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Levetiracetam can be effective in the treatment of restless legs syndrome with periodic limb movements in sleep: report of two cases

Restless legs syndrome (RLS) is an awake phenomenon characterised by an intense, irresistible urge to move the legs, sensory complaints, and motor restlessness. RLS is usually associated with periodic limb movements in sleep (PLMS). Clinical evidence suggests that dopaminergic agents are the treatment of first choice. Dopaminergic treatment is usually effective, but many patients develop augmentation.¹ Augmentation is the worsening of RLS symptoms attributable to a specific therapeutic intervention; its primary feature is a shift of RLS symptoms to an earlier time than was typical at symptom onset during the initial course of beneficial stable treatment.² Augmentation requires the withdrawal of dopaminergic agents. Anticonvulsants may be used if the response to dopaminergic agents is not adequate or if augmentation occurs.¹

We describe two patients affected by RLS with PLMS who became unresponsive to the traditional dopaminergic agents and

Table 1 Results of clinical and instrumental evaluations

	Baseline	Pramipexole	Augmentation	Levetiracetam
Patient no. 1				
IRSSG scale score	34	21	35	22
Suggested immobilisation test				
PLM index (events/h)	39	26	40	11
Epworth sleepiness scale	14	10	13	10
Polysomnography				
Sleep latency (min)	165	34	172	27
Sleep efficiency index (%)	77.3	90.5	78.4	89.3
PLM index (events/h)	41.5	23.1	45.6	10.9
Patient no. 2				
IRSSG scale score	27	15	31	18
Suggested immobilisation test				
PLM index (events/h)	45	29	47	21
Epworth sleepiness scale	12	9	13	11
Polysomnography				
Sleep latency (min)	194	35	125	32
Sleep efficiency index (%)	71.2	85.6	79.5	89.9
PLM index (events/h)	64.2	31.5	45.6	12.6

IRSSG, International Restless Legs Syndrome Study Group; PLM, periodic limb movements; PLM index, number of events per hour of time in bed. Sleep efficiency index: percentage of time in bed spent asleep. Sleep latency: interval between lights off and the first epoch of stage II NREM.

developed augmentation. Both patients were treated with the antiepileptic drug levetiracetam and showed a clear and persistent clinical improvement of both RLS symptoms and PLMS. The clinical assessment and follow up included: subjective evaluation of symptoms and their impact on everyday life by means of the International Restless Legs Syndrome Study Group (IRLSSG) rating scale; evaluation of daytime sleepiness with the Epworth sleepiness scale; a suggested immobilisation test (SIT); and overnight, laboratory based polysomnography (PSG). Patients gave written informed consent to the use of levetiracetam. Results are given in table 1.

Patient no. 1

Patient no. 1, a 58 year old man, had been affected by rheumatoid arthritis since the age of 34. He presented the first symptoms of RLS at the age of 40, characterised by a creeping sensation at rest, prevalent in the left lower limb, and severe insomnia. He had no familial history of RLS. Initially, he was treated with clonazepam with partial benefit, then with carbamazepine (600 mg) without success. In the following years he reported progressive worsening. RLS interfered with his work, since he was a manager, and he became unable to sit in meetings. He came to our attention at the age of 53. He reported severe RLS with sleep latency >3 h. EMG, and brain and spine MRI were normal. Ferritin levels were low (50 ng/ml); iron supplementation normalised the blood levels of ferritin, but symptoms did not remit. RLS was associated with PLMS (table 1). The patient complained of severe daytime sleepiness and depressed mood. Pramipexole (0.18 mg at bedtime) was started, with immediate clinical improvement which persisted for about 6 months. However, the patient then developed drug resistance and augmentation. Pramipexole was progressively titrated up to 2.1 mg and cabergoline (4 mg) was added. Since no amelioration occurred, the patient switched to ropinirole (5 mg), then gabapentin (1800 mg), L-dopa (500 mg), and again clonazepam and carbamazepine, all of which proved ineffective. Therefore, levetiracetam was started

(1000 mg at bedtime). Immediately, the patient presented a clear subjective benefit, consisting of a reduction in the restless sensation, a reduction in the time spent walking before sleep onset, and a subjective improvement in sleep quality as well as in daytime sleepiness. PLM index was decreased both in PSG and SIT. After 26 months the patient is still taking levetiracetam (1000 mg) at bedtime with satisfactory control of RLS symptoms.

