

## Case Report

# Late-onset recurrent mania as a manifestation of Wallenberg syndrome: a case report and review of the literature

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**Objective:** The aim of the present case report was to describe the late onset of recurrent mania in a patient after ischemic injury to the cerebellum and dorsolateral medulla.

**Methods:** We studied an 86-year-old male with no prior psychiatric history who developed recurrent episodes of mania following a brain stroke. Additionally, he had neurological symptom constellation typical of Wallenberg syndrome.

**Results:** Magnetic resonance imaging of the brain revealed infarction in the inferomedial right cerebellar hemisphere and the right dorsolateral medulla in the right posterior inferior cerebellar artery (PICA) distribution. He was successfully managed with a combination of antipsychotic and mood-stabilizer medications.

**Conclusions:** Post-stroke mania may be one of the rare manifestations of Wallenberg syndrome. This case adds to the emerging literature on cerebellar involvement in mood regulation and pathology of mania.

**Piyush Das<sup>a,b,c</sup>, Amit Chopra<sup>a,d</sup>,  
Abhishek Rai<sup>a,e</sup> and Preetha  
Sharone Kuppuswamy<sup>a</sup>**

<sup>a</sup>Department of Psychiatry and Psychology, Mayo Clinic College of Medicine, Rochester, MN, <sup>b</sup>Mental Health Clinic, VA Medical Center, Grand Island, <sup>c</sup>Department of Psychiatry, Creighton University Medical Center, Omaha, NE, <sup>d</sup>Department of Psychiatry, Allegheny General Hospital, Pittsburgh, PA, <sup>e</sup>Department of Psychiatry, St. Mary Mercy Hospital, Livonia, MI, USA

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Corresponding author:

Piyush Das, M.D.

Mental Health Clinic

VA Medical Center

2201 North Broadwell Avenue

Grand Island, NE 68803

USA

Fax: 308-389-5126

E-mail: drpiyushdas@yahoo.com

Late-onset mania occurs after 50 years of age and is usually secondary to an underlying organic etiology (1). The major causes of secondary mania include brain ischemia, demyelinating and neurodegenerative disorders, brain tumors and infections, brain trauma, cardiovascular disease, metabolic disturbances, endocrine dysfunction, medications, illicit drugs, and nutritional deficiencies (2). Ischemic events resulting in mania most commonly involve the orbitofrontal and lateral basotemporal cortex, ventral striatum, head of caudate, thalamus, and limbic system, with the right side of the brain being more commonly implicated than the left (3–5). The cerebellum is increasingly being recognized as an important brain

structure involved in the etiopathogenesis of bipolar disorder. Recurrent mania with delirium has been previously described in association with a combination of cerebellar and pontine stroke (6). We describe the first case of recurrent mania (without delirium) resulting from right posterior inferior cerebellar artery (PICA) ischemic stroke affecting the right cerebellum and right dorsolateral medulla oblongata.

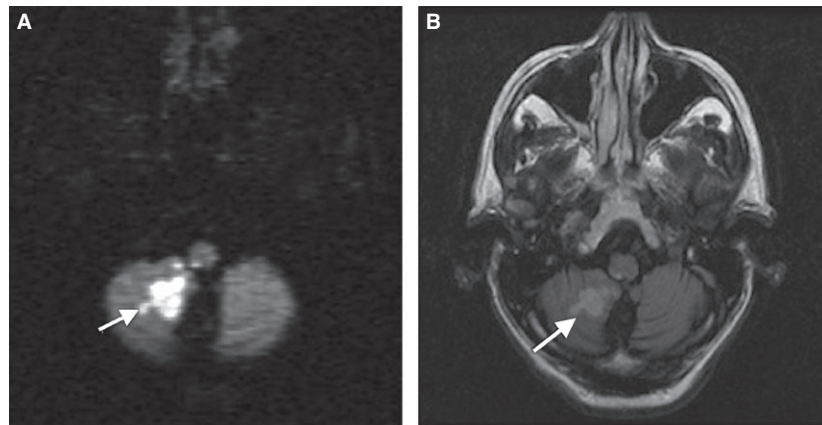
### Case report

Mr. X is an 86-year-old Caucasian male with no personal or family psychiatric history but a medical history significant for hypertension, hyper-

