Brief Report

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Effects of Rivastigmine on Patients with Spinocerebellar Ataxia Type 3: A Case Series of Five Patients

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Keywords
Ataxia · Spinocerebellar ataxia type 3 · Rivastigmine · Neurodegenerative disease

Abstract
Background: Rivastigmine is an acetylcholine esterase inhibitor which is commonly used as therapy for dementia in Alzheimer's disease and Parkinson's disease (PD). Recently, a randomized controlled trial demonstrated a positive effect of rivastigmine on gait function in nondemented PD patients. Disturbed gait is a shared hallmark of PD and ataxias. ***Objectives:*** We hypothesized that the effect of rivastigmine could be translated to spinocerebellar ataxia (SCA) improving gait function. ***Method:*** Five patients with SCA type 3 were treated with transdermal rivastigmine for 8 weeks. The patients were monitored using the Scale for the Assessment and Rating of Ataxia (SARA) and an electronic walkway system (GAITRite®). ***Results:*** Gait function was not changed by treatment, but 4 patients who continued treatment for 8 weeks showed improved coordination of extremities. The SARA sum score, which was 7.6 ± 2.2 at baseline, had dropped by 1.5 ± 1.9 after 4 weeks and by 2.1 ± 1.4 after 8 weeks. ***Conclusions:*** Contrary to our hypothesis, we observed no improvement of gait parameters as assessed by SARA and GAITRite®, but coordination abilities were improved. Rivastigmine was well tolerated, but known side effects of rivastigmine, such as deterioration of asthma, may appear. Further trials in larger cohorts are needed to confirm our findings.

Introduction

Rivastigmine is an acetylcholine esterase inhibitor which is commonly used as a symptom-therapeutic option for dementia in Alzheimer's disease and Parkinson's disease (PD). Recently, a randomized controlled trial demonstrated a positive effect of rivastigmine on gait function by reducing step time variability in nondemented PD patients [1]. Disturbed motor and gait function with increased step time variability is a shared hallmark of PD and ataxias. We therefore hypothesized that this effect of rivastigmine was not restricted to PD but could be translated to ataxias.

Spinocerebellar ataxias (SCAs) are a group of heterogeneous diseases of autosomal dominant inheritance.

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Table 1. Participants' characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	F	M	M	F	F
Age, years	52	56	48	37	61
Age at onset, years	43	46	45	36	46
CAG repeat length	68	64	73	72	56
SARA sum score at baseline	7	10.5	8.5	4.5	9
Comorbidities	none	none	none	none	allergic asthma

Leading disabilities include disturbed gait, coordination, oculomotor function, and speech [2]. SCA3, the most common form of SCAs worldwide, is caused by a CAG trinucleotide repeat extension leading to aggregation of the misfolded disease protein ataxin 3. The resultant clinical phenotype is highly variable and typically consists of ataxia in combination with various non-ataxia signs including peripheral neuropathy, parkinsonism, dystonia, spasticity, and ophthalmoplegia [2, 3].

At present, there is no effective drug treatment for ataxias in general, or specifically for SCA3. Pharmacological studies investigating the effect of the acetylcholine esterase inhibitor physostigmine in patients with mixed degenerative cerebellar diseases [4] and the partial acetylcholine receptor agonist varenicline in SCA3 were negative, although varenicline showed some promising results for axial features of ataxia [5]. Nonpharmacological interventions such as physiotherapy, speech therapy, whole body vibration, and noninvasive transcranial stimulation have shown some benefit, but final proof of efficacy is lacking [6, 7]. The present case series monitored the clinical response to rivastigmine in 5 SCA3 patients with ataxia.

Subjects and Methods

Five patients with genetically confirmed and clinically manifest SCA3 were treated with transdermal rivastigmine for a period of 8 weeks (4 weeks of 4.6 mg/24 h, followed by 4 weeks of 9.6 mg/24 h). Transdermal application was chosen because of tolerability and fewer adverse effects compared to the oral formulation, especially regarding gastrointestinal symptoms. Regular visits were scheduled at baseline (V0), at the 4-week follow-up (V1), and again after 8 weeks (V2) following initiation of treatment. Potential side effects and subjective reports of ataxia and falls were assessed at every visit.

