

CASE REPORT

SEROTONIN SYNDROME IN STROKE PATIENTS

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Objective: Serotonin syndrome is a potentially life-threatening condition that can be caused by administration of agents that increase serotonergic activity in the brain. We report here on 2 stroke patients who presented with serotonin syndrome following administration of dopaminergic agents.

Case report: Two stroke patients were administered ropinirole (patient 1) and carbidopa/levodopa (patient 2) during rehabilitation. Both patients exhibited the clinical features of serotonin syndrome, coinciding with an increase in dosage of each drug. Based on the clinical features included in revised Radomski's criteria, they presented with 3 major symptoms with 3 and 2 minor symptoms, respectively. The drugs that were thought to trigger serotonin syndrome were discontinued and the patients underwent conservative treatment. The patients recovered completely from the symptoms of serotonin syndrome appearing 2 days after administration of the trigger drugs.

Conclusion: Because a considerable number of stroke patients have some limitation in communication, and serotonin syndrome is a potentially life-threatening condition, clinicians should pay particular attention to the potential for development of serotonin syndrome when prescribing these drugs to stroke patients.

Key words: serotonin syndrome; stroke; dopaminergic agent.

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INTRODUCTION

Serotonin syndrome (SS) is a potentially life-threatening condition that can be caused by administration of agents that increase serotonergic activity in the central nervous system (1). Patients with SS present with a combination of various symptoms, including a sudden change in mental status, autonomic instability and neuromuscular hyperactivity (1). Previous studies have reported association of several types of antidepressants with SS (1, 2). However, recent studies have reported that other drugs, including dopaminergic agents, opioids, anti-emetics, and antibiotics, can also induce SS (2).

Dopaminergic agents are known to be effective in improvement of cognitive, language, motor, and executive function in stroke patients (3). Therefore, dopaminergic drugs are often prescribed for stroke patients during rehabilitation; however, administration of dopaminergic drugs is associated with the risk of inducing SS (1, 4, 5). Although SS has been reported in other brain pathologies, including depressive disorder and Parkinson's disease, little is known about SS in stroke patients (5).

We report here on 2 stroke patients who presented with SS after administration of dopaminergic agents.

CASE REPORT

Patient 1

A 52-year-old man underwent conservative treatment for a spontaneous bilateral pontine haemorrhage at the neurosurgery department of a university hospital; 43 days after onset he was transferred to the rehabilitation department of the same university hospital. At that time, he did not respond to simple verbal commands and could not maintain an alert state for more than 2 h during the day. He also exhibited complete weakness of all of his extremities (Medical Research Council 0/5). To improve these compromised functions, the patient was administered dopaminergic agents. Dopaminergic drugs were started with an initial dose of ropinirole 0.25 mg/day. After 2 days of treatment, the patient remained alert for more than 4 h during the day, and could intermittently follow simple verbal commands. In an attempt to achieve further improvements in alertness and cognitive function, the daily dosage of ropinirole was increased to 0.375 mg. On the afternoon of the same day, 5 h after administration of ropinirole, the patient presented with rigidity, diaphoresis, facial flushing, diarrhoea, hypertension (160/100 mmHg), tachycardia (118/min) and fever (38.5°C) (Table I). These symptoms satisfied 3 major and 3 minor symptoms of Radomski's criteria for SS (Table II). Laboratory and radiology tests performed in order to rule out other possible aetiologies did not show any abnormality: white blood cells (WBC, normal value: 4,000–10,000/ μ l) 7,780/ μ l, hemoglobin (Hb, > 14 g/dl) 9.8 g/dl, C-reactive protein (CRP, < 1.0 mg/dl) 0.827 mg/dl, aspartate aminotransferase (AST, 8–40 IU/l) 34 IU/l, alanine aminotransferase (ALT, < 45 IU/l) 27 IU/l, serum creatinine (CRE, 0.4–1.2 mg/dl) 1.02 mg/dl, serum iron (11.6–31.7 μ mol/l) 15.8 μ mol/l, thyroid stimulation hormone

Table I. Characteristics of the patients with symptoms and case criteria for serotonin syndrome (SS)

	Age, years/sex	Time to onset ^a , h	Presented symptoms	Trigger drug	Concomitant drugs
Patient 1	52/M	5	Diaphoresis ^b , diarrhoea ^c , fever ^b , shivering, rigidity ^b , tachycardia ^c , hypertension ^c	Ropinirole	Amantadine Carbidopa/levodopa Modafinil Methylphenidate
Patient 2	63/M	6	Diaphoresis ^b , diarrhoea ^c , tremor ^b , agitation ^c , dilated pupil ^c , rigidity ^b	Carbidopa/levodopa	Ropinirole Bromocriptine Amantadine Methylphenidate Venlafaxine Tianeptine

^aDuration between administration of the trigger drug and first presentation of symptoms of serotonin syndrome.

^bMajor symptoms of Radomski's criteria.

^cMinor symptoms of Radomski's criteria.

