

Clinical Profile and Predictors of Corticosteroid-Related Adverse Effects in Patients with Multiple Sclerosis

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ABSTRACT

High-dose intravenous methylprednisolone (IVMP) is widely recommended as first-line therapy for clinically significant relapses in multiple sclerosis (MS). Despite its well-established efficacy in accelerating neurological recovery, treatment is frequently accompanied by a variety of adverse effects that may influence patient comfort, adherence, and overall quality of life. However, the frequency, clinical spectrum, and determinants of these corticosteroid-related adverse effects have not been comprehensively evaluated in routine clinical practice.

To determine the frequency of corticosteroid-related adverse effects and identify independent predictors of the overall adverse effect burden in patients with multiple sclerosis receiving high-dose intravenous methylprednisolone. In this prospective observational study, 71 patients with clinically definite MS treated with high-dose IVMP for acute relapse were enrolled. Corticosteroid-related adverse effects were assessed using a standardized questionnaire, and demographic and clinical variables were analyzed using Spearman correlation and multivariable linear regression.

The most frequently reported adverse effects were fatigue (77.5%), metallic taste (70.4%), muscle weakness (66.2%), mood disturbance (53.5%), hot flushes (49.3%), and insomnia (46.5%). BMI showed a significant positive correlation with the total adverse effect score ($\rho = 0.362$, $p = 0.002$) and remained the only independent predictor of the overall adverse effect burden in the multivariable regression analysis (standardized $\beta = 0.361$, $p = 0.003$).

Corticosteroid-related adverse effects are common among patients with multiple sclerosis receiving high-dose intravenous methylprednisolone therapy. BMI was identified as the only independent predictor of the overall adverse effect burden, suggesting that patients with higher BMI may benefit from closer clinical monitoring during relapse treatment.

Keywords: Multiple sclerosis, Intravenous methylprednisolone, Corticosteroid-related adverse effects, Body mass index

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and immune-mediated disorder of the central nervous system characterized by demyelination, axonal damage, and progressive neurodegeneration (1). Although advances in disease-modifying therapies have substantially reduced inflammatory disease activity, acute relapses continue to represent an important cause of temporary neurological disability and impaired quality of life (1). Consequently, timely treatment of clinically significant relapses remains a fundamental component of MS management (2).

Current international guidelines recommend high-dose intravenous methylprednisolone (IVMP), most commonly 1000 mg daily for 3–5 days, as the preferred treatment for disabling MS relapses

(3). Corticosteroids reduce inflammatory activity through several complementary mechanisms, including stabilization of the blood-brain barrier, suppression of pro-inflammatory cytokines, inhibition of leukocyte migration into the central nervous system, and modulation of T-cell function. Although IVMP accelerates clinical recovery from relapses, it has not been shown to influence the long-term course of the disease (3).

Although high-dose corticosteroids are highly effective for the treatment of acute MS relapses, their use is frequently accompanied by a variety of adverse effects affecting multiple organ systems. Commonly encountered adverse effects include sleep disturbances, mood changes, gastrointestinal complaints, flushing, acne, weight gain, proximal muscle weakness, Cushingoid features, hyperglycemia, hypertension, electrolyte

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imbalance, and an increased risk of infection (4). While these adverse effects are generally mild and resolve after treatment, repeated exposure to corticosteroids may lead to cumulative toxicity, potentially compromising patient adherence and quality of life (4,5). Furthermore, the occurrence and severity of adverse effects are influenced not only by treatment-related factors, such as dose and duration, but also by individual patient characteristics (5).

Previous studies investigating corticosteroid safety in patients with MS have primarily focused on severe or long-term complications, such as avascular necrosis, osteoporosis, cardiovascular events, and serious allergic reactions (6). Although these complications are clinically important, they occur relatively infrequently and do not fully reflect the adverse effects encountered during routine clinical practice. In contrast, common but clinically relevant symptoms—including fatigue, metallic taste, insomnia, flushing, gastrointestinal discomfort, mood changes, and muscle weakness—have received considerably less attention (6,7). Furthermore, few studies have evaluated the overall burden of corticosteroid-related adverse effects using a comprehensive clinical assessment or investigated independent predictors that may identify patients at increased risk (7).

