ISSN: 2641-1911
DOI: 10.33552/ANN.2021.10.000750
Archives in Neurology & Neuroscience
Iris Publishers

Short Communication

Some Clinical, Psychological, Laboratory, and Genetic Aspects of Patients with Multiple Sclerosis in Upper Egypt

Hamdy Nageeb El Tallawy, Heba Mohamed Saad Eldin, Amal Mohamed Tohamy, Sara Eltellawy, Ali Mabrouk Bathalath and Mohamed Mostafa Shehab*

Department of Neurology and Psychiatry, Assiut University, Egypt

***Corresponding author:** Mohamed Mostafa Shehab, Department of Neurology and Psychiatry, Assiut University, Egypt.

Received Date: June 21,2021

Published Date: July 21, 2021

Abstract

Aim: Multiple sclerosis is the most prevalent chronic inflammatory disease of the central nervous system. The aim of the study is to show some clinical, cognitive, labarotory and genetic aspects in patients with multiple sclerosis in Upper Egypt.

Materials & Methods: 40 patients with MS recruited along the period from Jan.1st 2017 to Dec.31st2017 and 40 healthy controls were included in the study. Clinical, cognitive (depression, anxiety, and sleep), laboratory (25-hydroxyvitamin D), and genetic (TMEM106B, APOE2, and APOE1) aspcts were assessed.

Results and conclusion: Low serum 25(OH) D level is a major risk factor for MS in Upper Egypt. Vitamin D deficiency increases the risk of developing depression in MS patients. APOE1, APOE2 polymorphism alone, does not affect MS susceptibility.

Introduction

Multiple sclerosis (MS) is the most prevalent chronic inflammatory disease of the central nervous system (CNS), affecting more than 2 million people worldwide (at least 400,000 in the United States), (Neurological Disorders Collaborator Group, 2015) [1]. It is punctuated by fully or partially reversible episodes of neurologic disability, usually lasting days or weeks. Manifestations at presentation include, but are not limited to, monocular visual loss due to optic neuritis, limb weakness or sensory loss due to transverse myelitis, double vision due to brain-stem dysfunction, or ataxia due to a cerebellar lesion [2]. With a prevalence of 50–300 per 100 000 people, about 2·3 million people are estimated to live with MS globally [3]. The female to male sex ratio has increased markedly because of increased incidence of MS in women [4]. Most patients present in early adult life but there is increased awareness of presentation in childhood [5]. Interplay between environmental, genetic, and epigenetic factors have a causal role in MS [6]. Environmental risk factors such as vitamin D deficiency (either due to reduced exposure to sunlight or decreased natural production from sun exposure in ethnic groups with dark skin), diet, obesity in early life, and cigarette smoking may have a role in the development of MS [7]. Development of MS can also be associated with specific infections; for example, late infection as a young adult with Epstein-Barr virus increases the risk of subsequently developing the disease [8].

The increased heritability within families, and the directly proportional decrease in risk with degree of relatedness, provide evidence that genetic factors have a prominent role in the development of MS. Carriers of the HLA DRB1*15:01 allele

are about three times more likely to develop MS than are non-carriers [9]. A genome-wide association study (GWAS) from 2017, identified 31 independent associations within the extended MHC region, including some within class I genes and the non-classical HLA region [10]. The HLA locus accounts for 20–30% of the genetic susceptibility in MS [11]. In addition, GWAS showed that IL2RA and IL7RA re the first two non-HLA associations (International Multiple Sclerosis Genetics Consortium, 2007) [12]. Subsequent GWAS and a meta-analysis31 identified another dozen associations and brought the total number of associations to more than 200 [10].

