



## Distal myopathy with tubular aggregates: a new phenotype associated with multiple deletions in mitochondrial DNA?

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*J. Neurol. Neurosurg. Psychiatry* 2002;73;207-208  
doi:10.1136/jnnp.73.2.207

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## LETTERS

### Prolonged hemiplegic migraine associated with unilateral hyperperfusion on perfusion weighted magnetic resonance imaging

Hemiplegic migraine (HM) is an unusual subset of migraine with aura, in which headache is associated with unilateral motor deficits, thought to be attributable to an underlying calcium channelopathy.<sup>1</sup> In some cases the neurological dysfunction may outlast the headache and persist for many days. In the initial stages, hemiplegic migraine may mimic cerebral infarction. Within the first few hours after stroke, both computed tomography and magnetic resonance imaging (MRI) are often normal. However, more information can be gained using diffusion (DWI) and perfusion weighted imaging (PWI), which are much more sensitive to acute events in cerebral ischaemia. A recently reported post-processing technique (factor analysis of dynamic studies FADS) can be applied to PWI to generate images representing arterial ("early") and venous ("late") contributions to signal intensity.<sup>2</sup> This report outlines the findings arising from the application of multimodal MRI techniques to a patient with prolonged hemiplegic migraine.

#### Case report

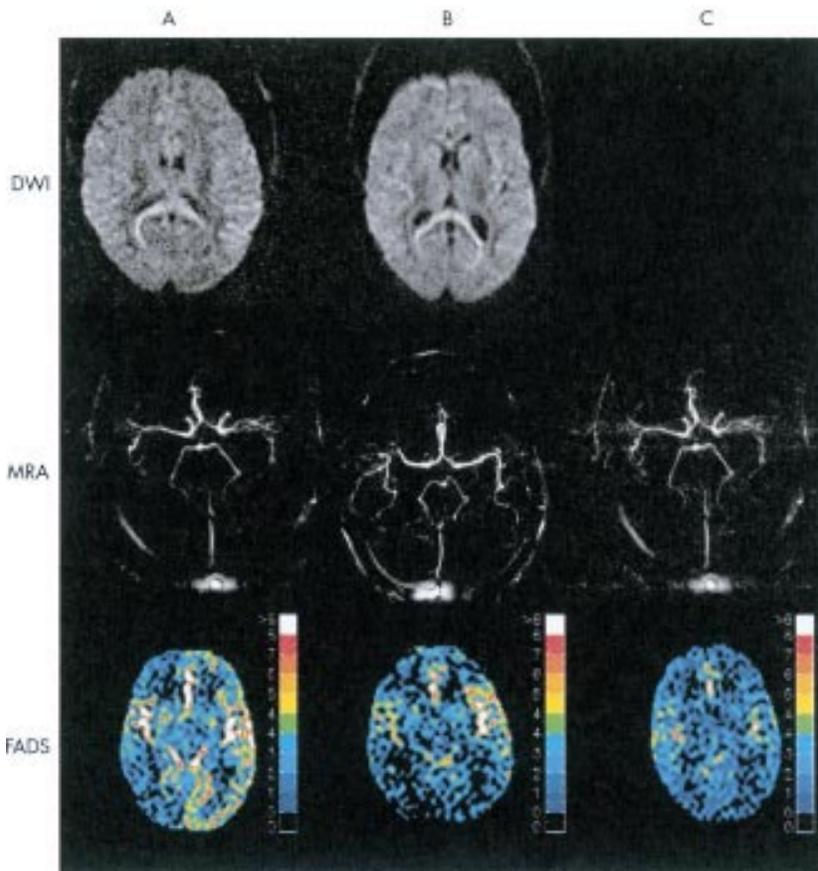
A 21 year old woman, with a long history of familial HM, presented with a six hour history of headache, nausea, right sided weakness, and expressive dysphasia. Her maternal aunt had also suffered with the condition. Genetic testing for CACNA 1A had not been performed. In previous episodes, her symptoms had resolved within four hours, so a clinical diagnosis of migraine related stroke was made and she underwent urgent T<sub>2</sub> weighted MRI and MR angiography with DWI and PWI. FADS was applied to the perfusion weighted images. These sequences revealed no large vessel obstruction and normal DWI, thus excluding infarction, but there was gross hyperperfusion of the left hemisphere on the early FADS images (fig 1A). The late FADS images, representing venous signal were unremarkable (data not shown).

Her headache persisted for the next 10 days. However, the right limb weakness improved over the next four days, but the dysphasia persisted. Repeat PWI on day four showed focal hyperperfusion of the inferior frontal lobe (fig 1B). A follow up scan at three months, at which time she was totally asymptomatic, showed complete resolution of these appearances (fig 1C).

#### Comment

This report demonstrates multimodal MRI findings in a case of HM and that by applying the techniques of DWI, PWI, and FADS, it was shown that hyperperfusion existed in the phase of neurological deficit thus excluding acute stroke.

There have been conflicting views regarding whether migraine is primarily attributable to vascular or neuronal dysfunction. One of the earliest models of its pathogenesis proposed that symptoms of migraine aura were related to hypoperfusion and ischaemia and that the subsequent headache was related to reactive hyperaemia. Initial studies of regional cerebral blood flow initially seemed to support



**Figure 1** Multimodal MRI findings during the course of an episode of hemiplegic migraine. (A) Day 1, 6 hours post-onset. Dense hemiparesis, aphasia, and severe headache associated with normal diffusion weighted imaging (DWI), magnetic resonance angiography (MRA), and gross hyperperfusion of the left hemisphere on factor analysis of dynamic studies (FADS). (B) Day 4. Weakness improving, dysphasic, persistent headache. Hyperperfusion of inferior frontal lobe on FADS. (C) Three months. Asymptomatic. Full resolution of perfusion changes. (DWI not repeated at three months).

this theory, demonstrating hypoperfusion in the aura phase and hyperperfusion in the headache phase. However, the observation by some authors that hypoperfusion may outlast the aura symptoms and extend into the headache phase makes a simple vascular pathogenesis less likely.

Our findings of normal DWI appearances associated with hyperperfusion in the context of neurological deficit and headache also argue against an ischaemic mechanism. The presence of hyperperfusion affecting the entire hemisphere and therefore not respecting anatomical boundaries is difficult to explain on a simple vascular model and may therefore be a secondary phenomenon resulting from underlying neuronal dysfunction. The concept of a primarily neuronal dysfunction in migraine has been drawn from parallels with the experimental phenomenon of "cortical spreading depression" (CSD) described by Leao.<sup>3</sup> The rate of propagation of CSD is similar to Lashley's estimate of the rate of progression of symptoms during the human migrainous visual aura.

