LETTERS

Focal hand dystonia after cervical whiplash injury

There is currently a general consensus of agreement that dystonia is a disease of the basal ganglia, although dystonic symptoms have been observed in association with lesions in various different sites of the sensory and motor pathways.¹ In particular, cervical intramedullary lesions have been reported as being a rare cause of focal hand dystonia,² although in these cases the pathogenesis of the movement disorder remains unclear. To help clarify this point, we report the case of a patient who developed dystonic features of the right hand after a cervical whiplash injury.

Case report

A 44 year old man developed sensory alterations and impairment of strength in the right hand immediately after a whiplash injury. Neurological examination showed proprioceptive and tactile anaesthesia of the first three fingers of the right hand, mild hypaesthesia on grasping, and adiadochokinesis of the right upper limb. Tendon reflexes, muscle tone, and plantar responses were normal, and thorough neurological examination of the upper left limb and lower limbs also yielded normal findings. Cervical magnetic resonance imaging (MRI) revealed a small right posterior C5-C6 lesion of the spinal cord (see fig 1). Brain MRI, nerve conduction studies, EMG, and transcranial magnetic stimulation were all normal. Two months later, the patient developed writhing movements of the first three fingers and a dystonic posture of the right hand, worsened by movement, and more evident when the eyes were closed. Ability to write, use a knife or fork, and hold a glass were moderately impaired, especially without visual guidance. Neurological examination at this time revealed slight cutaneous and proprioceptive hypaesthesia and paraesthesias of the first three fingers of the right hand, while grasping strength was normal and the EMG recording showed a pattern of co-contraction of the forearm flexor and extensor muscles. Median nerve sensory evoked potentials (SEPs) revealed normal peripheral and central conduction times, but spinal and cortical waves were larger in response to stimulation of the affected side. In particular, the cervical potential showed a right:left ratio of 1.2, while the right:left ratio for the cortical waves ranged from 1.8 to 2.4. The patient had no history of neuroleptic intake.

This is the first report of hand athetosis-dystonia after a cervical whiplash injury to the spinal cord. We are reasonably confident that the lesion was secondary to the trauma, rather than representing inflammation, because the symptoms appeared immediately after the whiplash injury and in view of the fact that MRI was performed within a couple of days and no signs of spinal cord oedema were detected. To date, only a few reports have described dystonic hand disorders in intramedullary cervical lesions, the vast majority being cases of syringomyelia, and occasionally spinal tumours, demyelinating lesions, and post-irradiation myelopathy.² The patient's involuntary movements may be interpreted as dystonia rather than pseudoathetosis, as they were also present when the eyes were open, and the simultaneous

recording of agonist and antagonist forearm muscles showed synchronised motor unit activation, whereas the pathogenetic mechanism of pseudoathetosis is a loss of postural tone secondary to the proprioception deficit. Proprioception was only slightly impaired at the time of onset of the movement disorder and the SEP data suggested the presence of a larger sensory input to the patient's central nervous system rather than deafferentation.

Various hypotheses have been adduced to explain hand dystonia secondary to cervical lesions. A dysfunction of spinal interneuronal circuits, resulting in a lack of reciprocal, recurrent spinal inhibition may be important in the pathogenesis of the symptoms, especially in centromedullary lesions such as syringomyelia. Supraspinal mechanisms, initiated by erroneous sensory inputs, might also lead to dystonia.

