MSJ Experimental Translational Clinical

Original Research Paper

Brain atrophy and employment in multiple sclerosis patients: a 10-year follow-up study

Multiple Sclerosis Journal—Experimental, Translational and Clinical

January-March 2020, 1–8

DOI: 10.1177/2055217320902481

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Abstract

Background: Multiple sclerosis is often associated with unemployment. The contribution of grey matter atrophy to unemployment is unclear.

Objectives: To identify magnetic resonance imaging biomarkers of grey matter and clinical symptoms associated with unemployment in multiple sclerosis patients.

Methods: Demographic, clinical data and 1.5 T magnetic resonance imaging scans were collected in 81 patients at the time of inclusion and after 5 and 10 years. Global and tissue-specific volumes were calculated at each time point. Statistical analysis was performed using a mixed linear model.

Results: At baseline 31 (38%) of the patients were unemployed, at 5-year follow-up 44 (59%) and at 10-year follow-up 34 (81%) were unemployed. The unemployed patients had significantly lower subcortical deep grey matter volume ($P < 0.001$), specifically thalamus, pallidus, putamen and hippocampal volumes, and cortical volume ($P = 0.011$); and significantly greater T1 ($P < 0.001$)/T2 ($P < 0.001$) lesion volume than the employed patient group at baseline. Subcortical deep grey matter volumes, and to a lesser degree cortical volume, were significantly associated with unemployment throughout the follow-up.

Conclusion: We found significantly greater atrophy of subcortical deep grey matter and cortical volume at baseline and during follow-up in the unemployed patient group. Atrophy of subcortical deep grey matter showed a stronger association to unemployment than atrophy of cortical volume during the follow-up.

Keywords: Multiple sclerosis, atrophy, employment, subcortical deep grey matter, biomarkers, MRI

Date received: 15 October 2019; revised: 23 December 2019; accepted: 6 January 2020

Introduction

Multiple sclerosis (MS) is a chronic, debilitating disease of the central nervous system. The disease onset is typically in young adulthood in patients' most vulnerable years, when obtaining an education, starting a family and establishing a career are key events in life. Employment status is an important part of the comprehensive assessment and unemployment is a considerable issue for MS patients. A large cross-sectional study conducted in 16 European countries showed that only approximately 50% of MS patients below retirement age were employed.[1] Several studies have explored the clinical determinants of work-related problems and unemployment,[2–5] but magnetic resonance imaging (MRI) pathology related to unemployment has been scarcely explored. Studies by Kadrnozkova et al.[6] and Tauhid et al.[7] thoroughly explore the relationship between lesion volumes, brain atrophy and employment status cross-sectionally and longitudinally, respectively. The cross-sectional study found increased lesion volume, increased T1 lesion volume and increased burden of T2 lesions showing T1 hypointensity, and decreased whole brain volume, all significantly associated with unemployment. Longitudinally, whole brain atrophy, T1 and T2 lesion load were predictors of unemployment after 12 years.[6] Further studies on

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this topic are warranted for the better understanding of unemployment in MS patients.

Traditionally, MS has been regarded as a disease of the white matter with multifocal lesions, evident by T2 hyperintense and T1 hypointense MRI lesions, causing axonal damage, and thereby leading to physical impairment. Extensive research during the past decades has greatly increased our knowledge of the pathomechanisms and symptoms of the disease. MS is not exclusively an inflammatory disease, as neurodegeneration and atrophy are apparent from the earliest stages of the disease.[8] The involvement of grey matter pathology is evident, contributing to both physical and cognitive impairment. The burden of physical and cognitive impairment affects the patients' total life situation profoundly, in which loss of employment is one of the consequences.[9] Brain atrophy is increasingly used as a marker of disease activity in research.[10] and regional and tissue-specific atrophy of the deep grey matter have been shown to correlate with clinical symptoms in several studies.[11,12] The association between subcortical deep grey matter (SDGM) atrophy and clinical disability has been shown in several studies.[9,12–15]

The aim of this paper was to investigate the relationship between grey matter atrophy and occupational status in MS patients cross-sectionally and over 5 and 10 years, and explore the effect of common MS symptoms on employment status over 5 and 10 years. Our hypothesis was that subcortical deep grey atrophy would be related to unemployment in MS patients.

