Trauma Monthly 2026; 31(3): 1864-1869

10.30491/tm.2026.588487.1950

Trauma Monthly

Research Article

Multiple Sclerosis and a History of Traumatic Brain Injury

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Received 2026-01-05 ; **Accepted** 2026-05-25; **Online Published** 2026-06-29

Abstract

Introduction: Given the potential impact of traumatic brain injury on the onset and severity of multiple sclerosis and its clinical importance, this study was conducted to compare the prevalence of multiple sclerosis in patients with a history of traumatic brain injury occurring before and after childhood and adolescence.

Method: This descriptive-analytical, cross-sectional study was conducted between 2024 and 2025 at the Multiple Sclerosis Center in Isfahan. The sample was selected through a census and included patients with a definitive diagnosis of multiple sclerosis during this period who were included in the study. Patients were interviewed using a checklist, and the severity of disability caused by multiple sclerosis was determined through examination. Finally, patients were divided into two groups, those with and without a history of traumatic brain injury, and compared.

Result: Significant differences were observed between the two groups in terms of age at MS onset, smoking, pregnancy history, and spinal injury history (P<0.05). The age of MS onset was notably lower in patients who sustained TBI during childhood. Furthermore, the number of smokers in this group was significantly higher than in the other groups (P<0.05). Pregnancy history was significantly less frequent among patients who experienced TBI during childhood. Conversely, spinal injury was significantly less common in this group. The mean time between TBI and MS onset differed significantly between the two groups (P<0.05). Patients who experienced TBI during childhood developed MS after an average of 18 years—a significantly longer interval than those in the other group.

Conclusion : Traumatic brain injury at a young age can be a factor in reducing the age of onset of MS.

Keywords: Traumatic Brain Injury, Multiple sclerosis, Severity of Disability.

Introduction

Multiple sclerosis (MS) reflects a complex interaction between environmental and genetic risk factors[1]. Some studies suggest an increased risk of developing MS following traumatic brain injury (TBI) after childhood, especially when the injury is repeated and requires extended hospitalization [2-4]. If TBI plays a role, it may do so by initiating etiological processes that lead to MS or by accelerating the clinical onset of a latent disease[5]. The hypothesized causal mechanism linking injury to MS involves the disruption of the blood-brain barrier. It is believed that TBI triggers a long-term secondary injury cascade driven by neuroinflammation, oxidative stress, and endoplasmic reticulum stress, all contributing to neurodegeneration[5,6]. Accordingly, reports indicate that TBI is often associated with neurodegenerative diseases, including early-onset Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and epilepsy[7,8]. Results from a 2014 meta-analysis showed a significant relationship between head injury before the age of 20 and the development of MS, particularly early-onset MS[9].

According to the World Health Organization (WHO), adolescence is defined as the period between 10 and 19 years of age, marking the transition from childhood to adulthood. Additionally, neurodevelopmental research has shown that brain maturation—particularly in the prefrontal cortex responsible for executive functions—

continues until late adolescence, approximately around 18 to 20 years of age[10,11].

Therefore, in this study, the age of 18 years was selected as the standard cut-off point to distinguish TBI occurring during the childhood–adolescence period from those occurring in adulthood, consistent with widely accepted clinical and epidemiological definitions.

Given the relative prevalence of TBI in children and the risk of its long-term complications, and due to the limited availability of comprehensive studies in this field, the present study was conducted to determine the prevalence of multiple sclerosis in patients with a history of traumatic brain injury occurring before and after childhood and adolescence.

Methods

The present study was a descriptive, cross-sectional, and comparative investigation that included newly diagnosed cases of multiple sclerosis in Isfahan. The sample was selected through a census method. It consisted of patients who had been definitively diagnosed with multiple sclerosis and referred to the Isfahan Multiple Sclerosis Center during the past year. A total of 400 patients were analyzed, 84 of whom (21%) reported a previous TBI. Among these, 37 individuals (44%) experienced traumatic brain injury between the ages of 0 and 18 years (G1). 47 individuals (56%) experienced TBI after age 18 years (G2) (Figure 1).