We believe that involvement of the somato-sensory pathway was the main determinant of the hand dystonia in our patient. This hypothesis is based on a number of findings. Firstly, MRI showed a cervical lesion involving the right posterior column and sparing the centre of the spinal cord. Secondly, the patient developed paraesthesias of the fingers, possibly attributable to a focus of ephaptic activity in the posterior cord, which is a mechanism known to cause positive symptoms in white matter lesions.³ The most intriguing finding, however, is that the SEP cortical waves were markedly larger in response to stimulation of the median nerve on the dystonic side, and the spinal potential was slightly larger on the affected side. The asymmetry of SEP amplitudes was not attributable to different intensities of stimulation on the two sides, as the intensity of the peripheral shock was the same, as was the amplitude of the afferent volleys recorded at the elbow and at the Erb's

point. A larger N30 potential has previously been described in dystonic patients, but this finding has not been replicated in other studies.⁴ It may seem strange to find larger SEPs associated with a sensory deficit, but the presence of ephaptic spread in the lemniscal pathway may account for the larger afferent input to the cortex, as well as for the paraesthesias. We may postulate that this larger sensory input may have triggered an abnormal motor command, resulting in a movement disorder with features favouring dystonia over those seen with sensory deafferentation (that is, pseudoathetosis). This report may confirm the central role of abnormal sensory processing in the pathogenesis of dystonic symptoms.⁵

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Encephalomyeloradiculopathy associated with wasp sting

Although stings from wasps can cause severe allergic reactions, including anaphylaxis, neurological complications of wasp stings are rare. There are, however, various interesting case reports of acute myelitis, acute encephalitis, encephaloradiculoneuritis, optic neuropathy,¹ cerebral infarction,² and acute inflammatory polyradiculopathy.³ We report here the case of a young man who developed encephalomyeloradiculopathy after being stung by a wasp.

Case report

An 18 year old man was referred to Ramathibodi Hospital with impaired consciousness and quadriplegia. He had been stung by a wasp 16 days previously on the right cheek and had mild swelling and tenderness over this area. On the following day, he suffered from headache, fever, and nausea and was admitted to a regional hospital. Three days later, he was drowsy and had urinary retention. Then he developed a generalised tonic-clonic seizure lasting two to three minutes. He was intubated and referred to us.

At Ramathibodi Hospital, he was comatose, quadriplegic, and areflexic. A lumbar puncture was done. The CSF pressure was 360 mm H₂O and fluid analysis showed mononuclear cells (9/mm³), a protein concentration of 160 mg/dL, and CSF/blood sugar concentrations of 4.38/13.38 mmol/L. CSF and serum were tested for

Figure 1 Cervical T2 sagittal section (A) and axial section at the level of the C5-C6 intervertebral space (B). The arrows indicate the small right posterior lesion.

Japanese encephalitis virus and dengue antibody with negative results. The erythrocyte sedimentation rate was 65 mm/h. Magnetic resonance imaging of the brain and cervical cord showed multiple ill defined scattered lesions of hypointense signal in T1 weighted (T1W) and inhomogeneous isohyperintense signal in T2 weighted (T2W) images involving both grey and white matter of medulla, pons, midbrain, basal ganglia, thalami, centrum semiovale, cortical grey matter, and cervical cord (fig 1). There was an absence of F waves in both median and ulnar nerves with absence of compound muscle action potentials on stimulating both tibial and peroneal nerves. Sensory nerve conduction was normal in median, ulnar, and sural nerves.

Methylprednisolone was given intravenously for five days. On the sixth day after starting treatment, he regained consciousness with limited eye movement and quadriplegia. A month later, a plasma exchange was performed. The power of the upper extremities gradually improved. Three months after admission, he was discharged with residual paraplegia with sensory level at T1 and urinary and fecal incontinence. The wasp was identified as *Vespa tropica*, a wasp commonly found throughout the country.

Comment

Allergic reactions to *Hymenoptera* stings range from local to severe systemic reactions or even death. These reactions are usually acute, beginning within minutes to hours in 76–96% of the patients. Nevertheless, there are reports of delayed responses that can occur days to weeks after the event. Of the 2606 reactions noted in the 1964 Academy of Allergy survey, 2.8% did not occur until several days after the sting. There have also been reports of neurological complications, hyperglobulinaemia, thrombocytopenic purpura, nephrotic syndrome, and hepatorenal syndrome.⁴ The neurological complications are infrequent but often serious and include clinical manifestations of damage to the central and peripheral nervous systems.

