

# The Role of Gender in Early Onset Relapsing Remitting Multiple Sclerosis

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## ABSTRACT:

### BACKGROUND:

Multiple sclerosis is an autoimmune inflammatory demyelinating disorder of the central nervous system. Multiple sclerosis is now universally found to be more prevalent in women than men

### OBJECTIVE:

The aim of the study is to clarify the role of gender in early onset multiple sclerosis

### PATIENTS AND METHODS:

This retrospective study was conducted in the multiple sclerosis clinic archive system in the Medical City Hospital in Baghdad, Iraq. Data collection was carried out between March 2008 and March 2009. The patients diagnosed to have relapse remitting multiple sclerosis according to the revised McDonald's diagnostic criteria for multiple sclerosis, and onset of disease must be before the eighteenth birthday. For each patient, the following information was gathered: age, gender, date of onset, and date of second attack, presenting symptom, and extended disability status scale and the date, and type and location of MRI lesions. A *p*-value <0.05 was considered the cutoff point to determine significant findings.

### RESULTS:

Forty-eight of the patients where females (62.3%) and 29 patients where males (37.7%), with a female: male ratio 1.6:1.

No significant difference was found regarding distribution of gender in each age group, and no significant difference was found when age at onset was compared between males and females, although in male patients a shift to children and a shift at adolescence in female were observed. The comparison of different radiological sites between males and females shows a significant difference with more males having infratentorial lesions compared with females (*P*=0.033).

No significant difference was found between the two genders regarding, age at onset the presenting symptom, mode of onset and no significant difference was found when interval between the first and second attack was compared between males and females.

### CONCLUSION:

Female preponderance was highest for subjects with disease onset at adolescents. No significant difference was found when age at onset was compared between males and females, although in male patients, a shift to children and a shift at adolescence in female were observed. A significant difference in the time, between first and second attack between males and females. A significant difference in the MRI findings was the finding that males had a higher incidence of infratentorial lesion than females.

**KEY WORDS:** gender, multiple sclerosis.

## INTRODUCTION:

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disorder of the central nervous system <sup>(1)</sup>. One of the most important epidemiological risk factors for autoimmune diseases, such as MS, is the female gender <sup>(2)</sup>.

MS is now universally found to be more prevalent in women than men <sup>(3-4)</sup>. Sexual dimorphism affects the physiological and a pathological response of the immune system is of considerable clinical importance <sup>(2)</sup>. This has led to extensive studies of differences in the immune system or nervous system between women and men, which might be caused by the effects of gonadal hormones, genetic differences, as well as different environmental exposures and modern lifestyle in men and women <sup>(1)</sup>.

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There is a considerable difference in the way MS affects females and males, as has been highlighted by epidemiology studies and MRI analyses<sup>(5-7)</sup>.

Several lines of evidence indicate that gender affects the susceptibility and course of MS with a higher disease prevalence and overall better prognosis in women than men<sup>(8)</sup>. The effect of gender on clinical features of MS is not as clear as the effect on MS prevalence; however, there is evidence that women generally have an earlier onset of disease, they have a slightly lower prevalence of primary progressive disease course and show in general less progression of disability than men<sup>(9)</sup>. The exact mechanism of these differences has not yet been established.

Surprisingly, the MS prevalence ratio of women to men has increased markedly during the last decades (2.3– 3.5:1), which indicates a true increase in MS among women but not men<sup>(3,4,10,11)</sup>. With a female to male ratio reaching (4:1) in Northern countries, according to recent epidemiological data in U.S. or Canada that consolidate estimates in Norwegian, U.S. and French cohorts<sup>(11,12-15)</sup>. Interestingly, the predominance in women varies also with latitude<sup>(16-17)</sup>. The causes of this widening gender gap do not seem to stem from diagnostic and ascertainment methods<sup>(15)</sup>. These observations should encourage efforts to identify potential environmental factors or habits accounting for the increased disease susceptibility in female<sup>(8)</sup>.

