Annals of Medical and Clinical Case Reports
Volume 1| Issue 8 | Case Report

Case Report: Investigating The Association Between Depression and Multiple System Atrophy

Huang M[2†], Zhou H[1†], Qiao Z[2], Li J[2], Kang L[2], Gao Q[2], Yang S[3*] , Ma X[1,2*]

[1]Yanan Medical College of Yanan University, Yanan, China;

[2]Department of Neurology, The First Hospital of Yulin, Yulin, Shaanxi, China 719000;

[3]Neuroscience Research Center, College of Basic Medicine, Chongqing Medical University, Chongqing, People's Republic of China.

***Corresponding author:** **Xingshun Ma, Yanan Medical College of Yanan University, Yanan, China; Department of Neurology, The First Hospital of Yulin, Yulin, Shaanxi, China 719000**

Shu Yang, Yanan Medical College of Yanan University, Yanan, China; Neuroscience Research Center, College of Basic Medicine, Chongqing Medical University, Chongqing, People's Republic of China.

Citation: Xingshun Ma and Shu Yang, Case Report: Investigating The Association Between Depression And Multiple System Atrophy., Ann Med Clin Case Rep, 2025; 1(8): 1-5.

Keywords: Depression; Multiple System Atrophy (MSA); Risk Factor

Published Date: 05-11-2025 Accepted Date: 03-11-2025 Received Date: 29-10-2025

Abstract

Depression commonly occurs as a secondary accompanying symptom in neurodegenerative diseases, including Multiple System Atrophy (MSA), and other chronic illnesses. To date, no studies have investigated the potential for depression to act as an independent risk factor and preclinical indicator of MSA. Consequently, the role of depression in the pathophysiology of MSA remains unclear. This report documents a case of a 53-year-old female patient diagnosed with major depression following significant emotional trauma, who later developed MSA. Through retrospective analysis, we observed a temporal correlation between the emergence of depressive symptoms and the subsequent development of neurological symptoms prior to the MSA diagnosis. This suggests that depression may not only be an early accompanying symptom of MSA but could also serve as an independent risk factor. Early identification and management of depressive symptoms might therefore help delay or prevent the progression of MSA. Close collaboration between neurologists and psychiatrists is crucial for identifying and treating such cases. The evaluation and treatment of depressive symptoms should not be isolated from the management of neurological disorders but should be integrated into the overall assessment.

1. Introduction

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by various combinations of autonomic dysfunction, Parkinson's syndrome, cerebellar ataxia, and extrapyramidal symptoms [1]. The average onset age of MSA is between 54 and 63 years old, with a higher prevalence in males and a median survival of approximately 6-11 years [2]. Studies have shown that depressive symptoms are more common in patients with neurodegenerative diseases and other chronic conditions. Although the data support an association between MSA and depressive symptoms, the precise role of depressive symptoms in the pathology of MSA remains uncertain.

2. Case Report

This report describes a 53-year-old female patient who was diagnosed with depression after experiencing major emotional trauma and subsequently developed MSA. The patient began exhibiting depressive symptoms, including low mood and anhedonia, five years after her son died in a traffic accident, leading to a formal diagnosis of depression. Over the following four years, she developed symptoms including gait instability, autonomic dysfunction, parkinsonism, and cerebellar ataxia. Imaging studies (CT and MRI) conducted before hospitalization did not reveal any significant abnormalities. Upon admission, a neurological examination revealed reduced facial expression, aggravated dysarthria, increased lower limb reflexes, and upper limb rigidity, rendering her unable to stand or walk independently. Brain MRI demonstrated significant atrophy in the frontal lobes, temporal lobes, cerebellum, and pons, along with the presence of the characteristic 'hot cross bun' sign (Figure1).

