Ocular neuromyotonia

Eric Ezra, David Spalton, Michael D Sanders, Elizabeth M Graham, Gordon T Plant

Abstract

Aims/Background—Ocular neuromyotonia is characterised by spontaneous spasm of extraocular muscles and has been described in only 14 patients. Three further cases, two with unique features, are described, and the underlying mechanism reviewed in the light of recent experimental evidence implicating extracellular potassium concentration in causing spontaneous firing in normal and demyelinated axons.

Methods—Two patients had third nerve neuromyotonia, one due to compression by an internal carotid artery aneurysm, which has not been reported previously, while the other followed irradiation of a pituitary tumour, a common association in the published reports. Selective activation occurred in both, where neuromyotonic activity was triggered by prolonged voluntary activation of specific extraocular muscles with or without spread of activity to other third nerve muscles. The other patient had fourth nerve involvement, where spasms of the superior oblique muscle were induced only by alcohol, a phenomenon which has not been described.

Results—The two patients with third nerve involvement responded to carbamazepine and in one, an improvement in a chronic partial third nerve paresis occurred. The other has not required treatment and remains asymptomatic by refraining from alcohol.

Conclusions—A careful examination, including the effects of prolonged voluntary muscle action is required to initiate episodes and to demonstrate selective activation. Imaging is mandatory to exclude compressive intracranial lesions, particularly where there is no history of pituitary fossa irradiation. A trial of anticonvulsants should be considered in all patients. Extracellular potassium may play a role in spontaneous firing and ephaptic transmission in ocular neuromyotonia.


In 1970 Ricker and Mertens described a patient with idiopathic paroxysmal diplopia. During episodes, they noted a tonic unilateral esodeviation with restriction of elevation and abduction due to overaction of the medial and inferior rectus muscles. Papas' in 1972 described a similar patient with involvement of the medial, inferior and superior recti, and the levator muscle. Electromyographic recordings in both patients during quiescent periods revealed a neurogenic pattern and they concluded that neuromyotonic activity resulted from spontaneous electrical activity in unstable motor nerve membranes, followed by ephaptic transmission of electrical activity to adjacent nerves, causing co-firing of different muscles supplied by the third nerve. This hypothesis was supported by the fact that both patients responded and became asymptomatic after treatment with carbamazepine, an anticonvulsant. The term 'ocular neuromyotonia' was used to describe the syndrome. Further reports in the literature have been sparse as summarised in Table I.

The condition is distinct from superior oblique myokymia, which is characterised by oscillopsia and microtremor due to phasic rather than tonic activity. It is also distinct from cyclical oculomotor spasm, which occurs in the setting of a congenital third nerve paresis, where cycles have characteristic pupillary involvement without tonic adduction. Although surgery or, more specifically, irradiation for pituitary fossa and other intracranial tumours is the usual aetiology, ocular neuromyotonia may occur with other intracranial compressive lesions, or in the absence of any causative factors. Any of the ocular motor nerves may be affected, often in the setting of a chronic nerve paresis and episodes may be elicited by sustained activity of the extraocular muscle supplied by the nerve involved or may occur spontaneously.

The diagnosis may be easily overlooked in a patient complaining of paroxysmal diplopia because a careful examination of ocular motility, including the effects of sustained action of individual muscles, is required. Furthermore, effective treatment with anticonvulsants is available. Our experience suggests that where the cause is not clear (particularly if there is no previous history of radiation therapy) all patients should be investigated for intracranial disease.

These points are illustrated with a description of three further cases.

Methods and patients

The three patients in this study were all referred following an initial examination by their ophthalmologist. All patients had a full ophthalmic, neurological, and general examination. Ophthalmic examination included careful assessment of ocular motility, with particular attention to the following:

(1) Ocular motility during quiescent periods, with careful documentation of chronic nerve pareses, including signs of oculomotor synkinesis ('aberrant regeneration') in third nerve involvement. A Hess examination was performed on all patients. Pupillary synkinesis
Table 1  Summary of the 17 cases of ocular neuromyotonia in the literature

