Paroxysmal symptoms as the first manifestations of multiple sclerosis

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SUMMARY Paroxysmal symptoms are described in 14 patients with undoubted or suspected multiple sclerosis (MS). In seven of the patients the paroxysms were the first symptom of the disease, although only one has developed definite MS so far. The clinical features have been compared with 153 patients previously reported in the literature which has been reviewed, with special reference to 36 in whom paroxysmal symptoms were the initial manifestations of MS. Attention has been focused on paroxysmal symptoms of brain stem and spinal cord origin of the following types: paroxysmal dysthria and ataxia, diplopia, tonic seizures, paroxysmal akinsia, paroxysmal sensory disturbances and pains. Examples of each type have been reported as the first symptoms of MS with remissions ranging from less than to 21 years before other manifestations of MS have developed.

Transitory neurological disturbances are not infrequently encountered in multiple sclerosis (MS) and may be precipitated by such factors as exercise, hot baths, smoking and emotion, neck flexion and eye movements. It is also of interest that many of the familiar manifestations of MS which typically have a duration of weeks or months may also occur in the form of short-lived repetitive paroxysms. The nature of the paroxysmal symptoms depends on their site of origin, which is usually in the brain stem or spinal cord. The main types that have been reported are tonic seizures, paroxysmal dysthria and ataxia, paroxysmal paraesthesiae and pains including trigeminal neuralgia, and paroxysmal akinsia. These may be distinguished firstly by their brevity, lasting usually for just a few seconds to one to two minutes, and secondly by recurring in a stereotyped fashion from a few times a day to several times an hour. Most come on spontaneously, but some are triggered by hyperventilation, anxiety, muscular activity and tactile stimuli. They continue to recur in this way for a few days, weeks or months whereupon remission ensues, but the response to treatment with carbamazepine is often dramatic.

Precise figures of the incidence of paroxysmal symptoms during the course of MS are not available although trigeminal neuralgia probably occurs in about 1-5%. Grand mal epilepsy due to cerebral plaques is also relatively rare and is not included with the other paroxysmal disturbances for the purposes of this paper. Trigeminal neuralgia is of course much more common as an idiopathic disorder in an older age group than with MS, but the possibility that paroxysmal symptoms may be associated with diseases other than MS must be considered. However, when paroxysms of brain stem or spinal cord origin occur in young adults and particularly if they remit spontaneously or respond to treatment with carbamazepine, MS is the most likely cause.

Occasionally, paroxysmal symptoms are the initial manifestations of MS, a fact that is not well known, and the purpose of this paper is to illustrate this point from our recent experience and from a review of the literature.

Patients

Fourteen patients (see table 1) with paroxysmal symptoms of the types encountered in MS, excluding epilepsy and trigeminal neuralgia, were seen by us in Derby and Nottingham Hospitals between 1968 and 1978. Four patients (1, 8, 9 and 10) had clinically definite MS, four (11–14)
latent MS and the remaining six (2–7) suspected MS, according to the classification of McDonald and Halliday. In the last group the paroxysmal symptoms have as yet been the only neurological manifestations. The ages of the fourteen patients ranged from 21–48 mean 33) years, the female to male ratio was nine to five. Paroxysmal symptoms have been the initial manifestations in seven of the patients (1–7) but so far only patient 1 has developed definite MS (see appendix). His first symptoms were paroxysms of dysarthria and ataxia, and were accompanied by neurological signs on examination. There followed a spontaneous remission lasting four years before further manifestations ensued and subsequent clinical developments made the diagnosis of MS indubitable. Paroxysmal symptoms were also the initial manifestations in patients 2–7, remitting spontaneously in patients 2–6 and responding to carbamazepine 600 mg daily in patient 7. The paroxysmal symptoms in these six patients (see table 1) were similar to those seen in MS and we believe they were the initial manifestations of this disease. However, as yet, with remissions ranging from one to eight (mean four) years, they have developed no other manifestations of MS nor of any other disease. Summaries of four of this group (patients 2, 4, 6 & 7) are given in the appendix. Patients 8, 9 and 10 (see table 1) have had typical manifestations of MS including paroxysmal symptoms which, although occurring quite early during the course of the disease, were not the initial manifestations. The paroxysms responded to carbamazepine 400 mg daily in patient 8 and remitted spontaneously in patients 9 and 10, the latter having been unable to tolerate carbamazepine. Their subsequent course left no doubt about the diagnosis of MS. The remaining four patients (11–14) had a single neurological episode which remitted and later they developed paroxysmal symptoms. Since then they have had no further manifestations of MS, the duration of remission ranging from three to eight years. However in view of the neurological episode preceding the paroxysmal symptoms in each case and the absence of evidence of any other disorder, we believe the diagnosis of MS will turn out to be correct. All four patients were treated with carbamazepine. Patient 11 did not respond to 600 mg but the other three responded well to relatively small doses.