Patients included in the study were diagnosed with MS by their treating physician, based on the McDonald criteria, and had a history of traumatic brain injury in childhood. Patients with mental health issues or conditions such as Alzheimer's or dementia were excluded. Patients who were admitted to hospitals outside the city of Isfahan following the trauma, as well as those for whom trauma-related information was not accessible, were also excluded from the study.

All patients were interviewed using a checklist at the time of admission. The checklist collected data on gender, age, age at MS onset, disability severity, and other relevant details.

After the patients confirmed having experienced trauma, information regarding the time, mechanism, and hospital of admission was obtained. Subsequently, data from the pre-hospital emergency system (for those involved in traffic accidents) and from the hospital information system where the patient had been admitted (for both traffic and non-traffic incidents) were used to collect details such as the Glasgow Coma Scale (GCS).

In fact, information related to the patients' trauma was recorded based on the patient's own statements, then followed up through her medical record at the hospital where she was sent or hospitalized.

The Expanded Disability Status Scale (EDSS) is a method used to assess the degree of disability caused by MS. A higher score on this scale indicates a more severe impact of MS.

A common classification of acute traumatic brain injury: Severe, GCS 3 to 8. Moderate, GCS 9 to 12. Mild, GCS 13 to 15.

The data were analyzed using SPSS software version 16, with a significance level of $P<0.05$. Quantitative data were reported as means and standard deviations, while qualitative data were presented as distributions and percentages. Finally, the data were compared between patients in the two age groups using chi-square and t-tests.

Ethical approval was obtained from Isfahan University of Medical Sciences under code IR.MUI.MED.REC.1400.147, and all guidelines of the Helsinki Declaration were followed. The study's objectives were fully explained to the patients, and written informed consent was obtained from all participants.

Results

The demographic and clinical characteristics of MS patients with a history of TBI are presented in Table 1. Significant differences were observed between the two groups in terms of age at MS onset, smoking, pregnancy history and spinal injury history ($P<0.05$). The age of MS onset was notably lower in patients who sustained TBI during childhood. Furthermore, the number of smokers in this group was significantly higher than the others ($P<0.05$). Pregnancy history was significantly less frequent among patients who experienced TBI during childhood. Conversely, spinal injury was significantly less common in this group.

The mean time between TBI and MS onset differed significantly between the two groups ($P<0.05$). Patients who experienced TBI during childhood developed MS

after an average of 18 years—a significantly longer interval than those in the other group.

For determining the impact of TBI on each of the MS-related variables, a univariate and multivariate regression analysis. Variables with a p-value of less than 0.05 in the univariate regression were included in the multivariate regression analysis. The results of the multivariate regression are shown in Table (2).

Figure 2 shows a significant relationship between the age at which TBI occurred and MS diagnosis (P = 0.0001<0.05). Three children, on average 6 years after experiencing a TBI, were diagnosed with multiple sclerosis MS.

Age at the time of traumatic brain injury (under 18 years) significantly influenced the type of multiple sclerosis in patients with an odds ratio of 2.4.

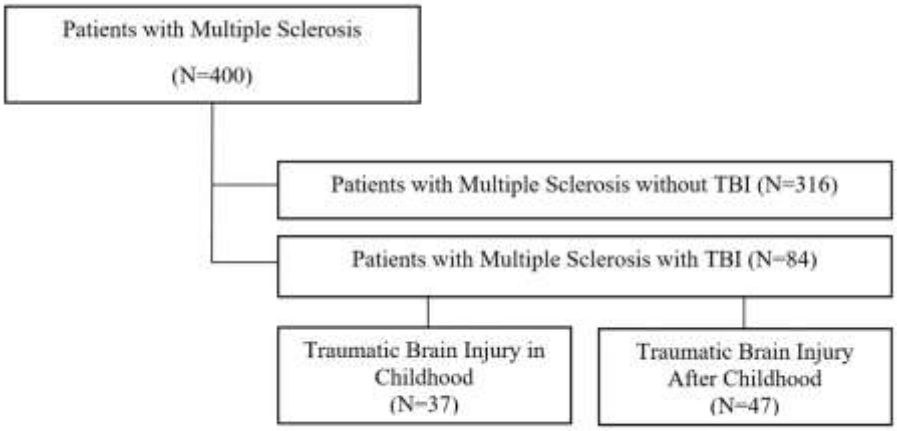

Fig.1 Subject's enrollment, randomization, and data gathering process in both groups

