

conduction studies revealed no abnormalities in the face, upper or lower extremities. Supramaximal stimulation of the tibial nerve elicited unusual late components in addition to F waves. Normal electrophysiological studies included blink reflex, median nerve somatosensory evoked potentials, brain stem auditory evoked potentials, visual evoked potentials and EEG.

The patient was given clonazepam, valproic acid and trihexyphenidyl without any relief of symptoms. Carbamazepine lessened the palatopharyngolaryngeal movement and also the muscle cramps in legs.

Ear clicks and palatopharyngolaryngeal involuntary movements seen in our patient can be clinically classified into "palatal myoclonus",¹ although the movements were not exactly rhythmic and recurred at a slower rate than the usual palatal myoclonus. Needle EMG showed myokymic discharges in the palatal and mylohyoid muscles in synchrony with the movement. These EMG findings differed from those reported in symptomatic "palatal myoclonus" showing rhythmic discharges at a faster rate,² although the previous EMG studies on "palatal myoclonus" did not disclose firing patterns of each jerk in detail. Myokymic discharges and muscle cramps in the legs relieved by carbamazepine in the present case may indicate that they arise from neuromuscular hyperexcitability rather than a central oscillator.

Ephaptic transmission resulting from demyelination can cause focal myokymia,³ but in our patient there was no evidence of organic lesions in the posterior fossa, nor other diseases suggesting diffuse injury or hyperirritability of the peripheral nerves, for example, in association with toxins, thyrotoxicosis, Guillain-Barré syndrome or polyneuropathy.³ Facial myokymia, though commonly seen in patients with pontine glioma, multiple sclerosis or Guillain-Barré syndrome, rarely involves the muscles innervated by lower cranial nerves.⁴

Myokymic discharges, also called grouped fasciculations, usually cause vermicular movements,³ but involvement of the dorsal interosseous muscles may cause tremor-like or flickering movements of the fingers.³ Myokymic discharges in the palatal muscles could therefore cause movements resembling "palatal myoclonus" or "tremor". Needle EMG is important to differentiate palatopharyngolaryngeal myokymia from the essential "palatal myoclonus",¹ which has a slower rate of movement than symptomatic "palatal myoclonus".

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Buspirone in progressive myoclonus epilepsy

Progressive myoclonus epilepsy is a clinical syndrome with obligate features of myoclonus and epilepsy and variable or inconstant features of dementia and ataxia. The most common is Unverricht-Lundborg disease (Baltic or Mediterranean myoclonus) but other types include Lafora disease and mitochondrial myopathy.

A serotonergic disturbance is suggested by reduced CSF5-HIAA in Baltic myoclonus and the antimyoclonic effect of L-tryptophan plus a monoamine oxidase inhibitor or 5-hydroxy-L-tryptophan in some patients.¹ The problem is that these observations do not point to a specific locus of abnormality in the 5-HT system.

Serotonin (5-HT) receptor pharmacology has advanced rapidly, identifying multiple 5-HT receptors types. Only a few have been studied in experimental myoclonus. In rats, the full 5-HT_{1A} receptor agonist 8-OH-DPAT induces myoclonus but partial 5-HT_{1A} agonists such as buspirone do not.

This pilot study was intended as a preliminary step in evaluation of the possible role of 5-HT_{1A} receptor abnormalities in progressive myoclonus epilepsy. The 5-HT_{1A} receptor is key to the 5-HT containing raphe neurons on which it is located, because its stimulation decreases cell firing. The activity of these neurons may be especially important in brainstem-mediated myoclonus, but the raphe nuclei also project widely to forebrain and spinal cord. Buspirone (Buspar) is the first clinically used 5-HT_{1A} agonist of its class, widely prescribed as an anxiolytic.² Since anxiety increases myoclonus in our patient population, we also hypothesised that they may benefit from an anxiolytic. Much evidence suggests buspirone exerts its clinical effect by stimulating pre-synaptic 5-HT_{1A} receptors.

