

the totals by response options. Therefore, the performance scores from this study are not directly comparable to other Agency for Healthcare Research and Quality quality reports and should be interpreted with caution.

In summary, telehealth was effective, widely used, and reported as satisfying by PwPD in the past year. Although telehealth may not be appropriate for every clinical service, the use of telehealth for PD appointments within a hybrid model of patient care should remain an option for PwPD, especially for SLP and mental health, and legislation should ensure the accessibility of this option in the future. ■

**Acknowledgments:** We thank our colleagues at the Parkinson's Foundation for their help and support, as well as those in the Parkinson's community whose tireless advocacy, support, and donations have made this work possible. We thank Dr. Yael Manor for providing information on telemedicine visits in the Tel Aviv Sourasky Medical Center.

### Data Availability Statement

Data available on request from the authors

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### Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

## Efficacy of Caffeine in ADCY5-Related Dyskinesia: A Retrospective Study

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**Relevant conflicts of interest/financial disclosures:** Aurélie Méneret and Emmanuel Roze hold a patent on compounds for use in the treatment of ADCY5-related dyskinesia (19305366.7).

**Funding agency:** ADCY5.org

**Received:** 10 December 2021; **Revised:** 8 February 2022; **Accepted:** 15 March 2022

**Published online 5 April 2022 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29006**

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**ABSTRACT: Background:** ADCY5-related dyskinesia is characterized by early-onset movement disorders. There is currently no validated treatment, but anecdotal clinical reports and biological hypotheses suggest efficacy of caffeine.

**Objective:** The aim is to obtain further insight into the efficacy and safety of caffeine in patients with ADCY5-related dyskinesia.

**Methods:** A retrospective study was conducted worldwide in 30 patients with a proven ADCY5 mutation who had tried or were taking caffeine for dyskinesia. Disease characteristics and treatment responses were assessed through a questionnaire.

**Results:** Caffeine was overall well tolerated, even in children, and 87% of patients reported a clear improvement. Caffeine reduced the frequency and duration of paroxysmal movement disorders but also improved

baseline movement disorders and some other motor and nonmotor features, with consistent quality-of-life improvement. Three patients reported worsening.

**Conclusion:** Our findings suggest that caffeine should be considered as a first-line therapeutic option in ADCY5-related dyskinesia. © 2022 International Parkinson and Movement Disorder Society

**Key Words:** ADCY5; paroxysmal dyskinesia; caffeine; dystonia; hyperkinetic

The ADCY5 gene codes for adenylate cyclase type 5 (AC5), an enzyme converting ATP to cyclic AMP, which is mainly localized in the striatum. Heterozygous mutations in ADCY5 induce a rare and disabling disease characterized by early-onset hyperkinetic movement disorders, comprising a variable association of chorea, dystonia, myoclonus, and tremor. Frequent associated signs include axial hypotonia, orofacial myoclonus, marked motor fluctuations, and paroxysmal dyskinesia of various types, with unusual occurrence during nighttime.<sup>1-5</sup> There is usually no intellectual deficiency, epilepsy, or cerebellar syndrome. Numerous treatments have been tried without notable efficacy so far, except for partial response to benzodiazepines or improvement in paroxysmal movements with deep brain stimulation (DBS) of the globus pallidus internus (GPi) in some patients.<sup>6</sup>

In the setting of routine care, 2 patients from the same family told us that caffeine had spectacular efficacy on their paroxysmal episodes. Caffeine is known to be an antagonist of A2A receptors, which activate AC5 and are preferentially located in striatal neurons that express dopamine receptors D2.<sup>7</sup> Therefore, caffeine likely induces AC5 inhibition. As most ADCY5 mutations are considered to induce hyperactivity of this protein, clinical improvement could reasonably be expected with this drug.<sup>8,9</sup> In addition, caffeine was shown to improve hyperactivity and locomotion in *Caenorhabditis elegans* mutants harboring mutations causing the closely related disorder of GNAO1-related dyskinesia, which likely result in AC5 activation.<sup>10</sup> Caffeine was therefore tried in other patients, with remarkable efficacy.<sup>11,12</sup> Due to the rarity of ADCY5-related dyskinesia and the fact that caffeine is an everyday consumer product, the conduct of a regular randomized study is extremely challenging: first, for most patients, stopping caffeine and possibly receiving a placebo for weeks was unconceivable; second, there was a risk of not achieving significance due to the high variability in doses and intervals, irrespective of weight, between patients. We thus opted for a real-life retrospective study to obtain further insight into the efficacy and safety of caffeine in ADCY5-related dyskinesia.