Axonal or neuronal loss, demyelination, and astrocytic gliosis are the hallmarks of MS pathology which leads to permanent clinical disability. Axonal loss may occur not only acutely in new inflammatory lesions, but also more slowly over time in chronically demyelinated lesions [13,14]. Early MS is usually characterized by acute episodes of neurological deficits known as relapses, that depend on both the location of the CNS region affected by the acute inflammatory demyelinating lesions and the extent of the inflammatory process. Clinical deficits caused by acute inflammatory demyelination could be reversible via restoration of nerve conduction. The restored nerve conduction is more continuous than saltatory, and is achieved because of several changes following demyelination, such as an increase in sodium channels. In addition, remyelination leads to new myelinated internodes, although these are shorter and thinner than normal [15]. Recovery of clinical symptoms could also be secondary to remyelination and cortical plasticity [16,17], which consists of a reorganization of the functional activation of cortical regions to maintain clinical function [18].

Clinical, imaging, and laboratory findings should be integrated for diagnosis of MS. Clinical expertise and MRI are necessary to demonstrate evidence of dissemination in time and space and, importantly, to exclude other neurological conditions [19]. The diagnostic criteria, known as the McDonald Criteria, have evolved as technology has improved to refine definitions, become simpler, and more accessible and applicable to a larger proportion of the population while maintaining specificity and sensitivity [20,13,14].

The majority of patients who develop MS begin with a single episode, termed a clinically isolated syndrome (CIS), and may have a second episode (or relapse), which marks the onset of clinically definite MS. Patients with at least 2 relapses are described as having relapsing remitting MS. 15% and 30% of them may develop progressive disability over a long-term follow-up, with or without superimposed relapses (described as secondary-progressive MS) [21,22]. About 15% of patients develop primary progressive MS from the outset [23]. Patients with incidental MRI findings consistent with MS, known as radiologically isolated syndrome (RIS), have been described [24]. 34% of patients with RIS develop a first acute clinical event consistent with CIS or MS within 5 years [25].

Cognitive impairment is a common feature in MS affecting approximately 43%-72% of patients and involving cognitive functions, such as memory, processing speed, attention, and executive function [26]. Rocca et al. [27] investigated the dynamic interaction between cognitive reserve and global/regional measures of brain white matter and gray matter damage and their effect on cognitive performance in 54 MS patients and 20 healthy controls using baseline and two-year three-dimensional T1-weighted scans. Initially, MS patients show atrophy of the deep gray matter nuclei, gray matter/white matter frontal-temporal-parietal-occipital regions, and left cerebellum [27].

In this study, clinical, imaging, and psychological assessment was done for MS patients. Cognitive functions, depression, anxiety, and sleep were assessed. Social support and psychological resilience were also assessed. Some biochemical tests and genetic analysis were done for patients and controls.

Patients and Methods

Forty patients with MS were recruited along the period from Jan.1st 2017 to Dec.31st2017 from inpatient neurology departments and outpatient neurology clinics of Assiut University hospitals in a multicenter case-control study.

Inclusion criteria: Patient were diagnosed according to revised McDonald's criteria (2017) [13,14]. The second group: 40 age and sex cross-matched healthy individuals were included as the control group.

Exclusion criteria: Patients proved to have autoimmune disease; Bechet disease and systemic lupus erythematosus and patients with other neurologic disorder mimic MS were excluded from the study.

Methods

Complete history taking, clinical examination and brain and spine magnetic resonance imaging with gadolinium enhancement were performed for all patients. Cognitive functions were assessed using Arabic form of Mini-mental state examination (MMSE) [28], the test was carried out as described in the original version [29], and Arabic version [30] of the Wechsler Adult Intelligence Scale–Revised (WAIS–R) [31]. Depression, anxiety, and sleep were assessed using Arabic version (West, 1985) of Beck Inventory Depression Score (BIDS), Arabic version of future anxiety scale, and Arabic version sleep disorder scale respectively. Arabic version of social support scale and psychological resilience scale were also applied to the patients. Patients were assessed using Timed 25-foot walk test and The Expanded Disability Status score (EDSS) [32]. Serum level of 25-hydroxyvitamin D was measured by enzyme linked immunosorbent assay (ELISA) technique. Genomic DNA was extracted from venous blood using a pure linked kit and the procedure recommended by the manufacturer (Vivantis). Extracted DNA was quantified using a nanodrop analyzer (ND-1000) spectrophotometer (Nanodrop Technologies Inc., Ortenberg,

Germany) for TMEM106B (rs1990622), APOE2 (rs429358), and APOE1 (rs 7412). Polymorphisms were analyzed by an Taqman allelic discrimination assay according to manufacturer's protocol (Applied Biosystems, Stepone Plus). Genotyping was performed using real-time PCR with a thermal profile of 60ºc for 30 sec., 95ºC for 10 min, 95ºC for 15 sec., and 60ºC for 90 sec.

