CASE REPORT

Serotonin syndrome following levodopa treatment in diffuse Lewy body disease

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SUMMARY

Serotonin syndrome results from an acute hyperserotonergic state. It is a rare and potentially fatal complication of drugs that affect the central nervous system serotonin levels. It is characterised by a triad of clinical features comprising altered sensorium, autonomic instability and neuromuscular hyperexcitability, in different combinations. We present an atypical case of serotonin syndrome related to levodopa use in a patient of probable Lewy body dementia. This case highlights the difficulty in diagnosis and management of cases with serotonin syndrome in the absence of history of a known serotonergic drug and the fact that levodopa can contribute to its occurrence.

BACKGROUND

Serotonin syndrome (SS) is a life-threatening neurological emergency. It occurs due to an overstimulation of 5-hydroxy-tryptamine (HT) 1A receptors in the central nervous system (CNS). The main culprits of serotonin syndromes are excess of 5-HT levels in the CNS, especially in the brainstem nuclei (raphe nucleus) from midbrain to medulla and spinal cord. Serotonergic mechanisms have been suggested as a pathophysiological mechanism SS. We present an interesting case of levodopa-induced SS in a patient of Lewy body dementia, which is rarely described in the literature.

CASE PRESENTATION

A 64-year-old man was diagnosed 3 months earlier as a case of probable diffuse Lewy body dementia (DLBD) with clinical presentations of parkinsonism, early dementia, recurrent visual hallucinations, and fluctuations in cognition and attention for the past 1 year. There was decreased uptake in fluro-deoxy glucose positron emission tomography scan in the bilateral parieto-occipital region. He was receiving levodopa-carbidopa (100/25 mg half tablet twice daily) and rivastigmine (3 mg twice daily) with good drug compliance during his 3-month illness. Three days prior to present hospital admission, he developed altered sensorium, tremulous movements of the whole body and stiffness of the limbs. He was treated empirically in a peripheral hospital with antibiotics (ceftriaxone 1 g twice daily), antimalarial (intravenous injection of artesunate 2.4 mg/kg/day) and intravenous fluid presuming infective pathology and possible malarial aetiology due to malarial endemicity in this locality. He was referred to us for further management due to history of DLBD. Enquiring as to further history, we found that 1 day prior to these symptoms his

levodopa-carbidopa dose had been increased to one tablet twice daily. Except for his history of Lewy body dementia, there was no history of fever, headache, convulsion, head trauma, toxin ingestions or any history of hypertension, diabetes mellitus, cardiac illness or substance abuse. Family history was insignificant. General physical examination revealed that the patient was stuporous with Glasgow Coma Scale (GCS) score of 11 (E₃M₃V₃), febrile (temperature 102.6°F) and tachypnoeic with profuse sweating. He was hypotensive (blood pressure 80/50 mm Hg) with heart rate of 128/min with autonomic variability. Cranial nerve examinations were grossly normal including fundii. There was tremulous movement of the whole body with intermittent myoclonus and mild rigidity of extremities. He had brisk deep tendon reflexes, spontaneous intermittent bilateral ankle clonus with flexor plantar response. Meningeal signs were absent.

INVESTIGATIONS

Investigations revealed white cell count of 21 510/mm³, random blood sugar 290 mg/dL, blood urea nitrogen 64 mg/dL, creatinine 1.5 mg/dL and creatine kinase level 1100 µ/L (N=60–400 µ/L). Arterial blood gas analysis and serum electrolytes were found to be within normal limits. Liver function test, peripheral thick and thin blood smear for malarial parasites, plasmodium lactate dehydrogenase dipstick test, blood and urine culture, chest X-ray and ultrasonogram of abdomen were unremarkable. ECG at the time of admission was normal with subsequent heart rate variability observed in cardiac monitoring during hospital stay. Cardiac enzyme (troponin T) was negative. Examination of cerebrospinal fluid for biochemical, cytology, Gram stain, India ink and acid-fast bacillus stains were unremarkable. EEG showed fast β activity with intermittent spikes and poly-spikes discharges corroborating myoclonus. Contrast-enhanced MR of the brain was normal.

DIFFERENTIAL DIAGNOSIS

In addition to SS, neuroleptic malignant syndrome (NMS), viral encephalitis and septic encephalopathy were considered as the closest possibilities. Absence of intake of neuroleptic drugs, rapid progression of disease, minimal limb rigidity, myoclonus, hyper-reflexia and significant autonomic instability pointed to SS rather than NMS. There was no evidence of CNS and systemic infections or metabolic alterations, which ruled out possible causes of encephalopathy.