The effects of gender on the clinical expression of MS and response to therapy have implications for follow up and treatment of patients with MS<sup>(18)</sup>. Thus, the effects of gender in MS especially the early onset need to be taken into consideration.

The aim of the study is to clarify the role of gender in early onset MS

### **PATIENTS AND METHODS:**

This retrospective study was conducted in the MS clinic archive system in the Medical City Hospital in Baghdad, Iraq. Data collection was carried out between March 2008 and September 2014. The patients referred to the clinic by neurologists, ophthalmologists, neurosurgeons, and other specialists. Their final diagnosis was reviewed by committee of five neurologists.

To be included, patients must first be diagnosed to have relapse remitting multiple sclerosis according to the revised McDonald's diagnostic criteria<sup>(19)</sup> for MS, and onset of disease must be

before the eighteenth birthday. The exclusion criteria included evidence for the diagnosis of another disease that explained the clinical picture, or age more than 18 years at onset. As this comprised retrospective data collection from the data system of the MS clinic, we did not require ethical approval or patient consent. The MS clinic was established in 2000 at Baghdad Teaching Hospital, which is geographically accessible by most of the population in Baghdad as well as from all over Iraq<sup>(20)</sup>.

The age limit was based on the WHO definition of "children" (under the age of 10) and "adolescents" (aged 10 and above but prior to the 18th birthday)<sup>(21)</sup>.

Neurological disability was assessed according to the Kurtzke extended disability status scale (EDSS) score, a seven functional systems score, which includes motor, sensory, cerebellar, brain stem, visual, mental and sphincter systems. The score ranged from normal examination ((0)) to death from MS ((10)), with a score of 6 representing moderate disability that needs assistance in walking a distance of 100 m<sup>(22)</sup>.

For each patient, the following information was gathered: age, gender, date of onset, and date of diagnosis, date of second attack, presenting symptom, and EDSS and the date, and type and location of MRI lesions. Initial MRI was performed with 1.5T, MRI data using a standardized procedure (sagittal, axial, and coronal and T1, T2, fluid attenuated inversion recovery FLAIR sequences and gadolinium enhancement) were collected from patients file records.

The data was analysed using minitab 17, where **Student's t test** was made to test the significance of difference between two means, **the Chi-square test** to test the significant association between discrete variables and **Z test** to test the significance of difference between 2 proportions. A *p*-value <0.05 was considered the cutoff point to determine significant findings.

**The progression index (PI)** was calculated for each patient according to the following formula (PI = EDSS / disease duration), and PI<0.5 was considered a significant prognostic indicator<sup>(22)</sup>.

### **RESULTS:**

Of the 2635 patients records surveyed for the research, 154 with the diagnosis of MS and onset of disease before their eighteenth birthday, (a prevalence of 9.4%) were eligible for the study. 96 of the patients were females (62.3%) and 58

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patients where males (37.7%), with a female: male ratio 1.6:1 (Table 1).

No significant difference was found regarding distribution of gender in each age group, and no significant difference was found when age at onset was compared between males and females, although in male patients a shift to children and a shift at adolescence in female were observed (Fig.1).

The peak for subjects with disease onset was at ages 13 (27 cases with female/male ratio 3.5:1) and at ages 14 (29 cases with female/male ratio 7.67:1).

No significant difference was found when PI was compared between male and females (table 2).

No significant difference was found between the two genders regarding the presenting symptom (table 3) and mode of onset (table 4).

Regarding time between 1<sup>st</sup> and 2<sup>nd</sup> attack the mean was 3.06 years (minimum 0.03 maximum 23.04 years). When interval between the first and second attack was compared between males and females the mean in females was 2.586 years and in males the mean was 3.87 years and statistically this difference was found to be highly significant (table 5). The distribution of patients according to gender and MRI findings are shown in (Table 6). This table shows the comparison of different radiological sites between males and females, and shows a significant difference with more males having infratentorial lesions compared with females. The study showed no other significant differences between males and females regarding other MRI findings.