Patient Characteristics

Two men and 3 women were recruited. The repeat lengths of the longer allele ranged from 56 to 73. The age ranged from 37 to 61 years, with a disease duration of 1–15 years (Table 1). The patients had no cognitive impairment, shown by Montreal Cognitive Assessment (MoCA) scores >26 [8].

Clinical Assessment

We used the Scale for the Assessment and Rating of Ataxia (SARA) as the primary measure of changes in ataxia severity. The SARA sum score ranges from 0 to 40, with "0" indicating complete absence of ataxia and "40" the most severe degree of ataxia [9]. SARA was applied unblinded by a single rater during routine neurological examination.

Spatial and temporal gait parameters were measured with the GAITRite® Electronic Walkway (CIR Systems, Inc., USA). Walk was assessed under four different conditions: slow, preferred, and fast speed plus dual task measurement with a serial subtraction exercise at the preferred speed. Each condition was repeated 8 times per visit. The first and the last walk were excluded from the statistical analyses to eliminate training and exhaustion effects. All analyses were performed using the R Software for Statistical Computing, version 3.5.1. (R Foundation for Statistical Computing, Vienna, Austria).

A subset of GAITRite® data (cadence [steps/min], velocity [cm/s], and double support time [s]) that reflect gait stability was used to calculate coefficients of variance, means ± standard deviations, and the 95% confidence limits (as shown in online suppl. Table 1; see www.karger.com/doi/10.1159/000510057 for all online suppl. material). Confidence intervals provide information about the range in which the true value lies with a certain degree of probability, as well as about the direction and strength of the demonstrated effect. To find statistically significant differences in gait parameters between baseline and follow-up, confidence limits were checked for overlap.

Results

Patient 5 terminated treatment with 4.6 mg/24 h rivastigmine after 2 weeks due to worsening of preexisting pollen-related asthmatic symptoms. Follow-up data are therefore not available from this patient, and the results are not shown in the graphics. The remaining 4 patients completed the 8-week treatment without reporting clinically significant adverse effects. Two of the 4 patients re-