Statistical Analysis

Continuous data are expressed as the mean ± standard deviation, and categorical data are expressed as numbers (percentages). Comparisons of differences in the categorical data were performed using the chi-squared test, and distributions of continuous variables were analyzed by a one-way ANOVA test and a binary logistic regression model. All tests were 2-tailed, and a p-value of less than 0.05 ($P < 0.05$) was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL, USA).

Results

Table 1: Baseline demographic data of MS patients.

		Cases		Controls		P-value
	(n= 40)		(n= 40)			
	No.	%	No.	%		
Sex:	Male	11	27.5	11	27.5	--
	Female	29	72.5	29	72.5	
Age: (years)	< 25	12	30	11	27.5	--
	25-30	14	35	13	32.5	
	> 30	14	35	16	40	
	Mean ± SD	29.37 ± 7.85		29.45 ± 7.30		0.965
Residence:	Rural	21	52.5	--	--	--
	Urban	19	47.5	--	--	
Occupation:	Working	19	47.5	--	--	--
	Not working	10	25	--	--	
	Housewife	11	27.5			--
Education:	Low education	10	25	--	--	--
	Middle education	16	40	--	--	
	High education	14	35	--	--	
Contraception use among married females	Yes	2	5	--	--	--
	No	38	95	--	--	
Smoking:	Yes	5	12.5	--	--	--
	No	35	87.5	--	--	
Consanguinity:	Yes	7	17.5	--	--	--
	No	33	82.5	--	--	
Family history of MS:	Yes	1	2.5	--	--	--
	No	39	97.5	--	--	
Comorbidities:	DM	2	5	--	--	--
	Drug abuse	1	2.5	--	--	
	No	37	92.5	--	--	

n: number, %: percentage

Table 2: Clinical data of MS patients.

		No. (40)	%
Duration of illness:	Less than 1 year	7	17.5
	1-5 years	23	57.5
	More than 5 years	10	25
	Mean ± SD	4.56 ± 5.75	
	Median (Range)	3.0 (0.2-28.0)	

Age of onset: (years)	< 20	6	15
	20-25	21	52.5
	> 25	13	32.5
	Mean ± SD	24.83 ± 6.80	
Total number of attacks:	One attack	16	40
	Two attacks	10	25
	Three attacks or more	14	35
	Mean ± SD	2.60 ± 2.09	
	Median (Range)	2.0 (1.0-9.0)	
Course:	Relapsing remitting	35	87.5
	Secondary progressive	1	2.5
	Primary progressive	4	10
Time between first and second attack: (months)	< 12	11	45.8
	≥ 12	13	54.2
	Mean ± SD	13.13 ± 12.03	
	Median (Range)	12.0 (3.0-60.0)	
Time between onset and diagnosis: (months)	< 6 months	18	45
	≥ 6 months	22	55
	Mean ± SD	10.33 ± 13.99	
	Median (Range)	6.0 (1.0-60.0)	
25-foot walk test impairment:	Normal	22	55
	Impaired	18	45

Table 3: Initial presenting symptoms of MS Patients.

Initial presenting symptoms	No. (40)	%
INO	13	32.5
Ataxia	12	30
Motor weakness	5	12.5
Trigeminal neuralgia	2	5
optic neuritis with weakness	1	2.5
ataxia with INO	2	5
trigeminal neuralgia with INO	1	2.5
INO with numbness	4	10

Table 4: MRI findings in MS patients.

