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Case Series

Unmasking the Mind-Organic Psychiatric Manifestations in Long-term Multiple Sclerosis: A Case Series

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Abstract

Multiple sclerosis (MS) is a chronic demyelinating disorder often accompanied by neuropsychiatric manifestations arising from fronto-limbic and prefrontal involvement. This case series describes four patients with long-standing MS who developed organic psychiatric syndromes independent of neurological relapse. Two patients presented with organic depressive disorder, one with organic anxiety disorder, and organic personality disorder. The MRI Brain scans of the cases revealed fronto-cingulate, orbitofrontal, or limbic demyelination, corresponding with the clinical features. They improved significantly with SSRI's, mood stabilizers, and psychotherapy. The findings highlight that psychiatric symptoms in chronic MS often reflect direct neurobiological consequences of demyelination rather than reactive psychological distress, emphasizing the importance of integrated neuropsychiatric assessment in MS management for aiding better functional and holistic outcomes.

Keywords: Multiple Sclerosis; Organic Depressive Disorder; Organic Anxiety Disorder; Organic Personality Disorder

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated demyelinating disease of the central nervous system (CNS) characterized by multifocal lesions leading to neurological and neuropsychiatric dysfunction. Psychiatric manifestations in MS are increasingly recognized as intrinsic to the disease process rather than mere psychological reactions to disability. Epidemiological data suggest that up to 50% of MS patients manifest with major depression, while anxiety disorders affect 30–40% during illness [1,2]. These symptoms often correlate with lesion burden in fronto-limbic and temporal regions rather than disease duration or physical disability [3,4]. It is crucial to distinguish organic psychiatric syndromes arising from brain pathology from reactive emotional, depressive and anxiety responses to chronic illness [4].

Organic psychiatric syndromes, including Organic Depressive Disorder (F06.32), Organic Anxiety Disorder (F06.4), and Organic Personality Disorder (F07.0), represent direct psychopathological consequences of brain pathology, often demyelination or atrophy in mood-regulating circuits. The pathophysiological basis lies in white matter disconnection and fronto-subcortical circuit dysfunction, disrupting serotonergic, dopaminergic, and noradrenergic pathways [5,6]. However, such syndromes are frequently underdiagnosed, especially when manifesting years after diagnosis and neurological stabilization.

This case series presents four patients with established MS of duration between 5 to 8 years who developed distinct psychiatric

manifestations. Through a detailed clinical and neuroimaging correlation, the series aims to emphasize the organic etiology of these syndromes, their neurobiological underpinnings, and the therapeutic implications of early identification.

Case Series

Case 1: Organic depressive disorder secondary to relapsing–remitting multiple sclerosis

A 37-year-old married woman with a six-year history of relapsing–remitting multiple sclerosis (RRMS), presented with persistent sadness of mood, loss of interest in her chores, and chronic fatigue for the last three months. She reported reduced concentration, low energy, early morning awakening, and feelings of helplessness, but denied suicidal ideation or psychotic symptoms. There were no recent relapses or psychosocial stressors. She had been diagnosed with RRMS at age 31 following episodes of optic neuritis and right-sided weakness, leaving mild left-leg weakness (EDSS 4.0). Neurological examination revealed mild spastic paraparesis with brisk reflexes, and cognitive screening (MoCA) scored 27/30. Mental status examination showed psychomotor retardation, depressed affect, reduced speech output, pessimistic ideas, and intact orientation and insight. MRI brain revealed chronic periventricular and juxtacortical demyelinating plaques with gliotic changes, prominently involving the left anterior cingulate (ACC) and dorsolateral prefrontal cortex (DLPFC). Thyroid profile, vitamin B12, and metabolic parameters were within normal limits. Considering the clear temporal association with established cerebral pathology, lack of psychosocial triggers, and neuroanatomical evidence, a diagnosis of Organic Depressive Disorder secondary to MS was made. She was started on Tab Escitalopram 10 mg/day, up titrated to 15 mg/day, along with structured Behavioral activation therapy and psychoeducation. Over twelve weeks, her Hamilton Depression Rating Scale (HAM-D) score improved from 26 to 8, with restoration of motivation and work efficiency. She maintained remission for over six months with ongoing Interferon therapy.

Case 2: Organic depressive disorder secondary to multiple sclerosis

A 50-year-old woman, with a seven-year history of relapsing–remitting multiple sclerosis (RRMS), presented with persistent pervasive low mood, reduced interest in her hobbies and social interactions, over the past five months. She reported reduced engagement with daily activities, diminished motivation, and feeling of fatigue, along with intermittent episodes of restlessness, excessive worry about her physical health, and sudden onset transient symptoms of palpitations and breathlessness with a feeling of impending doom lasting for 4-5 mins, occurring 5-6 times a week and resolved spontaneously. Family members described her as socially withdrawn, and emotionally unresponsive to routine events. She denied suicidal ideation, psychotic features, or recent psychosocial stressors. Her neurological history included two prior relapses, the last occurring two years earlier, leaving mild right-sided weakness but stable neurological function since then.