Our experience thus shows that paroxysmal symptoms may occur as the first as well as a later manifestation of MS. As we have not encountered the full range of paroxysmal symptoms in this series, we have reviewed the literature of the various types of paroxysmal disturbances other than epilepsy and trigeminal neuralgia which have been reported in MS, with particular reference to their occurrence as the first manifestation of the disease.

**Paroxysmal dysarthria and ataxia**

Paroxysmal bouts of dysarthria and ataxia have been reported previously in 47 patients (5–20) (see table 2) although clinical details have been given in only 27. The sex incidence is equal with a mean age of onset of 36 years. It was reported as the first symptom in nine patients, two each by Parker, Matthews, Osterman and Westerberg and one each by Espir and

### Table 1 Patients with paroxysmal symptoms (1968–1978)

<table>
<thead>
<tr>
<th>Patients No</th>
<th>Sex</th>
<th>Age</th>
<th>The first symptoms</th>
<th>Clinical diagnosis of MS</th>
<th>Response to carbamazepine</th>
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<tr>
<td>1 M</td>
<td>36</td>
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<tr>
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<td>3 F</td>
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<tr>
<td>4 M</td>
<td>37</td>
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<td>Diplopia</td>
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<td>+</td>
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<tr>
<td>5 F</td>
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<td></td>
<td>Paraesthesiae, limb weakness</td>
<td>(8)</td>
<td>+</td>
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<tr>
<td>6 F</td>
<td>25</td>
<td></td>
<td>Pain</td>
<td>(5)</td>
<td>+</td>
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<tr>
<td>7 F</td>
<td>27</td>
<td></td>
<td>Paraesthesiae</td>
<td>(8)</td>
<td>+</td>
</tr>
</tbody>
</table>

**Not the first symptoms**

| 8 M         | 28  |     | Dysarthria, ataxia | (4)                      | +                         |
| 9 F         | 23  |     | Dysarthria, ataxia | (1)                      | +                         |
| 10 F        | 47  |     | Pain, paraesthesiae | (2)                      | +                         |
| 11 F        | 48  |     | Pain               | (3)                      | +                         |
| 12 M        | 30  |     | Paraesthesiae      | (8)                      | +                         |
| 13 F        | 21  |     | Pain, paraesthesiae | (8)                      | +                         |
| 14 M        | 39  |     | Pain               | (5)                      | +                         |

Numbers in brackets indicate duration in years of remission between paroxysms and next symptom in patient 1, 8, 9 and 10 and of continuing remission since paroxysms in patients 2–7 and 11–14.
Each episode starts with slurring of speech which is usually accompanied by ataxia of gait and more rarely by incoordination of one or both upper limbs. The average duration of each attack is 15 seconds. Sensory symptoms accompanying the paroxysms of dysarthria have been reported by Matthews in six patients, all of whom reported a burning numbness or tingling sensation involving one side of the face at the onset of each attack. Three patients also had transient sensory disturbances involving one upper limb accompanying the dysarthria and ataxia. Diplopia occurring during the attacks of dysarthria is reported in three patients. Twenty one patients had noted precipitating factors and in 14 it was reported that the attacks of dysarthria and ataxia could be induced by hyperventilation. Despite this, most individual episodes occurred spontaneously. Successful treatment with carbamazepine (average dose 300 mg/day) was reported in 17 patients. Ten patients received phenytoin with a good response in two, two others obtained only partial relief and the remaining six did not respond. Voiculescu, Pruskauer-Apostol and Alecu described two patients treated successfully with acetazolamide.

