The eyelid motor disturbance in our patient was transient, with complete remission in 2 weeks. This finding may be related to the recovery of normal function that often occurs after ischemia, although some compensatory mechanisms also might have taken place during this time. For instance, in addition to an improvement of a possible edema of the internal capsule, the intact hemisphere could have taken over or even a functional reorganization of the ipsilateral cerebral cortex could have occurred.

In conclusion, unilateral striatal infarctions may cause a transient prominent reflex blepharospasm. These eyelid abnormalities may reflect a disruption of a common supranuclear pathway linking the nondominant cerebral hemisphere, the basal ganglia, and the brainstem, and emphasize the role of the striatum, particularly the putamen, in the pathophysiology of some eyelid motor disorders.

References


Survey on Cannabis Use in Parkinson’s Disease: Subjective Improvement of Motor Symptoms

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3Division of Clinical Toxicology and Mass Spectrometry, Department of Biochemistry, University Hospital Hradec Králové, Czech Republic

Abstract: An anonymous questionnaire sent to all patients attending the Prague Movement Disorder Centre revealed that 25% of 339 respondents had taken cannabis and 45.9% of these described some form of benefit. © 2004 Movement Disorder Society

Key words: cannabis; Parkinson’s disease; cannabinoid

The cannabis plant (Cannabis sativa) contains compounds called cannabinoids that are exclusive to the Cannabaceae family. These compounds exert their pharmacologic effect by acting on specific G protein-coupled cannabinoid receptors.
Two types of cannabinoid receptors have been isolated so far. CB₁ receptor is localized predominantly in the central nervous system (CNS), whereas CB₂ is found mostly in organs and cells of the immune system. To date, a number of endogenous agonists at cannabinoid receptors have been isolated that include anandamide and 2-arachidonyl glycerol (2-AG). The potential use of cannabis or cannabinoids in pharmacotherapy of various medical conditions including Parkinson’s disease (PD) and dyskinetic movement disorders has been discussed recently, substantiated by rich representation of cannabinoid system in the basal ganglia. The globus pallidus and substantia nigra pars reticulata contain the highest density of CB₁ receptors in the body. The concentration of anandamide in the globus pallidus and substantia nigra is three times higher than in other brain regions. Cannabinoid system therefore might play some physiological role in the basal ganglia control of movement and this is supported by the finding that CB₁ knockout mice exert lower locomotor activity.

The use of cannabis has been presented in Czech media as being possibly helpful in Parkinson’s disease, which was initiated mainly by one of our patients who objectively improved his PD symptoms after long-term use of cannabis. We realized that after this public information, some of our patients spontaneously started to take cannabis to alleviate their PD symptoms. The aim of this study therefore is to evaluate their possible experience with cannabis.

Subjects and Methods

The protocol was approved by the Research Ethics Committee of the General University Hospital in Prague and informed consent was obtained from all subjects participating in the analytical part of this study. All patients with PD registered at Prague Movement Disorders Centre were asked to anonymously complete a questionnaire about their possible experience with cannabis. For this purpose, we modified the questionnaire that Consroe and colleagues used to describe the effects of cannabis on multiple sclerosis symptoms. This questionnaire asks for basic personal data (age, gender, duration of PD), questions on the possible use of cannabis (if the patient uses cannabis, how frequently, how regularly, for how long, which part of the plant, whether there was an effect on cardinal motor symptoms of PD and on levodopa (l-dopa)-induced dyskinesias, and if any, when the effect had appeared), on the possible use of other drugs of abuse and current antiparkinsonian treatment. The terms muscle rigidity, bradykinesia, and dyskinesias were explained briefly. Patients were asked to rate the subjective changes in each symptom and dyskinesias as follows: substantial improvement, mild improvement, no change, mild worsening, substantial worsening, or I do not know. We have analyzed urine from 7 patients who had taken cannabis regularly for more than one year and a single patient who had only taken it 1 day before analysis. The patients had expressed their willingness to participate in further studies, had reported cannabis use, and were able to attend the hospital to submit urine samples. We carried out preliminary screening (EMIT II plus Cannabinoid Assay; Dade Behring, USA) followed by gas chromatography/mass spectrometry (GC/MS) quantitative analysis (ion 371 m/z was monitored in silylated 11-nor-Δ⁹-tetrahydrocannabinol-9-carboxylic acid; 11-nor-Δ⁹-THCOOH) on ion trap spectrometer Magnum (ThermoFinnigan) equipped with capillary column DB1ms (30 m; 0.25 µm; 0.25 mm; JW Scientific-Agilent, USA; silylation reagent: bis(trimethylsilyl)trifluoroacetamide) + trimethylchlorosilane 99.1%; standards: drugs of abuse control S1, S2 and S3 (Bio-Rad)). For extraction of cannabinoids, SPEC-C18-I Cartridges (Ansys, Inc., USA) and vacuum extractor Supelco Visiprep 24 were used.

