Unexpected outcome (positive or negative) including adverse drug reactions

Pathological gambling from dopamine agonist and deep brain stimulation of the nucleus tegmenti pedunculopontine

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Summary

In patients with Parkinson's disease, aberrant or excessive dopaminergic stimulation is commonly indicated as the trigger factor in unmasking impulse control disorders (ICDs) such as pathological gambling. We had the opportunity to follow a patient who experienced Parkinson's disease 7 years ago when he was using pramipexole and again, recently, when he was treated with levodopa (L-dopa) and low frequency stimulation of the nucleus of the pedunculopontine tegmentum (PPTg) but no dopamine agonists. The same patient had shown, when studied with fluorodeoxyglucose-positron emission tomography in the condition PPTg-ON, a peculiar increased activity in the left ventral striatum. This case report confirms that, in a predisposed personality, ICD may arise from the perturbation of endogenous pathways, which connect the brainstem to the basal ganglia.

BACKGROUND

An increasing range of 'reward-seeking' behaviours, reported as impulse control disorders (ICDs), has been described in patients with Parkinson's disease.^{1 2} ICDs, as hyper-sexuality, binge eating, compulsive shopping and pathological gambling, occur in about 5% of the total Parkinson's disease population and are commonly attributed to aberrant or excessive dopaminergic stimulation with particular regard to dopamine-agonists assumption. A large study—the DOMINION—carried out on more than 3000 Parkinson's disease patients is contributing to clarify how dopaminergic drugs interact with an underlying patient vulnerability in unmasking ICDs and dopamine dysregulation syndrome (DDS).³

Here, we describe the case of a Parkinson's disease patient who experienced pathological gambling under two rather different treatment conditions: pharmacological (association dopamine agonist/levodopa (L-dopa)) or pharmacological plus surgical (deep brain stimulation (DBS)).

CASE PRESENTATION

The case reports a 51-year-old patient affected by a severe form of Parkinson's disease (H&Y 3). No psychiatric problems were referred or noticed during his clinical follow-up apart from a stereotyped occasional ICD episode, consisting of a pathological gambling phase, which occurred when he was 43 years old after 4 years of disease duration. At that time, he was assuming L-dopa 250 mg plus pramipexole 3.5 mg/day. The discontinuation of dopamine agonist treatment, with concomitant L-dopa increase, promoted the complete resolution of pathological gambling.

Six years later, when the patient was 49 years old, the combination of motor fluctuations, unpredictable dyskinesias and freezing of gait suggested the stereotactic neurosurgery approach, which combined the implantation of the subthalamic nucleus (STN) and the nucleus of the pedunculopontine tegmentum (PPTg).⁴

INVESTIGATIONS

In the pre-surgical screening, the following tests were administered: Minnesota Impulsive Disorders Interview for ICD; Beck Depression Inventory for depression; Neuropsychiatric Inventory for psychopathologies; Mini-Mental State Examination and Frontal Assessment Battery for evaluation of cognitive abilities. No deficits in the explored psychiatric and cognitive domains emerged.

TREATMENT

Electrode implantations (medtronic 3389) were placed inside the two contemporary target areas for each hemisphere. For STN, we used standard sites.⁴ For the PPTg, co-ordinates were six lateral to the midline, 14 mm below posterior commissure; y=−2 mm below posterior commissure.⁵

OUTCOME AND FOLLOW-UP

Post-surgical follow-up (up to mid-2007), including steady state stimulation parameters in both nuclei, allowed us to assess mild motor benefits under PPTg-ON in the best stimulation protocol (lower bipolar contacts, 20 Hz). The patient was also manifesting a state of well-being occasionally perturbed by euphoria. Meanwhile, a significant

increase in verbal fluency and working memory as well as a dramatic restoration of rapid eye movement sleep phases were observed during PPTg-ON.^{4 6–7} To note, the positive effect of PPTg-DBS on Parkinson's disease non-motor aspects are in agreement with the increased attentiveness and the sleep quality improvement reported by other authors,^{8 9} despite obvious difference of trajectories in the 'pedunclopontine nucleus area'.

