DOI: 10.1590/0004-282X20160015

REVIEW

Brain atrophy in multiple sclerosis: therapeutic, cognitive and clinical impact

Atrofia cerebral en esclerosis múltiple: impacto clínico, cognitivo y terapéutico

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ABSTRACT

Multiple sclerosis (MS) was always considered as a white matter inflammatory disease. Today, there is an important body of evidence that supports the hypothesis that gray matter involvement and the neurodegenerative mechanism are at least partially independent from inflammation. Gray matter atrophy develops faster than white matter atrophy, and predominates in the initial stages of the disease. The neurodegenerative mechanism creates permanent damage and correlates with physical and cognitive disability. In this review we describe the current available evidence regarding brain atrophy and its consequence in MS patients.

Keywords: multiple sclerosis, brain atrophy, neurodegeneration.

RESUMEN

La esclerosis múltiple (EM) fue considerada históricamente como una enfermedad inflamatoria de la sustancia blanca. Hoy en día hay mucha evidencia que apoya, además, el compromiso de la sustancia gris y los mecanismos neurodegenerativos, que son al menos parcialmente independientes de la inflamación. La atrofia de la sustancia gris se desarrolla más rápido que la atrofia de la sustancia blanca y predomina en las etapas iniciales de la enfermedad. El mecanismo neurodegenerativo, crea un daño permanente y se correlacionaría con la discapacidad física y cognitiva del paciente. En esta revisión, se describe la evidencia disponible actual con respecto a la atrofia cerebral y su consecuencia en los pacientes con EM.

Palabras-clave: esclerosis múltiple, atrofia cerebral, neurodegeneración.

Multiple sclerosis (MS) is recognized as an inflammatory and neurodegenerative disease of the central nervous system (CNS)[1]. Axonal degeneration is thought to be responsible for the irreversible progression of the disability seen in affected patients[2,3,4]. The loss of brain volume, or brain atrophy, has been classically considered as a marker present in severe or advanced stages of the disease[4]. However, recent studies have demonstrated that this phenomenon also occurs in patients with clinically isolated syndromes suggestive of MS and also in the radiologically isolated syndrome[5,6].

In addition to these observations on disease progression and the course of atrophy in patients with MS, it is important to analyze the meaning that brain atrophy has in the clinical care of affected patients[3].

In the present review, we aim to assess the existing techniques for measuring brain atrophy and the impact that it has on disease progression and on the physical and cognitive impairment of patients with MS.

MOLECULAR BASES FOR AXONAL DEGENERATION IN MS

The axonal transection was demonstrated in 1998 by Bruce Trapp et al., whom with confocal microscopy and tridimensional reconstructions could identify oval shape terminal axonal lesions in the MS plaques[2]. The density of the damaged axons was 11.236/mm^3 in active lesions, 3.138/mm^3 in the edges of the chronic active hypercellular lesions and of 875/mm^3 in the

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Conflicts of Interest: Juan Ignacio Rojas has received honoraria from Novartis as a scientific advisor. He has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina, Novartis Argentina.

Liliana Patrucco has received honoraria for scientific and research grants from Teva Tuteur, Merck Serono, Biogen Idec and Bayer Schering.

J. Miguez declares no conflict of interest.

Edgardo Cristiano has received fees for consultations as a scientific advisory board member and for travel to meetings, conferences and clinical trials of the following companies: Avanir, Bayer, Biogen, Merck, Novartis and Teva.

Received 28 June 2015; Received in final form 06 November 2015; Accepted 16 December 2015.

hypocellular central areas of the chronic inactive lesions, thus being able to confirm that axonal loss correlates with the degree of inflammation in the disease, being present as from early stages of the disease[2]. Although the molecular mechanisms involved in the process of axonal damage are not exactly known, several hypothesis have been proposed[7]. It is known that myelin loss produces a failure in axonal action potential conduction, and this is sometimes seen from the clinical standpoint as neurologic deficit[8]. However, this axonal conduction can be recovered due to the expression and distribution of new sodium channels in the demyelinated axon, resulting in total or partial deficit remission[8]. This voltage – dependent sodium channels might probably play an important role in the neurodegenerative process seen in MS[9]. A consequence of axonal loss in a lesion is Wallerian degeneration along the fiber pathways that traverse it[2]. Axonal loss in lesions may therefore cause atrophy by two mechanisms: tissue loss within the lesion per se, and Wallerian degeneration in related fiber pathways. Given the large proportion that axons contribute to white matter volume, and evidence for considerable axonal damage in MS, axonal loss seems likely to be an important contributor to the atrophy observed in the disease[2,10,11].