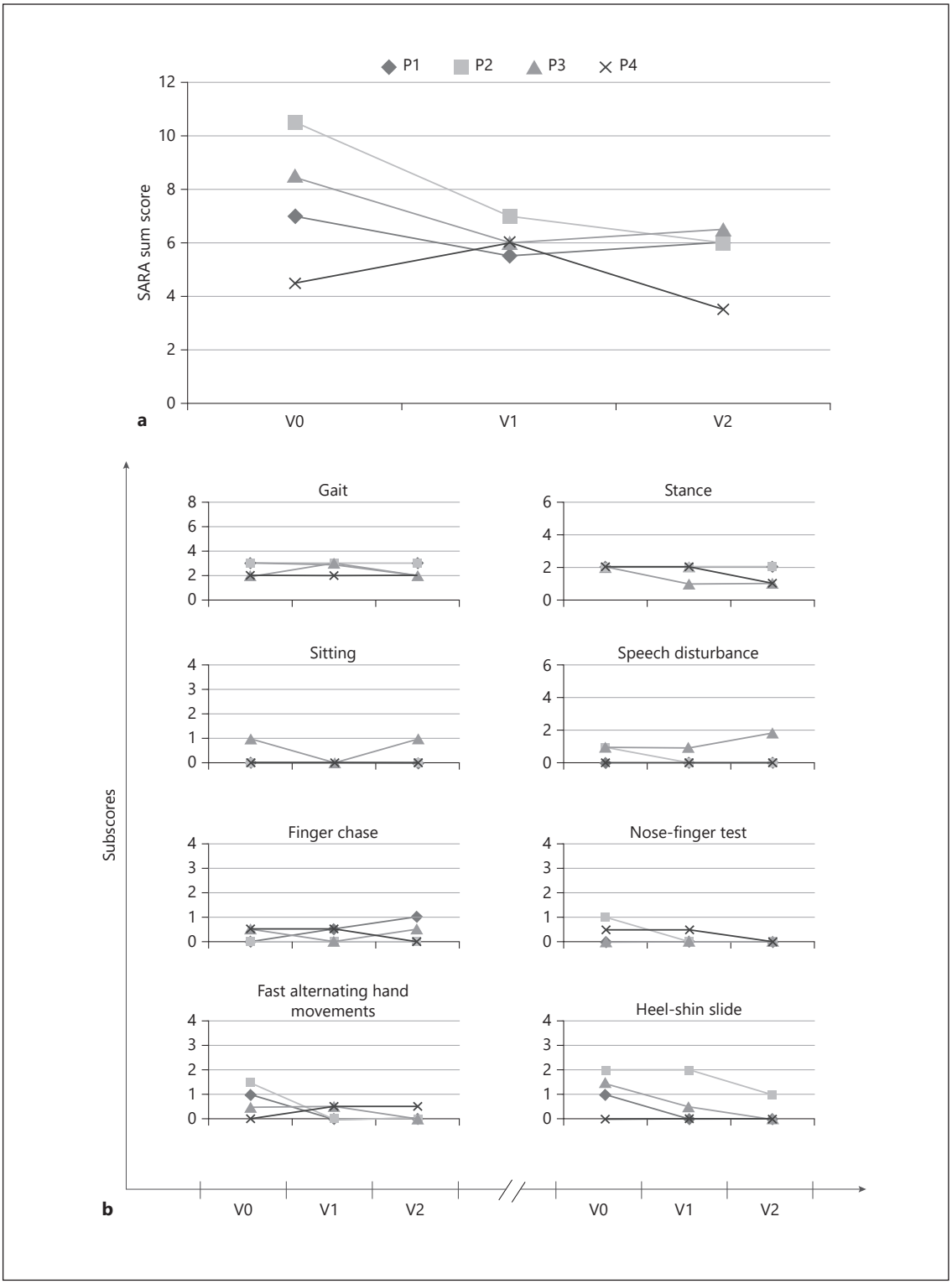

Fig. 1. a SARA sum score over time (patients 1–4) under treatment with rivastigmine. The SARA sum score ranges from 0 to 40, with higher scores denoting more severe ataxia. V0, baseline; V1, visit after treatment with rivastigmine at 4.6 mg/24 h for 4 weeks; V2, visit after treatment with rivastigmine at 9.5 mg/24 h for another 4 weeks. **b** SARA subscores over time under treatment with rivastigmine. Amelioration of the SARA sum score was mainly based on improved coordination (nose-finger test, fast alternating hand movements, and heel-shin slide, with no relevant change in finger chase).

