Comparison of familial and sporadic multiple sclerosis in Iraqi patients

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Summary:

Background: Multiple sclerosis (MS) is one of the increasing prevalent neurologic disorders. Epidemiologic and family studies implicate genetic and environmental factors in determining susceptibility to MS. The exact effect of the former is intended for investigation in our study.

Objectives: The objective of the study is to compare the demographic features, clinical presenting features, and clinical course between familial and sporadic cases of MS.

Materials and Methods: this is a retrospective cohort study conducted in Multiple Sclerosis Center in the Medical City in Baghdad. The records of the MS center in Baghdad Teaching Hospital were surveyed, and data from 13 patients with positive family history of MS, and 13 patients with out family history of MS was analyzed.

Results: Regarding the clinical presentation, for those with family history of MS the common presenting symptoms were sensory symptoms and transverse myelitis, and those without family history of MS was pyramidal, for those with family history of MS 11 patients had initial course of relapsing remitting MS (84.6%) ,of them 4 patients progressed into secondary progressive MS (36.4%); 2 patients had primary progressive MS as initial course, for those with negative family history of MS 12 patients had initial course of relapsing remitting MS, of them 5 patients progressed into Secondary progressive MS (41.6%); 1 patients had primary progressive MS as initial course (7.7 %.). No significant difference was found in the investigated parameters, except for the inverse relation between age of onset and lag time to diagnosis.

Conclusion: Familial MS do not significantly differ from sporadic MS in terms of the demographic patterns and clinical course and presentation. This is not the case for the relationship between the age of disease onset and lag time to diagnosis.

Key words: Multiple sclerosis and familial

Introduction:

Multiple sclerosis (MS) is a chronic heterogeneous inflammatory and degenerative disease of the CNS. It is a demyelinating and axonal degenerative disease of the central white matter. It is the most common cause of disability in young adults after trauma. The wide variety of clinical manifestations depends on the extent and the anatomical sites of demyelinating plaques. The functional prognosis of the disease is poor in the late phases of the disease. (1)

The incidence and prevalence of MS varies geographically. High frequency areas of the world include all of Europe (including Russia), southern Canada, northern United States, New Zealand, and southeast Australia. People of Asian, African, or American Indian origin have the lowest risk, with other groups showing intermediate risk levels. (2) There also appears to be an association between *

latitude and the risk of MS, with the risk increasing from south to north.(3)

Epidemiologic and family studies implicate genetic and environmental factors in determining susceptibility to MS. Evidence that these risk factors also influence phenotypic expression is less secure. The recurrence risk in relatives of individuals with MS is significantly increased compared to the background population. Knowledge of familial influences on disease expression therefore has significant implications for counseling families with several affected family members (4). Studies of familial MS underscore the genetic determination of susceptibility and often identify related individuals with pedigrees resembling those of mendelian or mitochondrial white matter diseases (5).

Although most MS cases occur sporadically, a considerable proportion, as many as 20 percent, of the patients are related by family. Previous attempts to assess the magnitude of the familial MS risk have arrived at variable estimates; the risk of MS has been reported to be increased from 12- to 38-fold in siblings, from 7- to 26-fold in parents, and from 6- to 25-fold in children of MS patients (6-12). Twin studies from different populations consistently indicate pair

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wise clinical concordance (20% to 30% in identical twin pairs compared with 2% to 5% in like-sex fraternal twin pairs and other siblings), providing additional evidence for a genetic etiology in MS.(13)
The clinical Course and severity of MS may also differ among ethnic groups, conceivably this phenotypic aggregation is due to genetic sharing. In multiplex families there may be a concordance for optic neuritis and/or spinal cord involvement as first and second manifestations of MS. In other studies, however, consistency of clinical presentation within families was not evident (14).