TECHNICAL CONSIDERATIONS IN BRAIN ATROPHY MEASUREMENT IN MS

Currently, global and regional brain atrophy can be assessed using a wide variety of techniques[4,12,13,14]. Some of these utilize manual methods for the quantitative analysis of the atrophy (such as bidimensional measurement of lateral ventricle diameter or of the third ventricle diameter, among others). Nevertheless, in spite of being simple and user friendly for an experienced operator, these methods carry important disadvantages because they not only require a prolonged analysis time but also demonstrate significant inter-observer variability[14]. As an alternative for this reproducibility hurdle, the automated segmentation techniques do not require interaction with the operator, they can process a larger number of images, and they eliminate the variability. The automation process of volumetric measurements has been possible because both MRI images (tridimensional sequences) and their processing through specific programs have improved[4]. These programs have allowed us to obtain more precise and reproducible measurements of brain atrophy in patients with MS. Automated or semi-automated measurement techniques can be divided in two groups: segmentation techniques (transversal) and registry techniques (longitudinal)[4].

SEGMENTATION BASED TECHNIQUES (TRANSVERSAL)

Segmentation based techniques (transversal) allow us to perform total brain volume measurements, either of white or gray matter, globally or regionally, in a certain time period[4,14]. One of the most commonly used techniques estimates brain parenchymal fraction (BPF), which is defined as the relationship between brain parenchyma volume and intra-cranial volume (obtained by the sum of the brain parenchyma and the cerebrospinal fluid (CSF)), or brain parenchyma/brain parenchyma + CSF[15]. The advantage of this technique is that both the brain parenchyma and the intra-cranial volume are measured in an automated fashion and skull size variability is considered for each patient separately.

REGISTRY BASED TECHNIQUES (LONGITUDINAL)

These registry based techniques allow us to perform longitudinal measurements of changes in brain atrophy[4,14]. The comparison of serial evaluations performed in a patient, or in a group of patients, quantifies changes that have occurred in brain volume during a certain time-frame. These techniques, which are largely automated, express results as a percentage of change in brain volume[4]. In Table 1 commonly techniques used for the measurement of brain atrophy can be seen, together with their main limitations and characteristics.

BRAIN ATROPHY AND THE EXISTING EVIDENCE CONCERNING ITS MEANING

Brain atrophy and the risk of disease progression

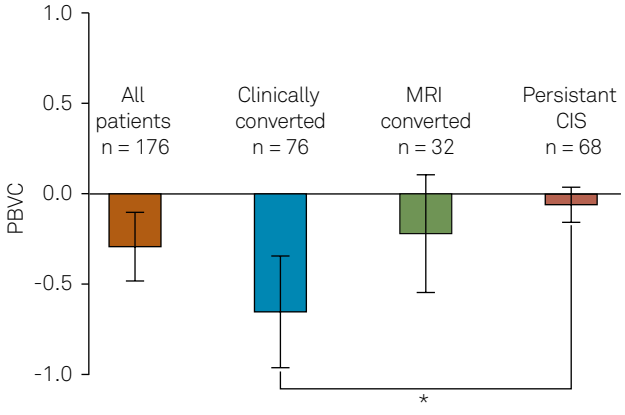
We have thoroughly evaluated the role of brain atrophy as a prognostic factor in the progression of the disease. As previously mentioned, brain atrophy is detected in the early stages of the disease, even in stages without clinical symptoms[16,17]. It has already been demonstrated that the rate of brain atrophy is greater in patients with a clinically isolated syndrome (CIS) that progresses to MS when compared with patients that do not worsen during the course of their disease. This impacts the early prognosis of the disease[18]. A sub-analysis from the ETOMS study that assessed the efficacy of [sc] interferon beta 1-a sc in patients with CIS showed a significant difference in mean annual percentage brain volume change (PBVC) between patients who had disease progression and those who did not (-0.92% and -0.56%, respectively)[19]. Similar findings were identified in an observational study done by Pérez-Miralles et al.[5] which showed a greater decrease of PBVC in 176 patients with CIS who progressed to MS when compared to those patients who did not progress (-0.65% compared to +0.059%, $p < 0.001$). These findings established a prognostic role for brain atrophy and MS conversion in patients who had a first demyelinating event. Di Filippo et al.[18] also demonstrated the prognostic role of brain atrophy and the risk of progression to MS after a first clinical event. In their studies, those patients with CIS that progressed to MS during a 6 year follow-up had an atrophy rate of 0.5% vs. -0.2% of those who did not, thereby making this an important prognostic factor for MS conversion[18] (Figures 1 and 2).