## Patients and Methods

We recruited 17 patients in France and 13 patients from other countries (Australia, Brazil, Canada, Germany, India, Italy, Russia, Slovakia, and the United States). Patients with a proven *ADCY5* mutation who had tried caffeine in the past or were currently taking caffeine were invited to participate. Patients aged 8 years or above in France (and their parents for minors) were sent information regarding the protocol. If they agreed to the study, they were contacted by phone to fill a questionnaire. Patients younger than age 8 years or from other countries were informed of the study according to their country's legislation but were not questioned. Their physician filled the questionnaire according to information already collected as part of their clinical care. Details are provided in Supplementary Information.

The key exploratory end point was the percentage of responders to caffeine, with response being defined as improvement in overall involuntary movements of 40% or more. Secondary objectives were to evaluate global improvement in hyperkinetic involuntary movements ranging from 0 to 10, and specific improvement in paroxysmal episodes of movement disorders with caffeine, in terms of duration and frequency of episodes. Change in quality of life was evaluated by the patients using the Clinical Global Impression—Improvement Scale.

## Results

### Demographics

A total of 30 patients (16 females and 14 males) were enrolled in the study. Ages ranged from 4 to 76 years (median age: 14.5); 90% (27 of 30) had baseline hyperkinetic movement disorders (dystonia, chorea, myoclonus, tremor, or various combinations), 93% (28 of 30) paroxysmal movement disorders (73% with nocturnal events), 60% (18 of 30) gait disorders, 50% (15 of 30) hypotonia, 63% (19 of 30) dysarthria, and 43% (13 of 30) attention deficits (Table 1).

### Caffeine Efficacy

Twenty-six patients (87%) reported an improvement in overall movement disorders of 40% or more and thus were considered to be caffeine responders. Only 1 patient reported low efficacy of caffeine (evaluated at 3/10 on the improvement scale). The three remaining patients reported worsening of their movement disorders (either baseline or paroxysmal).

Mean improvement of movement disorders on a scale of 0 to 10 was 6.7 among all patients. Baseline movement disorders were reported to be improved in 81% (22 of 27). Before treatment with caffeine, duration of paroxysmal episodes varied from a few seconds to hours, whereas frequency ranged from a few per month to 40 per day. Among the 25 patients who had paroxysmal episodes and reported improvement, data on episode frequency were

available for 22 and on episode duration for 19. Frequency reduction of 50% or more was reported by all 22 patients, including 6 in whom episodes completely subsided. Among patients who still had episodes, 7 patients reported a duration reduction of 50% or more, 6 reported no change, and 1 reported an increase from 1–2 to 5 minutes (albeit with frequency improvement).

Some patients reported additional benefits: improvement in gait ( $n = 10$ ), pain ( $n = 9$ ), dysarthria ( $n = 9$ ), attention and concentration ( $n = 8$ ), sleep ( $n = 7$ ), tone ( $n = 6$ ), fine motor skills ( $n = 6$ ), mood/anxiety ( $n = 5$ ), drooling ( $n = 2$ ), and reaching new milestones like standing up or walking ( $n = 3$ ).

Quality of life was reported to be improved by 87% (26 of 30) of patients (mean Likert score 2.4/7): very much improved in 7, much improved in 14, minimally improved in 5, much worse in 3 (who rapidly discontinued treatment), and unchanged in 1.

### Caffeine Doses and Tolerance

Twenty-seven patients were still on caffeine when the study was conducted. Doses and intervals varied greatly between patients, ranging from 60 to 800 mg a day, in one to five takes. Tolerance was very good, with 47% of patients (14 of 30) reporting mild side effects, including 4 patients only when they tried caffeine at higher doses: worsening of movement disorders in 3 patients; digestive issues in 5; sleep issues in 4; hyperactivity in 2; and tachycardia, dizziness, or irritability in 1 each.

### Other Treatments

A total of 114 therapeutic trials were performed with 30 different drugs in this cohort. Twenty-nine (25%) of these trials were reported to have an efficacy of 40% or more on movement disorders. Treatments most often considered to be effective were DBS of the GPi (3/4), clonazepam (5/15), diazepam (4/6), tetrabenazine (3/9), baclofen (2/4), levetiracetam (2/5), and trihexyphenidyl (3/13). Side effects such as drowsiness were frequent with benzodiazepines. Of note, tetrabenazine was reported to worsen movement disorders in 2 patients, levodopa was ineffective or worsened episodes in 13 of 14 trials, and acetazolamide was ineffective or worsened episodes in all eight trials.