**Paroxysmal diplopia**

Paroxysmal diplopia has already been referred to briefly in association with dysarthria and ataxia. However Osterman and Westerberg described three patients who experienced paroxysmal episodes of double vision unaccompanied by any other symptoms. The attacks occurred about 50 times per day and lasted approximately 60 seconds. In two, this was the first symptom, one of whom, a 25 year old female, had clusters of attacks for three years before other symptoms and signs of MS developed. It is interesting to note that in this patient, relatives observed strabismus during the attacks. She had a moderately good response to carbamazepine 800 mg daily with recrudescence of symptoms on withdrawal of the drug. Carbamazepine was reported to be effective in one other patient, although details are lacking.

**Other brain paroxysms**

A further constellation of brain stem symptoms were described by Osterman and Westerberg in two men who developed paroxysmal hemi-ataxia and paraesthesiae during the course of their disease. In each, the attacks started with an unpleasant prickling and sometimes painful sensation on the side of the face and ipsilateral arm followed immediately by ataxia of the contralateral arm and leg lasting between 10 and 30 seconds, and recurring about five times an hour. In the second patient, the attacks were accompanied by dysarthria. Both responded immediately to carbamazepine. We have not found reports of paroxysmal vertigo as an isolated or predominant symptom, perhaps because it is difficult to evaluate, although it commonly occurs in association with brain stem disturbances in MS.

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**Table 2 Author reference and paroxysms described**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Dysphonia</th>
<th>Diplopia</th>
<th>Hemianesthesiae</th>
<th>Tonic seizures</th>
<th>Paraesthesiae</th>
<th>Pain</th>
<th>Akinesia</th>
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</table>

Total: 47 3 2 64 7 9 3 18

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*This patient was reported by Espir et al in 1966 (case 6) when paroxysmal dysarthria, diplopia and ataxia responding to carbamazepine had been the sole manifestation. A year later other evidence of MS developed and the case was included by Espir and Millac in their 1970 paper.
Tonic seizures

Tonic seizures (TS) in MS were first described by Matthews and since then over 60 cases with various types of TS have been documented by others (see table 2). The mean age of onset of TS was 36 years with a slight female preponderance. TS was the first symptom in seven patients, three reported by Castaigne et al., two by Joynt and Green and two by Matthews. The duration of remission before other manifestations of MS developed in the six cases in which this was stated ranged from two months to four years. We have not ourselves encountered TS as the initial manifestation of MS.

The diagnosis of MS was in doubt in four of the patients reported by Matthews. Ekbom et al. described two patients with spinal sensory motor seizures, only one of whom had MS. Twenty-nine patients noted precipitating factors, the majority being triggered either by tactile stimulation or trunks movements. Each attack occurred without warning, the limb(s) going into tonic spasm without associated clonic movements or loss of consciousness. The spasms were painful in 25 patients.

Of 34 patients in whom details of the TS were described, the following characteristic patterns emerged: in 15 patients the arm was held in a tetany-like fashion with adduction at the shoulder, flexion at the elbow, wrist and metacarpophalangeal joints and extension at the interphalangeal joints. Simultaneous involvement of the ipsilateral lower limb was not invariable but when present Matthews reported varying degrees of hip and knee flexion, the feet and toes being held in spasm like the hand. Nine patients similar in many ways to the above, differed in some detail in that the hand was held with the fist clenched. Two reported by Matthews had a “claw hand” with extension of the metacarpophalangeal joints and flexion of the interphalangeal joints for the duration of each attack. Simultaneous bilateral involvement was described in 10 patients, the legs being more frequently affected alone, although in three patients, all four limbs were involved and in one both arms were affected simultaneously. Esquir and Mil lac also described a patient (case 2) with MS who had a bout of TS affecting first the right side, and two years later had a second cluster of TS affecting the left side.

Seven patients with TS reported by Shibasaki and Kuroiwa also had transient sensory disturbances in the involved limb preceding the attack and lasting only a few seconds. Castaigne et al. described TS with sensory symptoms in five patients, the sensory disturbances involving the contralateral limb in one, a feature also noted by Kreindler et al. and Ekbom et al. who described this as the “Brown-Sequard syndrome in reverse.” Matthews noted one patient whose left sided tonic seizures were preceded by a burning sensation behind the contralateral scapula. Other symptoms associated with TS include dysarthria reported in two by Matthews and one by Castaigne et al. while in one reported by Kuroiwa and Araki sweating of the ipsilateral limb immediately followed each attack. The efficacy of treatment of TS with carbamazepine is now well established and details are available of 18 patients treated successfully with this drug (average dose 400 mg per day). Six out of nine patients treated with phenytoin (average dose 300 mg per day) responded satisfactorily while four out of five were helped by phenobarbitone.