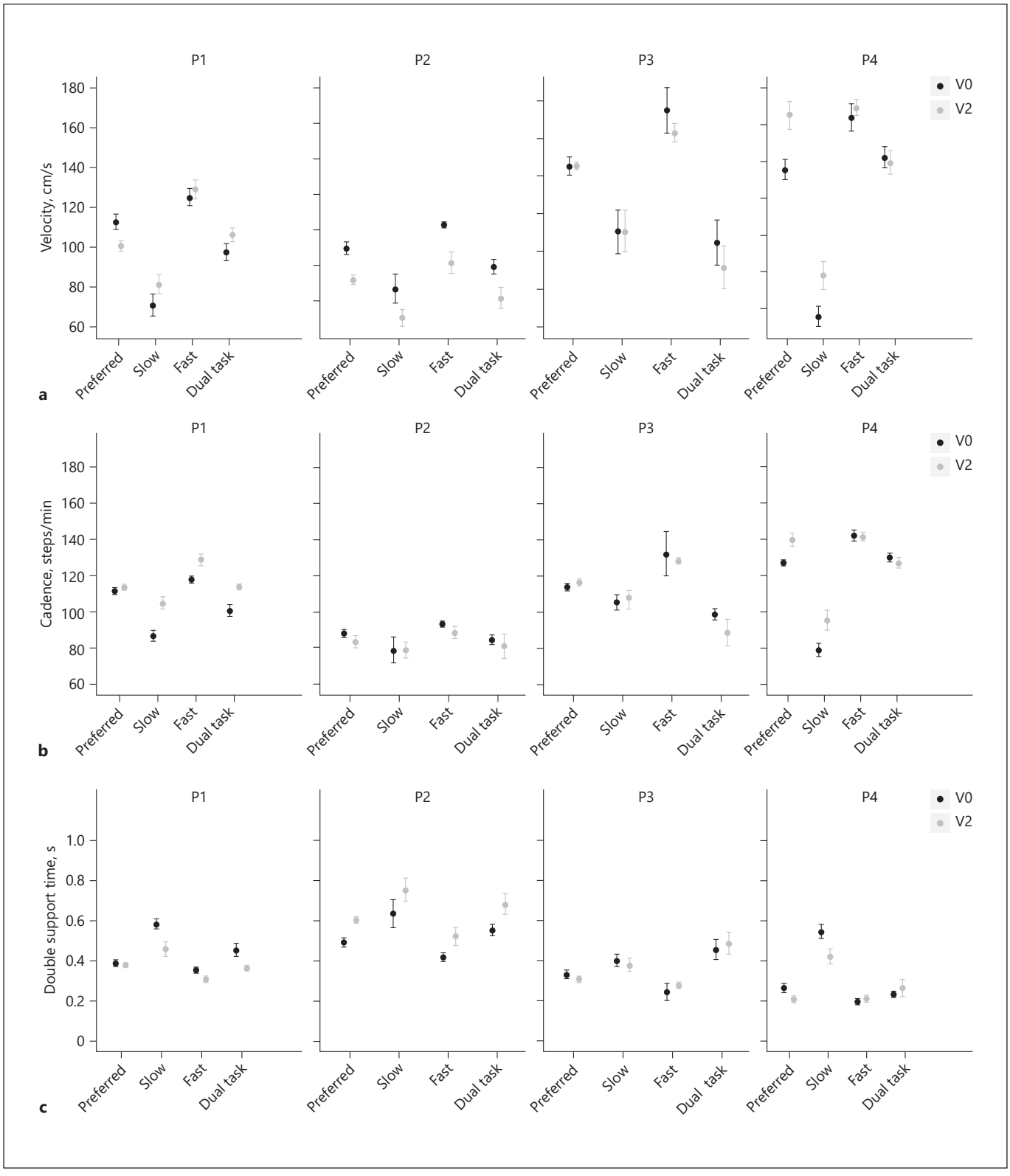

Fig. 2. Analysis of GAITRite® data obtained from 4 patients (P1–P4) who completed 8 weeks of therapy with rivastigmine. Shown are 95% confidence plots of parameter velocity (**a**), cadence (**b**), and double support time (**c**). Baseline data (V0, black) and follow-up data (V2, gray) on the four assessed walks (slow, preferred, fast, and dual task).

ported subjective improvement of gait stability, and all 4 patients reported that their relatives and partners noticed improved gait stability. Patient 2 observed a marked decrease in the frequency of falls during treatment (several times per week before treatment, reduced to once per week under treatment). Nevertheless, all patients discontinued treatment with rivastigmine (longest period 4 months) due to a subjectively insufficient clinical response over time.

On neurological examination, all 4 patients showed improvement in ataxia according to SARA sum score (Fig. 1; mean baseline SARA score, 7.6 ± 2.2; mean change in SARA score [improvement] – between V0 and V1, 1.5 ± 1.9, between V0 and V2, 2.1 ± 1.4). This change was mostly accounted for by improved coordination (SARA items 6–8: nose-finger test, fast alternating hand movements, and heel-shin slide). In contrast, SARA items 1–4 (gait, stance, sitting, and speech disturbance) as well as item 5 (finger chase) either remained unchanged or had even worsened slightly (Fig. 1, 2).

Considering the parameters velocity, step length, cadence, and double support time during assessment using GAITRite®, no treatment effect was detected during analysis when comparing baseline (V0) and follow-up (V2; Fig. 2; complete data in online suppl. Table 1). Two patients exhibited an increased cadence at different walking speeds, but this might have been due to increased velocity. During treatment, 1 patient (patient 1) displayed reduced double support time while slow-walking, as well as increased velocity and cadence under dual-task conditions. This effect did not occur at fast and preferred speed. The same effect was seen in a second patient at slow walking speed (patient 4).