Two male and two female patients, aged 15-22 years, with progressive myoclonus epilepsy who had failed conventional therapy were identified. Standard diagnostic tests had been performed including muscle enzyme histochemistry. All were taking one or more anticonvulsants (valproic acid, clonazepam, lorazepam, or phenobarbital) for control of seizures, but none of the drug doses were changed during the study. Each patient had prominent action myoclonus, some spontaneous myoclonus, and little or no cerebellar ataxia. None of the patients were seizure-free for more than a few months before the start of the study. All had therapeutic anticonvulsant levels before and during the study.

Patients were enrolled in an off label uncontrolled dose-ranging trial of buspirone using anxiolytic dose guidelines. The starting dose was 5 mg orally three times a day. The dose was increased every 3 days by 5 mg to a maximum of 60 mg/d. Two of the patients were videotaped performing a standardised battery of clinical tests including Archimedes's spirals. Repetitive motor tests and myoclonus were scored using established scales.^{3,4} In patients who were too neurologically impaired to comply with testing, a simple Likert scale was used to evaluate myoclonus: 0 = absent, + = mild, ++ = moderate, +++ = severe.

Myoclonus was unchanged in one patient and worsened in three (table). Patient 3 left the study at the starting dose reporting it made her more unsteady, and therefore she could not be tested. Patient 1, the only employed patient, could not go to work at 60 mg/day. On the Myoclonus Evaluation Scale, patient 1 went from 20% abnormality at baseline to 33-44% on buspirone; patient 2 from 43-56% to 47-53%, respectively. There were also no large differences on 10 timed motor tasks. Patient 4 was too impaired to comply with formal testing, but his action- and sensory-evoked myoclonus appeared to increase while spontaneous myoclonus was unchanged.

In all cases, the worsening of myoclonus was transient once the drug was stopped, and patients reported returning to their baseline level of function.

None of the patients experienced increased seizures compared with their baseline, even those with exacerbation of myoclonus. A brief head-shaking seizure occurred in patient 1 at 45 mg/d buspirone, a generalised convulsion in patient 2 at 30 mg/d and in patient 4 at 20 mg/d. No new dyskinesias were evoked.

The incidence of irritability and sedation in our patients was higher than the 2% and 10% of 477 cases in the Physician's Desk Reference, respectively. There may have been less dizziness (12% in PDR).

This uncontrolled observational study in a small number of patients suggests that buspirone does not help and may exacerbate myoclonus in progressive myoclonus epilepsy. Worsening of myoclonus was not explained by decreased anticonvulsant levels, and there are no experimental data to support an interaction between buspirone and anticonvulsants. Although a fluctuating baseline of patients with progressive myoclonus epilepsy could give the false impression of drug-induced exacerbation, the patients improved when buspirone was discontinued.

The data should be viewed as positive findings for several reasons. Any response to buspirone suggests that the 5-HT_{1A} somatodendritic autoreceptors are intact, and by inference, that 5-HT-containing raphe neu-

Table Effects of buspirone on myoclonus and seizures

Patient	Diagnosis	Days on drug	Threshold dose mg/day	Max. dose mg/day	Best dose/day	Effect of myoclonus		Side effects	Seizure frequency
						Subjective	Objective		
1	Baltic	60	15	60	35	worse	No change	Sedation Irritability Mood swings	1
2	Baltic	18	25	30	20	worse	worse	Sedation Lightheadedness	1
3	Baltic	3	15	15	—	worse	worse	—	0
4	Lafora	13	5	20	—	worse	worse	Sedation Irritability	1

Best dose/day may indicate merely least side effects.

rons are also present. It also implies that the 5-HT terminal is functional enough to mediate decreased 5-HT tone. This interpretation is supported by the finding of reduced CSF 5-HIAA in some patients.

The second observation was that buspirone did not exacerbate seizures unrelated to myoclonus in progressive myoclonus epilepsy. Drug-induced exacerbation of myoclonus may precipitate myoclonus-associated seizures, perhaps as in our case 2. This supports the clinical observation that myoclonus and epilepsy respond differently to drugs in progressive myoclonus epilepsy and the hypothesis that they have different regulatory mechanisms. The 5-HT_{1A} agonist 8-OH-DPAT has not been found to be an anticonvulsant in standard experimental models of epilepsy.⁵ Anticonvulsants could have masked a proconvulsant effect of buspirone since anticonvulsants are better able to block seizures than myoclonus in these disorders. There are no data to support a proconvulsant effect of buspirone, however, 8-OH-DPAT has a proconvulsant effect in mice⁵ and extremely high doses induce seizures in rats⁷ which may be unrelated to 5-HT neurotransmission.

