DOI: 10.7860/JCDR/2016/22248.9089

Case Report

Internal Medicine Section

Delirium in Parkinson's Disease: A Cocktail Diagnosis

ROBIN GEORGE MANAPPALLIL

ABSTRACT

Mental disturbances have been described in patients with Parkinson's Disease (PD). Of these, the common conditions are delirium and psychosis. Delirium has been attributed to change of environment, especially hospital stay and infections; while psychosis is due to drugs like dopamine agonists. This is a case of a 75 year old male, on levodopa therapy for PD, who presented with delirium and ended up with a cocktail diagnosis: Cryptococcal meningitis, Hashimoto's Encephalopathy (HE), Urinary tract infection with acute renal failure, Uremic encephalopathy and Levodopa induced psychosis. This case report, therefore, highlights the need to look for other causes of delirium in a patient with PD who is on levodopa therapy.

Keywords: Cryptococcal meningitis, Hashimoto's encephalopathy, Mental disturbances

CASE REPORT

A 75-year-old male retired government officer, presented in delirium and one day history of low grade fever. There were no other associated or systemic symptoms. He was diagnosed to have bipolar mood disorder at the age of 45, but is on irregular treatment and follow-up. At the age of 60, he was diagnosed to have Parkinson's Disease (PD) and has been on Levodopa100mg+Carbidopa 10mg thrice daily till date.

On examination, the patient was conscious but mildly disoriented and restless. His Glasgow Coma Scale (GCS) was E4V4M5. His vitals were stable with heart rate of 90beats/minute, blood pressure of 130/90mmHg, temperature of 99°F and respiratory rate of 24breaths/minute, with saturation of 94% at room air. He had a small bedsore in his left gluteal region which was healing. Neurological examination revealed bradykinesia, upper limb tremors, cogwheel rigidity, with normal deep tendon reflexes and flexor plantars. His pupils were bilaterally symmetrical and reacting to light. Ophthalmic fundus examination was normal. Mild neck stiffness was present which was attributed to his un-cooperative nature. His other systemic examinations were normal.

His complete hemogram showed elevated total counts (13,400cells/cmm with differential counts as N85 L12 E3), deranged renal functions (urea 120mg/dL, creatinine 3.5mg/dL) and plenty of pus cells on urine microscopy. His electrolytes, liver function tests and PT/INR were normal. Chest X-ray and ECG were also normal. His CT brain showed age related cerebral atrophy and a few small infarcts distributed over the arterial territory suggestive of Multi infarct state or Vasculitis. Anti-nuclear antibody, anti-double stranded DNA, anti-neutrophil cytoplasmic antibody (p and c) and viral markers like HBsAg, anti-HCV and HIV were negative. His thyroid profile was normal with TSH of 4.02mIU/L (0.34–4.25), FT3 2.78pg/mL (2.4 - 4.2) and FT4 1.2ng/dL (0.7–1.24). A provisional diagnosis of sepsis due to UTI with acute renal failure (pre-renal), and delirium secondary to either Levodopa therapy or complicated by urinary infection was considered. He was started on intravenous antibiotics (Piperacillin+Tazobactam 2.25gm qid). Levodopa was withheld and quetiapine (25 mg once daily) was started, as per advice by the psychiatrist. Bedsore dressings were done regularly. Urine culture grew *E.coli* (more than 100,000 CFU/ml) which was sensitive to Piperacillin+Tazobactam.

On day 3, his total counts and renal functions started normalizing. Patient was no longer restless, but continued to be disoriented. In view of CT brain showing vasculitis picture, anti-thyroid peroxidase antibody was measured, which was found to be elevated, i.e. 257IU/ml (<35). As a result, an additional diagnosis of Hashimoto's Encephalopathy (HE) was considered and steroid therapy was planned to be initiated once the patient was totally out of sepsis. Cerebrospinal fluid (CSF) analysis was done simultaneously, which revealed normal CSF pressure, with mild lymphocytic pleocytosis (lymphocytes 10), mildly decreased sugars (38mg%) but normal proteins (40mg%). His random blood sugar was 98mg%. Yeast cells were visualized in his CSF sample, which was also positive for India ink. CSF culture grew *Cryptococcus*. Blood test for cryptococcal antigen was also positive.

