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Neuropsychiatric Manifestations of Multiple Sclerosis in Egyptian Patients

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic inflammatory central nervous system (CNS) disease, arising from a complex interaction of both environmental and genetic factors. MS affects individuals during the most productive time of their lives, and directly limits their work capacity, leading to major social and economic consequences.

Objectives: The aim of the current work was to study neuropsychiatric manifestations in multiple sclerosis patients and to understand their correlation with the degree of clinical disability.

Patients and Methods: A cross-sectional randomized study included a total of 40 consecutive M.S. patients (26 female and 14 males with mean age ± SD 32.60 ± 10.01) attended at MS Outpatient Clinics of Al-Azhar University Hospitals (Al Hussein and Bab Elshierya) and 20 controls during the period from January 2018 until February 2019.

Results: The present study showed that there was a highly significant difference between patients and controls groups regarding Beck scale score for depression (p =0.005). There was 52.5% of MS patients had depression (while 25% of control subjects had depression). The study showed that there was significant positive correlation between beck scale score and EDSS scale score for disability a (p value =0.048 r=0.315). There was a highly significant difference between patients and control group regarding Hamilton scale score for anxiety as (P-value = 0.002).

Conclusion: An understanding of neuropsychiatric disorders in MS is important for all professionals involved in the care of people with MS. These disorders affect about half of patients.

Keywords: Neuropsychiatric Manifestations, Multiple Sclerosis

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory central nervous system (CNS) disease, arising from a complex interaction of both environmental and genetic factors **(1).**

MS affects individuals during the most productive time of their lives, and directly limits their work capacity, leading to major social and economic consequences **(2).** While Middle Eastern and North African (MENA) countries were previously considered areas of low– moderate risk of MS **(3),** there are evidences now that suggests a rising prevalence of MS in this region **(4, 5).**

MS comprises manifestations of acute, as well as chronically accumulating symptoms, including numbness, weakness, optic neuritis, incoordination, diplopia, vertigo and neuropsychiatric manifestations. Neuropsychiatric abnormalities are diverse, are reported in up to 60% of patients with multiple sclerosis (MS) and are among the main contributors to the morbidity and mortality associated with MS **(6).**

Major depressive disorder is the most common psychiatric disorder associated with MS with approximately five times the rate observed in the general population **(7).**

The coexistence of depressive and anxiety symptoms has been found to be associated with increased rates of physical symptoms, social dysfunction and suicidal ideation **(8).** Suicide is a significant cause of mortality with a 3% rate of completed suicide in individuals with MS **(9).**

Bipolar affective disorder prevalence in MS is approximately twice that in the general population **(10).**

Pseudobulbar affect, also known as 'pathological laughing and crying,' occurs in approximately 10% of individuals with MS **(11).**

The aim of the current work was to study neuropsychiatric manifestations in multiple sclerosis patients and to understand their correlation with the degree of clinical disability.

SUBJECTS AND METHODS

This cross-sectional randomized study included a total of 40 consecutive M.S. patients attending at MS Outpatient Clinics of Al-Azhar University Hospitals (Al Hussein and Bab Elshierya). **Approval of the ethical committee and a written informed consent from all the subjects were obtained.** This study was conducted between January 2018 until February 2019.

The included subjects were divided into two groups:

I- Patient group: Included 40 consecutive M.S. patients (26 female and 14 male with mean age ± SD 32.60 ± 10.01) fulfilling the following inclusion criteria:

1- Clinically definite M.S. patients diagnosed according to MacDonald Criteria of MS(2010).
2- The patients age between 15-55 years.
3- Sex: both sexes.
4- Patients were in clinical remission or after 3 weeks of acute relapse, to avoid the effect of steroids given for treatment of acute relapse, on mood.

Exclusion criteria

1- Patients with history of head trauma or C.N.S disorder other than MS, to avoid overlapping of these disorders with the effect of MS lesion.

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2- Patients with chronic medical disorders, which may affect mood.
3- Patients with past history of any psychiatric disorders.

II- Control group: Included 20 apparently healthy (10 male and 10 female with mean age ±SD 28.40 ± 8.21) with the same exclusion criteria other than patients relatives to escape the genetic aspects of susceptibility to psychiatric diseases. They were selected from the staff working in Al-Hussein University Hospital and other volunteers.

