LETTERS TO THE EDITOR

Treatment of paroxysmal symptoms in multiple sclerosis with bromocriptine

Paroxysmal symptoms are known to occur in multiple sclerosis and have a wide clinical range. We report two patients whose paroxysmal symptoms resolved with bromocriptine.

A 35 year old woman with a three year history of multiple sclerosis complained of paroxysmal upper and lower limb paresthesiae. She described these as "tingling sensations" beginning in her feet and ascending to her waist, and from her hands up to her shoulders, bilaterally. These sensations occurred in the upper and lower extremities simultaneously as well as independently. The symptoms lasted a few hours every day and remitted spontaneously. Occasionally, she complained of mild slurring of speech during these paroxysmal attacks. Neurological examination showed weakness of the hamstrings bilaterally and symmetric diffuse hyperreflexia.

Previous attempts to control her symptoms with carbamazepine, barbiturates and amitriptyline gave little relief. Bromocriptine at an initial dose of 2·5 mg twice a day was started, and led to appreciable reduction in the patient's symptoms. The dose was increased to 5 mg twice a day a week later, and the symptoms completely resolved. Discontinuation of bromocriptine six months later led to an immediate recurrence of her paroxysmal symptoms as described previously. Resumption of bromocriptine treatment was again successful in resolving her symptoms. Two further attempts to discontinue bromocriptine were unsuccessful, as the patient's symptoms recurred on each occasion. The patient tolerated bromocriptine well except for mild nausea.

She has since been maintained on 5 mg of bromocriptine twice a day and on follow up remains asymptomatic. Since the introduction of bromocriptine her dose of amitriptyline has been decreased from 75 mg to 30 mg at night.

A 38 year old man with multiple sclerosis for six years developed episodic numbness of the entire right half of his face. The numbness occurred daily, lasted a few hours, and remitted spontaneously. These paroxysmal attacks began two years ago. The patient had been unsuccessfully treated with amitriptyline. Neurological examination showed generalised hyperreflexia with mild impairment of tandem gait.

Bromocriptine at an initial dose of 2·5 mg twice a day was started and this was increased to 5 mg twice a day a week later; it resulted in resolution of his symptoms. The patient discontinued bromocriptine, and the paroxysmal facial numbness recurred within a day. Bromocriptine was resumed and this again resulted in resolution of his symptoms.

Six months later on follow up, the patient remained free of his paroxysmal attacks while taking bromocriptine at a dose of 5 mg twice a day.

This is the first report of bromocriptine in the treatment of paroxysmal symptoms in multiple sclerosis. A placebo response cannot be excluded.

There is evidence that the hormone prolactin, which is secreted by the anterior pituitary, has a stimulatory role on the immune function as first shown by the pioneer work of Nagy and Berczi.[1] Later work showed that bromocriptine, a dopaminergic agonist, selectively inhibits prolactin release.[2] Hauser *et al* showed that bromocriptine inhibited both the secretion of prolactin as well as the severity of acute rat experimental allergic encephalomyelitis (EAE),[3] a commonly used animal model in the study of multiple sclerosis. In the same study, it was shown that the clinical course of EAE was also modified and late relapses of EAE were significantly reduced.

Although ephaptic spread from a demyelinated lesion is widely accepted as the most plausible explanation of paroxysmal symptoms in multiple sclerosis,[4] the exact mechanism of such symptoms remains poorly understood. Suppression of the ephaptic spread seems to be the most likely mechanism of action of carbamazepine and phenytoin, two drugs commonly used to treat paroxysmal symptoms in multiple sclerosis. Other drugs, such as acetazolamide, have also been used to treat paroxysmal symptoms in multiple sclerosis.[5] One of us (OAK) has already reported that ibuprofen can be used to successfully treat paroxysmal symptoms in multiple sclerosis.[6] It remains unclear as to how agents such as bromocriptine, that may suppress the immune system, may also suppress paroxysmal symptoms in multiple sclerosis.

Paroxysmal symptoms can be seen in multiple sclerosis. This report of two patients whose paroxysmal symptoms were successfully treated with bromocriptine is encouraging and suggests the need for a clinical trial to investigate the efficacy of bromocriptine in the treatment of paroxysmal symptoms in patients with multiple sclerosis.