(TSH, 0.35–4.49 mIU/l) 1.8 mIU/l, free T4 (7–14.8 pmol/l) 10 pmol/l, total T3 (0.58–1.59 nmol/l) 1.0 nmol/l, urine leukocyte (–), urine WBC 0–1/high-power field (HPF), blood culture (–), urine culture (–), and chest X-ray (–). For management of the patient's symptoms, lorazepam (2 mg) was injected intravenously, and the patient was hydrated with normal saline. Muscle relaxants (dantrolene sodium 100 mg, baclofen 45 mg daily) were also administered for relief of rigidity. Ropinirole was discontinued, while administration of other neurotrophic drugs was maintained. The clinical symptoms associated with SS showed dramatic improvement. All of the symptoms, except for fever, disappeared within 8 h of discontinuing ropinirole. After an additional 15 h, no fever was observed, and the patient had recovered fully from SS.

Patient 2

A 63-year-old man underwent a decompressive craniectomy and external ventricular drainage for a spontaneous intracere-

bral haemorrhage on the left fronto-temporo-parieto-occipital lobe at the neurosurgery department of a university hospital. After surgery, the patient was transferred to a local medical rehabilitation centre in order to undergo rehabilitative management. Fifteen months later, the patient was admitted to the rehabilitation department of a university hospital for more active rehabilitation. At that time, he was able to follow 1-step verbal commands and he showed complete weakness of all of his extremities. Administration of neurotrophic drugs was commenced (initial dose: ropinirole 0.25 mg/day), with a gradual increase in the following dosages on the 13th day of admission: ropinirole 0.75 mg; bromocriptine 2.5 mg; amantadine 300 mg; carbidopa/levodopa 37.5/375 mg; methylphenidate 20 mg; donepezil 5 mg; venlafaxine 37.5 mg; and tianeptine 37.5 mg. On the 13th day of admission, the daily dose of ropinirole was increased from 0.625 mg to 0.75 mg. On the 15th day of admission, the daily dose of carbidopa/levodopa was increased to 50/500 mg. Diaphoresis and rigidity developed on the evening of the same day, after 6 h of administration of an increased dose of carbidopa/levodopa. The next day, diaphoresis and rigidity had worsened, and diarrhoea, facial flushing, pupil dilatation, tremor, and confusion with agitation were manifested (Table I). The patient's body temperature (36.5°C), pulse rate (78/min) and blood pressure (140/90 mmHg) were within normal ranges. The patient's symptoms fulfilled 3 major and 3 minor symptoms of Radomski's criteria for SS (Table II). Results of laboratory and radiology tests performed in order to rule out other possible aetiologies underlying these symptoms showed no abnormality (WBC 5,430/μl, Hb 12.4 g/dl, CRP 0.061 mg/dl, AST 12 IU/l, ALT 6 IU/l, CRE 0.72 mg/dl, serum iron 21.4 μmol/l, TSH 0.4 mIU/l, free T4 17 pmol/l, total T3 1.9 nmol/l, urine leukocyte (–), urine WBC 0–1/HPF, blood culture (–), urine culture (–), and chest X-ray (–)). The patient was hydrated with normal saline, and dantrolene (25 mg) and benzodiazepame (2 mg) were administered for management of rigidity. Most of the dopaminergic agents administered to the patient were reduced to approximately half their previous dosages (daily dose: ropinirole 0.5 mg; bromocriptine 2.5 mg; amantadine 200 mg; carbidopa/levodopa 25/250 mg; methylphenidate 5 mg). Approximately 12 h after initiating

Table II. Revised diagnostic criteria for serotonin syndrome

- A. Addition of a serotonergic agent to an already established treatment (or increase in dosage) and manifestation of at least 4 major symptoms or 3 major symptoms with 2 minor symptoms
- B. 1) Mental symptoms
 - Major – confusion, elevated mood, coma or semi-coma
 - Minor – agitation and nervousness, insomnia
- 2) Autonomic symptoms
 - Major – fever, hyperhidrosis
 - Minor – tachycardia, tachypnea and dyspnoea, diarrhoea, low or high blood pressure
- 3) Neurological symptoms
 - Major – myoclonus, tremors, chills, rigidity, hyper-reflexia
 - Minor – impaired co-ordination, mydriasis, akathisia
- C. These symptoms must not correspond to a psychiatric disorder, or its aggravation, that occurred before the patient took the serotonergic agent
- D. Infectious, metabolic, endocrine or toxic causes must be excluded
- E. A neuroleptic treatment must not have been introduced, nor its dose increased, before the symptoms appeared

Adapted from Radomski et al. (4).

