Familial MS cases are more severe than sporadic MS cases

C. Guaschino[1-2], F. Esposito[1-2], E. Mascia[2], S. Santoro[2], L. Moiola[1], V. Martinelli[1], G. Meola[3], G. Comi[1], F. Martinelli Boneschi[1-2].

•1 Department of Neurology, San Raffaele Scientific Institute - Milan (Italy); 2 Laboratory of Human Genetics of Neurological Diseases, CNS Inflammatory Unit & INSPE - Milan (Italy); 3 Department of Neurology, San Donato Hospital, Italy.

INTRODUCTION and PURPOSE

Epidemiological evidence indicates that multiple sclerosis (MS) is a multifactorial disease, caused by the interaction between genetic and environmental risk factors[1]. Relatives of MS patients have an increased risk of developing the disease compared to the general population[2]. In particular, it was shown that first-degree relatives of probands have a risk that is 30-50 times greater than the 0,1% risk of the general population. However, the comparison of demographic and clinical variables between familial and sporadic cases gave conflicting results. Romero-Pinel et al. demonstrated in a Spain cohort that there is a lower age at onset in familial versus sporadic MS and there is also an anticipation of the age at onset of MS in the younger generations of patients with familial MS[3]. On the other site, Gourraud et al. found no significant difference between probands of multicase families and probands of sporadic MS families in terms of gender, age of onset, disease duration, proportion with relapsing–remitting (RR) MS, and proportion with progressive MS in a cohort of American subjects[4].

The aim of this study was to compare demographic and clinical characteristics from an Italian cohort of familial MS cases (fMS), which were members of large multiplex families, with epidemiological data from an Italian cohort of sporadic MS patients (sMS).

METHODS

Patients: Twelve Italian families with at least three affected relatives (1 with 7, 5 with 4 and 6 with 3), two of which with a first-degree relationship, were recruited as part of a large Italian multicentric study. Another family with two cases only affected, one with a severe phenotype and a comorbidity for autoimmune disease, was also included in the study.

The pedigrees are reported in **Figure 1**.

