

# Treatment with 4-aminopyridine improves upper limb tremor of a patient with multiple sclerosis: a video case report

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## Abstract

The reversible potassium channel blocker 4-aminopyridine is effective in the treatment of numerous cerebellar dysfunctions, such as episodic ataxia type 2 and downbeat nystagmus syndrome. In 2011, its sustained release form, dalfampridine, was admitted in Europe for the treatment of walking difficulties in patients with multiple sclerosis (MS). Here we report the case of a 44-year old patient with a progressive MS whose upper limb tremor was markedly reduced under treatment with 4-aminopyridine, as documented in a Tremor Activities of Daily Living questionnaire and in the 9-Hole Peg test. Hand accelerations decreased in the left hand from 10.9 m/sec<sup>2</sup> to 2.2 m/sec<sup>2</sup> and in the right hand from 4.2 m/sec<sup>2</sup> to 0.9 m/sec<sup>2</sup>.

This case report indicates for the first time that 4-aminopyridine might be effective in the symptomatic treatment of tremor entities in patients with MS. The finding calls for further prospective studies to determine the usefulness of 4-aminopyridine or its sustained-release form dalfampridine in treating patients with tremor and MS.

## Keywords

Postural tremor; 4-aminopyridine, cerebellar ataxia, multiple sclerosis, case study, tremor therapy

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## Introduction

In March 2010, the US Food and Drug Administration (FDA) approved the sustained release form of 4-aminopyridine (4-AP), Fampyra® (dalfampridine), for the treatment of walking difficulties in patients with multiple sclerosis (MS). This drug improves gait speed in approximately 40% of MS patients.<sup>1</sup> The active ingredient, 4-AP, is a reversible potassium-channel blocker used in experimental neurophysiology for decades; over the last years, a number of studies have shown that 4-AP has the ability to improve specific cerebellar dysfunctions. In episodic ataxia type 2 (EA2), it prevents attacks and improves the patient's quality of life.<sup>2</sup> In two separate cases with EA2, gait variability became reduced and the subjective fall risk decreased during treatment with 4-AP.<sup>3</sup> In patients with downbeat nystagmus syndrome secondary to cerebellar floccular dysfunction, the intensity of nystagmus was reduced during treatment with 4-AP.<sup>4</sup>

## Case report

Here we report a single case in which there was a positive effect of 4-AP treatment on upper limb tremors. A 44-year-old woman with a progressive MS presented to the hospital with an Expanded Disability Status Scale (EDSS) score of 6.5. Besides spastic-ataxic walking impairments, her major presentations were the presence of a postural and intention tremor of the upper extremities and the trunk, leading to a severe reduction of upper limb function, e.g. while brushing her teeth or drinking a glass of water.

