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Great Minds.
Double-blind crossover trial of gabapentin in SPG4-linked hereditary spastic paraplegia

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Patients with hereditary spastic paraplegia (HSP) are often treated with antispastic drugs to relieve symptoms but documentation is lacking. In this study, gabapentin was tested in a double-blind crossover trial on a group of patients with HSP and linkage to the SPG4 locus. There was no difference between periods with gabapentin and placebo treatment in clinical assessment, self-reported parameters or paired transcranial magnetic stimulation evaluation of motor cortical excitability.

Introduction

The hereditary spastic paraplegia (HSP) is a heterogeneous group of inherited neurodegenerative disorders characterized by slowly progressive spasticity and weakness of the lower limbs. While neuropathological lesions predominate in the spinal cord, retrograde axonal degeneration of the corticospinal tracts and dorsal columns contributes to the underlying cause of symptoms. Most cases are transmitted in an autosomal dominant pattern (ADHSP) [1], and approximately 40\% are caused by mutations in the SPG4 gene on chromosome 2 (SPG4 locus) [2]. This locus encodes Spastin, which is a member of the AAA protein family [3], and although the exact pathogenic mechanism remains elusive, wild type Spastin has been shown to interact transiently with the microtubules [4].

Clinically, the major functional impairment is related to the severe lower limb spasticity, causing various degrees of gait disturbance. Different treatment regimens may alleviate this symptom; yet clinical drug trials in HSP have been very limited, leaving the choice of drug and dosage up to the personal experience and preferences of the individual physician.

Gabapentin has been reported to reduce spasticity in multiple sclerosis and spinal cord injury (SCI) [7,8], and may prove to be particularly useful in SPG4-linked HSP because gabapentin has the potential to reduce the increased intracortical excitability reported in these patients [6]. By modulating cortical interneuronal circuits, disturbances in efferent cortical output could be normalized, resulting in decreased spasticity.

In view of this, we decided to undertake a prospective double-blind randomized placebo-controlled crossover trial of a genetically homogenous patient population, investigating the effects of gabapentin on clinical disability and motor cortical excitability.

Patients and methods

Fifteen patients from nine different families with SPG4-linked ADHSP were originally recruited from the Institute of Medical Biochemistry & Genetics, University of Copenhagen. However, only 10 patients (seven males and three females; mean age 45.4 years, range 31–68 years) were included in the study as five patients failed to complete the full data collection program. SPG4 mutations were verified in six of the 10 included patients.

Inclusion criteria were: (1) definite clinical affection, (2) verified genetic linkage to the SPG4 gene [9] and (3) age between 18 and 68 years. Exclusions were made if patients were pregnant or had abnormal renal and liver parameters, abnormal white blood cell count or abnormal hemoglobin at pre-inclusion blood sampling. The ethics committee of Copenhagen (amendment toKF 01-142/94) approved the study and written informed consent was obtained from all participants before enrollment.

The study was performed as a prospective, two period crossover, placebo-controlled trial (Fig. 1). Assessments of outcome parameters (CE = clinical examination, SRP = self-reported parameters, MCE = paired transcranial magnetic stimulation (P-TMS) evaluation of motor cortical excitability) and blood samples (S-GA = S-gabapentin) were obtained at the...
first baseline level prior to the first treatment period (CE, SRP, MCE), at the second baseline level preceding the second treatment period (CE, SRP), and at the completion of the gabapentin and placebo treatment periods (CE, SRP, MCE). Subjects were randomly allocated to treatment regimens A and B. Group A received gabapentin during 2 months followed by a washout period of 10 days, a drug free interval of 1 month, and then placebo. Group B received the treatments in the opposite order. Gabapentin treatment consisted of a starting dose of 2400 mg daily, titrated up over 10 days to maximal dose of 4000 mg daily. Placebo treatment consisted of identically appearing capsules, given in the same manner as the active drug. All patients and data collectors were blinded as to the treatment assignment.

Outcome measures were rated according to the results of the clinical neurological examinations, self-reported health condition and P-TMS effects.

