Oraby *et al.*
Egypt J Neurol Psychiatry Neurosurg (2024) 60:47
https://doi.org/10.1186/s41983-024-00811-1

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH

Open Access

Syntaxin 1A gene polymorphism in multiple sclerosis: a case–control study

Mohammed I. Oraby[1*], Rasha H. Soliman[1], Noha A. Abdel Kader[2], Esraa M. Abdul Galil[1] and Mohammed M. Masoud[1]

Abstract

Background Syntaxin 1A is a member of a membrane-integrated nervous system-specific protein superfamily involved in the neuromediator release from synaptic vesicles and one of the proteins included in axonal integrity. Studies that discussed the role of Syntaxin 1A in multiple sclerosis are few and limited. Gene studying sometimes shows unexpected results in different populations. The aim of this work was to investigate Syntaxin 1A genetic polymorphism (rs1569061) in a sample of Egyptian patients with MS and the relation between Syntaxin 1A gene polymorphism and disease course and disability. A case–control study included 150 subjects; 75 Egyptian MS patients of different clinical courses and 75 age and sex matched healthy controls. Patients were subjected to clinical evaluation, assessment of disability, and cognition. Both patient and control groups were subjected to Syntaxin 1A genotyping.

Results There was no significant difference between different genotypes distribution for Syntaxin 1A (rs 1569061) between MS patients and controls.

No significant difference was found between genotypes and allele distribution for Syntaxin 1A (rs 1569061) among cases of MS regarding EDSS or results of BICAMS). There was no statistically significant difference between syntaxin genotypes among cases of MS regarding demographic or clinical characteristics of the disease.

Conclusion Here we show no statistically significant difference between MS patients and control regarding Syntaxin 1A genotypes and different alleles. Syntaxin 1A genotypes have no impact on clinical characteristics of the disease, disability, or cognition. These negative findings open the floor for the study of other MS related genes in Egypt.

Keywords Multiple sclerosis, Synaptopathy, Syntaxin 1A, Genotyping, Expanded Disability Status Score, Brief International Cognitive Assessment

Introduction

Multiple sclerosis (MS) is classically a chronic inflammatory demyelinating disease. However, accumulating studies have demonstrated the presence of axonal degeneration which may occur early in the disease course [1, 2].

Factors that can determine the development and progression of disability in multiple sclerosis patients are thoroughly under investigation as synaptopathy, accumulated oxidative stressors, axonal degeneration, and neuroplasticity [3, 4].

Experimental autoimmune encephalomyelitis is utilized as a model for developing novel therapies for multiple sclerosis. The levels of syntaxins in presynaptic terminals are reduced in experimental autoimmune encephalomyelitis [5, 6].

Synapsins play an important role in vesicular trafficking. They are neuronal phosphorylated proteins that are linked to cytoplasmic vesicle membranes in the synaptic regions [7].

*Correspondence:
Mohammed I. Oraby
Drm_Oraby@med.bsu.edu.eg
[1] Neurology department, Beni-Suef University, Beni-Suef 62511, Egypt
[2] Clinical Pathology Department, Beni-Suef University, Beni-Suef, Egypt

Autopsy studies conducted on various MS clinical phenotypes have revealed that the levels of synaptic proteins, such as synaptophysin and synaptotagmin, which act as presynaptic vesicle proteins and play an important role in synaptic vesicle release, are reduced. This decrease in synaptic proteins suggests the possible involvement of synaptopathy in the pathogenesis of MS [8].

Widespread synaptic loss has been reported in several human neuropathological studies, which may accompany or follow white and gray matter inflammatory lesions. Also, experimental models of neuroinflammation have demonstrated failure of synaptic plastic properties [9, 10].

Synapses are basic functional entities in cortical and subcortical brain networks. They are able to ensure learning processes and multi-modal information processing as they can express short and long-term plastic changes. Hence, the malfunction or loss of synapsis may lead to connection failure in the MS brain [11].

