Capgras Syndrome in a Patient with Parkinson’s Disease after Bilateral Subthalamic Nucleus Deep Brain Stimulation: A Case Report

Christina Rose Kyrtsos\textsuperscript{a}  Mark C. Stahl\textsuperscript{b, c}  Paul Eslinger\textsuperscript{b}  Thyagarajan Subramanian\textsuperscript{b}  Elisabeth B. Lucassen\textsuperscript{b}

\textsuperscript{a}College of Medicine and Departments of \textsuperscript{b}Neurology and \textsuperscript{c}Neural and Behavioral Sciences, Penn State Milton S. Hershey Medical Center, Hershey, Pa., USA

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Abstract
Capgras syndrome is a delusional misidentification syndrome (DMS) which can be seen in neurodegenerative diseases such as Lewy body dementia and, to a lesser extent, in Parkinson’s disease (PD). Here, we report the case of a 78-year-old man with a history of idiopathic PD who developed Capgras syndrome following bilateral subthalamic nucleus deep brain stimulation (DBS) implantation. As the risk of DMS has been related to deficits in executive, memory, and visuospatial function preoperatively, this case highlights the importance of continuing to improve patient selection for DBS surgery. Capgras syndrome is a rare potential complication of DBS surgery in PD patients with preexisting cognitive decline.

Introduction
Delusional misidentification syndromes (DMS) are relatively uncommon phenomena associated with both psychiatric and organic brain dysfunction. Capgras syndrome (CS) is a subtype of DMS in which a patient believes that a familiar person or place has been replaced by an imposter or duplicate [1–5]. This syndrome is highly associated with neurodegenera-
tive disorders, and in particular with Lewy body dementia; however, few reports have described it in association with idiopathic Parkinson's disease (PD) with or without dementia [3, 4, 6, 7].

The effect of subthalamic nucleus deep brain stimulation (STN DBS) on cognition and neuropsychiatric function in PD remains controversial, and it is unclear which factors are related to cognitive decline, dementia, and psychiatric disease after STN DBS [5, 8–11]. A recent study by Kim et al. [5] suggested that a dysfunction in the frontostriatal circuitry (as inferred from tests of executive function) at baseline was associated with a risk of subsequent global cognitive decline and dementia in patients with PD who underwent STN DBS. This study additionally identified preoperative mild cognitive impairment as a risk factor for dementia after STN DBS [5]. Several neuropsychiatric symptoms including mania, impulsivity, depression, and apathy are well known to emerge or to be exacerbated in the postoperative period, especially in patients with cognitive dysfunction [12]. To our knowledge, however, there have been no reported cases of CS following STN DBS implantation, which we describe here.

Case Presentation

The patient had a remote history of traumatic brain injury as a parachute jumper in the military with no apparent residual as well as remote heavy alcohol use. He was diagnosed with idiopathic PD at the age of 71 years. Tremor, rigidity, and bradykinesia were well controlled on a combination of carbidopa/levodopa, rasagiline, and amantadine. He never developed dyskinesias. Approximately 5 years after diagnosis, tremor worsened despite escalating medication doses, and he was referred for DBS implantation at the age of 76 years.

Preoperative magnetic resonance imaging (MRI) showed extensive ischemic microvascular disease but essentially normal brain volume for age (fig. 1a–c). Neuropsychological testing prior to DBS placement revealed mild cognitive difficulties with a Mini-Mental State Examination (MMSE) score of 25/30, Dementia Rating Scale-2 (DRS-2) test scaled score of 11 (average), Trail Making Test part A T-score of 43 (average), but an inability to complete Trail Making Test part B with multiple errors. This pattern is consistent with executive dysfunction and mild cognitive impairment. The family reported that he was independent in daily activities, driving locally, but no longer managing family finances. The patient was experiencing sleep disturbance, mild depression, and occasionally formed visual hallucinations, with variable insight, in which he reported seeing an intruder in his house. There was also paranoia that his wife was being unfaithful. Quetiapine 25 mg q.h.s. was started.

The patient elected to undergo bilateral STN DBS placement. A postoperative computed tomography (CT) revealed accurate electrode placement without hemorrhage (fig. 1d, e). His postoperative course was complicated by nearly 1 week of severe hallucinations and delirium, during which he assaulted a registered nurse and experienced delusions that the hospital staff wanted to murder him. He improved sufficiently to warrant discharge to home, but once there, he reportedly did not recognize his own house and became paranoid that people were trying to break in.

The DBS was activated 3 weeks later with stimulation parameters set symmetrically to an amplitude of 1.5 V, a frequency of 130 Hz, and a pulse width of 60 µs on the left and the right. He continued to have significant paranoia, mostly with regard to his wife, and some delusions of a home invasion. About 3 weeks after DBS activation, it became apparent to the family that the patient had come to believe that he was living with five or six doppelgängers.
of his wife, all of whom 'looked like her doing different jobs in the house, with the same name’. He easily recognized other family members.