All patients and controls were subjected to the following assessment procedures:
1- Full psychiatric and neurological history and clinical examination.
2- Expanded Disability Status Scale (EDSS).
3- Magnetic Resonance Imaging (MRI).
4- Psychometric study.
a) Beck depression Inventory (BDI)
b) Hamilton anxiety rating scale

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

Table (1): Age and Sex distribution of the studied cases

		Control group	Patients group	Test value	P-value	Sig.
		No. = 20	No. = 40			
Sex	Female	10 (50.0%)	26 (65.0%)	1.250*	0.264	NS
	Male	10 (50.0%)	14 (35.0%)			
Age (year)	Mean ± SD	28.40 ± 8.21	32.60 ± 10.01	-1.621•	0.110	NS
	Range	16 – 44	18 – 56			
Marital state	Single	7 (35.0%)	10 (25.0%)	1.078*	0.583	NS
	Married	13 (65.0%)	29 (72.5%)			
	Divorced	0 (0.0%)	1 (2.5%)			
Education	Not-educated	0 (0.0%)	3 (7.5%)	0.186*	0.666	NS
	Low	4 (20.0%)	7 (17.5.0%)			
	High	16 (80.0%)	30 (75.0%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

Table (1) shows that there was no significant difference between patients and control group regarding demographic data as (P value > 0.05).

Table (2): Comparison between control and patient groups regarding beck scale score

		Control group	Patients group	est value	-value	Sig.
		No. = 20	No. = 40			
Beck scale score	Median (IQR)	8 (5.5 – 10.5)	12 (8.5 – 22.5)	-2.786≠	0.005	HS
	Range	3 – 33	4 – 38			

Table (2) shows that there was a highly significant difference between patients and control group regarding Beck scale score as (P-value = 0.005).
More higher Beck scores were in MS patients. This means that the mood is significantly affected by MS.

Table (3): Relation between the clinical data of patients regarding Beck scale score

		Beck scale score		Test value	P-value	Sig.
		Median (IQR)	Range			
Sex	Female	19 (9 – 23)	4 – 38	-1.396ǂ	0.163	NS
	Male	10 (8 – 20)	5 – 34			
MS Type	2ryPMS	9 (8 – 15)	8 – 20	-1.019ǂ	0.308	NS
	RRMS	12 (9 – 23)	4 – 38			
Interferon	Not on interferon	9 (5 – 20)	4 – 38	-1.103ǂ	0.270	NS
	On Interferon	12 (9 – 23)	5 – 36			
MRI Spinal plaques	Negative	15 (6 – 23)	5 – 36	-0.041ǂ	0.967	NS
	Positive	12 (10 – 20)	4 – 38			
Suicidal ideation	Absent	10 (8 – 20)	4 – 38	-2.958ǂ	0.003	HS
	Present	34 (23 – 36)	22 – 36			
Suicidal attempts	Absent	12 (8 – 22)	4 – 38	-1.566ǂ	0.117	NS
	Present	36 (36 – 36)	36 – 36			

Table (3) shows that there was no significant statistical difference between sexes, MS types, interferon as DMT and suicidal attempts regarding Beck scale score as (P value > 0.05).

Also show that there is highly significant difference between suicidal ideation and Beck scale score as (p value = 0.003). That is mean increase of suicidal ideation with higher Beck score for depression.

Table (4): Correlation between the clinical data of patient group and beck scale score

	Beck scale score	
	r	P-value
Age of onset	-0.118	0.470
Disease Duration	0.137	0.399
No of relapses	0.206	0.202
EDSS scale score	**0.315***	**0.048**

Table (4) shows that there was no significant relation between Beck scale score and age of onset, disease duration and number of relapses as (P value > 0.05).

Table (4) shows that there was a significant positive correlation between Beck scale score and EDSS scale score in MS patients as (p value =0.048 r =0.315). This means that the more the degree of disability the more sever the degree of depression.

Table (5): Percentage of depressed MS patients receiving antidepressants.