The term "synaptopathy" refers to the modification of synaptic structure and function that have been reported in different neurological disorders, including Alzheimer's disease, autism, epilepsy, and recently, MS. Synaptopathy in MS is most probably an inflammatory dependent process and of particular interest because it is potentially reversible and could be a novel therapeutic target for MS [12, 13].

Syntaxin 1A is a presynaptic protein and forms the SNARE complex with VAMP2 and SNAP-25. SNARE complex is highly located in synaptic plasticity locations and plays a role in vesicle docking and fusion and as a result, mediating neurotransmitter secretion [14].

The results of genetic studies may vary according to the difference in population. The present study aims to investigate Syntaxin 1A genetic polymorphism (rs1569061) in a sample of Egyptian patients with multiple sclerosis and to assess the possible relation between Syntaxin 1A genetic polymorphism and disease course and disability.

Methods

A case–control study, was conducted at outpatient multiple sclerosis clinic, during the period between May 2021 and March 2022. The study was ethically approved by the authorized research ethical committee, was explained to all participants and informed consent was taken from them before starting the study.

The total number of participants was 150; patients group involved 75 Egyptian multiple sclerosis patients diagnosed according to the 2017 revised Macdonald criteria [15] on different lines of medical treatment. Inclusion criteria were: age more than 18 years, both genders. Exclusion criteria were: patients with clinically isolated syndrome and patients suffering from any inflammatory or other autoimmune diseases. And control group involved 75 healthy volunteers matched for age and sex.

MS patients were subjected to: history taking focusing on risk factors, age of onset of multiple sclerosis, disease duration, and total number of relapses. Medical examination including vital signs, cardiac, chest and abdominal assessment. Thorough neurological examination. The assessment of neurological impairment by Expanded Disability Status Score (EDSS) [16] which has steps from 0 (normal) to 10 (death due to MS), defined by functional system grades which include pyramidal, brain stem, cerebellar, bowel and bladder, sensory, cerebral, and visual. The assessment of cognitive impairment by brief international cognitive assessment in patients of multiple sclerosis (BICAMS) (Arabic version) [17] which is a reliable and valid tool for cognitive assessment of Arabic-speaking MS patients in different clinical and research settings. It included three tests: the California Verbal Learning Test (CVLT-II), the Symbol Digit Modalities Test (SDMT), and the revised Brief Visuospatial Retention Test (BVRT-R). The assessment of fatigue using the Fatigue severity scale (FSS) [18] which is a short questionnaire that asks the patient to rate her/ his level of fatigue. The FSS questionnaire contains nine statements that rate the severity of fatigue symptoms. The patient should read each statement and choose a number from 1 to 7, based on how precisely it reflects her/ his status during the past week.

The patient group was also subjected to magnetic resonance imaging (MRI) for the brain and spinal cord using a 1.5 Tesla Siemens Scanner Magnetom Aera, serial number 42612. The following protocols were used; T1-weighted images, T2-weighted images, Fluid attenuated inversion recovery (FLAIR) sequence, and Gadolinium enhanced T1-weighted images.

Both patients and control groups were subjected to DNA extraction and Syntaxin 1A gene (rs1569061) genotyping. Genomic DNA was extracted from EDTA-containing peripheral venous blood samples and genotyping Syntaxin 1A gene (rs1569061) (C > T) SNP was achieved using the MGB-TaqMan Allelic Discrimination method.

The TaqMan MGB probe/extension primers were VIC CTGGCGGCCCTGCCTGGGTCTGCTC to detect the allele 1 sequence and FAM TCGCTGTGCACACTG CATCACGCCC to detect the allele 2 sequences (Catalog number 4351379). The total volume of PCR reaction contained, 5 µl of genomic DNA, 12.5 µl of TaqMan master mix II (PN 1802052), 1.25 µl 20 × SNP assay mix and was adjusted to a final volume of 25 µl using 6.25 µl nuclease free water. PCR was performed by Step One™ real-time PCR. Applied Biosystems; (USA) (SN 2710004581, REF 4369074).