Table 1. Demographic and Clinical Characteristics of MS Patients

Variable	G1 (n=37)	G2 (n=47)	Total (n=84)	P value
Gender, Female, n(%)	27 (73)	40 (85.1)	67 (79.8)	0.169
Age, year, (mean±SD)	35.48±9.18	44.97±8.62	40.79±10	0.0001
Age of MS, year, (mean±SD)	28.54±7.37	38.40±8.81	34±9.5	0.0001
Age of TBI, year, (mean±SD)	10.62±5.10	31±8.45	22±12.44	0.001
BMI, (mean±SD)	23.78±4.3	24.21±3.46	24±3.83	0.613
Smocking, yes, n(%)	12 (32.4)	5 (10.6)	17 (20.2)	0.014
Pregnancy History/ Female, yes, n (%)	10/ 27 (27)	30/ 40 (75)	40/ 67 (59.7)	0.001
Vertebral Trauma, yes, n(%)	3 (8.1)	19 (40.4)	22 (26.2)	0.001
Type of TBI, n(%)				
Mild	21 (56.8)	27 (57.4)	48 (57.1)	0.973
Moderate	7 (18.9)	8 (17)	15 (17.9)	
Severe	9 (24.3)	12 (25.5)	21 (25)	
Type of MS, n(%)				
RRMS	35 (94.6)	41 (87.2)	77 (91.6)	0.343
PPMS	0	3 (6.4)	3 (3.6)	
SPMS	2 (5.4)	2 (4.3)	4 (4.8)	
EDSS, (mean±SD)	1.18±1.88	1.72±2	1.48±1.99	0.226
Duration Between TBI to MS, year, (mean±SD)	17.91±9.86	7.36±6.31	12±9.57	0.0001

n: number, TBI: Traumatic Brain Injury, SD: Standard Deviation, BMI: Body Mass Index, MS: Multiple Sclerosis, RRMS: Relapsing-Remitting MS, SPMS: Secondary-Progressive MS, PPMS: Primary Progressive MS, CIS: Clinically Isolated Syndrome, EDSS: Expanded Disability Status Scale, G1: traumatic brain injury in childhood (ages 0-18), G2: TBI after childhood (aged 18 and older).

Table 2. Multivariate regression

Variables (Type of MS)	Reference	Adjusted OR (95% CI)	P value
BMI	-	3.069 (0.389-24.234)	0.287
EDSS	-	0.117 (0.101-0.765)	0.036 *
Pregnancy History	Yes	9.885 (0.901-108.465)	0.061
Vertebral Trauma	Yes	1.145 (0.141-9.299)	0.899
Type of TBI	Severe	7.241 (0.369-142.169)	0.192
Age at TBI	<18	2.406 (2.030-5.410)	0.045 *
OR: Odds Ratio, CI: Confidence Interval, * Significant P value			