<table>
<thead>
<tr>
<th>Case/sex</th>
<th>Age/sex</th>
<th>Aetiology</th>
<th>Radiation (Gy)</th>
<th>Time to onset</th>
<th>Nerve</th>
<th>Chronic pain/ aberrant regeneration</th>
<th>Neuromyotonic muscle involvement (and triggering muscles)</th>
<th>Treatment response (symptoms)</th>
<th>Treatment response (chronic nerve palsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ricker</td>
<td>Nil</td>
<td>Nil</td>
<td>351</td>
<td>III</td>
<td>Nil</td>
<td>MR, IR</td>
<td>Full resolution</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Papst</td>
<td>Nil</td>
<td>4</td>
<td>9 Months</td>
<td>III</td>
<td>Nil</td>
<td>MR, IR, SR, LP</td>
<td>Full resolution</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Shults et al</td>
<td>60M</td>
<td>75</td>
<td>7 Years</td>
<td>III</td>
<td>AR lid only</td>
<td>MR, IR, SR, LP (triggered by MR, IR)</td>
<td>Full resolution</td>
<td>Full resolution</td>
</tr>
<tr>
<td>4</td>
<td>Pituitary adenoma, craniotomy</td>
<td>62F</td>
<td>50-4</td>
<td>3 Years</td>
<td>III</td>
<td>AR lid only</td>
<td>MR, IR, SR, LP (triggered by MR, IR)</td>
<td>No response</td>
<td>No response</td>
</tr>
<tr>
<td>5</td>
<td>Pituitary adenoma, craniotomy</td>
<td>52M</td>
<td>6</td>
<td>Nil</td>
<td>–</td>
<td>AR lid only</td>
<td>MR, IR, SR, LP (triggered by MR, IR)</td>
<td>Partial response</td>
<td>?</td>
</tr>
<tr>
<td>6</td>
<td>Nil</td>
<td>12M</td>
<td>66</td>
<td>3 Years</td>
<td>VI</td>
<td>Nil</td>
<td>LR (triggered by LR)</td>
<td>No response</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>46M</td>
<td>9</td>
<td>50-0-5</td>
<td>2 Years</td>
<td>III</td>
<td>Nil</td>
<td>SR</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>19F</td>
<td>10</td>
<td>54</td>
<td>11 Months</td>
<td>III</td>
<td>Nil</td>
<td>MR</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>11F</td>
<td>7</td>
<td>70-2</td>
<td>2 Months</td>
<td>VI</td>
<td>Partial VI</td>
<td>LR</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>Skull base sarcoma (no surgery)</td>
<td>12</td>
<td>40</td>
<td>4 Years</td>
<td>VI</td>
<td>Partial VI</td>
<td>LR</td>
<td>No treatment, partial resolution</td>
<td>–</td>
</tr>
<tr>
<td>11F</td>
<td>Skull base sarcoma</td>
<td>13</td>
<td>45</td>
<td>7 Years</td>
<td>III</td>
<td>Nil</td>
<td>IR, SR, LP</td>
<td>Full resolution</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>14F</td>
<td>36F</td>
<td>77</td>
<td>16 Months</td>
<td>VI</td>
<td>LR (triggered by LR)</td>
<td>No treatment, full resolution</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>14F</td>
<td>7M</td>
<td>36</td>
<td>9 Years</td>
<td>III</td>
<td>Partial III</td>
<td>MR, IR, SR, LR (triggered by MR, IR)</td>
<td>Partial response</td>
<td>Partial improvement</td>
</tr>
<tr>
<td>14</td>
<td>Thalamic glioma (no surgery)</td>
<td>Ezra et al (this study)</td>
<td>7</td>
<td>–</td>
<td>IV</td>
<td>AR</td>
<td>SO</td>
<td>No treatment, unchanged</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>15F</td>
<td>60M</td>
<td>7</td>
<td>36</td>
<td>III</td>
<td>Partial III</td>
<td>MR, IR, SR, LP (triggered by MR, IR)</td>
<td>Partial response</td>
<td>Partial improvement</td>
</tr>
<tr>
<td>16</td>
<td>16F</td>
<td>44M</td>
<td>46M</td>
<td>Nil</td>
<td>–</td>
<td>Partial III</td>
<td>MR, IR, SR, LP (triggered by MR, IR)</td>
<td>No treatment, unchanged</td>
<td>–</td>
</tr>
<tr>
<td>17</td>
<td>40M</td>
<td>400</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TSA = trans-sphenoidal adenohypophysectomy, AR = aberrant regeneration, MR = medial rectus, IR = inferior rectus, SR = superior rectus, LR = lateral rectus, SO = superior oblique, LP = levator palpebrae, P = pupillomotor, ? = unknown.

(case 2) was confirmed by pupillometry. Upper lid position and retraction on downgaze, a sign of upper lid synkinesis, were recorded.

(2) Episodes of neuromyotonic spasms were induced by prolonged voluntary activity of individual extracocular muscles in turn. Each muscle was tested to determine whether it could act as the triggering muscle.