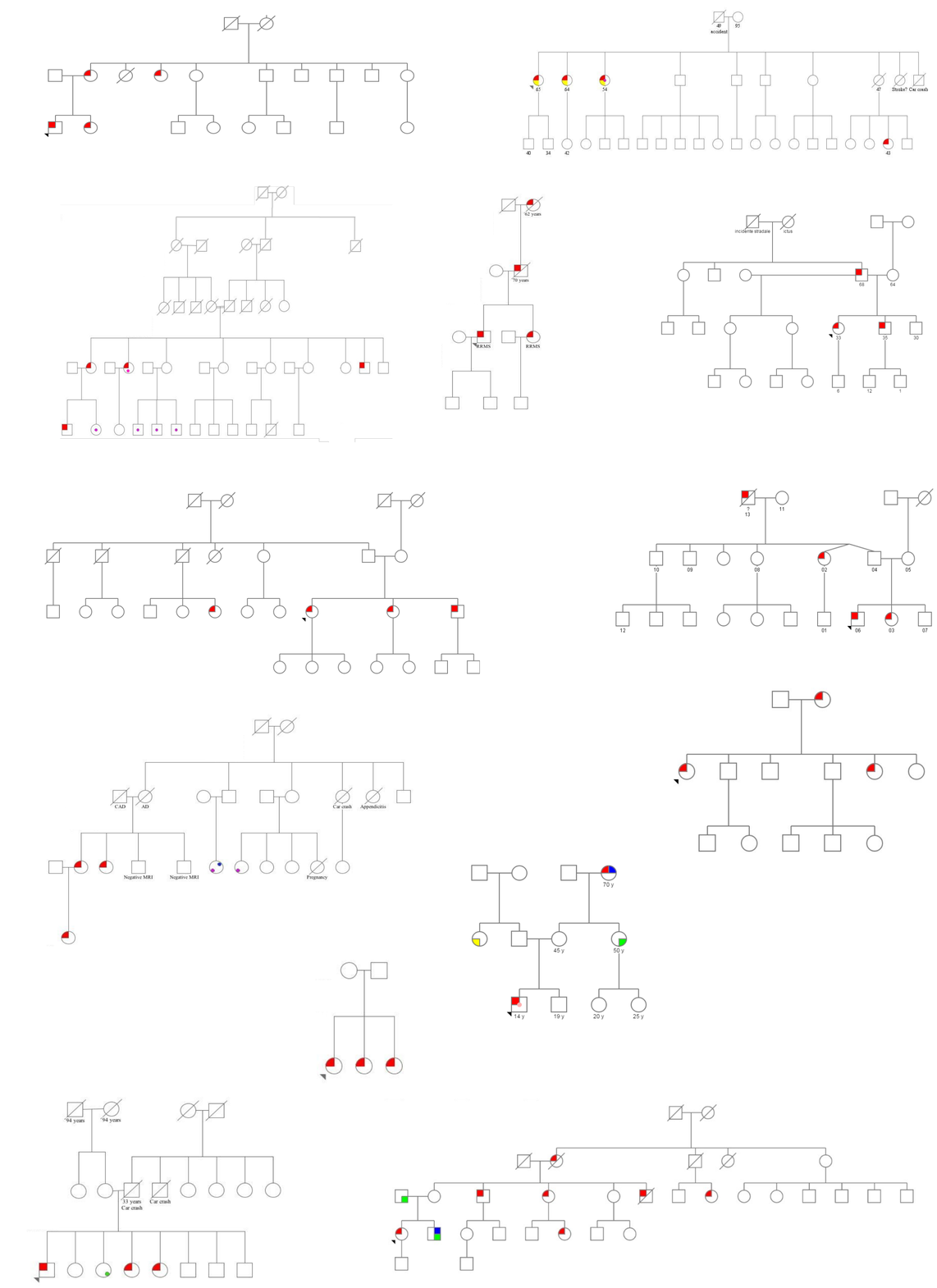

Figure 1: pedigrees of recruited families. MS patients are marked in red. Blue, green and yellow indicate other autoimmune diseases.

Demographic and clinical data including gender, age, age at onset, clinical phenotype, disease duration, Expanded disability Status Scale (EDSS), and MS Severity Scale (MSSS), were collected for 39 fMS and 461 sMS recruited in San Raffaele Hospital. Same assessment of familial history was recorded using a questionnaire focused on familiarity of MS and other autoimmune disease[5].

Statistical analysis:

•Demographic and clinical variables were compared between groups using the Mann-Whitney U-test for continuous variables and Pearson chi-square test for categorical variables.

•Within the familial MS group, fMS patients from different generations were selected. The age at onset between the members of the different generations were compared using Wilcoxon rank test in order to establish if there is anticipation of disease onset across generations.

RESULTS

Compared to sMS, fMS were older at age of recruitment (49.4 *vs* 39.4 years, p<0.0001), showed an higher prevalence of progressive (Pr) MS forms (12.8% *vs* 2.8%, p=0.001 **Figure 2**) compared to bout-onset MS (BOMS), had a significantly higher EDSS (median EDSS 3.0 vs 1.5, p<0.0001), longer disease duration (17.2 *vs* 10.5 years, p=0.003) and a more severe disease (mean MSSS 4.0 vs 2.3, p= 0.0003 **Figure 3**). No differences between the two groups were found regarding the gender proportion (p=0.27) and mean age at onset (31.7 years vs 28.7 years, p=0.15).

Demographic and clinical characteristics of fMS compared to sMS are summarized in **Table 1**.

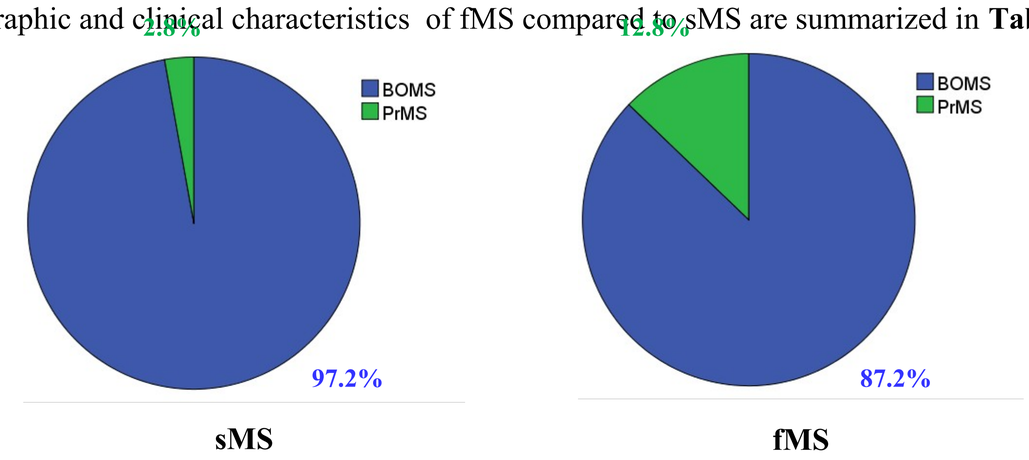

Figure 2: distribution of clinical courses in sMS and in fMS.