Therefore, the present study aimed to determine the frequency and clinical profile of corticosteroid-related adverse effects and to identify independent clinical predictors of the overall adverse effect burden in patients with multiple sclerosis receiving high-dose intravenous methylprednisolone therapy. We hypothesized that corticosteroid-related adverse effects are common in this patient population and that clinical characteristics may independently predict the burden of these adverse effects.

Materials and Methods

Study Design and Participants: This prospective observational study was conducted at the neurology outpatient clinics of two tertiary referral centers following approval by the local Institutional Ethics Committee.

Consecutive adult patients (≥ 18 years) with clinically definite multiple sclerosis (MS), diagnosed according to the 2017 revised McDonald criteria, who presented with an acute MS relapse requiring high-dose intravenous methylprednisolone (IVMP) treatment were prospectively enrolled.

Patients with medical conditions that could independently predispose them to corticosteroid-related complications, including previous major trauma, chronic alcoholism, pregnancy, oral contraceptive use, previous radiotherapy, coagulation disorders, or other disorders affecting bone metabolism, were excluded.

Data Collection: Demographic and clinical data were prospectively collected for all participants, including age, sex, body mass index (BMI), Expanded Disability Status Scale (EDSS) score, MS phenotype, duration of corticosteroid treatment, duration of corticosteroid exposure, relapse frequency requiring corticosteroid therapy, and disease-modifying treatment.

Following completion of IVMP therapy, corticosteroid-related adverse effects were systematically evaluated by the same neurologist using a standardized questionnaire specifically designed for this study. The questionnaire was administered using identical predefined questions in all patients, thereby ensuring consistency of data collection and reducing assessment bias. Patients were systematically questioned regarding each predefined adverse effect rather than relying solely on spontaneous self-reporting. The evaluated adverse effects included flushing, hot flushes, metallic taste, palpitations, dyspepsia, allergic reactions, skin rash, fatigue, muscle weakness, acne, hypertrichosis, weight gain, insomnia, mood disturbances, menstrual irregularities (in female patients), skin thinning, Cushingoid appearance, striae, osteoporosis, infections, and other clinically relevant adverse effects. Each predefined adverse effect was coded as either present or absent. An overall adverse effect score was subsequently obtained by summing the number of reported adverse effects for each participant.

Statistical Analysis: Statistical analyses were conducted using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Data distribution was evaluated by the Shapiro–Wilk test in combination with histogram inspection and normal probability (Q–Q) plots. Continuous variables are reported as mean $\pm$ standard deviation (SD) or median (Q1–Q3), according to their distribution, whereas categorical variables are presented as counts and percentages. Associations between clinical characteristics and the total adverse effect score were assessed using Spearman's rank correlation analysis. To determine independent predictors of the total adverse effect score, clinically relevant variables (age, sex, BMI, EDSS score, corticosteroid

treatment duration, duration of corticosteroid exposure, relapse frequency, and MS phenotype) were simultaneously entered into a multivariable linear regression model. Standardized regression coefficients (β), 95% confidence intervals (CI), and corresponding *p* values were reported. Variance inflation factors (VIFs) were calculated to assess multicollinearity. Statistical significance was defined as a two-tailed *p* value <0.05 .

Results

A total of 71 patients with multiple sclerosis who received high-dose intravenous methylprednisolone therapy were included in the study. The demographic and clinical characteristics of the study population are presented in Table 1. The mean age of the patients was 35.5 ± 10.0 years (range, 18–69 years), and 50 patients (70.4%) were female. The mean body mass index (BMI) was 24.7 ± 4.2 kg/m² (range, 17.8–36.4 kg/m²). The median Expanded Disability Status Scale (EDSS) score was 1.5 (Q1–Q3: 0.0–3.0), with values ranging from 0.0 to 6.0. The median duration of corticosteroid treatment was 5 days (Q1–Q3: 3–5 days), while the median duration of corticosteroid exposure was 1 year (Q1–Q3: 1–2 years). The median number of relapses was 1 (Q1–Q3: 1–2). Regarding disease phenotype, 58 patients (81.7%) had relapsing-remitting multiple sclerosis (RRMS), 7 (9.9%) had secondary progressive multiple sclerosis (SPMS), and 6 (8.5%) had primary progressive multiple sclerosis (PPMS).

