Tiagabine for treating painful tonic spasms in multiple sclerosis: a pilot study

Tiagabine (Gabitril, Paris, France) is a new antiepileptic drug that acts as a selective inhibitor of the γ-aminobutyric acid (GABA) transporter, GAT-3. It has recently been reported to be effective in diseases other than epilepsy, such as stiff man syndrome1 and neuropathic pain,2 conditions in which GABAergic mechanisms are supposedly involved. In multiple sclerosis, painful tonic spasms affect approximately 10% of patients and are usually treated with GABAergic drugs such as baclofen or gabapentin.1,2

We undertook an open label pilot study of tiagabine, in a dose range of 5 to 30 mg/day, in a group of seven multiple sclerosis patients with painful tonic spasms who were non-responsive or intolerant to established drug treatment. The patients had previously been treated with gabapentin, baclofen, diazepam, or clonazepam, and were being followed in the department of neurology, PA Micone Hospital, Genoa, Italy. Four subjects were female and three were male, with a mean age of 45.1 years, mean disease duration of 7.1 years, and mean expanded disability status score (EDSS) of 4.0. Four patients had relapsing-remitting, one had secondary progressive, and two had primary progressive disease. Painful tonic spasms were defined as transient painful extensor or flexor spasms in the lower limbs, with abrupt onset and brief duration (from a few seconds to a few minutes), with repetitive and stereotypical features. The subjective level of the painful tonic spasms was scored using a three point scale previously described: 0, no pain, no attack; 1, mild pain or discomfort, presents only a limited amount of time; 2, intermediate pain or discomfort: the duration moderates, or the different pathogeneses may reflect the inability of the scale to detect minor changes, or the different pathogeneses do not differ enough to make a difference.

Tiagabine was started at 5 mg daily and increased until spasms were relieved or to the maximum dosage of 30 mg. No other drugs with a potential influence on spasticity were allowed during the study period. The patients were clinically evaluated at baseline (T0), after pain relief was achieved (T1), and after three months from the beginning of the protocol (T2). The minimum follow up period was three months. All specific symptomatic drug treatments used previously were discontinued one week before treatment with tiagabine was begun.

The mean dose of tiagabine was 12.8 mg daily. Relief of painful tonic spasms was successful in four of the seven patients (minimum treatment period, three months). All four patients had complained and sustained recovery within one month of initiation of treatment (a reduction of two points on the pain scale); efficacy was maintained for a period of three months in all four subjects. The Ashworth score changed by one point in one subject. The clinical characteristics of the patients and the painful tonic spasm scores before and after treatment are given in Table 1.

Two patients (Nos 2 and 5) dropped out of the study because of adverse effects: one with nausea and dizziness, the other with drowsiness and weakness. These subjects had a longer disease duration and higher EDSS scores, suggesting a possible correlation between disease severity and adverse effects.

COMMENT

Typically, antiepileptic drugs are effective for treating paroxysmal symptoms in patients with multiple sclerosis at doses that are lower than those used in epilepsy. For this reason, we arbitrarily set the maximum dose of tiagabine at 30 mg/daily, while in epilepsy the maximum dose is usually 56 mg daily. Moreover, patients with multiple sclerosis treated with antiepileptic drugs more often report central nervous system side effects than patients with other diseases such as seizures or mood disorders.

The results of this study suggest a possible new treatment for painful tonic spasms in multiple sclerosis and support the postulated GABAergic mechanism of action as the key factor in the choice of drug therapy. The Ashworth scale, did not change during the study period, as reported in trials of other antispasticity drugs such as tizanidine. This may reflect the inability of the scale to detect mild changes, or the different pathogeneses of painful tonic spasms and spasticity. The frequency of side effects of this agent in patients with multiple sclerosis and its efficacy in the treatment of painful tonic spasms or spasticity must be confirmed in a larger study.

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References


Harlequin syndrome: an association with overlap parasomnia

We describe the novel association of Horner syndrome and autonomic paroxysmal flushing and sweating (Harlequin syndrome) with overlap parasomnia.

CASE 1

A 66 year old woman suffered right jaw and multiple limb fractures when she was 45. Since then she had recurrent sudden onset episodes of right hemifacial flushing and sweating, occurring with physical exertion and heat, rarely spontaneously, and lasting 20 to 30 minutes. Approximately one year after the trauma, her sleep became restless, being interrupted by excessive motor activity, seemingly purposeful and sometimes harmful, associated with vocalisation and a report of dreaming corresponding to the motor manifestations. Hypnagogic hallucinations and sleep paralysis could also rarely occur. Both facial flushing and sleep disturbances worsened after another accident to her face when she was 64.