Patient no. 2

Patient no. 2 was a 44 year old woman. Her mother and sister were affected by RLS. RLS symptoms started at the age of 30 and consisted of a burning sensation in her lower limbs and severe insomnia. Traditional sleep inducing drugs and carbamazepine provided no benefit. In the following years she reported a progressive worsening of restlessness, which spread to the upper limbs, and insomnia. She developed a nocturnal eating and drinking syndrome, which led to a 10 kg weight gain. She came to our observation at the age of 39. At that time, she reported severe RLS, with a sleep latency >2 h, and related daytime sleepiness. PSG revealed PLMS. Brain and spine MRI were normal. Ferritin levels were normal. Treatment with pramipexole (0.36 mg at bedtime) was effective. Eight months later she started to complain of re-occurrence of severe RLS symptoms, and pramipexole was increased to 1.4 mg without benefit. Ropinirole (5 mg), cabergoline (2.5 mg), L-dopa (750 mg), and gabapentin (1200 mg) were ineffective. Levetiracetam (500 mg at bedtime) was started, and the patient reported an almost immediate improvement in sensory symptoms associated with reduced sleep latency, increased sleep efficiency, and reduced daytime sleepiness. Currently, the patient is taking levetiracetam (1000 mg) at bedtime, and after a 21 month follow up no relapse of RLS has occurred.

Discussion

The present report concerns two patients with severe RLS with PLMS, who became unresponsive to dopaminergic treatment,

developed augmentation, and were then treated successfully with levetiracetam. Both patients showed no response to traditional anticonvulsants and agreed to test levetiracetam before opioid treatment. RLS was familial in one case and associated with iron deficiency in the other. Levetiracetam was well tolerated in both patients and induced a subjective improvement in the restless symptoms and daytime sleepiness. Objectively, it reduced the PLM index in polygraphic recordings.

Levetiracetam is employed as an adjunctive therapy for refractory partial epilepsy in adults. Its mechanism of action is not fully understood. None of the well established mechanisms of action of classic antiepileptic drugs can be hypothesised for levetiracetam. Recently, it has been demonstrated that the synaptic vesicle protein SV2A is the brain binding site of levetiracetam.³ Some neuropharmacological observations suggest levetiracetam may be useful in the treatment of RLS-PLMS, in the treatment of neuropathic pain,⁴ and in reducing L-dopa induced dyskinesias in Parkinson's disease.⁵ The choice of levetiracetam was justified by the need to test, in drug resistant patients, a non-dopaminergic agent, and in particular an anticonvulsant, as suggested by the management algorithms for RLS.¹

Our observations suggest that levetiracetam can be useful in the treatment of RLS unresponsive to traditional dopaminergic agents. The 2 year follow up suggests that the therapeutic effect may be long lasting; this is particularly interesting, since it is well known that the therapeutic efficacy of many drugs employed in RLS can be transient. More systematic evaluations of levetiracetam in controlled trials are needed to confirm these findings.

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BOOK REVIEWS

Palliative neurology

Edited by Ian Maddocks, Bruce Brew, Heather Waddy, Ian Williams. Published by Cambridge University Press, Cambridge, 2005, £29.99 (softcover), pp 252. ISBN 0-521-67249-x

This book is a well-written introduction to the ideas, philosophy and interventions of palliative care as applied to neurology. It joins a small but growing list of similar works, such as *Palliative Care in Neurology* (Volz et al, 2004). The focus of the book is around the meaning and application of supportive and palliative care. The first section gives an introduction to the basic tenants of palliative care such as the focus on the patient, communication, and effective team working. The historical background allows a discussion of supportive, palliative and terminal care for different disease trajectories and a recognition that these "phases" overlap. It does not specifically define specialist palliative care, apart from referral to a hospice, and perhaps misses an opportunity to discuss the often excellent multi-disciplinary work currently carried out in neurology and the role of specialists in palliative care (eg complex symptom management, terminal care, etc). It covers the trigger points for generalist palliative care, such as at diagnosis, change in physical or psychological condition or terminal phase, the common problems (poor team working, lack of clear documented communication, boundary working) and some common themes for good palliative practice (documentation of symptom control, carer support, etc).