Statistical analysis

Data were coded and entered using Microsoft Office Excel 2010. Statistical analysis was done using IBM SPSS version 24 (IBM Corporation, USA, Armonk, New York, 2016). Frequencies (number) and relative frequencies (percent) were used to summarize qualitative variables while mean, median, interquartile range, and standard deviations were used for quantitative variables. Comparison between groups was done using parametric tests (independent sample t-test and ANOVA) and non-parametric tests (Chi-square, Mann–Whitney test, and Kruskal–Wallis test) appropriately. P value less than or equal to 0.05 was considered significant.

Results

The age of MS patients ranged from 18 to 52 years with a mean value of 34.2 ± 9.03 years. While the age of controls ranged from 18 to 55 years with a mean value of 31.6 ± 10.3.8 years. There was no statistically significant difference between patients and controls ($P = 0.09$).

Table 1 Description of disease characters among MS group

Variables	Mean	SD	Range
Age of onset (years)	28.05	8.2	12–45
Disease duration (years)	6.19	5.8	1–25
	Median/IQR	Mean ± SD	Range
Total number of relapses	2/4	3.4 ± 2.7	1–15
Number of relapses in last 2 years	1/1	1.4 ± 0.9	0–5
MS severity degree	Mean	SD	Range
EDSS	3.38	2.1	0.5–7.5
FSS	4.19	1.5	1–8
BICAMS	Median/IQR	Mean ± SD	Range
SDMT	30/30	28.9 ± 17.3	3–66
CVLT	37/28	33.6 ± 15.6	8–36
BVRT	10/7	10.4 ± 4.5	3–18

MS multiple sclerosis, *EDSS* Expanded Disability Status Score, *FSS* Fatigue Severity Scale, *BICAMS* Brief International Cognitive Assessment, *SDMT* Symbol Digit Modalities Test, *CVLT* California Verbal Learning Test, *BVRT* Brief Visuospatial Retention Test

Regarding MS disease course, 55 patients (73.4%) were diagnosed with relapsing remitting multiple sclerosis (RRMS), 10 patients (13.3%) were diagnosed with secondary progressive multiple sclerosis (SPMS) and 10 patients (13.3%) were diagnosed as primary progressive multiple sclerosis (PPMS). Clinical characteristics of MS patients including; age of onset (years), disease duration (years), total number of relapses, number of relapses in last 2 years, EDSS, FSS, and BICAMS are shown in Table 1

The distribution of Syntaxin 1A rs1569061 genotypes and alleles frequencies in MS patients and controls were evaluated. Regarding MS patients, Syntaxin 1A genotype CC was found in 50 cases (66.7%), genotype CT in 22 cases (29.3%) and genotype TT in 3 cases (4%). Regarding controls, Syntaxin 1A genotype CC was found in 59 subjects (78.7%) while genotype CT was in 16 subjects (21.3%). There was no statistically significant difference between MS patients and control (Table 2).

T allele was more common in patients than controls (33.3% versus 21.3%) and C allele was lower in patients than controls (96% versus 100%). However, this association was not significant (Table 2).

On comparing RRMS, SPMS, and PPMS patients regarding Syntaxin 1A genotyping and different alleles, there was no statistically significant difference ($p > 0.05$) (Table 3).

On comparing the three genotypes of syntaxin regarding different clinical characteristics of MS (age of disease onset, duration, number of attacks, and MS severity degree (EDSS, and FSS), no statistically significant difference was found ($p > 0.05$) (Table 4).

Also, there was no statistically significant difference ($p > 0.05$) in comparing the cognitive functions among MS patients with different syntaxin genotypes (Table 5).

For syntaxin alleles, there was no statistically significant difference between the two alleles regarding different demographic, clinical, and radiological characteristics of MS ($p > 0.05$) (Table 6).

