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FIBROMYALGIA SYNDROME AMONG IRAQI PATIENTS WITH MULTIPLE SCLEROSIS

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ABSTRACT

Objective: To study the relationship between fibromyalgia syndrome (FMS) and relapsing remitting multiple sclerosis (RRMS) in Iraqi patients. **Patients and Methods**: The two stages classification process proposed by the 1990 American College of Rheumatology (ACR) multicenter criteria committee of FMS was applied after an objective assessment of multiple sclerosis (MS) patients and control group about full history and complete clinical examination. **Stage I:** A pain questionnaire was given to a sample of 140 (97 female and 43 male) consecutive patient with RRMS mean age 37.1 years (range 17-60 years) who were attending MS clinic in Baghdad Teaching Hospital. **Stage II:** All patients with chronic wide spread pain (CWP) where examined by the same examiner for 18 tender points. Another 140 healthy individuals matched for age and sex were examined as controls. **Results:** CWP was present in 83 of 140 (59.3%) RRMS patient compared to only 34 (24.3%) individual in the control group (P= 0.000). FMS was present in 20 of 140 (14.3%) RRMS patients by the 1990 ACR criteria as compared to only 6 (4.3%) individuals in the control group (P= 0.007). Female patients with RRMS have high percentage of CWP and FMS compared to male patients in the study group. There were positive correlations between FMS and RRMS patients with regards to age (P= 0.028), disease duration of more than five years (P= 0.000) and number of relapse attacks (P= 0.000) but no significant relation with Expanded disability status score (EDSS) or Body mass index (BMI). **Conclusions:** Chronic wide spread pain (CWP) and fibromyalgia syndrome (FMS) are positively correlated with Relapsing Remitting multiple sclerosis (RRMS) when compared with control group. FMS is more common in female patients who had disease duration ≥ 5 years with more disability status. Relapsing remitting multiple sclerosis having FMS showed more relapse attacks compared to those without FMS.

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INTRODUCTION

Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain and increased tenderness (Wolfe, 1995; Haq, 2005; Clauw, 2003). According to the American College of Rheumatology (ACR) 1990 criteria, diagnosis is based on tender points in a minimum of 11 of 18 specific sites and widespread pain, i.e., axial pain plus pain above and below the waist and in the right and left side of the body and for at least 3 months (Wolfe, 1990; Pongratz, 2000). In addition to wide spread pain, numerous other symptoms, such as fatigue, sleep disturbances, morning stiffness, irritable bowel syndrome headache, psychological distress and subjectively impaired cognitive function (Suhr, 2003; Hughes, 2006), FMS is defined as primary when there are no other coexisting diseases and secondary _ concomitant when it coexists with another disorder e.g. systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis (Hughes, 2006; Clauw, 2008) and bronchial asthma (AL_ Rawi, 2003).

Epidemiology: The prevalence of FMS ranges from 0.66% to 10.5%, higher in middle-age (Cavalcante, 2006), there is strong female predominance of around 9-10: 1 (Doherty, 2010). In Iraqi study, FMS occur in 1.5 % of Iraqi school children and adolescent (AL_Rawi, 2000).

Etiology, pathogenesis, and pathophysiology: Prospective, population-based studies have shown that physical and emotional stressors at the workplace and depressed mood are risk factors for the development of FMS. A variety of path physiological changes are associated with FMS without any

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clear causal relationship; among these are disturbances of central pain processing, hypo reactivity of the hypothalamic-pituitary-adrenal axis, disturbances of the growth hormone system, elevated pro-inflammatory and low anti-inflammatory cytokine profiles, and changes in the dopaminergic and serotonergic systems [13].

The diseases associated with fibromyalgia or, at least in part, may show some similar symptoms [14]

Rheumatic diseases
Lupus erythematosus
Rheumatoid Arthritis
Sjögren syndrome
Polymyositis
Polymyalgia rheumatica
Osteomalacia
Hypermobility syndromes
Regional Pain Syndromes
Neurologic Diseases
Carpal tunnel syndrome
Cervical radiculopathy
Multiple Sclerosis
Myopathies (dystrophies, metabolic, drug-as statin) .
Endocrine diseases
Hypothyroidism
Noninsulin Diabetes mellitus (NIDDM)
Hyperparathyroidism
Neoplasms
Multiple Myeloma
Metastasis (breast, lung, prostate)
Tapering of steroid .
Infections (Hepatitis C) .