Neuropsychological testing 3 months postoperatively showed little change in MMSE (24/30), but notable decline in DRS-2 (scaled score of 6, mildly impaired), Trail Making Test part A (T-score of 26), and continued difficulty with Trail Making Test part B. As he continued to have hallucinations and increasing delusions, the patient was tried on risperidone for 4 evenings before developing a severe psychotic episode which required a brief hospitalization. Amantadine and rasagiline were discontinued, without effect on his mental status. The DBS was then deactivated, but this failed to improve his cognition, hallucinations, or delusions and resulted in worsened motor function. He remained suspicious of the ‘women in his house’ who claimed to be married to him, sometimes demanding proof of their identity and accusing them of plotting to take his wealth. The DBS device was reactivated 1 month later and left on with only minor adjustments for nearly 2 years.

Six months postoperatively, a neuropsychological evaluation revealed further decline (MMSE score 14/30 and Trail Making Test part A T-score of 17, and the patient was now completely unable to perform the Trail Making Test part B). His quetiapine dosage was increased to 50 mg q.h.s. at this time, but the hallucinations and delusions persisted. His care was transferred to a Movement Disorders specialist here (E.B.L.), who added donepezil and switched his antidepressant from escitalopram to sertraline. These interventions correlated with improvement in his MMSE score and reduced symptoms of anxiety and depression. His dosage of quetiapine was further increased to 100 mg q.h.s. after he threatened one of the ‘versions’ of his spouse with a knife, believing she was preventing him from seeing his real wife. This improved his hallucinations, but the misidentification delusion about his wife persisted, though he could still be easily reoriented during this time.

Neuropsychological testing 1 year postoperatively indicated some modest improvement with an MMSE score of 20/30, DRS-2 scaled score of 4 (moderately impaired), and Trail Making Test part A T-score of 22, but continuing inability to perform Trail Making Test part B. The delusion of his wife being several different people became more pervasive, and the patient was harder to reorient verbally. He made increasingly violent gestures towards the various ‘versions’ of his wife. Quetiapine was increased to 100 mg b.i.d., with some improvement in his behavior at the expense of some sedation.

Neuropsychological testing 18 months postoperatively revealed an MMSE score of 18/30 and a DRS-2 scaled score of 2 (severely impaired). At this point, his wife reported that he needed a significant degree of assistance with feeding, chair-to-bed transfers, and other activities of daily living. For the continued delusions and violent outbursts, his psychiatrist started him on lamotrigine. Along with the quetiapine, this seemed to improve the delusions yet worsened cognition and functional status due to sedation. He became wheelchair bound. His wife indicated that the patient was often able to correctly identify her during the day, but that he would consistently misidentify her in the evenings before the q.h.s. quetiapine dose.

Twenty-six months after DBS placement, the patient experienced another acutely psychotic episode with delusions in which he became violent towards his wife. His wife was able to turn off the DBS and, remarkably, the patient’s delusions and violent behavior subsided considerably within about 30 min. The DBS was left off at this time and the patient enjoyed a period of substantially reduced delusions. The patient spent the next 4 weeks with the DBS deactivated, controlling his motor symptoms with his usual dose of carbidopa/levodopa. At this point, he passed away suddenly due to a cardiac arrhythmia before any further manipulation of his DBS device could be performed. Autopsy was not performed.
Written informed consent was obtained from the patient's family for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Discussion

CS is the most common form of DMS, affecting between 16.6 and 27.8% of individuals with Lewy body dementia, 15.8% of Alzheimer's disease patients, and 8.3% of patients with semantic dementia [3, 13]. It is less commonly associated with patients who have PD with or without cognitive decline and often presents years after the initial onset of dementia [1, 4]. It is also described in schizophrenia and with brain lesions (frontal, temporal, or parietal) due to trauma or to stroke [1, 14].

The defining feature of CS is the recurrent delusion that a person (often closely related or a spouse) has been replaced by an imposter having subtle physical differences. This may occur in patients who are otherwise quite lucid, such that the delusion can persist without detection unless specifically asked about or described by outside informants. Related forms of DMS include reduplicative paramnesia, in which the patient believes that his home, town, or other familiar place has been replaced with a near-identical simulacrum, and the Fregoli delusion, a belief that various strangers are actually a familiar person in disguise. These delusions stand in contrast to prosopagnosia (face-blindness) and nonverbal auditory agnosia, in which sufferers are simply unable to recognize the faces or voices, respectively, of familiar people. DMS of all types are associated with paranoid behaviors [2–4].

The exact pathophysiology in CS is not well understood, and no single impairment or pattern of lesions has been found to underlie all cases. CS has often been associated with either right hemispheric or bilateral lesions to the frontal and/or temporal lobes affecting limbic, paralimbic, and visual pathways involved in affective processing [1, 2, 4]. CS patients with parkinsonism often have frontal or global cerebral atrophy [1]. SPECT imaging of cerebral perfusion patterns in Capgras patients has demonstrated hypoperfusion of limbic and paralimbic structures [7]. Affected patients tend to have extensive lesions involving fairly large neocortical territories [4].