Methods

Patients

All patients diagnosed with MS in the south western parts of Norway in the years of 1998 to 2000 were invited to participate in the study, and were included at the time of diagnosis. The study population is described in an earlier paper.[13] The diagnosis of MS was made according to the current diagnostic criteria at that time, the criteria of Poser et al.[16]

We identified 108 patients eligible for inclusion, three of them had moved elsewhere, one had died and 11 declined participation, leaving 93 patients. From those, 81 patients went through the necessary testing, neurological examination and MRI of the brain, and were subsequently included in the study (Figure 1).

Follow-up assessments were performed after 5 and 10 years, and included clinical assessment and MRI of the brain.

At each time point, information regarding demographics, employment status, medical history and medication was collected. Clinical neurological examination with evaluation of the Kurtzke Expanded Disability Status Scale (EDSS) and cognitive testing using the symbol digit modalities test (SDMT) were performed at 5 and 10 years' follow-up. We investigated fatigue using the fatigue severity scale (FSS) at each time point.

The study was approved by the regional committee for medical and health research of western Norway and the Norwegian Data Protection Authority. Written informed consent was collected from all patients in accordance with the Helsinki Convention.

MRI acquisition and analysis

MRI scans were performed at 1.5 T (Siemens, Symphony/Philips Medical systems, Intera) units, in two different centers; at Haukeland University Hospital in Bergen and Stavanger University Hospital in Stavanger. The MRI protocol included a dual spin echo (SE) proton density (PD)/T2 weighted image (WI), a three-dimensional (3D) T1 WI and a SE T1 WI. On the Siemens scanner the voxel size for (SE) PD/T2 WI was $0.9 \times 0.9 \times 5.0\,mm^3$, for 3D

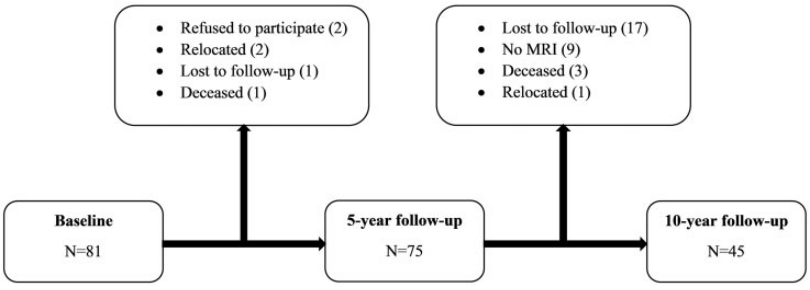

Figure 1. Flow chart of patient inclusion at baseline, 5-year and 10-year follow-up.

T1 WI $0.9 \times 0.9 \times 1.4\,mm^3$ and for SE T1 $0.9 \times 0.9 \times 5.0\,mm^3$. On the Philips scanner the voxel size for (SE) PD/T2 WI was $0.89 \times 0.89 \times 5.0\,mm^3$, for 3D T1 WI $0.89 \times 0.89 \times 1.2\,mm^3$ and for SE T1 $0.89 \times 0.89 \times 5.0\,mm^3$.

The protocol is described in detail elsewhere.[13]

Furthermore, the MRI scans were subsequently analyzed in order to calculate global and tissue-specific atrophy measures and lesion volumes. All baseline and follow-up images for a given subject were co-registered to its baseline T1 SE image using FMIRIB's FLIRT (FMRIB's linear image registration tool). Using co-registered images, T1 and T2 lesion volumes were calculated using a reliable semi-automated edge detection contouring/thresholding technique previously described.[17] The 3D T1 scans were first inpainted to minimize the impact of white matter lesions on grey matter volume measurements.[18] The normalized cortical volume was measured using SIENAX (V 2.6) as previously described.[19,20] For deriving cortical volumes at the follow-up time points, the SIENAX-MTP method was utilized.[21] Absolute volumes of the subcortical deep grey structures were estimated from inpainted 3D T1 images with FMRIB's integrated registration and segmentation tool (FIRST V1.2), a model-based segmentation/registration tool.[22] Normalized SDGM volumes were obtained by multiplying the estimated volumes from FIRST by the volumetric scaling factor from SIENAX.[19]

The process is described in detail elsewhere.[13]

Employment status assessment

At each time point employment status was assessed. We categorized the patients as employed or unemployed, including part time employment in the employed patient group. The patients were categorized as unemployed at the time when they received disability pension and permanently exited the work force. In Norway, during the time of inclusion and follow-up, being granted disability pension was a permanent decision.