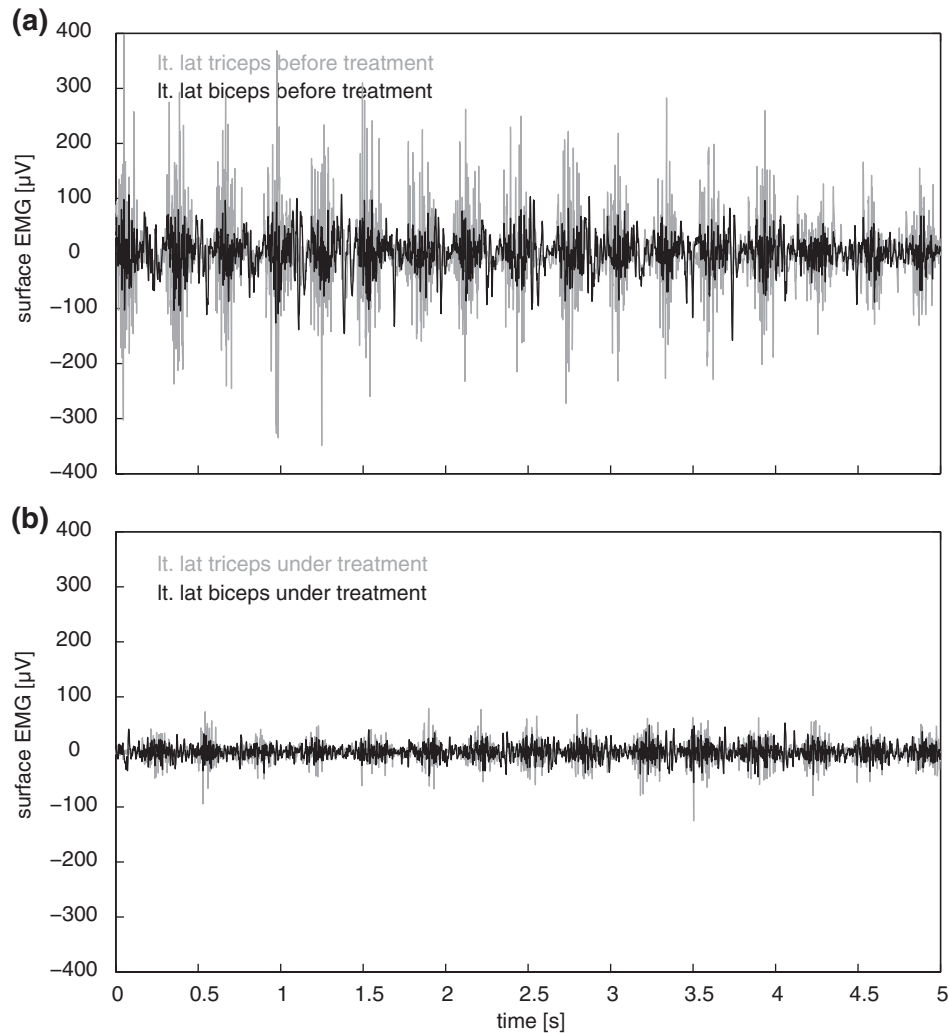
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**Figure 1.** Surface EMG recordings of the left proximal muscles.

(a) Compounding action potentials of the left arm over a 5-s time period, under the condition of holding, before 4-AP therapy;  
 (b) Compounding action potentials of the left arm over a 5-s time period, under the condition of holding, under the influence of 4-AP therapy.  
 4-AP: 4-aminopyridine; EMG: electromyography.

Assessment of the upper limb function included the 9-Hole Peg test. The time for completion of this test was 75 s, with the right hand. The test could not be completed by the patient with her non-dominant left hand. On a questionnaire-based tremor scale of activities of daily living, she rated 89 out of a maximum of 100 points. Tremor analysis using the Noraxon® system was performed using a surface electromyography (EMG) over bilateral antagonistic muscles, as well as 3-dimensional (3-D) accelerometers that were mounted bilaterally, at the dorsal surface of both hands. The accelerometer and EMG recordings were performed under the condition of holding the upper limbs against gravity, in a sitting position. Tremor intensity was calculated using a standard 3-D root mean square analysis. Her tremor intensities (hand accelerations) were 10.89  $\text{m/s}^2$  for the left hand and 4.23  $\text{m/s}^2$  for the right hand, with a frequency of 3.0 to 3.4  $\text{s}^{-1}$  (see Video 1, in the supplemental data).

The patient was symptomatically treated with 4-AP (5 mg t.i.d.). Only 24 hours after the first administration, the patient

reported there had been an improvement of her arm and hand tremors. Subjective scoring of the tremor-related activities of daily living improved from 89 to 77 points. With her dominant right hand, she completed the 9-Hole Peg test within 56s (a reduction of 19 s). Completion of the 9-Hole Peg test with her left hand was still not possible. After 62 h of treatment, the accelerometer recordings and video analysis were repeated, revealing a marked decrease in tremor intensity (see Video 1, supplemental data). Hand acceleration decreased by approximately 80% (left hand: reduction from 10.9  $\text{m/s}^2$  to 2.2  $\text{m/s}^2$ ; right hand: reduction from 4.2  $\text{m/s}^2$  to 0.9  $\text{m/s}^2$ ). Surface-EMG recordings showed a reduction of both distal and proximal arm muscle activity (for proximal muscles, see Figure 1). The frequency of the tremor remained unaffected.