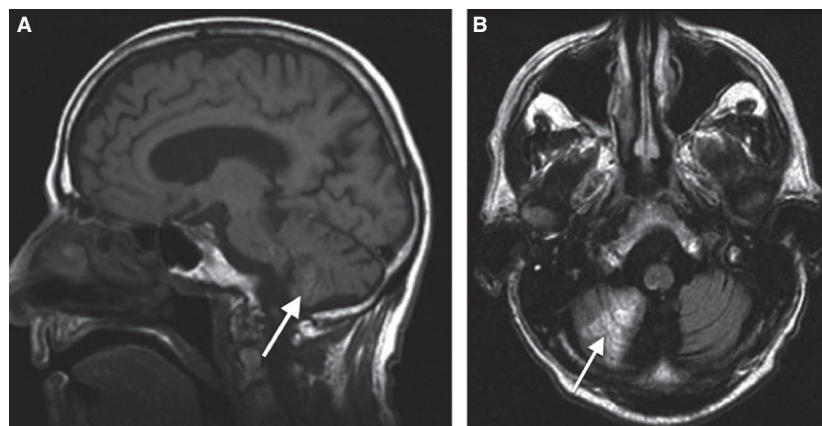
lipidemia, diabetes mellitus, coronary artery disease, left carotid stenosis (status post-stent placement), and postoperative encephalopathy following an aortic valve replacement three years earlier, who presented to an outside facility with symptoms of nausea, vomiting, vertigo, hiccups, and ataxia. He was diagnosed with posterior circulation stroke affecting the right cerebellar region, confirmed with a computed tomography (CT) scan. In the same month, he developed symptoms of hypomania for the first time in his life at 86 years of age. The symptoms included reduced need for sleep, increased talkativeness, and increased goal-directed activity. Quetiapine, 50 mg at bedtime, was initiated to treat hypomanic symptoms, with a good response.

A few months later, he presented to our facility with similar symptoms of vomiting, vertigo, hiccups, and ataxia. A repeat CT scan of the head

revealed the presence of a subacute right inferior cerebellar hemisphere infarction and chronic-appearing central pontine lacunar infarct. Magnetic resonance imaging (MRI) of the head showed the presence of a subacute infarction in inferomedial right cerebellar hemisphere and right dorsolateral medulla in the right PICA distribution (Fig. 1A and B). He was admitted for the treatment of stroke. A month later, his sister noted behavioral changes including anxiety, increased talkativeness, and increased goal-directed activities related to a pursuit of becoming an actor. Repeat MRI of the head at this time revealed an increase in the size of the previous cerebellar infarct consistent with the expected evolutionary changes in an infarct over time (Fig. 2A and B). Subsequently, he presented with multiple brief episodes of dizziness and nausea without associated weakness sec-



*Fig. 1.* Magnetic resonance imaging of the head, showing the presence of a subacute infarction in the inferomedial right cerebellar hemisphere and the right dorsolateral medulla in right posterior inferior cerebellar artery distribution. (A) Diffusion-weighted axial MRI image showing hyperintensity in inferomedial right cerebellar hemisphere and right dorsolateral medulla (see arrow), (B) T2 weighted fluid attenuation inversion recovery (FLAIR) axial MRI image showing hyperintensity in inferomedial right cerebellar hemisphere and right dorsolateral medulla (see arrow).



*Fig. 2.* Repeat magnetic resonance imaging of the head, showing an increase in the size of the previous cerebellar infarct consistent with the expected evolutionary changes in an infarct over time. (A) T2 weighted FLAIR sagittal MRI image showing hyperintensity in inferomedial right cerebellar hemisphere and right dorsolateral medulla (see arrow), (B) T2 weighted axial MRI image showing increase in hyperintensity in inferomedial right cerebellar hemisphere consistent with increase in size of the infarct (see arrow).

ondary to recurrent posterior circulation transient ischemic attacks and was recommended by his neurologist to continue taking antiplatelet drugs.

Approximately one year later, he presented to our psychiatry emergency department for evaluation of grandiose delusions, paranoia, and elevated mood for one week. He reported that he had tried to call several people, including the President, to seek help in spreading the word about his innovative ideas about producing a device to assist fool-proof computer documentation for medical insurance purposes, and his special abilities for 'vibration perception'. He also endorsed paranoid delusions that he was storing people's conversations so that they could not con him anymore. A mental status examination revealed flight of ideas, pressured speech, euphoric mood, paranoia, and grandiosity. A CT of the head at this time revealed an old infarct in the right inferior cerebellar hemisphere and right dorsolateral medulla, with the rest of the medical/neurological work-up being negative. Given his florid manic symptomatology, he was admitted to our psychiatric facility. During this psychiatric hospitalization, divalproex sodium was initiated at 250 mg twice daily, along with quetiapine 50 mg at bedtime and 50 mg three times daily as needed for agitation. Upon treatment, the patient showed steady improvement in thought process, delusional thoughts, grandiosity, and sleep. The divalproex sodium dose was titrated to a dose of 500 mg twice daily at the time of his dismissal, and during an outpatient psychiatric follow-up visit he was found to be asymptomatic, with a trough total valproic acid level of 61 µg/ml and a trough free valproic acid level of 8 µg/mL.