MRI	No. (40)	%
Periventricular lesions	40	100
Juxtacortical lesions	39	97.5
Brainstem lesions	17	42.5
Pericallosal lesions	14	35
Cervical spine lesions	9	22.5
Cerebellar lesions	8	20
Enhancement lesions	2	5

Visual evoked potential was normal in 15 patients (37.5%), while it showed mild, and moderate affection in 15 (37.5%) and 10 (25%) patients respectively. The mean MMSE score for MS patients was 28.58 ± 0.96. 55% of MS patients had average IQ performance, the mean 89.78 ± 10.01. The verbal performance 67.5% was average, the mean was 91.95 ± 9.75 and total mean was 93.58 ± 11.23. There was significant correlation between MMSE and Wechsler performance score as shown in Figure 1 and Tables 7-10.

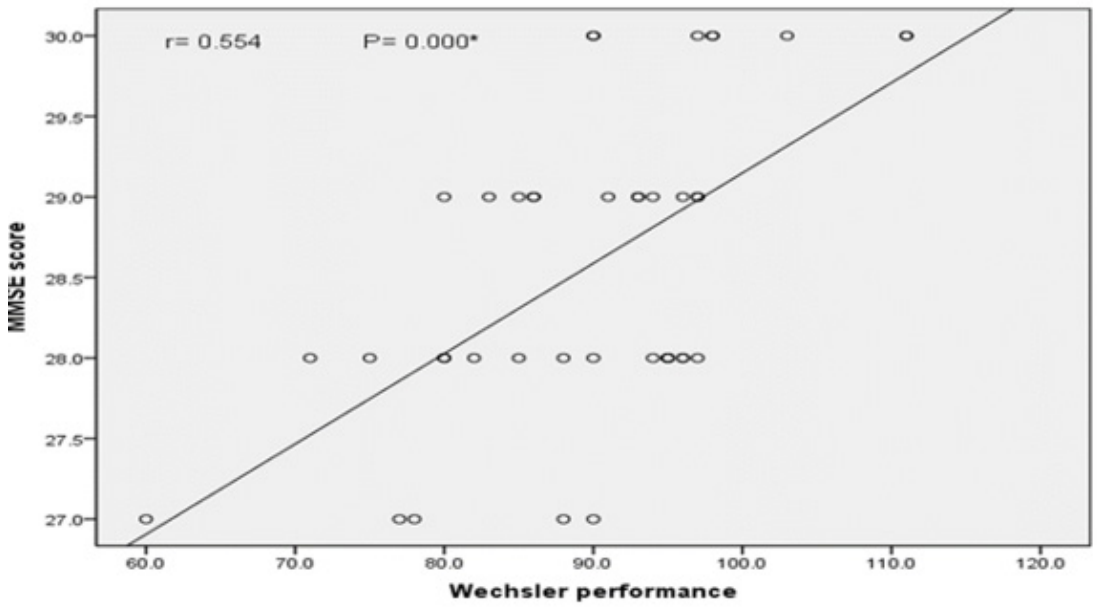

Figure 1: Correlation between MMSE and Wechsler performance score.

Table 5: Expanded disability status score (EDSS) groups.

EDSS score	No. (40)	%
Mild (0-3)	22	55
Moderate (3.5-5)	5	12.5
Severe (6 and more)	13	32.5
Mean ± SD	4.05 ± 2.47	
Median (Range)	3.0 (1.0-8.0)	

Table 6: Relation of degree of disability at time of interview to initial presenting symptom.

Mild 0-3 (N=22)		EDSS SCORE		
		Moderate 3.5-5 (N=5)	Severe 6 and more (N= 13)	
Initial first presenting symptoms	motor weakness (N=5)	4(18.2%)	0(0%)	1(7.7%)
	Ataxia (N=12)	4(18.2)	2(40.0%)	6(46.2%)
	INO (N=13)	10(45.5%)	2(40.0%)	1(7.7%)
	trigeminal neuralgia (N=2)	0(0%)	0(0%)	2(15.4%)
	optic neuritis with weakness (N=1)	0(0%)	0(0%)	1(7.7%)
	ataxia with INO (N=2)	0(0%)	1(20.0%)	1(7.7%)
	trigeminal neuralgia with INO (N=1)	0(0%)	0(0%)	1(7.7%)
	INO with numbness (N=4)	4(18.2)	0(0%)	0(0%)

