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CASE REPORT

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Tacrolimus-related nocturnal myoclonus of the lower limbs in elderly patients with rheumatoid arthritis

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Abstract Tacrolimus is an effective and well-tolerated treatment for rheumatoid arthritis (RA). We report three cases of strictly sleep-associated myoclonus in RA patients treated with tacrolimus. Although the high-dosage administration of tacrolimus in transplantation is known to cause diverse neurotoxic adverse effects, including myoclonus, no previous cases of myoclonus in RA, especially in association with sleep, have been reported. We suggest that this is not a rare adverse effect, particularly in elderly RA patients.

Key words Myoclonus · Neurotoxicity · Nocturnal · Rheumatoid arthritis · Tacrolimus

Introduction

The new immunomodulatory and anti-inflammatory agent tacrolimus is now widely accepted as an effective and well-tolerated oral therapy for rheumatoid arthritis (RA), even in elderly patients.[1,2] We report three cases of nocturnal myoclonus with or without pain of the lower limbs in patients with RA, induced by tacrolimus treatment. The development of nocturnal myoclonus did not correlate with blood tacrolimus levels or with the duration of tacrolimus administration.

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Case report

Case 1

A 69-year-old woman with poorly controlled RA since 1999 presented in December 2005. The case was complicated by depression and anxiety disorder, leading to a significant fear of disease-modifying anti-rheumatic drugs (DMARDs), particularly methotrexate. Tacrolimus was therefore started as second-line treatment at a dosage of 1.5 mg/day. On day 2, the patient was woken at midnight by sudden myoclonic jerks involving both lower limbs. She reported involuntary flexion at both knee joints, repeating one or two times per second, at times with collision of the knee joints. Myoclonus continued for several minutes despite voluntary efforts. Nocturnal myoclonic attacks then recurred almost every night until the cessation of tacrolimus. Thinking that these episodes were principally related to anxiety and neurosis, tacrolimus was subsequently restarted. However, nocturnal myoclonus reappeared, although the incidence gradually decreased to one episode a week and became tolerable. Neurological examinations did not reveal any abnormalities.

Case 2

A 63-year-old man with a history of refractory RA since 1986 presented in June 2005. Five months after therapy with tacrolimus (3.0 mg/day) was initiated, he experienced myoclonus of the lower limbs during sleep. These episodes were associated with prodromal symptoms, sometimes initially preceded by localized pruritus, but always triggered by unilateral stabbing thigh pain before the affected leg would start shock-like irregular contractions that could not be stopped voluntarily. The affected side varied between attacks. Stabbing pain was instantaneous and felt on the skin. He also reported that nocturnal myoclonus occasionally spread upward to the abdomen. Despite the scale of symptoms, the patient did not mention these episodes until careful questioning during follow-up, as he felt the symptoms

Table 1. Summary details of the three patients with tacrolimus-related nocturnal myoclonus

Case	Sex	Age (years)	Duration of RA (years)	Steinbrocker stage	ACR class	Nocturnal myoclonus	Pain	Other symptoms	Previous treatment	First symptoms	Blood tacrolimus (ng/ml)	Serum Ca/IP (ng/ml)	Serum Mg (ng/ml)
1	F	69	7	IV	3	Lower limbs	None	Anxiety depression fear of DMARDs	NSAIDs, PSL (6 mg/day)	2 days	ND	ND	ND
2	M	63	20	IV	3	Lower limbs/ abdomen	Stabbing thigh pain	Interstitial pneumonitis	NSAIDs, PSL (10 mg/day), DMARDs including methotrexate	5 months	1.7	8.5/2.9	1.7
3	F	82	40	IV	4	Lower limbs	Electric shock-like knee pain	None	NSAIDs, auranofin, salazosulfapyridine	6 weeks	2.2	8.4/4.2	1.9

Normal Ca level 8.2–10.0 ng/ml, normal IP level 2.5–4.5 ng/ml, normal Mg level 1.7–2.6 ng/ml
RA, rheumatoid arthritis; ACR, American College of Rheumatology; PSL, prednisolone; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs, ND, not done; F, female; M, male

were a nuisance but not of significant concern. Myoclonic attacks were predominantly nocturnal, but sometimes occurred during daytime naps, retaining an association with sleep. Seven months later, laboratory tests indicated liver dysfunction requiring withdrawal of tacrolimus. This completely resolved painful nocturnal myoclonus within 1 week. Neurological examinations did not reveal any abnormalities.