Statistical analysis

Descriptive statistics are presented as means and standard deviations (SDs), medians and interquartile ranges (IQRs), or as counts and percentages for continuous symmetric, continuous non-symmetric and categorical data, respectively. Between-groups comparisons were correspondingly performed using independent samples *t* tests, Mann–Whitney rank sum tests, or chi-square tests. The association between MRI characteristics and risk of unemployment were studied using generalized estimating equations (GEEs) logistic regression, with AR(1) working correlation and robust estimation of standard errors. Years of follow-up were included in the models as a continuous covariate, and adjustments were made for demographic (age, sex, study center and level of education) and clinical variables (MS course). Furthermore, cognition, fatigue and EDSS scores were included in the Supplementary analyses. For the patients employed at baseline, the association between unemployment at 5 and 10-year follow-up and, respectively, MRI volumes at baseline and percentage brain volume change between baseline and follow-up were investigated.

Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs), and with *P* values for the Wald tests of null effects.

All statistical analyses were performed using SPSS v. 24. Results with *P* values of 0.05 or less were considered statistically significant.

Results

Demographic, clinical and MRI characteristics at baseline

Demographic, clinical and MRI characteristics of the cohort at baseline, 5 and 10-year follow-up are shown in Table 1. At baseline, 31 of 81 (38%, 95% CI 0.28–0.50%) patients were unemployed. At the 5-year follow-up this number had increased to 44 of 75 (59%, 0.47–0.70%), and at the 10-year follow-up altogether 34 of 42 (81%, 0.35–0.91%) were unemployed.

Between baseline and the 5-year follow-up 18 patients became unemployed. Between the 5-year and 10-year follow-up four patients became unemployed. In the employed patient group there was a drop-out of 19 patients at the 10-year follow-up, and in the unemployed patient group there was a drop-out of 14 patients.

When comparing the employed and unemployed patient groups at baseline we found the unemployed patient group was older, having a higher EDSS score, longer disease duration, having more fatigue and cognitive impairment, higher T1/T2 lesion volumes and lower cortical and SDGM volumes (Table 1).

Table 1. Demographics, clinical characteristics and brain volumes split by employment status at baseline, 5 and 10-year follow-up.

	Baseline (n=81)			5-Year follow-up (n=75)			10-Year follow-up (n=42)		
	Unemployed	Employed	P value	**P value**	Employed	P value	Unemployed	Employed	P value
No. of patients (%)	31 (38.3)	50 (61.7)		44 (58.7)	31 (41.3)		34 (81.0)	8 (19.0)	
Age mean (SD)	47.3 (8.7)	38.3 (8.3)	**<0.001**	48.2 (9.4)	43.6 (8.8)	**0.035**	54.0 (9.2)	47.1 (6.8)	0.071
Women, n (%)	22 (71.0)	33 (66.0)	0.81	33 (75.0)	19 (61.3)	0.22	26 (76.5)	7 (87,5)	0.66
EDSS, median (range)	4.0 (2.0–6.0)	2.8 (0–6.0)	**<0.001**	4.0 (0–8.0)	2.5 (0–6.0)	**<0.001**	5.0 (1.5–8.0)	2.5 (1.5–6.0)	**0.015**
MS subtype, n									
RRMS	21	41	0.26	21	26	**0.006**	12	4	0.41
SPMS	5	6		16	3		16	4	
PPMS	5	3		7	2		6	0	
Disease duration in months, mean (SD)	134.0 (103.1)	76.0 (70.5)	**0.002**	163.8 (95.0)	149.0 (87.0)	0.51	230.6 (113.0)	193.2 (87.7)	0.66
DMT use, n (%)	3 (9.7)	8 (16)	0.42	19 (43.2)	14 (45.1)	0.87	23 (67.6)	6 (75.0)	0.69
FSS, mean (SD)	5.5 (1.7)	4.5 (1.7)	**0.003**	5.6 (1.3)	4.4 (1.9)	**0.003**	5.4 (1.5)	4.7 (1.3)	0.13
SDMT, mean (SD)	36.8 (11.3)	45.4 (12.6)	**0.002**	35.8 (13.4)	49.3 (12.1)	**<0.001**	39.3 (15.4)	55.5 (10.8)	**0.004**
Cortical volume	559 (557) [557]	585 (41.2) [582]	**0.011**	551 (46.9) [551]	577 (31.8) [574]	**0.013**	548 (39.8) [552]	534 (47.6) [517]	0.49
SDGM volume	42.1 (5.4) [40.3]	46.4 (5.0) [46.3]	**<0.001**	41.0 (6.2) [40.2]	45.6 (5.3) [45.6]	**0.003**	41.5 (6.0) [41.2]	43.3 (3.5) [41]	0.53
T2 LV, median (IQR)	17.3 (22.6)	6.22 (12.2)	**<0.001**	21.0 (25.9)	5.41 (14.4)	**0.002**	15.5 (17.4)	4.24 (6.0)	**0.025**
T1 LV, median (IQR)	6.9 (11.7)	1.9 (3.9)	**<0.001**	7.3 (14.1)	1.7 (4.5)	**0.002**	3.4 (8.9)	0.2 (1.9)	**0.034**