It would be premature to conclude that drugs acting at 5-HT_{1A} receptors are ineffective in progressive myoclonus epilepsy. A post-synaptically acting 5-HT_{1A} agonist might have a different effect on myoclonus from buspirone. Different partial 5-HT_{1A} agonists, such as gepirone or ipsapirone without buspirone's weak D₂ dopamine receptor antagonism, may also have a different effect on myoclonus. Continuous treatment with buspirone has effects on other neurotransmitter receptors such as 5-HT₂ receptors which could have influenced myoclonus. Pre- or post-synaptic 5-HT_{1A} antagonists are other therapeutic possibilities.

Further studies on the role of 5-HT receptor subtype involvement in myoclonus are indicated, particularly in Lance-Adams syndrome (post-hypoxic myoclonus) for which evidence is best for involvement of 5-HT systems.

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MATTERS ARISING

Balint's syndrome in subacute HIV encephalitis

I was interested to read the report of Dr Schnider *et al* on a 45 year old woman with Balint's syndrome complicating subacute HIV encephalitis.¹ Attributing her cognitive disorder to subacute HIV encephalitis in the absence of biopsy confirmation is presumptuous and likely to be incorrect. Focal neurological findings are distinctly unusual with this disorder. It is far more likely that progressive multifocal leukoencephalopathy (PML) was responsible. PML affects approximately 4% of all AIDS patients.² A predilection for the parieto-occipital region is typical and visual symptoms are a presented manifestation in 35% of patients.³ The radiographic characteristics of the white matter lesions in PML⁴ mirror those observed in their patient. Furthermore, the improvement with zidovudine hardly dispels the diagnosis of PML. Spontaneous recovery⁵ and improvement following the use of zidovudine⁶ have both been reported with HIV-associated PML.

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Schnider *et al* reply:

We appreciate the comments by Dr Berger regarding the histological nature of the lesions in our patient who presented with Balint's syndrome as the first neurological manifestation of AIDS.¹ Unlike some patients with Balint's syndrome due to stroke in whom visual movement perception is impaired,² she perceived movement particularly well. We ascribed this variant to a subcortical lesion site, as shown by MRI, that spares cortico-cortical connections between primary visual cortex and visual association areas. Both subacute HIV encephalitis and progressive multifocal leukoencephalopathy (PML) primarily involve subcortical white

matter³ and would explain the findings in our patient. The differential diagnosis was not elaborated in our article as it was not the primary objective. We favoured the former diagnosis because the MRI appearance with bilateral, extended, confluent lesions on T2-weighted images appeared more typical of subacute encephalitis⁴ and because of the response to zidovudine treatment.⁵ In the absence of a biopsy or necropsy, the histology of our patient's lesions remains conjectural and we agree with Dr Berger that PML is a serious consideration in this patient.

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Anti-acetylcholine receptor antibody measurement in myasthenia gravis

In a recent study,¹ Clarke *et al* reported a "deficiency of anti-acetylcholine receptor (AChR) antibodies measurement in myasthenia gravis (MG)". In their retrospective study, antibodies were detected in only 38% of 86 patients with MG, compared with 66-93% in other reports. The unusually low antibody detection rate is attributed by the authors to the use of staphylococcal protein-A for immunoprecipitation rather than anti-human IgG antiserum. To support their claim, the authors cite our early report of 36% detection in an assay employing protein-A.² In that study, however, we used denervated rat muscle AChR as the antigen. Later, we modified the system using *human amputation muscles AChR* which increased the detection rate to 88%, still using protein-A as the precipitating agent.^{3,4} These results agree with most reported series,^{5,6} which stress the notion that the assay efficiency (sensitivity and antibody titres) depends primarily on the quality of the antigen preparation. Thus protein-A is similar to anti-human IgG antisera for immunoprecipitation in the anti-AChR antibody assay and we feel that the authors should look for other methodological flaws to account for the low sensitivity of their assay. Finally, we completely agree with the authors that all laboratories engaged in routine antibody assays should be subject to a quality control audit, and we refer the authors to consult with "EuroEQAS for AChR antibodies".

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