Morvan’s syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels

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Summary
Morvan’s ‘fibrillary chorea’ or Morvan’s syndrome is characterized by neuromyotonia (NMT), pain, hyperhidrosis, weight loss, severe insomnia and hallucinations. We describe a man aged 76 years with NMT, dysautonomia, cardiac arrhythmia, lack of slow-wave sleep and abnormal rapid eye movement sleep. He had raised serum antibodies to voltage-gated K+ channels (VGKCs), oligoclonal bands in his CSF, markedly increased serum norepinephrine, increased serum cortisol and reduced levels and absent circadian rhythms of prolactin and melatonin. The neurohormonal findings and many of the clinical features were very similar to those in fatal familial insomnia, a hereditary prion disease that is associated with thalamic degenerative changes. Strikingly, however, all symptoms in our MFC patient improved with plasma exchange. The patient died unexpectedly 11 months later. At autopsy, there was a pulmonary adenocarcinoma, but brain pathology showed only a microinfarct in the hippocampus and no thalamic changes. The NMT and some of the autonomic features are likely to be directly related to the VGKC antibodies acting in the periphery. The central symptoms might also be due to the direct effects of VGKC antibodies, or perhaps of other autoantibodies still to be defined, on the limbic system with secondary effects on neurohormone levels. Alternatively, changes in secretion of neurohormones in the periphery might contribute to the central disturbance. The relationship between VGKC antibodies, neurohormonal levels, autonomic, limbic and sleep disorders requires further study.

Keywords: neuromyotonia; anti-VGKC antibodies; Morvan’s syndrome; paraneoplastic syndrome; fatal familial insomnia

Abbreviations: BP = blood pressure; FFI = fatal familial insomnia; HR = heart rate; MFC = Morvan’s fibrillary chorea; NMT = neuromyotonia; PE = plasma exchange; REM = rapid eye movement; VGKC = voltage-gated K+ channel; video-PSG = video-polysomnography

Introduction
In 1890, Morvan described a patient with myokymia (muscle twitching) associated with muscle pain, excessive sweating and disordered sleep [Morvan’s fibrillary chorea (MFC); Morvan, 1890]. The course was severe and the patient died 5 weeks after onset. A similar condition characterized by widespread myokymia and cramping, but without overt CNS involvement has since been described and is now referred to as neuromyotonia (NMT) (Mertens and Zschocke, 1965) or Isaacs’ syndrome (Isaacs, 1961). Acquired NMT is thought to be autoimmune in a high proportion of cases. It can be associated with thymoma (Newsom-Davis and Mills, 1993), and antibodies to voltage-gated K+ channels (VGKCs) are present in a proportion of patients (Shillito et al., 1995; Hart et al., 1997). Some patients have been shown to respond to immunotherapies, and mice injected with NMT immunoglobulins have prolonged neuronal action potentials and increased neurotransmitter release (Shillito et al., 1995). MFC, or Morvan’s syndrome (Serratrice and Azulay, 1994), is NMT with overt CNS involvement. It is probably also autoantibody-mediated (Halbach et al., 1987; Madrid et al., 1996; Heidenreich and Vincent, 1998; Lee et al., 1998; Barber et al., 2000), but the nature of the CNS dysfunction and the targets for the antibodies are not clear.

We describe a patient who had all the features of Morvan’s...
syndrome and raised levels of antibodies to VGKC. Detailed EEG and analysis of circadian hormone rhythms show for the first time the complexity of the underlying disturbance. Both the peripheral and central symptoms markedly improved with plasma exchange (PE).

**Clinical features**

A 76-year-old man presented with muscle weakness and fatigue, muscle twitching, excessive sweating and salivation, small joint pain, itching and weight loss. Over the next 12 months, he developed confusional episodes with spatial and temporal disorientation, visual and auditory hallucinations, complex behaviour during sleep and progressive nocturnal insomnia associated with diurnal drowsiness. There was also severe constipation, urinary incontinence and excessive lacrimation. The time-course of appearance of these symptoms is illustrated in Fig. 1.

