

Clusters of Onset Symptoms in Multiple Sclerosis: Characteristics, Comorbidities, and Risk Factors

Anurag Satpathy<sup>1</sup>, Babu Nayak<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of Neurology, Hi-Tech Medical College & Hospital, Bhubaneswar, Odisha, India

<sup>2</sup>Assistant Professor, Department of Nephrology, Hi-Tech Medical College & Hospital, Bhubaneswar, Odisha, India

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Corresponding author: Babu Nayak

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Conflict of interest: Nil

**Abstract:**

**Background:** Multiple Sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system, characterized by diverse and often debilitating symptoms that manifest in various clusters at disease onset. Understanding these symptom clusters, along with their associated comorbidities and risk factors, is critical for developing targeted interventions that can improve patient outcomes and slow disease progression.

**Aim:** This study aimed to identify and analyze clusters of onset symptoms in MS patients, exploring their associated characteristics, comorbidities, and risk factors, to inform more personalized treatment approaches.

**Methods:** A cross-sectional observational study was conducted involving 100 participants diagnosed with MS. Data were collected through patient interviews, medical record reviews, and standardized diagnostic tests. Symptom clusters were identified using cluster analysis, and associations with comorbidities and risk factors were explored using chi-square tests and logistic regression analyses. Statistical analysis was performed using SPSS version 23.0.

**Results:** Three distinct symptom clusters were identified: Sensory Symptoms (45%), Motor Symptoms (35%), and Visual and Cognitive Symptoms (20%). The Sensory Symptoms cluster had a significant female predominance and was mainly associated with relapsing-remitting MS (RRMS). The Motor Symptoms cluster showed a higher prevalence of smoking and was more often linked to primary progressive MS (PPMS). The Visual and Cognitive Symptoms cluster had the highest prevalence of depression. Significant associations were found between symptom clusters and both comorbidities and risk factors.

**Conclusion:** The study revealed distinct clusters of onset symptoms in MS, each with unique demographic characteristics, comorbidities, and risk factors. These findings suggest the need for personalized treatment strategies tailored to the specific symptom profiles of MS patients.

**Recommendations:** Further research should explore the longitudinal impact of these symptom clusters on disease progression and treatment outcomes. Clinicians are encouraged to incorporate these findings into the development of individualized care plans for MS patients, focusing on early intervention strategies that address both physical and mental health needs.

**Keywords:** Multiple Sclerosis, Symptom Clusters, Comorbidities, Risk Factors, Personalized Treatment

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## Introduction

The progressive loss of neurological function is the hallmark of (MS), a chronic immune-mediated illness of the central nervous system. Affected about 2.8 million people worldwide, it is the most prevalent non-traumatic debilitating neurological condition among young adults [1]. Numerous symptoms, including as deficits in motor, sensory, visual, and cognitive functions, are indicative of the condition and differ greatly from person to person. At the outset of the illness, these symptoms frequently occur in clusters, and each cluster may have an impact on the course of the disease as well as the patient's quality of life [2]. The key phase that determines the clinical trajectory of (MS) is when symptoms first appear. To create focused interventions that can halt the advancement of the disease and enhance patient outcomes, it is crucial to comprehend the patterns of these symptoms and the risk factors that are linked to them. The significance of detecting symptom clusters at the outset of an illness has been emphasised by recent studies, as these clusters may be predictive of future impairment and treatment response [3]. For example, individuals whose initial symptoms are mostly motor may become disabled more quickly than those whose initial symptoms are sensory [4]. Furthermore, it has been demonstrated that comorbid conditions including anxiety and depression decrease the prognosis overall and aggravate MS symptoms [5]. Comprehensive investigations that look at the link between comorbidities, risk factors, and symptom clusters at the outset are still necessary despite tremendous progress in MS research. Prior research has frequently concentrated on a single symptom type or certain comorbidities without thoroughly examining the intricate relationships that exist between these variables [6]. Furthermore, whereas lifestyle factors like smoking have been linked to the onset and progression of MS, little is known about how they affect certain symptom clusters

[7]. Particularly in the early phases of the disease, an understanding of these relationships may result in more individualised and successful treatment plans. This study aimed to identify and analyze clusters of onset symptoms in MS patients, exploring their associated characteristics, comorbidities, and risk factors, to inform more personalized treatment approaches.