Treatment

Treatment options for FMS include the followings:

- Cognitive behavioral therapy and operant therapy for pain including patient education.
- Aerobic endurance, training adapted to the patient's individual performance level.
- Pool-based exercise / aquatic jogging.
- Spa therapy (bathing in thermal springs).
- Amitriptyline 25-50 mg/d.
- Short-term: duloxetine 60–120 mg/d or fluoxetine 20–40 mg/d or milnacipran 100–200 mg/d or paroxetine 20–40 mg/d or pregabalin 150–300 mg/d.
- Short-term: complementary therapeutic techniques (homeopathy, vegetarian diet) [13].

Multiple sclerosis (MS): Multiple sclerosis (MS)is a disease of myelin, the insulating cover around the nerves of the central nervous system (CNS: brain, optic nerves, and spinal cord) that becomes damaged in MS. Multiple sclerosis most commonly begins in young adulthood and affects about twice as many women as men (Joseph, 2005) The annual incidence of MS varies by location and ranges between 1.5 and 11/100,000 people. The prevalence is estimated at 350,000 to 400,000 in the United States and more than 1,000,000 worldwide (Peter, 2005). The characteristic pathological feature of multiple sclerosis is the focal plaque or lesion. The lesions of multiple sclerosis were demyelination, relative preservation of axons, gliosis and a variable amount of inflammation. Furthermore, it is evident that the pathology of multiple sclerosis is not just confined to white matter lesions but involves the grey matter and macroscopically normal-appearing white matter (NAWM) (Siobhan Leary *et al*., 2009).

I	T-cell/macrophage associated
II	Antibody/complement associated
III	Distal oligodendrogliopathy
IV	Oligodendrocyte degeneration in the peri-plaque white matter

Types of multiple sclerosis: -Clinical disease activity in MS may manifest as relapses or insidious progression (Siobhan Leary, 2009).

Relapsing remitting multiple sclerosis:-Approximately 85% of individuals present with relapses and remissions. A relapse is defined as an episode of acute or subacute neurological dysfunction lasting a minimum of 24 hours (Siobhan Leary, 2009).

Secondary progressive multiple sclerosis:-Relapsing remitting multiple sclerosis may evolve into a gradually progressive course with accumulating irreversible neurological deficit and disability, classified as secondary progressive multiple sclerosis (Siobhan Leary, 2009).

Primary progressive multiple sclerosis:-there is insidious disease progression from onset, resulting in gradual accumulation of neurological deficit or disability, without relapse or remission. It accounts for approximately 10–15% of multiple sclerosis.

Progressive relapsing multiple sclerosis: Progressive relapsing multiple sclerosis refers to the small number of people who have progressive disease from onset with superimposed relapses, but the term is now rarely used. Insidious progression is the predominant feature and relapses are usually mild (Siobhan Leary *et al*., 2009).

Clinical features: Include optic neuritis, relapsing and remitting sensory symptoms, subacute painless spinal cord lesion, acute brain-stem syndrome, subacute loss of function of upper limb (dorsal column deficit), and 6th cranial nerve palsy (Siobhan Leary, 2009).

Diagnosis: Multiple sclerosis is a clinical diagnosis that requires appropriate expertise to confirm evidence of CNS lesions disseminated in time and space and to exclude other diseases. Investigations may be used to:

- Exclude other diseases;
- Provide evidence of dissemination in time and space;
- Provide evidence of immunological disturbance.