Brain volumes are presented in millilitres as mean, (SD), [median].
The differences between the employed and unemployed groups were calculated using Student's t test and Mann–Whitney rank sum test, as appropriate.
EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; RR: relapsing–remitting; SP: secondary progressive; PP: primary progressive; DMT: disease-modifying therapy; FSS: fatigue severity score; SDMT: symbol digit modalities test; SDGM: subcortical deep grey matter; LV: lesion volume.
Note. Bold values denote statistical significance at the $p < 0.05$ level.

MRI and clinical variables associated with employment status

We investigated MRI and clinical variables affecting employment status, specifically the cortical grey matter and the subcortical grey matter. Furthermore, we separately investigated the different deep grey matter structures.

The total effect of SDGM volume over the 10-year follow-up, when adjusting for age, sex, MS course, level of education and study center, was estimated as OR 0.87 (95% CI 0.80–0.95; $P = 0.002$), i.e. for every one cm^3 higher subcortical volume, the odds of being unemployed was reduced by 13% (Table 2). After adjusting for cognitive impairment (SDMT), fatigue (FSS) and physical disability (EDSS), the association was weaker and not significant ($P = 0.11$) see Supplementary Table 1).

Of the individual subcortical structures, all except for the caudate showed a significant effect on unemployment when adjusting for age, sex, MS course, level of education and study center. After adjusting for cognitive impairment, fatigue and physical disability, we found the atrophy to be mostly mediated through cognitive function and physical disability (see Supplementary Table 1).

When adjusting for SDMT, FSS and EDSS, only lower hippocampus volume showed a significant remaining effect on unemployment, with OR 0.59 (95% CI 0.38–0.93; $P = 0.021$) (Table 2).

The total effect of cortical volume over the 10-year follow-up, when adjusting for age, sex, MS course, level of education and study center, was estimated as OR 0.99 (95% CI 0.97–1.0; $P = 0.045$), i.e. for every one cm^3 higher cortical volume, the odds of being unemployed was reduced by 1%. After adjusting for cognitive impairment (SDMT), fatigue (FSS) and physical disability (EDSS), the association was weaker and not significant ($P = 0.51$) (Table 2).

Discussion

This prospective, longitudinal study of a cohort of MS patients identifies MRI markers of grey matter and associated clinical symptoms contributing to unemployment. SDGM atrophy showed the strongest association with unemployment, whereas cortical atrophy showed a weaker, yet significant relationship with employment status. Of the SDGM structures, lower volumes of thalamus, pallidus, putamen and hippocampus were associated with unemployment. This is in line with a cross-sectional study of 50 relapsing–remitting MS

Table 2. GEE model parameter estimates.