Means *et al* reported a case with a relapsing and progressive course of neurological symptoms and signs, including bilateral weakness and numbness of the arms and legs, following a sting by a yellow jacket (*Vespa pennsylvanica*).⁵ This patient had been alert

and oriented throughout her clinical course but she eventually died after sudden respiratory and cardiac arrest. Necropsy revealed massive pulmonary embolism which was the cause of death. Examination of the nervous system showed areas of demyelination throughout the central and peripheral nervous system associated with necrosis and inflammatory infiltrates in the brain stem and spinal cord. This is the only previous report of encephalomyeloradiculoneuritis in the English language literature. In contrast to this case, our patient had a more fulminant clinical course with a seizure and alteration of consciousness. It appears that there are occasional reports of acute myelitis, encephalitis, and encephalomyelopolyradiculoneuritis in the Russian and Romanian literature but the abstracts of those reports were not available for review.

Maltzman *et al* reported two cases and reviewed five other cases of optic neuropathy after bee and wasp stings.¹ Most cases had significant visual recovery after corticosteroid treatment. Bachman *et al* reported five cases presenting with acute inflammatory polyradiculopathy following *Hymenoptera* stings, with good recovery.³ Some cases had a sural nerve biopsy which showed segmental demyelination.

From early reports and our case, it appears that patients with neurological complications after *Hymenoptera* sting usually improve and some have complete recovery after high dose steroid treatment. According to some necropsy reports, the course of the disease, and the response to treatment, the pathogenesis—although not definitely known—could be an immune response to *Hymenoptera* sting. The nature and location of the sensitising agents involved in *Hymenoptera* are not entirely clear. The venom, venom sack, and insect body have all been shown to possess antigenic properties. *Hymenoptera* venom contains various non-myeelin proteins or peptides that could be encephalitogenic in some individuals. The antigens of the wasp may initiate production of antibodies that would cross react with myelin basic proteins. Alternatively, the phospholipase A activity of the venom could liberate encephalitogenic basic proteins or other antigens from myelin membranes of the central and peripheral nervous systems, inducing immune reactions.³ Although definitive evidence of the relation between an envenoming sting and neurological complications is often missing, this is true of many conditions that reflect delayed immune responses. It is hoped that a more detailed systematic evaluation of the consequences of severe stings by *Hymenoptera*, including serological and immunological testing, will solve these problems in the future.

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Debrisoquine hydroxylase gene polymorphism (CYP2D6*4) in dementia with Lewy bodies

After Alzheimer's disease, dementia with Lewy bodies (DLB) is probably the second most common cause of dementia among the elderly, having been shown to account for around 20% of cases at necropsy.¹ Pathologically, DLB is characterised by the presence of Lewy bodies within the cerebral cortex, especially the parahippocampal gyrus, cingulate gyrus and temporal neocortex, amygdala, and within brain stem nuclei, principally the substantia nigra and locus caeruleus.¹ Nonetheless, histopathological changes classically associated with Alzheimer's disease (amyloid plaques and neurofibrillary tangles) are frequently widespread within the cerebral cortex of patients with DLB.^{1,2}

Although most cases of DLB appear to arise sporadically, cases with a previous family history of similar disorder are known, suggesting that genetic factors may contribute to the risk of developing disease. It is well recognised that cases of DLB, especially male, show an increased frequency of APO E $\epsilon 4$ allele,^{2,3} though possession of this is generally associated with an accompanying Alzheimer's disease type pathology,² with DLB cases without Alzheimer's disease type pathology having a normal APO E $\epsilon 4$ allele frequency (Huckvale C *et al*, unpublished data). Hence, possession of APO E $\epsilon 4$ allele per se is unlikely to contribute to the generation of the Lewy body component of the pathological spectrum.

