

Prevalence of Seizure/Epilepsy in Patients with Multiple Sclerosis: A Systematic Review and Meta-Analysis

Abstract

Background: Seizure and epilepsy are among the initial symptoms of multiple sclerosis (MS), yet different prevalence rates are reported for them in the previous studies. The goal of this systematic review is to estimate the pooled prevalence of seizure and epilepsy in patients with MS. **Methods:** We searched PubMed, Scopus, EMBASE, Web of Science, google scholar, and gray literature including references from identified studies and conference abstracts published up to October 2019. The search strategy included the MeSH terms and text words as ((Epilepsies OR Seizure Disorder OR Seizure Disorders OR Awakening Epilepsy OR Epilepsy, Awakening OR Epilepsy, Cryptogenic OR Cryptogenic Epilepsies OR Cryptogenic Epilepsy OR Epilepsies, Cryptogenic OR epilepsy OR seizure) AND (Multiple Sclerosis OR Sclerosis, Multiple) OR Sclerosis, Disseminated) OR Disseminated Sclerosis) OR MS (Multiple Sclerosis)) OR Multiple Sclerosis, Acute Fulminating). **Results:** The literature review resulted in 4860 articles; 2593 articles remained after eliminating the duplicates. For the final analysis, 39 articles were included, 9 of which were conference abstracts. The pooled prevalence of seizure in MS cases was 2%, 95% confidence interval (CI)(1%-3%) ($I^2 = 91.8\%$, $P < 0.001$). The pooled prevalence of epilepsy in MS cases was 3%, 95% CI (2%-4%) ($I^2 = 92.9\%$, $P < 0.001$). The pooled prevalence of epilepsy in Asia, Europe, and America was 6%, 3%, and 3%, respectively. The level of heterogeneity decreased after subgroup analysis in Asian and American subgroups. Meta-regression analysis showed continent is not a source of heterogeneity (coefficient = -0.007, $P = 0.6$). **Conclusions:** The result of this systematic review shows that the pooled prevalence of seizure and epilepsy among MS patients is 2% and 3%, respectively.

Keywords: Epilepsy, multiple sclerosis, prevalence, seizures

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system, with a higher prevalence in women.^[1,2] It has a wide range of negative consequences on personal, social, occupational, and marital aspects of life.^[3] MS can present with a wide range of signs and symptoms based on the location of the lesions and other factors such as disease duration.^[4]

The prevalence of MS and its forms of presentation differ between nations and even between different geographical regions in a nation. It has been shown that seizure and epilepsy are more common in MS cases than that in the general population. Previous registry studies showed a higher incidence of seizure in MS cases.^[5,6]

The prognosis of a single seizure/epilepsy is important in patients with MS. Studies

show that drug-resistant seizure/epilepsy is less common in MS, while status epilepticus is more frequent.^[7-10] Magnetic resonance imaging (MRI) findings showed a positive correlation between cortico-subcortical lesions and presentation of seizure/epilepsy.^[11,12]

As seizure and epilepsy are among the prevalent symptoms of MS, it's important to study them. The prevalence of seizure/epilepsy has been reported variously in previous studies. So, we designed this systematic review to estimate the pooled prevalence of seizure and epilepsy in patients with MS.

Methods

Literature search

We searched PubMed, Scopus, EMBASE, Web of Science, google scholar and gray literature including references from

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identified studies, and conference abstracts published up to October 2019.

Inclusion criteria

The inclusion criteria were cross-sectional studies evaluating the prevalence of seizure or epilepsy in patients with MS, published in the English language.

Data search and extraction

The search strategy included the MeSH terms and text words as ((Epilepsies OR Seizure Disorder OR Seizure Disorders OR Awakening Epilepsy OR Epilepsy, Awakening OR Epilepsy, Cryptogenic OR Cryptogenic Epilepsies OR Cryptogenic Epilepsy OR Epilepsies, Cryptogenic OR epilepsy OR seizure) AND (Multiple Sclerosis OR Sclerosis, Multiple) OR Sclerosis, Disseminated) OR Disseminated Sclerosis) OR MS (Multiple Sclerosis)) OR Multiple Sclerosis, Acute Fulminating).

Two researchers independently assessed the resulted articles. In the case of discrepancy, a third researcher solved the problem. Data on the total number of participants, first author, publication year, country, mean patient age at MS onset, and a number of cases with seizure or epilepsy were extracted from the included studies.

Statistical analysis

All statistical analyses were performed using STATA (Version 13.0; Stata Corp LP, College Station, TX, USA). We used the inverse-variance approach with a random-effects model. Inconsistency (I^2) was calculated to estimate heterogeneity. Meta-regression analysis was conducted considering “continent” as a source of heterogeneity for the prevalence of epilepsy.