**Table 1: Distribution of patients according to their age at onset and gender**

AGE \ Gender	Under 10 years		From 10 to 18 years		P
	Number	Percent	Number	percent	
Male	4	28.6	54	38.6	0.704
Female	10	71.4	86	61.4	
Total	14	100	140	100	

**Table 2: Mean and standard deviation of Progression Index at different conditions.**

Progression Index	Mean ± SD	P
For the whole sample	1.436 ± 2.3	0.136
Gender		
Male	1.51 ± 3	
Female	1.39 ± 1.77	

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**Table 3: Distribution of patients according to their gender and presentation gender.**

	Male		Female		
	N	%	N	%	
Optic Neuritis	18	31	40	41.7	0.486
Brainstem	18	31	22	22.9	0.604
Sensory	8	13.8	20	20.8	0.640
Pyramidal	14	24.1	18	18.8	0.790
Transverse Myelitis	8	13.8	14	14.6	0.811
Sphincter disturbance	0	0	4	4.2	0.702
Cerebellar	8	13.8	2	2.1	0.123

**Table 4: Distribution of patients according to their gender and mode of onset of the disease.**

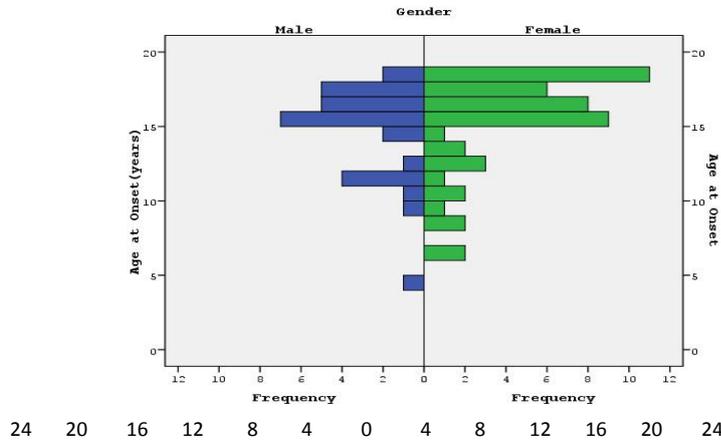
Mode \ Gender	Male		female		P
	Number	Percent	Number	percent	
Monofocal	48	82.8	70	72.8	0.323
Polyfocal	10	17.2	26	27.1	
Total	58	100	96	100	

**Table 5: the mean values of time (in years) between 1<sup>st</sup> and second attack in males and females and application of Least Significant Difference Test (LSD).**

Gender	Male	female	P
Time (years)	mean	Mean	
	3.87	2.586	0.000

**Table 6: Distribution of 154 Iraqi multiple sclerosis patients under the age of 18 according to their gender and some MRI findings.**

Findings	Male	Female	N	(%)	P-value
Periventricular	42	60	102	(66.0)	0.608
Brainstem	22	16	38	(24.6)	0.062
Spinal cord	10	10	20	(13.0)	0.598
Cerebellar	10	8	18	(11.5)	0.369
Centrum semiovale	8	22	30	(19.5)	0.467
Corpus callosum	8	4	12	(7.0)	0.258
Basal ganglia	2	6	8	(5.0)	0.979
Juxtacortical	2	8	10	(6.5)	0.711
Thalamic	0	4	4	(2.5)	0.686
Supratentorial (ST)	50	78	128	(83.0)	0.829
Infratentorial (IT)	28	30	58	(38.0)	0.033
Both (ST&IT)	22	22	44	(28.5)	0.260



**Figure1: Distribution of patients according to their gender and age at multiple sclerosis onsets.**

**DISCUSSION:**

145 patients had the onset of MS before the age of 18 years. The patients represented 6.8% of all 2635 patients recorded in the MS clinic in Baghdad. These results were close to the figure given by other studies (23-24). The mean age the patients at onset were  $14.9 \pm 3.2$  years that are close to the ages reported by other studies (12-13.7 years) (25-26).