The frequency and distribution of corticosteroid-related adverse effects are presented in Table 2. Fatigue was the most frequently reported adverse effect, occurring in 55 patients (77.5%), followed by metallic taste in 50 patients (70.4%) and muscle weakness in 47 patients (66.2%). Mood disturbance was observed in 38 patients (53.5%), while hot flushes and insomnia were reported by 35 (49.3%) and 33 (46.5%) patients, respectively. Less frequent adverse effects included flushing (29.6%), palpitations (28.2%), acne (28.2%), dyspepsia (26.8%), weight gain (26.8%), infection (21.1%), skin thinning (16.9%), Cushingoid appearance (16.9%), menstrual irregularity in 10 of 50 female patients (20.0%), allergy (14.1%), hypertrichosis (12.7%), and striae (5.6%).

Spearman correlation analysis demonstrated a significant positive correlation between BMI and the total adverse effect score ($\rho = 0.362$, $p = 0.002$) (Table 3). No significant correlations were identified between the total adverse effect score

and age, EDSS score, steroid treatment duration, cumulative steroid exposure, or number of relapses (all $p > 0.05$).

Multivariable linear regression analysis was performed to identify independent predictors of the total adverse effect score (Table 4). After adjustment for age, sex, EDSS score, steroid treatment duration, cumulative steroid exposure, number of relapses, and MS phenotype, BMI remained the only independent predictor of the total adverse effect score (standardized $\beta = 0.361$, $p = 0.003$). None of the remaining clinical variables demonstrated a statistically significant association with the total adverse effect score. The regression model explained 17.6% of the variance in the total adverse effect score ($R^2 = 0.176$; adjusted $R^2 = 0.054$), and no evidence of problematic multicollinearity was observed among the independent variables.

Discussion

The present prospective observational study demonstrated that corticosteroid-related adverse effects are highly prevalent among patients with multiple sclerosis receiving high-dose intravenous methylprednisolone therapy. Fatigue, metallic taste, muscle weakness, mood disturbances, hot flushes, and insomnia were the most frequently reported adverse effects. Among the evaluated clinical variables, body mass index (BMI) emerged as the only independent predictor of the overall corticosteroid-related adverse effect burden, whereas age, sex, disability level, disease phenotype, corticosteroid treatment duration, duration of corticosteroid exposure, and relapse frequency were not independently associated with adverse effect burden. These findings indicate that while corticosteroid-related adverse effects are common during routine relapse treatment, susceptibility to these adverse effects may be influenced more by individual patient characteristics than by disease-related or treatment-related factors.

In the present study, fatigue, metallic taste, and muscle weakness were the most frequently reported adverse effects following high-dose IVMP therapy, followed by mood disturbances, hot flushes, and insomnia. These findings are generally consistent with previous studies demonstrating that high-dose IVMP is commonly associated with a broad spectrum of transient but clinically relevant adverse effects during relapse treatment in patients with MS. In a prospective multicenter study by Peter Joseph Jongen et al.,

Table 1: Demographic and Clinical Characteristics of the Study Population (n = 71)

Variable	Value
Age (years), mean $\pm$ SD	35.5 $\pm$ 10.0 (18–69)
Female sex, n (%)	50 (70.4)
Male sex, n (%)	21 (29.6)
Body mass index (kg/m ²), mean $\pm$ SD	24.7 $\pm$ 4.2 (17.8–36.4)
EDSS score, median (Q1–Q3)	1.5 (0.0–3.0), range 0.0–6.0
Steroid treatment duration (days), median (Q1–Q3)	5.0 (3.0–5.0), range 1–10
Duration of corticosteroid exposure (years), median (Q1–Q3)	1.0 (1.0–2.0), range 1–6
Number of relapses, median (Q1–Q3)	1.0 (1.0–2.0), range 1–5
RRMS, n (%)	58 (81.7)
SPMS, n (%)	7 (9.9)
PPMS, n (%)	6 (8.5)

Abbreviations: BMI, body mass index; EDSS, Expanded Disability Status Scale; SD, standard deviation; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis. Continuous variables are presented as mean $\pm$ standard deviation (SD) with range or as median (Q1–Q3) with range, according to data distribution. Categorical variables are presented as number (%).