Subsequent studies have shown that in migraine with and without aura there is a similar spreading hypoperfusion across the cerebral hemispheres. This has also been demonstrated in HM.<sup>4</sup> However, hemispheric hyperperfusion during HM, correlating with contralateral hemiplegia has also been previously reported.<sup>5</sup> On the balance of available

evidence, it seems likely that in the early phase of migraine there is spreading cortical oligoemia and that this is linked to a neuronal dysfunction analogous to that reported in CSD. Oligoemia was not found in our patient although this may be because she was not scanned at the very onset of her attack.

HM has been linked to mutations in the CACNA 1A gene, which encodes a P/Q type calcium channel.<sup>1</sup> This channel is located on presynaptic membranes and is tightly coupled to neurotransmitter release. Conceivably, CACNA 1A mutations could cause neuronal membrane instability resulting in episodic loss of neural control of cerebrovascular tone and that, as neuronal membrane function recovers, neurogenic control of rCBF is regained. It is of interest, in this respect, that the recovery of neurological function in our patient was closely mirrored by the restoration of normal cerebral perfusion.

In conclusion, we show that the use of multimodal MR in a case of acute hemiparesis in a patient with HM was effective in excluding cerebral infarction. FADS analysis demonstrated reversible focal hyperperfusion of the cerebral cortex correlated with the clinical distribution of neurological deficit. Recovery was mirrored by the restoration of a normal vascular pattern.

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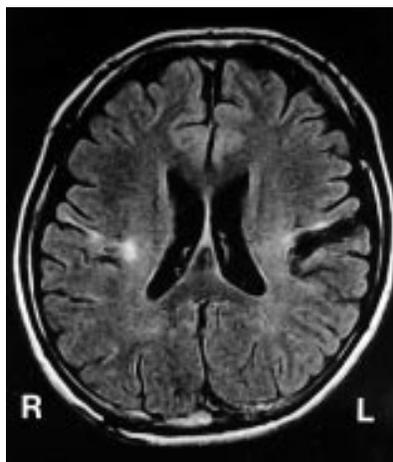
### Slowly progressive Foix–Chavany–Marie syndrome associated with chronic herpes simplex encephalitis

Foix–Chavany–Marie syndrome (FCMS) is characterised clinically by automatic voluntary dissociation of orofacial motility. It is caused by bilateral anterior opercular lesions and its aetiology is heterogeneous.<sup>1</sup>

Clinically, most cases of FCMS can be divided into three categories—*developmental*, *acute/subacute*, and *transient*.<sup>2</sup> The most common cause of the developmental form is congenital bilateral anterior opercular dysplasia. The acute/subacute form is usually caused by infection in the CNS or cerebrovascular disease. The underlying pathogenesis of transient form is epilepsy. Rare variant cases of FCMS presenting with a slowly progressive clinical course have also been reported.<sup>3</sup> We describe the clinical features of a patient with adult onset, slowly progressive FCMS, thought to be associated with chronic herpes simplex encephalitis.

A 29 year old Japanese woman developed epilepsy of generalised tonic-clonic type at the age of 15 and had been taking anti-convulsants for 14 years. She had had a normal pregnancy and delivery. Developmental assessment during schooling showed normal motor and psychological ability.

At the age of 27, she presented with dysarthria and dysphagia, which deteriorated gradually during the following 18 months. She also had difficulty with fine movements of her right arm at the age of 29. On admission, her voluntary orofacial motility was disturbed bilaterally, while emotional and involuntary facial movements were well preserved. Movement of the pharynx was slightly disturbed and gag and pharyngeal reflexes were reduced. She had difficulty in moving her tongue laterally. The other cranial nerves were normal. There was no sensory deficit or weakness in the limbs. Deep tendon reflexes of her right arm were slightly increased and her plantar responses were flexor. Rapid alternating movements of the right arm showed some clumsiness. A full scale IQ on the Wechsler adult intelligence scale, revised



**Figure 1** Magnetic resonance imaging on FLAIR sequences, showing linear high intensity lesions in the Rolandic area bilaterally and severe atrophy of the operculum bilaterally. Diffuse atrophy of the frontotemporal lobes was also observed.

(WAIS-R) was 80, with a verbal IQ of 85 and a performance IQ of 78. There was no similar disorder in her family members.

The concentration of IgG (7.9 mg/dl) and the IgG index (1.89) in the CSF were increased, while the protein level in the CSF (30 mg/l) and the cell count (2/mm<sup>3</sup>) were normal. IgG antibody titres for herpes simplex virus (HSV), measured by enzyme linked immunosorbent assay (ELISA) in the serum (64.6) and CSF (6.4), were also raised. The serum to CSF ratio of the HSV IgG titre was decreased at 10.1, and the IgG index for HSV was increased at 3.28. IgM was negative. Polymerase chain reaction (PCR) methods did not reveal genomes for HSV 1 or 2 in the CSF. Antibodies to other virus were not detected and antibody testing for HIV was negative in the serum.

An EEG showed generalised mild slowing without paroxysmal activity. Magnetic resonance imaging (MRI) on FLAIR sequences revealed bilateral linear high intensity lesions in the Rolandic area and severe atrophy of the operculum bilaterally, in addition to mild frontotemporal lobe atrophy (fig 1). These lesions on T1 weighted sequences showed no contrast enhancement after gadolinium administration. There was a partial defect in the body of the corpus callosum.

Treatment with acyclovir was begun but was suspended immediately because of a drug eruption. Treatment with intravenous vidarabine for 14 days was tried twice, and transient decreases of both IgG antibody titre and the IgG index for HSV in the CSF were observed on each occasion. There was no further deterioration in her neurological state after these treatments.

#### Comment

Neurological examination in our patient showed automatic voluntary dissociation of orofacial motility in addition to a disturbance of movement of the pharynx and tongue. An MRI study showed involvement of the opercular and Rolandic regions bilaterally. This combination of clinical and neuroradiological features is typical of FCMS. However, our patient is unusual for two reasons. First, the clinical course of the FCMS was of adult onset and was slowly progressive; this type of deterioration has not been reported previously either in

congenital dysplasia or in acquired acute/subacute CNS event such as stroke or infection.<sup>1</sup> Although some cases with adult onset and a slowly progressive course have been reported, the aetiology of those cases remained obscure.<sup>3</sup> Second, elevation of the IgG antibody titre and the IgG index for herpes simplex virus in the CSF showed the presence of chronic herpes simplex encephalitis. The temporal lobe is the favoured region for this. FCMS with an acute clinical course caused by herpes simplex encephalitis has been reported.<sup>4</sup>

Transient decreases in both IgG antibody titre and the IgG index for HSV after intravenous vidarabine were observed on both occasions the treatment was given. Although the correlation between increased IgG antibody for herpes simplex virus in the CSF and the chronic cerebral disturbance has not been verified, these observations support the view that chronic herpes simplex encephalitis remained active in our patient and could have been responsible for her neurological impairment. The clinical features—including the slowly progressive clinical course, the negative results of PCR testing for HSV, and the normal protein level and the cell count in the CSF—suggest that herpes simplex encephalitis was not the direct cause of the damage in the affected region. It is possible that persistent HSV infection may induce inappropriate activation of the immune system, resulting in neurocytotoxicity because of cross reactivity.

