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CORRESPONDENCE

Paradoxical caffeine-responsive paroxysmal nonkinesigenic dyskinesias

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Dear Sir

Paroxysmal dyskinesias (PxD) refer to a group of clinically and genetically heterogeneous disorders presenting with recurrent attacks of abnormal movements (mostly chorea, dystonia, or combination) of variable frequency, duration and etiology (genetic, metabolic, immunological, neurodegenerative and others). Clinically, based on the triggers of the attacks, three PxD subtypes have been delineated: paroxysmal kinesigenic dyskinesias (PKD) and paroxysmal exercise-induced dyskinesias (PED), in which attacks are brought on by rapid movements (PKD) or sustained exercise (PED), and paroxysmal nonkinesigenic dyskinesias (PNKD) where triggers include alcohol, caffeine, and stress [1]. Here we report the case of PNKD with dramatic and reproducible improvement after caffeine ingestion in the form of caffeine pills and green tea.

Case presentation

The 45 years-old businessman started to experience involuntary movements of the left arm and leg in his early twenties, often preceded by brief unspecific feelings in his body. His consciousness was never impaired. Initially, attacks occurred occasionally only (less than once in three months), but became very frequent (up to 30-times daily) over the time. Attacks lasted several seconds, typically less than two minutes. They occurred both, during the day and at night. Homemade videos demonstrated choreodystonic movements, always involving the left extremities (Video 1).

His interictal neurological examination was completely normal. His past medical history included only gastroesophageal reflux disorder treated with omeprazole. Family history was negative. Diagnostic work-up included a brain MRI, EEG, and comprehensive blood tests all of which were normal. Whole exome sequencing was unremarkable. The patient could not identify any clear trigger, except for emotional stress so a diagnosis of primary PNKD was made. Carbamazepine was effective, however, withdrew due to side effects. Notably, he reported improvement after caffeine intake: caffeine tablets (one tablet containing 100 milligrams of caffeine) or a cup of green tea or Coca Cola early in the morning considerably ameliorated his symptoms. Attacks became less frequent, shorter in duration, and also less severe. Caffeine did not interfere with his sleep habits. The effect of caffeine was recorded in his symptom diary (Fig. 1A).

Caffeine consumption led to reduction of attack frequency which decreased from several attacks per hour to none or several attacks a day (mostly one to six attacks daily). The intensity of his PNKD (scored from 0 to 5 by himself), showed mild improvement. Subsequently, the patient underwent a 14-days caffeine (100 milligrams twice daily) versus placebo (sacharose-based pill of similar physical properties

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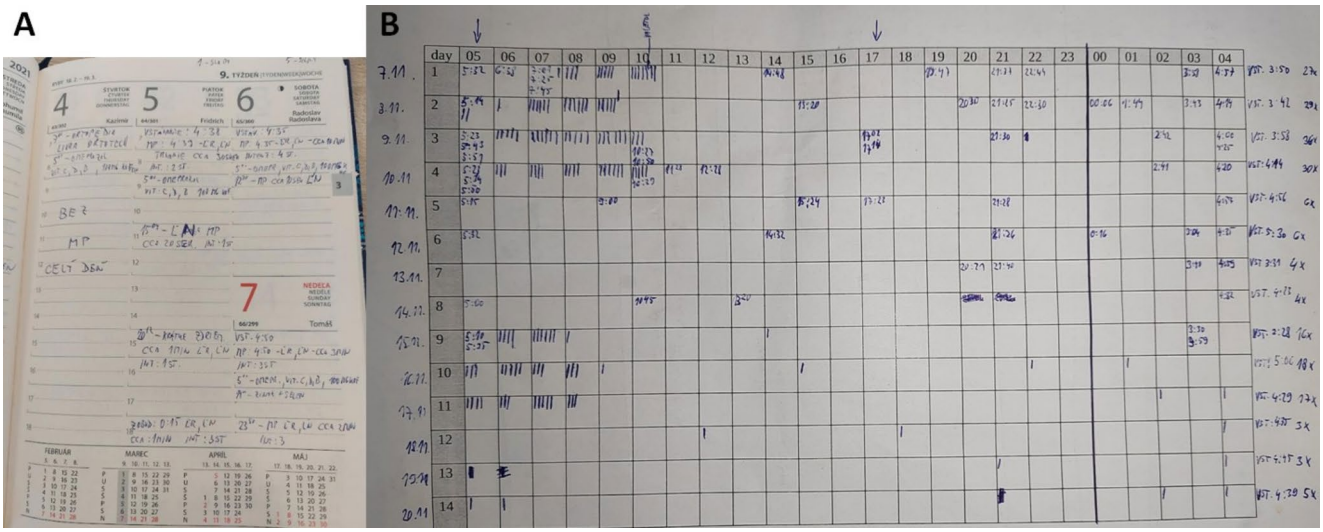

Fig. 1 (**A**) Patient´s home diary. (**B**) A table showing results of 14-days caffeine versus placebo clinical trial. Days 1–4: placebo, 5–8: caffeine, 9–11: placebo, 12–14: caffeine. Each single attack is shown as a single line. Compared to placebo, the number of attacks is significantly lower during caffeine treatment.

twice daily) blinded trial, confirming clear caffeine-responsiveness (Fig. 1B). His usual current dose consists of one third of 200 milligram caffeine tablet twice daily, sometimes in combination with one little cup of green tea, which leads to a good and consistent response.

Discussion

This case of PNKD is unusual, as caffeine, one of the typical triggers of PNKD, improved rather than triggered the attacks. Our observation resembles the case of 19 year-old female where a cup of coffee which had been given to induce an attack, led to significant improvement of PxD. This case was later found to have mutations in the proline-rich transmembrane protein 2 (*PRRT2*) gene, the most common cause of PKD [2]. More recently, considerable improvement after caffeine was reported in *ADCY5*-associated paroxysmal and non-paroxysmal dyskinesias. Therefore, caffeine should be considered a first-line treatment in this disorder [3]. Furthermore, caffeine-responsiveness was observed in animal models, i.e. in *Caenorhabditis elegans* mutants harboring mutations of GNAO1-related dyskinesia [4].

The etiology of PxD in our case remains undetermined. Mutations in *PRRT2*, *ADCY5*, *GNAO* and other PxD-related genes were excluded and whole exome sequencing was unremarkable.

Caffeine acts as an antagonist of adenosine 2 A (A2A) receptors located mainly in striatal neurons with D2 dopamine receptors. As these receptors activate adenyl cyclase 5, caffeine induces inhibition of this enzyme [3]. Notably, the A2A receptor antagonist such as theophylline can also ameliorate ADCY5-related dyskinesias [5].

Caffeine is a very practical therapeutic option in PxD, as it is widely available, inexpensive and well tollerated. Our patient continues to take caffeine tablets with great benefit. He reported a similar effect after drinking green tea (which contains both caffeine and theophylline). Based on this interesting case, we propose to offer a trial of caffeine in PNKD patients in whom caffeine does not trigger symptoms.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13760-024-02666-y.

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Author contributions Research project: (A) Conception, (B) Organization, (C) Execution; Statistical Analysis: (A) Design, (B) Execution, (C) Review and Critique; Manuscript Preparation: (A) Writing of the first draft, (B) Review and Critique.

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Data availability All datasets generated for this study are included in the article. The figures in our paper are original for this article, and we have permission to use it.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication We have obtained written informed consent from the patient for the publication of this case report.

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