Some genetic association studies in idiopathic Parkinson's disease^{4–5} have reported an increased frequency of the CYP2D6*4 allele of the debrisoquine hydroxylase gene (involving a G/A transition at the intron 3-exon 4 junction) which results in an inactive copy of the enzyme and a "poor metaboliser" phenotype. Other work has suggested that this same allelic variation may also occur more frequently in DLB,^{6,7} but not all studies agree.^{8,9}

We have examined the frequency of the CYP2D6*4 allele of the debrisoquine hydroxylase (DBH) gene in 53 patients with DLB. The clinical diagnosis of DLB was made in accordance with the consensus criteria of McKeith *et al*.⁹ Twenty five of the patients have died, and pathological examination of their brains (DMAM) confirmed the clinical diagnosis in every instance. Genomic DNA was extracted from blood (in living patients) or frozen brain tissue (in necropsy cases) by standard methods. DBH and APO E and genotyping were performed according to standard methods.^{4,10} Differences in APO E $\epsilon 4$ allele and DBH CYP2D6*4 allele frequency between patient and control groups were analysed by Fisher's exact test. As previously reported,^{2,3} the APO E $\epsilon 4$ allele frequency was significantly increased (compared to controls) in both clinic and pathological DLB groups, separately or combined (table 1). However, in agreement with previous reports,^{8,9} there were no significant differences in frequency of CYP2D6*4 allele of DBH gene between DLB cases (clinic or pathological groups (separately or combined)

Figure 1 Magnetic resonance imaging (T2 weighted) of the brain and cervical cord showing multiple ill defined scattered lesions of inhomogeneous isohyperintense signal involving both grey and white matter of medulla, pons, midbrain, basal ganglia, thalami, centrum semiovales, cortical grey matter, and cervical cord.

Table 1 Frequency of APO E alleles and DBH alleles and genotypes in different DLB groups and controls

	APO E alleles			DBH				
	ε2	ε3	ε4	Alleles		Genotypes		
				N	M	NN	NM	MM
DLB clinical	0.04	0.57	0.39*	0.88	0.12	0.8	0.16	0.04
DLB pathological	0.02	0.46	0.52*	0.85	0.15	0.75	0.21	0.04
DLB combined	0.03	0.52	0.45*	0.87	0.13	0.78	0.18	0.04
†Controls	0.06	0.8	0.14	0.81	0.19	0.66	0.3	0.04

†Control APO E data (n=35 cases) from Pickering-Brown *et al* [3]; control DBH data (n=720 cases) from Smith *et al* [4]

*p<0.01 v controls.

DLB, dementia with Lewy bodies; N, normal allele; M, mutant (CYP2D6*4) allele.

and control subjects. Neither were there any differences in age at onset of disease or (in the pathological cases) duration of illness between DLB cases with and without mutant CYP2D6*4 allele. Cases with CYP2D6*4 allele were no more likely to show any, or more severe, Alzheimer's disease type pathological changes than those without. Hence, in this present series of cases of DLB we have not been able to confirm possession of CYP2D6*4 allele in the pathogenesis of the disorder, either in terms of generating Alzheimer's disease or Lewy body type pathology or in influencing the age at onset or duration of the illness. We therefore conclude that possession of CYP2D6*4 allele of DBH gene does not act as a risk factor for DLB.

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Meningioma presenting as stroke: report of two cases and estimation of incidence

Meningioma is the most common extra-axial brain tumour in adults and frequently originates in the suprasellar, frontobasal, temporo-basal, sphenoid wing, or petroclival regions.^{1,2} Tumours situated in these locations often involve an intracranial portion of the internal carotid artery (ICA) and may compromise cerebral blood flow.¹ While transient cerebral ischaemia has been recognised as a complication of skull base meningiomas,^{3–7} to our knowledge, there are no documented cases of a meningioma causing stroke by ICA occlusion. We report two cases of meningioma presenting with cerebral infarction as a result of carotid artery compression and estimate the incidence of meningioma related cerebral ischaemia by this mechanism at our institution.