Antidepressant	MS patients
	Depressed
On	8 (38.1%)
Off	13 (61.9%)
Total	***21 (100.0%)***

Table (6): Comparison between control and patient groups regarding Hamilton scale score

		Control group	Patients group	Test value	P-value	Sig.
		No. = 20	No. = 40			
Hamilton scale score	Median (IQR)	4 (2 – 5.5)	8 (5 – 16)	-3.050≠	0.002	HS
	Range	2 – 26	2 – 35			

≠: Mann-Whitney test

Table (6) shows that there was a highly significant difference between patients and control group regarding Hamilton scale score for anxiety as (P-value = 0.002).
More higher Hamilton scores were in MS patients. That is mean the anxiety increase in patients with MS.

Table (7): Relation between the clinical data of patients regarding Hamilton scale score

		Hamilton scale score		Test value ǂ	P-value	Sig.
		Median (IQR)	Range			
Sex	Female	13.5 (6 – 17)	3 – 35	-2.053ǂ	0.040	S
	Male	6 (4 – 8)	2 – 18			
MS Type	2ryPMS	7 (5.5 – 11.5)	5 – 15	-0.385ǂ	0.700	NS
	RRMS	8 (4.5 – 16)	2 – 35			
Interferon	Not on interferon	5.5 (3 – 15)	3 – 24	-1.048ǂ	0.295	NS
	On Interferon	8 (6 – 16)	2 – 35			
MRI Spinal plaques	Negative	12 (4 – 17)	2 – 26	-0.615ǂ	0.538	NS
	Positive	7 (6 – 13)	3 – 35			
Suicidal ideation	Absent	8 (4 – 16)	2 – 26	-1.974ǂ	0.048	S
	Present	16 (15 – 24)	6 – 35			
Suicidal attempts	Absent	8 (5 – 16)	2 – 35	-1.481ǂ	0.139	NS
	Present	24 (24 – 24)	24 – 24			

Table (7) shows that there was no significant statistical difference between MS types, interferon as DMT, spinal MRI plaques and suicidal attempts regarding Hamilton scale score as (P value > 0.05).

But there was a significant difference between male and female regarding Hamilton scale score as (p value =0.040). Females were had more higher Hamilton score than males.

Also there was a significant difference between the presence of suicidal ideation regarding Hamilton scale score as (p value =0.048). That is mean increase of suicidal ideation with higher Hamilton score for anxiety.

Table (8): Correlation between the clinical data of patient group and Hamilton scale score

	Hamilton scale score	
	r	P-value
Age of onset	0.015	0.925
Disease Duration	0.067	0.680
No of relapses	0.143	0.379
EDSS scale score	0.162	0.319

Table (8) shows that there was no significant relation between Hamilton scale score and age of onset, disease duration , number of relapses and EDSS scale score as(P value > 0.05).

Table (9): Comparison between control and patients group regarding Suicidal ideation and Suicidal attempts

		Control group	Patients group	Test value	P-value	Sig.
		No. = 20	No. = 40			
Suicidal ideation	Absent	19 (95.0%)	35 (87.5%)	0.833*	0.361	NS
	Present	1 (5.0%)	5 (12.5%)			
Suicidal attempts	Absent	20 (100.0%)	39 (97.5%)	0.508*	0.476	NS
	Present	0 (0.0%)	1 (2.5%)			

Table (9) shows that there was no significant difference between control and patient group regarding the presence of suicidal ideation and attempts as (P value > 0.05).

DISCUSSION

Multiple sclerosis (MS) is a chronic inflammatory central nervous system (CNS) disease, arising from a complex interaction of both environmental and genetic factors [1].

MS affects individuals during the most productive time of their lives, and directly limits their work capacity, leading to major social and economic consequences [2].

Persons with MS appear to have a higher prevalence of a number of psychiatric symptoms and disorders. Depression and anxiety, in particular, have been associated with decreased functional status [3], and quality of life [4].

The present study show that there was 52.5% of patients group had depression while 25% of control subjects had depression. That's mean MS patients complaining of more depressive symptoms.

Lobenteinz and Vivek records that the life time prevalence of depression in MS patients ranged from 40%-60% [5, 6].

Siegert and Abernethy [7] and **Minden** [8] reported that almost one in two MS patients will experience clinically significant depression in their lifetime (overall lifetime frequency of 25–50%), which equals approximately three times the prevalence rate in the general population.