The patient was started on intravenous Amphotericin B (0.5mg/kg/day), which was given for 7days and stopped, since his renal parameters started showing mild derangements. Intravenous Dexamethasone (8mg thrice daily) was given for 2 days, followed by oral Prednisolone 1 mg/kg/day for 10 days; and then tapered and stopped. Oral Fluconazole (450mg/day) was started; and by day10, his sensorium improved. He was asked to continue Fluconazole for 10 weeks. He was also restarted on low dose Levodopa. Patient was advised to do weekly reviews, but he never turned up after discharge, probably due to financial restraints.

DISCUSSION

Delirium can be defined as an acute organic brain syndrome presenting with cognitive impairment, attention deficits, decreased level of consciousness, varied psychomotor activity and wake-sleep rhythm disorders [1]. Meningitis, septicemia, head injury, subarachnoid hemorrhage, neoplasms, alcohol withdrawal, drug intoxication are some of the common etiologies [2]. There is a consensus that delirium increases with age and rates as high as 60% have been reported in hospitalized elderly patients [1,3].

Parkinson's Disease (PD) is a form of progressive neurodegenerative disorder; with rest tremor, rigidity and bradykinesia being the three cardinal features [4]. It mostly affects elderly age group; and delirium has been reported in 5–25% of Parkinson patients treated with Levodopa [5]. High doses of Levodopa can lead to confusion and psychosis. Dopamine dysregulation syndrome and punding are other behavioural abnormalities encountered with Levodopa therapy [4]. Deficits in the neurotransmitters like dopamine and acetylcholine, and systemic inflammation have also been proposed in the pathophysiology of delirium in PD [6].

There are also reports which suggest a probable link between Urinary Tract Infection (UTI) and delirium in elderly population. However, the exact mechanism remains unknown [7-9].

HE is a rare neurological disorder of unknown aetiology; with depression being an infrequent manifestation [10]. The disorder is commonly seen between 44 to 46 years of age with female preponderance. The clinical manifestations have two major patterns of presentation: 75% of patients exhibit a diffuse progressive pattern of slow cognitive deterioration with dementia, confusion and hallucinations; while 25% present with a stroke-like pattern of recurrent episodes of focal neurologic deficits with a variable degree of cognitive dysfunction and impaired consciousness [11]. However, recently a third type in the form of relapsing-remitting pattern has been described which also includes cognitive decline and psychiatric problems [12]. The patients may experience focal or generalized tonic-clonic seizures or even status epilepticus. Other features include myoclonus, tremors, hypereflexia, psychosis, visual hallucinations and paranoid delusions. The diagnosis of HE requires the presence of elevated levels of antithyroid antibodies, which portray thyroid autoimmunity. Positive anti-thyroid antibodies are seen in 95% of Hashimoto thyroiditis and 85% of Grave's disease. Low antibody titers are present in more than 10% of normal population and the value increases with age. Other conditions include papillary follicular carcinoma of thyroid, subacute thyroiditis (for a brief period) and primary thyroid lymphoma [13]. Autoimmune conditions like rheumatoid arthritis, systemic lupus erythematosus and myasthenia gravis may also show elevated titers [14-16]. Lymphocytic pleocytosis and elevated protein levels may be seen in the CSF analysis of HE patients [11]. EEG abnormalities include a nonspecific slow background activity, focal spikes or sharp waves and transient epileptic activity [17]. The MRI brain findings include ischemic lesions, demyelination, vasogenic oedema and atrophy. However, the MRI can also be normal [18]. Once the diagnosis of HE is confirmed, corticosteroid treatment usually provides a dramatic recovery [12].

Meningitis, an infection of the subarachnoid space, can be of bacterial, viral, fungal or rickettsial aetiology. Confusional psychosis has been reported in cryptococcal meningitis. *Cryptococcus* makes use of levodopa as substrate to produce melanin, which in turn gives resistance against host defense [19,20].

CONCLUSION

With regard to the patient being reported the question is "What was the cause of delirium?" Was it levodopa induced or due to UTI with contribution of uremia or HE or Cryptococcal meningitis or a combination of all giving rise to a delirium cocktail. This case report, therefore, highlights the multi-factorial causes of delirium, other than levodopa therapy, in a patient with PD.