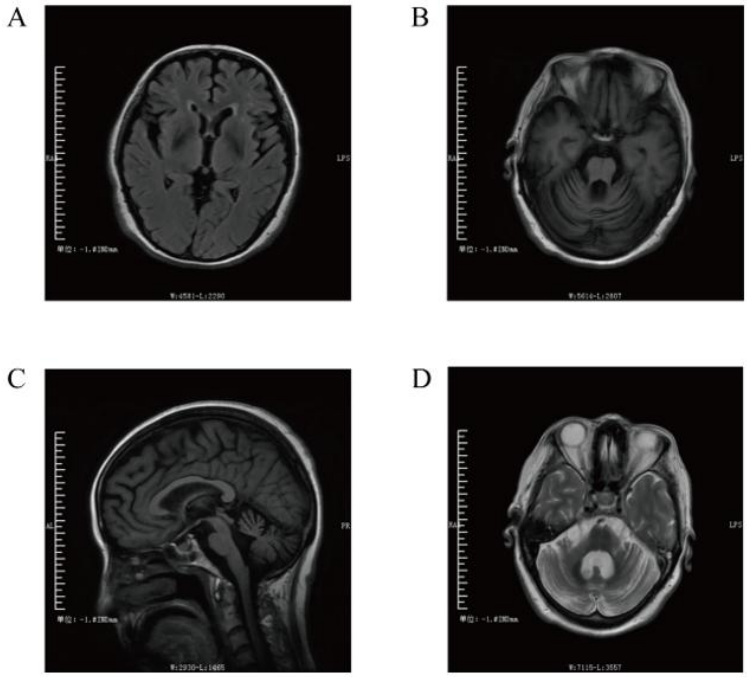

Figure 1: Brain MRI findings consistent with multiple system atrophy： (A) Magnetic resonance images show atrophy of the cerebral cortex with frontal lobe and temporal lobe. (B) Magnetic resonance images show atrophy is prominent in cerebellum. (C) Magnetic resonance images show atrophy is the basis pons, medulla and cerebellum. (D) Magnetic resonance image showing the “hot cross bun” sign.

4. Discussion and Conclusion

The diagnosis of MSA is clear from the patient's presentation. Interestingly, depressive symptoms appeared before any obvious neurological deficits. This observation suggests that depression might be a risk factor for the development of MSA.

Through retrospective analysis, we found that the onset of depressive symptoms prior to MSA diagnosis was time-related to the development of subsequent neurological symptoms. After analyzing cases of MSA diagnosed at our hospital between January 2015 and April 2024, we focused particularly on two patients whose circumstances resembled those described in our case report. The first was a 55-year-old female who had been in a prolonged depressive state following the sudden death of her son in 2012. Approximately one year later, she began experiencing symptoms of low blood pressure, urinary incontinence, and constipation, with progressively unstable gait. After thorough clinical observation and assessments, including an MRI scan and autonomic nervous system evaluations conducted in July 2015, she was diagnosed with MSA according to the diagnostic criteria set forth by the International Parkinson and Movement Disorder Society. The second case involved a 64-year-old man who attempted remarriage after his wife's death but faced conflicts with his children. During which period, he presented with symptoms of depressed mood, insomnia, and a generalized burning sensation. Despite treatment with alprazolam and diazepam, the symptoms did not improve. Six months later, he manifested gait instability, hyperreflexia, limb rigidity, along with autonomic symptoms such as urinary

incontinence and constipation. Two years later, brain MRI demonstrated atrophy of the basal pons and cerebellum, along with an increased signal intensity at the base of the pontine transverse fibers.

In many studies related to MSA, depressive symptoms are frequently documented but are typically regarded as an early concomitant symptom of MSA [3]. One study found that the comorbidity of MSA and depression reached 43%; whereas the incidence of mood disorders increases with the progression of MSA [4]. Neurodegenerative diseases may affect the synthesis or metabolism of mood-related neurotransmitters. However, in our cases, depression was more likely related to environmental factors, rather than being indicative of MSA. Firstly, depressive symptoms had emerged six months to a year before the onset of neurological symptoms. Secondly, the depression occurred in conjunction with significant life events, rather than as a reaction to neurological dysfunction. This suggests that in these particular cases, depression demonstrated a stronger association with significant environmental factors than with neurodegenerative changes. Of course, this does not rule out the possibility of an individual's genetic predisposition to depression. It is worth considering the relationship between depression and MSA—why do elderly patients with depression, who do not initially exhibit neurological symptoms, develop MSA within six months to a year? The pathological mechanisms shared by depression and MSA—including neurotransmitter depletion, pathological protein accumulation, inflammatory responses, and alterations in neuroprotective factors—may interact in multiple biological processes.