Structured objective clinical examinations and self-reported parameters were assessed (1) at the first baseline level prior to starting, (2) after completion of the gabapentin treatment period, (3) at the second baseline level and (4) at the completion of the placebo treatment period (Fig. 1).

Objective clinical measures were rated according to a combination of the MS Impairment Scale [10] and the SPATAAX diagnostic form [11]. The examination included lower limb patellar reflexes (0 = normal, 1 = enhanced, 2 = very brisk), severity of paresis (0 = normal muscle strength, 1 = muscle strength reduced by 25%, 2 = muscle strength reduced by 50%, 3 = movement of joint against gravity possible, 4 = movement of joint possible when gravity is eliminated, 5 = muscle contraction visible, but no movement of joint), muscle tone (0 = normal, 1 = hyperactive tendon reflexes with extended zones or clonus, 2 = spasticity detectable at fast movements only, 3 = spasticity detectable even at slow movements, 4 = full passive movement is possible only with major effort, 5 = full passive movement not possible even at major effort), disability score (0 = no functional handicap, 1 = no functional handicap, but signs at examination, 2 = mild, able to run, walking unlimited, 3 = moderate, unable to run, limited walking without aid, 4 = severe, walking with one stick, 5 = walking with two sticks, 6 = unable to walk, requiring wheelchair, 7 = confined to bed) and ambulatory scoring (the sum of the number of meters traveled in 5 s with and without aid). Self-reported parameters included assessment of the severity of sphincter disturbances (0 = none, 1 = mild, 2 = moderate, 3 = severe) and Visual Analogue Scale score (0 = death; 100 = optimal health condition) of current life quality.

Intracortical motor excitability was quantified at the first baseline level, and at the completion of both treatment periods as described previously [12].

Due to the small number of patients and presence of ordinal data, statistical analyses were performed using nonparametric tests. Gabapentin versus placebo treatment effects on clinical data and self-reported measures were evaluated, comparing effect scores (drug – baseline values) during the two treatment periods with the Wilcoxon signed rank test. Order effects were tested accordingly comparing sums of effect scores (gabapentin + placebo) in treatment regimens A (gabapentin followed by placebo) and B (placebo followed by gabapentin) using the Mann–Whitney U-test.

P-TMS data were evaluated with the Wilcoxon signed rank test, comparing gabapentin and placebo average amplitude ratios during inhibitory and facilitatory interstimulus intervals separately. The significance level was 5%.

**Results**

Blood sample results showed an increase in S-gabapentin in all the patients during the gabapentin treatment (mean 48.0 mmol; range 17–79 mmol), and no significant active drug was observed during placebo treatment (< 2 mmol S-gabapentin).

Median scores of self-reported and clinical ratings at the different treatment assignments are shown in Table 1. No statistically significant differences were recognized comparing gabapentin to placebo effect.
Priebe et al. [8] proposed that treatment effects of gabapentin in SCI are dosage dependent, and that doses up to 3600 mg daily cause clinical improvement. Our decision of 4000 mg of gabapentin daily is therefore most likely adequate, albeit beneficial effects of further dose elevation cannot be ruled out.

While spasticity generally is more pronounced than weakness in the lower limbs in HSP, absence of improved ambulatory scores does not necessarily relate to lack of treatment effects. In some cases gait function may be worsened by a reduction in muscle tone, unmasking coexisting paresis and reducing limb-stability. This phenomenon was suspected in a previous study of HSP [14] reporting five of 10 patients with only minimal improvement of gait function after intrathecal bolus injections of baclofen. In our study however, no significant decreases were observed in muscle tone scores, rendering destabilizing tone reduction less likely to affect ambulatory outcome.

Mechanisms causing spasticity are complex and inadequately understood, and different rating scales have been used in the literature to quantify this symptom. We employed a variety of parameters focusing both on performance deficits; signs of spastic hypertonia and self-reported health condition. This multifaceted approach is imperative, as improvement of single components not necessarily results in improved functional ability.