Our patient had both a partial defect of the corpus callosum and epilepsy. This combination is often observed in patients with congenital cerebral dysplasia. However, the onset of developmental FCMS is always in the early infant period and is usually associated with delayed psychomotor milestones or mental retardation.<sup>2</sup> Thus the pathogenesis in our patient is very unlikely to be explained on the basis of simple congenital dysplasia. The association between a partial defect of the corpus callosum and epilepsy in FCMS could be explained by the presence of herpes simplex virus infection dating from the fetal period. Although a necropsy proven case of FCMS that was probably caused by chronic herpes simplex encephalitis has been reported before,<sup>2</sup> the clinical course in that case was not slowly progressive. In fact there have been no previous reports of slowly progressive FCMS associated with chronic viral infection.

In conclusion, this is the first report of a case of FCMS associated with chronic herpes simplex encephalitis. Further similar cases would establish this as a variant type of FCMS.

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### Lesion responsible for WEMINO syndrome confirmed by magnetic resonance imaging

WEMINO (wall eyed monocular internuclear ophthalmoplegia) syndrome is a rare neurological impairment involving disconjugate ocular movements.<sup>1</sup> Neuroradiological findings of the lesion responsible for WEMINO syndrome have not been reported to date. We report a case of the syndrome in which cerebral magnetic resonance imaging (MRI) clearly showed a tiny isolated lesion causing this impairment.

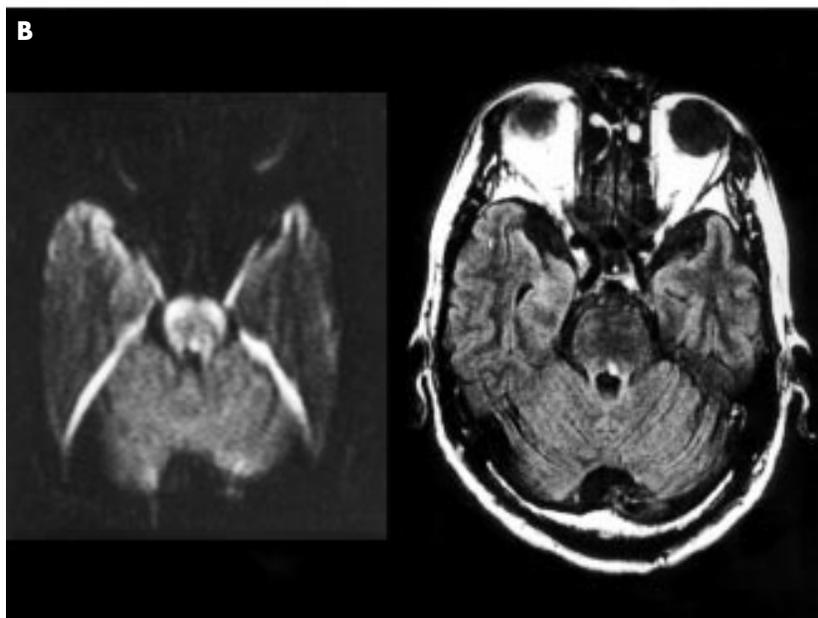
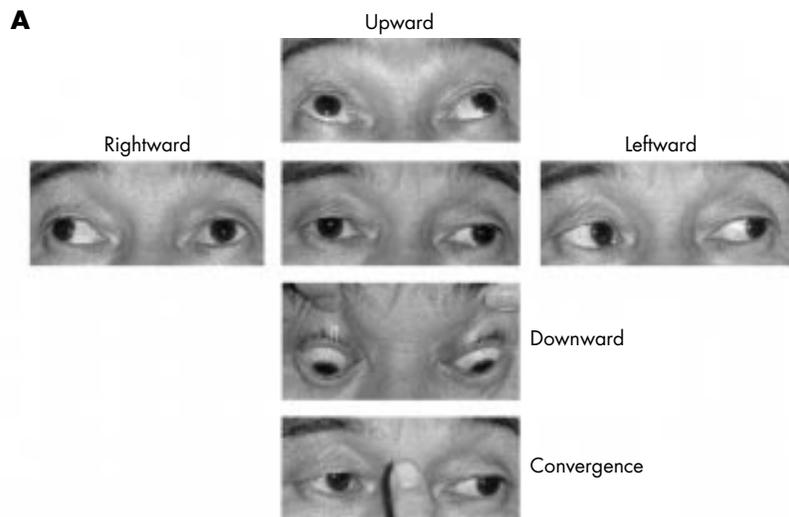
The patient was a 61 year old Japanese man who had been admitted to hospital for surgery for mitral regurgitation. He had a two year history of mitral incompetence, and mitral valve plasty was completed successfully on 21 September 2000. There were no postoperative problems.

On the afternoon of 27 September, one week after the operation, he suddenly experienced double vision, and was found to have left exotropia without blepharoptosis. On neurological examination, adduction of left eye was disturbed and it could not move beyond the midline of orbit, although full abduction was possible. Bilateral upward nystagmus was noted on forward gaze. Right ocular movement was not disturbed in any direction, but horizontal nystagmus appeared on rightward gaze. There was deficiency of left convergence. No ptosis occurred at any time. His pupils showed isocoria and responded promptly to light. Vertical ocular movement was not disturbed in either eye (fig 1A). Other neurological findings were completely normal. His ocular symptoms were summarised as comprising a left internuclear ophthalmoplegia with ipsilateral exotropia; these findings have been termed WEMINO syndrome.<sup>1</sup>

Cerebral computed tomography, undertaken immediately after onset, did not show any abnormalities.

We considered that he might have had a cerebral embolus caused by microthromboembolism following the heart surgery, but echocardiography did not show any obvious thrombus. We speculated that the responsible lesion was isolated in the area that included the medial longitudinal fasciculus because his impairments were limited to the ocular symptoms described above. He had been given warfarin potassium since 25 September, but the anticoagulant effect was insufficient on the day of symptom onset. Thus heparin sodium was begun intravenously in a dose of 10 000 units/day, and the dose of warfarin was gradually increased.

