 10. Right fourth cranial nerve palsy, showing reduced depression of the right eye in adduction, (a) caused by paresis of the superior oblique muscle. b. On left gaze the right eye points superiorly caused by unopposed action of the inferior oblique muscle (supplied by the third cranial nerve).

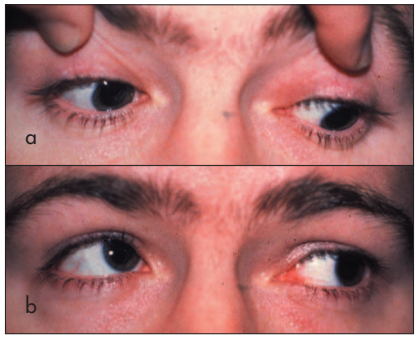
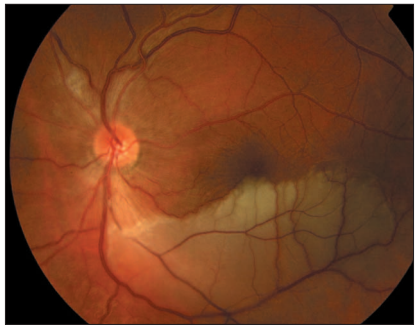


Figure 11. Fundus photograph showing left inferior branch retinal artery occlusion.



ing elderly patients, with systemic and ocular manifestations (Chan et al, 2001). It can lead to arteritic anterior ischaemic optic neuropathy (AION), which appears as a pale and swollen optic nerve head with small splinter-shaped haemorrhages and an altitudinal field defect (affecting the inferior or superior hemifield without crossing the horizontal midline). AION in the absence of GCA is caused by a microvasculopathy and is then said to be non-arteritic, often in the presence of hypertension and diabetes.

Other ocular manifestations of GCA include retinal artery occlusion and cranial nerve palsies. Systemic symptoms include headache, scalp and temporal artery tenderness, jaw claudication, proximal muscle stiffness, weight loss, malaise, and widespread arteritis. Although a very high erythrocyte sedimentation rate >60 mm/hr and positive temporal artery biopsy help to confirm the diagnosis, both may still be normal. High-dose corticosteroid must be started immediately if GCA is suspected to prevent involvement of the other eye.

Nutritional and drug-related neuro-ophthalmic disease

Toxic amblyopia is an optic neuropathy associated with excess alcohol and tobacco intake, leading to a secondary deficiency in B vitamins and amino acids (Kline and Bajandas, 2001). Excessive alcohol leads to thiamine deficiency and causes Wernicke's encephalopathy, associated with ophthalmoplegia, ataxia and confusion.

Optic neuropathy can be caused by therapeutic agents such as ethambutol, while antiepileptic agents are associated with gaze-evoked or upbeat nystagmus (Mejico et al, 2000). Vigabatrin is also used in epilepsy, but causes field defects which may be irreversible. Opiates and cholinergic agents cause miosis, while CNS stimulants, e.g. amphetamines and cocaine, anticholinergic agents and phenothiazines, are associated with mydriasis. Corticosteroids, tetracycline and the oral contraceptive pill have been implicated in the aetiology of benign intracranial hypertension.

Infection

Infective processes can affect both the eye and nervous system, often with systemic involvement (Acheson and Riordan-Eva, 1999). Examples include gram positive and negative bacteria, syphilis, tuberculosis, Lyme disease, herpes simplex and zoster viruses, cryptococcus and toxoplasmosis. This may take the form of an atypical optic neuritis, meningitis, encephalitis, or manifest through the effects of an intracranial space-occupying lesion, leading to papilloedema and varied clinical signs depending on the anatomical location. Cranial nerve palsies, particularly the sixth and third nerves, may also occur.

Phakomatoses

The phakomatoses comprise a range of diseases with multiple hamartomas, which all have both ocular and neurological manifestations (Kerrison, 2000). For example neurofibromatosis type I is associated with optic nerve glioma, posterior segment hamartomas, multiple neurofibromas, Lisch nodules of the iris, congenital glaucoma and pulsating exophthalmos caused by sphenoid dysplasia. Von Hippel–Lindau syndrome is characterized by retinal angiomatosis and cerebellar haemangioblastoma, as well as other systemic tumours.

Retinal astrocytomas are typically found in tuberous sclerosis, together with systemic hamartomas and intracranial lesions causing epilepsy. Sturge–Weber syndrome is associated with a facial angioma involving the first and second division of the trigeminal nerve, congenital glaucoma, choroidal and calcifying occipitoparietal leptomeningeal angiomata.

Pupillary disorders

Abnormalities in pupil size and response can be a manifestation of neurological disease, the pathways responsible involving both parasympathetic and sympathetic nervous systems as well as other higher cortical input (Acheson and Riordan-Eva, 1999; Kline and Bajandas, 2001).

Parasympathetic defects: Central lesions are typically compressive, presenting with a large, unreactive pupil, absent accommodation and oculomotor nerve paresis. Atropinergic substances may be present in commercial gardening products and cause a postganglionic defect, with a dilated pupil unreactive to light and accommodation. Adie's pupil typically affects young women and is caused by demyelination of short ciliary nerves, with aberrant regeneration later causing sluggish sectoral 'vermiform' contraction and relaxation of the so-called 'tonic' pupil.