Case reports

Patient 1

A 49 year old right handed man experienced two weeks of left upper extremity weakness. Brain magnetic resonance imaging (MRI) reportedly revealed a right sided mass involving the cavernous sinus, and the patient was referred for a neurosurgical consultation. Two days later the patient noted a sudden increase in symptom severity and presented to an outside hospital. Neurological examination showed a left facial droop, left hand weakness of 2/5 (MRC scale), left proximal upper extremity weakness of 4/5, and decreased sensation on the left hand.

Brain MRI demonstrated a subacute right middle cerebral artery (MCA) territory infarct. In addition, there was a mass in the right cavernous sinus, consistent with a meningioma, which encased the ICA (fig 1A). Cerebral angiography demonstrated occlusion of the right cavernous ICA with radiographic blush from the surrounding meningioma (fig 1B). Flow in the supraclinoid ICA was reconstituted from the external carotid artery via the

ophthalmic artery, and there was cross filling to the right hemisphere via the anterior communicating artery. Transoesophageal echocardiography was normal without evidence of embolic source. Neuro-ophthalmological examination revealed no signs of emboli. A comprehensive serum hypercoagulable panel revealed no abnormalities.

The patient underwent focused radiation therapy of the meningioma and his symptoms gradually improved. However, about six months later he experienced worsening left leg weakness. Brain MRI revealed an acute right MCA and right watershed distribution infarct. There appeared to be fresh thrombus in the right cavernous ICA. The patient was given anticoagulation and has had no further neurological events in over 30 months of follow up.

Patient 2

A 31 year old right handed man had acute onset of complete visual loss in his right eye. The event was painless, and as the patient felt that he could compensate sufficiently, he did not seek medical attention. One morning, about two years later, he experienced sudden onset of left sided numbness, collapsed, and was unable to sit up. Brain MRI revealed a right parietal region infarct, as well as a large mass, consistent with a meningioma, originating from the olfactory groove and encasing the right ICA at the apex of the right orbit (fig 1C). The mass also compressed the right optic nerve. Cerebral angiography demonstrated near occlusion of the right distal ICA (fig 1D) with the majority of perfusion to the right hemisphere being supplied by cross filling from the left ICA. Transoesophageal echocardiography was normal without evidence of embolic source. Neuro-ophthalmological examination revealed no signs of emboli. A comprehensive serum hypercoagulable panel revealed no abnormalities. The patient underwent complete tumour resection. Over the next several weeks he recovered most neurological function but was left with no vision in the right eye and persistent left arm numbness.

Discussion

Meningiomas are prevalent brain tumours commonly located at the skull base.^{1,2} By virtue of their position, these tumours have the potential to affect portions of the ICA and compromise cerebral blood flow. Previous reports have suggested that meningioma compression of the carotid artery may produce transient neurological symptoms including loss of consciousness, hemiparesis, parasthesias, and global amnesia.^{3–7} To our knowledge, however, there has never been a documented case of cerebral infarction as a result of meningioma related ICA compression.

We present two patients with cerebral infarction attributable to meningioma ICA involvement. In case one, imaging after the first ischaemic episode demonstrated a large cavernous sinus meningioma surrounding and occluding the right ICA. MRI after the second ischaemic episode suggested stump thrombosis in the cavernous ICA. The stroke was probably attributable to both haemodynamic hypoperfusion as well as artery to artery embolisation. In case two, imaging demonstrated a large olfactory groove meningioma encasing the right ICA with near occlusion of the vessel. It seems his stroke also occurred because of a combination of hypoperfusion and thromboembolism. Neither of these patients had evidence of vasculopathy or another aetiology for stroke.

Figure 1 (A) Coronal T1 weighted MRI with gadolinium demonstrating a meningioma encasing the internal carotid artery (ICA) within the right cavernous sinus. (B) Cerebral angiography with right common carotid artery (CCA) injection demonstrating occlusion of the right ICA and radiographic blush from the surrounding meningioma. (C) Coronal T1 weighted MRI with gadolinium demonstrating a meningioma encasing the right ICA at the apex of the right orbit. (D) Cerebral angiography with right CCA injection demonstrating virtual occlusion of the distal right ICA.