Materials and methods:
Study Design: The study was a retrospective cohort study, with the family history being the exposure of interest here. The sampling technique was convenience sampling for patients with positive family history (including all of them), and systematic random sampling for patients with no family history of MS. Settings: The study was conducted in Multiple Sclerosis Clinic archive system at the Medical City in Baghdad teaching hospital over the period of July 1st 2008 to March 30th 2009.
Patients: Patients attended MS center in Baghdad from all over Iraq referred by neurologists, ophthalmologists, neurosurgeons and other specialists (the diagnosis is reviewed by a committee of three neurologists in most cases). Patient included must first be diagnosed to have (MS) according to the revised McDonald`s diagnostic criteria for multiple sclerosis.(15)
Tools: The tool of data collection was a questionnaire form that was administered and filled by the researcher through reviewing all the records (1125 records) since the establishment of the center in 2000. This questionnaire was developed by the researcher and the supervisor.
For each patient the following information were gathered: age, sex, date of onset, date of diagnosis, date of second attack, presenting symptom, degree of recovery from the first attack(complete partial or non) course of disease, relapsing remitting MS (RRMS) or Primary progressive (PPMS), secondary progression and its date and extended disability status scale (EDSS). Neurologic disability was assessed according to the EDSS score a seven functional score system. This score included motor, sensory, cerebellar, brain stem, visual, mental and sphincter impairment. The score ranged from 0=normal examination to 10= death from MS. A score of 6 for example represents moderate disability with need for assistance in walking distance =100 meter.(16) Statistical Analysis: The statistical package of social sciences (SPSS) version 15 was used for data input and analysis. Parametric statistics were used, as well as the Kaplan–Meier method (to test the significance of developing secondary progression in relation to time using pooled

log rank). Findings of alpha ≤ .05 are considered significant.

Results:
Of the 1125 patients record surveyed for the research, 26 patients were eligible for the study, with the diagnosis of MS or possible MS; 13 patients had family history of MS, and 13 patients had no such history. Distribution of patients according to their family history and certainty of diagnosis: For patients with positive family history, 11 had a diagnosis of MS (84.6%) and 2 patients had a diagnosis of possible MS (15.4%). For those without family history of MS, all 13 patients had a diagnosis of MS. Mean (SD) age at onset was 30 (9.9) years for those with positive family history of MS. Patients without this history had a mean (SD) age of 32.2 (8.9) years. No significant difference was found when age at onset was compared between the two groups of patients. Mean (SD) lag time to diagnosis (calculated as the time difference between date of onset and date of diagnosis) was 2.9 (6.5) years for those with positive family history, and 5.1 (7.6) years for those without family history of MS. Again, the relation was not statistically significant. We found that the mean time between the first and second attack was 3.4 years for those with family history and 2.6 years with for those without family history, no significant difference was found. Distribution of patients according to their gender: Three of those with family history were males (23.1%) and 10 patients were females (76.9%). Also three of those without family history of MS were males (23.1%) and 10 patients were females (76.9%), no significant difference was found regarding distribution of patients according to their family history and gender. Clinical presentation: for those with positive family history of MS ; 3patients (23.1%%) with transverse myelitis,3 patients (23.1%) with sensory symptoms, 2 patients presented with optic neuritis (ON) (15.4%), 2 patients(15.4%) with symptoms referred to a brain stem lesion, 2 patients (15.4%) with pyramidal, and one patient with bladder symptom (7.7%); and those without family history of MS, 1 patient (7.7%%) with transverse myelitis, 2 patients (15.4%) with sensory symptoms, 2 patients presented with ON (15.4%) , 4 patients (30.8%) with pyramidal, 3 patients (23.1%) with cerebellar lesion, and one patient with facial pain (trigeminal neuralgia) (7.7%), no significant difference was found regarding distribution of patients according to their family history and the clinical presentation(Table 1).
The course of the disease: of those with positive family history of MS, 11 patients had an initial course of relapsing remitting MS (RRMS) (84.6%), of those 4 patients progressed into SPMS (36.4%) after a mean (SD) duration of 8.4 (3.8) years, and 2 patients had PPMS as initial course 15.4%. Of those with negative family history of MS, 12 patients had an initial course of relapsing remitting MS (RRMS) (92.3%), of which

