

## LATE ONSET PSYCHOTIC DEPRESSION IN MULTIPLE SCLEROSIS: A CASE REPORT

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### INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated inflammatory and demyelinating disease of the central nervous system characterized by diverse neuropsychiatric signs and symptoms, which may have a progressive course in young adults. The majority of MS patients suffer from psychiatric conditions which may occur on both the onset and the course of MS and they frequently need psychiatric treatment (Feinstein 2011). Depression is one of the most frequent psychiatric conditions associated with MS (Brozek et al. 2017). Psychotic symptoms or disorders are rarely observed (Marrie et al. 2015).

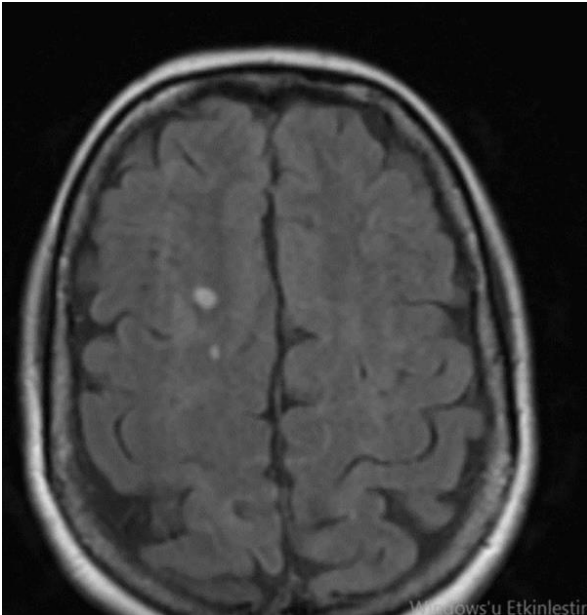
The lifetime prevalence of major depressive disorder (MDD) in MS patients is in a range of 15-50%. MDD is also associated with poor quality of life, cognitive problems, suicidality, difficulties in social relationships and reduced treatment compliance in MS patients (Catic et al. 2020, Murphy et al 2017). Hence, effective treatment of mood disorders and mental well-being were reported to have significant positive effects on functional status, quality of life and treatment compliance in MS (Duka Glavor et al 2019; Patten et al 2005). Psychotic depression (PD) was determined as a severe subtype of MDD with psychotic features that differ from non-psychotic MDD in terms of diagnosis, treatment, and also prognosis (Johnson et al 1991). However, recent studies indicated that psychosis is an independent trait that may accompany mood disorders of varying severity (Dubovsky et al 2021). Patients experience psychotic symptoms as delusions and/or hallucinations that are frequently consistent with depressive themes of worthlessness and guilt. The lifetime prevalence of PD in general population is 0.4-0.5% and the pathogenesis of the disease remains unclear. The neurobiology of psychotic MDD was suggested to be associated with dysregulation of the hypothalamic-pituitary-adrenal axis (Rothschild 2009). However, there is little data on the risk factors for PD (Jääskeläinen et al. 2018).

The prevalence of psychosis in MS is relatively rare, however, was reported to be higher in the MS population than general population (Marrie et al. 2015). The causative relation is still not clear; and the possible exacerbating effect of corticosteroids should be kept in mind just as the possible coincidental coexistence of both diseases (Camara-Lemarroy et al. 2017). In this report we aimed to present a MS case with PD as a rare and severe neuropsychiatric condition and review the possible etiologic factors such as the lesion locations in MS patients.

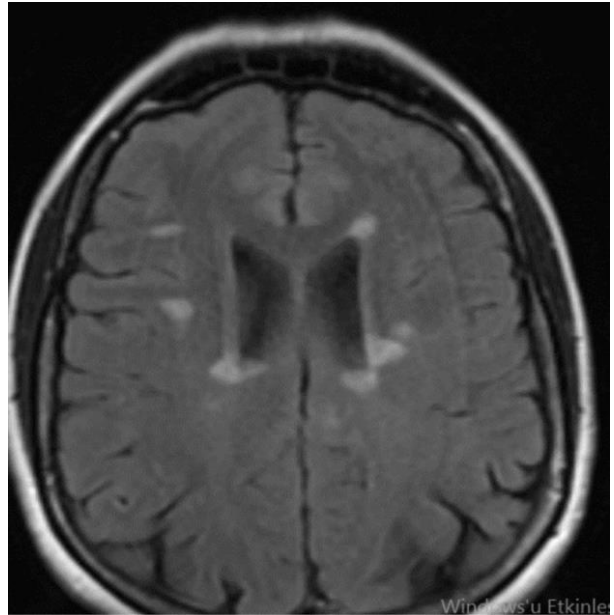
### CASE DESCRIPTION

A 55-year-old female patient was brought to the psychiatric emergency department by her family members. She was having psychological complaints such as depressive mood, irritability, insomnia and agitation which have gradually increased since two months after a conflict with her mother, and psychotic symptoms as delusions and auditory hallucinations appeared since five-six days before the hospital admission.