Results

The literature search resulted in 4860 articles, but 2267 were duplicates and were eliminated. From 2593 remaining articles, 2554 were either not cross-sectional studies or not published in English. Thus, 39 articles were included for final analysis [Figure 1], 9 of which were conference abstracts [Table 1].

The included studies were published between 1972 and 2019 in Asia ($n = 5$), Europe ($n = 29$), and America ($n = 5$). The sample sizes ranged from 63 to 15810.

The pooled prevalence of seizure in MS cases was 2%, 95% confidence interval (CI)(1%-3%) ($I^2 = 91.8%$, $P < 0.001$) [Figure 2].

The pooled prevalence of epilepsy in MS cases was 3%, 95% CI (2%-4%) ($I^2 = 92.9%$, $P < 0.001$) [Figure 3].

The pooled prevalence of epilepsy in Asia, Europe, and America was 6%, 3%, and 3%, respectively [Figure 4]. The level of heterogeneity decreased after subgroup analysis in Asian and American subgroups. However,

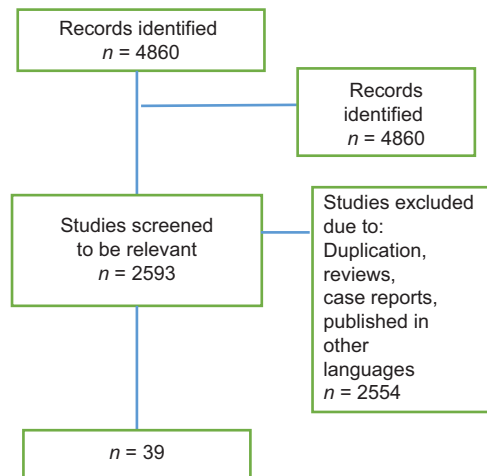


Figure 1: Flow diagram summarizing the selection of eligible studies

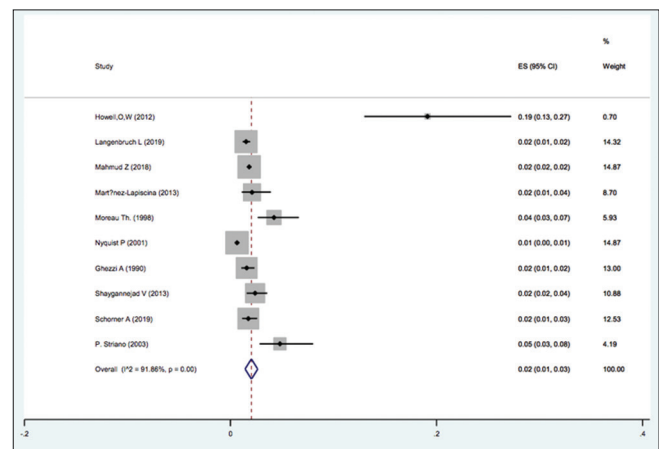


Figure 2: The pooled prevalence of seizure in multiple sclerosis cases

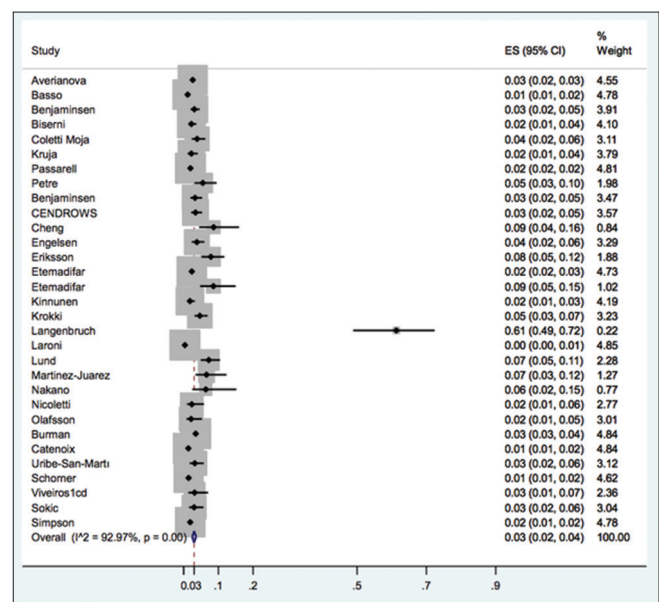


Figure 3: The pooled prevalence of epilepsy in multiple sclerosis cases

Meta-regression analysis showed continent is not a source of heterogeneity (coefficient = -0.007, $P = 0.6$).

