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Sunihidi Ramesh
Thomas Jefferson University

Jeffrey Ratliff
Thomas Jefferson University

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Brief Report

Improved Cotard Delusion and Motor Function in Parkinson's Disease following Electroconvulsive Therapy (ECT)

Sunidhi Ramesh, BS [a], Jeffrey Ratliff, MD [a,b]

[a] Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA
[b] Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease caused by depletion of dopaminergic neurons in the basal ganglia, with a myriad of non-motor features. Comorbid psychiatric conditions, including psychotic disorders and mood disorders, among others, are common. (Rihmer et al., 2014)

Outside of PD, depression can be complicated by psychotic features and is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM). Within PD, depression and psychosis are two common psychiatric complications, (Rihmer et al., 2014) with prevalence ranging from 20 to 40% and 15–30% respectively. (Rihmer et al., 2014) Their co-incidence in PD is estimated to be about 10%, which has been calculated to not be higher than that expected by chance, suggesting that both depression and psychosis are distinct neurobehavioral disorders in PD. (Weintraub et al., 2006) Typical hallucinations in psychosis associated with PD are characterized by visual hallucinations while typical delusions are paranoid. (Factor and Molho, 2004)

The Cotard Delusion is a unique syndrome (Debruyne et al., 2009) characterized by a "nihilistic delusion" that the whole or part of one's self is dead, necrosing, or has stopped existing. Attempts to clinically categorize Cotard Delusion are available, where Type I is a purely psychotic disorder lacking an association with depression, and Type II is a mixture of anxiety, depression, and characteristic "nihilistic delusions." A third type was felt to be a form of *psychotic depression*, with clinical features of anxiety, auditory hallucinations, and melancholic delusions of guilt but lacking significant nihilistic delusions. (Berrios and Luque, 1995) Case reports have described Cotard Delusion in patients with PD (see Table 1). (Weintraub et al., 2006; Solla et al., 2015)

Electroconvulsive therapy (ECT) is an electrical stimulation-based treatment for a range of psychiatric conditions, including medication-refractory depression. It is thought that iatrogenic induction of seizures can improve brain remodeling and thus symptoms. (Madsen et al., 2000) Prior literature has indicated that electroconvulsive therapy may be an effective and safe treatment for PD patients who are not optimally responding to first-line motor therapies. (Takamiya et al., 2021) Additional studies have suggested benefit in patients with PD and comorbid depression who have continued remission of their motor and depressive symptoms with monthly ECT. Other psychotic symptoms in PD have also been reported to improve following ECT. (Solla et al., 2015)

Herein, we present a case of a patient with PD complicated by depression and Cotard Delusion with significant motor and psychiatric benefit following ECT; we will use this case to summarize the role of Cotard Delusion in PD from the literature.

2. Case presentation

A 63-year-old right-handed man presented for management of PD. He had developed left-handed tremor and rigidity two years prior. Previous Ioflupane I123 SPECT (DaTscan®) showed reduced right striatal uptake. He had an initial motor response to levodopa. His clinical course was complicated by medication-refractory depression approximately one year after diagnosis. He developed the belief of his "fingers and muscles being liquefied" within his body. He held the belief that his body was rotting, and his bones were broken. He developed concurrent worsening of his motoric parkinsonism with poor response to increasing doses of levodopa.

Presenting to our clinic two years post-diagnosis, he demonstrated bilateral Parkinsonism with rest tremor, rigidity, and bradykinesia on exam. Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) score was 46, indicating significant Parkinsonism on his examination. His mental status examination demonstrated a severely blunted affect and intact orientation, attention, fund of knowledge, and recall. However, he displayed an expressed belief that his bones and organs were internally broken, consistent with Cotard Delusion. His marked associated depression was supportive of a Type II Cotard Delusion. (Berrios and Luque, 1995) He had auditory hallucinations of voices telling him he would "never get better." Medications at the time included 450 mg of total daily levodopa, 150 mg daily quetiapine, 225 mg daily venlafaxine, and 30 mg nightly mirtazapine. We recommended increasing his

E-mail address: sunidhi.ramesh@jefferson.edu (S. Ramesh).

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Levodopa to 600 mg total daily dose with a consideration for further increases to 800 mg. We initiated a prescription for pimavanserin, but this medication was never begun.

Two months following our evaluation, he presented to an outside hospital for worsening depressive symptoms and was admitted for inpatient psychiatric care. During this admission, he underwent six total sessions of ECT. On follow up in our clinic, two months following ECT treatment, the patient demonstrated profound improvement in his PD symptoms. His depression and Cotard Syndrome were entirely resolved. He had self-discontinued Levodopa entirely without developing bothersome motor symptoms. He remained on 150 mg quetiapine, 150 mg venlafaxine, and 15 mg mirtazapine, with intentions to wean them under the care of a psychiatrist. On exam, he had resting tremor in his left hand, moderate left-sided rigidity, and moderate left-sided bradykinesia. His UPDRS Part III score was 17. His mental status exam revealed intact cognition as before, with interval improvement in his affect and the absence of any delusional thought content.

