ignated β -amyloidopathy (APP 717).³ We screened 85 cases of early onset AD to estimate the frequency of this mutation.

The patients were collected from an ongoing genetic study on early onset AD. The clinical diagnosis was based on a standardised protocol, fulfilling NINCDS-ADRDA criteria.⁷ The age of onset of patients was < 60 years, with a mean (SD) of 54.0(4.9). Sixty four cases had no affected first or second degree relatives, 21 were familial with at least one first or second degree relative with AD.

DNA was extracted from blood leucocytes, and exon 17 of APP gene was amplified by the polymerase chain reaction (PCR), according to Goate *et al.*² Since the (APP 717: Val->Ile) mutation creates a BclI restriction site allowing its direct detection,² the PCR product was digested with the BclI restriction enzyme and analysed on a 2% agarose gel. The enzyme did not recognise the mutant BclI site in any of our cases, whereas it digested the PCR product of an in vitro generated exon 17 with the (APP717: Val->Ile) mutation. This agrees with the studies of Van Duijn *et al.*⁸ and Schellenberg *et al.*⁶ including patients with a higher age of onset. Combining the results of all studies on early onset patients of Caucasian origin,^{2,4,6,8} it may be concluded that for a confidence interval of 95%, less than 2.6% of isolated cases, and between 0.3 and 5.3% of familial cases, would have this mutation.

Two other missense mutations have, however, also been found in the same codon of APP gene^{9,10} supporting the hypothesis of allelic heterogeneity in early onset AD. We cannot therefore exclude the presence of another APP gene mutation in our sample. Even if the (APP 717: Val->Ile) mutation is of poor diagnostic value, the identification of other mutations within the same gene will establish a clear molecular classification and contribute to the understanding of the pathogenesis of the disease.

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Palatopharyngolaryngeal myokymia resembling "palatal myoclonus"

"Palatal myoclonus" consists of rhythmic movement of pharyngeal, laryngeal and palatal muscles at the average rate of 100 jerks/minute.¹ Usually seen in association with brain stem lesions, the hypertrophically degenerated inferior olive seems to serve as the central oscillator. Some patients with "palatal myoclonus", however, have no organic lesions in the posterior fossa.¹

We report a patient with palatopharyngolaryngeal involuntary movement resembling "palatal myoclonus" in synchrony with myokymic discharges recorded on needle EMG.

A 57 year old housewife complained of hearing ear clicks and experienced an involuntary twitch in the throat. Beginning insidiously, the symptoms have neither worsened nor remitted for 18 months. She also noted occasional muscle cramps in lower extremities. She had no history of cerebrovascular disease, encephalitis or trauma. None of her family had neurological disorders.

Neurological examination revealed "palatal myoclonus" consisting of involuntary up and down movements of the uvula at a rate of 40-80 beats/minute. Clicking sounds in association with the movements was audible by the examiner. Incessant rippling of the skin in the anterior neck reflecting the contraction of the pharyngeal and outer laryngeal muscles was observed. Laryngoscopic examination

Figure Surface EMG in successive sweeps recorded from a pair of electrodes placed on the right lateral part of the soft palate (A) showing nonrhythmic spontaneous group discharges. Needle EMG recorded from the right palatal (B) and mylohyoid (C) muscle showing myokymic discharges.

showed twitches of the inner laryngeal muscles. These movements, showing no temporal relationship with either respiration or heart beat, did not change with posture, sleep or when the patient held her breath. She had normal costoabdominal respiration without disturbance of phonation or swallowing. Ocular movements were full without pendular nystagmus. There was no spontaneous contraction in facial, masseter, tongue, sternocleidomastoid, diaphragmatic or limb muscles. Examination of the muscles revealed normal tonus without atrophy or weakness. She had intact sensation and normal reflexes and had no ataxia, hyper-sweating, myotonia, or Trousseau or Chvostek signs.

Normal laboratory data included total and ionised serum calcium and magnesium, thyroid and parathyroid functions, and immunological studies. Brain MRI showed no abnormalities. Surface EMG recorded from the right lateral part of the soft palate showed nonrhythmic group discharges of varying durations (fig A). Simultaneous recording from different sites of the anterior neck revealed asynchronous firing. Studies with a concentric needle electrode placed in the palatal and mylohyoid muscles confirmed the presence of single or grouped fasciculation potentials or myokymic discharges (fig B, C), firing at 60-120 beats/minute. Careful search disclosed neither fibrillation potentials nor positive sharp waves. The facial, masseter, sternocleidomastoid and limb muscles were normal with no evidence of myokymic discharges at rest or even after hyperventilation. Motor and sensory nerve

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 CSF 5-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.