Besides the effect on the hand tremors, the patient's gait performance (gait speed, stride length, gait variability) improved under 4-AP treatment (data not shown).

After a follow-up period of 4 weeks, all improvements in subjective, clinical and neurophysiological measurements remained stable (data not shown). The patient is continuing the 4-AP treatment, which has lasted for more than 18 months now. She has refused to switch her medication from 4-AP to dalfampridine, citing both its beneficial effects and an absence of side effects.

## Discussion

The symptomatic treatment of MS patients with cerebellar tremor remains a challenge for clinicians. Pharmacotherapeutic strategies are described in several small, short-duration studies<sup>5,6</sup> but evidence is conflicting. Deep brain stimulation, mainly of the ventral intermediate thalamic nuclei, may obtain tremor reduction, but this is associated with potentially serious side effects.<sup>7</sup>

This case report indicates for the first time the usefulness of 4-AP in improving the upper limb tremor of a MS patient. Thus, besides its positive effect on walking performance in MS patients, 4-AP may also be considered as a new option for the symptomatic treatment of tremor in patients with MS.

Aminopyridines were previously tested in the symptomatic treatment of tremor patients. A prospective, double-blinded cross-over trial with 3,4-diaminopyridine in 19 patients with essential tremor did not show any positive effects.<sup>8</sup> Our case report indicates that aminopyridines may be effective in treating MS tremor, secondary to pathologies of the cerebellum. Our patient showed a high burden of disease within the cerebellum and cerebellar peduncles (Figure 2). Clinical testing revealed a marked cerebellar ataxia and the criteria for a cerebellar tremor (low frequency, postural and intention tremor) were fulfilled.

Supported by animal studies, the putative mode of action of 4-AP on cerebellar functions is thought to be an improvement of Purkinje cell function. The drug 4-AP improves the excitability and the precision of cerebellar Purkinje cells.<sup>9</sup> Moreover, 4-AP reduces the excitability of olivary neurons, at least in the guinea pig, which in turn are thought to be the rhythm pacemakers in the harmaline-induced tremor model.<sup>10</sup>

Taking these findings into account, one can argue that 4-AP may have the potential to improve any tremor entities

that are linked to cerebellar dysfunctions. This further implies that our observation should encourage us to further investigate the usefulness of 4-AP, or its sustained release formulation dalfampridine; in a systemic, controlled trial in patients with MS tremor, especially when cerebellar symptoms are present.

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## Conflict of interest

The authors declare that there are no conflicts of interest.

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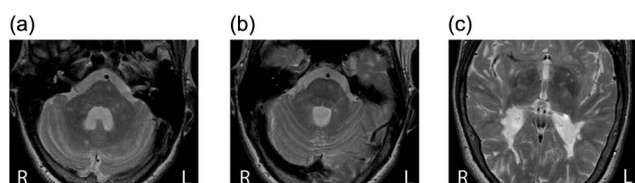
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## Contributorship statement

1. Research project: A. Conception B. Organization C. Execution  
2. Manuscript: A. Writing of the first draft B. Review and Critique  
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**Figure 2.** T2 sequences of the brain of the patient, prior to treatment, using a Siemens® MRI Scanner at 1.5 Tesla.

- (a) T2 (3mm) sequence of the cerebellum, inferior cerebellar peduncles and brainstem  
 (b) T2 (3mm) sequence of the cerebellum, middle cerebellar peduncles and brainstem  
 (c) T2 (3mm) sequence of the inferior thalamus  
 MRI: magnetic resonance imaging;