(3) During neuromyotonic episodes the following were recorded: (i) duration and symptoms, particularly the nature of the diplopia; (ii) which muscles were co-firing – this could be determined by ocular deviation in all positions of gaze and by eliciting mechanical restriction of the antagonists; (iii) upper lid position in primary gaze and the effects of downgaze, which accentuates any spasm of the levator palpebrae; (iv) pupillary spasm; (v) globe retraction due to co-firing of extracocular muscles; (vi) the presence of torsional diplopia, intorsion, and hypodeivation were taken as a sign of superior oblique spasm (case 3) and microtremor was sought by slit-lamp examination.

(4) In case 3, episodes could not be elicited during several examinations. The patient was therefore asked to drink approximately 100 ml of spirit in order to allow observation of an episode.

All patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) with contrast, and MRI cerebral vessel angiography was performed to confirm suspected vascular lesions (case 1). All patients also had neurological examination, including full blood screening. An edrophonium (Tension) test to exclude myasthenia gravis, was performed in all patients, where an intravenous injection during a quiescent period was followed by a careful examination of ocular motility to determine whether edrophonium could abolish neuromyotonic triggering.

Results

CASE 1

A 60-year-old man was referred with a 1 year history of right supraorbital pain. The family had noted that, from time to time, his right eye would appear to stare. Direct questioning revealed episodes of intermittent diplopia, with variable horizontal and vertical components and no precipitating factors of which the patient was aware. He also had a history of hypertension, ischaemic heart disease, and peripheral vascular disease. Alcohol consumption had been high, in excess of 40 units per week for several years, though episodes were not related to alcohol consumption. Neuro-ophthalmic examination showed a partial right third nerve palsy and signs of oculomotor synkinesis, with upper lid retraction on downgaze (Fig 1 A–C) and pupillary synkinesis. The right corneal reflex was reduced but there were no other abnormal neuro-ophthalmic or neurological signs. Systemic examination revealed bilateral carotid bruises and hypertension but was otherwise unremarkable.

Sustained elevation of the right eye resulted in paroxysmal spasm of the right levator muscle, the upper lid becoming markedly
retracted, particularly on attempted downgaze (Fig 1 C-E). Ocular motility and pupillary responses remained unchanged during these episodes. A different pattern of activity could be provoked by sustained adduction of the right eye. During these episodes, paroxysmal spasm of the medial rectus would occur, with restriction of abduction, and unaffected lid position (Fig 1 F-I). Both types of episodes typically lasted between 2 and 3 minutes. The clinical pattern reflected levator and medial rectus involvement, although simultaneous overaction of these could not be elicited in a single episode and co-firing of other muscles supplied by the third nerve did not occur. Both types of episodes could be easily reproduced.

A T1 MRI scan revealed a supracallosal mass on the right, with a mixed signal suggestive of a partially thrombosed aneurysm (Fig 2). This was confirmed by MRI angiography which showed an aneurysm of the internal carotid artery at its junction with the posterior communicating artery, impinging on the roof of the right cavernous sinus where the third nerve enters the sinus (Fig 3). Treatment with carbamazepine 200 mg twice daily resulted in full resolution of symptoms within a week, but the partial third nerve paresis remained unchanged. An attempt to reduce the dosage resulted in recurrence of symptoms and the original dose was recommenced. He has had no further attacks on treatment after 1 year.

CASE 2
A 44-year-old man with headache, right visual disturbance and gynaecomastia was found to have visual acuities of 6/12 right and 6/6 left, with a bitemporal hemianopia, a right central scotoma, and right optic disc pallor and afferent pupillary defect, suggesting anterior chiasmal compression. Ocular motility and neurological examinations were unremarkable and general examination revealed signs of panhypopituitarism. A CT scan confirmed the presence of a large pituitary fossa mass with suprasellar extension, and a markedly raised serum prolactin indicated a prolactinoma. At the time, bromocriptine therapy was not available and he underwent a frontal craniotomy and hypophysectomy, followed by postoperative irradiation with 36 Gy. Thereafter, he remained well on endocrine replacement therapy and showed improvement in visual fields and acuity of the right eye.

