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Original Article

Factors Affecting Prognosis in Patients with Relapsing Remitting Multiple Sclerosis.

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ABSTRACT

Background: Multiple sclerosis (MS) is an autoimmune neurodegenerative disease of central nervous system characterized by inflammation, demyelination, as well as neuro-degeneration. The aim of the study is to detect factors affecting the degree of disability in multiple sclerosis patients for early identification and prognosis estimation.

Methods: Ninety relapsing remitting multiple sclerosis (RRMS) patients (36 males and 54 females) were included in this retrospective cohort study in the period from February 2020 to October 2022 in Zagazig University hospital and outpatient MS clinic. Full general and neurological assessments were done to all patients. Severity was evaluated by expanded disability status scale (EDSS). Physical and psychological MS impact scales were also done. Magnetic resonance imaging (MRI) for brain and spine were done with gadolinium enhancement; visual evoked potential was done for the patients.

Results: Among 90 patients with RRMS, 52 (57.8 %) patients had EDSS ≤3 (group A), while 38 patients (42.2%) had EDSS >3 (group B). Multi-logistic regression analysis showed that black holes, total cholesterol (TC) and disease modifying therapy (DMT) use were the independent factors affecting disability in RRMS patients. There was significant positive correlation between EDSS and Visual evoked potential (VEP) latency of RT eye and there was a negative correlation between EDSS and VEP amplitude of the RT eye.

Conclusions: Black holes, TC and DMT use were independent factors affecting prognosis of RRMS that help early estimation and intervention.

Key words: multiple sclerosis, total cholesterol, black holes, disease modifying drug, EDSS, prognosis

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease that is considered as a leading reason of non-traumatic disability in young adult worldwide **(1).**

In early disease course, patients have an intermittent course, which advance later into a progressive form and can seriously affect the quality of life **(2)**.

Progression of disease disability needs to be observed to predict accurate prognosis **(3).**

Expanded disability status scale (EDSS) is the gold standard to assess disability as it is a common, accepted and used scale for detecting prognosis **(4).**

The aim of this study is to detect factors affecting the degree of disability in multiple sclerosis patients for early identification and prognosis estimation.

METHODS

The data from the files of 90 patients with RRMS admitted to Neurology Department and MS outpatient clinic in Zagazig University hospitals in the period from February 2020 to October 2022 were retrospectively reviewed.

There were 36 males and 54 females. Their age was ranging from 17 to 50 and mean age (±SD) of 34.4± 10.5.

The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving

humans. The study was approved by the Ethical Committee of our Faculty (ZU-IRB# 4164/22-11-2017). All patients who agreed to participate in our study were informed and a written consent was obtained from them.

Diagnosis of MS patients was done according to recent modified McDonald criteria 2017 **(5)** and patients with Expanded disability status score (EDSS) between 1.5- 6 to include ambulatory patients **(6).**

Relapsing Remitting patients were classified according to disability into 2 groups: Group A included patients whose EDSS is equal or less than 3 and included 52 patients and group B included patients whose EDSS is more than 3 and included 38 patients.

We excluded patients with known history of other neurologic diseases (i.e. cerebrovascular stroke, brain tumor, neurodegenerative disorders and other demyelinating diseases), patients with concomitant medical diseases such as hypertension, diabetes mellitus, liver diseases, renal diseases, pulmonary diseases, patients with present infection and female who was pregnant and patients with progressive MS.

Detailed medical and neurological history according to MS sheet with attention to medical disease, complete general and neurological examination, criteria of MS (duration of disease, annualized relapse rate, total number of relapses, and disease modifying therapy (DMT) use or not) were assessed to all patients. Annual relapse rate (ARR) was calculated according to **Siomon and colleagues,** by dividing total number of relapses by disease duration **(7).**

Assessment of disease disability was assessed using EDSS **(6).** Disease activity was assessed using disease activity scale and criteria which include physical and psychological Multiple Sclerosis impact scale **(8)**.