On examination, she had a reduced facial expression and slowed psychomotor activity. Mental status examination revealed a pervasively depressed affect, reduced spontaneity, thinking suggestive of helplessness, and bleak views of the future with preserved orientation and cognition (MoCA score 28/30). MRI brain demonstrated multiple chronic periventricular demyelinating plaques, with prominent involvement of bilateral orbitofrontal (OFC) and anterior cingulate regions (ACC). Routine laboratory investigations, including thyroid function, vitamin B12, and metabolic profile, were normal.

A diagnosis of Organic Depressive Disorder secondary to MS was made, based on the clear temporal relationship with established cerebral disease, absence of psychosocial precipitants, and lesion localization in mood-related neural circuits. She was initiated on Tab Sertraline 50 mg/day, up-titrated to 100 mg/day over four weeks, along with psychoeducation, activity scheduling, and relaxation therapy in the form of Jacobson's Progressive Muscle Relaxation (JPMR). By 12 weeks, her depressive symptoms and panic attacks had significantly improved, with HAM-D scores reducing from 22 to 7, accompanied by improved social engagement and affective responsiveness.

Case 3: Organic anxiety disorder secondary to multiple sclerosis

A 36-year-old woman with a five-year history of RRMS presented with persistent symptoms of restlessness, palpitations, fatigue,

and episodes of tearfulness for last two months. She described excessive worries about her health associated with tremulousness, sweating, poor concentration, sleep disturbance and even became fearful of her possible death. She had been given steroids and was presently on Glatiramer acetate subcutaneous therapy with no relapses. There were no family history of anxiety or mood disorder and no identifiable psychosocial precipitant. On neurological examination, she had left internuclear ophthalmoplegia with intention tremors and broad-based unsteady gait. Mental status examination revealed anxious affect, with increased psychomotor activity as she was fidgety and restless, thinking revealed health-related worries and fear of death. MRI brain revealed chronic demyelinating plaques in the right insular cortex and limbic regions. Biochemical investigations were normal. In view of the absence of psychosocial stress, structural cerebral involvement, and prominent anxiety symptomatology, a diagnosis of Organic Anxiety Disorder was made. She was managed with Tab Escitalopram 10 mg/day with a short course of Tab Clonazepam 0.5 mg twice a day, psychoeducation, relaxation, and Cognitive Behavior Therapy (CBT). At ten weeks, there was a significant improvement in subjective anxiety, and her HAM-A score reduced from 18 to 5. Follow-up MRI after six months showed no new plaques.

Case 4: Organic personality disorder secondary to multiple sclerosis

A 46-year-old man with an eight-year history of relapsing–remitting multiple sclerosis (RRMS) was referred by his family for noticed behavioral changes over the past year. He had become increasingly irritable, emotionally unpredictable, and withdrawn, showing reduced interest in social interactions and diminished empathy towards the family members. His wife described him as "rigid", "argumentative", and "indifferent", with periods of emotional coldness alternating with sudden tearfulness or anger. Previously known for his calm, organized personality, he now displayed poor adaptability to minor frustrations and a marked loss of initiative, preferring to remain reclusive. There was no history of euphoria, disinhibition, excessive spending, or socially inappropriate behavior. He denied substance use or prior psychiatric illness.

Neurological examination revealed mild spastic paraparesis (EDSS 5.0). On Mental status examination, he appeared apathetic and mildly irritable, with restricted affect punctuated by occasional emotional lability. Thought form was goal-directed but concrete; insight into behavioral change was partial. Cognitive screening (MoCA = 21/30) with slow impaired attention, memory and visuospatial deficit. MRI brain demonstrated bilateral dorsolateral and orbitofrontal demyelinating plaques with mild cortical atrophy. Metabolic and endocrine parameters were within normal limits.

Given the acquired alterations in affect, impulse modulation, motivation, and interpersonal conduct occurring in the context of established cerebral disease and not attributable to other psychiatric conditions, a diagnosis of Organic Personality Disorder (F07.0) secondary to MS was made. He was managed with Tab Sodium Valproate 1000 mg/day, insight-oriented psychotherapy, and cognitive remediation measures. Family members were psychoeducated on the biological basis of personality change and were advised to maintain structured daily routines and ensure consistent feedback with regular follow-up. Over four months, there was progressive improvement in mood stability, emotional engagement and functional outcomes.