Diagnostic investigations

- **Magnetic resonance imaging:** The plaques of white matter demyelination in multiple sclerosis are readily visualized on MRI.
- **Cerebrospinal fluid:** In clinically definite multiple sclerosis, intrathecally synthesized oligoclonal immunoglobulin G (IgG) bands are found in approximately 90% of patients (Siobhan Leary, 2009)

- **Evoked potentials:** A markedly delayed P (potential) 100 wave of normal amplitude.
- **Auto antibodies:** No autoantibody has been confirmed to be diagnostic for multiple sclerosis to date. A recent study of CIS (clinically isolated syndrome) patients – who also had MRI abnormalities and CSF oligoclonal bands indicating a high likelihood for multiple sclerosis – reported that the presence of antimyelin antibodies in serum substantially increased the risk for developing clinically definite multiple sclerosis (Siobhan Leary, 2009)

Prognosis: MS is a heterogeneous disease, with a variable clinical course. Patients can progress rapidly over several months to death, or may have a few relapses and then remain clinically stable for many decades.

Treatment: Agents used to treat MS decrease the clinical relapse rate and accompanying inflammation within the CNS. These agents include interferon beta-1b, interferon beta-1a, glatiramer acetate, mitoxantrone, and natalizumab. Various medications are utilized for symptomatic treatment of pain, muscle spasms, fatigue, depression, sexual dysfunction, and bladder and bowel dysfunction. Possible febrile infections require vigilance as they may exacerbate MS. Potential exacerbations during the postpartum period can often be managed by initiating immunomodulatory therapy soon after delivery (Siobhan Leary, 2009).

Aim of the study: We aimed to study the possible association between fibromyalgia syndrome and relapsing remitting multiple sclerosis; a study that is to the best of our knowledge was not done earlier.

Patients and Methods:- One hundred forty MS patients diagnosed according to Mc Donald criteria [(15)] whom course of the disease is Relapsing Remitting (RRMS), a clinically stable phase, were studied in the MS Clinic at Baghdad Teaching Hospital during the period between December 2009 and June 2010.

Each patient was interviewed and assessed according to a protocol paper (Appendix 1). Expanded disability status scale (EDSS) were used to assess the severity of the disease(Appendix 2).

Patients with RRMS were excluded from the study if they are

- Receiving corticosteroid treatment in the last 6 weeks.
- Getting exacerbation within the last 6 weeks.

One hundred forty age and sex matched healthy controls (mainly relatives of MS patients) were interviewed and assessed by using the same protocol paper. Full history, complete clinical examination, and the American college of Rheumatology (ACR) 1990 criteria for fibromyalgia were applied for individuals in both groups by the same physician.They were questioned about presence of chronic wide spread pain (CWP),sleep disturbance, headache, fatigue, numbness, anxiety, depression, irritable bowel syndrome (recurrent episodes of abdominal cramping and diarrhea alternating with constipation). Patients were subsequently examined for 18 tender points by digital palpation with an approximate force of 4kg (the amount of pressure required to blanch the nail) (Appendix 3), the former concept of control points previously described as area of the body that should not be tender has been abandoned (Clauw, 2008). A point was considered tender if there was a spontaneous verbal affirmation of pain, or physical wince/evasion maneuver from the patient, in response to firm pressure. A signed consent was taken from all patients and controls included in the study.

Statistical analysis: Statistical analysis was carried out using statistical package for social sciences (SPSS v.17) used for data input and analysis. chi- square test for independence used to analyze the association between discrete variables. Finding with P value ≤ 0.05 were considered significant.

RESULTS

The demographic distribution of both MS patients and controls is shown in (Table I). There were 140 patients with MS, 97 female (69.3%), and 43 male (30.4%). One hundred forty healthy controls, 96 female (68.6%),and 44 male (31.4%), with a female to male ratio of 2/1 both groups. The mean age for MS patients and controls was 34.1 and 38.6 year respectively. Most of MS patients and individuals in the control group had normal body mass index (BMI) 109 (77.9%), and 101 (72. 1%) respectively while the rest were over weight or obese. As shown in Table I. FMS was reported in 20 (14.3%) patients in MS group compared to 6 (4.3%) individuals in the control group (P =0.007) as shown in (Table II).