Paroxysmal paraesthesiae

Paroxysmal sensory disturbance occurring as the predominant symptom are described in seven patients (see table 2). Reference has already been made to the sensory symptoms occurring in association with both tonic seizures and paroxysmal dysarthria and ataxia. Sensory paroxysms were the first manifestation of MS in two patients. One was a man aged 45 who was successfully treated with carbamazepine for over 12 months. He developed further manifestations of MS shortly after the onset of these attacks. In the other, a man aged 33, the attacks ceased spontaneously after seven months, and he later developed undoubted MS.

The mean age of onset of paroxysmal sensory disturbances was 47 years. The paraesthesiae had an average duration of 15 seconds, usually affected one limb only and occasionally had an unpleasant quality. In one patient both legs and in another the unilateral arm and leg were involved simultaneously. Four patients treated with carbamazepine responded satisfactorily.

Paroxysmal pain

Repeated shortlived attacks of severe pain usually involving one limb are the hallmark of this variety which has been described in nine patients (see table 2). Seven of whom were males. The mean age of onset was 38 years. In two patients it was the first symptom. In one, a man aged 46 years there was a two year interval, when pain was controlled with carbamazepine and acetazolamide, before further manifestations.
of MS developed. The other, a man aged 28 developed right sided paraesthesiae three months after the painful paroxysms had remitted spontaneously.17 Few details are reported on the quality of pain other than its severity although Osterman and Westerberg17 described the discomfort as an “ache” occurring in brief attacks of five to ten seconds duration up to 12 times daily. The pain was accompanied by minor sensory and motor disturbances in the affected limb in three patients reported by Espir and Millac18 and in one reported by Voiculescu.18 Seven patients were treated with carbamazepine (average dose 500 mg per day) five responding almost completely and two partially, although the latter were unable to tolerate doses in excess of 400 mg per day). However similar brief episodes of pain may accompany conditions other than MS31 and may respond partially or completely to treatment with carbamazepine, irrespective of aetiology.

Paroxysmal itching
Paroxysmal itching was described in three patients all female.19 32 In one it was the first symptom lasting for two months and occurring three years before she developed further manifestations of MS. The itching was intense and not relieved by scratching or pinching the affected area. The upper limbs were affected in two patients while the third had trunkal involvement in a T7 and T8 distribution. Attacks could be precipitated by sensory stimuli in all patients and occurred up to 80 times daily, each paroxysm lasting an average of five minutes. All responded to carbamazepine (average dose 800 mg per day) although in two the relief was only partial.

Paroxysmal akinesia
Zeldowicz23 described 12 patients with “paroxysmal motor episodes” and since then six further patients with MS have been reported appearing under a variety of names as “les manifestations motrices paroxystiques,”12 “paroxysmal loss of use”16 and “paroxysmal akinesia.”17 The mean age of onset was 31 years. In those reported by Zeldowicz, all twelve patients presented with akinetic attacks as the first symptom of their disease. The time lapse to the diagnosis of MS ranged from 2-21 years (mean 9 years) with a mean age of onset of 33-5 years. Castaigne et al12 reported one patient (case 8), a 22 year old female, in whom this was the first manifestation of her disease. There was then a remission for two years before further symptoms of MS developed.

Characteristically there is sudden loss of power of a limb or limbs described by the patients as “knees locking,” “legs collapsing,” “legs don’t go,” “unexpected falls,” followed by rapid recovery. The legs were more frequently involved, although Castaigne12 described one patient whose right hand would become weak for 10–20 seconds while playing the piano. The paroxysmal nature of those described by Zeldowicz is undoubtedly reflected by recovery from each attack did take “a few minutes.” In the remaining patients from the above authors, recovery was more typical taking from between a few seconds to two minutes and the attacks recurred as frequently as four per hour. Four out of five patients treated with carbamazepine responded satisfactorily. In one only17 were details given of the dosage used and treatment was withdrawn after two weeks following the development of a rash.