## Methodology

### Study Design

This study is a cross-sectional observational study design.

### Study Setting

The study was conducted at Tertiary Care Hospital, a leading neurological research center specializing in (MS) treatment and research. The hospital is equipped with advanced diagnostic tools and a team of experts in neuroimmunology and MS. The study was carried out over a period of 12 months, from January 2023 to December 2023.

### Participants

A total of 100 participants diagnosed with (MS) were recruited for this study. All participants were patients at the neurological research center, ensuring that they had access to uniform diagnostic criteria and care.

### Inclusion Criteria

- Adults aged 18-65 years.
- Diagnosed with (MS) according to the McDonald criteria.
- Onset of symptoms within the past 5 years.
- Able to provide informed consent and participate in the study procedures.

### Exclusion Criteria

- Individuals with other neurological disorders that could confound the diagnosis of MS.

- Participants with severe cognitive impairment that would prevent accurate self-reporting.
- Patients who have participated in other MS-related clinical trials within the past year.
- Pregnant or breastfeeding women.

### Bias

To minimize selection bias, participants were randomly selected from the patient database of the neurological research center. To address information bias, standardized questionnaires and diagnostic tools were used for data collection. Confounding factors such as age, gender, and comorbidities were controlled using statistical adjustments during data analysis.

### Data Collection

Data were collected through a combination of patient interviews, medical record reviews, and standardized diagnostic tests. Participants were asked to complete a detailed questionnaire covering their symptom onset, comorbid conditions, lifestyle factors, and medical history. Clinical data, including MRI findings and laboratory results, were extracted from medical records.

### Procedure

The study began with obtaining informed consent from all participants. After consent, participants were interviewed using a structured questionnaire. Clinical data were then collected from the participants' medical records. Data collection was completed in one session for each participant to minimize recall bias and ensure consistency.

### Statistical Analysis

Data were analysed with SPSS 23.0. Demographic and clinical factors were described by means, standard deviations, and frequencies. Cluster analysis was used to detect MS symptom clusters at onset. Chi-square testing and logistic regression examined symptom clusters, comorbidities, and risk variables. A p-value under 0.05 was significant.

### Results

A total of 100 participants were included in the study, with a mean age of 35.4 years (SD = 8.7). Of these, 60% were female (n = 60) and 40% were male (n = 40). The majority of participants (70%) were Caucasian, 20% were African American, and 10% belonged to other ethnic groups. The mean duration since the onset of (MS) symptoms was 3.2 years (SD = 1.1).

**Table 1: Demographic Characteristics of Participants**

Demographic Characteristic	Number of Participants (n = 100)	Percentage (%)
<b>Gender</b>		
Male	40	40%
Female	60	60%
<b>Ethnicity</b>		
Caucasian	70	70%
African American	20	20%
Other	10	10%
<b>Mean Age (years)</b>	35.4 (SD = 8.7)	
<b>Mean Duration of MS (years)</b>	3.2 (SD = 1.1)	

### Symptom Clusters

Cluster analysis revealed three distinct clusters of onset symptoms among the participants:

1. **Cluster 1: Sensory Symptoms (n = 45, 45%)**
  - Participants in this cluster predominantly reported sensory disturbances, such as numbness,

tingling, and paraesthesia. The mean age of participants in this cluster was 34.8 years (SD = 7.9), with a female predominance (70%, n = 31). The majority of participants in this cluster (65%) were classified as having relapsing-remitting MS.

## 2. Cluster 2: Motor Symptoms (n = 35, 35%)

- This cluster was characterized by motor deficits, including muscle weakness, spasticity, and gait disturbances. The mean age was 36.2 years (SD = 9.1), with an equal gender distribution (50% male, 50% female). A higher proportion

of participants in this cluster (40%) were classified as having primary progressive MS.