Examination at age 66 showed partial ptosis of the left eyelid, bilateral conjunctivitis, episodic right hemifacial flushing and sweating (Harlequin syndrome) and contralateral paroxysmal facial flushing. We describe the novel association of Horner syndrome and autonomic paroxysmal flushing and sweating (Harlequin syndrome) with overlap parasomnia.

Table 1

<table>
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<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>EDSS</th>
<th>Dose (mg)</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>Type</th>
<th>Duration (years)</th>
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</table>

EDSS, expanded disability status scale; F, female; M, male; PP, primary progressive; RR, relapsing-remitting; Se, side effects; SP, secondary progressive; T0, study entry; T1, at pain relief; T2, after 3 months.

Competing interests: none declared.

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NREM sleep activity. During NREM sleep an EEG showed short sequences of REM-like patterns (sawtooth waves and desynchronised high frequency/low amplitude activity), sometimes with chin muscle atonia. During REM (rapid eye movement) sleep, her EEG showed typical elements but also frequent intrusions of spindles and K complexes, with partial chin atonia on electromyography (EMG) and bursts of phasic EMG activity associated with vocalisation and facial movements. These transitional patterns of "mixed EEG" accounted for about 20% of total REM and S2 sleep time (fig 1). During a subsequent 48 hour Vivotap® evaluation, which confirmed the presence of "mixed EEG patterns," the patient reported vivid dream contents related to awakenings from both REM and NREM sleep. A multiple sleep latency test showed borderline daytime somnolence (mean sleep latency, 8 minutes and 48 seconds) with frequent early microsleeps during all sessions. Chin EMG was unstable during each session, without a clear cut relation to the microsleeps.

**CASE 2**

A 52 year old woman presented with a two year history of sudden sweating and flushing of the left hemiface. Physical exercise and heat could cause these episodes, which also occurred spontaneously. Lacrimal and gustatory sweating were absent. At this time, abnormal motor activities had appeared during sleep, associated with vocalisation resulting from vivid frightening dreams which the patient could report after waking. During admission, episodes characterised by sudden arousal during nocturnal sleep with screaming and fearful vocalisation were observed by room mates. From this time, nocturnal sleep became non-refreshing and was interrupted by brief and abrupt awakenings; there was excessive daytime sleepiness. On physical examination, the right pupil was smaller than the left and did not dilate to light. Right iris heterochromia with 0.01% eye drops did not change the size of the right pupil. A body heating test with alizarin powder application showed absent sweating in the right hemiface. Brain and spinal cord MRI and neurophysiological investigations including neuroregulatory tests as in patient 1 were all normal.

Twenty four hour video PSG showed long sequences in which NREM and REM PSG features were intermingled: in particular runs of rapid eye movements and sawtooth waves intruded during stage 2 sleep associated with chin EMG fluctuations, and K complexes and sleep spindles were observed during REM sleep patterns. Chin muscle atonia was not complete during REM sleep, with brief sudden twitches and tonic EMG bursts; full blown REM sleep behaviour disorder (RBD) could not be recorded; chin muscle atonia could also appear suddenly during NREM sleep, randomly or before a leg movement. These intermingled NREM-REM sleep PSG patterns occupied 33.5% of total REM and stage 2 NREM sleep time.

**COMMENT**

Our patients had anhydrosis of one side of the face and long standing ipsilateral Horner’s syndrome associated with both spontaneously occurring and heating/exertion induced paroxysmal facial sweating, consistent with Harlequin syndrome. They probably suffered a lesion of the first sympathetic neurone. While the negative dilute epinephrine eye drop test result suggested an absence of adrenergic supersensitivity secondary to a third sympathetic neurone lesion, absent lacrimal and gustatory sweating excluding a second or third sympathetic neurone lesion at the exact site lesion, however, eluded us because of the negative MRI findings. In addition, our patients suffered abnormalities of nocturnal sleep, with recurrent seemingly purposeful motor activities like extractions, intrusions into NREM and REM sleep, and PSG patterns characterised by an admixture of wake, NREM, and REM sleep EEG elements. Thus our patients had evidence for both a disorder of arousal and RBD because, from a behavioural point of view, they presented with atypical sleep with frequent muscle twichings, vocalisation, and dream-like mentation on waking. Such a mixed state of wakefulness and sleep is typical of the state dependent failure of control of the so called “parasomnia overlap” syndrome. Hypnagogic hallucinations and sleep paralyses were also reported by patient 1. Remarkably, the Harlequin syndrome was temporarily linked and preceded the parasomnia overlap syndrome by one year, suggesting a possible connection between the two. Overlap parasomnia has been noted after lesions, even transient, of the brain stem and forebrain regions, but ours is the first report of an association between Harlequin syndrome and sleep disorders in the form of overlap parasomnia syndrome. Our findings emphasise the need for an integrated approach to patients with autonomic and sleep disorders.