Table 7: Psychological resilience scale among studied MS patients and control groups.

		patients		Controls		P-value
	(n= 40)		(n= 40)			
	No.	%	No.	%		
Personal competence:	Low (less than 29)	40	100	0	0	0.000*
	High (more than 29)	0	0	40	100	
	Mean ± SD	24.18 ± 1.99		31.03 ± 1.94		0.000*
Problem solving:	low (less than 24)	39	97.5	1	2.5	0.000*
	high (more than 24)	1	2.5	39	97.5	
	Mean ± SD	17.70 ± 2.37		25.42 ± 1.39		0.000*

Flexibility:	Low (less than 31)	40	100	0	0	0.000*
	High (more than 31)	0	0	40	100	
	Mean ± SD	24.17 ± 1.41		35.28 ± 2.64		0.000*
Managing emotion:	Low (less than 21)	39	97.5	1	2.5	0.000*
	High (more than 21)	1	2.5	39	97.5	
	Mean ± SD	16.80 ± 2.03		23.15 ± 1.89		0.000*
Optimize:	Low (less than 18)	39	97.5	0	0	0.000*
	High (more than 18)	1	2.5	40	100	
	Mean ± SD	15.52 ± 2.76		20.02 ± 1.48		0.000*
Social relation:	Low (less than 28)	38	95	0	0	0.000*
	High (more than 28)	2	5	40	100	
	Mean ± SD	24.90 ± 1.26		30.38 ± 1.71		0.000*
Faith:	Low (less than 30)	40	100	0	0	0.000*
	High (more than 30)	0	0	40	100	
	Mean ± SD	27.60 ± 0.59		31.72 ± 1.54		0.000*
Total SRS:	Low (less than 180)	40	100	0	0	0.000*
	High (more than 180)	0	0	40	100	
	Mean ± SD	150.35 ± 5.04		197.00 ± 5.80		0.000*

Table 8: Sleep disorders scale among studied MS patients and control groups.

Sleep disturbance		**patients**		**Controls**		**P-value**
	(n= 40)		**(n= 40)**			
	Mean ± SD		**Mean ± SD**			
Insomnia		14.75 ± 3.61		16.03 ± 3.22		0.1
Hypersomnia		10.23 ± 3.05		10.88 ± 2.32		0.287
Interrupted sleep		9.35 ± 1.59		10.25 ± 1.58		0.013*
Night mare's		6.75 ± 1.24		9.80 ± 1.32		0.000*
Night terrors		5.15 ± 0.36		7.25 ± 1.51		0.000*
Sleep walking		4.00 ± 0.00		6.07 ± 1.12		0.000*
Total Sleep disorders scale		49.43 ± 7.65		59.97 ± 6.66		0.000*
Total Sleep disorders scale	No sleep disturbance (36-71)	40	100	40	100	-
	Sleep disturbance (72-100)	0	0	0	0	

Table 9: Serum levels of 25-hydroxy vitamin among studied MS patients and control.

25 –hydroxy vit D	**patients**		**Controls**		**P-value**
	(n= 40)		**(n= 40)**		
	No.	**%**	**No.**	**%**	
Sufficient (30-100 ng/ml)	2	5	14	35	0.000*
Insufficient (10-29 ng/ml)	27	67.5	26	65	
Deficient (<10 ng/ml)	11	27.5	0	0	
Mean ± SD	14.59 ± 9.40		31.10 ± 7.19		0.000*
Median (Range)	12.0 (5.0-50.0)		29.0 (21.0-50.0)		

Table 10: Genetic analysis of APOE1, APOE2 and TMEM106B among MS patients and control groups.

		patients		**Controls**		**P-value**
	(n= 40)		**(n= 40)**			
	No.	**%**	**No.**	**%**		
APOE1:	Homogenous1=CC= wild	38	95	33	82.5	
	Homogenous2=TT= mutant	0	0	0	0	
	Heterogeneous= CT=carrier	2	5	7	17.5	