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TREATMENT

The empirical antibiotic (ceftriaxone 1 gm twice daily) was continued until infective pathology was excluded, along with supportive treatment with intravenous fluids, vasopressors (norepinephrin) and antipyretics (acetaminophen). Oral cyproheptadine 4 mg thrice daily was started on the second day of admission through a nasogastric tube considering SS. To avoid the development of acute dopamine depletion syndrome, the levodopa-carbidopa dose was tapered instead of being suddenly withdrawn. The rivastigmine dose was also reduced.

OUTCOME AND FOLLOW-UP

The sensorium of the patient improved (GCS score of 14, E₄M₆V₄) and the myoclonus decreased on the second day of administration of cyproheptadine. Biochemical parameters were normalised. However, marked variability in blood pressure and heart rate was noted. The patient developed sudden cardiac arrest late at night on the third day of admission from which he could not be resuscitated.

DISCUSSION

Serotonin behavioural syndrome was initially demonstrated in animal pharmacology and was later recognised in humans by Insel *et al*¹ as SS in 1982. Subsequently, Sternbach described the clinical review of SS. He also formulated the first diagnostic clinical criteria in his publication. The Sternbach diagnostic criteria of SS includes history of administration or increase of serotonergic drugs plus 3 of the following 10 symptoms: (1) mental status change, (2) agitation, (3) hyper-reflexia, (4) diaphoresis, (5) myoclonus, (6) tremors, (7) shivering, (8) diarrhoea, (9) problems with coordination and (10) fever. The condition should not be explained by other causes nor by any history of administration of a neuroleptic.² Subsequently, the Hunter serotonin toxicity criterion was proposed to overcome the diagnostic difficulties in certain situations.³

CNS serotonergic neurons are found in the raphe nuclei located in the brain stem. The rostral midbrain part of the nucleus regulates wakefulness, affective and sexual behaviour, thermoregulation, food intake and vomiting. In the lower pons and medulla, it assists in regulation of motor tone as well as nociception. The peripheral serotonin system is helpful in the regulation of vascular tone as well as gastrointestinal motility.⁴ SS is mainly due to excess administration of tryptophan containing substances, excess release of 5-HT (eg, amphetamines), decreased reuptake (eg, selective serotonin reuptake inhibitors, fluoxetine and tricyclic antidepressants), reduced metabolism (eg, monoamine oxidase inhibitors) and administration of 5-HT agonists as well as opioids and psychomimetics.

There are several CNS regions of 5-HT and dopamine interaction: (1) at the level of brainstem where the substantia nigra and ventral tegmental area is located, (2) at the level of nigrostriatal and mesocorticolimbic dopaminergic systems and (3) at the level of nucleus accumbens and the prefrontal cortex. The interaction can be due to direct effect mediated by 5-HT receptors located on the cell body and/or on nerve terminals of dopaminergic neurons or indirect effect mediated by 5-HT receptors located in the interneurons or in the feedback loops.⁵ Increased brain serotonin concentration following levodopa and bromocriptine therapy has been postulated as the plausible mechanism of levodopa induced myoclonus in SS.⁶ Levodopa is decarboxylated into dopamine in serotonergic neurons and displaces the endogenous serotonin into the synaptic cleft producing secondary dysregulation of striatal serotonin activity.⁶ It is possible that a spillover of this effect may actually translate into full blown SS.

SS is an adverse drug reaction representing a continuum ranging from mild unnoticed symptoms to a potentially life-threatening state to death.⁷ The diagnosis of SS is primarily based on clinical history of intake or change in schedule of serotonergic drugs. Mental status change, autonomic instability, neuromuscular hyperexcitability and rapidity of the symptoms and responsiveness to antiserotonergic drugs such as cyproheptadine point towards the diagnosis of SS.

So the present case is likely to be associated with sudden alteration in levodopa dosage, which clinically corresponds to SS as described in Hunter serotonin toxicity criteria. Iqbal *et al*⁸ and Sandyk⁶ also described the association of L-dopa in SS. It needs mention that patients of DLBD have been shown to have abnormal reactivity to even slightest changes in the neurotransmitter levels, but whether this has any bearing on the development of SS in our patient is conjectural.

Delay in diagnosis as well as under appreciation of levodopa-associated SS and severe autonomic disturbances made the condition fatal in our case. In the absence of any diagnostic laboratory test, early clinical suspicion is valuable along with timely withdrawal of the offending drugs with supportive and specific treatment for a better outcome.

Learning points

- ▶ Serotonin syndrome is a life-threatening situation resulting from overdose or interaction of serotonergic drugs.
- ▶ Levodopa may be the potential cause of serotonin syndrome.
- ▶ It is important to recognise a hyperserotonergic state, and early intervention may avoid the progression to fulminant state.

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