



## Beneficial effects of fluvoxamine for hemiballism in a patient with depressive disorder: a case report

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### Introduction

Hemiballism (HB) is an involuntary, irregular and poorly patterned movement disorder having wide amplitude. HB can mostly result from a focal vascular lesion in the contralateral basal ganglia. In the absence of an identifiable focal vascular lesion, metabolic derangements, brain neoplasm, and infectious diseases of the central nervous system (eg., human immunodeficiency virus infection) are considered to be the more common causes. Among metabolic causes, nonketotic hyperglycemia has been described as an unusual metabolic cause of this abnormal movement disorder. The involuntary movement usually affects only one side of the body; the term hemiballism is used to describe unilateral ballism (1, 2).

Extrapyramidal system diseases such as akathisia, tardive dyskinesia, chorea, and HB are all associated with dopaminergic dysregulation on the basal ganglia or their pathways (3). Considering the role of the effects of sigma-1 receptors on akathisia (4, 5), we hypothesized that fluvoxamine might be effective in the treatment of hyperkinetic disorder. Here, we report a case of depressive disorder in which fluvoxamine was effective in ameliorating both HB and the major depressive disorder.

### Case report

A 47-year-old man was consulted to psychiatry out-patient clinic from the neurology department with complaints of feelings of helplessness and hopelessness, loss of interest in daily activities, significant weight loss, insomnia, feeling of agitation, restlessness, trouble in focusing on something, suicidal ideas, difficulty in moving the limbs voluntarily, being unable to stand still and to sit, and abnormal movements involving the right side of his

body. In the past, the patient had been admitted to our emergency department with complaints of right-sided abnormal movement. The abnormal movement had begun two days before coming to the emergency and had been jerky, irregular, and nonsuppressible, but it had resolved during sleep. He had no history of hypertension, headache, parkinsonism, or other neurological diseases and no family history of movement disorders. On examination in emergency, he had been alert as well as fully orientated, and there had been no obvious focal motor or sensory deficit. The pertinent abnormality had been a right-sided hemiballismus (HB) type movement disorder affecting the right side of his body. His random plasma glucose level had been significantly elevated; measuring 586 mg/dl with HbA1c of 13.2%, but there was no evidence of ketoacidosis or hyperosmolar state. The MR image had showed high-signal intensities in the posterior parietal subcortical area and in the sigmoid sinuses in T2-weighted images that had been consistent with chronic infarction and thrombosis of transverse sinus (Fig. 1). However, brain MR venography had revealed hypoplasia of transverse sinus (Fig. 2). He had been hospitalized by the neurology department with a diagnosis of hyperkinetic movement disorder (HB). He had been referred to the endocrinology department and his serum glucose had been regulated with insulin treatment. Combination of reducing plasma serum glucose levels with haloperidol 4.5 mg/day had resulted in moderate improvement of the right-sided abnormal movement, and he had been discharged in this condition from the neurology clinic. However; after two weeks, the patient had come back to the neurology outpatient clinic with symptoms of depressive disorder, sustained contractions of the muscles and abnormal movements of the right side of the body, difficulty in moving the limbs voluntarily, and he had been consulted to our outpatient



FIG. 1. — The MR image demonstrates high-signal intensities in the posterior parietal subcortical area.

clinic. During psychiatric examination, depressed mood, anhedonia, poor appetite, insomnia, low self-esteem, distractibility, feelings of hopelessness, suicidal thoughts, and akathisia, were noted. A neurological examination showed bradyimia, bradykinesia, rigid, abnormal, jerky, and irregular movement of the right side of the body. Deep tendon reflexes were symmetrically hypoactive. The remaining results of the examinations were unremarkable. Blood sample tests revealed no abnormality. EEG was performed twice and findings of both were normal. The initial scores of Hamilton Depression Rating Scale (HDRS), Brief Psychiatric Rating Scale, and Barnes Akathisia Rating Scale (BARS) were 31, 19, and 13. He was diagnosed as having “Major Depressive Disorder Due to General Medical Condition” and “Medication Induced Movement Disorder Not Otherwise Specified”, according to Diagnostic and Statistical Manual of Mental Disorders Text Revision (DSM-IV-TR) (6) and “Hyperkinetic Movement Disorder” (HB). Because of extrapyramidal side effects, haloperidol 4.5 mg/day was stopped gradually and biperiden, 4 mg/day oral treatment was started. Three days after biperiden treatment, extrapyramidal symptoms such as bradykinesia, bradyimia, and rigidity were resolved; however symptoms of akathisia did not disappear (BARS: 7) and jerky, irregular, and non-suppressible movement of the right side of body ap-