UPDRS Part III remained stable on no levodopa at eight months following ECT. Quetiapine was able to be reduced to 100 mg daily without worsening symptoms. One year following ECT he was off quetiapine and levodopa and managed with 150 mg venlafaxine and 15 mg mirtazapine. He had no mood symptoms nor any further delusional beliefs. UPDRS Part III score showed progress of motor deficits and a total score of 34. Given his high functioning, the patient elected to defer re-initiation of dopaminergic therapy.

3. Discussion

3.1. The clinical benefit of ECT on PD and Cotard delusion

This case describes sustained improvement in motoric and complex neuropsychiatric derangements following ECT in a patient with PD. As previously mentioned, coincidence of depression and psychosis in PD is probably due to chance, rather than indicative of an associated neurobehavioral syndrome. (Weintraub et al., 2006) However, in this case, the nihilistic Cotard Delusion and pessimistic auditory hallucinations are more consistent with those seen in Type II Cotard Delusions that are more commonly a function of depression rather than the visual hallucinations and paranoid delusions more characteristic of PD-related psychosis. (Weintraub et al., 2006)

The clinical benefit of ECT on motoric and affective symptoms in PD has been described, though without systematically controlled trials. (Cumper et al., 2014; Cunningham et al., 2016; Kellner and Kellner, 2015) In a series of PD patients undergoing ECT for PD-related psychosis, Calderón-Fajardo et al. found that "all patients showed a statistically significant improvement in the Brief Psychiatric Rating scale (reduction of 52% points) and the Hamilton Depression Rating Scale (reduction of 50% points) independent of the presence of psychosis, depression, or both." (Calderon-Fajardo et al., 2015)

The precise mechanism(s) of benefit of ECT in PD is still being defined. PD involves changes in dopaminergic transmission and neuronal dopamine response. For this reason, the effect of ECT on reducing PD symptoms is thought to be mediated through dopamine in the striatum. (Cumper et al., 2014) Other research suggests that ECT may have "effects on [dopamine] release, receptor sensitivity, and other modulatory mechanisms." (Cumper et al., 2014) It may also upregulate dopamine receptors in the striatum and disrupt the permeability of the blood-brain barrier to dopamine and levodopa. (Calderon-Fajardo et al., 2015) Recent animal data has suggested a number of effects that may occur in striatal dopamine function, such as augmented dopamine release or stimulation-induced hypersensitivity of dopamine receptors. (Baldinger et al., 2014) Ultimately, ECT likely modulates many neurotransmitters, and a single neurochemical pathway that explains its therapeutic benefits across its indications is improbable.

3.2. Theory for mechanism behind type I vs. II Cotard

Cotard Delusions occur in the context of both primary psychotic disorders (Type I) and with depressive disorders (Type II). Regardless of type, a number of pharmacologic therapies have been observed to benefit patients suffering from Cotard Delusion. These therapies include serotonergic antidepressants, dopamine receptor *blocking* antipsychotics as well as dopamine receptor *agonist* medications. (Madsen et al., 2000) Thus, consensus on whether this psychotic state represents a hypo- or hyper-dopaminergic state remains elusive.

A robust number of clinical reports suggests that ECT is more effective than medication therapy for the treatment of Cotard Syndrome. (Berrios and Luque, 1995) The variability in pharmacologic response and the association with both primary psychotic and depressive disorders implies that clinical sub-types of Cotard, while similar, may result from different underlying pathophysiology. There is, however, no **consistent treatment** for Type 1 vs. Type II Cotard (Table 1).

Factor and Molho (2004) presented a PD patient with psychosis (and without co-morbid depression) who heard "the voice of God telling her to stop her medications" and felt "she was dead and did not require her medications." This patient was categorized to have Type I Cotard (in light of the *lack of depression*) and responded to dopamine antagonist (quetiapine 400 mg qd) therapy. Takahashi et al. (2010) reported a patient diagnosed to have PD in addition to severe depression with psychotic features who stated: "My mind is completely blank with no thoughts, and there seems to be no brain in my head." She was categorized to have Type II Cotard (in light of her mood symptoms) and treated with dopamine agonist (pramipexole 0.75 mg qd) therapy. A report by Ramirez-Bermudez et al. (2010) includes a patient much like ours, who had Type II Cotard successfully treated with ECT. This constellation of reports suggests that Type II Cotard Delusion is perhaps related to deficient dopaminergic signaling, supported by its response to dopaminergic stimulation either via ECT or pharmacologic enhancement.

However, upon further review of the literature, this conclusion is **not** upheld. Solla et al., (2015) report a patient with a **history of depression** and PD (suggesting Type II Cotard) who presented with a sudden onset of nihilistic delusion; the ultimately effective therapy in this patient was dopamine antagonist (quetiapine 75 mg qd) therapy.