Discussion
In this paper we describe a further 14 patients who developed paroxysmal neurological symptoms and in whom the diagnosis of MS is (clinically) definite, probable or suspected. Previous reports of 153 patients with paroxysmal disturbances other than trigeminal neuralgia and epilepsy have been reviewed.

It is difficult to establish the incidence of paroxysmal symptoms in MS. Osterman and Westerberg17 reported 22 out of 235 suspected or definitely diagnosed patients over an eight year period (excluding trigeminal neuralgia). Espir and Millac32 saw 23 out of 600 patients over a similar period. The incidence of the Japanese on the other hand claim a frequency as high as 17% with painful tonic seizures being the most frequently encountered.20 It is equally difficult to establish the incidence of paroxysmal symptoms as the first manifestation of MS. In a previous series,15 six out of 23 patients with paroxysms other than trigeminal neuralgia presented in this way. Of the 153 patients in this present review of the literature, 36 have had paroxysmal symptoms as the initial manifestation of MS. The duration of remission before subsequent manifestations of MS developed (in those recorded) ranged from two months to 21 years (see table 3).

In our present series, seven out of 14 patients had paroxysmal symptoms as the first manifestation of their illness. Although the diagnosis of MS has not yet been established in all our cases, the paroxysms are of the types encountered in patients known to have MS, and similar to those we have reviewed. It is of course conceivable that
The paroxysms may precede other symptoms by months or years, the mean interval being 5-6 years in those patients reported in the literature. Thus in the absence of a specific diagnostic test for MS, the awareness that paroxysmal symptoms may be the first clinical manifestation of MS is important, particularly in view of their response to carbamazepine and in anticipation of specific treatment being available and effective in the early stages of the disease in future.

The pathophysiology of these paroxysmal attacks remains conjectural. A cerebral origin with cortical epileptic discharges seems unlikely; the clinical, electroencephalographic and autopsy evidence does not support such a hypothesis. Matthews21 was initially impressed by the "tetanic" posture adopted during tonic seizures although he modified this view in his 1975 paper. This feature and the fact that attacks can readily be precipitated by hyperventilation led him to postulate that reduction in ionised calcium may be relevant. This is known to facilitate transmission through plaques of demyelination.34-35 Kuroiwa and Araki24 suggested that "inflammatory irritation" was likely to be responsible for the symptoms, and Ekborn et al28 postulated a transversely spreading activation of axons at the affected level in the spinal cord possibly triggered by afferent sensory stimuli. Osterman and Westerberg17 elaborated on this hypothesis and used it to correlate the symptoms of each paroxysm with the anatomical localisation of the plaque. Zeldowicz33 alluded to the possibility that "sudden and transient anoxia whether due to vascular or biochemical disturbances" might be relevant. Espir and Millac13 postulated that "paroxysms result from a degree of demyelination insufficient to give persistent deficit, but rendering axons hypersensitive to minor stresses." The sensitivity to hyperventilation suggested that the resultant metabolic changes or decrease in blood flow and minor degrees of hypoxia might be sufficient to trigger the affected neurones.

**Drug treatment**

The response of all types of paroxysms to carbamazepine is often dramatic, and of the 58 patients reported in sufficient detail (see table 4)
all responded, although six obtained only partial relief. Carbamazepine was withdrawn and substituted by placebo in 11 patients and in each, symptoms returned rapidly to be relieved once more on restarting therapy. Side effects due to carbamazepine were not troublesome and were reported in only eight patients. Treatment with carbamazepine was reported in only five of the 36 in whom the paroxysms were the first manifestation of MS. In our present series the efficacy of carbamazepine was confirmed; of the seven patients treated, five obtained relief, in one the drug had to be withdrawn owing to a rash and only one had no benefit. Seven patients did not receive treatment as their symptoms had regressed spontaneously. It is interesting that in our present series, treatment with carbamazepine was given to only one of seven patients whose paroxysmal symptoms were the first manifestation of MS, but to six of the seven patients who had paroxysmal symptoms preceded by other manifestations of MS.