Radiological investigations were done for all patients including Magnetic resonance imaging (MRI) of the brain and cervical and dorsal spinal cord. A standardized protocol of MRI comprising T2-weighted and T1-weighted gadolinium enhancing (T1Gd+) were performed using 1.5 tesla (Achieva, Philips Medical System).

Laboratory investigations include lipid profile (total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL)), CRP and uric acid. TG was performed with enzymatic method: glycerol-3-phosphate (GPO)-peroxidase (POD), TC was done by cholesterol oxidase method, HDL and LDL by direct method.

STATISTICAL ANALYSIS

Data were transferred to SPSS for analysis **(9)**. A *t*-test; chi-square test was used to compare the qualitative data between the groups. Statistically significant differences factors between the two groups were subjected to multiple logistic regression analysis (the model was established using stepwise regression). Statistically significant (S) was considered as P value < 0.05, highly statistically significant (HS) was considered as P < 0.01 and P ≥ 0.05 was considered none statistically significant (NS).

RESULTS

This retrospective cohort study included ninety patients with RRMS, they were divided into 2 groups; group A included 52 patients whose EDSS was 3 or below and group B included 38 patients whose EDSS more than 3.

The mean age of group A was 34.4± 10.5 while the mean age of group B patients was 37.0±7. Group A patients has 35.6% male and 65.4% females, while group B had 47.4% males and 52.6% females, group B had highly statistically significant higher disease duration than group A. The number of patients with initial motor manifestations is considered highly statistically significant increased in group B than group A, both groups showed statistically significant difference regarding disease modifying therapy (DMT) use, there was highly statistically significant increased total number of relapses among group B patients while higher annualized relapse rate in group A than group B with no statistically significant difference **(Table 1)**.

There was statistically significant higher total cholesterol (TC), triglycerides (TG) and low density lipoproteins (LDL) in group B than group A patients **(Table 2)**.

A statistically significant increase number of cervical cord atrophy was found in group B patients and there was highly statistically significant increase in black holes and brain atrophy in the same patients **(Table 3)**.

A significant positive correlation between EDSS and Visual evoked potential (VEP) latency of RT eye and a negative correlation between EDSS and VEP amplitude of the RT eye was found **(Table 4)**. There was a statistically significant increased physical MSIS in group B patients than group A **(Table 5)**.

Multiple logistic regression analysis revealed that TC, number of black holes and DMT usage were independent factors manipulating the degree of patients' disability in RRMS with the difference between factors being statistically significant **(Table 6)**.

Table (1) Demographic and clinical characteristic data of studied groups:

	Group A N=26		**Group B N=19**		**Test of significance**	**P**
Age X±(SD)	34.4± 10.5		37.0±7		t=1.2	0.22
Gender	N	%	N	%	χ^2=1.49	0.22
male Female	18 34	34.6 65.4	18 20	47.4 52.6		
BMI (KG/m^2)	29.4± 4.2		30.2± 3.8		t= 0.69	0.46
Duration X±(SD)	1.25±1.0		4±2.35		t=5.36	<0.0001**
Initial manifestation	N	%	N	%	χ^2=19.49	<0.001**
Motor	26	50.0	32	84.2*		
Sensory	14	26.9	0	0.0		
Cerebellar	2	3.8	0	0.0		
Brainstem	0	0.0	2	5.3		
Visual	10	19.2	4	10.5		
DMD use	42	72.4	12	37.5	5.24	0.02*
TRN X±(SD)	2.01±0.27		4.47±2.7		t=4.45	<0.001**
ARR X±(SD)	2.81± 1.79		2.5±1.5		t=1.2	0.16

EDSS : Expanded Disability Status Scale; TRN : total relapse number; ARR : annualized relapse rate; DMD: disease modifying drug; * significant, **highly significant.