Although gabapentin was originally designed as a structural analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), subsequent studies have questioned the GABAergic effects of the drug, and currently there is little agreement among investigators regarding the exact molecular target of gabapentin [17]. Instability of GABAergic inhibition has been proposed to underlie the increased intracortical facilitation in SPG4-linked HSP however [5], hence true GABAergic drugs like vigabatrin and baclofen may still prove to be efficient in these patients.

Intrathecal baclofen was in fact reported to have a beneficial effect on gait in highly selected patients [14,15] whereas methylpendidate did not show any effect on gait or muscle tone [15]. Botulinum toxin

### Table 1 Self-reported measures and clinical ratings median scores

<table>
<thead>
<tr>
<th>Treatment assignment</th>
<th>VAS (0–100)</th>
<th>DIS (0–7)</th>
<th>AMB (m/5 s)</th>
<th>Urge</th>
<th>Incont.</th>
<th>Paresis (0–6)</th>
<th>Tendon reflexes (0–2)</th>
<th>Tone, 0–5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline prior to placebo</td>
<td>55.0</td>
<td>3.5</td>
<td>4.5</td>
<td>1.5</td>
<td>0.5</td>
<td>2.5</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Baseline prior to gabapentin</td>
<td>65.0</td>
<td>3.5</td>
<td>4.1</td>
<td>1.5</td>
<td>0.5</td>
<td>2.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>59.0</td>
<td>3.0</td>
<td>4.5</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>67.5</td>
<td>3.5</td>
<td>4.6</td>
<td>1.5</td>
<td>0.5</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
</tr>
</tbody>
</table>

VAS, Visual Analog Score; DIS, Disability Score; AMB, Ambulatory Score (distance in meters walked without support during 5 s). n = 9 in AMB as one patient missed assessment during placebo treatment.

scores, and no order effects were identified for the randomization sequences.

Accordingly no evidence was found of altered intracortical excitability, comparing data from the two treatment regiments.

**Discussion**

In this placebo-controlled, double-blinded crossover trial, we did not find a therapeutic effect of gabapentin on SPG4-linked HSP, and the lack of clinical improvement was further substantiated by unchanged intracortical excitability during treatment.

This outcome was surprising given the fact that gabapentin is a well-known therapy for spasticity associated with SCI [8,13]. However, as this is the first placebo-controlled study investigating oral antispastic treatment in a HSP population, no previous studies support our conclusion, and various circumstances may explain the lack of outcome. Most notable is the observation of S-gabapentin levels below 20 mmol in two individuals at completion of the active treatment (17 and 18 mmol, respectively). This suggests poor medication compliance in some patients, which could instigate a lesser effect on outcome parameters. As only two individuals at completion of the active treatment observation of S-gabapentin levels below 20 mmol in

instigate a lesser effect on outcome parameters. As only two individuals at completion of the active treatment in respect of genetic linkage, yet mutations in SPG4 were only verified in six patients from four families. As increased intracortical facilitation has been shown previously in patients chosen from the linkage criteria [5] an effect on P-TMS was expected regardless of an actual mutation in SPG4. Due to the small number of individuals included in the present study, a comparison between subsets of patients with and without verified mutations in SPG4 were unfeasible. However, no obvious differences in outcome parameters were seen between the groups.

Another issue concerns the choice of dosage and influence of dose level on the outcome parameters. Priebe et al. [8] proposed that treatment effects of mutations in SPG4 were unfeasible. However, no actual mutation in SPG4. Due to the small number of individuals included in the present study, a comparison between subsets of patients with and without verified mutations in SPG4 were unfeasible. However, no obvious differences in outcome parameters were seen between the groups.

Another issue concerns the choice of dosage and influence of dose level on the outcome parameters. Priebe et al. [8] proposed that treatment effects of
has been tried in a case report on one patient with improvement of gait and muscle tone [16]. It is not unlikely that gabapentin like intrathecal baclofen may have an effect on highly selected HSP patients, although the group remains elusive. Studies on larger patient groups with more extensive rating scales are needed to explore the effect of gabapentin in SPG4-linked HSP further.

Conflicts of interests and funding

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References