MRI performed 20 hours after onset showed a tiny isolated lesion at the left paramedian pontine tegmentum just adjacent to the fourth ventricle on both fluid attenuated inversion recovery (FLAIR) imaging and diffusion weighted MRI (fig 1B). This corresponds to the anatomical area of the medial longitudinal fasciculus. The tiny lesion showed high signal



**Figure 1** (A) Ocular impairment in the patient at the time of onset. Left exotropia was present on forward gaze without blepharoptosis. Adduction of left eye was disturbed and it never reached beyond the midline of the orbit, although full abduction was possible. Right ocular movement was not disturbed in any direction, but horizontal nystagmus appeared on rightward gaze. There was deficiency of left convergence. Vertical ocular movement of both eyes was undisturbed. (B) Cerebral magnetic resonance imaging (MRI): a tiny isolated lesion was present at the left paramedian pontine tegmentum just adjacent to the fourth ventricle on both axial fluid attenuated inversion recovery (FLAIR) imaging (right) and diffusion weighted MRI (left). The tiny lesion causing WEMINO syndrome showed high signal intensity on both MRI modes.

intensity on FLAIR imaging and diffusion weighted MRI, and low signal intensity on T1 weighted MRI. These MRI findings are typical of an acute lesion resulting from cerebral infarction. Other parts of the brain showed no abnormalities. Cerebral magnetic resonance angiography showed neither stenosis nor occlusion of any of the major vessels.

The ocular impairment began to improve by the third day after onset. On the seventh day, the left exotropia on forward gaze had disappeared, and the left internuclear ophthalmoplegia had begun to improve. By the 13th day, eye position and ocular movement were completely normal, and on the 14th day the high signal intensity on FLAIR MRI had diminished.

There are various syndromes that involve disconjugate ocular movement and eye position simultaneously. WEMINO syndrome consists of symptoms similar to internuclear ophthalmoplegia with ipsilateral exotropia.<sup>1</sup> There are two other syndromes supposedly involving a combination of injury to the medial longitudinal fasciculus and exotropia; these are paralytic pontine exotropia (PPE),<sup>2,3</sup> and non-paralytic pontine exotropia (NPPE).<sup>4,5</sup> However, WEMINO syndrome can be discriminated from both PPE and NPPE, because the latter show exotropia on the side contralateral to the injured medial longitudinal fasciculus. There have been few reports describing WEMINO syndrome, and up to

now no lesions in the central nervous system have been identified as a cause of the syndrome. Johnston and Sharpe reported that the neuropathological findings in one case of WEMINO syndrome were confined to a lesion of the pontine tegmentum, sparing the oculomotor nucleus.<sup>1</sup> As the exotropia in our WEMINO patient disappeared within a short space of time, the symptom could be regarded as an acute phase phenomenon accompanying injury to the medial longitudinal fasciculus. Thus exotropia in patients with WEMINO syndrome might not be confirmed at an appropriate stage, as in PPE and NPPE patients.<sup>2,3</sup>

Cerebral MRI in our patient showed a tiny isolated lesion corresponding to the medial longitudinal fasciculus in the pontine tegmentum. This report is the first in which MRI has shown that WEMINO syndrome can arise from damage confined to the area of the medial longitudinal fasciculus.

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## A relapsing-remitting type of ocular myasthenia gravis without typical muscle fatiguability

Myasthenia gravis (MG) is an autoimmune disorder causing postsynaptic impairment of neuromuscular transmission.<sup>1–3</sup> Ocular,

bulbar, or proximal limb muscles are most frequently affected, and weakness worsens during exercise. Recently, variants of MG have been described that deviate notably from the typical clinical presentation of MG, including “MG of respiratory muscles” and a “distal type”.<sup>4</sup>

The neurological department of the Innsbruck University Hospital serves as a single referral centre for all cases of MG in the state of Tyrol. Over the past 20 years we have been prospectively following 84 patients with MG, corresponding to a prevalence rate of 116 per million.

Our patient series includes five men and women with an unusual relapsing-remitting variant of ocular MG that lacks muscle fatiguability and most typical laboratory features of neuromuscular junction disorders and, thus, may evade correct diagnosis. All these patients reported acute or subacute onset (overnight in three cases) of non-fluctuating diplopia with gradual spontaneous remission over a 2–20 week period. Further episodes (one to six)—none of which was provoked by infection, immunisation, or medication—emerged at intervals of 1–80 months. The pattern of ocular muscles involved varied from episode to episode. Ptosis was usually mild or absent. Extensive laboratory investigations involving blood analysis (erythrocyte sedimentation rate, antinuclear, antiacetylcholine receptor, and antistriated muscle antibodies, circulating immune complexes, routine blood tests, thyroid hormones, etc), analysis of cerebrospinal fluid (three patients), an edrophonium (Tensilon Roche Laboratories, Nutley, New Jersey, USA) test, electrophysiological examinations, magnetic resonance imaging of orbita, sinus cavernosus, and cerebrum and computed tomography of the chest were all unremarkable or negative. Oral pyridostigmine (180 mg daily) was tried in one patient over a period of two weeks but it had no clinical effect. Table 1 summarises the main clinical and laboratory characteristics of the patients. Because of the unusual clinical presentation, especially the absence of muscle fatiguability—the clinical hallmark of MG—and the normal results of standard laboratory procedures (Tensilon test, repetitive nerve stimulation, and measurement of acetylcholine receptor antibodies), MG was not diagnosed in any of the patients initially. All were assumed to suffer from recurrent cranial nerve palsy or midbrain lesions (table 1). Later in the course of disease

the correct diagnosis was established by single fibre electromyography of the right extensor indicis muscle (pathological jitter) and the observation of a few episodes of typical ocular MG. All patients responded excellently to a medium dose of prednisone and remained asymptomatic under a low maintenance dose (4–8 mg) but relapsed weeks to months after further tapering or discontinuation of corticosteroids (four of the five patients). None developed generalized MG during follow up.

Except for a few anecdotal case reports,<sup>5</sup> this unusual presentation of MG has not yet been addressed in the literature or mentioned in standard neuromuscular textbooks.<sup>1–3</sup> Our five patients represent 10% of all subjects with ocular MG seen in the single referral centre for the state of Tyrol, suggesting a significant minimal prevalence of this type of disease. Single fibre electromyography is necessary to establish an early diagnosis and, thus, should be an obligatory component in the diagnostic investigation of patients with diplopia or ptosis of unknown origin, even in the absence of muscle fatiguability.