Table 1: Characteristics of the included studies

First author	Publication year	Country	F/M ratio	Mean age at onset of MS (range) Epilepsy MS	Sample size	Number of seizure patients	Number of epilepsy patients	Prevalence of seizure/epilepsy	Country
Averianova, L. ^[13]	2017	Russia			1850		48	2.59	2
Basso, P. ^[14]	1989	Italy			2353		27	1.14%	2
Benjaminsen, E. ^[9]	2019	Norway			658		20	3.1%	2
Biserni, P. ^[15]	1993	Italy	2.33/1		630		14	2.22%	2
Coletti Moja, ^[16] M.	2003	Italy			365		14	4.1%	2
Howell, O. W. ^[17]	2012	UK	1.73/1		115	22			2
Kruja, J. ^[18]	2009	Albania	1.6/1		412		9	2.1%	2
Passarell, M. ^[19] A.	2017	Spain	2.3/1		5548		109	1.96%	2
Petre R ^[20]	2016	Romania			200		11	5.5%	2
Benjaminsen E ^[9]	2017	Norway	2.14/1	41.2±13.7	431		14	3.2%	2
CENDROWSKI W ^[21]	1972	Poland	1.5/1	28.9 (10-41)	500		17		2
Cheng M ^[4]	2012	Taiwan	3/1	28.38	93		8	8.6%	1
Engelsen B ^[22]	1997	Norway	1.5/1	25.2±5.6	423		16	3.8%	2
Eriksson M ^[23]	2002	Sweden		26.2	255		20	3.5%	2
Etemadifar M ^[24]	2012	Iran	3.37/1	28.54±11.22 (8-57)	3522		81	2.3%	1
Etemadifar M ^[25]	2012	Iran	5.16/1	2.1±1.1 (7-16)	117		10	8.5%	1
Kinnunen E ^[26]	1986	Finland	1.8/1	31.9	599		11	1.8%	2
Krokki O ^[27]	2014	Finland	2.3/1	29.4 (15-49)	491		23	4.7%	2
Langenbruch L ^[28]	2019	Germany			4078	62	38	1.5%/0.9%	2
Laroni A ^[29]	2017	Italy	1.87/1		1877		7	0.4%	2
Lund C ^[8]	2014	Norway	1.7/1	30.1 (19-48)	332		24	6.6%	2
Martinez-Juarez I ^[30]	2009	Mexico			122		8	6.55%	3
Mahmud Z ^[31]	2018	Sweden			15810	289		1.8%	2
Martínez-Lapiscina ^[32]	2013	Spain		29.2 _ 10.3	428	9		2.1%	2
Moreau Th. ^[12]	1998	France	1.48/1		402	17		4.25%	2
Nyquist P ^[33]	2001	USA			5715	37		0.64%	3
Ghezzi A ^[34]	1990	Italy			1459	23		1.57%	2
Nakano H ^[35]	2013	Japan	1.8/1	18.5±9.5	63		4	6.3%	1
Nicoletti A ^[36]	2003	Italy			170		4	2.35%	2
Olafsson, E ^[37]	1999	USA			188		4		3
Burman, J ^[6]	2017	Sweden	2.45/1		14545		502	5-year prevalence: 1.7%	2
Shaygannejad V ^[38]	2013	Iran		32.6±6.23	920	22		2.3%	1
Catenoix H ^[7]	2010	France		26.7 (7-49)	5041		67	1.3%	2
Uribe-San-Martín R ^[39]	2013	Chile	2.3/1	25 (15-40)	310		10	3.2%	3
Schorner A ^[40]	2019	Germany		25.3±8.7 (14-42)	1267	22	18	1.74%/1.42%	2
Viveiros CD ^[41]	2010	Brazil	3/1		160		5	2.5%	3
Striano P ^[42]	2003	Italy	4.4/1	16-48 (28.7)	270	13		4.8%	2
Sokic D ^[43]	2001	Yugoslavia			268		8	3%	2
Simpson R ^[44]	2014	UK	3.9/1		3826		72	1.9%	2

Discussion

To our knowledge, this is the first systematic review and meta-analysis on the prevalence of epilepsy in MS patients. Our results showed that the pooled prevalence of seizure and epilepsy was 2% and 3%, respectively. Subgroup analysis showed different prevalence rates of epilepsy between continents, while according to advance analysis, the continent was not a source of heterogeneity.