## 3. Cluster 3: Visual and Cognitive Symptoms (n = 20, 20%)

- Participants in this cluster primarily experienced visual disturbances, such as optic neuritis, and cognitive impairments, including memory loss and difficulty concentrating. The mean age was 35.9 years (SD = 9.3), with a slight female predominance (55%, n = 11). Most participants in this cluster (75%) had relapsing-remitting MS.

**Table 2: Symptom Clusters in Participants**

Symptom Cluster	Number of Participants (n = 100)	Percentage (%)	Mean Age (years)	Gender Distribution	MS Type Distribution
Cluster 1: Sensory Symptoms	45	45%	34.8 (SD = 7.9)	70% Female	65% RRMS
Cluster 2: Motor Symptoms	35	35%	36.2 (SD = 9.1)	50% Male, 50% Female	40% PPMS
Cluster 3: Visual and Cognitive Symptoms	20	20%	35.9 (SD = 9.3)	55% Female	75% RRMS

## Comorbidities and Risk Factors

The study also explored the prevalence of comorbidities and risk factors among the different symptom clusters. The most common comorbidities were depression, anxiety, and hypertension. Smoking was identified as a significant risk factor, especially in participants from the motor symptoms cluster.

- Depression** was more prevalent in Cluster 3 (Visual and Cognitive

Symptoms), with 60% of participants reporting a history of depression.

- Anxiety** was most common in Cluster 1 (Sensory Symptoms), affecting 50% of participants.
- Hypertension** was evenly distributed across all clusters, with an overall prevalence of 25%.
- Smoking** was reported by 30% of participants in Cluster 2 (Motor Symptoms), which was statistically significant ( $p = 0.03$ ) compared to the other clusters.

**Table 3: Prevalence of Comorbidities and Risk Factors across Symptom Clusters**

Comorbidity/Risk Factor	Cluster 1: Sensory (n = 45)	Cluster 2: Motor (n = 35)	Cluster 3: Visual & Cognitive (n = 20)	Total (n = 100)	p-value
Depression	18 (40%)	10 (29%)	12 (60%)	40%	0.04
Anxiety	22 (50%)	12 (34%)	6 (30%)	40%	0.06
Hypertension	12 (27%)	9 (26%)	4 (20%)	25%	0.08
Smoking	8 (18%)	10 (30%)	2 (10%)	20%	0.03

## Discussion

The participants were predominantly female (60%), with a mean age of 35.4 years. The study identified three distinct symptom clusters: Sensory Symptoms, Motor Symptoms, and Visual and Cognitive Symptoms, each presenting unique demographic characteristics and clinical profiles. The **Sensory Symptoms cluster** (45% of participants) was the largest group, characterized primarily by sensory disturbances such as numbness and tingling. This cluster had a significant female predominance (70%) and was mostly associated with the relapsing-remitting form of MS. The relatively high predominance of anxiety in this group (50%) suggests a possible link between sensory disturbances and psychological distress, which may require integrated therapeutic approaches that address both physical and mental health aspects.

The **Motor Symptoms cluster** (35% of participants) was notable for its even gender distribution and a higher incidence of primary progressive MS (PPMS), which is generally associated with a more aggressive disease course. This cluster also had the highest prevalence of smoking (30%), a statistically significant finding that suggests smoking may exacerbate motor-related MS symptoms or contribute to a more severe disease trajectory. The association between smoking and motor symptoms underscores the importance of smoking cessation interventions in MS management, particularly for patients presenting with motor deficits.

The **Visual and Cognitive Symptoms cluster** (20% of participants) was the smallest group but exhibited the highest predominance of depression (60%), which was significantly more common than in the other clusters. This finding suggests that visual and cognitive impairments in MS may be closely linked to mental health challenges, particularly depression. The predominance of MS in this group, along with the high depression rates, indicates

that patients with visual and cognitive symptoms may benefit from early psychological support and monitoring to prevent or mitigate depressive symptoms.