Summary of cases

Case No.	Age (yrs)/ Gender	MS Duration	Psychiatric Diagnosis	MRI Lesion Locations	Treatment	Outcome
1	37/Female	6 years	Organic Depressive Disorder	Left ACC and DLPFC	Tab Escitalopram 15 mg/day & Behavioral activation therapy	HAM-D: 26 (severe)→ 8 (mild); Remission maintained for 6 months
2	50/Female	7 years	Organic Depressive Disorder	Bilateral OFC and ACC	Tab Sertraline 100 mg/day, JPMR, and Activity scheduling	HAM-D: 22(moderate)→ 7(normal)
3	36/F	5 years	Organic Anxiety Disorder	Right insular cortex and limbic regions	Tab Escitalopram 10 mg/day, Tab Clonazepam 0.5 mg bd, CBT, and Relaxation therapy	HAM-A: 18(moderate)→ 5 (normal); remission; Functional and radiological improvement
4	46/M	8 years	Organic Personality Disorder	Bilateral DLPFC and OFC plaques with mild cortical atrophy	Sodium Valproate 1000 mg/day + Insight-oriented psychotherapy + Cognitive remediation	Improved mood stability over 4 months and Functional improvement

Discussion

Neuropsychiatric manifestations in Multiple Sclerosis (MS) encompass a wide spectrum, including mood and anxiety disorders, as well as cognitive and personality changes. Among these, depression is the most prevalent psychiatric comorbidity. Emerging neuroimaging evidence indicates that depression in MS may arise independently of psychosocial adversity, resulting instead from demyelination within fronto-limbic, orbitofrontal, and anterior cingulate circuits [7]. Both Case 1 and Case 2 in this series illustrate this mechanism—each presented with depressive–apathic syndromes several years post-diagnosis, with radiological correlations confirming organic etiology. The apathic subtype reflects orbitofrontal–subcortical disconnection, disrupting motivation and affective expression while preserving emotional insight [8].

Anxiety in MS, though frequently underdiagnosed, significantly affects quality of life and treatment adherence [9]. Case 3 demonstrated prominent anxiety symptoms associated with right insular and limbic demyelination—regions implicated in interoceptive awareness and autonomic regulation. Prior studies have linked insular and amygdalar involvement with heightened autonomic arousal and somatic anxiety in MS [10,11]. The patient's favorable response to SSRIs and relaxation therapy underscores that anxiety in MS often responds to standard psychotropics when its neurobiological underpinnings are appropriately recognized.

Case 4 highlights an organic personality change—an underreported yet clinically significant manifestation. Features such as disinhibition, irritability, emotional lability, and social tactlessness reflected orbitofrontal and ventromedial prefrontal involvement [12]. These symptoms are often misattributed to stress or maladaptive coping, leading to under-recognition, inadequate treatment, and family distress. Neuroimaging findings in this case substantiated the organic basis, consistent with prior neuropathological evidence [13].

The neurobiological mechanisms linking demyelination to psychiatric syndromes involve white matter disconnection, neuroinflammation, and altered neurotransmitter dynamics. Inflammatory cytokines such as IL-1β and TNF-α modulate serotonin metabolism and neuroplasticity, contributing to depressive and anxiety phenotypes. Demyelination within prefrontal and limbic pathways further disrupts fronto-thalamo-striatal circuits, impairing mood regulation, motivation, and impulse control [14].

Therapeutically, SSRIs, SNRIs, and mood stabilizers remain effective, though careful selection is essential to minimize interactions with disease-modifying therapies (DMTs]. Behavioral activation, cognitive retraining, and psychoeducation complement pharmacological management by enhancing coping, adherence, and functional recovery [15]. Sustained remission in the present cases underscores the value of integrated neuropsychiatric care in MS.

These observations reinforce that psychiatric syndromes in MS are not merely "reactive" but constitute intrinsic neurobiological expressions of the disease. Early recognition of these manifestations facilitates timely intervention, improves outcomes, and promotes holistic patient care. Education of patients and clinicians alike is vital to reduce stigma, foster adaptive coping, and advance comprehensive neurorehabilitation [16].

Conclusion

This case series highlights that organic psychiatric syndromes—particularly depression, anxiety, and personality change—can emerge in long-standing multiple sclerosis (MS), even during periods of neurological stability. Recognition of these syndromes requires clinical vigilance and neuroimaging correlation, as lesions in fronto-limbic, orbitofrontal, and insular cortices appear pivotal in shaping specific psychopathological profiles. Timely, lesion-informed intervention with appropriate psychotropics and psychosocial therapies led to notable improvement in affective and functional outcomes, underscoring the need for an integrated neuropsychiatric management model including Neurology, Psychiatry, and psychosocial rehabilitation is essential for holistic management of MS. These findings underscores the clinical relevance of recognizing organic psychiatric syndromes in MS as integral neurological manifestations rather than reactive states, highlighting their importance in training clinicians to integrate neuropsychiatric assessment and imaging interpretation for ensuring early identification, comprehensive management and substantially enhance the prognosis and quality of life of patients of MS.

Future research should focus on longitudinal imaging and biomarker studies to elucidate mechanistic pathways linking demyelination and neuropsychiatric expression, thereby enhancing personalized therapeutic strategies.

Ethics Considerations

Informed consent was taken from the patients before publishing this article. Participation of the patients is voluntary, and their confidentiality and anonymity have been maintained at every step.

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Conflict of Interest

Nil.

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