Nine years later he presented with episodes of paroxysmal vertical and horizontal diplopia, associated with a 'pulling' sensation in the right eye usually occurring while driving long distances and looking in the rear mirror or when tired or under extreme stress. During these episodes he invariably noted that the right eye would 'stare'. Typically, episodes would last between seconds and minutes and resolve spontaneously, with several occurring over a period of several hours. At the time, ocular motility and eyelids were reported as normal, though the effects of sustained muscle activity were not sought. Visual field and CT examination on three occasions failed to show any change or tumour recurrence. Over the next 3 years, episodes became increasingly frequent, to the extent that he was no longer able to drive without symptoms. He also developed a mild chronic third nerve paresis, a 2 mm ptosis, pupillary dilatation, and oculomotor synkinesis (aberrant regeneration), with lid retraction on downgaze and pupillary synkinesis confirmed by pupillometry.
Attacks could be provoked by sustained adduction and depression of the right eye. During episodes, the right eye would become tonically deviated in adduction, with restriction of all ocular movements, particularly abduction and elevation, and marked upper lid retraction due to levator overaction. In addition pupillary involvement would occur, the pupil becoming fixed in partial miosis, failing to react to light or accommodation. The patient reported vertical and horizontal diplopia, without torsion, during these attacks, which lasted a variable period from seconds to minutes. The clinical pattern therefore reflected co-firing of pupillomotor, levator and medial, inferior and superior rectus muscle fibres, triggered by sustained voluntary activity of the medial and inferior recti.

Treatment with carbamazepine 200 mg twice daily resulted in a dramatic improvement of symptoms within a week. In addition, the chronic third nerve paresis improved markedly (Fig 4), with only mild limitation of upgaze, and mild upper lid retraction on downgaze remaining after 2 months of treatment. Although he reported occasional symptoms on treatment, no further attacks could be elicited.

**CASE 3**

A 40-year-old man was referred with a 4 year history of paroxysmal vertical diplopia. Episodes typically lasted between 10 and 20 seconds and would occur repetitively after moderate to high alcohol consumption. He did not report any oscillopsia or eyelid abnormalities during attacks. No relevant medical history was elicited.

Neuro-ophthalmic and neurological examination proved unremarkable initially, but after consumption of about 100 ml of spirit under observation, a series of attacks occurred over the space of 20 minutes. During episodes, which occurred spontaneously and independently of eye position, he would develop a right hypotropia due to superior oblique overaction with torsional and vertical diplopia. No oscillopsia or microtremor occurred and eyelid position and pupillary reactions remained normal throughout. Each episode was extremely short lived, thereby precluding a more detailed examination. Activity could not be induced in the absence of alcohol.

MRI studies failed to reveal any intracranial abnormality and an edrophonium test during
an episode proved negative. He did not receive treatment and remains asymptomatic if he abstains from alcohol.

Discussion
All 17 cases of ocular neuromyotonia in the literature,\(^1\)\(^-\)\(^8\) including the three reported here, are summarised in Table 1. Eleven had intracranial tumours treated with surgery and/or radiotherapy, the period between treatment and onset of symptoms ranging from 2 months to 9 years. Four patients had no identifiable cause and two associations were reported here for the first time — oculomotor nerve compression (case 1) and an association with alcohol consumption (case 3). Case 1 in our series is the first patient with ocular neuromyotonia to be described in association with a compressive lesion. However, the patient described by Bateman and Saunders,\(^10\) a patient with a suprachiasmatic aneurysm, a chronic third nerve paresis with synkinesis, and paroxysmal third nerve spasm was interpreted as having a cyclical oculomotor palsy but may well have been a case of ocular neuromyotonia, as has been suggested by previous authors.\(^3\)

Eleven patients had involvement of the third nerve, two of the fourth nerve, and four of the sixth nerve. Ten patients in total received anticonvulsant therapy, eight showing a reduction in the frequency of symptoms. Perhaps more remarkably, three patients, our case 2 and two patients described by Shults et al,\(^3\) showed improvement of chronic nerve paresis on treatment. Of the 11 patients with third nerve involvement, six had evidence of a chronic nerve paresis with signs of oculomotor synkinesis and five had normal ocular motility during quiescent periods, eight had levator involvement, nine medial rectus, eight superior rectus, and eight inferior rectus involvement during episodes. Only two patients had pupillary involvement.

In the two patients we have described with third nerve neuromyotonia, the phenomenon of selective activation occurred, that is to say sustained action of certain muscles provoked the spasms. This was also described in four of the six patients in the series of Shults et al,\(^3\) with activation most commonly occurring through action of the medial and inferior recti. In case 2 medial and inferior rectus overaction resulted in co-firing of the other muscles. Case 1 showed two quite distinct patterns of neuromyotonic activity, where sustained upgaze triggered overaction of the levator and activity of the medial rectus triggered overaction of that muscle only. Activity did not ‘spread’ from the medial rectus to the levator or vice versa. This pattern has not been previously reported and some degree of co-activation is the rule.