5 progressed into SPMS (93.9%) after a mean (SD) duration of 6.8 (4.6) years, and 1 patient had PPMS as initial course 7.7 %.(Table 2) Resolution of the first attack: for those with family history of MS, 11 patients had complete improvement (84.6%), in 2 patients there was no improvement (15.4%). Of those with negative family history, 10 patients had complete improvement (76.9%), 2 had partial improvement (15.4%), and 1 patient there was no improvement (7.7%), no significant difference was found here. We used the Kaplan–Meier method to estimate the time to secondary progression in relation to family history of MS; mean (SE) time in patients with positive family history of MS was 7.974 (2.626) years, patients with negative family history of MS time was 6.251 (2.565) years (p=0.997), no significant difference was found when time was compared between the two groups of patients (Tables 3 and 4) (Figures 1and 2). We also compared different parameters and correlation to each other was estimated. Over all, there was an inverse correlation between lag time to diagnosis and age at disease onset (p=0.007) (the younger age the longer lag time to diagnosis), and there was direct correlation between lag time to diagnosis and time to second attack (p=0.05) (the longer to second attack longer lag time to diagnosis). The individual groups did not vary significantly in this regard.
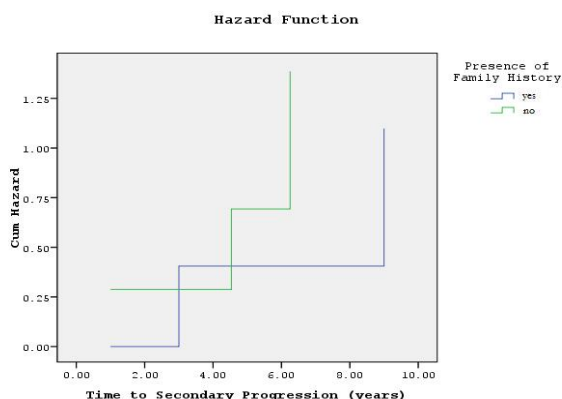

Figure 1: Kaplan-Meier e plot for the cumulative risk of developing secondary progression with time in patients of MS

Figure 2: Kaplan-Meier plot for the cumulative survival with time (in years) from developing the second attack in patients of MS.

Table1: Distribution of patients according to their family history of MS and their presentation.

Presenting Episode	Positive Family History		No Family History		P***
	N	%	N	%	
Transverse Myelitis	3	23.1	1	7.7	0.586
Sensory	3	23.1	2	15.4	0.999
Optic Neuritis	2	15.4	2	15.4	---
Brainstem	2	15.4	0	0	0.1461
Pyramidal	2	15.4	4	30.8	0.461
Cerebellar	0	0	3	23.1	0.219
Others	1*	7.7	1**	7.7	---
Total	13	100	13	100	

*bladder
**facial pain
***Z test for difference in proportions.
Total number of patients is 26
Data are number (%)

Table2: Distribution of patients according to their family history, recovery from the first attack and course of the disease

Recovery from the first Attack	Positive Family History					No Family History					P(d)
	All		Course of the disease			All		Course of the disease			
			Initial	SPMS(c)				Initial	SPMS		
	N	%		N	%	N	%		N	%	
complete	11	84.6	RRMS(a)	4	36.4	10	76.9	RRMS	4	40	0.589
partial	0	0	---	---	---	2	15.4	RRMS	1	50	0.461
no recovery	2	15.4	PPMS(b)	---	---	1	7.7	PPMS	---	---	---
Total	13	100.0	---			13	100.0	---			---

aRelapsing remitting multiple sclerosis.
bPrimary progressive multiple sclerosis.
cSecondary progressive multiple sclerosis.
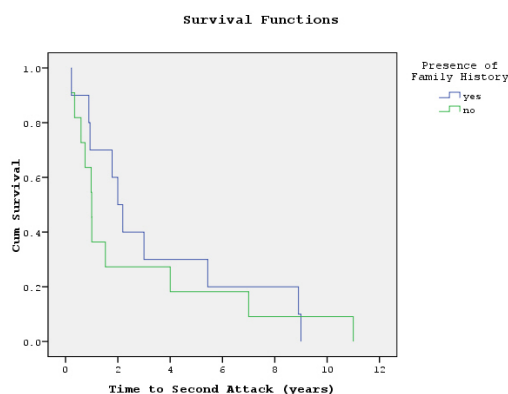dZ test for difference in proportions.
Data are number (%)

Table 3: Time to secondary progression (in years) in relation to having a family history of MS

Family History	Number of patients	Minimum	Maximum	Median	Mean	Standard Deviation	P*
Present	4	3.0	11.9	9.2	8.4	3.8	0.594
Absent	5	1.0	13.2	6.3	6.8	4.6	

*t test for two independent samples.