## Discussion

This retrospective real-life study indicates that caffeine is efficacious and well-tolerated in most patients with *ADCY5*-related dyskinesia, as 87% of our cohort reported improvement in their hyperkinetic involuntary movements of at least 40%. Improvement was noted in frequency and duration of paroxysmal movement disorders but also in baseline movement disorders and other features such as gait disorder, hypotonia, dysarthria, pain, attention and concentration, sleep quality, mood, fine motor skills, and drooling.

**TABLE 1** Characteristics of the patients and caffeine response

Patient	Age (y)	Gender	ADCY5 mutation	Caffeine daily dose (mg)	Improvement in MD (0–10)	Quality of life	Improvement in frequency of episodes	Improvement in duration of episodes	Side effects
1	27	F	R418Q	100–400	7	2. Much improved	100%	100%	0
2	39	F	R438P	175	8	2. Much improved	50%	ND	Possible worsening of insomnia
3	76	M	R418W (mos)	400	9.5	1. Very much improved	>50%	>50%	0
4	40	F	R418W	75	7	3. Minimally improved	ND	ND	Loss of appetite at higher doses
5	46	M	c.2088 + 1G > A	200	7	2. Much improved	50%–75%	0	0
6 <sup>11</sup>	13	M	c.2088 + 1G > A (mos)	400	8	2. Much improved	90%	>50%	0
7	31	M	R418W	500–600	7	3. Minimally improved	50%	0	Acid reflux
8	18	M	c.2081_2082insAAA/p.Lys694dup	300	5.5	3. Minimally improved	60%	60%	0
9	35	M	L720P	50	0	6. Much worse	NA	NA	Worsening of dystonia
10	15	F	R418W	100	4	2. Much improved	50%	0	Hyperactivity at higher doses
11	12	F	R68Q	100 mg	8	2. Much improved	50%	0	Insomnia, irritability at higher doses
12	13	F	L720P	100–200	0	6. Much worse	NA	NA	Triggering of episodes
13	19	F	R418Q	150–300	6	3. Minimally improved	50%	0	0
14	17	M	R418W (mos)	800	7	2. Much improved	75%	0	0
15	13	F	c.2088 + 2 T > G	300	5	2. Much improved	NA	NA	0
16	7	F	R418W (mos)	200	9	1. Very much improved	80%	0	0
17	6	M	S567R	300	7	2. Much improved	100%	ND	0
18	43	F	R418W	300	10	2. Much improved	100%	100%	0
19	5	M	R418W	25	0	6. Much worse	NA	NA	Neurological worsening, jitteriness
20	14	M	K691N	100	6	4. No change	100%	ND	0
21	13	F	R418W	225	9	1. Very much improved	80%	98%	Suppressed appetite, mild tachycardia, weight loss
22	9	M	R418Q	150	9	2. Much improved	80%	Longer duration	Slight insomnia
23	5	F	M696K	200	9	1. Very much improved	80%	50%	Abdominal pain, reflux
24	6	M	R418Q	100	7.5	2. Much improved	70%	80%	0

(Continues)

**TABLE 1** Continued

Patient	Age (y)	Gender	ADCY5 mutation	Caffeine daily dose (mg)	Improvement in MD (0–10)	Quality of life	Improvement in frequency of episodes	Improvement in duration of episodes	Side effects
25	27	F	R418W	600	10	1. Very much improved	100%	100%	0
26	10	F	R418W	120–160	8.5	2. Much improved	50%	ND	Nausea, worsening of awakening episodes, insomnia if late intake
27	4	F	R418Q	60	7	2. Much improved	ND	ND	Hyperactivity, loss of energy
28	15	F	R418W	300	3	3. Minimally improved	ND	ND	Hyperactivity, dizziness at higher doses
29 <sup>12</sup>	32	M	R418W	200	9	1. Very much improved	95%	75%	0
30	4	M	R418W	200	9	1. Very much improved	NA	NA	0

Abbreviations: MD, movement disorders; F, female; ND, not determined; M, male; NA, not applicable; mos, mosaic.