Model		Unadjusted			Model A			Model B			Model C	
Predictor	n/obs	OR (95% CI)	*P* value	n/obs	OR (95% CI)	*P* value	n/obs	OR (95% CI)	*P* value	n/obs	OR (95% CI)	*P* value
Cortical	81/173	0.98 (0.97, 1.00)	0.003	76/163	0.99 (0.97, 1.00)	0.037	76/161	0.99 (0.97, 1.00)	0.045	74/146	1.00 (0.98, 1.01)	0.51
Subcortical	81/173	**0.87 (0.82, 0.94)**	**<0.001**	76/163	**0.87 (0.80, 0.95)**	**0.001**	76/161	**0.87 (0.80, 0.95)**	**0.002**	74/147	0.93 (0.84, 1.02)	0.11
Thalamus	81/173	**0.71 (0.58, 0.87)**	**0.001**	76/163	**0.68 (0.52, 0.89)**	**0.005**	76/161	**0.68 (0.51, 0.89)**	**0.006**	74/147	0.81 (0.59, 1.11)	0.19
Pallidus	81/173	**0.29 (0.13, 0.63)**	**0.002**	76/163	**0.22 (0.09, 0.53)**	**0.001**	76/161	**0.24 (0.10, 0.58)**	**0.002**	74/147	0.43 (0.14, 1.38)	0.16
Putamen	81/173	**0.57 (0.44, 0.75)**	**<0.001**	76/163	**0.61 (0.46, 0.83)**	**0.001**	76/161	**0.61 (0.45, 0.83)**	**0.002**	74/147	0.73 (0.50, 1.05)	0.090
Caudate	81/173	**0.60 (0.39, 0.91)**	**0.017**	76/163	0.68 (0.41, 1.15)	0.15	76/161	0.67 (0.40, 1.15)	0.15	74/147	0.93 (0.51, 1.69)	0.80
Hippocampus	81/173	**0.44 (0.28, 0.68)**	**<0.001**	76/163	**0.47 (0.30, 0.74)**	**0.001**	76/161	**0.48 (0.31, 0.76)**	**0.002**	74/147	**0.59 (0.38, 0.93)**	**0.021**

Model A: adjusted for baseline covariates: center, sex, age and education.
Model B: adjusted for baseline covariates: center, sex, age and education; and time-varying MS course.
Model C: adjusted for baseline covariates: center, sex, age and education; time-varying MS course; and time-varying symbol digit modalities test, fatigue severity score and Expanded Disability Status Scale.
GEE: general estimating equation; OR: odds ratio; CI: confidence interval; MS: multiple sclerosis.
Note. Bold values denote statistical significance at the $p < 0.05$ level.

patients showing significantly more thalamic atrophy in unemployed patients.[9]

Some cross-sectional studies have explored the correlation between MRI biomarkers and employment, and both lesion load, whole brain volume and central atrophy were associated with unemployment.[7,9] However, only a handful have explored the contribution of brain atrophy to unemployment longitudinally.[6] This paper can be viewed as an important addition to the current knowledge, exploring the role of brain atrophy in more detail. To the best of our knowledge, this paper is one of the first to explore the relationship between brain atrophy of the SDGM structures and employment status longitudinally. Compared to SDGM atrophy, a weaker association was seen between cortical atrophy and unemployment in our study. This is in line with several studies concluding with atrophy of the deep grey matter being strongly associated with disability[12,13,23] and cognitive impairment.[9,14] Cortical atrophy has in several studies been found to be associated with clinical symptoms, namely cognitive dysfunction[11] and neurological disability.[13] The underlying pathology causing deep grey matter atrophy is not fully understood, and several mechanisms are probably present. Most of the deep grey matter regions are central hubs with widespread connections to several regions of the brain, including the cortex, making them especially vulnerable.

We found an unemployment rate of 38.3% at baseline, and the unemployment rate increased over the 10-year follow-up. The proportion of unemployed MS patients varies considerably in different studies. In a recent study with almost 17,000 patients in 16 European countries, the proportion of patients not employed due to MS was between 20% and 64%,[1] and a recent meta-analysis found an average employment rate of 44% across 33 cross-sectional studies. The great difference in reported unemployment is most likely caused by different patient groups (hospital vs. outpatient clinic), different diagnostic criteria used, disease duration and social service systems. In comparison, overall 7.8% of the population aged 18–67 years in the county of Rogaland were receiving disability pension in the year 2015.[24] Hence, MS affects the employment ability profoundly in western Norway.

Clinical correlates of unemployment are well explored in several studies, showing unemployed patients having more physical disability, cognitive impairment, depression and fatigue, and lower quality of life.[2–5,25,26]

SDMT is as a measure of processing speed, and we chose it as a measure for cognitive impairment, as it has been shown to be a valid and reliable method to measure cognitive impairment in MS patients.[27,28] The unemployed patients had a significantly worse SDMT score compared to the employed group at baseline and 5-year follow-up. In the GEE analysis, worsening processing speed, as measured by SDMT, was the clinical parameter best associated with unemployment. This is in line with a study conducted on 60 relapsing–remitting MS patients showing decreased volumes of thalamus, hippocampus and putamen being associated with reduced cognitive performance, especially in terms of processing speed.[15]

