



## Case report

## Should a psychotic or manic episode be considered an early manifestation of Multiple Sclerosis? A multiple case study



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## ABSTRACT

**Background:** Early manifestations of Multiple Sclerosis (MS) can be atypical and misleading, and several case report studies have highlighted that MS onset sometimes takes the form of a psychotic or manic episode.

**Methods:** All neurologists belonging to the French Multiple Sclerosis Observatory network were contacted by email and were asked to find patients with MS who presented with a history of psychiatric episode(s) near MS onset.

**Results:** Seventeen patients were selected that met the criteria of presenting with psychotic or manic symptoms either before the diagnosis of MS ( $N=8$ ), or at the time of the first neurological episode or shortly after ( $N=9$ ). Patients with a history of a psychiatric episode occurring before the first neurological episode were diagnosed on average 7 years later than patients with either a first neurological or a mixed (both neurological and psychiatric) episode. However, psychiatric symptoms in the first group and the first neurological symptoms of MS in the second group occurred at a similar age.

**Conclusion:** Based on this multiple case study, we question whether past psychotic or manic episode should be considered equivalent to a first manifestation of MS.

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## 1. Introduction

Psychotic and manic disorders have a higher prevalence in patients with Multiple Sclerosis (MS) than in the general population (Benros et al., 2014; Kang et al., 2010; Patten et al., 2005, but see also Brenner et al., 2014; Johansson et al., 2014), and several case report studies have highlighted that MS onset can take the form of a psychotic or manic episode (Asghar-Ali et al., 2004; Blanc et al., 2010; Jongen, 2006). However, most of these studies describe patients presenting with psychiatric symptoms occurring at the same time as the neurological symptoms of MS. In contrast,

little data has been reported on psychotic or manic symptoms preceding the onset of MS (Blanc et al., 2010).

In fact, it is known that inflammatory processes and axonal loss usually begin several years before the first neurological episode, which is conventionally used to define MS onset (Wolfson and Wolfson, 1993). Both transient neurological symptoms and episodes of depression have also been reported in a period of 1 to 10 years preceding the first neurological episode of MS (Feinstein et al., 2014). However, because the prevalence of depression is high in the general population and its origin is multi-determined, it would be difficult to assert that past episodes of depression in fact represent true earlier MS attacks in patients with a first neurological episode evocative of MS. In contrast, psychotic and manic disorders are more rare in the general population and are therefore more readily related to brain lesions and/or inflammatory processes (Leboyer et al., 2012; Patten et al., 2005).

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This evidence led us to question whether a previous psychotic or manic episode should be regarded as a first MS attack in patients with MS.

Interpreting a history of a psychotic or manic episode as related to MS inflammatory processes would lead to the assumption that MS has started at the time of the first psychiatric symptoms. The onset and severity of MS in terms of the number of episodes should thus be evaluated differently, particularly in patients presenting with neurological symptoms evocative of MS, as this has potential implications for diagnosis and treatment.

We report here the cases of patients diagnosed with MS who presented with a history of a psychotic or manic episode before the first neurological episode of MS. Considering that MS associated with psychotic or manic symptoms may represent a particular form of the illness, these patients were compared to other MS patients who also experienced psychotic or manic symptoms, but whose symptoms occurred either at the first episode of MS or after MS onset.

We examined the age of the first psychiatric or neurological manifestations as well as the age at diagnosis of MS with a particular focus on the possible delay of diagnosis in patients with psychiatric symptoms preceding the first neurological episode of MS.

## 2. Method

All neurologists belonging to the French Multiple Sclerosis Observatory network were contacted by email and were asked to find patients with MS who presented with a history of psychiatric episode(s) before MS onset or near MS onset (during the first or second episode of MS). The Observatory network was developed after approval of ethics committee and all patients gave included in the Observatory network gave their informed consent with respect to the anonymous analysis and publication of their clinical data. Seven neurologists responded to the invitation and a sample of 30 patients (15 women) was obtained. All patients were diagnosed with MS according to McDonald et al.'s revised criteria (Polman et al., 2011). For each patient, FBe called the referent neurologist to get more precise information about the characteristics of the psychiatric episode(s) and its(their) time course with regard to the first neurological episode. The patients' psychiatrists were also called if a patient had already met with one. Based on the information gathered, two psychiatrists (FBe and PV) independently attributed a DSM-IV (American Psychiatric Association, 2000) diagnosis for each patient with good inter-rated reliability ( $\kappa=0.89$ ). Conflicts were resolved after discussion.