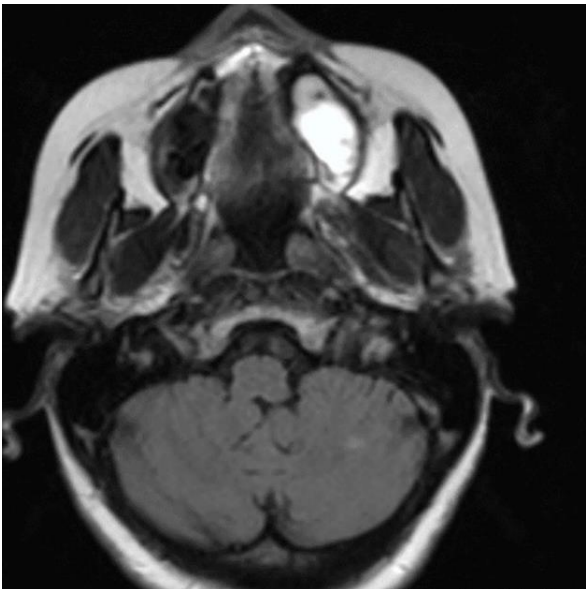
Before visiting our emergency department, she had thrown away the glasses and bowls from the balcony and torn off her clothes at her home. She was repeatedly screaming aloud that "Kill me, I'm worthless, I'm nothing!". She was having delusions of guilt, blaming herself in every respect, and was also agitated, and refused to collaborate with the staff. The patient was transferred to the short-stay unit of the emergency department, and haloperidol 5 mg and biperiden 2.5 mg were administered for agitation. The patient had no previous history of psychiatric disorder. She was diagnosed with MS for six years with a relapsing-remitting course. Initial symptoms of MS were dysarthria and weakness and numbness on the right side of the body. She had no psychiatric symptoms at the onset. Following treatment of the initial attacks with 1 gr/day methylprednisolone, she was administered fingolimod 0.5 mg/day and was stable for a couple of years. Her MS relapses were usually triggered after stressful life events.



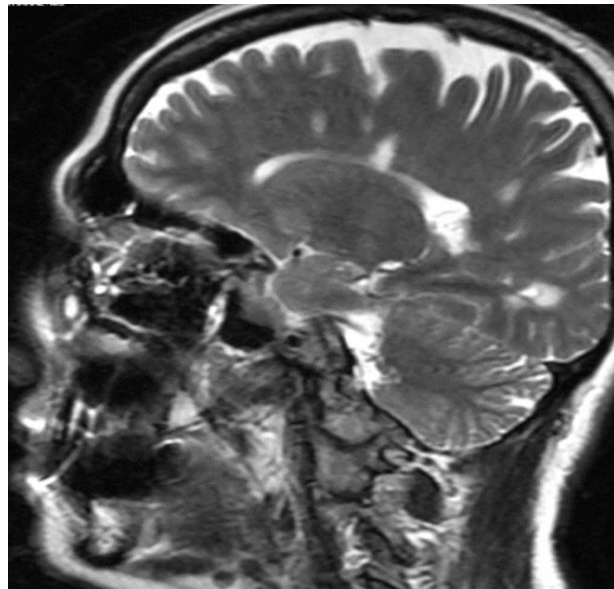
**Figure 1.** Frontoparietal subcortical area



**Figure 2.** Parietal lobe involvement



**Figure 3.** Infratentorial area of cerebellum



**Figure 4.** Periventricular Dawson's finger sign

## MANAGEMENT/TREATMENT

The brain magnetic resonance imaging (MRI) showed multiple T2 hyperintense lesions in the frontoparietal subcortical area, parietal lobe, and in the cerebellum without contrast enhancement (Figure 1, 2, 3, 4). There was no new lesion in her MRI compared to the past MRI scans. Patient had no history of MS relapse and corticosteroid treatment recently. There was no significant finding in the neurological assessment and laboratory investigation.

Thereafter the acute psychiatric treatment, the patient's agitation improved and became tranquilized, and she was more collaborative with the staff. The patient was diagnosed with late onset PD due to MS; however, she and her relatives refused hospitalization. As she had no active suicidal or homicidal ideation, or other symp-

toms requiring compulsory hospitalization, outpatient treatment planned with escitalopram 10 mg/day, olanzapine 2.5 mg/day and lorazepam 1 mg/day. Patient referred to the outpatient psychiatric unit and had a good outcome. Lorazepam was ceased at the end of the first week, and her symptoms were fully remitted within four weeks after the first admission.