Table 2: Frequency of Corticosteroid-Related Adverse Effects in Patients with Multiple Sclerosis Receiving Intravenous Methylprednisolone Therapy

Adverse effect	n	%
Fatigue	55	77.5
Metallic taste	50	70.4
Muscle weakness	47	66.2
Mood disturbance	38	53.5
Hot flushes	35	49.3
Insomnia	33	46.5
Flushing	21	29.6
Palpitations	20	28.2
Acne	20	28.2
Dyspepsia	19	26.8
Weight gain	19	26.8
Infection	15	21.1
Skin thinning	12	16.9
Cushingoid appearance	12	16.9
Menstrual irregularity*	10	20.0
Allergy	10	14.1
Hypertrichosis	9	12.7
Striae	4	5.6

Abbreviations: IVMP, intravenous methylprednisolone. Data are presented as number (n) and percentage (%). Percentages were calculated based on the total study population (n = 71), except for menstrual irregularity, which was evaluated only in female patients (n = 50); therefore, its percentage was calculated using the female subgroup as the denominator

change in taste, facial flushing, gastrointestinal discomfort, and sleep disturbance were among the most frequently reported adverse effects following

IVMP administration, highlighting that subjective symptoms occur in the majority of treated patients (8). Similarly, a more recent review of relapse

Table 3: Spearman Correlation Analysis Between Total Adverse Effect Score and Clinical Variables

Variable	Spearman's correlation coefficient (ρ)	p value
Age	-0.151	0.210
Body mass index (BMI)	0.362	0.002
EDSS score	-0.173	0.149
Steroid treatment duration (days)	0.001	0.994
Duration of corticosteroid exposure (years)	0.019	0.875
Number of relapses	0.058	0.630

Abbreviations: BMI, body mass index; EDSS, Expanded Disability Status Scale.

Spearman's rank correlation analysis was performed to evaluate the association between the total adverse effect score and clinical variables. Statistically significant correlations ($p < 0.05$) are shown in bold

management in MS identified metallic taste, hot flushes, anxiety, and insomnia as the most common short-term adverse effects of high-dose corticosteroid therapy (9). Although the relative frequencies of individual adverse effects differed slightly between studies, likely reflecting differences in study design, assessment methods, treatment regimens, and patient populations, the overall pattern consistently indicates that corticosteroid treatment is accompanied by a high burden of predominantly transient adverse effects. These observations emphasize the importance of systematically informing patients about expected adverse effects before treatment and actively monitoring these symptoms during and shortly after IVMP administration to improve treatment tolerance and adherence.

The most notable finding of the present study was that BMI emerged as the only independent predictor of the overall adverse effect burden following high-dose IVMP therapy. To our knowledge, few studies have specifically evaluated BMI as a determinant of patient-reported corticosteroid-related adverse effects in patients with MS, making direct comparisons with previous reports difficult. Nevertheless, several biological mechanisms may explain this association. Obesity has been shown to alter glucocorticoid pharmacokinetics and pharmacodynamics, and obese individuals may exhibit increased sensitivity to the metabolic and systemic effects of corticosteroids despite variable drug exposure (10). In addition, obesity is characterized by a chronic low-grade inflammatory state mediated by adipokines such as leptin and pro-inflammatory cytokines, which may enhance susceptibility to treatment-related adverse effects and influence symptom perception. In patients with MS, obesity has also been associated with increased inflammatory activity and worse clinical

outcomes, suggesting that excess adiposity may modify the biological response to corticosteroid therapy (11). Although the exact mechanisms remain uncertain, our findings support the hypothesis that BMI may influence susceptibility to corticosteroid-related adverse effects following high-dose IVMP therapy (12).

In contrast to BMI, age, sex, disability level, disease phenotype, corticosteroid treatment duration, duration of corticosteroid exposure, and relapse frequency were not independently associated with the overall adverse effect burden in the present study. These findings are broadly consistent with previous reports demonstrating considerable heterogeneity in the frequency and severity of corticosteroid-related adverse effects among patients with MS receiving IVMP therapy, suggesting substantial interindividual variability in treatment response (8). This observation may indicate that patient-specific biological factors, including differences in glucocorticoid sensitivity, genetic susceptibility, psychological factors, and symptom perception, contribute more substantially to the experience of adverse effects than conventional clinical measures such as EDSS score or relapse history. Accordingly, routine clinical characteristics alone may be insufficient to identify patients at increased risk of corticosteroid-related adverse effects during relapse treatment (8).