In contrast, patient 2 showed reduced walking speed across all tasks, with consecutively prolonged double-support time, but no change in cadence. No effects were seen in patient 3. Taken together there was no clear-cut improvement of gait functions assessed by GAITRite® after treatment.

Discussion

Despite patient-reported subjective improvement of gait stability and a marked reduction of falls in 1 patient, treatment with rivastigmine did not yield a positive effect on gait function in SCA3 patients as assessed by SARA and the GAITRite® system. However, SARA showed improvement of coordination in extremities in all 4 of the treated patients, evident in a mean reduction in SARA sum score of >2 points, which is considered clinically relevant [10] and larger than the placebo effect in a previous drug trial on SCA3 [5]. Interestingly, the positive effect as measured by SARA was already noticeable at the low dose of 4.6 mg/24 h in 3 of the 4 patients. Nevertheless, all patients stopped treatment in the further course because of subjectively insufficient efficacy.

Deterioration of preexisting asthmatic symptoms was the only adverse effect reported in this case series; however, asthmatic symptoms are a known side effect of rivastigmine. This case series included only a small number of patients, and no blinded control was established. We cannot rule out that the improvement in SARA sum score was due to a placebo effect, due to subjectivity as a consequence of unblinded testing, or the consequence of natural fluctuations in the severity of ataxia, as frequently reported by many patients. Due to the limitations of this case series, the improvement in SARA sum score should be interpreted cautiously, and confirmation of our findings should be obtained in larger trials.

The mechanism of action underlying possible clinical improvement after treatment with rivastigmine is unclear. Although much is known about cholinergic projections, the involved receptors, and their distribution in the brain, the exact function of the cholinergic cerebellar system remains unresolved. Zhang et al. [11] speculated that the cerebellar cholinergic afferents may occupy a modulatory role in influencing the final outputs. This modulatory nature may be subject to habituation and might explain the missing subjective treatment effect over time. Possible strategies for rescuing any benefit might comprise the prescription of higher doses or drug holidays, both of which were not investigated in our patients. To date, no direct connection between the cerebellar cholinergic system and the regulation of motor control has been demonstrated, and further fundamental research (e.g., using imaging studies) is needed for a better understanding of the underlying mechanism.

In PD, severe gait dysfunction is a common problem in later stages of the disease, and cholinergic neurons are believed to be involved in its pathophysiology [12]. The degeneration of networks maintaining rhythmicity of gait might cause gait to become a cognitive task, which could explain a positive effect of rivastigmine in PD [1, 13]. Recently, degeneration of cholinergic fibers in the pedunculopontine nucleus (PPN) has been identified as a potential cause of gait dysfunction in PD [14]. Intriguingly, atrophy of the PPN is also evident in SCA2 and 3 [15].

We hypothesized that the loss of cholinergic neurons due to atrophy of the PPN in SCA3 could be compensated by rivastigmine, resulting in a clinical amelioration of ataxia. Unexpectedly, gait functions per se remained unchanged. However, we observed an improvement in the coordination of extremities. Again, a rise in attention may also be attributed to the improved coordination abilities in our patients, although this may be mediated by the cerebellar cholinergic system rather than the PPN.

Conclusions

This is the first report on potential treatment effects of rivastigmine in ataxic patients. Contrary to our hypothesis, we observed no improvement of gait parameters as assessed by SARA and GAITRite® in a genetically homogeneous SCA3 cohort, but coordination abilities were improved. Rivastigmine was well tolerated, but known side effects of rivastigmine, such as deterioration of asthma, may appear. Our finding may contribute to treatment options for ataxia, given that our observations can be confirmed in future trials.

Statement of Ethics

Written informed consent of all patients was obtained to publish this case series, and all procedures were conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Informed consent for individual off-label treatment and consent for anonymous publication including clinical data was obtained from all patients. This report represents a case series, reporting our clinical experience in treating SCA3 patients with rivastigmine. Hence, no ethics approval was required.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Conceptualization: O. Kaut. Clinical supervision and collection of data: M. Grobe-Einsler, I.R. Vogt, and O. Kaut. Data analysis: T. Schaprian, I.R. Vogt, and M. Grobe-Einsler. Writing and review of the manuscript: M. Grobe-Einsler, R. Hurlemann, T. Klockgether, and O. Kaut.

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