FIG. 2. — The brain MR venography shows hypoplasia of transverse sinus.

peared markedly. Fluvoxamine 100 mg/day was administered for treating depressive symptoms and biperiden treatment was stopped gradually. On the fourth day of fluvoxamine treatment, jerky, irregular, and nonsuppressible movements improved. Ten days after treatment, akathisia improved and HB also had disappeared. The patient was scheduled for a follow-up appointment in the psychiatry and neurology outpatient clinic. On outpatient clinic controls, symptoms of depressive disorder, akathisia, and HB were observed as remitting.

### Discussion

Various structural lesions have been associated with ballism (7), however; damage to dopaminergic pathways, which includes the subthalamic nucleus and the pallidsubthalamic pathways, appears to play a critical role in the expression of this hyperkinetic movement disorder (8). The pathophysiology of hyperglycemia-induced HB is not fully elucidated, although several different mechanisms have been proposed. One of the proposed mechanisms is hyperviscosity related to nonketotic hyperglycemia and underlying cerebrovascular disease (8). Because our patient had chronic cerebrovascular infarct and saggital sinus hypoplasia, the probable etiology of HB may be discussed as above.

HB should not be confused with focal motor seizure, which has a rhythmic, episodic quality and tends to be more localized (2). Since characteristics of abnormal movement of our case are irregular,

jerky, rhythmic, and not localized; and also EGG findings were normal, and he had no history of seizure, we excluded the diagnosis of motor focal seizure.

In the treatment of ballism, dopamine receptor-blocking drugs such as perphenazine, haloperidol, chlorpromazine, pimozide, and atypical neuroleptics have been used most frequently (9). Reserpine and tetrabenazine, which are dopamine depleting drugs, have also been used successfully. Some clinicians consider tetrabenazine to be the preferred drug for its rapid onset of action and its effectiveness, without the danger of inducing tardive dyskinesia if chronic antidopaminergic treatment is needed (11). Our patient had been benefited from haloperidol treatment; however because of extrapyramidal side effects, we could not continue this treatment.

The endoplasmic reticulum protein sigma-1 receptors play an important role in  $Ca^{2+}$  signaling and cell survival, and have been shown to regulate a number of neurotransmitter systems in the central nervous system (12). Furthermore, sigma-1 receptors play important roles in  $Ca^{2+}$  signaling and bioenergetics within the cell (13). The selective serotonin reuptake inhibitor fluvoxamine is a very potent agonist at sigma-1 receptors (4). A study that used a selective sigma-1 receptor agonist [ $^{11}C$ ]SA4503 and positron emission tomography showed that fluvoxamine binds to sigma-1 receptors in the living human brain at therapeutic doses, suggesting that sigma-1 receptors might play a role in the mechanism of action of fluvoxamine (14). There are also evidences that sigma-1 agonist agents might increase and also reduce dopamine levels in striatum (15, 16). The sigma-1 receptor is particularly concentrated in specific areas of limbic system and brainstem motor structures. The caudate putamen, septum, nucleus accumbens, and amygdala showed moderately concentrated with sigma-1 receptors in mice (17). Although Furuse and Hashimoto reported anti-psychotic induced akathisia cases who were resolved by sigma-1 receptor agonist fluvoxamine; the probable mechanism of benefit was suggested to be unclear due to complex pathophysiology of akathisia (4, 5). Faherty *et al.* reported that chronic fluvoxamine administration presipate dystonia experimentally by sigma receptor agonism which is in the line of the classical treatment of ballism (18). Possibly, a potent sigma-1 agonist fluvoxamine might act as a reducer of dopamine in striatal area in our case.

To our knowledge, this is the first case report showing that fluvoxamine is effective in the treatment of HB. This case report suggests that fluvoxamine may serve as an alternative option in the

treatment of ballism without severe side effects such as extrapyramidal side effects by antipsychotic drugs. More detailed, double-blind studies should be performed to clarify the role of fluvoxamine in the treatment of hyperkinetic movement disorders.

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