Ajdacic-Gross et al. (2021) used latent class analysis to group the different clusters of (MS) onset symptoms into six classes. These classes included more specialised ones like those with solitary onset symptoms like paraesthesia and visual issues, as well as a "multiple symptoms" class with high probabilities across a range of symptoms. The study discovered that various comorbidities and risk factors were linked to particular symptom clusters. For example, the fatigue-weakness and numerous symptoms classes were linked to problems like angina, skin diseases, migraines, and a greater prevalence of smoking, whereas the multiple symptoms class had higher comorbidity with other autoimmune disorders [9].

In a related study, Tao et al. (2018) investigated the impact of lifestyle factors on MS patients' age at symptom onset (ASO), namely marijuana and tobacco usage. The researchers found that whereas marijuana usage was connected to an earlier ASO by roughly six years, a history of tobacco use was associated with a delayed ASO by about three years. Additionally, compared to relapsing-onset MS cases, progressive-onset MS cases had an ASO that was over five years later, demonstrating the substantial impact of behavioural factors on the time of MS beginning [10].

Briggs et al.'s (2019) study looked at the variability in MS onset and how it relates to other risk factors, such as heredity, obesity, and smoking. According to the study, smoking, having a higher genetic risk score (GRS), and possessing the HLA-DRB1\*15:01 variant were all linked to an earlier age of onset. In addition, the onset age of primary progressive MS was often higher in men, obese people, and those with lower levels of education. These results highlight the intricate interactions between

distinct traits in the onset and development of (MS) [11].

### Conclusion

The study's findings highlight the heterogeneous nature of MS and the importance of personalized treatment strategies. Each symptom cluster presents distinct challenges that require tailored interventions, such as addressing anxiety in patients with sensory symptoms, promoting smoking cessation in those with motor symptoms, and providing mental health support for patients with visual and cognitive impairments. These results also suggest that lifestyle factors like smoking can significantly influence the clinical presentation and progression of MS, making lifestyle modification a critical component of comprehensive MS care.

### References

- Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of (MS) worldwide: Insights from the Atlas of MS, third edition. *Mult Scler J*. 2020 Dec;26(14):1816-1821.
- Filippi M, Amato MP, Centonze D, Gallo P, Gasperini C, Inglese M, Patti F, Pozzilli C, Preziosa P, Trojano M. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. *Journal of Neurology*. 2022 Oct;269(10):5382-94.
- Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of (MS) - success from bench to bedside. *Nat Rev Neurol*. 2019 Dec;15(12):761-776.
- Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet*. 2018 Apr 21;391(10130):1622-1636.
- Marrie RA, Reider N, Cohen J, Stuve O, Trojano M, Sorensen PS, et al. A systematic review of the incidence and prevalence of sleep disorders and seizure disorders in multiple sclerosis. *Mult Scler J*. 2018 Sep;24(10):1600-1606.
- Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep*. 2010 Aug 1;33(8):1061-1071.
- Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol*. 2017 Jan;13(1):25-36.
- Ajdacic-Gross V, Steinemann N, Horváth G, Rodgers S, Kaufmann M, Xu Y, et al. Onset Symptom Clusters in Multiple Sclerosis: Characteristics, Comorbidities, and Risk Factors. *Front Neurol*. 2021;12:693440.
- Tao C, Simpson S, Taylor B, Blizzard L, Lucas R, Ponsonby A, et al. Onset Symptoms, Tobacco Smoking, and Progressive-Onset Phenotype Are Associated With a Delayed Onset of Multiple Sclerosis, and Marijuana Use With an Earlier Onset. *Front Neurol*. 2018;9:418.
- Briggs F, Yu J, Davis MF, Jiangyang J, Fu S, Parrotta E, et al. (MS) risk factors contribute to onset heterogeneity. *Mult Scler Relat Disord*. 2019;28:11-16.