Table 2 Comparisons of syntaxin1a genotypes and alleles in different study groups

Syntaxin genotypes	Cases ($N = 75$)		Control ($N = 75$)		*P*-value	Sig.
	No	%	No	%		
CC	50	66.7	59	78.7	0.09	NS
TT	3	4	0	0		
CT	22	29.3	16	21.3		
Syntaxin genotypes alleles						
T Allele	25	33.3	16	21.3	0.1	NS
C Allele	72	96	75	100	0.2	NS

NS nonsignificant

Table 3 Syntaxin 1A genotypes and alleles in different MS types

Syntaxin genotypes	Relapsing remitting (*N* = 55)		1ry progressive (*N* = 10)		2ry progressive (*N* = 10)		*P*-value	Sig.
	No	%	No	%	No	%		
CC	37	67.3	6	60	7	70	0.7	NS
TT	2	3.6	0	0	1	10		
CT	16	29.1	4	40	2	20		
Syntaxin genotypes alleles								
T Allele	18	32.7	4	40	3	30	0.8	NS
C Allele	53	96.4	10	100	9	90	0.5	NS

NS nonsignificant

Table 4 Comparison between different syntaxin genotypes regarding MS disease characters

Disease characters	Syntaxin genotypes						*P*-value	Sig.
	CC		TT		CT			
	Mean	SD	Mean	SD	Mean	SD		
Age of onset (years)	28.2	8.8	21.7	4.9	28.6	6.9	0.4	NS
Disease duration (years)	6.5	5.9	2.7	2.1	5.9	6.01	0.5	NS
Total number of attacks	3.7	2.9	3	1.7	2.7	2.3	0.4	NS
Number of attacks in last 2 years	1.5	0.9	1.7	0.57	1.1	0.64	0.2	NS
MS severity degree								
EDSS	3.6	2	2.8	2.3	3	2.3	0.5	NS
FSS	4.2	1.6	5.2	0.81	4.03	1.4	0.5	NS

EDSS Expanded Disability Status Score, *FSS* Fatigue Severity Scale, *NS* nonsignificant

Table 5 Cognitive assessment in different syntaxin genotypes among MS patients

Cognitive assessment	Syntaxin genotypes						*P*-value	Sig.
	CC		TT		CT			
	Mean	SD	Mean	SD	Mean	SD		
CVLT	33.7	15.9	32	8.9	33.5	16.1	0.9	NS
SDMT	29.6	17.8	42.7	3.1	25.6	16.5	0.3	NS
BVMT	10.8	4.5	14.3	2.1	8.9	4.1	0.07	NS

SDMT Symbol Digit Modalities Test, *CVLT* California Verbal Learning Test, *BVRT* Brief Visuospatial Retention Test, *NS* nonsignificant

To summarize, there was no significant difference between genotypes and different alleles distribution for Syntaxin 1A (rs 1569061) between MS patients and controls. Also, there was no significant difference between clinical phenotypes of MS (RRMS, SPMS and PPMS) regarding genotypes and different alleles distribution of Syntaxin 1A (rs 1569061).

Discussion

Multiple sclerosis is a chronic inflammatory disease that results in demyelination and axonal degeneration affects mainly young adults and may cause significant disability [19].

