



## Cerebrovascular Comorbidities in Multiple Sclerosis: Analysis of the Nationwide Inpatient Sample

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### Abstract

**Objective:** To evaluate the risk of cerebrovascular comorbidities in Multiple Sclerosis (MS) in the US.

**Methods:** A retrospective cohort analysis from 1988 to 2012 of the Nationwide Inpatient Sample. Records were identified with a primary diagnosis of cerebrovascular disease (ischemic stroke, hemorrhagic stroke and non-ruptured aneurysm) and a secondary diagnosis of MS. Prevalence of MS in this cohort versus the general population was compared using indirect adjustment. We calculated the Standardized Prevalence Ratio (SPR), adjusted for sex and age.

**Results:** Among 2,574,503 admissions for cerebrovascular events, 0.18% had MS. When corrected to age and gender and the SPR of MS among patients with ischemic stroke was 1.6218 (95% confidence interval [CI] 1.6188, 1.6249); for hemorrhagic stroke 1.3030 (1.2966, 1.3095); and unruptured aneurysm was 3.2359 (3.1943, 3.2781).

**Conclusion:** In this national US hospital cohort, the prevalence of MS in the population with cerebrovascular events was overrepresented, suggesting that MS may increase the risk for cerebrovascular events.

**Keywords:** Multiple sclerosis; Stroke; Ischemic stroke; Hemorrhagic stroke; Aneurysm

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### Introduction

Multiple Sclerosis (MS) is considered to be an autoimmune inflammatory demyelination disease of the central nervous system that leads to destruction of the myelin sheath and axonal loss and resulting in progressive accumulation of disability. Previous nationwide studies have reported an increased risk of stroke in patients with MS compared to the normal population [1-4]. The cause of this increase has not been determined.

Ischemic stroke in MS has been found to be elevated in multiple national studies in Taiwan [1], Sweden [2,3] and Denmark [4]; however, no nationwide study of stroke in MS has been done in the US. Other cerebrovascular events, including Intracerebral Hemorrhagic Stroke (ICH) and unruptured aneurysms, have not been previously studied at a national level. Understanding if and which other cerebrovascular comorbidities are increased in MS may help explain why ischemic strokes are increased and how to prevent them in the MS population. Because the national prevalence of cerebrovascular disease among people with MS has not been studied in the US population, we explored this using the Nationwide Inpatient Sample (NIS, AHRQ.gov).

The purpose of this study was to analyze all admissions for cerebrovascular events over the last 24 years to determine if the prevalence of MS is increased in these cases compared with the general population.

### Methods

A retrospective cohort analysis of the NIS from 1988 to 2012 was used to identify all admissions for cerebrovascular events. The NIS is a stratified 20% sample of all acute care hospitalizations in the US and is available from 1988. It is the largest publicly available all-payer hospital inpatient database in the US. It is used to study health care utilization, access, charges, quality, outcomes and disease burden [5]. Clinical Classification Software (CCS) redacts the 13,000 + International Classification of Diseases Ninth Revision (ICD9) diagnostic codes into 260 categories. CCS was used to identify admission records with a primary diagnosis of stroke (CCS 109). Then ICD9 was used

to further refine the primary diagnosis, identifying admissions with a primary diagnosis of ischemic stroke (ICD9 code 434.xx), ICH (ICD9 codes 431 and 432) and unruptured aneurysm (ICD9 code 437.3). The secondary diagnosis of MS was identified using CCS 80 (ICD9 340).

**Data cleansing and statistical analysis**

The initial cohort was 2,922,817 admissions. Records with missing data for age, gender and disposition were culled [6,7]. The initial age range was 0 to 123 years. We eliminated the bottom and top 5% of cases based on age as these were highly likely to be miscoded, resulting in a range of 29 to 95 years. In a similar fashion records with a length of stay >57 days (99<sup>th</sup> percentile) were dropped since the data were skewed (mean length of stay=7.4 days, median=5, range 0 to 364). Because race and ethnicity were suppressed in ~35% of the NIS records we did not use this to calculate the Standardized Prevalence Ratio (SPR).

Statistical analysis was performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA). Comparison of categorical data was done using the chi-square test. Wilcoxon rank sums were used to compare continuous variables likely to be skewed. Unique subject identifiers are used in the NIS, which conceal the identity of the subjects and prevents identification of multiple admission of the same patient.