Although meningiomas commonly involve the ICA, they rarely present with symptoms of cerebral ischaemia. These tumours typically do not change vascular patency even when completely encasing the ICA and its bifurcation into the MCA and anterior cerebral artery. It may be possible that meningiomas, being slow growing and non-invasive, do not exert sufficient external force to significantly compress the high pressure arterial vasculature. In addition, the ICA vessel wall is thick with a muscular media segment, thereby offering substantial resistance to vascular compromise. By comparison, cortical veins and dural sinuses, being low pressure compartments with thin walls, are frequently compromised by meningiomas.⁸ The tumour's slow growth rate, however, allows for development of substantial collateral drainage, and as a result, cortical infarction attributable to venous insufficiency has only been reported postoperatively after injury to these compensatory pathways.⁹

The rate at which meningiomas present with symptoms of cerebral ischaemia is unknown. In an attempt to estimate the incidence at which meningiomas manifest symptoms of cerebral ischaemia by ICA compression, we reviewed retrospectively the medical records of 1617 patients with meningiomas evaluated by the surgical neuropathology service at our institution from 1985 to 2001. We identified three patients with meningeal involvement of the ICA as well as neurological symptoms that could be attributed to ICA compression. The first patient had a

parasellar/medial sphenoid wing meningioma that narrowed the right ICA within the cavernous sinus and presented with progressive left hemiparesis. The second patient had a petroclival meningioma that encased the left ICA and presented with right upper extremity paresthesias. The third patient had a frontobasal meningioma that involved the right ICA and presented with evolving left hemiparesis. Thus, while meningiomas frequently involve intracranial portions of the ICA, we estimate the incidence of meningioma related cerebral ischaemia by carotid artery compression to be only 3 of 1617 tumours or 0.19%.

In conclusion, we describe two cases of cerebral infarction as a result of carotid artery compression by a meningioma. We hypothesise that meningiomas typically do not compromise the ICA significantly because of the slow growth rate and non-invasive nature of the tumour, as well as the high arterial pressures of the ICA. Consequently, cerebrovascular insufficiency is an exceedingly uncommon presentation for meningioma.

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Parkinsonism associated with a serotonin and noradrenaline reuptake inhibitor, milnacipran

Milnacipran is a new class of antidepressant, a dual serotonin (5-HT) and noradrenaline (norepinephrine) reuptake inhibitor (SNRI).¹ It shows no affinity for neurotransmitter receptors.¹ The use of selective serotonin reuptake inhibitor (SSRI) has been associated with the occurrence and worsening of parkinsonism.^{2,3} However, SNRI induced parkinsonism has not been reported. A case is reported here in which severe parkinsonism occurred in association with the use of milnacipran.

A 83 year old woman was prescribed 200 mg of etidronate disodium once daily, and 0.25 µg of calcitriol for osteoporosis. In July 2001, she was prescribed 15 mg of milnacipran twice daily to alleviate her depressive state. Four months after starting milnacipran, she developed gait disturbance and tremors of the fingers and hands. Her family noticed tilting of her trunk to the left. The gait gradually deteriorated. In December 2001, she became unable to walk unaided. No other medications had been previously prescribed. She was referred to our clinic.

On examination, she was alert. Her face was expressionless, and she spoke in a low voice. Her cranial nerve functions were intact. Barré arm sign was negative. Bradykinesia and plastic rigidity were evident in her four limbs, which showed no obvious laterality. The rigidity was more marked in the proximal musculature. She had resting and postural tremors in the fingers and hands on both sides. Tendon reflexes were normal. Pathological reflexes were negative. The complete blood count, electrolytes, blood urea nitrogen, creatinine, liver function tests, and glucose were normal. Cranial magnetic resonance images demonstrated multiple small infarcts in the thalamus, basal ganglia, and cerebral white matter on both sides.