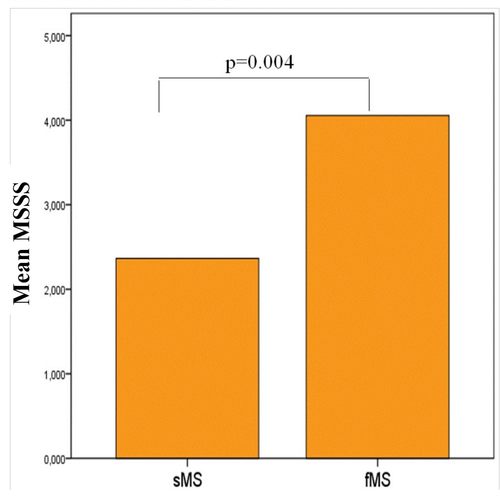

Figure 3: mean MSSS in sMS and in fMS.

	fMS (n=39)	sMS (n=461)	p value
Clinical course (BOMS:PrMS)	34:5	448:13	0.001
Sex ratio F:M	2.9:1 (29:10)	1.9:1 (303:158)	n.s.
Mean Age (years)	49.4±13.9	39.4±10	<0.0001
Mean Age at onset (years)	31.7±10.9	28.7±9.1	n.s.
Mean Disease duration (years)	17.2±12.3	10.5±6.7	<0.0001
Median EDSS	3.0	1.5	<0.0001
Mean MSSS	4.0±2.5	2.3±1.9	0.004

Table 1 shows the demographic and clinical characterstics of fMS compared to sMS.

Within the familial MS group, a trend for a mean lower age at onset in the younger generation was found (25.5 [SD=5.0] compared to 35.2 [SD=13.4]) in older generation, but without reaching statistical significance (p value = 0.176) (**Figure 4**).

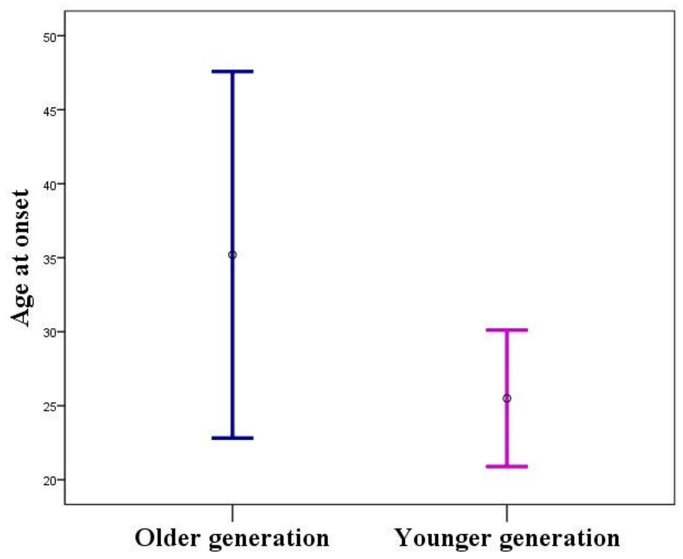

Figure 4: Error bar showing mean age of onset in older (blue bar) and younger (violet bar) generations.

CONCLUSIONS

- **In our Italian cohort, no major differences were observed between sporadic and familial cases from large Italian multiplex families in terms of gender and age at onset in agreement with a previous report from a US cohort[4].**
- **However, familial cases have a higher proportion of PrMS subjects and a more severe disability (quantified using MSSS) compared to sMS.**
- **Despite not statistically significant, our study seems also to suggest that in fMS, onset of the disease might occur earlier in the younger generations.**
- **These data suggest that shared environmental and genetic factors in multiplex families might negatively influence the disease course in fMS, but data should be confirmed in larger datasets from additional Italian families and replicated in other cohorts with different genetic background.**

REFERENCES

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2) Compston et al., Lancet 2008
3) Romero-Pinel et al., European Journal of Neurology, 2010
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5) Esposito et al., Neurology, Neuroimmunology and Neuroinflammation, 2015