Results

Out of 630 questionnaires sent by mail, 339 (53.8%) were returned (195 men, 139 women; 5 without answer regarding gender). The responders’ mean age was 65.7 years (age range, 36–92 years) and the mean PD duration was 8.5 years (range, 1–30 years). Cannabis use was reported by 85 patients (25.1% of returned questionnaires; 55 men, 29 women, 1 without answer), most of them using approximately half a teaspoon of fresh or dried leaves orally (only 1 patient inhaled), usually before taking it to alleviate PD symptoms. None had been advised to use cannabis by a doctor, and all patients continued using the antiparkinsonian therapy recommended by their neurologist. After cannabis, 39 patients (45.9%) described mild or substantial alleviation of their PD symptoms in general, 26 (30.6%) improvement of rest tremor, 38 (44.7%) alleviation of

| TABLE 1. Mean age and duration of Parkinson’s disease in patients who had used and not used cannabis to alleviate symptoms |
|--------------------|--------------------|----------------|
| Parameter          | Used cannabis      | Never used cannabis |
| Mean age, yr (range) | 63.9 (45–83)      | 66.4 (36–92) |
| Mean duration of PD, yr (range) | 8.3 (<1–28) | 9.3 (<1–30) |

<table>
<thead>
<tr>
<th>Duration of cannabis use</th>
<th>Overall symptoms (n)</th>
<th>Tremor (n)</th>
<th>Bradykinesia (n)</th>
<th>Rigidity (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improved</td>
<td>Not improved</td>
<td>No answer</td>
<td>Improved</td>
</tr>
<tr>
<td>&lt;3 mo.</td>
<td>27</td>
<td>5</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>≥3 mo.</td>
<td>54</td>
<td>33</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>No answer</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>39</td>
<td>33</td>
<td>13</td>
</tr>
</tbody>
</table>

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TABLE 3. Relationship between the frequency of cannabis doses and number of patients reporting improvement in dyskinesias

<table>
<thead>
<tr>
<th>Dose frequency</th>
<th>Total</th>
<th>Improvement in dyskinesias (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Not every day</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>≥Once/day</td>
<td>54</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>12</td>
</tr>
</tbody>
</table>

bradykinesia, 32 (37.7%) alleviation of muscle rigidity, and 12 (14.1%) improvement of L-dopa-induced dyskinesias (Table 2 and 3). Only 4 patients (4.7%) reported that cannabis actually worsened their symptoms.

According to the information obtained from the patients, this alleviation occurred 1.7 months in average (range, 1 hour to 6 months) after their first cannabis use. Patients using cannabis for at least 3 months reported significantly more often a mild or substantial alleviation of their PD symptoms in general (P < 0.001, χ² test), improvement of resting tremor (P < 0.01, χ² test), bradykinesia (P < 0.01, χ² test), and muscle rigidity (P < 0.01, χ² test) (Table 2). Although there was no relationship between the length of cannabis use and the effect on dyskinesia, patients using cannabis on a regular basis at least once a day reported an improvement in their dyskinesias significantly more frequently than did those who were taking cannabis less than once a day (Table 3, P < 0.05, χ² test). We did not find any influence of patients’ age (χ² test), duration of PD (χ² test), part of the plant used (Kruskal-Wallis test) or whether fresh or dried plant was used (χ² test).

Only 2 patients used cannabis for purposes other than alleviation of PD symptoms: 1 patient used cannabis “to relieve depression” and 1 “to have more energy.” None of the respondents ever used cannabis to experience hallucinations, to relieve anxiety, or to relax; however, the questionnaire did not ask directly if they had experienced any psychoactive effects when using cannabis. Three patients reported that they had discontinued using cannabis because of unspecified side effects.