CLINICAL IMPACT OF BRAIN ATROPHY IN PATIENTS WITH MS

A study from Fisher et al.[20] published in 2002 showed the relationship between brain atrophy and physical impairment during an 8-year follow-up. This study also stated that brain atrophy had a clinical impact: worsening expanded disability status scale (EDSS) and progression to disability. A correlation between atrophy rate and physical disability was performed and suggesting that progression to atrophy in relapsing remitting multiple sclerosis (RRMS) was clinically relevant and may be a useful marker to predict disease progression[20]. Following this line of research, Fisniku et al.[21] evaluated whether physical disability during follow-up was related to white and gray matter brain atrophy. The study included 73 patients with CIS who were followed up for almost 20 years showed that atrophy of gray matter was related to an increase in EDSS ($p < 0.001$) and a worsening in the functional assessment of the patients ($p < 0.001$) in a higher proportion than in the atrophy of the white matter[21]. Sailer et al.[22] identified that a greater thinning of the global cortical thickness, and specially the motor cortex, related to worse performance in physical assessment and an increase in EDSS ($p = 0.001$) during follow-up in patients with MS. These studies support the finding that more significant brain atrophy correlates with a worsening of physical

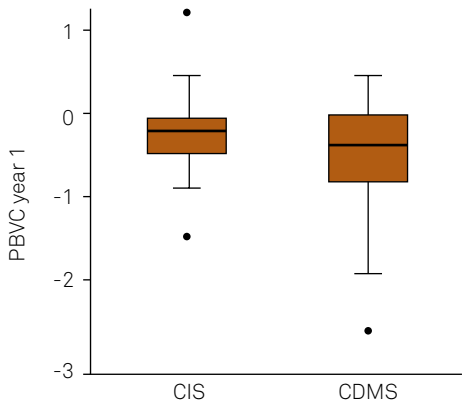
Table 1. Techniques used to measure brain atrophy.

Technique	Degree of automation	Characteristics	Limitations
BSI www.sourceforge.net/projects/bsintegral/	Semi-automated	Measures changes in brain volume using pairs of images	Does not distinguish between brain tissue
FIRST http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/	Automated	Volumetry and analysis of deep gray matter	Analysis in a certain time point
FreeSurfer http://freesurfer.net/	Automated or manual	Volumetry of deep gray matter; cortical thickness; simultaneous analysis in multiple time points	Prolonged calculation time needed
Nifty-Seg http://cmic.cs.ucl.ac.uk/home/software/	Automated	Measures cortical thickness	Analysis in a certain time point
SepINRIA http://www-sop.inria.fr/asclepios/software/SepINRIA/	Automated	Measures changes in brain volume using pairs of images	Does not distinguish between brain tissues
SIENA http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/	Automated	Measures changes in brain volume using pairs of images	Does not distinguish between brain tissues
SIENA-R http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/	Automated	Analysis of brain focal atrophy in groups of patients using pairs of images	Does not distinguish between brain tissues
SPM-Longitudinal VBM www.fil.ion.ucl.ac.uk/spm/	Automated	Analysis of brain focal atrophy in groups of patients using pairs of images	Can only be applied in a group
TOADS-CRUISE www.nitrc.org/projects/toads-cruise/	Automated	Measurement of cortical thickness changes	-



PBVC: percentage brain volume change; CIS: clinically isolated syndrome.