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Competing interests: none declared

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**Table 1** Clinical and laboratory characteristics of five patients with an unusual variant of ocular myasthenia gravis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Clinical features					
Age at onset (years)	40	50	44	37	63
Sex	F	M	F	F	M
Prominent ptosis	–	–	+	–	–
Muscle fatiguability (at disease onset)	–	–	–	–	–
Subacute disease manifestation	+	+	+	+	+
Number of episodes	7	5	2	4	4
Mean duration of episodes (weeks)*	3	12	2	9	6
Generalisation	–	–	–	–	+
Concomitant diseases	–	–	Hypothyreosis	–	–
Diagnostic findings at disease onset					
MRI lesions in orbita/cerebrum	–	–	–	–	–
Tensilon test	–	–	–	–	–
Decrement in repetitive nerve stimulation (5 Hz)	–	–	–	–	–
Anti-AChR antibodies	–	–	–	–	–
Diagnosis initially proposed	Midbrain lesion	Incomplete external oculomotor nerve paresis	Bilateral external oculomotor nerve paresis	Abducens nerve paresis	Tolosa-Hunt syndrome

\*Episodes without corticosteroid therapy only. –, Absent or negative; AChR, acetylcholine receptor; F, female; M, male; MRI, magnetic resonance image.

## Acute dopaminergic challenge tests to assess postural/kinetic tremor of different origin: a case report

In Parkinson's disease, a postural/kinetic tremor may occur in association with the classical resting tremor. According to the consensus statement of the Movement Disorder Society on tremor,<sup>1</sup> this association is classified as type I (classical parkinsonian tremor) if the difference between the frequencies of postural/kinetic tremor and resting tremor is less than 1.5 Hz; and as type II if this difference is more than 1.5 Hz. In type I tremor, resting tremor and postural tremor share common pharmacological properties, responding to levodopa.<sup>2,3</sup> Type II tremor (that is, a predominant postural/kinetic tremor associated with a resting tremor of a lower frequency) is considered to be a combination of essential tremor and parkinsonian tremor, and is reported in between 3% and 24% of the patients diagnosed as having Parkinson's disease.<sup>3</sup> Though postural/kinetic tremor and resting tremor may show some overlap in their electrophysiological properties in Parkinson's disease, the postural/kinetic component does not respond to levodopa.<sup>3</sup> Nevertheless, clinical criteria may be insufficient to differentiate between Parkinson's disease and essential tremor.

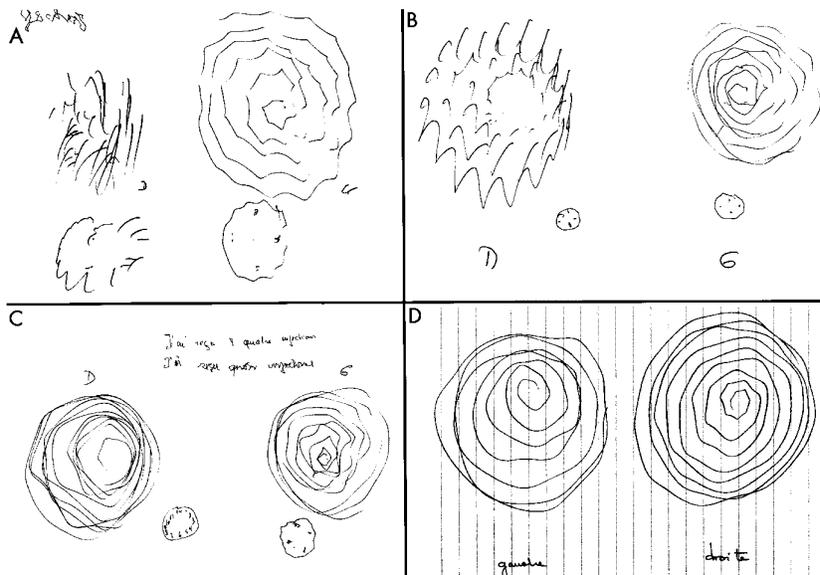
We report a case of a 70 year old patient affected by essential tremor and Parkinson's disease, in whom acute dopaminergic challenge tests allowed us to differentiate between the two components of severe bilateral arm tremor.

Acute dopaminergic challenge tests, which are well accepted as a diagnostic tool in Parkinson's disease, may be helpful in various clinical settings—for example, postural/kinetic tremor of mixed origin—by identifying the parkinsonian component and predicting the responsiveness of the tremor to dopaminergic treatment.

A 70 year old right handed woman was referred to us because of disabling postural tremor and resting tremor of both hands. At age 61, the patient had developed a postural/kinetic right handed tremor. Two years later, she had also developed resting tremor in the same limb. The resting tremor and the postural/kinetic tremor worsened progressively, with significant impairment of her daily activities and social life. Two months before our first evaluation, she had started to notice a postural/kinetic tremor of her left upper arm.

On neurological evaluation, she had mild asymmetrical parkinsonism with a bilateral resting tremor, a postural/kinetic tremor of the upper limbs, and a moderate voice tremor. The UPDRS motor score (items 18–31) in the off-state was 27. The upper limb right sided resting tremor was constant, of moderate amplitude, and with a frequency of 5 Hz on surface EMG; the left sided resting tremor was intermittent and milder than on the right. A postural/kinetic tremor of both upper limbs was also present; this was marked and disabling on the right, mild and constant on the left (fig 1, panel A). The kinetic tremor was more pronounced than the postural component on the left.

The patient underwent acute dopaminergic challenge tests, including a test with a single dose of levodopa-carbidopa 200/50 mg, and on the next day, a sequential test with increasing doses (1.5 mg, 3 mg, 4.5 mg, 6 mg) of subcutaneous apomorphine. Clinical evaluation was performed before each single dose



**Figure 1** Changes in postural/kinetic tremor as shown by drawing a spiral under different conditions: (A) off-state; (B) after a levodopa acute challenge test; (C) after an apomorphine (6 mg) acute challenge test; (D) under chronic treatment with levodopa, pergolide, and primidone.

(off-state), and after one hour for levodopa and 30 minutes for apomorphine by the UPDRS scale (motor examination, items 18–31) and writing (writing a phrase and drawing a spiral) (fig 1, panels B and C).

The levodopa/carbidopa test mainly improved akinesia and rigidity, the right sided postural/kinetic tremor and resting tremor being improved by only 33%. The left sided resting tremor and postural/kinetic tremor did not change significantly. A progressive improvement in the tremor was observed with increasing doses of apomorphine, with total disappearance of the right sided resting tremor at a dose of 6 mg, and of the left sided resting tremor at 1.5 mg. The right postural component was reduced by 60% by 1.5 mg of apomorphine and disappeared at the 6 mg dose, while a mild kinetic tremor persisted unchanged. The left sided postural/kinetic tremor did not change.