The findings of the present study have several potential clinical implications. Given the high frequency of patient-reported adverse effects following high-dose IVMP therapy, clinicians should routinely inform patients about the expected short-term adverse effects before initiating treatment and actively inquire about these symptoms during follow-up. Early recognition and appropriate management of corticosteroid-related adverse effects may improve

Table 4: Multivariable Linear Regression Analysis for Factors Associated with Total Adverse Effect Score

Variable	Standardized β	SE	95% CI	p value	VIF
Age	-0.004	0.061	-0.124 to 0.121	0.985	2.78
Male sex	-0.084	0.949	-2.478 to 1.317	0.543	1.41
Body mass index (BMI)	0.361	0.087	0.095 to 0.444	0.003	1.01
EDSS score	-0.168	0.465	-1.211 to 0.648	0.548	5.73
Steroid treatment duration (days)	0.012	0.208	-0.396 to 0.436	0.923	1.09
Duration of corticosteroid exposure (years)	-0.062	0.477	-1.150 to 0.757	0.682	1.67
Number of relapses	0.048	0.557	-0.934 to 1.294	0.748	1.66
SPMS (vs RRMS)	0.045	1.820	-3.165 to 4.115	0.795	2.21
PPMS (vs RRMS)	-0.053	2.015	-4.628 to 3.432	0.768	2.36

Model statistics

$R^2 = 0.176$

Adjusted $R^2 = 0.054$

$F = 1.444$

Overall model $p = 0.190$

Abbreviations: BMI, body mass index; EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; VIF, variance inflation factor.

treatment tolerance, reduce patient anxiety, and enhance adherence to relapse therapy (13). Furthermore, the identification of BMI as an independent predictor of the overall adverse effect burden suggests that patients with higher BMI may benefit from closer clinical monitoring and individualized counseling during corticosteroid treatment. Current recommendations for the management of MS relapses emphasize not only the prompt initiation of high-dose corticosteroid therapy but also careful patient education and monitoring to optimize treatment outcomes and minimize treatment-related complications (13).

Several limitations of the present study should be acknowledged. First, although the study was prospectively conducted, it included a relatively small sample size despite recruitment from two tertiary referral centers, which may limit the generalizability of the findings. Second, adverse effects were assessed using a standardized patient questionnaire rather than objective clinical or laboratory measures; therefore, the assessment of adverse effect burden remained dependent on

subjective symptom reporting. Third, the study focused primarily on commonly encountered short-term adverse effects following IVMP therapy, whereas uncommon but potentially serious complications were not specifically evaluated (12,13). Finally, although BMI emerged as the only independent predictor in the multivariable regression analysis, the regression model included several covariates relative to the sample size, resulting in a noticeable difference between R^2 and adjusted R^2 . Therefore, the possibility of model overfitting cannot be excluded, and the association between BMI and the overall adverse effect burden should be interpreted with caution until confirmed in larger prospective cohorts. In addition, the overall explanatory power of the model was modest, suggesting that additional biological, treatment-related, and patient-specific factors not evaluated in the present study are also likely to contribute to the overall burden of corticosteroid-related adverse effects. Future multicenter studies with larger cohorts incorporating objective clinical,

laboratory, and biological assessments are warranted to further clarify the determinants of corticosteroid-related adverse effects in patients with multiple sclerosis.

In conclusion, corticosteroid-related adverse effects are common among patients with multiple sclerosis receiving high-dose intravenous methylprednisolone therapy, with fatigue, metallic taste, muscle weakness, mood disturbances, hot flushes, and insomnia being the most frequently reported symptoms. Among the evaluated clinical variables, body mass index emerged as the only independent predictor of the overall adverse effect burden, suggesting that individual patient characteristics may influence susceptibility to corticosteroid-related adverse effects. These findings highlight the importance of systematic assessment and proactive management of adverse effects during relapse treatment and suggest that patients with higher BMI may benefit from closer clinical monitoring and individualized counseling. Further prospective multicenter studies are needed to validate these findings and to better identify patients at increased risk for corticosteroid-related adverse effects.

Ethics Committee Approval: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Van Yüzüncü Yıl University Clinical Research Ethics Committee (Date: 16.08.2023; Decision No: 03).

Conflict of Interest: The authors declare that they have no conflict of interest.

Patient Consent: Written informed consent was obtained from all participants prior to enrollment.

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