On admission, he was confused, restless and disoriented in time and space. When left alone, the patient would slowly lapse into a stuporous state with dreamlike episodes characterized by complex and quasi-purposeful gestures and movements (enacted dreams). When awakened, he could report the content of his dreams. Marked hyperhidrosis and excessive salivation and lacrimation were evident. Neurological examination disclosed diffuse muscle twitching and spontaneous and reflex myoclonus, slight muscle atrophy in the limbs, absence of tendon reflexes in the lower limbs and diffuse erythema especially on the trunk with scratching lesions of the skin. Pinprick, touch and vibration sensitivities and muscle strength were normal; plantar reflexes were flexor. All routine investigations were normal including paraneoplastic antibodies and tumour markers. Erythrocyte sedimentation rate was 49 mm/h. CSF had a normal protein, glucose, white blood cell and IgG index but there were weak oligoclonal bands, absent in the blood.

Brain MRI showed age-associated high intensity lesions in the white matter of both cerebral hemispheres. A biopsy of the left vastus lateralis muscle showed scattered angular and atrophic fibres of both fibre types probably due to mild

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### Table: Clinical Course of the Disease, Timing of Plasma Exchange, and Investigations

<table>
<thead>
<tr>
<th>EXAMINATIONS</th>
<th>EVOLUTION TIME (months)</th>
<th>CLINICAL FEATURES</th>
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<tbody>
<tr>
<td><strong>ONSET</strong></td>
<td></td>
<td>small joints pain; hyperhidrosis; itching; excessive salivation; asthenia; muscular twitching weight loss</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>myokymia; hallucinations; enacted dreams</td>
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<tr>
<td></td>
<td>-2</td>
<td>insomnia</td>
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<td></td>
<td>-3</td>
<td>incontinence</td>
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<td></td>
<td>-6 PE</td>
<td>improvement of sleep; disappearance of hallucinations and skin lesions</td>
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<tr>
<td></td>
<td>-16</td>
<td>worsening of insomnia and diurnal drowsiness</td>
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<tr>
<td></td>
<td>-17</td>
<td>improvement of sleep disturbances</td>
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<tr>
<td></td>
<td>-21</td>
<td>hyperhidrosis; reappearance of skin lesions</td>
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<tr>
<td></td>
<td>-22</td>
<td>reappearance of small joints pain; itching; enacted dreams; worsening of muscular twitching and skin lesions</td>
</tr>
<tr>
<td></td>
<td>-25</td>
<td>DEATH</td>
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</tbody>
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Fig. 1 Clinical course of the disease, timing of plasma exchange, and investigations. AI = autonomic investigations; HCR = hormonal circadian rhythms; video-PSG = video polysomnographic study; EMG = electromyography; PE = plasma exchange.
Morvan’s syndrome

Fig. 2 Electrophysiological recordings before and after plasma exchange. (A) The wake EEG was characterized by theta activity intermingled with alpha and fast activities (C3 and O2 leads). Mylo EMG and recordings from limb muscles show typical spontaneous or continuous fibre activity of NMT and abundant myoclonic activity. Frequent extrasystoles are evident in the ECG. (B) After plasma exchange, the wake EEG is characterized by normal alpha activity. The EMGs show no evidence of myoclonus and reduced continuous fibre activity. ECG abnormalities are no longer present.

Course and treatment

The patient was treated with haloperidol (6 mg/day) with some improvement in the psychomotor agitation and hallucinations, but even high doses of carbamazepine did not improve the spontaneous muscle activity. Antibodies to VGKC were detected (see below) and the patient underwent 10 sessions of PE of 2 l each. After the third session his itching, sweating, mental disturbances and complex nocturnal behaviour improved and these symptoms completely disappeared after the sixth session, with improvement in insomnia and reduced muscle twitching. At this time, neuropsychological tests showed no abnormality.

One month after the sixth PE session, there was a progressive worsening of insomnia and diurnal drowsiness, which promptly disappeared after another two PE sessions. Two months later, hyperhidrosis and skin lesions reappeared, followed within a few months, by confabulation during drowsiness and sleep and marked vigilance swings during the daytime; fasciculations and myokymia were more pronounced.

A new course of PE was begun, but symptoms abruptly worsened during the second session, and within a few hours the patient died. A complete autopsy was performed 24 h after death and disclosed a pulmonary adenocarcinoma; the remainder of the examination, including the adrenal glands, was normal for age. Brain neuropathology is described below.