Ocular neuromyotonia of the fourth nerve has only been described in two patients, including case 3 in our series, and typically involves spontaneous superior oblique overaction without microtremor or oscillopilia, reflecting the tonic, rather than phasic, nature of the neural discharges in neuromyotonia. This patient is the only case of ocular neuromyotonia provoked by alcohol. The case described by Clark\(^11\) as superior oblique overaction without oscillopilia or microtremor, was probably the first case of fourth nerve neuromyotonia to be described in the literature, as has been pointed out by previous authors.\(^5\)

As a clinical syndrome, fourth nerve neuromyotonia may be differentiated from superior oblique myokymia. In addition to a hypothropia, the symptom of oscillopilia, in association with microtremor and intorsion, which are best observed by slit-lamp examination, is typical of myokymia and reflects phasic neural activity other than the tonic activity seen in neuromyotonia. However, both conditions may represent a spectrum of disease with a common underlying mechanism, with the distinction being purely clinical.

Sixth nerve neuromyotonia has been described in four patients. It involves intermittent exotropia with restriction of adduction, and is triggered by sustained action of the lateral rectus muscle. The patient described by Barroso and Hoyt\(^6\) is unique in that this is the only reported case where resolution of neuromyotonia occurred spontaneously without anticonvulsant therapy. Metz and Sterns\(^12\) described a woman with a chronic sixth nerve paresis, following pituitary surgery and irradiation, who developed 'variable esotropia-exotropia'. The clinical picture would be consistent with sixth nerve neuromyotonia.

In ocular neuromyotonia the spontaneous firing results from sustained neural firing in a single neuron or a group of neurons supplying the activating muscle or muscles. Interneural transmission to other neurons supplying the same or other muscles may then occur resulting in a self perpetuating circuit.\(^13\) This would explain 'selective activation' by specific muscles and subsequent co-firing of other muscles in third nerve neuromyotonia and tonic activity in fourth and sixth nerve involvement.

Support for this mechanism has come from evidence in other neurological conditions such as radiation plexopathy,\(^13\) peripheral neuropathy,\(^14\)\(^-\)\(^15\) traumatic neuropathy,\(^16\) facial nerve palsy,\(^17\) where spontaneous firing has been shown to occur in segmentally demyelinated axons. Patients with limb myokymia due to radiation plexopathy exhibit similar electromyographic activity to those with ocular neuromyotonia.\(^13\)

In experimental models, spontaneous firing in demyelinated axons has been demonstrated in rat spinal root axons,\(^18\) cat dorsal columns,\(^19\) and rat trigeminal nerve.\(^20\) Ectopic action potentials also occur in normal, myelinated mammalian axons where extracellular potassium concentration has been elevated\(^21\) including following sustained tetanic activation.\(^22\) In ocular neuromyotonia, therefore, it is possible that damaged axons become susceptible to spontaneous firing. Extracellular potassium may be elevated when axons are subjected to sustained activity, thus explaining the triggering that occurs with sustained muscle activity. For co-firing of neurons supplying other muscles to be initiated interneural electrical
transmission must occur; perhaps this may also occur as a result of changes in extracellular potassium.

In ocular motor synkinesis, it has previously been argued that aberrant regeneration or axonal misdirection may not account for co-firing. Two alternative mechanisms have been proposed.\textsuperscript{23} The first is ephaptic (lateral) transmission between axons and the second involves central synaptic reorganisation following injury. As most patients with third nerve neuromyotonia also show signs of synkinesis during quiescent periods ephaptic transmission may be relevant to both phenomena. This may account for the disappearance of synkinesis in case 2 following anticonvulsant therapy – its disappearance has also been described following treatment of a lymphoma causing ocular motor nerve synkinesis.\textsuperscript{24} It would be difficult to explain these observations if the synkinesis were due to a 'hard wired' aberrant regeneration.

The role of alcohol consumption in precipitating attacks in patient 3 is unknown. Studies examining the effects of alcohol on human peripheral nerve function have not shown similar effects in peripheral nerves.\textsuperscript{25-27} Finally, the marked improvement in basal nerve function with anticonvulsant treatment in case 2 and in the two other patients described in the literature,\textsuperscript{3} implies that chronic paresis is at least in part due to nerve membrane instability. The improvement of such a paresis may have wider implications for the treatment of other peripheral and central neuropathies and demyelinating disorders.

We are grateful to Dr Rais Kapoor for his contribution to the discussion and to the orthoptic department at St Thomas's Hospital for their contributions.