**References**

An expansion in the ZNF9 gene causes PROMM in a previously described family with an incidental CLCN1 mutation

In 1997 Mastaglia et al described a two generation family of Macedonian origin with phenotypic features of PROMM and an incidental CLCN1 mutation. Affected individuals had mild myotonia, predominantly proximal muscle weakness, and cataracts, consistent with a diagnosis of proximal myotonic myopathy (PROMM). Molecular genetic studies showed that the proba
did not have the chromosome 19 myotonic dystrophy (DM1) CTG expansion, but did have the R894X mutation in exon 23 of the muscle chloride channel gene (CLCN1). However, she had only passed the R894X mutation to one of her two affected offspring. Thus the CLCN1 gene mutation did not segregate with the disease. We can now confirm that a definite genetic cause for PROMM has been identified in this family.

In 1998 a locus for a second type of myotonic dystrophy (DM2 or PROMM) was mapped to chromosome 3q21. In 2001 it was shown that DM2/PROMM was caused by a CCTG repeat expansion located in intron 1 of the zinc finger protein 9 (ZNF9) gene. Inheritance of the microsatellite markers D3S1589, D3S3606, D3S1541, and D3S684—flanking the DM2 locus—was compatible with DM2 being the disease in the family described by Mastaglia et al. The DM2 repeat expansion is difficult to demonstrate because of its very large size, but the presence of an expansion can be inferred by the non-inheritance of the normal sized allele from the affected parent, as in other expansions. The proposa
to the family reported by Mastaglia et al shows only one normal sized allele for the tetranucleotide repeat region of the ZNF9 gene, and by inference she has an expanded allele. This may occur through the proposa
either being homozygous for the same sized normal allele or through having one normal sized allele and one expanded allele. Her two affected offspring also have one normal sized allele, and in both of them this is different in size from the normal sized allele of their mother. Thus they have not inherited a normal sized allele from their mother, but have inherited different normal sized paternal alleles. This family is thus suffering from DM2/PROMM.

The proband was 49 years old when initially described, her score had been symptomatic for 15 years. In the six years since that description, there has been minimal worsening of symp
toms, with the patient reporting a little more difficulty in climbing stairs and rising from low chairs. However, there was no deterioration in strength or increased myotonia on examination. Repeat psychometric testing has not shown further reduction in either verbal or performance IQ (74 and 75, respectively), but she had become significantly depressed, requir
ing treatment. A second brain magnetic reso
nance imaging (MRI), five years after the initial one, showed some increase in the extent of the periventricular white matter disease, but this was not significant. We are confident and there was no atrophy of the parenchyma. Some subtle signal abnormality was seen for the first time in the pons.

The proband’s offspring remain clinically asymptomatic with respect to cataracts, muscle problems, and cognition, at the ages of 34 and 24 years. In the initial description both were shown to have myotonic discharges on electromyography, and this has not been repeated. However, they have now each had brain MRI scans reported as being within normal limits. The younger sibling has the incidental CLCN1 mutation. The R894X mutation has been described in association with the autosomal recessive form of myotonia congenita, and a more recently described mutation to one of her other CLCN1 allele— would not be expected to cause a disease phenotype. However, some CLCN1 muta
tions can cause either a recessive or a dominant mode of transmission, depending on supplemental genetic factors. Thus the coexistence of the ZNF9 and the CLCN1 mutations may conceivably cause a more severe phenotype. At the present time, neither sibling has any abnormality; thus this theory cannot be proven or disproven.