A diagnosis of essential tremor and Parkinson's disease was made, and antiparkinsonian treatment with levodopa/benserazide 100/25 mg three times daily and pergolide 0.25 mg three times daily was started. On this treatment, the resting tremor improved on the right side and disappeared on the left. In contrast, the postural/kinetic tremor persisted unchanged on the left, though it clearly improved on the right, allowing the patient to perform most of her daily activities. A therapeutic trial with primidone (Mysoline) was started, and this resulted in substantial improvement in the left sided tremor and a further positive effect on the right sided residual postural/kinetic tremor (fig 1, panel D).

Our patient presented with a combination of essential tremor and Parkinson's disease, with a differential response of the tremors to acute dopaminergic challenge tests. The opposite lateral predominance of the tremors (right for Parkinson's disease and left for essential tremor) allowed us to differentiate the pharmacological response of the two tremors more easily; the resting tremor responded to apomorphine, disappearing at the highest dose on the right side and at lower

doses on the left side, while the postural/kinetic tremor showed a different response on the two sides, nearly disappearing on the right (except for a mild kinetic tremor), while persisting almost unchanged in both its postural and kinetic components on the left. The dopaminergic tests clearly indicated the presence of a postural/kinetic tremor which did not respond to dopaminergic stimulation and which was diagnosed as essential tremor. In accordance with the results of the acute challenge tests, chronic treatment with dopamine agonists and levodopa significantly improved the parkinsonian tremor (both the resting and the postural component) on the right side, while the left sided postural/kinetic tremor responded selectively to primidone.

The different pharmacological response of essential tremor and parkinsonian tremor confirms that they are separate pathophysiological entities, often difficult to distinguish on a clinical basis.<sup>3</sup> The mainstays of treatment for essential tremor include  $\beta$  adrenergic blocking drugs and primidone. The response of parkinsonian tremor to antiparkinsonian treatment is variable. Both the resting tremor and the postural tremor, which share similar electrophysiological properties (as in type I tremor) seem to respond to antiparkinsonian treatment (L-dopa or dopamine agonists)—providing an adequate dosage is given—but not to primidone or  $\beta$  blockers. When both types of tremor (essential tremor and parkinsonian tremor) coexist, combined treatment is necessary, in line with their different pathophysiology.

Dopaminergic acute challenge tests are a well accepted diagnostic tool for diagnosis and evaluation of dopaminergic responsiveness in Parkinson's disease, including parkinsonian tremor.<sup>4,5</sup> Our observations show that in particular clinical settings, such as when both essential tremor and parkinsonian tremor are suspected, acute dopaminergic challenge tests may differentiate these two entities and define the best treatment strategies.

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### Distal myopathy with tubular aggregates: a new phenotype associated with multiple deletions in mitochondrial DNA?

Multiple deletions of mitochondrial DNA (mtDNA) are recognised in association with a number of clinical phenotypes, including chronic progressive external ophthalmoplegia (CPEO) and myoneurogastrointestinal encephalopathy (MNGIE). The abnormality may be sporadic or inherited in a recessive or autosomal dominant fashion and is generally considered to be secondary to an abnormality of nuclear DNA.<sup>1</sup>

Tubular aggregates (TA) are histological bodies consisting of densely packed, double walled tubules 50–70 nm in diameter, originating from the lateral sacs of the sarcoplasmic reticulum.<sup>2</sup> Their functional significance remains controversial: in a small group of progressive myopathies, TA form the dominant or even the sole structural abnormality, but more commonly they appear as an accessory histopathological feature in a wide variety of neuromuscular disorders, both inherited and acquired. The strongest association appears to be with periodic paralysis and myotonic disorders, but the finding is by no means consistent, and TA are never more than a minor element of the overall myopathology.<sup>2</sup>

To the best of our knowledge, an isolated late onset distal myopathy has never been described in association with multiple mtDNA deletions, and high densities of TA have not previously been described in association with mitochondrial myopathy. The present case therefore illustrates two original clinicopathological observations and may be a novel clinical phenotype.

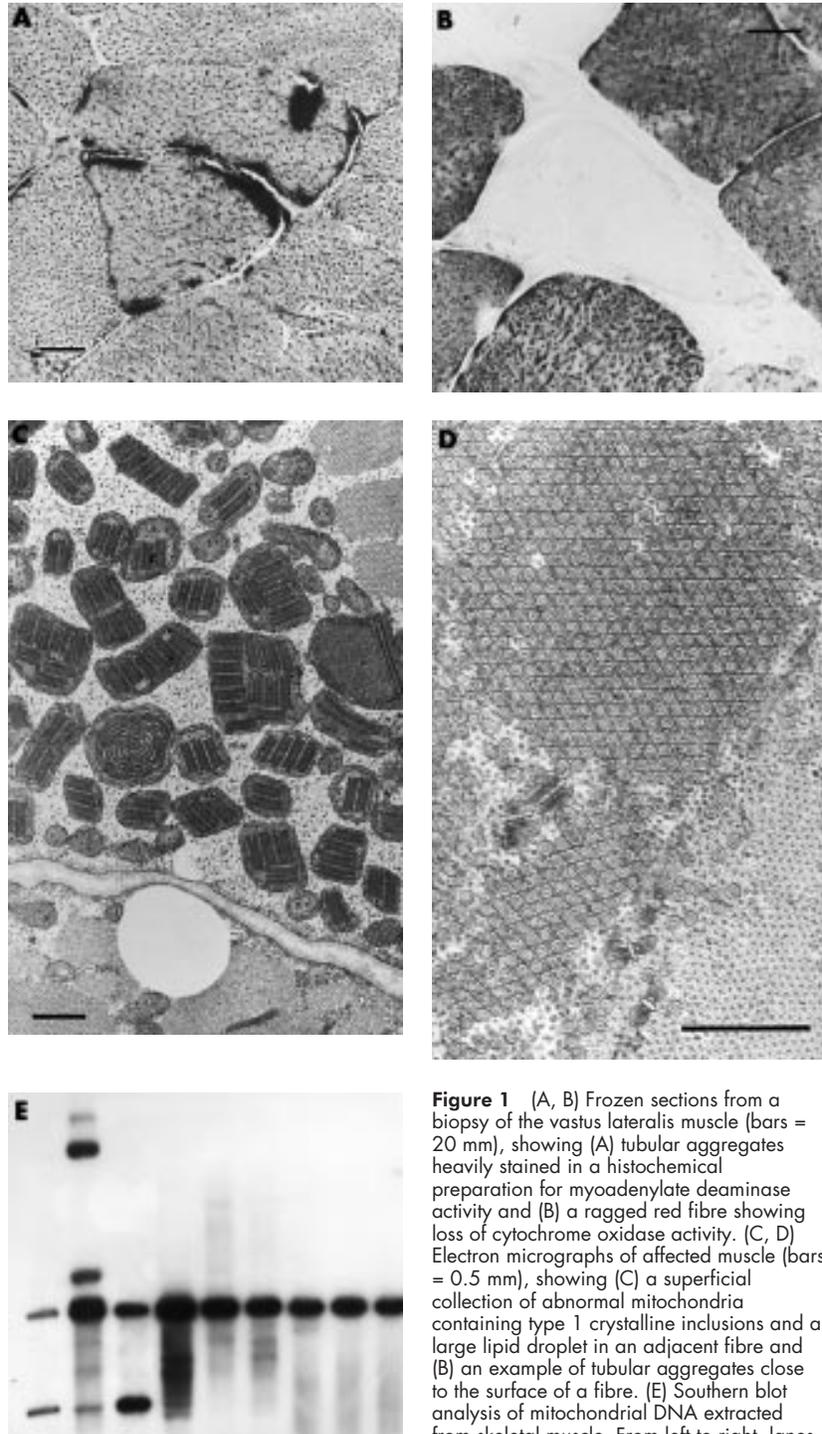
A 73 year old man presented with a history of diffuse muscular pain and progressive gait disturbance over two years. The pain, which preceded the gait disturbance, affected his lower back, buttocks, and upper thighs, was maximal when he was supine, and was not exercise induced. He later noticed that his walking was becoming slower, and then he developed a tendency to drag his feet and trip over. Subsequently, arm elevation and fine finger movements became mildly affected. There were no symptoms of bulbar or sphincter dysfunction. Over the previous five years he had begun to suffer from mild angina and