There were high proportion female with MS 18 (18.6%) having FMS compared to male patients 2 (4.7%). Their mean age was 37.1 year (range 17-60 years). As shown in Table III. There were significant statistical differences in the distribution of FMS between MS patients below and above the age of 40 years (Table III), there were no significant statistical differences in the distribution of FMS among MS patients below and above BMI 25 kg /m2 (Table III). MS patients with FMS had a mean disease duration of 7 years (range 2-12 years) the least disease duration was 2 years, MS patients with disease duration $\geq$ 5 years were more prone to have FMS with significant statistic relationship (P=0.000) as shown in (Table IV). The mean EDSS is 4.5 (range 0-10) MS patients with EDSS $\geq$ 3.5 were more frequent to have FMS with no significant statistical relationship (Table IV). The mean relapse attacks in patients with multiple sclerosis (MS) were 2 per year (rang 1-3) the least number of relapse attack was 1/year. FMS among MS patients were more prone for recurrent relapse attacks compared to MS patients without FMS (p = 0.000) as shown in (Table IV). Other variables like sleep disturbances, headache, fatigue, numbness, anxiety, depression, chronic wide spread pain, and tender points, showed statistically significant differences between patients and controls,whilst irritable bowel syndrome have no significant relationship between patients and controls as shown in (Table V).

DISCUSSION

The classification and treatment of FMS symptoms complex are controversial matters, not only with in and among the medical specialty societies but also among patients and their families (Hauser, 2009) Many rheumatologists, neurologists, and pain specialist, as well as many patients, consider FMS to be a distinct illness associated with pathological changes in the muscles and connective tissue and with characteristic functional abnormalities of the CNS (Hauser, 2009).

Table 1. Demographic distribution of MS patients and controls by age, gender & BMI

	MS Patients	Controls	P value
	N = 140(100.0%)	N = 140(100.0%)	
Age			0.105
< 20	5(3.6)	11(7.9)	
20 - 29	30(21.4)	26(18.6)	
30 - 39	53(37.9)	40(28.6)	
40 - 49	37(26.4)	40(28.6)	
50 - 59	14(10.0)	16(11.4)	
60^{+}	1(0.7)	7(5.0)	
Range	17 - 60	17 - 69	0.243
Mean ± SD	37.1 ± 9.9	38.6 ± 11.5	
Gender			0.897
Female	97(69.3)	96(68.6)	
Male	43(30.7)	44(31.4)	
BMI			0.154
Under weight	0(0.0)	0(0.0)	
Normal	109(77.9)	101(72.1)	
Over weight	21(15.0)	19(13.6)	
Obese	10(7.1)	20(14.3)	

MS= multiple sclerosis; BMI= body mass index

Table 2. Distribution of study sample according to the presence of Multiple Sclerosis (MS) and Fibromyalgia Syndrome (FMS)

	FMS Present	FMS Absent	Total	
	N (%)	N (%)	N (%)	P
MS group	20 (14.3)	120 (85.7)	140 (100.0)	0.007
Control group	6 (4.3)	134 (95.7)	140 (100.0)	

MS= multiple sclerosis; FMS= fibromyalgia syndrome; N= number; (%)=percent

Table 3. The prevalence of FMS among MS patients by age, gender & BMI

	FMS Positive	FMS Negative	total	P
	N=20 (14.3%)	N=120(85.7%)	N=140(100.0%)	
Gender				
female	18 (18.6)	79 (81.4)	97(100.0)	0.056
Male	2 (4.7)	41 (95.3)	43(100.0)	
Age (year)				
< 40	9 (9.4)	87 (90.6)	96(100.0)	0.028
≥ 40	11 (25.0)	33 (75.0)	44(100.0)	
BMI (Kg/m^2)				
< 25	17 (17.5)	80 (82.5)	97(100.0)	0.166
≥ 25	3 (7.0)	40 (93.0)	43(100.0)	

Table 4. Comparison between MS patients with and without FMS according to duration of the disease, EDSS, and number of relapsing attacks of MS

