Two determinants of late disability progression in multiple sclerosis: early inflammatory disease and old age in damaged brain

Fulvia Fanelli (1), Maura Danni (2), Paola Cavalla (3), Valeria Barletta (1), Luca Prosperini (1), Lorenzo Pinessi (3), Leandro Provinciali (2), Carlo Pozzilli (1).

(1) Dept. of Neurology and Psychiatry, S. Andrea Hospital, Sapienza University, Rome, Italy
(2) Neurological Clinic, Ospedali Riuniti, Marche Polytechnic University, Ancones, Italy
(3) Dept. of Neurosciences, S. Giovanni Battista Hospital, University of Turin, Italy

INTRODUCTION

Natural history studies have suggested that the disability progression due to multiple sclerosis (MS) is a "two-stage" process, i.e. in the earlier stage inflammation and disability progression are associated, while in the later stage these two phenomena are independents. Nonetheless, the relationship between relapses and disability is still debated.

OBJECTIVE

To investigate the influence of relapses and paraclinical signs of inflammation detected at magnetic resonance imaging (MRI) on disability progression from an Expanded Disability Status Scale (EDSS) score of 3.5 (+/-0.5) to 6.0 or more.

METHODS

Data of patients regularly attending 3 tertiary MS centres in Italy (Rome, Ancones and Turin) were analyzed. The characteristics of patients included are shown in *Table 1*.

A Cox proportional hazard model was built to assess the influence of some covariates on the risk of progression to EDSS =/>6.0 (main outcome).

These covariates included gender; age, MS duration, relapse rate and MRI activity at EDSS 3.5 (+/-0.5); onset symptom; time to first relapse; exposure to disease-modifying treatments (time-dependent covariate). The follow-up period was calculated as time elapsed from EDSS 3.5 (+/-0.5) to the main outcome, or the last available visit, whichever came first.

Table 1: Patients' characteristics (N=611)

Gender, n (%)	
Female	409 (67%)
Male	202 (33%)
Age (years) at disease onset	30.4 (9.9)
Onset symptom, n (%)	
Afferent	247 (40%)
Efferent	239 (39%)
Multifocal	125 (21%)
Time to first relapse, months	31.5 (35.8)
Age (years) at fixed EDSS 3.5-4.0	42.5 (9.8)
Disease duration (years) at fixed EDSS 3.5-4.0	12.2 (7.5)
N. Relapses at fixed EDSS 3.5-4.0	5.9 (3.4)
Disease-modifying drugs, n (%)	
none	53 (9%)
first-line	137 (22%)
second-line	421 (69%)
Site	
Rome	326 (53%)
Ancone	177 (29%)
Turin	108 (18%)

All data are expressed as mean (SD) unless indicated otherwise

RESULTS

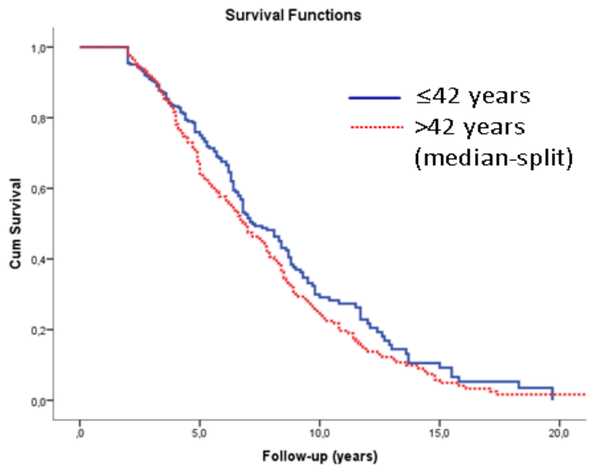
During a median follow-up time of 5 years (range 2-23), 361 patients reached an EDSS score =/>6.0. Out of these, 232 (64%) patients developed disability with superimposed relapses or paraclinical (i.e. gadolinium-enhancement) signs of inflammation, while 129 (36%) patients did not show any disease activity despite disability progression. Those patients presenting superimposed clinical/MRI activity were younger, had shorter MS duration and higher relapse rate at EDSS 3.5 (+/-0.5) than those without activity (all p-values<0.01, see also Table 2).

Table 2: subgroup analysis of patients (n=361) who reached the disability outcome

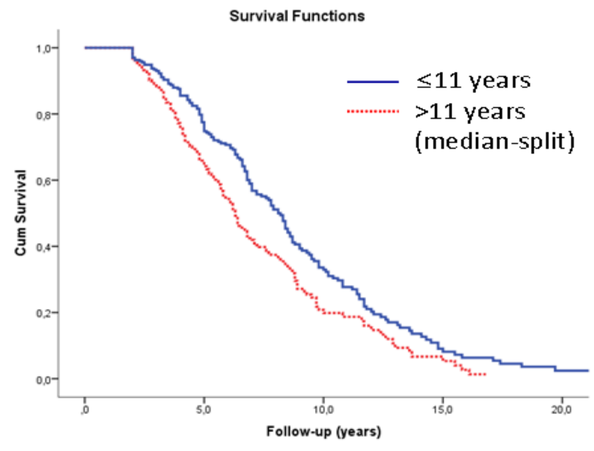
	Age at EDSS 3.5-4.0	Disease duration at EDSS 3.5-4.0	No of relapses at EDSS 3.5-4.0
Superimposed relapses and/or GD-enhancement **N=232 (64%)**	47.0 (9.4)	11.6 (7.2)	6.5 (3.8)
Absence of relapses and/or GD-enhancement **N=129 (36%)**	46.2 (8.9)	13.8 (7.4)	5.5 (2.7)
P-value	***<0.001***	***0.02***	***0.004***

The Cox regression model showed that the risk of disability progression to EDSS score =/>6.0 was associated with older age (HR=1.024, p<0.001) and shorter MS duration (HR=0.972, p=0.001) at EDSS 3.5 (+/-0.5) (see also the Figure below).

Risk of reaching EDSS of 6.0 or more according to age at EDSS 3.5



Risk of reaching EDSS of 6.0 or more according to MS duration at EDSS 3.5



DISCUSSION

Our findings suggest that the occurrence inflammation may lead to disability progression even in the later disease stage in about two thirds of the patients, especially if younger, with shorter MS duration and higher relapse rate. However, the multivariate analysis confirms the "Confavreux's hypothesis" that aging is an independent risk factor for disability progression and may play a role in the chronic diffuse neurodegeneration due to MS.

REFERENCES

1. Confavreux C, Vukusic S. *Age at disability milestones in multiple sclerosis*. Brain. 2006
2. Friese MA et al, *Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis*. Nat Rev Neurol. 2014
3. Filippi M. *MRI measures of neurodegeneration in multiple sclerosis: implications for disability, disease monitoring, and treatment*. J Neurol. 2015