In the group of 7 patients who were using cannabis consistently over several months, an effect of urine level of 11-nor-δ-9-THCOOH (major δ-9-THC metabolite in the urine) on bradykinesia and rigidity was apparent. In all patients in which urine levels (Table 4) of 11-nor-δ-9-THCOOH were higher than 50 ng/ml (4/7), there was a reported improvement in bradykinesia or rigidity. In contrast, in patients where 11-nor-δ-9-THCOOH levels were lower than 50 ng/ml (3/7), there was no reported improvement in either. It is of interest that 1 patient who did not take cannabis regularly but who had taken it the day before analysis had higher urine levels of 11-nor-δ-9-THCOOH (132.2 ng/ml), but reported no improvement in symptoms, a finding consistent with the conclusions of the questionnaire, which were that chronic use of cannabis might be required to obtain a subjective improvement in symptoms.

### Discussion

Possible involvement of the cannabinoid system in PD pathophysiology was shown in several experimental animal models of PD and in one postmortem study. Potential use of cannabinoids in PD is controversial. Some authors suggest that CB₁ receptor antagonists could prove useful in the treatment of parkinsonian symptoms and L-dopa-induced dyskinesia, whereas CB₂ receptor agonists could have value in reducing L-dopa-induced dyskinesia, which was also demonstrated in a recent clinical study. In an earlier clinic report, however, no effects of smoked cannabis were observed in parkinsonian tremor.

The aim of our study was to evaluate the frequency and patterns of cannabis use in PD patients, focusing especially on possible subjective changes in cardinal motor symptoms and L-dopa-induced dyskinesias. The results obtained from the questionnaires show that bradykinesia seems to be the symptom most commonly improved by cannabinoids, followed by muscle rigidity and tremor. In addition, 14% of our patients reported alleviation of dopaminergic-induced dyskinesias with cannabis use. Unfortunately, we do not know how many patients in the anonymous study actually suffered from dyskinesias. In fact, many PD patients are not aware of dyskinesias and thus cannot evaluate accurately any possible antidysetic effects of therapies.

The late onset of cannabis action is noteworthy. Because most patients reported that improvement occurred approximately 2 months after the first use of cannabis, it is very unlikely that it could be attributed to a placebo reaction. The results from the analytical part of the study (GC/MS) also support our observation that long-term regular use of cannabinoids is crucial. Possible explanations include gradual accumulation of low doses of highly lipophilic δ-9-THC before reaching higher concentrations necessary for stimulation of movement, or regulations on the level of CB₁ receptors. This observation is in contrast with the study of Sieradzan and

### TABLE 4. Relationship between the concentration of 11-nor-δ-9-THCOOH in urine and change of symptoms in a subset of PD patients with long-term cannabis use

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>11-nor-δ-9-THCOOH (ng/ml)</th>
<th>Regular/infrequent user</th>
<th>Tremor</th>
<th>Bradykinesia</th>
<th>Rigidity</th>
<th>Dyskinesia</th>
<th>Pain</th>
<th>Other effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;10</td>
<td>Regular</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>43.10</td>
<td>Regular</td>
<td>Improved</td>
<td>No change</td>
<td>No change</td>
<td>Improved</td>
<td>No change</td>
<td>Relaxation</td>
</tr>
<tr>
<td>3</td>
<td>47.50</td>
<td>Regular</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>50.68</td>
<td>Regular</td>
<td>Not present</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Not present</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>96.27</td>
<td>Regular</td>
<td>No change</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Relaxation</td>
</tr>
<tr>
<td>6</td>
<td>107.63</td>
<td>Regular</td>
<td>No change</td>
<td>Improved</td>
<td>No change</td>
<td>Improved</td>
<td>No change</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>147.43</td>
<td>Regular</td>
<td>Improved</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Stimulation</td>
</tr>
<tr>
<td>8</td>
<td>132.3</td>
<td>Infrequent</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Not present</td>
<td>No</td>
</tr>
</tbody>
</table>
colleagues,\(^2\) where the action of synthetic cannabinoid agonist occurred within minutes or hours after administration. The design of these two studies, however, including the doses used, was very different. Although in regular users the subjective improvement of symptoms seemed to correlate well with concentrations of the major metabolite of 6-9-THC found in urine, the actions of other plant cannabinoids have to be considered because they may substantially influence the effect of 6-9-THC alone.\(^2\)\(^7\)\(^8\) The most likely is cannabidiol, which inhibits uptake and hydrolysis of anandamide and acts as a vanilloid receptor (VR\(_1\)) agonist.\(^2\)\(^9\) Cannabinoids may also have a protective role in slowing down progression of a neurodegenerative process.\(^3\)\(^0\)\(^–\)\(^3\)\(^2\)

The present study evaluating spontaneous use of natural cannabis in PD patients suggests that cannabis may improve PD symptoms and \(\text{dopa}\)-induced dyskinesias. Due to the illegal status of cannabis in the Czech Republic, it was impossible to run a proper clinical trial and we had to use an anonymous retrospective questionnaire-based study; we are well aware of its limitations. Questionnaires are used quite commonly in clinical research because they enable obtaining data from a large group of patients; however, results from this type of study cannot be conclusive and should rather serve as a baseline for future research. Even though a possible placebo reaction and other confounders (e.g., concomitant antiparkinsonian therapy, non-standardized plant material) have to be taken into account, it seems that various cannabinoids or other compounds targeting the endogenous cannabinoid system might be useful in the treatment of PD symptoms or drug-induced dyskinesias and this field definitely deserves further research.