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Onset symptoms of multiple sclerosis

The date of the clinical onset of multiple sclerosis is routinely used for epidemiological studies of incidence and prevalence. To date there are no uniform criteria to be used for that purpose, making comparisons between various studies difficult. Patients, and often their physicians, may date the onset of the disease to such non-specific symptoms as headaches, backaches, seizures, nervousness, or tremulousness. This article attempts to standardise the method of dating the clinical onset of the disease by establishing a list of definite and possible symptoms. These symptoms can be used only in cases that have been diagnosed as definite or probable multiple sclerosis.[1]

The proposed list of symptoms is based on the author's long clinical experience and that of the multiple sclerosis experts who were consulted.

With rare exceptions the date of symptomatic onset is obtained from the patient's history. In some instances, such as optic or retrobulbar neuritis, transverse myelitis, or acute monoparesis, the patient will almost certainly have sought medical attention at that time, so that documentation might be available. In other situations, the potential relevance of a particular symptom may not have been recognised by either the patient or the physician and may have been ignored or initially ascribed to another cause.

Because epidemiological studies must be based exclusively on patients who have been diagnosed as having definite or probable multiple sclerosis, the symptoms listed here are only a few of the constellation of symptoms and signs that develop later and form the basis for the diagnosis. Because the diagnosis of multiple sclerosis can never be established on the basis of the first episode, information about onset symptoms must be obtained retrospectively, and patients must be carefully questioned about these symptoms to determine their accuracy. The availability of medical records confirming the existence of these symptoms, perhaps when associated with abnormalities of the neurological examination, will greatly increase the value of the data.

The symptoms have been divided into *definite* and *possible* (table). *Definite* symptoms must have been present for a minimum of 24 hours. To be considered as *possible* symptoms of onset, a *definite* symptom must have appeared within two years.

To establish the importance of these symptoms, confirmatory information will have to be obtained by carefully questioning the patients.

Optic/retrobulbar neuritis is almost invariably preceded by pain in or behind the affected eye, associated with a decrease of monocular vision. Clearly, as with all the other symptoms listed, other causes must have been ruled out before the symptom is accepted as signifying the onset of the disease. Bilateral optic/retrobulbar neuritis is unusual in multiple sclerosis and, in this context, must be interpreted with caution.

Acquired monocular colour blindness, oscillopsia, and acute unilateral loss of hearing are extremely rare but, when present, practically pathognomonic for multiple sclerosis.[2] True binocular diplopia can be established only if the double image disappears when closing either eye. Tic douloureux must not be confused with simple facial pain. It is characterised by lightning pains usually occurring in series but each lasting for no more than one or two seconds.

Transverse myelitis, like optic/retrobulbar neuritis, may well be a symptom of an acute postinfectious or postvaccinal encephalomyelitis.

Onset symptoms of multiple sclerosis

Definite:
These symptoms must last for at least 24 hours.

- Unilateral optic/retrobulbar neuritis
- Acquired monocular colour blindness
- Oscillopsia
- True binocular diplopia
- Tic douloureux (under age 40)
- Hemifacial spasm (under age 40)
- Acute unilateral diminution of hearing (under age 40)
- Transient acute non-positional vertigo (under age 40)
- Transient scanning speech
- Transverse myelitis
- Lhermitte symptom
- Gait ataxia
- Unilateral dysmetria/intention tremor/incoordination
- Sensory useless hand syndrome
- Transient weakness/paraesthesiae of one entire limb
- Transient painless urinary retention (under age 40)
- Transient painless urinary urgency/incontinence in men (under age 40)

Possible:
For these symptoms to be used as onset markers, they must be followed by a definite symptom within two years.

- Unilateral facial palsy
- Transient painless urinary frequency in men (under age 40)
- Transient hemiparesiss (under age 40)
- Organic erectile dysfunction
- Painful tonic seizures

To accept a Lhermitte symptom, it is desirable, although not required, that the symptom be transient. More important, however, is the fact that other causes for this symptom, in particular herniated nucleus pulposus or spondylosis in the cervical region, must have been ruled out. Gait ataxia and unilateral dysmetria/intention tremor/incoordination may be manifestations of involvement of the cerebellum or of the posterior columns with loss of position sense. Unusual clumsiness, dropping things, changes in handwriting, and inability to perform fine hand movements or activities such as sewing, embroidery, or fine instrument manipulation, may be the expression of these problems affecting the hands. The reason that they must be unilateral to indicate multiple sclerosis is to rule out familial essential tremor or the fine tremor of hyperthyroidism, which are invariably bilateral.