Case 3

An 82-year-old woman had refractory RA since 1966. Six weeks after starting tacrolimus administration (2.0 mg/day), she woke at midnight with instantaneous pain and myoclonus of the legs. She described the pain as an electric shock, occurring superficially on the skin around the knee. This pain was then followed by myoclonic jerks of both legs, flexing both knees, at an irregular rate of one or two times per second, and lasting for several minutes. The episodes initially occurred every night, but sometimes pain and myoclonus occurred independently. The frequency of nocturnal myoclonic attacks gradually decreased, disappearing completely within 3 months. However, pain continued and subsequently spread from the knees to the ankles and even began to appear during daytime. The subsequent reduction of tacrolimus (1.5 mg/day) resulted in a complete elimination of the pain.

We regarded the leg contractions described earlier as myoclonus, not tremor, cramp, or other involuntary movements, caused by the shock-like, rapid, irregular movements with knee flexion, and the absence of painful muscle spasm.

No significant differences were noted between the mean ages of the three affected and eight unaffected patients in our clinic (71.3 ± 9.7 years vs. 64.9 ± 17.3 years, respectively). Serological examination revealed no abnormalities of electrolyte levels including calcium, magnesium, and phosphate during tacrolimus treatment in all patients. Renal function, hemoglobin levels, and blood pressure were also routinely checked during follow-up. No correlation was identified between the appearance of nocturnal myoclonus of the lower limbs and measured blood tacrolimus concentrations, and all levels were within normal limits at the onset of episodes. The time between the first appearance of nocturnal myoclonus and the initial administration of tacrolimus varied from 2 days to 5 months (Table 1).

Discussion

Tacrolimus is an immunosuppressive macrolide similar to cyclosporine A, and is known to suppress the enzymatic activity of calcineurin. Several studies have reported the efficacy of tacrolimus against RA,[1,3,4] even in elderly patients.[2] Tacrolimus is also used for immunosuppression following organ transplantation, and is known to cause a number of adverse effects related to neurotoxicity, including tremors, headache, itching, insomnia, nightmares,

paresthesia, visual disturbances, seizures, myalgia, calcineurin-inhibitor-induced pain syndrome, posterior reversible encephalopathy syndrome, and coma.[5–15] Myoclonus has been reported as a rare adverse event with tacrolimus treatment following liver transplantation.[9–11] Although tremors, cramp, muscle convulsions, headache, anxiety, paresthesia, visual disturbances, and seizures have been reported with RA, myoclonus has not previously been reported.[1–3,16,17] Myoclonus may have been included under the larger heading of muscle convulsions, cramp or even seizures in some earlier reports, but discriminating myoclonus from these symptoms is difficult because of a lack of detailed description of events and the latent ambiguity of borderline cases.

In Case 1, the sudden onset of nocturnal myoclonus provoked significant anxiety, and the patient independently decided to stop taking tacrolimus. Withdrawal led to spontaneous resolution of episodes, whereas restarting tacrolimus produced prompt relapse. Similarly, in Case 2, the discontinuation of tacrolimus resulted in complete resolution of nocturnal myoclonus and associated pain. None of these patients had ever experienced similar sleep-related myoclonus or pain prior to administration of tacrolimus, and none were concurrently taking any other medications known to be associated with myoclonus. In addition, none of the 129 RA patients treated without administration of tacrolimus in our clinic reported any incidents involving nocturnal myoclonus. Routine tests during follow-up excluded significant electrolyte disorders including hypomagnesemia, hyperkalemia, hypokalemia, and hypophosphatemia, and no other neurological signs or suggestions of infection were apparent in these patients. Magnetic resonance imaging of the head and the spine excluded any significant intracranial or spinal lesions associated with myoclonus (Fig. 1). These findings thus suggest that tacrolimus induced nocturnal myoclonus of the lower limbs, sometimes in association with pain.

Tacrolimus-related myoclonus in RA has not been reported in two large-scale studies[1,4] or in any previous case reports. Although one small-scale study reported muscle convulsions as an adverse effect of tacrolimus treatment in elderly RA patients,[2] whether the authors included myoclonus within this category is unclear. This latter study reported a frequency of 3.7% (2 of 54) in a population with a mean age of 70.2 years[2] but did not provide detailed descriptions of adverse events in terms of the affected body part, severity, or any potential relation to sleep as evidenced in our cases. On the basis of our own observations, tacrolimus-related nocturnal myoclonus is not a rare event, with an incidence of 27.3% (3 of 11) in patients attending our clinic in Saitama. The mean age of affected patients (71.3 years) in our clinic may be significant, given the mean age of 55.7 years in a previous large-scale study that did not report similar adverse effects,[1] suggesting that nocturnal myoclonus may be much more frequent in elderly tacrolimus-treated RA patients. An association with disease severity may also be present because the cases reported were all suffering from advanced or highly active RA that had proved refractory to several DMARDs, including methotrexate.