He presented to the emergency department again a year later for evaluation of a fall on his left side. A thorough medical work-up, including blood laboratory results, a CT of the cervical spine, thoracolumbar plain films, a chest x-ray, and a pelvic x-ray, were normal. A CT of the head showed no acute intracranial hemorrhage, mass, mass effect, or fracture. Psychiatry service was consulted after his sister reported the onset of paranoia, grandiose delusions, tangential speech, and insomnia over a period of several days in the setting of discontinuation of quetiapine by an outpatient psychiatrist owing to dizziness that was presumed to be resulting from quetiapine therapy. He was taking divalproex sodium extended release (ER) 500 mg once daily prior to this presentation. His sister reported that he had been talking non-stop and planning to call the President and Bill Gates to get financial assistance for the project that he claimed he had been working on, and to call the navy to buy a barge and then put his house on the barge and 'go floating

down the Mississippi River'. A mental status examination revealed pressured speech, elevated mood, and delusional thinking, with normal cognitive abilities (Mini-Mental State Examination score = 28/30). As a result of his manic presentation, he was hospitalized to our facility for the second time. During this hospitalization, olanzapine was initiated and titrated to a total dose of 12.5 mg at bedtime, and divalproex sodium ER was titrated up to a total dose of 1250 mg once daily (the trough total valproic acid level was 53 µg/mL), with a significant improvement in manic symptomatology. He was dismissed from our facility on a regimen of divalproex sodium ER 1250 mg and olanzapine 12.5 mg, both at bedtime. In the outpatient setting, the patient was noted to have excessive daytime sedation, as a result of which olanzapine was discontinued, and haloperidol was initiated at 0.5 mg in the morning and 1 mg in the evening, along with a reduction in the dose of divalproex sodium to 750 mg at bedtime. The patient continued to do well on this psychotropic medication regimen, with good control of his mood and psychotic symptoms, and no further psychiatric hospitalizations until his demise at the age of 90 years due to non-psychiatric multiple medical conditions.

### Discussion

Mania resulting from an ischemic brain injury or post-stroke mania is a relatively rare occurrence, with an estimated prevalence of less than 1% (7). Steffens and Krishnan (4) defined post-stroke or vascular mania as mania with clinical (a history of stroke or transient ischemic attack and/or focal neurological signs and symptoms), neuro-radiological (signal hyperintensities, cortical or subcortical infarcts), or neuropsychological (impairment in cognitive domains such as executive function, memory, and speed of information processing) evidence of cerebrovascular disease. They also proposed a few supportive criteria (not needed for diagnosis), including onset or change in illness course at the age of 50 years or older, an absence of family history of mood disorder, and marked disability in activities of daily living. Wijeratne and Malhi revised these criteria and defined vascular mania as mania with onset at or after 50 years of age, with clinical evidence of transient ischemic attack or cerebrovascular accident, or at least two systemic diseases which are vascular risk factors for stroke, including hypertension, hyperlipidemia, coronary heart disease, and diabetes mellitus, along with supportive criteria including neuroimaging and neuropsychological changes greater than expected for age (5).

Santos et al. (8), in their systematic review on mania and stroke, mentioned that the 'orbitofrontal circuit', comprising the orbitofrontal cortex (a subdivision of the prefrontal cortex), basotemporal region, thalamus, and caudate nucleus, is a central circuit in mood regulation and social behavior. Lauterbach (9) described the cerebellum as having connections with the limbic system (hippocampus, fornix, septum, and amygdala), ventral tegmental area, locus coeruleus, substantia nigra, corpus striatum, pallidum, pedunculopontine nucleus, thalamus, temporal lobe, and prefrontal cortex, and that these structures project to basal ganglia–thalamic circuits which are considered relevant in bipolar disorders.

Post-stroke mania appears to occur most often with right hemispheric lesions, especially the right orbitofrontal region or the right thalamus. Babinski was the first person to describe an association between elevated mood state (or euphoria) and right hemispheric brain injury (10). A study by Starkstein et al. (3) indicated that right hemispheric stroke patients with mania differed from those who did not develop mania, in that the former had a higher bifrontal ratio (based on a CT scan measurement of subcortical atrophy at the level of the frontal lobes) and a higher third ventricle to brain ratio (based on a measurement of atrophy in diencephalic areas).

The cerebellum has also been suggested to play a significant role in the pathophysiology of schizophrenia. A dysfunctional prefrontal–thalamic–cerebellar circuitry has been proposed to exist in patients with schizophrenia (11). A brief discussion about schizophrenia is important here as there is a large body of evidence indicating a significant overlap (including, but not limited to, genotypic and phenotypic features) between schizophrenia and bipolar disorder (11, 12).