Methods

Electrophysiological studies

Routine EMGs were performed on the right abductor pollicis brevis, right abductor digiti quinti and right tibialis anterior muscles, and conduction velocity studies on the median and tibial nerves. A regional block of the right median nerve was performed, with infiltration of 2% lidocaine at the wrist.

Twenty-four-hour video-polysomnography (video-PSG)

Recordings were performed before and after PE. Identification of sleep stages according to the standard criteria of Rechtschaffen and Kales was prevented by the dominance of a transitional condition between wake and sleep (see below) (Rechtschaffen and Kales, 1968). The other sleep stages were scored according to Rechtschaffen and Kales with allowance for rapid eye movement (REM) sleep without atonia.

Autonomic investigations

These were performed in a temperature controlled (23 ± 1 °C) room and included continuous monitoring of EEG, systemic blood pressure (BP), heart (HR) and respiratory rates. The head-up tilt, Valsalva manoeuvre, deep breathing and sustained handgrip tests were performed according to
Bannister and Mathias (Bannister and Mathias, 1988), with blood sampling for plasma norepinephrine and epinephrine levels. Catecholamines were measured using high performance liquid chromatography with electrochemical detection (Anton and Sayre, 1962).

**Hormonal circadian rhythms**

A 24-h study session was performed after the sixth PE, under carefully controlled conditions and during a 24-h video-PSG recording. At this time, the patient was drug-free and without sedating medications. Results were compared with six age-matched controls undergoing a 24-h study session with the same protocol, and eight patients with fatal familial insomnia (FFI) (unpublished observations). Commercial radioimmunoassay kits were used to measure serum cortisol (Diagnostic Products Corp., Los Angeles, Calif., USA) and growth hormone (HGH Liso-phase; Sclavo, Verona, Italy). Immunoradiometric assay kits were used for ACTH (adrenocorticotropic hormone) and melatonin (Nichols Institute Diagnostic, San Juan Capistrano, Calif., USA) and prolactin (MAIA Clone; Ares Serono Diagnostics, Milan, Italy).

**Immunological tests**

Antibodies to VGKC were measured by immunoprecipitation of 125I-dendrotoxin labelled VGKCs (labelling types kv1.1, 1.2 and 1.6) as previously described (Shillito et al., 1995; Hart et al., 1997). Indirect immunohistochemistry was performed with serum diluted 1:200 to 1:800 on frozen paraformaldehyde-fixed, saponin-permeabilized, rat brain tissue (pre-perfused in phosphate-buffered saline). Screening for paraneoplastic antibodies was performed on frozen, acetone-fixed rat cerebellum (for details, see Amyes et al., 2001). The presence of IgG bound to the patient’s CNS in situ was determined by direct immunohistochemistry on acetone-fixed frozen sections of blocks of brain taken at post-mortem from the right side. In each case, bound IgG antibodies were detected with biotin-anti-human IgG, streptavidin-peroxidase and AEC producing a red stain. Images were captured using a Nikon Coolpix 990 digital camera, Nikon Corporation, Tokyo, Japan, attached to a Nikon E400 light microscope, Nikon Corporation, Tokyo, Japan.

**Neuropathology**

The left half of the brain was examined grossly and microscopically. Microscopic examination included sections of the superior and inferior frontal lobe, anterior basal ganglia, anterior temporal lobe, mid portion of basal ganglia, amygdaloid nucleus, anterior, middle and posterior thalamus, hippocampus and posterior temporal lobe, superior and inferior parietal lobe, occipital lobe, cerebellum, brainstem, upper, middle and lower cord and dorsal root ganglia. Sections were immunostained for $\tau$- and $\beta$-amyloid. Congo red staining was done in the spinal arachnoid.

**Results**

**Electrophysiological studies**

In the examined muscles, no abnormal insertional activity or fibrillation potentials were noted. Various patterns of spontaneous repetitive motor unit action potentials (MUPs) were recorded: doublets, triplets and multiplets, and myokymic discharges with an intraburst firing rate from 5 to 40 Hz and duration of up to 13 s (Fig. 2A). There were also complex repetitive discharges and paired discharges. Quantitative MUP analysis was normal. The spontaneous MUPs were not abolished by lidocaine nerve block indicating their distal origin. Nerve conduction studies were normal and there was no decrement on repetitive stimulation. After PE, quantitative analysis of the spontaneous activity showed a 60% reduction compared with the recording before PE (Fig. 2B).