## 3. Results

Among the 30 patients, 8 (5 women, 62.5%) had presented with one psychotic or manic episode before the first neurological episode of MS. These patients had a median age of 28.5 years at first psychiatric episode and a median age of 35.2 years at MS diagnosis. The time interval between two episodes ranged from 3 months to 13 years. Nine other patients from the same sample (3 women, 27.5%) had presented with psychotic or manic symptoms either at the time of the first neurological episode ( $N=5$ ) or close after the first episode of MS ( $N=4$ ). These patients had a median age of 26.0 years at first neurological episode and a median age of 28.0 years at MS diagnosis. The time interval between two episodes ranged from 12 months to 12 years. As shown in Table 1, two patients in this group did not exhibit later episodes of their illness in the period of clinical observation available, whereas all other patients presented with at least one more neurological episode.

The episode characteristics for both groups of patients are presented in Table 1. The remaining 13 patients were not included in the present analysis because they did not present with psychotic or manic symptoms (major depressive disorder,  $N=5$ ; minor depressive disorder,  $N=1$ ; obsessive-compulsive disorder,  $N=1$ ) or because information was not sufficient to assign DSM-IV diagnosis ( $N=6$ ).

## 4. Discussion

This study examined a very particular subset of patients presenting with a psychotic or manic episode before or close to MS onset and represents the largest multiple case study of these rare patients. We showed that patients with a history of a psychiatric episode occurring before the first neurological episode were diagnosed about 7 years later than patients with either a neurological or a mixed (both neurological and psychiatric) first episode. Delayed diagnosis was observed despite the finding that the first psychiatric symptoms in the first group occurred at a similar age (28.0 years) as the first neurological symptoms of MS in the second group (26.0 years).

Before reflecting further on these results, some obvious limitations of our work must be acknowledged that arise from the retrospective nature of the analysis. In fact, assessing the age of first clinical manifestations is a challenging issue that concerns both neurological and psychiatric chronic illnesses (Goulding et al., 2013; Miller et al., 2012). Moreover, our sample size was small due to the particular rarity of the patients who were the focus of this study. Systematic and prospective studies must thus be conducted in larger samples in the future to confirm the hypothesis that we present. Furthermore, we must also acknowledge that neurological examination was either reported as normal or not available in the four patients with a first "pure" psychiatric episode, and we cannot completely rule out the possibility that neurological symptoms of MS may have not been adequately recognized. Finally, previous studies have shown that diagnosis of physical illness (Chang et al., 2014; Reilly et al., 2015), including MS (Butler et al., 2009; Hayhow et al., 2015), is frequently delayed in patients with psychiatric illness. Therefore, the delayed diagnosis reported in our multiple case study may also reflect poorer access to somatic health care in patients with severe mental illness.

From a clinical perspective, such cases indicate that careful neurological examination is needed in patients presenting with a first psychotic or manic episode, and that MRI should be rapidly proposed in case of either neurological or atypical psychiatric symptoms (Lyoo et al., 1996). Psychotic disorders occurring during the course of MS often resemble true psychotic disorders (Patten et al., 2005) when only the psychiatric symptoms are considered, particularly at the beginning of illness. For example, T2 hypersignals indicating possible MS were found in 0.86% of patients admitted to a psychiatric hospital when systematic MRI was proposed (Lyoo et al., 1996).

From a pathophysiological perspective, it could be tempting to consider psychotic or manic episodes occurring before MS diagnosis as early misleading presentations of MS onset, due to their possible common pathophysiological inflammatory mechanisms (Borovcanin et al., 2012; Inglese and Petracca, 2015; Miller et al., 2011). The fact that psychiatric manifestations occurred at a very similar age as the first neurological symptoms fits with this hypothesis, and the probability of having a psychotic or manic episode before a first neurological MS episode is low enough to suggest that the association cannot be viewed as purely accidental (Benros et al., 2014; Carta et al., 2014; Leboyer et al., 2012; Patten et al., 2005). However, we cannot firmly label them "episodes of MS" in our patients, given that no MRI was done at the time of

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