The primary purpose of this study was to see if MS is overrepresented in the cerebrovascular disease population. We used an indirect standardization, taking the prevalence of MS based on the National Health Interview Survey by Noonan et al. [8] to determine the number of MS patients expected based on each separate cohort of cerebrovascular event. This was calculated based on age and gender and compared to actual number of cerebrovascular events in each group to determine the Standardized Prevalence Ratio (SPR). Noonan’s prevalence of MS in the US study was chosen due to its partial overlap with our cohort as it covered 1982 to 1996.

**Results**

A total of 2,574,503 cerebrovascular admissions were identified and 4,568 (0.18%) had a secondary diagnosis of MS. The MS patients in the ischemic stroke cohort were significantly younger, more likely to be female and had a significantly shorter length of stay. Mortality was less for the MS patients who were more likely to be discharged to a skilled nursing facility. The MS patients in the ICH cohort were significantly more likely to be female, to be younger and the length of stay and discharge disposition were not significantly different. The MS patients in the non-ruptured aneurysm cohort were significantly younger, more likely to be female, and the length of stay and disposition were not significantly different (Table 1).

The SPR of MS among patients with ischemic stroke, when adjusted for age was 1.6218 (95% confidence interval [CI] 1.6188, 1.6249) and when matched for gender and age was 1.7182 (1.7150, 1.7214). The SPR for MS among ICH patients, adjusted for age was 1.3030 (1.2966, 1.3095) and for gender and age was 1.4118 (1.4049, 1.4188). The SPR of MS in patients with unruptured aneurysm, adjusted for age was 3.2359 (3.1943, 3.2781) and for gender and age was 2.8022 (2.7661, 2.8387).

**Discussion**

The data from this retrospective study of hospital admission in

**Table 1: Demographics.**

|                                       | MS          | Non-MS      | P                     |
|---------------------------------------|-------------|-------------|-----------------------|
| <b>Ischemic CVA (n)</b>               | 3870        | 2,209,462   |                       |
| Female (%)                            | 68.5        | 53.86       | <0.0001 <sup>†</sup>  |
| Mean age (SD)                         | 61.7 (12.9) | 72.5 (12.7) | <0.0001 <sup>††</sup> |
| LOS (median, interquartile range)     | 4 (3-7)     | 5 (2-8)     | <0.0001 <sup>††</sup> |
| Disposition (%):                      |             |             | <0.0001 <sup>†</sup>  |
| Died                                  | 4.27        | 6.61        |                       |
| Routine/home                          | 36.22       | 40.26       |                       |
| Transfer to other hospital            | 3.83        | 3.28        |                       |
| SKNF                                  | 42.41       | 39.07       |                       |
| Home Health/Hospice                   | 12.25       | 10.21       |                       |
| <b>Intracranial Hemorrhage (n)</b>    | 470         | 314,978     |                       |
| Female (%)                            | 67.87       | 51.02       | <0.0001 <sup>†</sup>  |
| Mean age (SD)                         | 59.2 (12.0) | 69.9 (14.3) | <0.0001 <sup>††</sup> |
| Median LOS (interquartile range)      | 5 (2-10)    | 5 (2-10)    | NS <sup>††</sup>      |
| Disposition (%):                      |             |             | NS <sup>†</sup>       |
| Died                                  | 28.42       | 30.76       |                       |
| Routine/home                          | 16.88       | 20.88       |                       |
| Transfer to other hospital            | 4.91        | 4.91        |                       |
| SKNF                                  | 43.59       | 37.06       |                       |
| Home Health/Hospice                   | 5.98        | 5.92        |                       |
| <b>Non-ruptured Cerebral Aneurysm</b> | 228         | 45,495      |                       |
| Female (%)                            | 86.4        | 73.17       | <0.0001 <sup>†</sup>  |
| Mean age (SD)                         | 53.0 (9.6)  | 56.9 (12.7) | <0.0001 <sup>††</sup> |
| Median LOS (interquartile range)      | 3 (1-5)     | 3 (1-6)     | NS <sup>††</sup>      |
| Disposition (%):                      |             |             | NS <sup>†</sup>       |

<sup>†</sup>χ<sup>2</sup>  
<sup>††</sup>Wilcoxon two-sample test  
<sup>†</sup> Disposition is not shown. The HCUP Data Use Agreement prohibits any table with a cell size of 10 or less.  
 LOS=Length of Stay, SKNF=Skilled Nursing Facility.