The present study showed that there is no significant difference between patients on interferon as DMT and patients not on interferon regarding depression.

This is agree with the PRISMS study (Prevention of Relapses an disability by Interferon beta 1-a Subcutaneously in MS), which did not reveal any differences in the levels of depression among the active treatment and placebo group [9].

Patten *et al.* [10] reported that rates of depression are the same for patients treated with IFN and for patients treated with glatiramer acetate in clinical settings.

On the other side several clinical trials have reported an increase in depression in patients during the first two to six months of treatment with both interferon beta-1b [11] and interferon beta-1a [12], but it appears that these increases in depressive symptoms are more related to pretreatment levels of depression than to the administration of IFN [13].

The present study showed that higher Beck scale scores increase presence of suicidal ideation in MS patients. This in the line with **Carson *et al.*** [14] who noted that depression in MS has been shown to be highly correlated with suicidality, but depressive symptoms are often undetected and untreated.

The finding of a significant relationship between depressive symptoms and suicide ideation has added to the few studies in this area that have reported similar findings [15, 16].

Alternatively, **Caine and Schwid** [17] suggest that suicide ideation in MS may not be identified because patients tend to minimise these thoughts during assessment in order to provide superficial reassurance to their clinicians that they will not harm themselves.

As regard the relation between Beck scale score for depression and type of MS, Findings from the present study suggested that there was no significant difference between relapsing remitting and secondary progressive types [18].

Whereas **Filippi *et al.*** [19] reported that there is a significant increase in the prevalence of depressive symptoms in the progressive type of MS.

As regard the relation between Beck scale score for depression and number of relapses, Findings from the present study suggested that there was no significant correlation between depression and number of relapses. These finding agree with that of **Chwastiak *et al.*** [18] who attributed this finding to the adaptation of the patients by the time.

The present study show there is significant positive correlation between depression and disability. This means that the more the degree of disability the more sever degree of depression.

Our study was in line with **Chwastiak *et al.*** [18] who found that the severity of multiple sclerosis was associated with depressive symptoms as they recorded that patients with intermediate and advanced illness according to EDSS, were 3 and 6 times more depressed respectively than mildly affected patients. Also, there were several other studies have confirmed this association [20, 21, 22, 23].

On the other side **Dalos *et al.*** [24] and others found that the frequency or severity of depressive episodes among multiple sclerosis patients is independent of the severity of multiple sclerosis, as reflected by the patient's score on the Expanded Disability Status Scale [25].

Whereas data on the relationship between depression and physical disability, as measured by the Expanded Disability Status Scale (EDSS), are contradictory [18, 26].

In the present work there was only 38.1% of depressed MS patient on antidepressant that's agree with **Feinstein *et al.*** [13] who noted that two-thirds of MS patients with current major depression were not receiving antidepressants.

Even though depression is one of the strongest predictors of reduced quality of life, it is often not detected nor treated in MS [10], although as a rule the symptoms respond well to standard treatment [27]. The treatment of depression and mood changes is generally based on various psychological interventions and antidepressants [28].

The present work suggested that there were 30% of MS patients group had anxiety while 15% of control subjects had anxiety.

This means that the anxiety was significantly higher in patients with MS. Our findings agree with **Beiske *et al.* [29], Janssens *et al.* [30] and Korostil *et al.* [31]** who found that the prevalence of anxiety disorders in MS populations varies from 14% to 41%, with a female preponderance.

An increase in frequency of reported anxiety symptoms is often recorded soon after announcement of the diagnosis to MS patients **[32].**

Anxiety often co-occurs with depression and is associated with increased suicidal ideation, more physical complaints, greater social dysfunction, and excessive alcohol consumption [33].

In the present study the relation between anxiety and various disease prameters as regared age of onset, disease duration, number of relapses, types of MS and sevirty of symptoms (EDSS), did not show any significant correlation.

This is in agreement with **Janssens *et al.* [30]** and **Zorzon *et al.* [32]** who found anxiety to be associated with disease activity (active relapse) but not with duration or severity of MS. Whereas, Stenager found significant correlations with neurologic disability but not with disease course **[33].**

Our study showed there in no significant difference between patient and control groups regarding the presence of suicidal ideation and attempts.