was treated successfully with metoprolol, but his medical history was otherwise unremarkable—specifically, there was no history of gastrointestinal problems. There was no family history of neurological illness.

On examination, cranial nerves were normal, with no ophthalmoplegia or facial weakness. There was symmetrical weakness of proximal and distal muscles in all four limbs, which was most pronounced distally, espe-

cially affecting ankle dorsiflexion (graded 3/5), giving rise to a pronounced foot-drop gait. The small hand muscles were wasted but no fasciculations were seen. All deep tendon reflexes were brisk but symmetrical and the toes downgoing.

Preliminary investigation found that the full blood count, erythrocyte sedimentation rate, renal, liver, and thyroid function, serum glucose and calcium, creatine kinase, vitamin



**Figure 1** (A, B) Frozen sections from a biopsy of the vastus lateralis muscle (bars = 20 mm), showing (A) tubular aggregates heavily stained in a histochemical preparation for myoadenylate deaminase activity and (B) a ragged red fibre showing loss of cytochrome oxidase activity. (C, D) Electron micrographs of affected muscle (bars = 0.5 mm), showing (C) a superficial collection of abnormal mitochondria containing type 1 crystalline inclusions and a large lipid droplet in an adjacent fibre and (B) an example of tubular aggregates close to the surface of a fibre. (E) Southern blot analysis of mitochondrial DNA extracted from skeletal muscle. From left to right, lanes 1–3 (deletion control): PVU digest, *Sna*BI digest, *Bam*HI digest; lanes 4–6 (patient): PVU digest, *Sna*BI digest, *Bam*HI digest; lanes 7–9 (normal control): PVU digest, *Sna*BI digest, *Bam*HI digest.

B12 and red cell folate, immunoglobulins and electrophoresis, prostate specific antigen, an autoimmune screen, antineuronal antibodies, and antibodies against voltage gated calcium and potassium channels were all normal or negative. A chest radiograph and echocardiogram were both normal. Magnetic resonance imaging of the brain, spinal cord, lumbar roots, and plexus was normal. Cerebrospinal fluid examination showed an increased protein concentration (0.97 g/l, range 0.15–0.45), but other constituents were normal and oligoclonal bands absent.

Routine sensory and motor nerve conduction studies of the upper and lower limbs did not find any evidence for a peripheral neuropathy. All F latencies were within normal limits. Repetitive stimulation of the right median nerve showed no significant amplitude decrement. Electromyographic sampling of distal lower limb muscles showed an excess of low amplitude polyphasic units of brief duration and a full interference pattern (< 1 mV) during a weak contraction. The same features were noted in an upper limb forearm muscle. Other muscles sampled also showed similar though less pronounced changes suggesting a patchy but diffuse myopathic process.

A therapeutic trial of corticosteroids (prednisolone 60 mg/day) resulted in a significant reduction in pain but no change in the weakness and walking difficulties. Pain returned when the prednisolone was withdrawn after two months. Some months later a left vastus lateralis muscle biopsy was performed and showed changes of mitochondrial pathology (1% ragged red and 8% cytochrome oxidase negative fibres) together with accumulations of neutral lipid and TA in 12% of fibres (fig 1A–D). Muscle respiratory chain analysis was consistent with a reduction in complex IV activity. Serum lactate concentration was increased at 3.12 mmol/l (range 0.5–1.65), with a lactate to pyruvate ratio of 29 (range 10–20). mtDNA analysis by Southern blotting was positive for multiple deletions (fig 1E).

Mitochondrial myopathy is characterised by the presence on muscle biopsy of ragged red fibres and abnormal mitochondria with paracrystalline inclusions. The cardinal clinical features consist of proximal muscle weakness and exercise intolerance, which may be accompanied by a variable degree of resting or exercise induced lactic acidosis. Neither pain nor distal weakness is a typical feature.

From a genetic perspective, the disorder may be related to a single mtDNA deletion, a point mutation, or multiple mtDNA deletions probably secondary to defects in nuclear genes critical to intergenomic communication.<sup>1</sup> This last group has shown great clinical heterogeneity: to date, the phenotypes described are an autosomal dominant form of (CPEO),<sup>2</sup> disorders of neuromuscular function and intestinal motility (MNGIE) associated with mutations in the thymidine phosphorylase gene,<sup>4</sup> progressive encephalomyopathy,<sup>5</sup> skeletal and cardiac myopathy in a patient with consanguineous parents,<sup>6</sup> and a familial syndrome of myopathy and parkinsonism in Sephardic Jews.<sup>7</sup>

Our patient's clinical presentation was characterised by late onset, slowly progressive myalgia without exercise induced cramps and a predominantly distal pattern of muscle weakness in the absence of gastrointestinal disturbance, cardiomyopathy, or disturbances of eye movement. In the presence of multiple mtDNA deletions, such a combination of clinical findings constitutes a novel phenotype.