**Twenty-four-hour video-PSG**

Before PE, the EEG figures which characterize non-REM sleep (spindles, K complexes and delta waves) were undetectable. The EEG was dominated by ‘wakefulness’ (Fig. 2A) and ‘subwakefulness’ alternating or intermingled with short ($<1$ min) atypical REM sleep phases, characterized by loss of muscle atonia. The ‘subwakefulness’ state was characterized by 4–6 Hz theta activity intermingled with fast activity and desynchronized lower voltage theta activity, behaviourally associated with sleep-like somatic and autonomic behaviour (Guilleminault et al., 1993). Behaviourally, the patient oscillated between a state of relative calm with a pre-sleep-like behaviour to severe agitation with delirium or enacted dreams. Concomitant audio-visual analysis showed that the abnormal, hallucinatory behaviour, which occurred at night-time or during diurnal naps, appeared during periods of abnormal REM sleep without atonia, arising directly from ‘wakefulness’ or ‘subwakefulness’.

After PE, video-PSG recording disclosed a normal wake state was characterized by non-REM sleep stages, averaging 23% of total bedtime (normal value 50%), recognizable by the reappearance of sleep spindles and K-complexes. Short REM sleep episodes with atonia were more common and not associated with dream-like behavioural episodes. ECG also normalized at this time (Fig. 2B).

**Autonomic investigations**

Before PE, BP was 145/60 mmHg. Plasma norepinephrine was elevated (810 pg/ml; 11 age- and sex-matched controls, 270 ± 155 pg/ml), whereas plasma epinephrine
Morvan’s syndrome

Fig. 3 Autonomic and circadian disturbance. (A) Norepinephrine plasma levels during head-up tilt test (healthy controls – mean values ± SEM). (B) Circadian rhythms of norepinephrine, cortisol, ACTH, melatonin, PRL and growth hormone, compared with six age-matched healthy controls (mean values ± SEM) and the findings in eight FFI patients. The results in the Morvan’s syndrome patient are very similar to those found in FFI patients.

was normal (23 pg/ml; 11 age- and sex-matched controls, 37 ± 41 pg/ml). The response to head-up tilt was characterized by a mild decrease in BP (~15/10 mmHg), an increase in norepinephrine (+389 pg/ml) (Fig. 3A) and epinephrine (+17 pg/ml), and increase in the frequency of supraventricular extrasystoles. The HR changes induced by the Valsalva manoeuvre and deep breathing could not be analysed because of the continuous heart arrhythmia. The rise in diastolic BP induced by isometric handgrip was normal.

After PE, the patient, while supine, had a regular HR without any extrasystole (70 beats/min) (Fig. 2B); BP was 140/65 mmHg; plasma norepinephrine was still higher than normal (710 pg/ml) and epinephrine was normal (21 pg/ml). After head-up tilt test, BP decreased (~25/5 mmHg) and HR showed a mild increase (~5 beats/min). Norepinephrine (Fig. 3A) and epinephrine levels increased (~478 pg/ml; ~9 pg/ml). The Valsalva manoeuvre did not induce reflex bradycardia (Valsalva Rate, VR = 1.03), and there was no rise in HR during the hypotension phase. The respiratory arrhythmia induced by deep breathing was absent.
**Hormonal circadian rhythms**

Neurohormones were only measured between the first two courses of six PEs (Fig. 1) when the patient was beginning to deteriorate again. There were striking changes in neurohormone levels (Fig. 3B). Serum levels of melatonin were substantially lower than normal, and the circadian rhythm was absent. Serum levels of prolactin were also low and showed no detectable nocturnal increase. Growth hormone levels were relatively normal, but during the day there were peaks not related to sleep. Plasma levels of norepinephrine were high throughout the 24-h period, without the physiological nocturnal decrease. Blood levels of ACTH and cortisol were slightly raised at night but the physiological early morning increases were preserved. Importantly, these results were almost identical to those of eight patients with FFI (Fig. 3B).

**Immunological studies**

Serum antibodies to VGKC were strongly positive at presentation (3000 pM; controls < 100 pM; see Fig. 1); serum antibodies to acetylcholine receptor, voltage-gated calcium channels, glutamic acid decarboxylase and gangliosides were negative. One month after the sixth PE, VGKC antibodies were 2100 pM, a relatively small drop suggesting that the titre may have been rising steeply before PE. At this time, the VGKC antibodies were not detectable in the CSF. Serum levels rose to 2700 pM 4 months later, and to 3600 pM 1 month before death (Fig. 1).