Our findings not in the line with **Patten *et al.* [10] and Ghaffar *et al.* [34]** who reported that Suicide is a significant cause of mortality with a 3% rate of completed suicide in individuals with MS, which is approximately 7.5 times higher than that of the general population and significantly higher than that reported in individuals experiencing other neurological or chronic medical disease disorders.

There was one study examined correlations between suicidal ideation and MS, found that among a sample of 104 women and 36 men attending an outpatient MS clinic, 28.6% endorsed lifetime suicidal ideation **[13].**

This difference may be attributed to the fact that most of our patients do not know full information about their illness as regard nature, prognosis, possibility of future disability, and even if the disease is completely curable or not.

So the disease is not perceived as a stressful threatening situation and so, there is minimal fear**.** Also, religious adaptation and social support in our community play an important role to reduce the level of stress put on our patients.

In the present work there is no significant difference between EDSS scale for disability and presence of suicidal ideatin that's agree with Feinstein who did not find a significant association**[13].**

However, two studies reported that self-reported bladder or bowel difficulties, and communication and swallowing difficulties were risk factors for suicide ideation **[16]** and in addition, **Turner *et al.* [35]** found that mobility problems and a higher level of perceived disability was associated with suicide ideation**.**

This contradiction could be explained by the small number of patients, the differences in community expectations and the presence of social support.

CONCLUSION

Neuropsychiatric changes are common in MS and are often considered core symptoms of this prevalent neurologic disorder. An understanding of neuropsychiatric disorders in MS is important for all professionals involved in the care of people with MS. These disorders affect about half of patients.

Depression and anxiety disorders are highly prevalent among persons with MS and have been associated with decreased quality of life. These symptoms may be equally or more important than physical disability in the prediction of quality of life. Therefore, early recognition and effective management of depression and other neuropsychiatric symptoms are essential parts of optimal care for patients with MS.

Physical disability of MS can be reduced by early diagnosing such patients and providing them with proper treatment.

REFERENCES

1. **Ascherio A (2013):** Environmental factors in multiple sclerosis. Expert Rev Neurother., 13(12):3–9.
2. **Jennum P, Wanscher B, Frederiksen J *et al.* (2012):** The socioeco-nomic consequences of multiple sclerosis: a controlled national study. Eur Neuropsychopharmacol., 22(1):36–43.
3. **Tsivgoulis G, Triantafyllou N, Papageorgiou C *et al.* (2007):** Associations of the Expanded Disability Status Scale with anxiety and depression in multiple sclerosis outpatients. Acta Neurologica Scandinavica, 115(1):67-72.
4. **Amato MP, Ponziani G, Rossi F *et al.* (2001):** Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. Multiple Sclerosis Journal, 7(5):340-4.
5. **Lobentanz IS, Asenbaum S, Vass K *et al.* (2004):** Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. Acta Neurologica Scandinavica, 110(1):6-13.
6. **Vivek PS, Pawar G, Miller LA *et al.* (2010):** Impact of visual impairment on health-related quality of life in multiple sclerosis. International Journal of MS Care, 12(2):83-91.
7. **Siegert RJ, Abernethy DA (2005):** Depression in multiple sclerosis: a review. Journal of Neurology, Neurosurgery & Psychiatry, 76(4):469-75.