Table III. *Drugs that increase serotonergic activity in the central nervous system*

<i>Dopamine agonists</i>
Amantadine (PK-Merz)
Bromocriptine (Parlodel)
Burporpion (Wellbutrin)
Levodopa
<i>Dopamine serotonin receptor agonists</i>
Buspirone
Lysergic acid diethylamide
Sumatriptan (Imitrex)
Lithium
Meta-chlorophenylpiperazine
<i>Increase serotonin synthesis</i>
L-tryptophan
<i>Decrease serotonin metabolism</i>
Monoamineoxidase inhibitors
Phenelzine
Tranylcypromine
Reversible inhibitors of MAO-A
Moclobemide
Other
Isocarboxazid
Selegiline
<i>Increase serotonin release</i>
Amphetamines
Cocaine
Fenfluramine
Reserpine
<i>Inhibit serotonin uptake</i>
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Serotonin noradrenaline re-uptake inhibitors
<i>Anti-emetics</i>
Metoclopramide (Reglan)
Ondansetron (Zofran)
<i>Analgesics</i>
Cyclobenzaprine
Fentanyl
Meperidine

Information from (2, 5).

management of SS, symptoms associated with SS had almost completely disappeared. After an additional 12 h the patient had recovered completely from SS.

DISCUSSION

We reported on 2 stroke patients who showed the clinical features of SS after administration of dopaminergic agents. For diagnosis of SS, we used Radomski's criteria for diagnosis of SS (4). Radomski's criteria require the presence of at least 4 major clinical features or 3 major symptoms with 2 minor symptoms (major symptoms: confusion, elevated mood, coma or semi-coma, fever, hyperhidrosis, myoclonus, tremors, chills, rigidity, hyper-reflexia; minor symptoms: agitation and nervousness, insomnia, tachycardia, tachypnea and dyspnoea, diarrhoea, low or high blood pressure, impaired co-ordination,

mydriasis, akathisia), and historical coincidence of addition, or a recent increase in dosage of drugs that activate the serotonergic system (Table III). In the current report, 2 patients satisfied 3 of the major symptoms with 3 and 2 minor symptoms included in Radomski's criteria, respectively. In addition, symptoms of neuroleptic malignant syndrome (NMS) are similar to those of SS; thus, SS is easily confused with NMS. However, unlike SS, NMS usually presents after prolonged exposure to neuroleptics or withdrawal of dopamine agonists and the onset of NMS is usually slow (days to weeks). In our patients, neuroleptic drugs were not administered, and we did not taper dopaminergic drugs before the development of SS-related symptoms. In addition, after dopaminergic agent was elevated, SS symptoms developed immediately on the same day. Therefore, we were able to confirm that the patients' symptoms were the result of SS.

It appears that SS in the 2 patients in our report was triggered by ropinirole and carbidopa/levodopa, respectively. Ropinirole acts predominantly as a dopamine D₂, D₃ and D₄ receptor agonist; however, it is also active at the 5-HT receptor (6). Therefore, it appears that administration of ropinirole to patient 1 accompanied the over-activation of the serotonergic system, leading to development of SS (5). Upon entry into the brain, levodopa is assisted by carbidopa, which passes through the blood-brain barrier, and, in the brain, levodopa is taken up by serotonin neurones (7). Levodopa in serotonin neurones is converted to dopamine, and dopamine pushes serotonin into synaptic clefts (8). Thus, administration of carbidopa/levodopa to patient 2 may have induced hyperactivation of the serotonergic system, leading to development of SS. Although other neurotrophic drugs that were administered to these patients, along with ropinirole and carbidopa/levodopa, may also have contributed to development of SS, we could not rule this out completely because there is no definite diagnostic tool for use in determination of whether a specific drug can induce SS. Also, in our patients, discontinuation of the dopaminergic drugs and administration of benzodiazepines or muscle relaxant with fluid therapy were sufficient to manage the patients' symptoms. In addition, 5-HT 2A antagonists, such as cyproheptadine, methysergide, chlorpromazine or beta-blockers, such as propranolol, for treatment of hyperthermia may be considerable in patients with uncontrolled symptoms of SS.

To the best of our knowledge, this is the first report on SS in stroke patients. SS was first described in 1960, by Oates & Sjoerdsma (9), in depressed patients as a consequence of administration of high doses of tryptophan in combination with monoamine oxidase inhibitors (MAOI). Since the study by Oates & Sjoerdsma, several studies have reported on induction of SS by antidepressants (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants and MAOI) in patients with major depressive disorder (1, 2). In addition, 2 studies have reported on SS triggered by dopaminergic agents (5, 10). In 1986, Sandyk (10) reported SS in a parkinsonian patient, which was triggered by the combined administration of carbidopa/

levodopa (75/750 mg daily) and bromocriptine (20 mg daily). In 2002, Avarello & Cottone (5) reported on a case of SS in a patient with major depressive disorder and Parkinson's disease. They concluded that SS was the result of co-administration of an antidepressant (a SSRI) and a Parkinson's disease drug (levodopa), via over-activation of 5-HT receptors. Therefore, to the best of our knowledge, this is the first report on SS in stroke patients following administration of dopaminergic agents.

Recently, in several countries, such as Korea, Japan, Poland, and Sweden, dopaminergic agents have been widely prescribed for stroke patients during rehabilitation. Because a considerable number of stroke patients have some limitation in communication, and SS is a potentially life-threatening condition, clinicians should pay particular attention to the occurrence of SS when prescribing dopaminergic drugs to stroke patients. Further studies are warranted in patients with mild functional impairments.

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