Table 6 Comparisons between syntaxin alleles regarding different MS variables

Variables	C allele		*P*-value	Sig.	T allele		*P*-value	Sig.
	No	Yes			No	Yes		
	Mean ± SD	Mean ± SD			Mean ± SD	Mean ± SD		
Age (yrs)	24.3 ± 5.7	34.7 ± 8.9	0.06	NS	34.7 ± 8.9	33.3 ± 9.3	0.5	NS
Age of onset (yrs)	21.7 ± 4.9	28.3 ± 8.2	0.2	NS	28.2 ± 8.8	27.8 ± 7.1	0.8	NS
Disease duration (yrs)	2.7 ± 2.1	8.3 ± 5.9	0.3	NS	6.5 ± 5.9	5.5 ± 5.7	0.5	NS
Total number of attacks	3 ± 1.7	3.4 ± 2.7	0.8	NS	3.7 ± 2.8	2.7 ± 2.1	0.2	NS
Number of attacks in last 2 years	1.7 ± 0.6	1.4 ± 0.9	0.6	NS	1.5 ± 0.97	1.1 ± 0.66	0.2	NS
MS severity degree								
EDSS	2.8 ± 2.3	3.4 ± 2.1	0.6	NS	3.6 ± 2	2.9 ± 2.3	0.2	NS
FSS	5.2 ± 0.81	4.2 ± 1.5	0.3	NS	4.2 ± 1.6	4.2 ± 1.4	0.9	NS
MRI plaques								
Cortical and juxta cortical	7.3 ± 2.5	7.7 ± 2.7	0.8	NS	7.5 ± 2.6	8 ± 2.8	0.4	NS
Peri-ventricular	4.7 ± 1.5	5.1 ± 2.6	0.8	NS	5.1 ± 2.9	4.9 ± 2.03	0.9	NS
Infra-tentorial	0.33 ± 0.6	0.42 ± 1.3	0.9	NS	0.42 ± 1.5	0.4 ± 0.6	0.9	NS
Spinal cord	0.67 ± 0.6	0.61 ± 0.6	0.8	NS	0.64 ± 0.7	0.56 ± 0.6	0.6	NS
Cognitive assessment								
CVLT	32 ± 8.9	33.7 ± 15.9	0.8	NS	33.7 ± 15.9	33.3 ± 15.3	0.9	NS
SDMT	42.7 ± 3.1	28.4 ± 17.4	0.2	NS	29.6 ± 17.8	27.7 ± 16.5	0.7	NS
BVMT	14.3 ± 2.1	10.3 ± 4.5	0.1	NS	10.8 ± 4.5	9.6 ± 4.3	0.2	NS

EDSS Expanded Disability Status Score, *FSS* Fatigue Severity Scale, *BICAMS* Brief International Cognitive Assessment, *SDMT* Symbol Digit Modalities Test, *CVLT* California Verbal Learning Test, *BVRT* Brief Visuospatial Retention Test, *NS* nonsignificant

Multiple variations interact and affect the patient clinical presentation, response to different disease-modifying medications, disease progression, and disability [20].

Although the hallmark of MS pathology is demyelination, accumulating evidence indicates that axonal degeneration may occur in the early stages of the disease. Axonal damage may be secondary to chronic inflammation and demyelination, or it can be a direct immune attack against the axon itself [21, 22].

Syntaxin 1A protein is one of the neuronal phosphorylated proteins and plays a crucial role in vesicular trafficking in the synaptic region and is particularly related to cytoplasmic vesicle membranes. With VAMP2 and SNAP-25 proteins, Syntaxin 1A protein forms the SNARE complex which is involved in several critical fundamental functions [3].

The potential role of synaptic dysfunctions has been reported not only in the pathogenesis of primary CNS degenerative disorders, but also in neuroinflammatory brain disorders such as MS [23, 24].

Many neurological disorders have genomic etiology which affects their clinical presentation, disease progression, and response to therapeutic agents [25, 26].

This variability creates a need to identify characteristics within different populations as such genes can affect drug pharmacokinetics, therapeutic efficacy, and even adverse drug reactions [27].

As far as we know, our study was the first Egyptian and the second worldwide study to assess the relation between the Syntaxin 1A gene and MS disease. We evaluated the association between Syntaxin 1A single nucleotide polymorphism (rs1569061) and MS risk in an Egyptian sample as a new geographical area for MS gene research. In addition, we investigated the possible relation to disease course, disability, cognitive affection, fatigability, and MRI findings.

This study was conducted on 75 Egyptian MS patients of different clinical courses and 75 healthy controls from the same geographical area which was age and sex matched with cases.

There was no significant difference between genotypes and different alleles distribution for Syntaxin 1A (rs 1569061) between MS patients and controls. (We measured the frequency of appearance of each of the genotypes [the homozygous (CC), (TT) and the heterozygous (CT) also the C and T alleles]).

Studies that discussed the role of Syntaxin 1A in multiple sclerosis are few and limited. Gene studying sometimes shows unexpected results in different populations.