8. **Minden SL, Schiffer RB (1990):** Affective disorders in multiple sclerosis review and recommendations for clinical research. Archives of Neurology, 47(1):98-104.
9. **Patten SB, Metz LM (2001)**: InterferonB-1a and depression in relapsing-remitting multiple sclerosis: an analysis of depression data from the PRISMS clinical trial. Mult Scler., 7: 243–248.
10. **Patten SB, Beck CA, Williams JVA *et al.* (2003):** Major depression in multiple sclerosis: a population-based perspective. Neurology, 61:1524–7.
11. **Neilley LK, Goodin DS, Goodkin DE *et al.* (1996):** Side effect profile of interferon beta-lb in MS: results of an open label trial. Neurology, 46(2):552-3.
12. **Mohr DC, Dick LP, Russo D *et al.* (1999):** The psychosocial impact of multiple sclerosis: Exploring the patient's perspective. Health Psychology, 18(4):376.
13. **Feinstein A, O'Connor P, Feinstein K (2002):** Multiple sclerosis, interferon beta-1b and depression. Journal of Neurology, 249(7):815-20.
14. **Carson AJ, Best S, Warlow C *et al.* (2000):** Suicidal ideation among outpatients at general neurology clinics: prospective study. BMJ., 320(7245):1311-2.
15. **Turner AP, Williams RM, Bowen JD *et al.* (2006):** Suicidal ideation in multiple sclerosis. Archives of Physical Medicine and Rehabilitation, 87(8):1073-8.
16. **Viner R, Fiest KM, Bulloch AG *et al.* (2014):** Point prevalence and correlates of depression in a national community sample with multiple sclerosis. General Hospital Psychiatry, 36(3):352-4.
17. **Caine ED, Schwid SR (2002):** Multiple sclerosis, depression, and the risk of suicide. Neurology, 59:662–663.
18. **Chwastiak L, Ehde DM, Gibbons LE *et al.* (2002):** Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. American Journal of Psychiatry, 159(11):1862-8.
19. **Filippi M, Horsfield MA, Morrissey SP *et al.* (1994):** Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. Neurology, 44(4):635-.
20. **Anhoque CF, Domingues SCA, Carvalho T *et al.* (2011):** Anxiety and depressive symptoms in clinically isolated syndrome and multiple sclerosis. Arquivos de neuro-psiquiatria, 69(6), 882-886.
21. **Arnett PA, Barwick FH and Beeney JE (2008):** Depression in multiple sclerosis: review and theoretical proposal. Journal of the International Neuropsychological Society, 14(05): 691-724.
22. **Beal CC, Stuifbergen AK and Brown A (2007):** Depression in multiple sclerosis: a longitudinal analysis. Archives of Psychiatric Nursing, 21(4): 181-191.
23. **Da Silva AM, Vilhena E, Lopes A *et al.* (2011):** Depression and anxiety in a Portuguese MS population: associations with physical disability and severity of disease. Journal of the Neurological Sciences, 306(1): 66-70.
24. **Dalos NP, Rabins PV, Brooks BR *et al.* (1983):** Disease activity and emotional state in multiple sclerosis. Annals of Neurology, 13: 573–577.
25. **Rabins PV (1990)**: Euphoria in multiple sclerosis. In S. M. Rao (Ed.), Neurobehavioral aspects of multiple sclerosis. New York: Oxford University Press, Pp. 180–185.
26. **Figved N, Klevan G, Myhr KM *et al.* (2005):** Neuropsychiatric symptoms in patients with multiple sclerosis. Acta Psychiatrica Scandinavica, 112: 463–468.
27. **Minden SL (2000):** Mood disorders in multiple sclerosis: diagnosis and treatment. J Neurovirol., 6(2): 160–167.
28. **Thomas PW, Thomas S, Hillier C *et al.* (2007):** Psychological interventions for multiple sclerosis (review) The Cochrane Library. John Wiley & Sons: Chichester, Pp. 1–51.
29. **Beiske AG, Svensson E, Sandanger I *et al.* (2008):** Depression and anxiety amongst multiple sclerosis patients. European Journal of Neurology, 15(3):239-45.
30. **Janssens E, Dauwe T, Pinxten R *et al.* (2003):** Effects of heavy metal exposure on the condition and health of nestlings of the great tit (Parus major), a small songbird species. Environmental Pollution, 126(2):267-74.
31. **Korostil M, Feinstein A (2007):** Anxiety disorders and their clinical correlates in multiple sclerosis patients. Multiple Sclerosis Journal, 13(1):67-72.
32. **Zorzon M, de Masi R, Nasuelli D *et al.* (2001):** Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects. Journal of Neurology, 248(5):416-21.
33. **Stenager EN, Wermuth L, Stenager E *et al.* (1994):** Suicide in patients with Parkinson's disease: an epidemiological study. Acta Psychiatrica Scandinavica, 90(1):70-2.
34. **Ghaffar O, Feinstein A (2007)**: The neuropsychiatry of multiple sclerosis: a review of recent developments. Curr Opin Psychiatry, 20: 278–285.
35. **Turner AP, Williams RM, Bowen JD *et al.* (2006):** Suicidal Ideation in Multiple Sclerosis. Archives of Physical Medicine and Rehabilitation, 87(8): 1073-1078.