To the best of our knowledge, myoclonus has not been specifically reported as an adverse event of tacrolimus treatment for RA, particularly in terms of a strict association with sleep. In organ transplantation cases, tacrolimus is used at significantly higher dosages, and the neurotoxic effects reported may be dosage dependent,[18,19] whereas the frequency of nocturnal myoclonus in RA appears to have no relationship with the blood levels of tacrolimus. The signs of neurotoxicity previously reported in organ transplantation have usually been reversible on dosage reduction or withdrawal of tacrolimus,[11,14,15,20] in agreement with our own observations of nocturnal myoclonus in RA patients. The potential onset of events in RA is extremely early (2 days in Case 1), and our observations suggest that nocturnal myoclonus is not a rare adverse effect in elderly RA patients. Taken together, these observations on tacrolimus-related nocturnal myoclonus in RA suggest that separate and distinct etiologies may exist for these adverse effects in

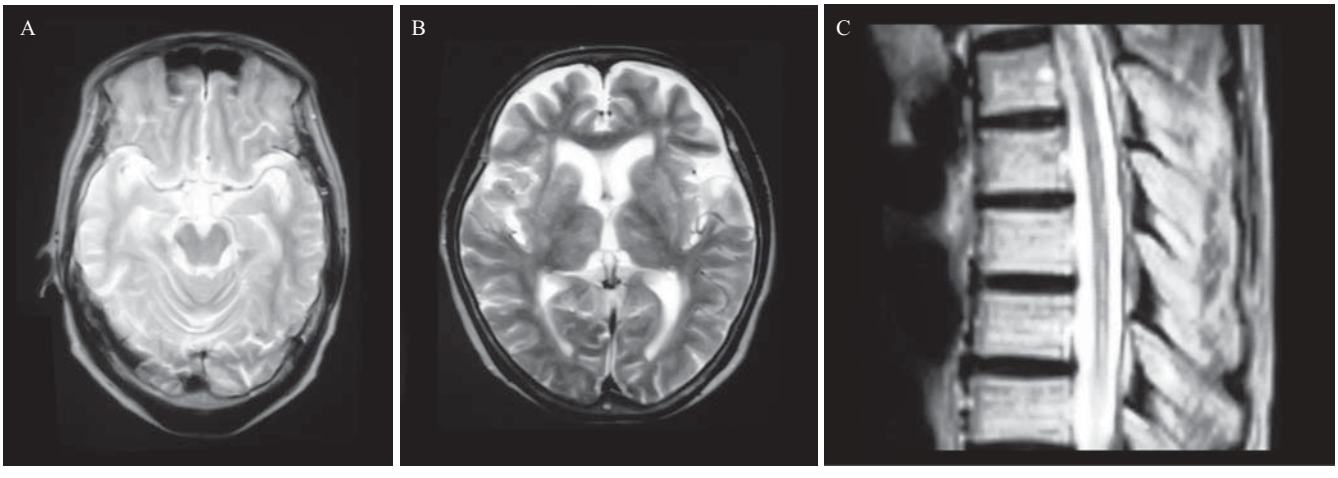

Fig. 1. Representative T2-weighted images from head and spine magnetic resonance imaging. Scans performed on Case 3 (**a**), Case 2 (**b**, **c**) did not reveal any significant intracranial or spinal lesions associated with myoclonus

different patient groups. The symptoms reported in RA were confined to sleep, particularly deep sleep, when patients were likely to consider adverse events as the effects of nightmares, fail to remember them in the morning, or otherwise disregard them. Such symptoms may also be a source of significant anxiety, as in Case 1, but patients may not associate them with a new medicine unless prompted by a physician during follow-up.

In summary, we believe that this represents the first detailed report of nocturnal myoclonus in association with tacrolimus treatment in patients with RA. Although these initial observations are based on the experience of a small number of RA patients treated with tacrolimus, we believe that a larger study is warranted to confirm these observations and further to characterize this tacrolimus-related nocturnal myoclonus. We recommend a detailed review during follow-up for early identification of these adverse effects, particularly in elderly RA patients.

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