Table 4: Kaplan-Meier estimates of Means and Medians for Time to Secondary Progression in relation to family history of MS.

Presence of Family History	Mean				Median				P(a)
			95% CI				95% CI		
	Estimate	SE(b)	Lower	Upper	Estimate	SE	Lower	Upper	
yes	7.974	2.626	2.827	13.122	8.999	4.898	.000	18.599	0.997
no	6.251	2.565	1.224	11.277	4.537	2.626	.000	9.683	
Overall	6.989	1.728	3.603	10.376	6.253	2.248	1.848	10.659	---

a Pooled over all log rank by Kaplan-Meier Survival Analysis.
b Standard Error.
Data are mean (SE)

Discussion:

13 patients with positive family history of MS were included, this represent 1.1% of the 1125 patients involved in the MS clinic. These results were different to the figure given by Weinshenker, *et al*(17) 12.1%, and 18.9% in Eber CG *et al* (18) , this high figure because familial aggregation of MS is a well-known phenomenon in high prevalence areas (4) and it is considered very rare in Asia, a low prevalence area(19) however, the few studies that have addressed the familial risk of MS in low prevalence areas have been seriously limited by modest numbers of MS patients (20,21). Mean age at onset was 30 years for those with positive family history of MS; and 32.2 years for those without family history of MS, which was consistent with Weinshenker *et al,* who divided patients into 1 of 4groups: "sporadic"- no affected relatives; "1st degree"-a single affected 1st degree relative; "2nd or 3rd degree"-l or more affected 2nd- or 3rd-degree relatives; "1st degree plus"-Multiple affected relatives including at least one 1st-degreerelative. Mean age at onset was 30.49 years for sporadic and 31.74 years 1st degree relative, 30.261st degree plus, 28.95 2nd or 3rd degree. (17). Familial factors influence susceptibility to multiple sclerosis but it is unknown whether there are additional effects on the natural history of the disease (4). Mean lag time to diagnosis was 2.9 years for those with positive family history, and 5.1years for those without family history of MS; also no significant difference was found when mean lag time to diagnosis was compared between the two groups of patients, and we could not found other study to compare with them. Mean time between the first and second attack was found to be

3.4 years for those with positive family history and 2.6 years with for those without family history, no significant difference was found, also Weinshenker *et al* (17) did not found significant difference between the 4 group mentioned previously (3.85 for sporadic, 5.05 for first degree plus, 4.55 for first degree, and 4.43 2nd or 3rd degree) although their figures were higher than ours. This may be due to higher number of patients at Weinshenker *et al* and the different method of statistical analysis.

When presenting symptoms were analyzed the most common presenting symptoms for positive family history patients were sensory complaints and transverse myelitis (23.1% for both), followed by ON and pyramidal symptoms (15.4 for both). The difference was not significant. According to Weinshenker,(17) the most common presenting symptoms were sensory (46% for sporadic, 65% for 1st degree plus, 47% for first degree, and 46% for 2nd or 3rd degree), followed by ON (17% for sporadic, 26% 1st degree plus ,14%1st degree,20% 2nd or 3rd degree). Eber CG et al,(18) divided patients also into 4 groups: "sporadic" having no affected relatives; "1st degree"-a single affected 1st degree relative; "2nd or 3rd degree" having one or more affected 2nd- or 3rd-degree relatives. The results were very close to that of Weinshenker, the sensory symptoms being the presentation for 48% of the sporadic, 46% of the 1st degree, and 51% of the 2nd or 3rd degree. This was followed by ON (17% of the sporadic, 18% of the 1st degree, and 18% of the 2nd or 3rd degree. Both of the studies found no difference. In our study high percentage of transverse myelitis in those with positive