The role of the cerebellum in bipolar disorder has been suggested as cerebellar atrophy is seen in patients with bipolar disorder (13–16). Schmahmann and Sherman (17) have described a condition called 'cerebellar–cognitive affective syndrome' (CCAS), consisting of cognitive impairments (executive dysfunction, visuospatial deficits, and language symptoms) and behavioral–affective disturbances associated with an interruption of cerebellar connections with cerebral association cortices (with the posterior cerebellar lobe) and the neocortex–limbic system (with the posterior vermis), respectively (17, 18). The posterior vermis ('putative limbic cerebellum') lesions disrupting cerebellar communication with the neocortex and the limbic system can result in neuropsychiatric symptoms (18). The cerebellar vermis area is radio-

logically demarcated into V1 (anterior lobe), V2 (superior posterior lobe), and V3 (inferior posterior and flocculonodular lobes) areas (19). DelBello et al. (19), in their pilot study involving MRI analysis of the cerebellum in patients with bipolar disorder, found that the V3 area, which has extensive connections with the limbic system, has a smaller volume in patients with recurrent manic episodes than in patients with first episodes. The authors proposed this to be a neurodegenerative process following each affective episode.

In 2007, Moorhead et al. (20) showed that patients with bipolar disorder lose cerebellar gray matter at an accelerated rate compared to healthy control subjects. A more recent study (21) demonstrated sexual differences in vermis morphology, with males with bipolar disorder having a larger vermis volume compared to healthy controls, while females with bipolar disorder showed no significant difference from healthy females.

Functional changes in the cerebellum of patients with bipolar disorder have also been reported. A functional MRI study of an explicit facial emotion recognition task involving fear, disgust, and neutral emotions identified hyperactivity in the hippocampus, inferior parietal and superior temporal cortices, and cerebellum among ten female euthymic patients with bipolar disorder compared to matched controls (22). Loeber et al. reported that patients with bipolar disorder have lower cerebellar regional cerebral blood flow compared to schizophrenics and healthy controls (23). Reduced activity of specific isoforms of phosphodiesterase-4A (PDE4A5 and PDE4AX) has been shown in the cerebella of patients with bipolar disorder in comparison to matched controls, with no significant changes in the cerebella of patients with schizophrenia or major depression (24).

Wallenberg syndrome, also known as lateral medullary syndrome and posterior inferior cerebellar artery syndrome, is a disease in which patients have a constellation of symptoms which can result from infarction in the distribution of the PICA. The signs and symptoms result from the infarction of the posterolateral medulla oblongata, with or without involvement of the cerebellum (25). The most common symptoms are impairment of pain and thermal sensation over the contralateral side of the trunk, limbs, and ipsilateral face; Horner syndrome; dysphagia; dysphonia; nausea and vomiting; vertigo; nystagmus; ataxia; and intractable hiccups (25). First, our patient met both Steffens and Krishnan, and Wijeratne and Malhi criteria for post-stroke mania. Second, he met the criteria for Wallenberg syndrome as he had an infarct in the distribution of the right PICA (MRI evidence),



affecting the posterolateral/dorsolateral medulla (right side) and inferior medial right cerebellar hemisphere, with symptoms including vertigo, nystagmus, diplopia, nausea, ataxia, and hiccups. Additionally, he developed his first episode of manic symptoms after the stroke, affecting the brain areas implicated in lateral medullary or Wallenberg syndrome. Subsequently, he had a recurrent episode of mania without the occurrence of more strokes in that area or elsewhere. Hence, his presentation may be considered as a unique and previously unreported manifestation of Wallenberg syndrome. Another unique feature of this case is that ischemic injury to the medulla oblongata may have played a synergistic role in the causation of mania. It has been suggested that the medulla oblongata is involved in the neural regulation of mood, given its adrenergic projections to several neuroanatomical regions, including the locus coeruleus, raphe nuclei, hypothalamus, periaqueductal gray, paraventricular nucleus of the thalamus, amygdala, and ventral tegmental area (26, 27). The nucleus of the tractus solitarius (NTS) in the medulla oblongata projects into regions such as the thalamus, hypothalamus, amygdala, and hippocampus, which are regions involved in the neural circuitry implicated in bipolar disorder (28). Additionally, NTS has connections with the anterior cingulate cortex, the activation of which is speculated to increase during mania (29).

The present case report implicates Wallenberg syndrome as a novel putative cause of post-stroke mania. It adds to the emerging literature on the neurobiological basis of bipolar disorder, and strengthens the previously reported cerebellar involvement in the pathology of secondary mania. Additionally, this case also illustrates the possible role of the medulla oblongata in affective regulation and adds to the sparse literature previously available on this particular function of the medulla oblongata. Further studies are needed to strengthen the association of secondary mania and bipolar disorder with the cerebellum and medulla oblongata.

### Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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