APOE2:	Homogenous1=CC= wild	2	5	0	0	
	Homogenous2=TT= mutant	38	95	40	100	
	Heterogeneous= CT=carrier	0	0	0	0	
TMEM106B:	Homogenous1= CC=mutant	1	2.5	6	15	
	Homogenous2= TT=wild	33	82.5	34	85	
	Heterogeneous= CT=carrier	6	15	0	0	

Discussion

Multiple sclerosis (MS) is a progressive demyelinating and neurodegenerative disease of the central nervous system (CNS). The pattern of symptoms of MS is complex, variable and unpredictable. MS has sensorimotor, cognitive, affective, autonomic, special sense, and many other manifestations. This study tried to show the various manifestations of MS in a group of 40 patients with studying some biochemical and genetic aspects.

The female: male ratio was 2.9:1. This is in agreement with many previous studies, which showed that MS is more prevalent in the female more than male similar to the corresponding ratios measured previously in Egypt 2.57:1 (Zakaria et al., 2016). For unknown reasons, approximately three quarters of people with multiple sclerosis are female, as is common in diseases that are considered autoimmune [33]. The range of age of the patient with MS was 17-48 years (29.37 ± 7.85). These results agree with many other studies such as Tutuncu et al, (2013) [34] that found most individuals are diagnosed with MS at age 20–50 years [34].

In this study, 35 patients (87.5%) presented with relapsing remitting course, 4 patients (10%) presented with primary progressive course and 1 patient (2.5%) presented with secondary progressive course. Tamás Biernacki et al. [35] showed that 65.71% of their patients had relapsing–remitting course, 24.29% had secondary progressive course, 7.14% had primary progressive disease course and 2.86% patients were diagnosed with CIS [35]. In this study, only one male patient has positive family history of MS (his sister). Akkad et al. study reported that the risk of MS incidence in first-degree relatives is increased (3.4–5.13%) in Canada, England, Scotland and Belgium. Twin studies demonstrated genetic susceptibility in monozygotic twins with 25–30% concordance rate and 0.25–0.76 heritability index [36]. The most frequent neurologic manifestations along whole MS course were motor manifestations (57.5%), followed by sensory manifestations (55%). 15% of patients had manifestations of optic nerve affection. Azadvari et al (2020) in their study showed that 28% of MS patients suffering from neurogenic bladder are of older age or have longer duration of disease [37]. The mean EDSS score of patients was 4.05 ± 2.47 (Table 5). It is nearly similar to a new registry in Egypt (3.6) as reported by (Zakaria et al., 2016). It was nearly similar to that reported in North Tonawanda, the mean of EDSS was 5.02 ± 1.67 [38]. The mean MMSE score for MS patients was 28.58 ± 0.96. These results agree with Shamsian et al. [39] where the mean of MMSE score was 27.23 ± 3.27 in MS patients compared to 28.96 ± 2.00 in control group [39]. Beck Depression Inventory (BDI) score was significantly higher in all types of MS patients in comparison to control group. 82.5% of MS patients had depression with different degrees of severity with 25% of patients had severe depression. The mean of the patients was 21.90 ± 9.61. There was positive significant correlation between depression assessed by BDI score and MS disability assessed by EDSS. This is in agreement with many other studies [40,41].

Future Anxiety Scale was significantly higher in all types of MS patients in comparison to control group. The mean of total future Anxiety Scale for patients was 51.35 ± 11.85. Wallis et al. [42] found that almost half of the patients (42%) had clinically significant anxiety symptoms. Wallis et al. [42] Other studies also reported that anxiety and depression are very prevalent in MS patients. Prevalence of both conditions range between 25–50%, which is much higher than the general population [43,44].