family history may be because of fewer numbers of patients. The initial disease course in patients with positive family history of MS was RRMS in 84.6%, while 15.4% had an initial course of PPMS. Patients without such a history showed RRMS course in 92.3%, and 7.7% had initial course of PPMS. In the current study this percentage is consistent with what is observed in the general population (22). Nevertheless, Weinshenker found RRMS course in 32% of sporadic, 39% of 1st degree plus, 24% of 1st degree, and 37% of 2nd or 3rd degree cases. They found PPMS in 33% of sporadic, 26% of 1st degree plus, 36% of 1st degree, and 27% of 2nd or 3rd degree cases. Eber *et al* observed RRMS in 28% of sporadic, 19% of 1st degree plus, 25% of 1st degree, and 32% of 2nd or 3rd degree. PPMS was seen in 21% of sporadic, 15% of 1st degree plus, 21% of 1st degree, and 19% of 2nd or 3rd degree (18). Again they found no difference when they compared the 4 groups, but the percentages were higher in comparison with our study. Of the patients with RRMS 36.4% evolved into SPMS after a mean period of 8.4 years (this for the patients with positive family history of MS), while patients without family history of MS 41.6% evolved onto SPMS after a mean period of 6.8 years. Weinshenker recorded that 25% of sporadic, 22% of 1st degree plus, 31% of 1st degree, and 26% of 2nd or 3rd degree evolved onto SPMS after a mean period of 5.69 years for sporadic, 7 years for 1st degree plus, 7.19 years for 1st degree, and 6.8 years for 2nd or 3rd degree cases. Regarding the disability mean, EDSS score was 3.6 for those with positive family history of MS, and 3.7 for those with negative family history; No significant difference was found regarding the disability. Weinshenker also conducted survival curves using EDSS 3 and 6 as end points, yielding no significant difference in outcome. A significant inverse correlation between lag time to diagnosis and age at onset (p=0.007) was found in this study, this may indicate that there is a lower index of suspicion regarding the disease diagnosis in younger age group or because there was a direct correlation between lag time to diagnosis and time to second attack (p=0.05) and an inverse though insignificant correlation between time to second attack and age at onset the lag time to diagnosis may be explained by the longer time to second attack that is required in many cases. Also because time to second attack is of prognostic value (13) this may mean that the disease carry amore favorable course with younger age at onset this consistent with Hauser *et al* that states that Patients less than 40 at onset (but not beginning in childhood) carry favorable prognosis .

The difference between sporadic and familial MS in the current study,may give the impression that although the number of the cases is low the familial MS is environmental rather than genetic which can be explained the geographical distribution of the disease in the country that the number of the cases in the north more than that in the middle and the south which could be to the latitude difference. One proposed explanation for the association with latitude is that exposure to sunlight may be protective, either because of an effect of ultraviolet radiation or of vitamin D (3). In support of this hypothesis, a case-control study in Tasmania that assessed sun exposure both by questionnaire and by solar damage to skin found that higher sun exposure during childhood and early adolescence was associated with a reduced risk of MS (23), and a study of monozygotic twins from North America reported that the frequency of childhood sun exposure, assessed by questionnaire, was inversely associated with the likelihood of developing MS (24).

Conclusions: :
Patients with familial MS did not differ from those with sporadic MS. We were unable to find any support for differences between familial and sporadic MS within the parameters studied. The only exception was the significantly inverse relation between mean age at onset and lag time to diagnosis.

This study is one of very few conducted on MS patients in Iraq, while proud to be so; this indicates the need to better examine our MS population, integrating the results to what is continuously being known worldwide.

Being one of the first studies, we were faced with several limitations, some of which is the small number of informative records, as well as the limited financial and human resources allocated for us.

Our study was a retrospective cohort one, future studies can overcome several challenges that we had to go through. For example, using the records as a source of information may have resulted in information bias as it depended on the observer's interpretation of the record. Also, having incomplete or misleading records often lead to excluding potentially beneficial sources of information. Stronger study designs where patients are followed up in person by the researchers can reveal ample information that can aid in further investigations, especially that the information will be gathered by the researchers, so what may go usually unrecorded will be noted and the defect can be overcome either in the same interview or in subsequent interviews. Also this can help recruit larger number of participants for the study (given that people who were registered were over 1,000). Such a pool can be extremely helpful and can yield more accurate and reliable results.