The useless hand syndrome[2] has an acute or subacute onset and consists of paraesthesiae and numbness in one arm and a decreased ability to use the hand properly. Men often report that they cannot use that hand to identify coins in their pocket, and the same applies to women trying to search for objects in their purse. Handwriting is usually impaired as well.

Transient paraesthesiae are understood to involve only one entire limb to differentiate them from the much more common carpal tunnel syndrome, as well as from the frequent complaint of bilateral numbness of the arms and hands on awakening or involving both legs with lumbosacral spine disease. Painless urinary urgency or incontinence in women is very often a symptom of bladder infection and therefore is relevant only when it occurs in men. Acute urinary retention occurring under the age of 40 distinguishes it from the problems caused by prostatic enlargement and some gynaecological difficulties in women.

Symptoms considered as "possibly relevant" should be counted only if a definite symptom as listed here occurs within two years. Facial palsy is a very common problem but rare as a presenting symptom of multiple sclerosis. In men urinary frequency and transient hemiparesis, both occurring under the age of 40, are fairly specific, but other conditions causing these same symptoms occur often enough to dictate caution in using them in this set of criteria. Impotence to be classified as organic erectile dysfunction must include the lack of morning erection. It does not, however, include the inability to achieve orgasm. Finally, painful tonic seizures again are nonspecific although probably more frequent in patients with multiple sclerosis than in any other conditions.

The original lists were reviewed by the following multiple sclerosis specialists: Johan Aarli, Bergen, Norway; Peter Behan, Glasgow, UK; John Benedikz, Reykjavik, Iceland; Alastair Compston, Cambridge, UK; Floyd Davis, Chicago, USA; Geoffrey Dean, Dublin, Eire; John Kurtzke, Washington, DC, USA; Brian Matthews, Oxford, UK; Ian MacDonald, London, UK; Donald Paty, Vancouver, Canada; Sigrid Poser, Göttingen, Germany; Giulio Rosati, Sassari, Italy; Randall Schapiro, Minneapolis, USA; Labe Scheinberg, New York, USA; and Donald Silberberg, Philadephia, USA. Many useful comments and suggestions were made, most of which were incorporated into the final list. Endorsement of the lists of symptoms by these specialists is not implied.

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Multiple sclerosis in the Parsis

During the course of a search for patients with multiple sclerosis among Asian immigrants resident in England, five Parsis have been found with definite multiple sclerosis, one male and four female. The Parsi are Zoroastrians who left Persia (Iran) and settled in India, mostly in Bombay. They are a closely knit community. According to the Religious and Cultural Centre of the Parsi and Irani Zoroastrian community there are around 5000 Parsis resident in England and Wales and most of the adult members of the community came to England from the Indian subcontinent or East Africa.

By contrast with the Parsis multiple sclerosis is very uncommon among ethnic Indian immigrants to England and Wales,[1-3] and also among Indians in India.[4,5] During a 25 year search for patients with multiple sclerosis among Asian immigrants to England only 23 patients have been found among ethnic Indian immigrants, although in 1981 there were 383 000 immigrants from India and a further 193 000 immigrants from East Africa resident in England and Wales and most of these immigrants were of Indian ethnic origin.

The prevalence of multiple sclerosis in the Parsis of Bombay is also much higher than among ethnic Indians.[4-6] The high prevalence of multiple sclerosis among Parsi immigrants to England, by contrast with the very low prevalence among ethnic Indian immigrants, may be an important clue to the genetic and environmental factors responsible for the disease.

We would be most grateful if any doctor who knows of a Parsi with multiple sclerosis would, with the permission of the patient, notify Dr Geoffrey Dean at the address below.

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A new treatment of spasticity with repetitive magnetic stimulation in multiple sclerosis

Electromagnetic fields easily penetrate tissues, independent of tissue density and resistance. This property is applied in transcranial magnetic stimulation of neocortical neurons used to evaluate motor pathway function. Similarly, deep seated neurons in the spinal cord can be evoked by non-invasive trans-spinal magnetic stimulation. We designed a magnetic stimulator with repetitive stimulation capability to study the effect of magnetic stimulation on spasticity in multiple sclerosis.

The study was performed as a comparison of pretreatment and post-treatment

Onset symptoms of multiple sclerosis.

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Notes