Table (2) Laboratory findings in studied groups:

	Group A N=26	**Group B N=19**	**Test of significance t test**	**P**
Total cholesterol	154.7± 26.1	179.6±25.9	3.16	0.002*
triglycerides	124.3±26.2	146.2± 32.7	2.49	0.016*
LDL	86.1± 23.9	110.6 ±32.9	2.89	0.005*
HDL	68.26± 14.7	67.3± 21.6	0.16	0.86
CRP	2.6±3.7	2.2±1.78	0.46	0.64
Uric acid	4.7± 1.2	4.7±1.3	0.03	0.97

LDL: Low density lipoprotein; HDL: High density lipoprotein; CRP: C-reactive protein.

Table (3) Radiological finding in studied groups:

	Group A N=52		**Group B N=38**		**Test of significance χ^2**	**P**
	N	%	N	%		
Black holes	4	7.7	28	73.7	41.73	<0.001**
Brain atrophy	0	0.0	10	26.3	12.85	<0.001**
Enhanced brain lesions	26	44.8	16	50.0	1.57	0.2
Cervical cord atrophy	8	15.4	16	42.1	4.01	0.004**

Table (4): Correlation between EDSS and VEP:

VEP	r	P
Latency		
RT	**0.33**	**0.04***
LT	**0.23**	**>0.05**
Amplitude		
RT	**- 0.32**	**0.05***
LT	**- 0.22**	**>0.05**

VEP: Visual evoked potential; EDSS: Expanded disability status score

Table (5): Multiple sclerosis impact scale among groups:

	Group A N=26	Group B N=19	Test of significance t test	P
physical	46.96± 15	62.6±20.3	2.97	0.004*
psychological	54.4±17	65.6± 21.87	1.94	0.058

Table (6): Multiple logistic regression analysis of factors affecting disability in RRMS patients

	ß± SE	95% CI	P
Black holes	0.36± 0.16	0.03- 0.69	<0.005
TC	0.03±0.002	0.001-0.009	<0.005
DMD use	0.04± 0.002	0.001- 0.009	<0.005

RRMS: relapsing remitting multiple sclerosis; TC: total cholesterol; DMD: disease modifying drug.

DISCUSSION

The progressive neurodegenerative characteristic of MS that lead to irreversible disability **(3)** could be markedly reduced by early and appropriate treatment **(10).** We conducted this study to detect factors affecting prognosis and degree of disability in relapsing remitting multiple sclerosis patients for early identification and prognosis estimation.

In our study, group B which carry worse prognosis had more age than group A (37± 7 versus 34.4± 10.5), but with no significant difference. In line with our results, **Manouchehrinia and colleagues** showed that higher age was associated with more disability **(11)**.

Male to female ratio in Group B was more than group A (34.6%**:** 65.4% versus 47.4%**:** 52.6%) but with no difference between both groups. In accordance with our result, other studies reported that male carry worse prognosis and faster disability accumulation than females **(12-14)**.

Regarding initial manifestations, we found that 84% of patients in group B initially manifested with motor manifestations, but 50% of group A were initially manifested with motor symptoms with highly statistically significant correlation between initial motor attack and EDSS, initial visual symptoms were more common in group A (19.2% VS 10.5 % in group B). Initial sensory symptoms were first manifestation in 26.9% of group A but 0% in group B, this indicating that first attack with sensory manifestations carry good prognosis. These results go with previous studies estimated that aggressive disease course was associated with pyramidal affection in the first year of disease **(3, 15, 16)**.

On the contrary, **Uludag and colleagues** did not find any correlation with first attack symptoms and disease progression over 10 years of follow up **(17)**.

A highly significant correlation was found between duration of disease and EDSS (P<0.001), these results agree with those of **Xue and colleagues (2)** and **Manouchehrinia and colleagues (11)**.

We notice that patients with higher total relapse number had higher EDSS with statistically significant correlation, this go in line with **Ulundag and colleagues;** who reported significant association between frequent relapses in the first 5 years of the disease with disease progression. **Ulundag et al.** demonstrated that gender, age and first attack symptoms were not associated with the increase in EDSS **(17)**.