	FMS Positive	FMS Negative	Total	P
	N=20 (14.3%)	N=120 (85.7%)	N=120 (100%)	
Duration of MS				
< 5 years	4 (5.2)	73 (94.8)	77 (100.0)	0.000
≥ 5 years	16 (25.4)	47 (74.6)	63 (100.0)	
EDSS				
< 3.5	7 (9.2)	69 (90.8)	76 (100.0)	0.061
≥ 3.5	13 (20.3)	51(79.7)	64 (100.0)	
No. of relapse attacks / year				
1	4 (5.2)	73 (94.8)	77 (100.0)	0.000
≥ 2	16 (25.4)	47 (74.6)	63 (100.0)	

In this study the prevalence rate of FMS among MS patients was reported in 14.3% of the sample studied, an association which is to the best our knowledge not previously reported. FMS was recorded in association with many other medical illnesses, this result showed that FMS was reported in association with RRMS less frequently than with what was noted in some other medical diseases. FMS was reported in 25% of patients with Rheumatoid Arthritis (Wolfe, 1984), and hemophilia-A (Ma'youf, 2010), 50% of patients with Sjogren syndrome, (Bennett, 1997) 30% of patients with SLE (Middleton, 1994), but it is comparable to the prevalence of Diabetes mellitus 17%, (Tishler, 2000). It's higher when compared to a prevalence rate of FMS in chronic hemodialysis 7.4% (Tolga Enver, 2005) bronchial asthma 8.3% (AL_ Rawi, 2003), and Behcet's disease 8.9% (Al-Izzi, 2001). There was also high prevalence of CWP (59.3%) among MS patients compared to that of the controls (24.3%) which is in agreement with other study (Robert, 2008). In this study females with MS outnumber male patients reflecting the sex ratio conventionally observed in the general MS population (Doherty, 2010). There were a high proportion of female with MS having FMS compared to male patient (ratio 9:1) also CWP was encountered more in female patients which is in agreement with other study (Kevin, 2001). CWP does not absolutely correlate with the presence of FMS as most patient with CWP have fewer than 11 of 18 tender points (Giles, 2000).The high prevalence of FMS found in our study may be explained by the age of our inclusion sample (17-60 years old)

Table 5. Comparison between Multiple Sclerosis (MS) patients and control variables

Variables	MS patients	Control	P
	N=140 (100%)	N = 140 (100%)	
Sleep Disturbance			
No	63(45.0)	120(85.7)	0.000
Yes	77(55.0)	20(13)	
Headache			
No	40(28.6)	93(66.4)	0.000
Yes	100(71.4)	47(33.6)	
Fatigue			
No	50(35.7)	123(87.9)	0.000
Yes	90(64.3)	17(12.1)	
Numbness			
No	55(39.3)	133(95.0)	0.000
Yes	85(60.7)	7(5.0)	
Anxiety			
No	90(64.3)	135(96.4)	0.000
Yes	50(35.7)	5(3.6)	
Depression			
No	109(77.9)	129(53.8)	0.000
Yes	31(22.1)	11(46.3)	
Irritable Bowel Syndrome			
No	111(79.3)	120(85.7)	0.156
Yes	29(20.7)	20(14.3)	
Chronic Wide Spread Pain (CWP)			
No	57(40.7)	106(75.7)	0.000
Yes	83(59.3)	34(24.3)	
Tender points			
<11 points	120(85.7)	134(95.7)	0.004
>11 points	20(14.3)	6(4.3)	

where FMS more frequent in age of ≥ 40 years (P=0.028). Indeed, studies consistently show that FMS is more common in middle age individuals (Carmona, 2001). Most of our patients are with BMI between 18.5-24.9 kg/m^2 and no statistical significant increase on the prevalence of FMS among MS patients with BMI while FMS was reported mainly in female which showed increased BMI (Munshid *et al*., 2010). FMS was frequent among high disability status with no statistical significant differences, where EDSS is an independent but moderate determinant of depression and anxiety in MS patient (Tsivgoulis, 2007). MS patients with disease duration more than five years were more prone to have FMS, high proportion of our patients with FMS were had MS for more than 5 years with significant relation ship (P0.000), where diffuse pain that has been present for years is likely to be due to FMS (Clauw, 2008). The average relapse frequency in RRMS is approximately one relapse per year (Lebrun, 2009), number of relapse attacks were found in medical records of patients in MS clinic.