Social support scale was significantly higher in family support and in total social support among MS patients with comparison to control group. The mean of social support in family for patients 59.18 ± 11.54. In addition, the mean for control 70.75 ± 5.66. Also the mean of total support for the patient is 125.85 ± 20.56. Also there was significant correlation between Social support scale in family support and out family support among patients and level of education. Mikula et al. [45] suggested that social support may had a buffering effect, and that in case of a long-term health threatening condition, social support from family, friends, and significant others may protect MS patients from more severe depression [45]. Psychological resilience scale was significantly lower in all types of MS patients in comparison with control group (P. value 0.000*). Another study, included 185 patients with early MS, showed that high psychological resilience was associated with better objective performance on the MS and motor outcomes, especially gross motor function (i.e. grip strength, gait endurance). This relationship of psychological resilience to outcomes was independent of mood and fatigue [46].

Garland et al. [47] have found sleep disorders to be four times higher in patients with MS as compared to healthy populations [47]. In a previous Chinese study, Sleep disorders among patients with MS was 64.9% [48]. In this study, levels of vitamin D among total and all phenotypes of MS patients (14.59 ± 9.40) were significantly lower than controls (31.10 ± 7.19). Zamazam et al. [49,50] studied the status of vitamin D in MS Egyptian patients and reported a significant vitamin D insufficiency in Egyptian patients

with MS (65.7%) as well as in controls 21.2% [49,50]. Behrens et al. [51] reported vitamin D deficiency already in very early phases of MS [51]. A cross-sectional study of 50 RRMS patients revealed a vitamin D deficiency with a mean of 22.3 ng/ml /ml [52]. In a Moroccan study of 113 MS patients, 97.3% of patients were vitamin D deficient with a mean of 11.69 ng/ml [53]. Bäcker-Koduah et al. [54] found vitamin D deficiency is common in RRMS patients living in the north-eastern part of Germany [54]. There is an ongoing debate whether vitamin D deficiency represents a risk factor for MS or whether this association is rather due to reverse causality, i.e., low vitamin D levels are a result of MS, for example as a consequence of reduced outdoor activities. In a study on a different cohort of early MS or CIS patients, there was vitamin D deficiency already in very early phases of MS [51] which also supports the interpretation that vitamin D deficiency is rather a cause than a consequence of MS.

In the current study, a negative but insignificant correlation was found between serum level vitamin D and disease disability as measured by EDSS. Our results agreed with Rito et al. [52] who found no correlation between vitamin D levels and EDSS scores, or duration of disease. The lack of significance in our study might be related to small sample size and the reliance on EDSS only as a marker for disease severity. In our study, the more deficient 25-hydroxy Vitamin D, the more severity of depression. This agree with Kotb et al. [41] who demonstrated that lower vitamin D levels are associated with higher depressive scores.

In the present study, there were significant difference between patients and controls regarding TMEM106B gene (P-value .008). There was no significant difference between patients and controls regarding APOE1 and APOE2 genes. These results agree with many other studies for APOE1 and APOE2 such as Flowers et al (2020) and Yamazakiet al (2019) [55,56] who found that APOE alleles are not associated with MS risk or severity [55,56]. Schrewe et al. [57] studied linear regression analyses of MS and APOE rs7412 and rs429358. In the overall analyses, 3237 MS patients did not reveal statistically significant association with MS severity and APOE [57]. A total of 552 participants from the German National MS cohort, a multicenter, prospective, and observational study, were included. The putative role of APOE polymorphisms on the cognitive outcome parameters in patients with MS had been assessed. Neither APOE2 carrier status nor APOE4 heterozygosity showed an influence on the evaluated cognitive outcome parameters [58,59].

Conclusion

In conclusion, the most robust predictor of MS disability is MS course outcomes. Low serum 25(OH) D level is a major risk factor for MS in Upper Egypt. Vitamin D deficiency increases the risk of developing depression in MS patients. APOE1, APOE2 polymorphism alone, does not affect MS susceptibility as we cannot exclude other HLAG polymorphic sites which may work together to regulate MS risk. Further studies on larger number of are needed to study the role of TMEM106B gene polymorphism in pathogenesis of MS. This study highlights the importance of focusing research on identifying different clinical, psychological, biochemical, and genetic biomarkers capable of characterizing the course and severity of MS.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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