REFERENCES

[1] Lipowski ZJ. Update on delirium. *Psychiatric Clin N Am* 1992;15: 335–46.
[2] Ropper AH, Samuels MA. Delirium and other acute confusional states. Adams and Victor's Principles of Neurology. 9th ed. McGraw Hill education 2009.pp 405-06.
[3] Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Inter Med.* 1990;113:941–48.
[4] Mahon RD, Jorge LJ. Parkinson's Disease and Other Extra pyramidal Movement Disorders. In :Fauci, Braunwald, Kasper, Hauser, Longo, Jameson, Loscalzo eds. Harrison's Principles of Internal Medicine. 17th ed. McGraw Hill education 2008. pp. 2559.
[5] Noe´-Sebastia´n E, Irimia-Sieira P, Pomares-Arias E, Martı´nez-Vila E, Luquin-Piudo MR. Neuropsychiatric disorders in parkinson's disease. *Rev Neurol.* 2001;32:676–81.
[6] Vardy ER, Teodorczuk A, Yarnall AJ. Review of delirium in patients with Parkinson's disease. *J Neurol.* 2015;262(11):2401-10.
[7] Balogun SA, Philbrick JT. Delirium, a symptom of UTI in the elderly: Fact or fable? A systematic review. *Canadian Geriatrics Journal*. 2014;17(1):22-26.
[8] Eriksson I, Gustafson Y, Fagerström L, Olofsson B. Urinary tract infection in very old women is associated with delirium. *Int Psychogeriatr.* 2011;23(3):496-502.
[9] Manepalli J, Grossberg GT, Mueller C. Prevalence of delirium and urinary tract infection in a psychogeriatric unit. *J Geriatr Psychiatry Neurol.* 1990;3(4):198-202.
[10] Rolland F, Chevrollier JP. Depression, antithyroid antibodies and Hashimoto encephalopathy. *Encephale*. 2001;27(2):137-42.
[11] Chong J, Rowland L, Utiger R. Hashimoto encephalopathy: syndrome or myth? *Arch Neurol.* 2003;60:164-71.
[12] Watemberg N, Greenstein D, Levine A. Encephalopathy associated with Hashimoto thyroiditis: Pediatric perspective. *J Child Neurol*. 2006;21(1):1-5.
[13] Wallach J. Endocrine Diseases. Interpretation of Diagnostic Tests. 8th ed. Wolters Kluwer (India) Pvt., Ltd. pp 662.
[14] Yavasoglu I, Senturk T, Coskun A, Bolaman Z. Rheumatoid arthritis and anti-thyroid antibodies. *Autoimmunity*. 2009;42(2):168–69.
[15] Tsai RT, Chang TC, Wang CR, Lee SL, Wang CJ, Tsay GJ. Thyroid peroxidase auto-antibodies and their effects on enzyme activity in patients with systemic lupus erythematosus. *Lupus*.1995;4(4):280-85.
[16] Nakamura H, Usa T, Motomura M, Ichikawa T, Nakao K, Kawasaki E, et al. Prevalence of interrelated autoantibodies in thyroid diseases and autoimmune disorders. *J Endocrinol Invest*. 2008;31(10):861-65.
[17] Rodrigez A, Jicha G, Steeves T, Benarroch E, Westmoreland B. EEG changes in a patient with steroid responsive encephalopathy associated with antibodies to thyroperoxidase (SREAT, Hashimoto's encephalopathy). *J Clin Neurophysiol*. 2006;23:371-73.
[18] Chen N, Qin W, Wei C, Wang X, Li K. Time course of Hashimoto's encephalopathy revealed by MRI: Report of two cases. *J Neurol Sci.* 2011;300(1-2):169-72.
[19] Sa'adah MA, Araj GF, Diab SM, Nazzal M. Cryptococcal meningitis and confusional psychosis. A case report and literature review. *Trop Geogr Med.* 1995;47(5):224-26.
[20] Manappallil R. Cryptococcal meningitis - A silent culprit behind delirium in a patient with Parkinson's disease, on levodopa, presenting with urinary tract infection. *Italian Journal of Medicine*. 2016;10:619.

PARTICULARS OF CONTRIBUTORS:
1. Consultant – Physician, Department of Internal Medicine, National Hospital, Calicut, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Robin George Manappallil,
Consultant – Physician, National Hospital, Calicut, Kerala-673004, India.
E-mail: drrobingeorgempl@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 22, 2016**
Date of Peer Review: **Aug 12, 2016**
Date of Acceptance: **Sep 29, 2016**
Date of Publishing: **Dec 01, 2016**