Fatigue was significantly more pronounced in the unemployed patient group at baseline and 5-year

follow-up. We found that fatigue to some extent was explained by loss of SDGM volume. Other papers have suggested that the basal ganglia partly contribute to fatigue.[29] A recent systematic review suggested that the cortico-striato-thalamo-cortical loop has close connections with the development of central fatigue.[30]

Disability, as measured by EDSS, was significantly more pronounced in the unemployed patient group at all time points. A higher EDSS, suggestive of greater physical disability, was in our findings to some extent explained by loss of SDGM volume, in particular thalamus, putamen and hippocampus volumes. Several studies have shown an association between grey matter atrophy and physical disability,[13,23] and the contribution of physical disability to unemployment is well established.[5,31–33]

The greatest strength of this paper is that we were able to follow an unselected cohort of patients newly diagnosed with MS over 10 years. It is of interest that the patients were largely untreated in the first part of the follow-up, thus providing insight into the evolution of atrophy in absence of the newer, more efficient treatment options.

This study has some limitations. We had a relatively small sample size, and a considerable drop-out of 30 patients over the 10-year follow-up. At the 10-year follow-up a considerable drop-out of 61% of the group employed at 5 years, compared to a drop-out of 31% of the patients that were unemployed at the 5-year follow-up. Hence, caution should be exercised when interpreting the 10-year follow-up results. The MRI was performed by two different scanners, but when detecting longitudinal volume changes the effect of different scanners is rather small.[34] We nevertheless adjusted for center in the statistical analysis to account for this issue. Moreover, all scans were acquired on 1.5 T MRI systems, whereas 3T acquisitions may result in somewhat more reliable volumetric segmentations.[35]

We categorized the patients as unemployed at the time of receiving disability pension. This is a strict definition, and the majority of these patients were completely or partly unable to perform paid work before disability pension was granted. However, this represents the time point the patient is found permanently unfit to continue work on the basis of a thorough evaluation. Unfortunately, our data do not differentiate whether other conditions contributed to the patients becoming unable to perform paid work. The unemployed patient group was on average 9 years older than the employed patients. Knowing the effect of age on brain atrophy and clinical symptoms, the effect on our results is difficult to account for fully in the analysis, and should be taken into consideration when interpreting the results.

Employment has been proposed as a comprehensive marker of the function and wellbeing of MS patients.[31] Being employed is associated with greater quality of life in several studies. Depression is shown to be associated with unemployment, and is suggested to be a result of, rather than causing, unemployment.[26] Current markers, such as disability measures like EDSS, used to monitor disease progression and severity of disease are at best inadequate. The state of employment can provide added information on the level of function of MS-patients.

MRI markers that can help detect patients at risk of exiting the workforce are useful, as proactive intervention can possibly aid in preventing, or at least delaying, unemployment. In the future, in our opinion, the detection of deep grey matter atrophy will possibly be a marker for disease activity, prompting early, efficacious disease-modifying treatment. The predictive value of SDGM atrophy on later unemployment would be of interest to explore, unfortunately a lack of statistical strength did not allow us to perform these analyses.

Conclusion

Atrophy of the SDGM structures showed a strong association with unemployment, whereas a weaker association was seen with cortical atrophy. As atrophy starts early in the disease course, an early focus on measures to keep MS patients in the workforce is warranted.

Conflicting of Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CJ received speaker honoraria from Novartis. RZ received personal compensation from EMD Serono, Genzyme-Sanofi, Celgene and Novartis for speaking and consultant fees. He also received financial support for research activities from Genzyme-Sanofi, Novartis, Celgene, Mapi Pharma, Keystone Heart, V-WAvE-Medical and Protembis. KMM has received grants and personal fees from Biogen Idec and Novartis; personal fees from Genzyme, Roche, Almirall and Merck; personal fees and non-financial support from Teva, outside the submitted work. TOD, ID and NB have nothing to disclose. EF participated in advisory boards and received speaker honoraria from Biogen, Genzyme, Merck,

Novartis, Roche, Sanofi-Aventis and an unrestricted grant from Novartis.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: CJ was supported by a grant from Novartis. KMM received funding from the Norwegian Research Council, grant no. 288164. TOD was supported by a grant from Biogen Idec.

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Supplemental material

Supplemental material for this article is available online.

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