The amygdala (AMY) is a crucial hub in the emotional processing network of the brain and is involved in the pathogenesis and progression of depression according to neurobiological models [5]. Task-based fMRI studies have shown that in patients with severe depression, AMY activity increases in response to negative emotional stimuli such as faces, pictures, and words [6]. Additionally, studies have found that functional connectivity (FC) dysfunction in the AMY-ventromedial prefrontal cortex circuit correlates positively with the severity of symptoms in women who exhibit early life stress and depression [7]. Post-mortem brain examinations in MSA also reveal severe atrophy of the AMY, highlighting potential dysfunction in AMY related to depression in MSA patients.

In MSA, studies have identified significant reductions in dopamine and norepinephrine in key brain areas such as the striatum, septal nuclei, substantia nigra, locus coeruleus, hypothalamus, and septum [8]. Dysfunctions in the catecholaminergic systems within these regions, particularly in the striatum, are crucial for regulating emotional and cognitive functions [9]. Neurotransmitter disturbances in MSA patients with depressive symptoms predominantly stem from disruptions of dopaminergic neurons, which are compounded by dysfunctions of serotonin, norepinephrine, and other neurotransmitters [10]. Thus, this extensive depletion of neurotransmitters not only indicates the presence of MSA but may also represent a biological basis for the onset of depression.

Research indicates that in the brains of patients with depression, the pathological accumulation of proteins such as amyloid, tau, and α-synuclein is associated with neurodegenerative changes [11]. These abnormal protein aggregates, linked to symptoms akin to Alzheimer's disease [12], may also trigger the development of MSA [13]. Chronic depressive states may lead to aberrant expression and accumulation of these proteins in the brain [14], thereby accelerating the neurodegenerative process.

Depression is associated with enhanced inflammatory responses and reduced levels of neurotrophic factors such as BDNF (brain-derived neurotrophic factor) [15, 16]. These biological changes not only play a role in the development of depression but may also increase the risk of MSA [17, 18]. An increase in microglial cell activation and number is characteristic of MSA [19]. In states of depression, elevated inflammatory cytokines and reduced neuroprotective factors may further damage neural cells, leading to accelerated progression of neurodegenerative diseases [20].

Future research should further explore the specific biological mechanisms linking depression and MSA, as well as how these mechanisms vary among individuals. Studies should also investigate how interventions targeting depression could potentially influence the developmental pathway of MSA, as well as the practical efficacy and clinical applicability of these interventions. Additionally, since there may be biological links between depression and MSA, exploring these connections is crucial for developing early diagnostic methods and preventative strategies. For instance, early identification and management of depressive symptoms could serve as a means to mitigate or prevent the progression of MSA. Moreover, treatments targeting neurotransmitter balance, pathological protein processing, and inflammation control could have dual efficacy for patients with depression and MSA.

Importantly, close collaboration between neurologists and psychiatrists is essential for the identification and management of such cases. The assessment and treatment of depressive symptoms should not be isolated from the management of neurological diseases but should be integrated into the overall evaluation.

In summary, depression is not only a potential early accompanying symptom of MSA but may also be an independent risk factor. The association between depression and MSA could be mediated by multiple biological mechanisms, such as neurotransmitter depletion, pathological protein accumulation, inflammatory responses, and changes in neuroprotective factors. Therefore, understanding these biological links is essential for the early diagnosis and treatment of both MSA and depression.