The second section focuses on specific symptom control, such as fatigue, pain and others. All common symptoms are dealt with, the breadth allowing only the briefest of pathophysiology, complications and other interactions to be discussed. However, suggested treatments are clearly, sometimes simplistically, presented with dosing regimes, which would make for easy reference. The third section reviews the specific palliative care and terminal care needs of 11 different neurological conditions, such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), and dementia. Each condition is briefly introduced, assuming a wider knowledge of the neurology, and concentrates on specific areas of palliative care. For example, in the ALS chapter it is divided into the Palliative phase: breaking the bad news, end of life discussion, the supportive phase: fasciculation, hypoxia, communication, dysphagia, constipation and psychological issues and the terminal phase: pain, immobility, choking fears, requests for euthanasia.

No book would be complete without a more concentrated discussion on the ethical dilemmas and issues surrounding proxy-decision making, euthanasia, advanced directives, decisions in non-competent adults and terminal sedation. These areas are handled clearly, with some useful examples of advanced directives, definitions and some points that inform the arguments on both sides. The final part of the book are the appendices giving more details of the practical aspects of palliative home care, team organisation, education, drugs with common doses and further reading.

The book is a useful addition to the few already available. It is aimed at neurologists who wish to know and understand more about general palliative care. It carefully suggests that the principles of good palliative care can and should be part of all neurology care, although it perhaps falls short of discussing where and when specialist palliative medicine/care may be of help. However, as an introduction to the principles and practical integration of palliative care into neurology it succeeds.

C E Urch

Neurologic disease in women, second edition

Edited by Peter W Kaplan. Published by Demos Medical Publishing, New York, 2005, \$165.00 (hardcover), pp 454. ISBN 1-888799-85-4

That women have particular health issues, often in relation to childbearing, and that some conditions have a female preponderance is not new. However, it is good to see a work that recognises the gender difference and deals with it in some detail. This is the second edition of the book, which is multi-authored, all USA based, with some interesting choices of topics—for example, women, law and neurological disease, frailty in women.

The editor divides the book into three main sections – General issues in women's health, Life stages and neurological disease expression in women and, finally, Neurologic disorders in women. The first section on general issues highlights differences between male and female regional brain structure and metabolic activity largely based on imaging techniques. These differences may contribute to the gender differences in disease processes and alter risk. There are also sociological and epidemiological topics and, more usefully for the physician, a chapter on drug treatments, especially antiepileptic drugs with emphasis given to teratogenicity and changes in metabolism in pregnancy and lactation. There is much useful information in this section.

The chapter on Women, law and neurologic disease is interesting but may not be as helpful as it might have been as the case law quoted is American. However, the chapter does raise issues found in many cultures where no doubt equivalent case law exists.

The section on Life stages takes the reader through from childhood to frailty in elderly women, the latter being an aspect that might appear to be no different in women from men. However, there does seem to be some evidence suggesting that oestrogens are important in maintaining muscle strength with age, an area for more work. Pregnancy, menopause and their association with neurological conditions are explored in some detail within this section.

The last section covers predictable specific groups of disorders—migraine, epilepsy, autoimmune disease—for example, in relation to women. There is a useful section on pelvic floor disorders.

Overall this book has taken a broad and interesting approach to the topic of women and neurology, a field that is likely to expand as we begin to understand more about hormonal influences on disease processes. The information is well referenced and clearly set out with good easily readable tables. With about 50% of the population and hence our