## DISCUSSION

Here we present a middle aged woman with MS, who developed PD after six years of her diagnosis as MS. The prevalence of MDD and psychosis in MS have been reported as 15-50% and 2-4%, respectively, which are much higher than found in the general population (Feinstein 2011; Murphy et al. 2017). However, the prevalence of PD in MS remains unclear. Late onset PD

previously reported to be associated with structural brain lesions especially with vascular and degenerative lesions in a study with small sample size by Lesser et al.; however, no patient was reported to be diagnosed with MS and related disorders among those with late onset PD (Lesser et al. 1991).

The link between MS and psychotic symptoms and psychotic disorders has also not been fully established. Unfortunately, studies on psychosis often do not discriminate between psychotic symptoms in general or specific psychotic disorders. Additionally, the incidence of psychosis is not still reported (Camara-Lemarroy et al. 2017). Psychotic symptoms in MS are suggested to be considered as follows; (i) they could be resulted from a common pathophysiological process related to the underlying disease of the central nervous system, rather than a comorbidity of the separate diseases; (ii) they could be manifested as a side effect of, or are exacerbated by medications such as corticosteroids used in the treatment of MS; (iii) or they may reflect regional demyelination (Kosmidis et al. 2010). Furthermore, the co-existence of these two disorders may also have resulted from the psychological distress of having a severe chronic illness that could worsen psychological conditions. Regarding inflammatory responses, a significant increase in the plasma levels of interleukin-6 and c-reactive protein was previously reported, as inflammatory biomarkers in patients with psychotic disorders (Hashimoto 2017). Increased activity of inflammatory signaling pathways (such as NF- $\kappa$ B pathways) and altered anti-inflammatory activity may be considered as common factors in the pathophysiology of MS and psychotic disorders (Leibowitz & Yan 2016).

The relation of the localization of MS lesions and neuropsychiatric symptoms are previously investigated in many studies. However, to date, a clear association has not been detected (Murphy et al. 2017). In earlier, it was thought that MS with psychiatric disorders were associated with temporal lobe lesions (Honer et al. 1987). A recent study investigating MS patients reported that patients with mood disorders had a predominance of frontal lobe involvement, whereas patients with psychotic disorders had a predominance of temporal lobe involvement (Camara-Lemarroy et al. 2017). Psychotic symptoms has been suggested to be associated with MS neuropathology in periventricular white matter, and temporal and fronto-temporal regions (Murphy et al. 2017). Delusions and thought disorders, and flattened affect were associated with greater pathology in the temporoparietal region (Ron & Logsdail 1989). It is most likely that involvement of both temporal and frontal regions often overlaps.

Regarding MDDs, the key findings reported in a imaging study of MS and depression were that; the depressed MS patients had “more hyperintense lesions in the left inferior medial frontal regions” and “greater atrophy of left anterior temporal regions” (Feinstein et

al. 2004). In another study, authors suggested a possible predisposition of depression in MS with greater neuropathology in the left anterior temporal/parietal region (Siegert & Abernethy 2005). Our case was having frontoparietal and parietal involvements in MRI which may be related with both depressive and psychotic symptoms; however, as discussed above, the relationship between these symptoms and lesion localization is still unclear.

Psychotic symptoms are expected to disappear after the remission of the MS relapse and/or cessation of the associated drug treatment. However, chronic psychosis after MS relapse is also reported (Cheema et al. 2019). While haloperidol is generally recommended for psychotic symptoms in case reports, recent studies have revealed the benefit of new generation antipsychotics such as olanzapine and risperidone as in our case.

Regarding depressive symptoms; drugs such as tricyclic antidepressants should be prescribed cautiously, as they may cause severe anticholinergic side effects. Selective serotonin reuptake inhibitors (SSRIs) could be important treatment options in PD in MS patients. Accordingly, SSRIs such as escitalopram, sertraline, fluvoxamine and fluoxetine are reported to be effective on MDD in MS patients in several open-label studies since they have a safe drug-drug interaction profile and relatively lower side effects (Havle et al. 2010, Skokou et al. 2012).

## CONCLUSION

Psychotic symptoms in MS were usually associated with corticosteroid use or new-onset active lesions in frontal and temporal regions. However, our case suggests that chronic lesions in frontoparietal region may also be considered a potential risk factor for PD in MS patients and may be associated with the late onset of this condition.

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### Ethical considerations:

In this publication the WHO guidelines for good clinical practice were followed. The patient has consented that his data can be published anonymously by the author.

**Conflict of interest:** None to declare.

### Contribution of individual authors:

Nihal Taştekin & Betül Kırşavoğlu: study design, literature review, writing original draft.

Murat Yalçın & Özdem Ertürk Çetin: study design, literature review, supervision, critically review of the manuscript.

All authors approval of the final version.

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