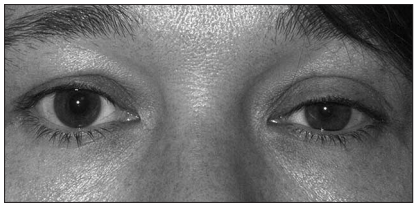
Horner's syndrome: Horner's syndrome is a result of disruption to the sympathetic supply of the eye (*Figure 12*). Clinical findings are a miotic but reactive pupil, small upper lid ptosis and an 'upside-down' ptosis of the lower lid, with reduced ipsilateral sweating in preganglionic lesions. Iris heterochromia is also present in congenital Horner's syndrome. Acquired causes may be classified by anatomical location:

1. Central: syringomyelia, brainstem vascular disease, demyelination
2. Preganglionic: Pancoast's tumour of the lung, cervical rib, carotid artery dissection, lesions in the neck
3. Postganglionic: trauma, cavernous sinus lesion.

Pharmacological tests exist to ascertain the anatomical site of the lesion, but these are only occasionally used.

Light-near dissociation: This occurs when the pupillary light reflex is diminished but the near reflex remains intact. This is seen with compressive lesions of the dorsal midbrain e.g. pinealomas, which are thought to initially affect the fibres serving the near reflex as they lie dorsal to those serving the light reflex, which are more ventral and thus relatively spared. Others causes of light–near dissociation include aberrant regeneration following a third nerve palsy, Adie's pupil and Argyll–Robertson pupil, which is classically associated with neurosyphilis.

Figure 12. Left Horner's syndrome with miosis and mild left ptosis.



Extraocular motility

Ocular motor nerve palsies: Extraocular movement and position are affected by palsies of the third, fourth and sixth cranial nerves, clinical features of which have already been described.

Gaze palsies: Defects in supranuclear pathways lead to gaze disturbances, which are pathological changes in versional (conjugate) and vergence (disconjugate) eye movements. For example, disturbances in horizontal gaze include internuclear ophthalmoplegia, horizontal conjugate gaze deviation, one-and-a-half syndrome and skew deviation. Deficits in vertical upgaze are caused by lesions of the periaqueductal and dorsal midbrain region, usually a pinealoma. Further signs include upper eyelid retraction, pupillary light–near dissociation and convergence-retraction nystagmus, together comprising Parinaud's dorsal midbrain syndrome.

Nystagmus: Nystagmus is an involuntary rhythmic oscillation of the eye, consisting of fast and slow phases, the direction being denoted by the fast phase. Pathological nystagmus may be the result of ocular problems, but is often a manifestation of underlying neurological disease, e.g. downbeat nystagmus is seen in the Arnold–Chiari malformation, upbeat nystagmus in posterior fossa lesions and see-saw nystagmus in chiasmal disease. Other oscillatory abnormalities include square-wave jerks in demyelinating disease and ocular bobbing in comatose patients with massive pontine lesions.

Ocular myopathies: The ocular myopathies include myasthenia gravis, myotonic dystrophy, chronic progressive external ophthalmoplegia and related hyperkinetic disorders such as essential blepharospasm. Myasthenia gravis is an autoimmune disorder caused by autoantibodies against the postsynaptic acetylcholine receptor at the neuromuscular junction of skeletal muscle (*Figure 13*).

Ocular symptoms include ptosis and diplopia, symptoms being worse toward the end of the day or when fatigued. Proximal muscles can also be involved, leading to difficulty with swallowing or breathing. The diagnosis can be confirmed by improvement of ptosis following the Tensilon test or after placing an ice pack over the affected eye. Further evidence is provided by testing for acetylcholine receptor-binding antibodies and, in equivocal cases, by electromyography.

Myotonic dystrophy is a dominantly inherited disease characterized by myotonia of peripheral muscles, making release of handgrip difficult. Ocular features include bilateral ptosis, premature cataract, pigmentary retinopathy, pupillary light–near dissociation and rarely gaze restriction. Wasting of facial muscles causes a characteristic 'mournful' myotonic facies.

Chronic progressive external ophthalmoplegia is a mitochondrially inherited disorder which is characterized by slowly progressive bilateral ptosis and restriction of all extraocular muscles (Riordan-Eva, 2000). These features are found together with heart block and pigmentary retinopathy in Kearns Sayre syndrome.

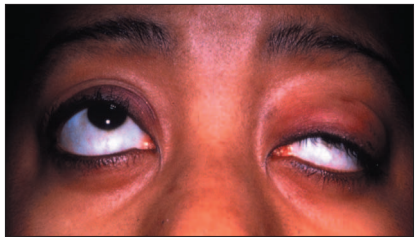
Hyperkinetic facial nerve syndromes may also present with ophthalmic symptoms, including essential blepharospasm and hemifacial spasm (Acheson and Riordan-Eva, 1999). Treatment of such disorders has been revolutionized by the use of botulinum toxin. This is injected subcutaneously into the orbicularis oculi muscles and significantly reduces facial spasms within a few days, lasting for an average of 3 months.

Inherited disorders

There are several hereditary forms of optic atrophy, the most common of which is autosomal dominant, with autosomal recessive forms being much rarer and associated with additional neurological and systemic abnormalities. Mitochondrially-inherited Leber's hereditary optic neuropathy usually affects males, causing sudden central visual loss in the second to third decade of life. Peripapillary telangiectasia may be present in the acute phase, but recovery is slow and depends on the type of primary mutation present.

Retinitis pigmentosa is a group of inherited retinal dystrophies characterized by progressive loss of photoreceptor and retinal pigment epithelial function. It is associated with several systemic disorders, many of which have neurological symptoms, such as abetalipoproteinaemia, Refsum's disease and Usher's syndrome. **HM**

Figure 13. Myasthenia gravis with marked left ptosis, worsened on fatigue testing with prolonged upgaze.



The authors would like to thank Mr J Acheson, Mr V Menezo and the Medical Illustration Department, Moorfields Eye Hospital, London, for their assistance in the preparation of figures.

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