The initial categorization of Cotard syndrome was developed by a landmark paper by Berrios and Luque, (1995) in which the authors analyzed 100 cases (not specific to PD) of Cotard syndrome; in the paper, the authors write:

> *"Cotard Type l patients… showed no loadings for depression or other disease and included most of the complete cases (on the Cotard index); these patients are likely to constitute a pure Cotard syndrome, and it is suggested here that their nosological origin is in the delusional and not in the affective disorders; the therapeutic implication of this view is that such patients are less responsive to antidepressant treatment. Type 2 patients showed anxiety, depression and auditory hallucinations and constitute a mixed group."*

These definitions developed by Berrios et al. have provided a lasting foundation for the categorization of Cotard syndrome. They, however, do not specify the temporality of the patients' depression specifically in Type I Cotard; this may be the cause of *some* of the inconsistency of patients' clinical response to dopaminergic agonist vs. antagonist therapy in Type I vs. Type II Cotard. That is, perhaps we are simply not categorizing them correctly.

Does "history of depression" differ from "current depressive state"? Would the latter still qualify the patient for *Type I* Cotard and the former for *Type II*? If this were the case, Solla et al.'s patient would indeed have *Type I* Cotard, explaining their ultimate response to dopamine antagonistic therapy (Table 1). It should also be noted that the mechanism of Cotard may be different in patients with PD as compared to patients

Table 1
Cases of Cotard delusion and Parkinson's disease.

Authors	Associated Psychiatric Features	Suspected Cotard Type	Ultimately Effective Therapy
Factor and Molho (2004)	psychosis; auditory hallucinations with no visual component; no co-morbid depression *She heard "the voice of God telling her to stop her medications" and later felt "she was dead and did not require her medications."*	I	*dopamine antagonist* quetiapine 400 mg daily
Takahashi et al. (2010)	severe depression with psychotic features; suicidal ideation, anxiety, loss of interest and pleasure, agitation, weight loss of 6 kg in 2 months, and depressive mood *"My mind is completely blank with no thoughts, and there seems to be no brain in my head."*	II	*dopamine agonist* paroxetine 20 mg daily augmented with pramipexole 0.75 mg daily
Ramirez-Bermudez et al. (2010)	severe depression with psychotic features; depressed mood, anhedonia, anorexia with a loss of 20 pounds over several weeks; loss of interest in self-care, ideas of self-loathing *He rejected hospitalization with the argument that he was "already dead." He later stated: "I am no longer myself, I feel like an automaton, like if the world did not exist; I am completely eliminated."*	II	*augmented dopamine release or stimulation-induced hypersensitivity of dopamine receptors* ECT
Solla et al. (2015)	psychosis; sudden onset of nihilistic delusion, mainly during the "wearing-off" condition and associated with end of dose dyskinesias and akathisia; history of depression *She "complained of having lost both of her eyes, mouth, nose, and ears. Often during these events, she insisted to have a mirror to see herself. She expressed the false belief that she did not have the whole body and that nothing existed, including herself, without any insight."*	I?	*dopamine antagonist* quetiapine 75 mg daily
Our Case	severe depression with psychosis; auditory hallucinations of voices telling him he would "never get better" *He believed his "fingers and muscles were being liquefied" and that his body was rotting on the inside.*	II	*augmented dopamine release or stimulation-induced hypersensitivity of dopamine receptors* ECT

without it.

Nonetheless, other case reports of Cotard Delusion outside of PD have also suggested a similar mismatch between the Cotard subtype and the ultimate successful treatment. De Berardis et al. (2010) report a patient with depressed mood, poor concentration, and subsequent Cotard syndrome; this, according to the initial Berrios et al. definitions, would qualify as Type II Cotard. However, she was successfully treated with dopamine antagonistic therapy. The authors suggest that this may be the case because the psychotic symptoms were "more prominent" than the depressive ones. This report supports our recommendation that the modern categorization of the two syndromes requires further research and elucidation. Of note, our pre- and post-assessments of the patient were limited to clinical assessments and subjective reports but did not include quantitative tests of his cognition/mood; this could represent a limitation in our ability to fully measure the degree of his improvement post-ECT.

4. Conclusions

Our case reinforces the existing literature that ECT can be an effective therapy in patients with PD for the management of refractory motor and neuropsychiatric symptoms. We postulate that the upregulation of dopamine signaling from ECT may underlie the clinical improvement in PD patients with Type II Cotard. However, the current definitions of Type 1 vs. Type II Cotard do not account for the temporality of the patients' depressive symptoms (Berrios and Luque, 1995). That is, while Berrios et al. described the subtypes of Cotard, a clearly defined clinical diagnostic criterion or treatment strategy (with either pharmacologic or electroconvulsive therapies) has not been well validated for patients presenting with the syndrome. While this case report may serve to move us towards a clinical validation, our modern categorization of the two syndromes requires further clarification through more in-depth research. Ultimately, further study is needed to validate this theory, perhaps including functional neuroimaging of dopamine functioning in patients with variable sub-types of Cotard Delusion.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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