The pattern of abnormality on his muscle biopsy was also of interest: the density of TA seen was in keeping with a diagnosis of "myopathy with TA",<sup>2</sup> yet the finding was clearly accompanied by a second pathological process (mitochondrial myopathy). Although multiple mtDNA mutations are sometimes seen in inclusion body myositis (a condition that shares many of the clinical features of the present case and may be missed histologically), it is difficult to provide an independent explanation for TA (the known drug associations do not include prednisolone or metoprolol), suggesting that the two pathologies may be in some way linked. Animal models have suggested that structural changes in the sarcoplasmic reticulum in affected muscle may be the end product of a range of functional abnormalities, including genetic anomalies, hormonal influences, and intracellular calcium ion regulation.<sup>8</sup> The role of ATP in controlling the calcium release channel of sarcoplasmic reticulum and the importance of mitochondria to cellular calcium signalling may suggest a link between the two pathologies.

This case adds to the growing list of clinical phenotypes associated with multiple mtDNA deletions. Moreover, the clinical features cannot easily be accommodated into any of the recognised subtypes of either mitochondrial or TA myopathy, suggesting that the classification of these conditions is incomplete. Finally, although the co-occurrence of two extremely rare conditions may be random, it seems more likely that the coincidence of TA with mitochondrial dysfunction provides a clue to the functional significance of these poorly understood histological bodies.

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## Topiramate induced manic episode

Topiramate is a novel antiepileptic drug (AED) that has been in use for several years, mainly as add on treatment for partial and secondarily generalising seizures that are otherwise refractory to treatment.<sup>1</sup> Despite the good efficacy of topiramate, dizziness, ataxia, double vision, and somnolence have been noted as the main side effects. While older AEDs such as carbamazepine and sodium valproate are now routinely used for the treatment of mood disorders, recent studies suggest that novel AEDs, such as lamotrigine, gabapentin, tiagabine, and topiramate, have mood stabilising efficacy as well.<sup>2</sup> Exacerbation of psychotic symptoms has been reported but mostly in patients with pre-existing psychiatric disorders.<sup>3,4</sup> However, more patients than previously assumed may be affected by a broader range of side effects. We present a case of a patient taking topiramate who presented with an acute manic episode, lacking any previous history of affective disorders or episodes.

A 57 year old woman with a history of temporal lobe epilepsy was referred to our hospital by her local general practitioner due to suicidal ideation and the intention of killing her husband. In the preceding weeks, her relatives had noted a progressive change of personality with verbal attacks, lack of sleep, expensive purchases, and the recurrent desire to give her house to a distant acquaintance. On admission, she was fully oriented, agitated, restless, suspicious, and laughing inappropriately. She refused any medical help and in turn was convinced that her spouse was mentally ill and needed urgent medical advice. Her speech was hasty, with pompous, overbearing, and self important utterances, obvious "flight of ideas", and high "pressure of thoughts". She boastfully admitted ideas about a relationship with a younger man and her own irresistible attractiveness, and threatened the psychiatrist verbally and physically during the initial interview. She had partially lost coherence of thought and she was "talking past the point". She denied hearing voices or other hallucinations; nevertheless, it was impossible to complete a full psychiatric interview. At this time, the patient scored 37 out of 44 points on the young mania rating scale (YMRS).

The patient had a well documented history of seizures (including video encephalographic monitoring), which had started 18 years previously with 7–10 attacks per month (on average) and were classified as single and complex partial seizures without secondary generalisation. Neuropsychological testing showed a pattern of medial temporal lobe dysfunction, and brain magnetic resonance imaging showed left hippocampal sclerosis. According to both the referring physician and her relatives, she had never experienced any psychiatric symptoms in her life. Apart from hypertension there was no relevant medical or neurological history. Reviewing her medication, we noted that 12 weeks before her admission topiramate had been added to her antiepileptic regimen of tiagabine (40 mg/day for more than one year), beginning with

50 mg once daily. In retrospect, her husband noted first unusual arguments and a short temper while she was taking 100 mg/day topiramate for about two weeks. First psychotic symptoms were noted when the topiramate dose was adjusted to 200 mg/day three weeks before admission (blood concentration 8 µg/ml).

We discontinued antiepileptic treatment with topiramate immediately after admission and treated her extreme manic symptoms with haloperidol (up to 40 mg/day) and intravenous diazepam (20 mg/day). After four days haloperidol was replaced with olanzapine (20 mg/day, blood concentration 0.02 µg/ml) and after 21 days with risperidone (6 mg/day). Tiagabin (40 mg/day) and clobazam (20 mg/day) were finally used for antiepileptic cover. Extreme manic symptoms abated within one day after neuroleptic treatment and discontinuation of topiramate. Other indices of psychotic symptoms, however, were alleviated rather slowly: the YMRS score was 8 after one month and 2 after two months. Interestingly, concomitantly with aggravation of manic symptoms, seizures were declining and stopped nearly completely with add on treatment of 200 mg/day topiramate.

Topiramate is a novel AED, which is almost exclusively used as an add on. It acts by a state dependent blockade of sodium channels, potentiation of  $\gamma$ -aminobutyric acid mediated

neurotransmission, and antagonism of glutamate by blocking  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors.<sup>4</sup> Although in clinical trials the incidence of psychosis with topiramate treatment was not significantly different from placebo,<sup>1</sup> concerns remain about its use, particularly in predisposed patients. Reports of paranoid delusions, auditory hallucinations, and cognitive impairment with topiramate treatment are scanty.<sup>3,5</sup> While previous accounts have suggested that these adverse effects may occur mainly in patients with pre-existing psychiatric conditions, our report illustrates a rare case of an actual manic episode in a patient without respective psychiatric history. Although she had been receiving tiagabine for a long time, the close temporal relation of the introduction of topiramate and the onset of manic symptoms, as well as their disappearance after termination of topiramate treatment, indicates an adverse effect of topiramate (although an interaction can, of course, not be excluded).

This case is illustrative of a potentially severe side effect of topiramate. A careful determination of psychiatric history and neuropsychiatric assessment may be useful in identifying patients who are particularly prone to this side effect. Prescribing physicians need to recognise and treat affective and psychotic symptoms appropriately. Although topiramate and other novel AEDs have been

used to treat mood disorders, their range and frequency of adverse effects will ultimately limit clinical use.<sup>2</sup>

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Competing interests: none declared

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