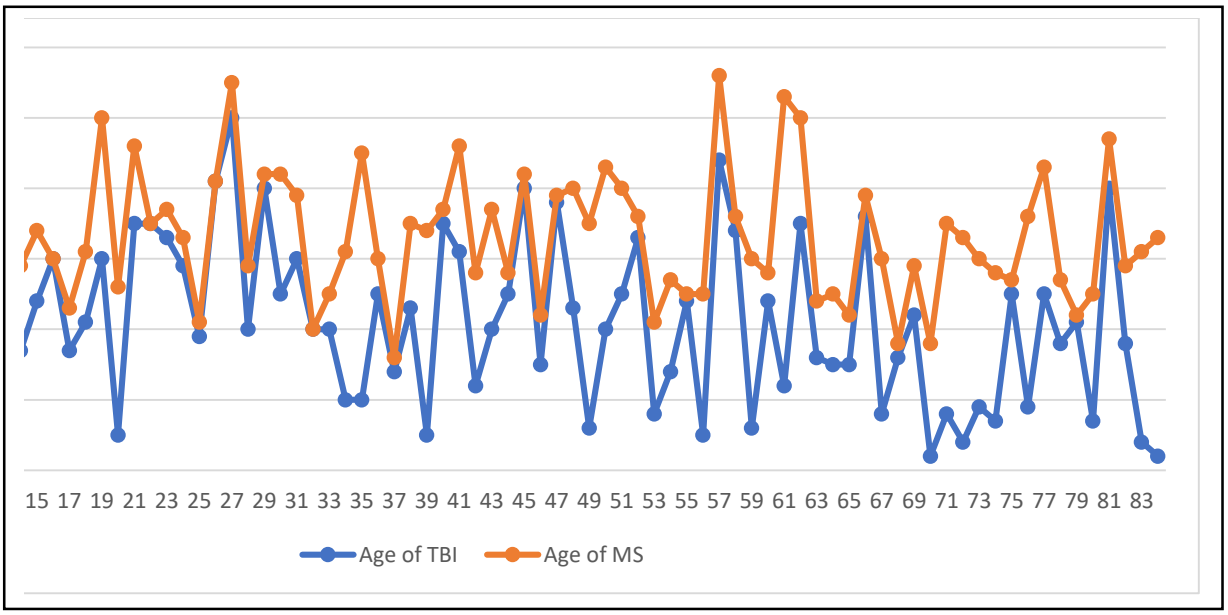

Figure 2. TBI and MS

Discussion

The exact cause of MS remains unknown, and previous studies have presented conflicting results regarding the relationship between MS and head or spinal cord injuries[8,9]. This study aimed to explore the association between MS and a history of TBI. Patients diagnosed with MS were divided into two groups: one group included patients who had experienced TBI during childhood, while the second group comprised those who sustained TBI after childhood. The results showed a significant correlation between the age at which the TBI occurred and the age of MS diagnosis.

According to Etemadifar (2016)[13], the mean (±standard deviation) age of MS onset in Iran was 33.1 (±9.5) years. The present study similarly demonstrated a mean age of MS diagnosis of 34 years among all patients. A notable finding was that patients who had sustained TBI during childhood were diagnosed with MS at an average age of 28 years, while those who had experienced TBI after childhood were diagnosed at an average age of 38 years—both earlier and later than the national average for MS onset, respectively.

Fattahi (2021)[14], in a study conducted in Tehran, observed that the incidence rate of MS follows an upward trajectory starting at 20 years of age, peaking at

25 years. After this peak, the incidence rate begins to decline, reaching its lowest point between the ages of 55 and 59. Eskandarieh (2023)[15] found that the average age of MS onset is 29 years. Similarly, Ghajarzadeh (2020)[16], in a study conducted in Qazvin, reported that the average age of MS onset in that city was also around 29 years, consistent with the diagnosis age of patients who had experienced TBI during childhood in this study. However, the diagnosis age for the other group was higher than that observed in the Qazvin study.

In another study conducted in Chaharmahal and Bakhtiari, Omrani (2023)[17] reported an average age of MS diagnosis of 37 years, which is consistent with the diagnosis age of patients who had experienced TBI after childhood in the current study. However, the age of MS diagnosis in the other group was lower than that observed in the Chaharmahal and Bakhtiari study. Cheraghmakani (2020)[18] reported an average age of MS onset of 32 years in Mazandaran .

Johansson (2024)[19] A Swedish population-based case-control study found that a history of head trauma was associated with a 30% increased risk of future MS, and that the risk of MS increased with the number of head traumas. Finally, head trauma in individuals with genetic risk factors was associated with an 18-fold increased risk of MS compared with individuals with neither genetic risk factors nor a history of head trauma. One limitation of this study is that, due to the nature of the study, it was not possible to use a control group.

Conclusion

Traumatic brain injury at a young age can be a factor in reducing the age of onset of MS.

Conflict of Interest Disclosures Funding Sources

The authors declare no conflict of interest.

Authors' Contributions

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical Statement

The current study was approved by the Isfahan University of Medical Sciences Ethics Committee with the code of IR.MUI.MED.REC.1400.147.

Declaration of Generative AI and AI-assisted technologies

During the preparation of this work, the authors did not use Chatgpt to write the manuscript.

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