In our study 25. 4% of FMS among MS patients had frequent relapse attacks per year (P<0.05) reflect the association with an increased risk of relapse, which is in agreement with other studies as stress affect relapse activity (Siobhan Leary, 2009). In our study there is significant relation among variables like (sleep disturbance, headache, fatigue, numbness, anxiety, depression) between MS patients and controls (P0.000) which is in agreement with other studies (Lebrun, 2009; Mendes, 2000; Fuso, 2010; Petruzzello, 2009; Stanton, 2006). This significant relationship of variables are strongly related to FMS (Clauw, 1995). Apart from these variables, irritable bowel syndrome was more detected in MS patients group in comparison to control group but without significant differences which may be due to effect of interferon beta (β) (Fitzgerald, 2008). A true increase in intensity of those variables in our study in comparison to other studies (Lebrun, 2009; Mendes, 2000; Fuso, 2010; Petruzzello, 2009; Stanton, 2006) may be related to FMS or attributed to MS, but chronic disease per se (MS) does not increase general symptoms of variables reported (Bjorkegren, 2009). FMS patients had more general symptoms than rheumatoid arthritis, osteoarthritis and other pain syndrome (Bjorkegren, 2009). .

Many hypotheses might explain FMS, CWP among MS patients:

- Both middle age and female gender are known risk factors for chronic pain determined by biological and social factors, non paid work (e.g. house hold work) is per se a risk factor for pain (Ana Assumpcao, 2009).
- Decrease physical and social activities is reported in MS patients, they became more sedentary. Eventually this may predispose to anxiety, depression and tiredness (Croft, 1993), which may predispose to FMS (Clauw, 1995) .
- Although the status of acute relapse and demyelinated lesions in person with RRMS was not examined in this study, increased pain may be attributed to an underlying inflammatory process or demyelination of the brain and spinal cord (Hauser, 2005).
- Pain and fatigue may share the same CNS pathways, there by increasing catecholamine and cortical levels in response, the sympathetic nervous system is an overload leading to a vicious cycle of more fatigue (Reyes, 2003).
- Pain and depression may be processed in the somatosensory pathways of the brain and spinal cord (Delgado, 2004) these areas are often affected with atrophy and demyelination in MS (Bair, 2003).
- sleep disturbance could explained by the pathophysiology of RRMS, demyelination lesion and inflammatory responses may disrupt the sleep wake

cycle by interfering with response of suprachiasmatic nucleus of the brain, in addition patient with RRMS reported more day time sleepiness, poor sleep quality (Attarian, 2004).

- The adverse impact of depression, fatigue, and sleep disturbance on mental quality of life is significant (Miller, 2006).
- FMS, Depression and neuropathic pain are all associated with altered sympathetic / parasympathetic balance, neuroendocrine disturbances, characterized by insufficient hypothalamus – pituitary adrenal axis regulation and altered immune function (University of south Carolina, 2009).

Unusually severe fatigue is a peculiar symptom of MS, often transient and more likely to occur when there is fever or other evidence of disease activity (Ropper, 2005). The concems about interferon-beta treatment and depression may have undue (Zephir, 2003). The association of MS and FMS may pose diagnostic dilemmas, where may contribute to a misinterpretation in initial diagnosis and relapse attacks leading to over treatment since FMS had more neurological symptoms with moderate correlation between symptoms and signs (Watson, 2008. also this association lead to frequent physician visits, early retirement, loss of income, and social isolation (Pittack, 2004). Treatment is by education, certain medications cognitive behavioral therapy and exercise (AL_ Rawi, 2003). Effective pain management may decrease intensity of fatigue depression, and sleep disturbance in all RRMS patients. In addition treatment of depression may improve mental quality of life where as treatment of fatigue may improve physical quality of life (Pamela, 2009). FMS recognition in MS is fundamental for adequate treatment of patients who hold both diseases at the same time.

Conclusions

Chronic wide spread pain (CWP) and FMS are positively correlated with Relapsing Remitting MS, an association not previously reported. FMS is more common in female who had disease duration ≥ 5 years with more disability status. Patients with RRMS having FMS are more prone to relapse attacks compared to those without FMS.