References

1. Cohen J, Low P, Fealey R, Sheps S, Jiang NS. Somatic and autonomic function in progressive autonomic failure and multiple system atrophy. Ann Neurol. 1987 ;22(6): 692-699.
2. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology, 1996; 46(5): 1470.
3. Wenning GK, Colosimo C, Geser F, Poewe W. Multiple system atrophy. Lancet Neurol. 2004;3(2):93-103.
4. Burns MR, McFarland NR. McFarland, Current Management and Emerging Therapies in Multiple System Atrophy. Neurotherapeutics. 2020;17(4):1582-1602.
5. Zhang LY, Cao B, Zou YT, et al. Depression and anxiety in multiple system atrophy. Acta Neurol Scand. 2018; 137(1): 33-37.
6. Schrag A, Sheikh S, Quinn NP, et al. A comparison of depression, anxiety, and health status in patients with progressive supranuclear palsy and multiple system atrophy. Mov Disord. 2010; 25(8): 1077-1081.
7. Hamann S. Cognitive and neural mechanisms of emotional memory. Trends Cogn Sci. 2001; 5(9): 394-400.
8. Young KD, Siegle GJ, Bodurka J, Drevets WC. Amygdala Activity During Autobiographical Memory Recall in Depressed and Vulnerable Individuals: Association With Symptom Severity and Autobiographical Overgenerality. Am J Psychiatry. 2016; 173(1): 78-89.
9. Padgaonkar NT, Lawrence KE, Hernandez LM, Green SA, Galván A, Dapretto M. Sex Differences in Internalizing Symptoms and Amygdala Functional Connectivity in Neurotypical Youth. Dev Cogn Neurosci. 2020; 44: 100797.
10. Spokes EG, Bannister R, Oppenheimer DR. Multiple system atrophy with autonomic failure: clinical, histological and neurochemical observations on four cases. J Neurol Sci. 1979; 43(1): 59-82.
11. Westbrook A, Frank MJ, Cools R. A mosaic of cost–benefit control over cortico-striatal circuitry. Trends Cogn Sci. 2021; 25(8): 710-721.
12. Fetoni V, Soliveri P, Monza D, Testa D, Girotti F. Affective symptoms in multiple system atrophy and Parkinson's disease: response to levodopa therapy. J Neurol Neurosurg Psychiatry. 1999; 66(4): 541-544.
13. Wu KY, Lin KJ, Chen CH, et al. Decreased Cerebral Amyloid-β Depositions in Patients With a Lifetime History of Major Depression With Suspected Non-Alzheimer Pathophysiology. Front Aging Neurosci. 2022; 14: 857940.
14. Wang SM, Kim NY, Um YH, et al. Default mode network dissociation linking cerebral beta amyloid retention and depression in cognitively normal older adults. Neuropsychopharmacology. 2021; 46(12): 2180-2187.
15. Laferrière F, Claverol S, Bezard E, Ichas F, De Giorgi F. Similar neuronal imprint and no cross-seeded fibrils in α-synuclein aggregates from MSA and Parkinson's disease. NPJ Parkinsons Dis. 2022; 8(1):10.
16. Radford R, Wong M, Pountney DL. Neurodegenerative Aspects of Multiple System Atrophy. In: Kostrzewa RM, ed. Handbook of Neurotoxicity. 2nd ed. Cham: Springer International Publishing; 2022: 1869-1892.
17. Tran AA, De Smet M, Grant GD, Khoo TK, Pountney DL. Investigating the convergent mechanisms between major depressive disorder and Parkinson's disease. Complex Psychiatry, 2021; 6(3-4): 47-61.

18. Scaini G, Mason BL, Diaz AP, et al. Dysregulation of mitochondrial dynamics, mitophagy and apoptosis in major depressive disorder: Does inflammation play a role? Mol Psychiatry. 2022; 27(2): 1095-1102.
19. Emon MPZ, Das R, Nishuty NL, Shalahuddin Qusar MMA, Bhuiyan MA, Islam MR. Reduced serum BDNF levels are associated with the increased risk for developing MDD: a case–control study with or without antidepressant therapy. BMC Res Notes. 2020; 13: 83.
20. Yuan X, Wan L, Chen Z, et al. Peripheral Inflammatory and Immune Landscape in Multiple System Atrophy: A Cross-Sectional Study. Mov Disord.2024; 39(2): 391-399.
21. Zhang L, Cao B, Hou Y, et al. Fatigue in patients with multiple system atrophy: a prospective cohort study. Neurology. 2022; 98(1): e73-e82.
22. Stefanova N, Wenning GK. Review: Multiple system atrophy: emerging targets for interventional therapies. Neuropathol Appl Neurobiol. 2016; 42(1): 20-32.
23. Stefanova N, Georgievska B, Eriksson H, Poewe W, Wenning GK. Myeloperoxidase inhibition ameliorates multiple system atrophy-like degeneration in a transgenic mouse model. Neurotox Res. 2012; 21(4): 393-404.