Journal of the Neurological Sciences 396 (2019) 119–120

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Treatment of intractable resting tremor of spinocerebellar ataxia 42 with zonisamide

ARTICLE INFO

Keywords:
Spinocerebellar ataxia
CACNA1G
T-type calcium channel
Tremor
Zonisamide

1. Introduction

Zonisamide (ZNS) was originally developed as an antiepileptic drug and is a T-type calcium (Ca) channel inhibitor. A previous clinical trial found that ZNS shortened the duration of "off" time in patients with Parkinson's disease [1]. ZNS is also effective in resting tremor in patients with Parkinson's disease in which dopamine is not effective [2]. Moreover, ZNS was useful for the treatment of essential tremor. Several basic research studies have reported that other T-type Ca channel blockers were effective in treating experimental tremors [3]. Therefore, it could be speculated that the effect of ZNS on resting tremor is caused by suppression of T-type Ca channels.

Here, we present a case in which ZNS was effective for treating intractable resting tremor of a patient with spinocerebellar ataxia 42 caused by a mutation in *CACNA1G*.

2. Case report

A 32-year-old Japanese woman presented with dysarthria, limb ataxia, ataxic gait, and resting tremor (especially tremor in the head), from the age of 18 years; these symptoms gradually worsened (2-III-1 in Fig. 1A, from reference 4). Her resting tremor was exacerbated by tension. Epilepsy, muscle atrophy, pyramidal tract sign, and parkinsonism other than tremor were absent. Her grandfather, mother, uncle, and twin sister also presented with these symptoms. Her sister also suffered from resting tremor, but the other family members did not. Brain computed tomography showed cerebellar atrophy (Fig. 1). Linkage analysis and consequent exome sequencing resulted in a diagnosis of autosomal dominant spinocerebellar ataxia (SCA) 42, caused by a mutation in *CACNA1G*, which encodes the low-threshold voltage-dependent Ca channel $Ca_v3.1$ (T-type Ca channel). This gene is a new causative gene of SCA, as previously reported (SCA42 [MIM: 616795]) [4,5]. Her resting tremor was refractory to treatment with clonazepam, alprazolam, propranolol, and trihexyphenidyl hydrochloride (Supplemental movie). However, by adding low-dose ZNS (25 mg), her resting tremor improved markedly (Supplemental movie). Along with the reduction in resting tremor, her walking stability improved to some extent. ZNS treatment has been well tolerated, and improvement of her tremor persists after 2 years of follow-up.

3. Discussion

We have reported a case in which ZNS was effective for treating the resting tremor in a patient with SCA42. In Japan, ZNS is generally used as an antiepileptic drug and as a remedy for Parkinson's disease. In addition, it has been reported that it may be useful for the treatment of migraine, neuropathic pain, and essential tremor [6], but it has not been reported to date that ZNS is effective for treating SCA-related resting tremor. Interestingly, the therapeutic dose of ZNS was 100–200 mg/day for essential tremor [6] and typically 200–400 mg/day for epilepsy, whereas in this case, a low dose of ZNS was effective, as it is in Parkinson's disease.

Most patients with SCA42 caused by a mutation in *CACNA1G* present with a pure form of cerebellar ataxia, but the patient and her twin sister were characterized by resting tremor, in addition to cerebellar ataxia. $Ca_v3.1$ is expressed at high levels in the cerebellum and the inferior olive nucleus. Park et al. showed that the T-type Ca channel of the inferior olive nucleus is involved in the generation of tremor [7]; hence, the resting tremor of the patient and her twin sister may be the result of the $Ca_v3.1$ mutation. T-type Ca channel inhibitors are effective in suppressing harmaline-induced tremor. Harmaline is often used as an agent to induce tremor in animal experiments, and it is speculated that its tremor-generating mechanism involves the T-type Ca channels in the cerebellum and the inferior olive nucleus. It has also been reported that T-type Ca channel inhibitors improved tremor in several basic research studies [3].

In the present case, low-dose ZNS was effective in treating the resting tremor of a patients with SCA42 caused by a mutation in *CACNA1G*. It is unclear whether ZNS treatment (especially low-dose therapy) would be effective for tremor in other types of SCA. Further studies are needed to evaluate the safety and efficacy of ZNS for the treatment of intractable resting tremor not only in patients with SCA42 caused by a mutation in *CACNA1G*, but also those with other types of SCA.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2018.11.013.

https://doi.org/10.1016/j.jns.2018.11.013
Received 17 September 2018; Received in revised form 8 November 2018; Accepted 9 November 2018
Available online 10 November 2018

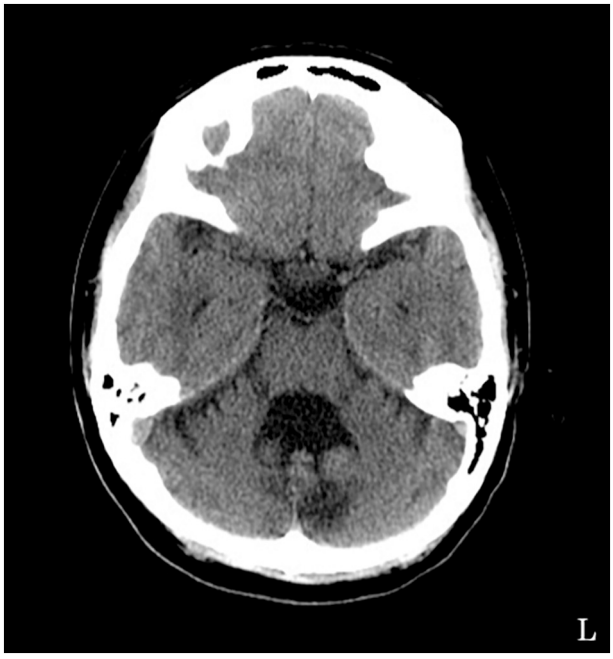

Fig. 1. Brain computed tomography image showing the cerebellar atrophy (especially affecting the vermis).

Acknowledgements

We thank Mr. H. Matsumoto for editing the movie data.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying data.

Study funding

This study was supported by research grants from the Japan Society for the Promotion of Science KAKENHI (Grant Number 17K17907).

Conflict of interest

Hirofumi Maruyama reports grants from Daiichi Sankyo Co., Ltd., which is unrelated to the submitted work.

All other authors declare that they have no conflicts of interest.

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