Quality of life was reported to be improved by 87% of patients. Caffeine was overall well tolerated, even in children. Notably, caffeine rarely induced sleep disorders, even when taken in the evening. Considering its remarkable tolerance profile and ease of use, we thus state that caffeine should be considered as a first-line therapeutic option, regardless of age, in all patients with ADCY5-related dyskinesia. Physicians should however be aware of the possibility of reversible worsening in a small subset of patients (10% in our study). Besides, our findings further support the possibility of targeting striatal cyclic adenosine monophosphate metabolic pathways to find new treatments for hyperkinetic disorders.<sup>13</sup>

The principal limitation of this study is its retrospective and nonrandomized design, which leaves the possibility that the result we observed could merely be due to a placebo effect. However, no comparable and generalized results were found with other treatments in our cohort, which strongly suggests that this is not the case. Of 114 therapeutic trials conducted with 30 different drugs (including DBS), only 25% were reported to have an efficacy of 40% or more on movement disorders, with low reproducibility. Best results were obtained with benzodiazepines, frequently at the cost of debilitating side effects, or DBS, which is an invasive procedure. Coadministration of other drugs could be a confounding factor, but doses were unchanged during the caffeine titration period. Another limitation to the study is its sample size, of 30 patients. However, this is a relatively high number considering the rarity of the disease, which could be achieved only by including patients from multiple centers in various countries. In addition, even though we specifically aimed to include any patient who had previously tried caffeine, we cannot exclude a possible recruitment bias toward responders. Finally, due to the retrospective nature of the study and its focus on caffeine response, there were some missing data and no detailed phenotypic description of all patients. As chorea, myoclonus, tremor, and dystonia are often mixed and difficult to differentiate in these patients, we chose to use the broad term “hyperkinetic movement disorders.”

Of the 3 patients who reported worsening with caffeine, 1 had the common R418W mutation. The fact that he tried only very small doses (25 mg) raises the possibility of a threshold effect. In our experience, trying doses too low for a particular patient may lead to falsely conclude regarding caffeine inefficacy, whereas doses too high may worsen movements in others. The other 2, who presented with much clearer and reproducible worsening of their movement disorders, shared the same mutation (L720P), which was not found in any other patient. This suggests that the L720P mutation could have different consequences, possibly through a loss of function phenomenon. A parallel could be made with GNAO1-related disorders, which may be due to either loss- or gain-of-function mechanisms, suggesting contrary effects of a given drug depending on the underlying mutation.<sup>14,15</sup> Further



pharmacogenomics investigations should be conducted in these disorders, opening the door for personalized medicine.

This study further supports the empirical- and pathogenesis-driven hypothesis that caffeine could be beneficial in patients with *ADCY5*-related dyskinesia. The large disparity in effective doses (60–800 mg a day) and intervals (one to five times daily) of caffeine among patients, regardless of weight, indicates that (1) self-tailored treatment regimens with close monitoring are mandatory and (2) flexible doses should be preferred in the prospect of a future clinical trial. ■

**Acknowledgments:** We would like to thank Assistance Publique - Hôpitaux de Paris and Inserm for their support, as well as all the participants in our study.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

## Diabetes, Glycated Hemoglobin (HbA1c), and Neuroaxonal Damage in Parkinson's Disease (MARK-PD Study)

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**Funding agencies:** CUC was supported by an Else Kröner Exzellenzstipendium from the Else Kröner-Fresenius Stiftung (grant number: 2018\_EKES.04). RS was supported by an Else Kröner Exzellenzstipendium from the Else Kröner-Fresenius Stiftung (grant number: 2020\_EKES.16).

**Relevant conflicts of interest/financial disclosures:** MU, SL, RS, and SM have nothing to declare. CB served on scientific advisory boards for Bial, Desitin, Kyowa Kirin, Merz, STADA Pharm, and Zambon and received honoraria for lectures from Abbvie, Bial, Desitin, TAD Pharma, UCB Pharma, and Zambon. MPN received lecture fees from Abbvie, Abbott, and Boston Scientific and served as consultant for Medtronic, Boston Scientific, Licher, Zambon, and Abbvie. CG reports personal fees from AMGEN, Boehringer Ingelheim, Novartis, Daiichi Sankyo, Abbott, Prediction Biosciences, and Bayer. JK received speaker fees, research support, travel support, and/or served on advisory boards for Swiss MS Society, Swiss National Research Foundation (320030\_189140/1), University of Basel, Progressive MS Alliance, Bayer, Biogen, Celgene, Merck, Novartis, Octave Bioscience, Roche, and Sanofi. CUC reports personal fees from Pfizer and Zambon.

**Received:** 2 December 2021; **Revised:** 2 February 2022; **Accepted:** 28 February 2022

Published online 6 April 2022 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29009