Because drug induced parkinsonism was suspected, milnacipran was withdrawn. In a

few days, she could walk without assistance. Four weeks after withdrawal of the drug, she had slight rigidity and mild bradykinesia. Treatment with 300 mg of L-dopa and 30 mg of carbidopa failed to further improve her motor function. Thus, it was unlikely that she had Parkinson's disease. A rechallenge procedure with milnacipran was not done, for she was no longer depressive. Because the temporal relation between the ingestion of milnacipran and the occurrence of parkinsonism was so noticeable, it is highly probable that milnacipran caused the severe parkinsonism. Because milnacipran is not metabolised by the hepatic cytochrome P450 system,¹ it is unlikely that concurrent use of etidronate disodium and calcitriol affected plasma concentration of milnacipran.

Although several lines of evidence suggest that dopamine release in the striatum is regulated by serotonin, the effects of serotonin and SSRI on dopamine release in the striatum of normal animals are disputed. Some studies have demonstrated that stimulation of the 5-HT(1A) receptors inhibits dopamine release and tyrosine hydroxylation in the striatum. In the striatum of the animals with nigrostriatal dopaminergic denervation, 5-HT(1A) receptor density was upregulated.⁴ The density of dopamine D2 receptors in the striatum was increased after repeated administration of milnacipran.⁵ Infarcts in the basal ganglia might have impaired such adaptive changes in the dopaminergic system, rendering the patient susceptible to milnacipran induced parkinsonism. To my knowledge, this is the first reported case of parkinsonism associated with the use of SNRI. Clinicians should be aware that not only SSRI but SNRI can cause severe parkinsonism.

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The relation between daytime sleepiness, fatigue, and reduced motivation in patients with adult onset myotonic dystrophy

Daytime sleepiness, apathy, and lack of motivation are established clinical manifestations of myotonic dystrophy.^{1,2} A recent study showed that modafinil reduced daytime sleepiness and average sleep latency in a group of nine patients with myotonic

dystrophy.³ This finding suggests that daytime sleepiness in patients with myotonic dystrophy and without obstructive sleep apnoea might be central in origin. A magnetic resonance imaging study indeed found evidence for a possible association between cerebral abnormalities in myotonic dystrophy and excessive daytime sleepiness.⁴ Although several studies have measured levels of fatigue with validated questionnaires in different neurological patient populations,^{5,6} fatigue questionnaires have not yet been related to the symptoms of daytime sleepiness in myotonic dystrophy. With the results of the modafinil study mentioned above in mind, our goal was to test the relations between excessive daytime sleepiness, experienced fatigue, and reduced motivation.

Methods

Patients

The study was conducted at the outpatient clinic of the Neuromuscular Centre Nijmegen, based at the Institute of Neurology of the University Medical Centre Nijmegen in the Netherlands. Consecutive ambulant patients with a genetically confirmed diagnosis of (adult onset) myotonic dystrophy and an expanded CTG repeat on chromosome 19q13.3 (DM1) were invited to take part. Fatigue was not a criterion for inclusion, and the patients came to the hospital for their regular visits. Those willing to participate were asked to complete the questionnaires at home and then send them back to the hospital.

Data were collected on 32 patients (16 female/16 male), mean age 43.8 years (range 22 to 73), and mean complaint duration 10.1 years (range 1 to 35). Myotonia and muscle weakness were rated using the five point muscular disability rating scale (MDRS).⁷ The scores in this group ranged from 0 (absent myotonia and muscle weakness) to 4 (severe proximal muscle weakness and wheelchair dependence), and the mean (SD) MDRS score for the group was 2.3 (1.1) (range 0 to 4).

Measurements

Daytime sleepiness

Three items (Nos 2, 5, and 7) of the subscale sleep/rest of the sickness impact profile refer specifically to increased daytime sleepiness.⁸ These three items ("I feel continuously like dozing off"; "I am often hanging around half asleep"; "I sleep more during the day") were summed, and a score > 0 was taken as an indication of increased sleepiness.