Turkish study of Yalın and colleagues [28] was conducted on 123 MS patients against 192 healthy controls for the assessment of Syntaxin 1A genetic polymorphism and other synaptic genes. They found a significant association between MS and syntaxin1a (CT) and (CC)

genotypes. Syntaxin1A/synaptotagmin XI genes, CT and CC haplotypes, and SNAP-25 MnlI/SNAP-25 DdeI GC haplotype were found to be associated with an increased risk of MS development. This Turkish study was the first study to evaluate the associations between MS disease and the SNARE complex genetic polymorphisms.

A German study reported that whether the polymorphisms rs133946 nor rs133945 in the promoter region of the Synapsin III (SYN3) gene were associated with Multiple Sclerosis in German patients. Association of the SYN3 variations and haplotypes with MS is not evident in German MS patients [29], and this confirms that the difference in population may affect results of genetic studies.

According to Otaegui and colleagues [30], Two SNPs (rs133945 and rs133946) in the promoter region of the SYN3 gene were analyzed in 221 Spanish MS patients with a cluster of 72 Basque patients and 373 controls with a cluster of 138 controls of a Basque origin. The SNPs were distributed differently in the two populations. Surprisingly, they found that the CC genotype in rs133946 and the GG genotype in rs133945 could be protective factors against MS in the Basque population.

Another Italian study selected two polymorphisms within the SYN 35'-promoter region which were assessed in a group of MS patients from southern Italy. They found an inverse association between MS and the g-631C > G polymorphism [31].

The difference between results may be explained by; the ethnic and phenotypic disparities among the population studied, the difference in geographical area, different numbers of MS patients, and clinical phenotypes included, also the influence of disease-modifying therapy could not be eliminated.

This study was the first worldwide to compare clinical types of MS regarding syntaxin1A (rs1569061) single nucleotide polymorphism and different alleles distribution. We found no significant difference in genotypes and different alleles distribution for Syntaxin 1A (rs 1569061) between types of MS (RRMS, SPMS, and PPMS) regarding the frequency of appearance of each of the genotypes [the homozygous (CC), (TT) and the heterozygous (CT) also the C and T alleles].

Initial autopsy American studies of patients with RRMS, PPMS, and SPMS have reported decreased levels of other synaptic proteins, including synaptotagmin and synaptophysin. Synaptophysin is a presynaptic vesicle protein that plays a role in synaptic vesicle release [8].

On the other hand, in the Turkish study by Yalın and colleagues [28], the number of patients with secondary progressive and primary progressive multiple sclerosis patients was small and could not be analyzed separately as most of their patients were of the relapsing remitting type.

As discussed before, heterogenicity may be likely attributed to the difference of the number and clinical phenotypes of MS patients, the difference in genetic backgrounds and ethnic variations also, disease-modifying drugs could affect gene expression.

In the current study, there was no significant difference between genotypes and allele distribution for Syntaxin 1A (rs 1569061) among cases of MS regarding age, and sex. Also, there was no significant difference between syntaxin1A (rs1569061) genotypes and allele distribution among cases of MS and disease characters (age of disease onset, disease duration, number of MS attacks).

Neurological disability is the main determinant of global and selective domains of quality of life in MS patients. The Expanded Disability Status Scale which was originally described by Kurtze (1983), is a commonly used scale for assessing the level of disability in people with multiple sclerosis [32].

To our knowledge, this work was the first to study the association between syntaxin SNP and MS disease severity using the EDSS scale, FSS, and cognition affection using BICAMS. There was no significant difference between genotypes and allele distribution for Syntaxin 1A (rs 1569061) among cases of MS regarding EDSS. Also, there was no significant difference between genotypes and allele distribution for Syntaxin 1A (rs 1569061) among cases of MS regarding neither FSS nor cognition affection using BICAMS.

The main limitation of our study is the relatively small number of patients, genetic studies should include a larger number of patients but financial resources should be taken into consideration. Also, this study is a single-center study, a multicenter study with more geographical areas in Egypt is recommended.