References:
1. *Hasan ZN.Disability and prognosis of relapsing remitting multiple sclerosis, is it different in Iraqi patients?.Neurosciences 2011; Vol. 16 (3): 233-236.*
2. *Ebers, GC. Environmental factors and multiple sclerosis. Lancet Neurol 2008; 7:268.*
3. *Ascherio, A, Munger, KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Ann Neurol 2007; 61:504*

4. *Hensiek AE, Seaman SR, Barcellos LF, Oturai A, Eraksoi M, Cocco E,et al. Familial effects on the clinical course of multiple sclerosis. Neurology 2007;68:376–383.*

5. *Kalman B, Leist TP. Familial multiple sclerosis and other inherited disorders of the white matter. The Neurologist 2004;10: 201–215*

6. *Sadovnick AD, Baird PA, Ward RH. Multiple sclerosis: updated risks for relatives. Am J Med Genet 1988; 29:533–41.*

7. *Dyment DA, Ebers GC, Sadovnick AD. Genetics of Multiple sclerosis. Lancet Neurol 2004; 3:104–10.*

8. *Carton H, Vlietinck R, Debruyne J, et al. Risks of multiple sclerosis in relatives of patients in Flanders, Belgium. J Neurol Neurosurg Psychiatry 1997; 62:329–33.*

9. *Grasso MG, Frontali M, Bernardi S, et al. Multifactorial inheritance and recurrence risks of multiple sclerosis in Italian patients. Neuroepidemiology 1989; 8:300–7.*

10. *Montomoli C, Prokopenko I, Caria A, et al. Multiple sclerosis recurrence risk for siblings in an isolated population of Central Sardinia, Italy. Genet Epidemiol 2002; 22:265–71.*

11. *Robertson NP, Fraser M, Deans J, et al. Age-adjusted recurrence risks for relatives of patients with multiple sclerosis. Brain 1996; 119:449–55.*

12. *Sadovnick AD, Baird PA. The familial nature of multiple sclerosis: age-corrected empiric recurrence risks for children and siblings of patients. Neurology 1988; 38:990–1.*

13. *Green A, Waubant E. Genetic and epidemiology of multiple sclerosis. Continuum Lifelong Learning Neurol. 2007; 13(5):63–85.*

14. *Barcellos LF, Oksenberg JR, Green AJ, et al. Genetic basis for clinical expression in multiple sclerosis. Brain. 2002; 125:150–158).*

15. *Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the ''McDonald Criteria.'' Ann Neurol 2005; 58(6):840–846.*

16. *Pinhas-Hamiel O. juvenile multiple sclerosis clinical features and prognostic characteristic .J pediatr. 1998; 132:735-7.*

17. *Weinshenker BG, Bulman D, Carriere W, Baskerville J, Ebers GC. Comparison of sporadic and familial multiple sclerosis. Neurology 1990; 40:1354–1358.*

18. *Ebers GC, Koopman WJ, Hader W, et al. The natural history of multiple sclerosis: a geographically based study: 8: familial multiple sclerosis. Brain. 2000; 123:641–649.*

19. *Rudick, RA, Whitaker, JN. Cerebrospinal fluid tests for multiple sclerosis. In P. Scheinberg (Ed.), Neurology/neurosurgery update series, Vol. 7, CPEC, Princeton, NJ, 1987; p 1.*

20. *Tan CT. Multiple sclerosis in Malaysia. Arch Neurol 1988;45:624–7*

21. *Bansil S, Singhal BS, Ahuja GK, et al. Comparison betweenmultiple sclerosis in India and the United States: a case-controlstudy. Neurology 1996;46:385–7*

22. *Hauser, Stephen (Ed.) (2006) Harrison`s Neurology in Clinical Medicine .16th Ed. New York :McGrow-Hill.*

23. *Van der Mei, IA, Ponsonby, AL, Dwyer, T, et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. BMJ 2003; 327:316.*

24. *Islam, T, Gauderman, WJ, Cozen, W, Mack, TM. Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. Neurology 2007; 69:381.*