We looked for evidence that these antibodies could bind CNS tissue using indirect immunohistochemistry on frozen sections of rat midbrain. Control serum showed no binding (lack of pink stain in Fig. 4A and B), whereas the patient’s serum IgG bound quite strongly to most neuronal cells. This was particularly evident on neuronal dendrites in the hippocampus (Fig. 4C), and neurones in the thalamus (Fig. 4D). Binding was predominantly cytoplasmic but not homogeneous (Fig. 4E and F). In the striatum (Fig. 4G), again, binding was clearly different from that of healthy control serum (Fig. 4H) or antibodies to the small cell cancer-associated Hu antigen, which bound strongly to cell nuclei (Fig. 4I). The antibody binding to hippocampus, thalamus, striatum and cerebellum (not shown), was similar to that previously reported for rabbit antibodies against the Kv1.2 subtype of VGKCs (Rhodes et al., 1997).

**Neuropathology**

The left half of the brain was grossly unremarkable. Histological examination showed a remote microinfarct of Sommer’s sector of the left hippocampus. Other findings that were considered within the normal range for age included hypertensive cerebral vascular changes, minimal perivascular inflammatory infiltrates, focal hyalination and thickening of the arachnoid of undetermined nature at various levels of the spinal cord. Immunostaining for τ- and β-amyloid was negative. Congo red staining was negative in the spinal arachnoid. There were no apparent white matter changes.

To see whether there was any evidence of immunoglobulin deposition in the patient’s brain, we performed direct immunohistochemistry on frozen sections of the post-mortem brain tissue (Fig. 5), washing the sections particularly carefully in order to remove antibody that might have leaked into the tissue post-mortem. The sections were examined ‘blind’ by two independent observers. In the thalamus (Fig. 5A and C) and striatum, there were areas of substantial leakage of IgG and diffusion into the parenchyma of the brain with evidence of antibody bound to neuronal cells. In sections of cortex, by contrast, there was evidence of antibody in the blood vessels with only mild leakage into the surrounding tissue (Fig. 5B and D). Unfortunately, control human tissue was not available for comparison, and these observations must be interpreted with caution since it is difficult to exclude the possibility of post-mortem artefact (Sillevis Smitt et al., 1995).

**Discussion**

We describe a case of Morvan’s syndrome with widespread neurological involvement affecting the peripheral nervous system (NMT), the autonomic system (cardiac arrhythmia, severe constipation, urinary incontinence, hyperhidrosis, excessive lacrimation and salivation) and the CNS (spatial and temporal disorientation, hallucinations, impairment of recent memory, severe insomnia and complex nocturnal behaviours). These features were associated with raised serum levels of antibodies to VGKCs as found in acquired NMT, antibodies binding to brain neurones and marked changes in circadian serum levels of neurohormones. The striking clinical improvement in peripheral and central symptoms, including electrophysiological changes, following PE demonstrates that the condition is caused by serum factors; probably, but not necessarily exclusively, autoantibodies.

Evidence of NMT and histopathological changes were similar to those previously described in NMT and MFC (Madrid et al., 1996; Lee et al., 1998). Dysautonomic symptoms characterized by excessive sweating, constipation, urinary incontinence and tachycardia have been described in patients with MFC (Lee et al., 1998), and tachycardia has been described in NMT (Isaacs, 1961) and MFC (Roger et al., 1953), but autonomic investigations of the cardiovascular system have not been previously performed. The abnormally increased plasma level of NE with a normal response to stress in the tilt test, demonstrates a sympathetic overactivity in our case. Increased plasma levels of NE may be due to an increased release, a reduction of re-uptake or kidney failure (Polinsky, 1988). In our patient, there was no evidence of kidney failure and the return of NE blood levels to baseline values after the tilt test excluded an impairment of re-uptake. Therefore, the high plasma levels of NE suggest an increased release, probably of central origin since levels...
Fig. 4 Binding of antibodies to rat brain. (A and B) Control serum shows no binding (absence of pink stain). The MFC patient’s serum antibodies bind to the hippocampus (C) and thalamus (D) sparing the white matter. At higher magnification, (E and F), the binding is diffuse throughout the cytoplasm but variable between cells. Binding in the striatum (G) is also present compared with control serum (H), and different in distribution to that shown by antibodies to the paraneoplastic antigen, Hu (I).
A remarkable feature in our case was the frequent supraventricular extrasystoles associated with the tachycardia. Genetic defects of VGKC function are responsible for cardiac arrhythmias such as the slow Q–T syndrome (Ackerman and Clapham, 1997), and it is possible that antibodies to VGKCs may be responsible for similar abnormalities. The fact that the extrasystoles disappeared after PE while the raised NE levels persisted, suggests a possible dissociation between serum antibodies acting on the cardiac conduction system and those factors that are responsible for increased NE levels.