As well as confirming the genetic basis of the disease in this family, this report also confirms PROMM as being a very slowly progressive and relatively benign disease. Although the MRI changes and other neuro
dergenerative diseases such as CAGASIL can predict the clinical signs by more than 10 years (personal observation), this would not appear to be the case with PROMM. Although there has been a recent report of a patient with PROMM and schizophrenia who was intolerant of neuroleptics and susceptible to malignant hyperthermia, the proband has had several general anaesthetics without mishap. However, she has developed a psychiatric disorder in the form of depression, which is the third report of psychiatric dysfunction in PROMM patients.
Here we describe loss of the feeling or emotion produced by music itself. Musical emotion can be considered at a number of levels. At the most fundamental level, dissonance produces a perception that is unpleasant to most listeners. More variable is the intense pleasure that certain music may evoke in particular listeners, often described as a "chill", or "chills", which is likely to represent a more complex aesthetic response. We describe a patient with selective loss of this emotional response to music, due to a focal brain lesion.

A 52 year old right handed radio announcer collapsed in February 2000. He was found afterwards to have a total loss of speech comprehension and output, and a right hemiplegia. His speech recovered well, such that 12 months after the event he had only subtle output phonological problems. Motor functions recovered completely and he had no residual lateralising motor signs. However, he reported a persistent alteration in his auditory experience. He was in the habit of listening to classical music, to relax after working his night shift at the radio station, and had derived particular pleasure from listening to Rachmaninov preludes. He experienced an intense, altered emotional state or "transformation" when he did this. In common with other subjects who have this experience, the transformation was only

Figure 1  Use of counting backwards from 100 in sevens and spelling WORLD backwards in clinical practice.

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References

"When the feeling's gone": a selective loss of musical emotion

Loss of "feeling" is a common lament in popular music:

Tragedy: when the feeling's gone and you can't go on (Tragedy as performed by the Bee Gees. Spirits have flown, 1979.)

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produced by particular pieces, and he did not describe such an experience in response to music other than Rachmaninov’s, nor to other sensory experiences. This emotional response to the music was lost following the acute event, and remained absent during the period of testing between 12 and 18 months after the stroke. During this period he was able to enjoy other aspects of life, and reported no biological features of depression. He had noticed no change in his hearing, and was still able to identify speech, music, and environmental sounds normally.

When assessed in April 2001, pure tone audiometry, auditory filter widths, speech audiometry, prosody perception, and music perception were all normal. Musical perception was examined using a battery of tests during which subjects are required to make same/different judgments on melody pairs that can show differences in melodic structure, rhythm, and metre. Our patient showed normal scores on tests of scale (28/30), contour (27/30), interval (28/30), rhythm (28/30), metre (29/30), and incidental memory (27/30); see http://www.fas.umontreal.ca/psy/GRPLABS/lnmcg/website/index.html for normative data. Structural MRI revealed infarction involving the left insula and extending anteriorly into the left frontal lobe and inferiorly into the left amygdala. After normalisation to the standard stereotactic space of Talairach, the infarcted areas showed a close correspondence with left hemisphere areas activated during emotional response to music in normal subjects (fig 1).

In a case such as this it is impossible to prove that the stroke produced a new deficit in the emotional reaction to music without direct evidence of the emotional reaction and its autonomic effect both before and after the stroke. The interest of this investigation accrues from the subjective report of the patient alone. Nevertheless, this is the first documented case of such a deficit of which we are aware, completing an important double dissociation between musical cognition and emotional processing. Such a dissociation would require the presence of distinct substrates for musical cognition and emotion.

The cerebral basis for musical emotion has only recently been the subject of systematic study. In the clinical literature, an impaired emotional response to music is generally accompanied by disordered musical perception (amusia). However, one previously reported patient had impaired recognition of music despite a preserved affective response. In contrast, our patient strikingly illustrates the reverse dissociation, with normal recognition of music but loss of the emotional response to music. Together, these two cases complete a double dissociation between the perceptual and emotional components of music processing. This double dissociation suggests that the emotional effect of a piece of music is not determined by simple acoustic properties (which were processed normally in our patient).

Accumulating evidence from functional brain imaging studies in normal individuals suggests that functionally and anatomically separable neural networks mediate music perception and emotion. The perception of music involves the superior temporal lobes and inferior frontal lobes. In contrast, emotional processing of music engages a distributed brain network that is also recruited by other powerful emotional stimuli that produce autonomic arousal. This network includes bilateral medial limbic structures, insula, ventral striatum, thalamus, midbrain, and widespread neocortical regions. The present study enables us to conclude that the left insula is involved in normal musical emotional processing of music.

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References

"When the feeling's gone": a selective loss of musical emotion

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