Conclusion

There was no significant difference between genotypes and different alleles distribution for Syntaxin 1A (rs 1569061) between MS patients and controls. Also, there was no significant difference between clinical phenotypes of MS (RRMS, SPMS, and PPMS) regarding genotypes and different alleles distribution of Syntaxin 1A (rs 1569061). Syntaxin 1A genotypes have no impact on clinical characteristics of the disease, disability, or cognition. The results of this study may limit the role of Syntaxin 1A (rs 1569061) as a biomarker for multiple sclerosis.

The results of genetic studies may vary according to the difference in population. This study opens the floor for the study of MS genetics in Egypt, which will help to understand the effect of genomic etiology on clinical

presentation, disease progression, and the response of MS patients to different therapeutic agents.

Abbreviations

BICAMS	Brief International Cognitive Assessment
BVRT	Brief Visuospatial Retention Test
CVLT	California Verbal Learning Test
EDSS	Expanded Disability Status Score
FSS	Fatigue Severity Scale
MS	Multiple sclerosis
PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SDMT	Symbol Digit Modalities Test
SPMS	Secondary progressive multiple sclerosis

Acknowledgements
Not applicable

Author contributions
MO participated in the study design, sequence alignment, and analysis of the data and helped to draft the manuscript. RS participated in the study design, sequence alignment, and analysis of the data and helped to draft manuscript. NA performed the laboratory work and helped to draft the manuscript. EA participated in the study design, collection of the data and helped to draft the manuscript. MM participated in the study design, sequence alignment, and analysis of the data and helped to draft the manuscript. All authors read and approved the final manuscript.

Funding
The authors did not receive any funding for this work.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request with the permission of Faculty of Medicine, Beni-Suef University, Egypt.

Declarations

Ethics approval and consent to participate
A written informed consent was obtained from each participant in this study and the study was approved by the authorized ethical committee in Faculty of medicine, Beni-Suef University (FMBSUREC/01092020/Hassan in 1st of September 2020).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 18 May 2023 Accepted: 14 February 2024
Published online: 25 March 2024