Also, **O'Connor and colleagues** reported higher relapse rate in first 2 years was associated with accumulation of disability **(18)**. The study of **Xue and colleagues** showed that number of relapses, ARR and disease duration were important factors affecting disability **(2)**. In contrary, many studies reported that relapse rate has no relation with prognosis **(3, 19)**. Our study demonstrated that the ARR in group A was more than group B with

no significant difference. Although other studies supported that higher relapse rate was associated with higher disability **(20, 21).** This may be due to longer disease duration in group B than group A leaded to more ARR in group A than group B.

Further analysis with multivariate logistic regression showed that black holes, TC and DMTs use were independent factors associated with disability progression in MS patients. Currently more than one disease modifying therapy approved be FDA for treatment of RRMS, studies suggest that DMTs can reduce disability risk **(22)**.

In our study, we found that interferon beta 1B was the most drug used, followed by fingolimod and dimethylfumarate, then teriflunomide and rituximab; and there was statistically significant correlation between number of patients who received DMTs and the EDSS, since 72% of group A were on DMT and 37.5% of group B were on DMTs. Our results go with **Healy and colleagues** and **Eissa and colleagues,** who found that DMTs diminished the risk of disability worsening **(3, 23)**.

Patients` lipid profile was a factor that affects degree of disability in RRMS. We noticed that total cholesterol, triglycerides and LDL were statistically significant higher in group B than group A**. Tetty and colleagues** and **Jorissen and colleagues** observed this correlation **(24, 25)**. It stimulates production of inflammatory cytokines that lead to accumulation of active monocytes in the site of lesion and further exacerbate the demyelination. Moreover, **Tetty and colleagues** reported that high TC/HDL ratio were associated with disability progression **(26)**. In contrast, TG was reported to be not related to the degree of disability in MS patients in another study **(27)**.

As regard imaging in the present study, there was highly significant correlation between number of patients with black holes on T1 and high EDSS (P<0.0001). This matched with **Hickman and colleagues** and **Abdelhafeez and colleagues (28, 29).**

A study was conducted in Egypt and divided patients into three groups according to the EDSS score (mild from 0-3, moderate from 3.5-6 and severe more than 6) found highly significant correlation of EDSS with T1 hypointense lesions **(29)**.

Brain atrophy is gradual loss of brain volume, it arises early in the disease course and accelerate with disease progression **(30).**

In the present study, a significant number of patients with whole brain atrophy with high disability. Similarly, many studies found disability progression over 10 years follow up was associated with increase cortical atrophy and enlarged ventricular CSF spaces and not related to number of relapses or T2 lesion load **(31, 32)**.

Also spinal cord atrophy represent an important element in disability, a statistically significant higher incidence of cervical cord atrophy in group B patients was found, this coincides with **Kearny and colleagues (33) and Kolind and colleagues (34).**

Visual evoked potential (VEP) has a helpful role in the early detection of sub clinical changes of nerve tract demyelination and monitoring the signs of axonal damage **(35-37).**

There was strong positive correlation between EDSS and VEP latency in the right eye, but there is a negative correlation between EDSS and VEP amplitude in the right eye. This coincides with **Kantorova and colleagues** who found relationship between EDSS and VEP latencies in both eyes but amplitudes did not associated with EDSS **(38)**.

The Multiple Sclerosis Impairment Scale (MSIS) is a measure of deficits accumulation assessed by neurological examination, it measures disease impact on normal daily life. In our study, the physical impact scale has positive significant correlation with EDSS, as shown in **table (5)**, but no correlation was found between psychological impact score and EDSS this coincides with **Mc Guigan and Hutchinson (39)** and **Costelloe et al (40)**, they found highly significant correlation between EDSS and physical MSIS (P< 0.001).

CONCLUSION

In conclusion, the degree of disability is influenced by several factors and there is no particular independent factors affect it, so monitoring, early intervention and early DMTs administration help to improve prognosis and quality of life in patients with MS. other prospective and larger size samples studies are needed to confirm the results of this study.

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