Fatigue severity

The subscale "fatigue severity" of the checklist individual strength (CIS) measures the experience of fatigue associated problems during the previous two weeks. The CIS-fatigue severity scale contains eight items that can be scored on a seven point Likert scale. Scores can range between 8 and 56; higher scores indicate higher levels of fatigue, and scores exceeding 40 points are considered to indicate severe fatigue.^{5,6,9}

Reduced motivation

The CIS subscale "reduced motivation" contains four items that are also scored on a seven point Likert scale (score range 4 to 28). Higher scores (range 4 to 28) are indicative of taking less initiative and of decreased motivation.⁹

Statistics

Independent *t* tests were used to compare the groups of patients with and without sleepiness symptoms with respect to their mean

CIS-fatigue, CIS-lack of motivation, and MDRS scores. Significance testing was two sided, with α set at 0.05.

Results

Ten (31%) of the 32 patients answered positively on one or more of the three sleepiness items. The patients were then divided into a group which reported at least one of the three sleepiness symptoms (sleepiness; *n* = 10) and a group which reported no sleepiness symptoms (non-sleepiness; *n* = 22). Independent *t* test showed no significant differences between the mean CIS-fatigue scores of the two groups (sleepiness, 44.6 (7.5); non-sleepiness, 41.0 (10.2); *t* = 0.98, *p* = 0.33), but there was a significant difference for the CIS-reduced motivation score. The sleepiness group reported a significantly greater reduction in motivation than the non-sleepiness group (sleepiness, 22.5 (3.5); non-sleepiness, 15.1 (4.8); *t* = 4.35, *p* < 0.001). The groups did not differ with respect to their MDRS scores (mean MDRS in the sleepiness group, 2.2 (1.5); in the non-sleepiness group, 2.4 (1.0); *t* = -0.4, *p* = 0.69). The MDRS score was also not significantly correlated with the CIS-fatigue score (Spearman ρ = 0.19, *p* = 0.32).

Discussion

Almost one third of this group of consecutive, ambulatory, adult onset myotonic dystrophy patients reported daytime sleepiness. This proportion is comparable with that in the study by Rubinshtein *et al.* in which 39% of 36 adults with non-congenital myotonic dystrophy were identified as hypersomnolent.² Another study also found that patients with myotonic dystrophy or Charcot-Marie-Tooth disease reported more daytime sleepiness than healthy controls, but that the majority of patients with myotonic dystrophy had daytime sleepiness scores below the proposed cut off on the Epworth sleepiness scale.¹⁰ In the two daytime sleepiness studies mentioned in our introduction, only small numbers of patients were studied (9 and 11),^{3,4} so comparisons of the incidence of daytime sleepiness are rather difficult. However, the fact that we studied consecutive patients makes a bias towards those with fewer symptoms of daytime sleepiness unlikely.

The mean fatigue scores of both the sleepiness group and the non-sleepiness group exceeded the cut off for abnormal fatigue and thus warrants a more extensive study of possible determinants of abnormal fatigue in this multisystem disorder. The findings that the fatigue scores were increased independently of sleepiness, and the fact that neither symptom was associated with the MDRS, suggests that different pathophysiological mechanisms underlie these clinical manifestations. Further assessment of the relation between these independent symptoms and, for example, the endocrinological and neurological status of the patients is required. Post hoc assessment of 21 of our group of patients showed that none of them suffered from thyroid dysfunction, while the prevalence of abnormal sleepiness (38%) and the mean fatigue score of these 21 patients resembled those of the 11 other patients on whom no thyroid function data were available. These findings suggest that abnormal sleepiness or fatigue may occur in myotonic dystrophy despite normal thyroid function.

In the light of these results we would like to advocate the simultaneous use of both daytime sleepiness and fatigue outcome measures in future treatment and fatigue studies.

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