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References

Stuttering and Gait Disturbance After Supplementary Motor Area Seizure

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Abstract: Acquired stuttering is an uncommon speech disorder. Supplementary motor area (SMA) lesions have been reported to be directly or indirectly related to acquired stuttering and various types of motor dysfunction. We report on a patient who presented with both acquired stuttering and long-lasting gait disturbance after SMA seizure. © 2004 Movement Disorder Society

Key words: supplementary motor area; stuttering; gait disturbance

Stuttering has been defined as a disruption in the fluency of verbal expression, which is characterized by involuntary repetitions or prolongations in the utterance of short speech elements—namely, sounds, syllables, and words of one syllable.1 Developmental stuttering typically begins in childhood or early adolescence.2,3 The etiology of developmental stuttering remains elusive. New stuttering in adulthood, or acquired stuttering, has been reported in a variety of diseases, including strokes,4–12 Parkinson’s disease,13,14 progressive supranuclear palsy,14 Alzheimer’s disease,15 and trauma.6,12,15

The supplementary motor area (SMA) corresponds to the medial aspect of Brodmann area 6 on the medial wall of the frontal lobe, which is essentially related to the initiation and execution of the movement.16,17 It has been shown that SMA lesions cause various abnormalities of speech and motor function.18–20

We recently observed a patient who developed both acquired stuttering and long-lasting gait disturbance after apparent SMA seizure. His stuttering and gait disturbance gradually improved and almost completely resolved over 1 month.

Case Report

A 37-year-old, right-handed man was admitted because of speech and gait disturbances. He had been in good health until 28 months earlier, when he had a left anterior cerebral artery territorial infarction involving the left SMA and cingulate gyrus (Fig. 1A–C). At that time, he had experienced speech arrest and weakness of his right leg, which resolved over 10 days. The etiology of the stroke was not determined, and he was discharged from the hospital on aspirin.

Eighteen months after the stroke, he had what was considered a left SMA seizure, which consisted of sudden speech arrest, head deviation to the right, tonic posturing of the right leg, and preserved consciousness. After the seizure, he had difficulty with speech and walking that resolved gradually over 15 days. Subsequently, he was referred to our hospital for further evaluation of this episode.

He denied any speech problems when he was a child. There was no history of cardiaco diseases, hypertension, diabetes, or trauma. He had no family history of stuttering. On neurologic examination, the cranial nerves, speech, motor power, and sensation were normal. On awakening 3 days after hospital admission, he was unable to walk alone; postural stability was markedly impaired with generalized paucity of body movement. Motor strength was normal. He was barely able to make steps and only with assistance. His gait improved gradually and normalized over 20 days. During this episode, he showed no speech disturbance. An electroencephalogram (EEG), brain magnetic resonance angiogram (MRA), transcranial Doppler, and echocardiogram were all normal. Although the exact etiology of his gait disturbance was not found, it was clinically suspected that this episode was a postictal manifestation of an SMA seizure. The patient was placed on valproic acid and aspirin and did well without recurrent seizures or any other problems for the next 9 months.

On the day of his second admission, he developed sudden speech and gait disturbances after the SMA seizure that lasted for approximately 5 minutes. On examination, he showed severe stuttering with an abnormal protruding movement of his lips when he tried to speak (see video Segment 1). The stuttering did not improve with repetitive practice. It was similar in severity on both spontaneous speech and with repetition. The stuttering was accompanied by severe slowness of orolingual and velopharyngeal movement. The dysfluency of his speech was noted through entire sentences, but mainly at the beginning of words, phrases, or sentences. When he read a book aloud, the severity of the stuttering diminished and speech was monotonous. The speech disturbance was also noted when he sang a familiar song. We also detected severe bilateral body bradykinesia and gait disturbance. The bradykinesia was initially generalized but later was noted mainly in the lower extremities. He was initially...