Hence, during most of 2007 and the beginning of 2008, in light of the prominent effect on sleep architecture, PPTg was maintained ON only at night-time. During 2008, our patient was challenged again with continuous stimulation of both targets (chronic 185 Hz STN-DBS plus 20 Hz PPTg-DBS and L-dopa 450mg but no dopamine agonists). A few weeks after the prolonged continuous PPTg plus STN-DBS the patient experienced a severe DDS characterised by pathological gambling (up to 13 000 Euros lost in 3 weeks), compulsive buying of useless items, hypersexuality and drug 'craving'. The same tests used for the pre-surgical screening revealed personality trait abnormalities but no cognitive decline. As a first strategy, we have tapered L-dopa and changed the STN-DBS setting, but this was of no help; only switching OFF PPTg-DBS abated ICD. Consistently, in the last 12 months the abnormal behaviour has not re-emerged since maintaining STN-ON plus a stable L-dopa regimen (500 mg/day).

DISCUSSION

So far, the impact of PPTg-DBS on ICD has been never investigated, while the effects of STN-DBS are quite variable.^{10 11} Here we document the risk of unmasking impulsive disruption through PPTg stimulation in the absence of dopamine agonists.

To note, fluorodeoxyglucose-positron emission tomography studies had revealed that PPTg-ON (but not STN-ON) increased the metabolic activity of unilateral ventral striatum; which is reminiscent of the hypothesis of a robust activation of ascending 'limbic' circuits in Parkinson's disease gamblers.¹²

Learning points

- Our case indicates that a reward system malfunction may be exacerbated not only as a iatrogenic consequence of treatment affecting D2/D3 binding sites but also as the result of an electrical activation of dysfunctional circuitries, which connect the brain-stem (namely the PPTg-ventral tegmental area pathway) to the basal ganglia (ventral striatum/accumbens) and orbitofrontal pre-frontal areas.
- The importance of cognition analysis in exploring the emotional domain in pedunclopontine nucleus surgery.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Dodd ML**, Klos KJ, Bower JH, *et al*. Pathological gambling caused by drugs used to treat Parkinson's disease. *Arch Neurol* 2005;**62**:1377–81.
2. **Voon V**, Hassan K, Zurowski M, *et al*. Prospective prevalence of pathological gambling in Parkinson's disease. *Neurology* 2006;**66**:1750–2.
3. **Weintraub D**, Koester J, Potenza MN, *et al*. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 2010;**67**:589–95.
4. **Stefani A**, Lozano AM, Peppe A, *et al*. Bilateral deep brain stimulation of the pedunclopontine and subthalamic nuclei in severe Parkinson's disease. *Brain* 2007;**130**:1596–607.
5. **Mazzone P**, Sposato S, Insola A, *et al*. Stereotactic surgery of nucleus tegmenti pedunclopontini. *Br J Neurosurg* 2008;**22**:S33–S40.
6. **Stefani A**, Galati S, Pierantozzi M, *et al*. Non motor effects of PPN-DBS in PARKINSON'S DISEASE patients; insights from intraoperative electrophysiology. In: Groenewegen **HJ**, Vroom P, Berendse HW, Mulder AB, Cools AR, eds. *The Basal Ganglia IX, Advances in Behavioral Biology*. New York: Springer 2009:573–87.
7. **Stefani A**, Ceravolo R, Brusa L, *et al*. Non-motor functions in parkinsonian patients implanted in the pedunclopontine nucleus: Focus on sleep and cognitive domains. *J. Neurol Sci* 2010;**289**:44–8.
8. **Androulidakis AG**, Mazzone P, Litvak V, *et al*. Oscillatory activity in the pedunclopontine area of patients with Parkinson's disease. *Exp Neurol* 2008;**211**:59–66.
9. **Lim AS**, Moro E, Lozano AM, *et al*. Selective enhancement of rapid eye movement sleep by deep brain stimulation of the human pons. *Ann Neurol* 2009;**66**:110–4.
10. **Lim SY**, O'Sullivan SS, Kotschet K, *et al*. Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. *J Clin Neurosci* 2009;**16**:1148–52.
11. **Ardouin C**, Voon V, Worbe Y, *et al*. Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. *Mov Disord* 2006;**21**:1941–6.
12. **Steeves TD**, Miyasaki J, Zurowski M, *et al*. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. *Brain* 2009;**132**:1376–85.

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