the US over a 24-year period suggest there is an increased risk of ischemic stroke and ICH in people with MS. This suggests people with MS are at a higher risk of ischemic stroke, and at younger age than the general US population. The risk of ischemic stroke has been found to be elevated in other studies [1-4]. In the Taiwan study, the authors found the adjusted hazard ratio of ischemic stroke in the MS population to be elevated at 4.02 [1]. The ratio was also much higher in their group of patients under the age of 40 at 12.7 [1]. A Swedish study, looking at the risk of cardiovascular disease in MS, found all cardiovascular disease to be elevated as well as ischemic stroke at the adjusted relative risk of 1.32 and 1.37 respectively [2]. Increase in ischemic stroke was partially attributed to a selection bias due to increased imaging [2]. Another Sweden-based MS study found the incidence ratio of ischemic stroke was 1.71 (95% CI 1.46 to 2.00) as compared to those without MS, as well as, an increase in myocardial infarction and heart failure, which were particularly prominent in women even after stratification for age, sex and country of birth [3]. A population-based cohort involving Danish citizens showed an elevated adjusted Incidence Rate Ratio (IRR) of MI to be 1.84 (95% CI 1.28 to 2.65) and ischemic stroke’s adjusted IRR to be 1.96 (95% CI 1.42 to 2.71) during the first year and in the subsequent 2-30 year follow-up the IRR of MI was decreased at 1.10 (95% CI

0.97 to 1.24) and ischemic stroke remained elevated at 1.23 (95% CI 1.10 to 1.38) [4]. Data has been conflicting on the prevalence of atherosclerosis in MS. While some studies report a lower prevalence of coronary artery disease in patients with MS except in the first year after diagnosis, in which it was increased [4,9]. Other studies suggest cardiovascular disease is higher in the MS population [3,10]. Some of the possible mechanisms of increased ischemic strokes include endothelial dysfunction, chronic inflammation and change from Disease Modifying Therapies (DMTs) [11]. Individuals with MS often have reduced mobility and occasionally are immobilized by their disease which also increases cardiovascular risk. But while there is an increased risk of ischemic stroke in MS, no corresponding increase in myocardial infarction has been found [10]. Perhaps the most intriguing hypothesis to explain this would be that the endothelial dysfunction and perivascular inflammation identified in MS causes vessel abnormalities which lead to thrombosis or occlusion of the vessels in the brain [12,13]. Another possibility includes side effects from medications, particularly corticosteroids and disease modifying therapies [11]. Hypertension and elevated plasma glucose were found to be higher in patients on beta-interferons and glatiramer acetate (Copaxone, Teva Pharmaceutical Industries, Ltd., Petah Tiqva, Israel) when compared to MS patients that were treatment naïve [11]. Corticosteroids are well known to cause dysregulation of the blood glucose, as well as, elevated blood pressure and altered electrolyte balance; however, in most cases of MS corticosteroids are used only short term for relapses. Most recently beta-interferons were found to have an elevated adjusted odds ratio of 1.83 for ischemic stroke [14]. Another explanation would include lifestyle changes caused by the disabling features of MS, including a more sedentary lifestyle. Other studies have shown that hypertension is a common comorbidity in MS; studies of type-2 diabetes and hyperlipidemia in patients with MS have been in conclusive [10]. Some accepted triggers for causing and worsening MS are also risk factors for stroke including cigarette smoking [15] and obesity [16]. A previous study also found that the proportion of deaths due to stroke was the same in the MS population compared to the age-matched general population [17]. Of note: this was prior to the introduction of any DMTs, as well as major changes in lifestyle, such as the reduction in smoking in the general population, and a greater emphasis in treatment of hyperlipidemia. Another older study based on autopsies showed no difference in the incidence of myocardial infarction or cerebral hemorrhage in MS compared to the general population [18]. Since the first DMTs were developed in 1993, most of our study epoch includes the years after the development of DMTs. The now-seen increase in ischemic stroke could likely be related to our current therapies, increased comorbid conditions, and/or increased imaging. All of which should be further studied.

The rate of ICH in patients with MS was 1.4 times greater than rate expected in the general population. This suggests that those with MS are at a higher risk of ICH. The incidence of hemorrhagic strokes has not been previously reported. There are case reports, one of which involved an ICH in the setting of beta-interferons and corticosteroids [19]. There have also been reports of ICH with fingolimod (Gilenya, Novartis Pharma AG, Basel, Switzerland) use in MS [20,21]. The proposed mechanisms of increased risk of ischemic stroke with MS, as well as poor balance and increased falls, would also increase the risk for ICH. We suspect some of the hemorrhages could be caused by trauma from falls. Falls are more common in MS patients because of postural instability, numbness, and weakness [22]. Patients who

have an increased fall risk may benefit from interventions particularly physical therapy and appropriate assistive walking devices. By identifying these patients and decreasing their fall risk we may decrease the number of ICH in MS.