References

1. Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009;132(Pt 5):1175–89.
2. Gilmore CP, Donaldson I, Bö L, Owens T, Lowe J, Evangelou N. Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord. J Neurol Neurosurg Psychiatry. 2009;80(2):182–7.
3. Xue H, Yang Z, Wang L, Jiang Y, Li J, Wu M, Wang G, Zhang Y, Zhang M. Factors influencing the degree of disability in patients with multiple sclerosis. Front Neurol. 2021;13(12):714631.
4. Lublin FD, Häring DA, Ganjgahi H, Ocampo A, Hatami F, et al. How patients with multiple sclerosis acquire disability. Brain. 2022;145(9):3147–61.
5. Mix E, Meyer-Rienecker H, Hartung HP, Zettl UK. Animal models of multiple sclerosis–potentials and limitations. Prog Neurobiol. 2010;92(3):386–404.
6. Constantinescu CS, Farooqi N, O'Brien K, Gran B. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). Br J Pharmacol. 2011;164(4):1079–106.
7. Gitler D, Takagishi Y, Feng J, Ren Y, Rodriguiz RM, Wetsel WC, et al. Different presynaptic roles of synapsins at excitatory and inhibitory synapses. J Neurosci. 2004;24(50):11368–80.
8. Dutta R, Chang A, Doud MK, Kidd GJ, Ribaudo MV, Young EA, et al. Demyelination causes synaptic alterations in hippocampi from multiple sclerosis patients. Ann Neurol. 2011;69(3):445–54.
9. Bellingacci L, Mancini A, Gaetani L, Tozzi A, Parnetti L, Di Filippo M. Synaptic dysfunction in multiple sclerosis: a red thread from inflammation to network disconnection. Int J Mol Sci. 2021;22(18):9753.
10. Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 2015;14(2):183–93.
11. Wegner C, Esiri MM, Chance SA, Palace J, Matthews PM. Neocortical neuronal, synaptic, and glial loss in multiple sclerosis. Neurology. 2006;67(6):960–7.
12. Mandolesi G, Gentile A, Musella A, Fresegna D, De Vito F, Bullitta S, et al. Synaptopathy connects inflammation and neurodegeneration in multiple sclerosis. Nat Rev Neurol. 2015;11(12):711–24.
13. Lepeta K, Lourenco MV, Schweitzer BC, Martino Adami PV, Banerjee P, Catuara-Solarz S, et al. Synaptopathies: synaptic dysfunction in neurological disorders - a review from students to students. J Neurochem. 2016;138(6):785–805.
14. Söllner TH. Regulated exocytosis and SNARE function (Review). Mol Membr Biol. 2003;20(3):209–20.
15. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.
16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444–52.
17. Rahman TT, El Gaafary MM. Montreal Cognitive Assessment Arabic version: Reliability and validity prevalence of mild cognitive impairment among elderly attending geriatric clubs in Cairo. Geriatr Gerontol Int. 2009;9(1):54–61.
18. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121–3.
19. Ghasemi N, Razavi S, Nikzad E. Multiple sclerosis: pathogenesis, symptoms. Diagn Cell-Based Ther Cell J. 2017;19(1):1–10.
20. Holford N. Treatment response and disease progression. Transl Clin Pharmacol. 2019;27(4):123–6.
21. Filippi M, Bozzali M, Rovaris M, Gonen O, Kesavadas C, Ghezzi A, et al. Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis. Brain. 2003;126(Pt 2):433–7.
22. Papiri G, D'Andreamatteo G, Cacchiò G, Alia S, Silvestrini M, Paci C, et al. Multiple sclerosis: inflammatory and neuroglial aspects. Curr Issues Mol Biol. 2023;45(2):1443–70.
23. Di Filippo M, Portaccio E, Mancini A, Calabresi P. Multiple sclerosis and cognition: synaptic failure and network dysfunction. Nat Rev Neurosci. 2018;19(10):599–609.
24. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. Signal Transduct Target Ther. 2023;8(1):267.
25. Lopez C, Tucker S, Salameh T, Tucker C. An unsupervised machine learning method for discovering patient clusters based on genetic signatures. J Biomed Inform. 2018;85:30–9.
26. Boone PM, Wiszniewski W, Lupski JR. Genomic medicine and neurological disease. Hum Genet. 2011;130(1):103–21.
27. Silgado-Guzmán DF, Angulo-Aguado M, Morel A, Niño-Orrego MJ, Ruiz-Torres DA, Contreras Bravo NC, et al. Characterization of ADME gene variation in colombian population by exome sequencing. Front Pharmacol. 2022;30(13):931531.
28. Yalın OÖ, Gökdoğan Edgünlü T, Karakaş Çelik S, Emre U, Güneş T, Erdal Y, Eroğlu ÜA. Novel SNARE complex polymorphisms associated with

multiple sclerosis: signs of synaptopathy in multiple sclerosis. Balkan Med J. 2019;36(3):174–8.
29. Akkad DA, Gödde R, Epplen JT. No association between synapsin III gene promoter polymorphisms and multiple sclerosis in German patients. J Neurol. 2006;253(10):1365–6.
30. Otaegui D, Zuriarrain O, Castillo-Triviño T, Aransay A, Ruíz-Martinez J, Olaskoaga J, et al. Association between synapsin III gene promoter SNPs and multiple sclerosis in Basque patients. Mult Scler. 2009;15(1):124–8.
31. Liguori M, Cittadella R, Manna I, Valentino P, La Russa A, Serra P, et al. Association between Synapsin III gene promoter polymorphisms and multiple sclerosis. J Neurol. 2004;251(2):165–70.
32. Fernández-Jiménez E, Arnett PA. Impact of neurological impairment, depression, cognitive function and coping on quality of life of people with multiple sclerosis: a relative importance analysis. Mult Scler. 2015;21(11):1468–72.

Publisher's Note