In a previous Norwegian study, Benjaminsen *et al.* found that the prevalence of focal epilepsy in MS cases

was 3.2%, which was 4.5-fold higher than that in the general population.^[9] According to their results, active epilepsy increased the risk of conversion from RRMS to SPMS. Engelsen *et al.* reported the prevalence of epilepsy as 4% in MS patients, which was near four times higher than the prevalence reported in the general population.^[22] In a study conducted by Eriksson in Sweden, the prevalence of epilepsy in MS individuals was found as 3.5%, while in the general population, it was reported as 0.53%-0.64%.^[45] In another Swedish study by Mahamud *et al.*, the 10-year risk of epilepsy was 51.4% in MS patients and 41.3% in

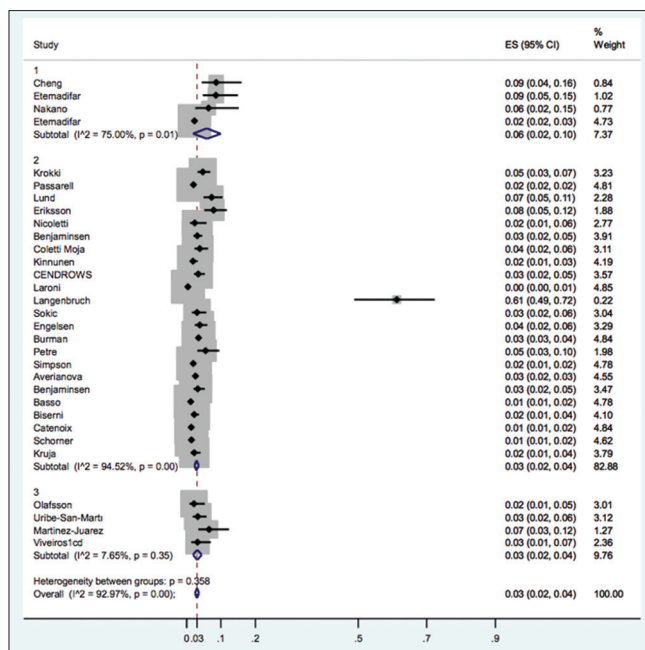


Figure 4: The pooled prevalence of epilepsy in multiple sclerosis cases in each continent

controls. The risk for SPMS and RRMS cases was 60% and 46%, respectively.^[31] Krokki *et al.* indicated epilepsy as the most prevalent comorbidity in MS, which was found in 4.7% of 491 definite MS patients.^[27] Langenbruch *et al.* assessed 4078 MS patients and reported seizure in 1.5% and epilepsy in 0.9%.^[28] In a Japanese study conducted by Nakano *et al.*, the prevalence of epilepsy in MS patients was twice the prevalence in neuromyelitis optica patients.^[35]

The cause of seizure in MS is not clear, however cortical and juxtacortical inflammation, demyelination, and atrophy are considered to play a role in the development of seizures/epilepsies in MS.^[46,47]

Seizure or epilepsy could occur at any time during the disease. All types of seizures have been reported in MS.^[32] Some researchers believe the most common type of seizure in MS is focal seizure (FS) followed by secondary generalization, while others consider primary generalized tonic-clonic seizures as the most frequent type.^[7,42,48,49] Martínez-Lapiscina *et al.* reported epilepsy in 3% of their MS cases and focal seizures in 80%.^[32]

Some authors believe that epilepsies are common in relapsing-remitting form of MS, but there are controversies over it.^[30,42] One reason for seizures in MS patients might be the locations of MRI lesions. Some authors believe lesions extended to the cortex are the risk factors of seizures in MS. Calabrese *et al.* reported that intra-cortical lesions are five times more prevalent in RRMS patients with seizures than in those without it.^[46] Another study on MRI examinations confirmed a higher number of cortical and juxtacortical lesions in MS individuals who experienced seizure compared to other MS patients. This

study also showed that cortical and juxtacortical lesions were independent predictors of seizures, by controlling the total number of lesions and brain atrophy.^[32] More intensive inflammation was reported in the cortex of MS cases with epilepsy than in those without epilepsy.^[46] Waxman suggested the role of demyelination in the sodium channel gene activation, which would result in hyperexcitability.^[50]

Seizure/epilepsy can be the first symptom of MS, the incidence rate of which increase with the longer duration of the disease or the higher number of lesions.^[9] However, no relationship has been found between the severity of MS and epilepsy.^[26,34]

The prognosis of seizure in MS patients is highly controversial.^[42,48,49] Administration of antiepileptic medications is recommended to prevent new seizures and status epilepticus.^[22]

Conclusions

The result of this systematic review shows that in MS patients, the pooled prevalence of seizure and epilepsy is 2% and 3%, respectively.

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Conflicts of interest

There are no conflicts of interest.

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