62.3% of the patients were females close to 65.1% reported by Simone et al. (27). No significant difference in age at onset between male and female patients was noted (Male =  $14.705 \pm 3.134$ , Female =  $15.105 \pm 3.265$ ), although in male patients a shift to younger age was observed despite younger age at puberty in female. The female preponderance was highest

for subjects with disease onset at ages 13 with female/male ratio 3.5:1 and at ages 14 with female/male ratio 7.67:1). Although numbers are small, these data support the theory that hormonal changes related to puberty, especially sex hormones, may play an important role in MS onset.

The first published study regarding gender in MS shows a tendency for the disease to present with a 1:1 ratio before the age of 12, and a female 2:1 preponderance thereafter (28). In the latter years, this tendency has been observed by the KIDSEP Study Group, with a female-male ratio of 1.2:1 in patients under 10 years of age, which increases to 1.8:1 in the older pediatric population (29). When evaluating prognostic factors, female gender was related with a higher frequency of severity (30).

The nervous system is sexually dimorphic, with gender-specific anatomical differences affecting various behavioral, physiological and hormonal responses. While some adult patterns of sexual dimorphism are present at birth (31), gonadal hormones still remain important for maintaining brain sex-specific differences later in life (32-33). This sex dimorphism may be explained by sex chromosome effects and effects of sex steroid hormones on the immune system, blood brain barrier or parenchymal central nervous system cells (8). The most striking evidence for CNS sexual dimorphism possibly related to MS gender difference is that women have less cerebral white matter, which comprises the myelinated connecting axons (34-36). These anatomical differences may render female brain more susceptible to myelin attack in MS (8), which is further supported by observations of changes in disease symptomatology with alterations in sex hormone levels during pregnancy (37) and the significant difference in the time, between 1<sup>st</sup> and second attack between males and females (table 5).

There is evidence that sex hormones can affect the immune system and that female and male hormones act in opposing ways (38-39) and have bimodal effects on the immune system and the anti- vs. proinflammatory effects of estrogen in particular depend of the dose and the time point of estrogen administration in relation to the state of the inflammatory disease (8).

Shift during puberty may support the theory of hormonal but this not enough and may be age-related rather than hormonal change but not prove yet.

A significant difference in the MRI findings was the finding that males had a higher incidence of infratentorial lesion than females ( $p=0.033$ ). This higher male rate may be related to the fact that the pons myelinates faster in males than female individuals (40).

Differences in MRI measurements regarding gender have been studied, observing gray matter and central atrophy more prominently in men, whereas women present with more white matter atrophy (41). There are no studies analyzing these changes in early onset MS. Bellis et al studied the effect of sex hormone on brain maturation which can highlight the MRI changes. Specifically, males had more prominent age-related gray matter decreases and white matter volume and corpus callosal area increases compared with females. The findings suggest that there are age-related gender differences in brain maturational processes (40). Significant age-related reductions in cerebral gray and increases in white matter volumes and corpus callosal areas were evident, while intracranial and cerebral volumes did not change significantly (42). Significant gender by age interactions was seen for cerebral gray and white matter volumes and corpus callosal areas (43-44). Brain development during childhood and adolescence is characterized by both progressive myelination and regressive pruning processes (40). The study of age-related gender differences in cerebral pruning and myelination may aid in understanding the mechanism of MRI difference between two genders in early MS.

In conclusion female preponderance was highest for subjects with disease onset at adolescents. No significant difference was found when age at onset was compared between males and females, although in male patients, a shift to children and a shift at adolescence in female were observed. A significant difference in the time, between first and second attack between males and females. A significant difference in the MRI findings was the finding that males had a higher incidence of infratentorial lesion than females.

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