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APPENDIX 1:

Fibromyalgia in patient with multiple sclerosis

- **Patient's number :**
- **date : /**
- **Consent :**

Age:

Sex:
Wt :

Occupation

Occupation

Ht :

- **Fibromyalgia features:**

Duration of wide spread pain:
Tender point:

- **Associated features:**

Sleep disturbance

Head ache: Anxiety

Fatigue Depression

Numbness Irritable bowel

- **Drugs**
- **Investigations:**

CBP ESR
LFT RFT
S.Ca S.K S.A.P

- **multiple sclerosis**

Duration - Diagnosis category:

MS Suspected MS

No. of relapse attacks per year

Disease course:

RRD PPD SPP RP C/S

APPENDIX 2

EDSS
Kurtzke Expanded Disability Status Scale

0.0 = Normal neurological examination. (All grade 0 in functional system [FS]; cerebral grade 1 acceptable).
1.0 = No disability, minimal signs in one FS (i.e. grade 1 excluding cerebral grade 1).
1.5 = No disability, minimal signs in more than one FS(more than one grade 1excluding cerebral grade 1).
2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5 = Minimal disability in one FS (tow FS grade 2, others 0 or 1).
3.0 = Moderate disability in one FS(one FS grade 3, others 0 or 1), or mild disability in three or four FS(three/four FS grade 2, others 0 or 1) though fully ambulatory.
3.5 = fully ambulatory but with moderate disability in one FS(one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2(others 0 or 1).
4.0 = Ambulatory without aid or rest for>/= 500 m.
4.5 = Ambulatory without aid or rest for>/= 300 m.
5.0 = Ambulatory without aid or rest for>/= 200 m.
5.5 = Ambulatory without aid or rest for>/= 100 m.
6.0 = Unilateral assistance required to walk about 100 m with or without resting.
6.6 = Constant bilateral assistance required to walk about 20 m without resting.
7.0 = Unable to walk beyond 5 m even with aid; essentially restricted to wheelchair; wheels self and transfers alone.
7.5 = Unable to take more than few steps; restricted to wheelchair; may need aid to transfer.
8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of the day; retains many self-care functions; generally has effective use of arms.
8.5 = essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions.
9.0 = helpless bed patient; can communicate and eat.
9.5 = totally helpless bed patient; unable to communicate or eat.

10.0 = death due to MS.

APPENDIX 3 :

Criteria for the classification of fibromyalgia+

1. History of widespread pain / definition. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist, an addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side, low back pain is considered lower segment pain.
2. Pain in 11 of 18 tender points on digital palpation. *definition. Pain on digital palpation, must be present in at least 11 of the following 18 tender point sites:

- Occipit : bilateral, at the suboccipital muscle insertion.
- Low cervical: bilateral, at the anterior aspect of the intertransverse spaces at C5-C7.
- Trapezius: bilateral at the midpoint of the upper border.
- Supraspinatus : bilateral, at origins, above the scapula spine near the medial border.
- Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
- Lateral epicondyle: bilateral 2 cm distal to the epicondyles.
- Gluteal : bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
- Greater trochanter: bilateral, posterior of the trochantric prominence.
- Knee: bilateral, at the medial fat pad proximal to the joint.

+ For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present at least 3 months. The presence of a second clinical disorder dose not exclude the diagnosis of fibromyalgia.

*Digital palpation should be performed with an approximate force of 4kg. for a tender points to be considered positive the subject must state that the palpation was painful. ”tender” is not to be considered “painful”.

List of abbreviations

ACR	American college of rheumatology
BMI	Body mass index
CNS	Central nervous system
CSF	Cerebrospinal fluid
CWP	Chronic wide spread pain
EDSS	Expanded disability status score
e.g.	For example
FMS	Fibromyalgia syndrome
Kg	Kilogram
M2	Meter square
mg	Milligram
MS	Multiple sclerosis
No.	Number
RRMS	Relapsing remitting multiple sclerosis
SLE	Systemic lupus erythematosus
Wt.	Weight

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