Unifying mechanistic theories to explain CS include disconnection (via destructive, functional, or degenerative lesions) between the occipito-temporal cortex, where facial recognition occurs, and limbic circuits associated with emotion. Under this paradigm, facial recognition or a sense of familiarity may occur, but in the absence of the full emotional context that uniquely marks and supplies identity to the specific features of persons close to the patient [14]. Similarly, disruption of frontal-temporal or frontal-limbic circuits could result in a disconnection between the cognitive pathways responsible for recognizing a face seen many times and other processes critical for placing it as a unique identity with a shared personal and emotional history [2].

The subthalamic nucleus regulates multiple neural networks via inhibitory signals that pass through it from various cortical areas. Motor circuits are modulated in the dorsolateral area, limbic circuits in the ventromedial region, and frontal-associative modulation in the intermediate zone [12]. It is hypothesized that STN DBS improves motor symptoms by impeding the inhibitory signals to the motor cortex. However, inadvertent stimulation of frontal-associative or limbic circuits could conceivably affect these functions which are hypothesized to be important in DMS as described above. Alternately, STN electrode-induced disconnection between the frontal lobe and other lobes or a disconnect between the inferotemporal cortex and the amygdala could potentially have triggered the CS in our patient.
The Capgras delusion only appeared after his surgery. He had mild cognitive dysfunction preoperatively, which steadily worsened in the postoperative period and coincided with the severity of the Capgras delusions. As initially turning off the DBS did not help the symptoms abate, it is possible that a lesional effect was responsible for these symptoms rather than the stimulation itself. Alternately, the stimulation may have triggered a delusional state that was sustained by his ongoing psychosis, and turning off the stimulation once the quetiapine was started may have been helpful, as it seems to have ultimately been. We speculate that his history of prior head injury and baseline executive dysfunction, with possible damage to the frontostriatal circuitry, and/or the moderate white matter disease present before surgery may have been risk factors that predisposed him to develop CS in the context of STN DBS. In retrospect, tractography with diffusion tensor imaging would have been of interest in this patient.

CS is important to recognize in part because of the significant risk of violence against the person who is misidentified. The risk to a significant other or family member is increased in patients who are male, in those whose delusions have existed for longer periods of time, and in patients with concomitant paranoia or substance abuse [1]. In this case, the treating team was made aware of at least one episode in which the patient threatened his wife with a knife, and it is fortunate that the patient did not have access to a firearm. In some instances, acute placement of a patient into a psychiatric facility may be needed. Although in this case CS presented in the context of frank paranoia, some patients are otherwise rational and CS could go undetected unless it was specifically considered.

CS has been successfully treated with neuroleptics including quetiapine, olanzapine, mirtazapine, pimozide, and risperidone [1]. In cases of CS in patients with Lewy body dementia, typical antipsychotic agents should be avoided as these can acutely worsen parkinsonism, increase sedation, or cause a neuroleptic malignant syndrome-like condition which can be fatal [15]. In general, quetiapine and clozapine are preferred agents for treating psychosis in patients with parkinsonism of any type due to the relative lack of extrapyramidal side effects.

This patient was diagnosed by a neurologist as having idiopathic PD at the age of 71 years. However, he never experienced motor fluctuations or drug-induced dyskinesias. He had significant microvascular changes in the brain preoperatively. He also developed cognitive changes relatively quickly. These features do raise the question of whether the patient suffered from idiopathic PD, an alternate diagnosis of Lewy body dementia, or a combination of idiopathic PD and vascular dementia. Unfortunately, pathological confirmation is not available. This case also illustrates the need for clinicians to approach patients and their families for autopsy diagnosis whenever possible to advance the care of patients in the future.

**Conclusion**

To our knowledge, this is the first case report of CS initially presenting after bilateral STN DBS implantation in a patient with idiopathic PD. As the risks of DMS are still under investigation, this case highlights the importance of identifying the potential importance of
cognitive, neuropsychiatric, and neuroimaging factors that may contribute to complications after DBS surgery. That is, patients with certain preexisting neurocognitive and neuropsychiatric symptoms may not be the optimal candidates for bilateral STN DBS implantation. It can be important to recognize such misidentification syndromes because they may precipitate dangerous situations.

Disclosure Statement

The authors declare that they have no competing interests.

References

Fig. 1. a Preimplantation coronal-section T2-sequence MRI. b Preimplantation axial T2-sequence MRI. c Preimplantation axial T2-sequence MRI demonstrating atrophy and extensive white matter disease. d Postimplantation coronal-section CT demonstrating bilateral STN lead placement. e Postimplantation axial-section CT demonstrating bilateral STN lead placement.