Other anticonvulsant drugs have been tried but relatively few patients have responded to them as well as to carbamazepine, and double blind studies have not been reported. Voiculescu et al. reported successful treatment of brain stem and spinal cord paroxysms with acetazolamide. Although this was not a double blind study, in four cases withdrawal of medication was followed by immediate recurrence of the attacks. They claim an efficacy equal to that of carbamazepine but the rationale for using acetazolamide was not discussed.

Since first reported to Blom, carbamazepine has become the drug of choice in the treatment of tic douloureux and the often dramatic response of the paroxysmal disorders of MS to this drug suggests some similarity between these conditions. The mode of action of carbamazepine in paroxysmal disturbances is not clear. In the experimental animal carbamazepine is known to depress synaptic transmission in the spinal trigeminal nucleus. Depression of ephaptic transmission through and around demyelinated plaques would seem a credible explanation for the efficacy of carbamazepine in treating paroxysmal disturbances.

We wondered whether there might be a correlation between the anatomical site of the paroxysms and response to treatment, that is whether paroxysms of brain stem origin were more susceptible to the effects of carbamazepine than those originating in the spinal cord. This hypothesis might be justified on simple anatomical grounds, in that minute areas of demyelination being more likely to cause symptomatic dysfunction by disrupting afferent impulses in the complex structures of the brain stem while larger areas might have to be involved to exert an effect at spinal cord level. However the site of origin of paroxysmal symptoms did not appear to influence the response to therapy in individual patients and their occurrence from any level within the central nervous system warrants a trial of treatment with carbamazepine.

Differentiating these attacks from focal epilepsy or transient cerebral ischaemia may prove difficult in early cases, particularly if the paroxysmal disturbance is the presenting manifestation of MS. A relatively young age of onset, no evidence of cardiovascular disease, a normal EEG during attacks, and response to carbamazepine or spontaneous remission all favour underlying demyelination. However, the diagnosis will frequently remain in doubt until other symptoms and signs of MS become evident.

Appendix

Patient 1 BD, a 36 year old male, was first seen in 1973 when he gave a four month history of attacks of slurred speech with associated incoordination. These lasted for about 15 seconds and occurred up to 10 times per day. On examination there was slight incoordination of both legs with hyper-reflexia and bilateral extensor plantar responses. Investigations included cerebro-spinal fluid (CSF) examination, skull X-rays, EEG and isotope brain scan, which were normal. The paroxysms remitted spontaneously after four months and he remained well for almost four years when he developed increasing ataxia and lower limb weakness. On examination then, he was euphoric with pallor of both optic discs. There was nystagmus on lateral gaze to the left and right with incoordination of both arms and legs. Tone was increased in the legs with hyperreflexia and bilateral sustained ankle clonus. Both plantar responses were extensor. Further investigations in 1977 included a normal CAT scan and negative WR. CSF contained no excess of cells, protein was 45 mg/1 with a high level of immunoglobulins (15-5 mg%); Lange colloidal gold test 2111000000. There was a prolonged latency of the visually evoked response in the right eye. He improved following a course of physiotherapy and has had no further relapses or paroxysmal symptoms.

Patient 2 BD, a 43 year old female, was seen in 1976. She gave a four month history of episodes of dysarthria each lasting a few seconds and
recurring up to 50 times daily. Neurological 
examination was normal. As the attacks had 
subsided spontaneously, no treatment was given. 
She has remained well since.

Patient 4 DR, a 37 year old male, attended in 
1976 complaining of episodes of diplopia lasting 
a few seconds and occurring up to ten times 
daily. There was no abnormality on neurological 
or general examination. The attacks subsided 
without treatment and he has since remained 
symptom free.

Patient 6 MP, a 25 year old female, was seen in 
1973. She complained of bouts of sharp pain in 
her left arm and hand lasting two to three min-
utes, recurring approximately every 30 minutes 
for about eight months. Physical examination 
was normal. Her symptoms resolved sponta-
neously and no therapy was given.

Patient 7 BG, a female aged 27 years, was seen 
in 1970. She complained of episodes of para-
esthesiae involving the left side of the face, arm 
and leg. Less frequently the right side was 
involved. Each episode lasted five to 30 seconds 
and occurred up to 14 times daily. There were 
no precipitating factors. Physical examination was 
normal. She was started on carbamazepine 600 mg 
daily which markedly reduced the number of 
attacks. Nine months later she was symptom free 
and has remained well since.

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