The greatest overrepresentation was in the aneurysmal cohort which was 3.2 times greater than expected. Many of the previously discussed mechanisms for ischemic stroke including endothelial dysfunction, hypertension, and cigarette smoking are also risk factors for cerebral aneurysms. A more likely explanation is frequent imaging increases the detection of asymptomatic aneurysms, thus falsely elevating the perceived risk.

The limitations on using administrative datasets include the inability to examine socio-economic risk factors, medications, functional status, severity, duration of MS and diagnostic accuracy. Diagnostic accuracy varies in administrative datasets and it is not uncommon for acute MS lesions that have restricted diffusion on MRI to be misdiagnosed as stroke even when the diagnosis of MS has already been established [23]. Acute demyelination may demonstrate restricted diffusion on MRI, particularly in more inflammatory demyelinating lesions where it may be mistaken for ischemic stroke; however, it is more common that the lesion will appear bright on diffusion-weighted imaging and not have a decrease in apparent diffusion coefficient [24]. It is also for this reason that we used MS as the secondary diagnosis and not the primary diagnosis to attempt to limit the number of cases that may have previously had a misdiagnosis of stroke. While misdiagnosis of an MS lesion for an ischemic stroke may have falsely elevated the SPR for ischemic stroke, ICH is easily distinguished from MS.

It was found that the highest risk group for all cerebrovascular events was women in their 4<sup>th</sup> or 5<sup>th</sup> decade and the lowest risk was women over the age of 70. This pattern may further support the theory of direct endothelial damage from inflammation, which inflammation is well known to decrease later in the MS disease process. It may also support the risk of the treatments for MS, which are not as frequently used after the 7<sup>th</sup> decade of life. It may be that the rest of the population has caught up in risk by the 7<sup>th</sup> decade. This pattern and possible explanations should be researched further.

## Conclusion

While there is much speculation on the cause for increased ischemic strokes and many possible explanations, we feel that the recognition that strokes may be increased in the MS population may lead to improved diagnosis and treatment of acute stroke, particularly in the older population. It is important to get a clear history from the patient, and those who have a very sudden exacerbation should be evaluated for the possibility of stroke. It is also important for the MS population, that neurologists and other health care providers recognize comorbid conditions and attempt to lower the associated risks. However, care should be taken in charting a course of action. Statins have remained controversial in MS. They have shown a negative impact in laboratory on oligodendrocytes and myelin formation [10,25]. They have also shown possible harm in relapsing remitting MS with an increase in T2 lesions and brain atrophy but no change in disease progression, but have also shown potential benefits in secondary progressive MS with a decrease in brain atrophy and disease progression [26]. Therefore, we feel that statins should be used with caution in the setting of MS and based on an individual patient's need. Additionally, aspirin and other anti-platelet agents

should be carefully evaluated considering the increase in ICH in the MS population [27]. We also feel that the focus should start with women in their 3<sup>rd</sup> and 4<sup>th</sup> decades addressing multiple risk factors through diet, exercise, and lifestyle changes, before they become an issue in their 5<sup>th</sup> decade of life.

Increased prevalence of these cerebrovascular diseases among patients with MS warrants further investigation to determine if the association is related to MS treatments, other comorbidities, endothelial dysfunction, or chronic inflammatory state. Better management of these conditions may very well lead to improvement in quality of life in our MS patients.

## Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors received no financial support for the research, authorship, and/or publication of this article.

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We feel our article is unique and, to our knowledge, this is the first US nationwide study of ischemic stroke as well as other vascular complications in multiple sclerosis. We feel *Neurological Disorders and Stroke International* is the best journal to reach all general neurologists, MS and vascular specialists to inform them of the prevalence of vascular complications in multiple sclerosis.

This manuscript has not been published elsewhere and is not under consideration by another journal. The findings were presented as a poster at the ECTRIMS 2015 annual meeting in Barcelona, Spain. All authors have approved the manuscript and take full responsibility for the content including data, analyses, and interpretation. We agree to the conditions outlined in the Authorship and Contributorship. Thank you for considering our work, Scott Belliston.

## Author Contribution

Dr. Belliston conceptualized and helped design the study; Dr. Dubinsky helped design the study, provided the data, carried out the biostatistical analysis, and interpreted the data; and Dr. Belliston, Dr. Dubinsky and Dr. Lynch all contributed to drafting and revising the manuscript.

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