Sleep disturbances in MFC have been described in the literature but polysomnographic studies have been performed in very few cases (Fischer-Perroud et al., 1974; Murri et al., 1976). Patients with mild insomnia associated with anxiety and mood depression have been described, while others have complained of severe total insomnia of long duration (agrypnia) associated with decreased vigilance, mental confusion, hallucinations, motor agitation and complex motor behaviour mimicking dreams, and autonomic activation. This pattern, which was very evident in our patient, has been called ‘agrypnia excitata’ (Lugaresi and Provini, 2001).

Antibodies to VGKC appear to be implicated in the pathogenesis of MFC. Serum VGKC antibodies are found in NMT (Shillito et al., 1995; Hart et al., 1997) and were reported to be present in one patient with thymoma-associated MFC (Lee et al., 1998), and in a patient with spontaneously reversing MFC (Barber et al., 2000). Moreover, the serum antibodies from our patient bound strongly to the hippocampus in a distribution similar to that of antibodies to known VGKCs (Rhodes et al., 1997). The decreased vigilance, mental disorientation and ‘psychosis’ of MFC are similar to the manifestations of limbic encephalitis (Corsellis et al., 1968). Although this condition is usually associated
with autoantibodies directed against the neuronal antigens Hu or Ma2 (Voltz et al., 1999), no paraneoplastic antibodies were detected in our patient by routine immunohistochemistry, and patients with CNS paraneoplastic disorders seldom show a striking response to PE. Moreover, VGKC antibodies, with similar distribution of antibody binding sites, were recently demonstrated in two cases of reversible limbic encephalitis (Buckley et al., 2001). The absence of morphological alterations of the brain pathology, the suggestion of diffusion of IgG into the thalamus and striatum, more marked than in the cortex (consistent with effects on the thalamolimbic system), the oligoclonal bands in the CSF and the amelioration after PE all strongly support an antibody-mediated basis for the condition, although the lack of VGKC antibodies in the CSF is surprising. Strikingly, the clinical, behavioural and neuroendocrine disturbances were very similar to those in FFI, a hereditary prion disease characterized by ‘agrypnia excitata’, sympathetic overactivity and somatomotor manifestations (myoclonus, ataxia, dysarthria and spasticity) (Lugaresi et al., 1986; Silber et al., 1995). In FFI, brain histopathology shows neuronal loss in the anteroverentral and dorsomedian thalamic nuclei and in limbic and paralimbic cortical regions (Gambetti et al., 1994). Even though our patient lacked structural pathological abnormalities in the thalamolimbic system, we speculate that, in analogy with FFI, his CNS and autonomic symptoms were caused by impaired corticolimbic control of the subcortical structures regulating the sleep–wake and autonomic functions (Lugaresi et al., 1998).

In NMT, VGKC antibodies are thought to lead to neuronal hyperexcitability by reducing the number of functioning VGKCs that are necessary for repolarization of the motor nerve (Sinha et al., 1991; Shillito et al., 1995; Hart et al., 1997). Although there is no direct evidence, effects of VGKC antibodies on secretory tissue could be responsible for the excessive salivation, lacrimation and sweating that appear to be common in MFC and in some cases of limbic encephalitis (Buckley et al., 2001). However, it is possible that there are also other antibodies contributing to the peripheral and central dysfunction in this case of MFC and further studies are in progress to define more precisely the binding sites for the antibodies and their molecular targets.

Finally, the possibility that some of the central disturbances in MFC result not directly from the autoantibodies, but indirectly from the peripheral effects of the antibodies on secretion of neurohormones will also need to be carefully investigated.

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References


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