Figure 1. Percentage of brain volume change and prediction of multiple sclerosis (MS) conversion in patients with CIS. In this study, those patients with greater atrophy rate after diagnosis presented a higher risk of MS conversion, defined either clinically or by images during follow-up[5].



PBVC: percentage brain volume change; CIS: clinically isolated syndrome; CDMS: clinically definity multiple sclerosis.

Figure 2. Box plots that show in another study the risk of multiple sclerosis (MS) conversion during follow-up in patients with CIS. Higher atrophy during the first year of disease implies a greater risk[18].

disability in patients with MS. The remainder of the evidence concerning this issue is explained in detail in Table 2.

BRAIN ATROPHY AND COGNITIVE IMPACT IN MS PATIENTS

The impact of brain atrophy in the cognitive field can be seen as from the pre-morbid stage of the disease, known as the radiologic isolated syndrome (RIS)[16]. Amato et al. reported that 27.6% of these patients had signs of cognitive deterioration and that cortical brain volume reduction related to a worse performance in cognitive tests ($p = 0.043$)[35]. In patients with RRMS, the finding of regional atrophy has been related to specific functional involvement. For example, atrophy of the corpus callosum (CC) has been related to a worsening in verbal fluency tests as well as in attention tests, as measured by the Symbol Digit Modality Test

Table 2. Brain atrophy in multiple sclerosis (MS): prognostic factor and impact on physical disability in patients with clinically isolated syndrome (CIS) and MS.

Author	Aim of the study	N patients	Result variable	Brain atrophy measurement (software used)	Comment
Jacobsen et al.[23]	Assess atrophy as marker of progression of physical disability in 5-10 year follow up	81 with MS	Disease progression measured by EDSS	Longitudinal PBVC and tissue specific transversal volumes changes (SIENA, SIENAX y FIRST)	Patients with disability progression have more putaminal and cortical brain atrophy
Hofstetter et al.[24]	Assess gray matter changes as a marker of disability progression.	239 with MS	EDSS progression and MSFC worsening	Longitudinal changes in gray matter (VBM SPM5)	Physical disability was associated with greater gray matter atrophy
Pérez-Miralles et al.[5]	Evaluate brain atrophy as prognostic factor in CIS	176 with CIS	MS conversion in patients with CIS	Changes in PBVC (SIENA)	The decrease in global brain volume foresaw MS conversion in patients with CIS
Zivadinov et al.[25]	Assess atrophy of the thalamus as prognostic factor in CIS	216 with CIS	Conversion to MS in patients with CIS	PBVC and subcortical structures changes (SIENA y FIRST)	Atrophy of the thalamus and of global brain structures was associated with an increase in the risk of conversion to MS in patients with CIS
Popescu et al.[26]	Evaluate whether brain atrophy predicts physical disability in a 10 year follow up period	261 with MS	Disability progression quantified by EDSS	PBVC longitudinal changes and transversal measurements (SIENA/SIENAX)	Brain atrophy might play a significant role in predicting long term disability in patients with MS
Rojas et al.[27]	Assess if brain atrophy predicts physical disability in a 7 year follow up period.	26 with RRMS	Physical disability progression measured by EDSS	PBVC longitudinal changes (SIENA)	Greater brain atrophy during the early stages of the disease was associated with greater physical disability during follow up
Di Filippo et al.[18]	Evaluate if brain atrophy during the first year of CIS predicted the clinical status at 6 year follow up	99 with CIS	Physical disability progression measured by EDSS and MS conversion	Longitudinal changes in PBVC (SIENA)	Brain atrophy was associated with MS conversion in patients with CIS, and not with physical disability during follow up
Lukas et al.[28]	Assess the predictive value of central atrophy in relation to the risk of physical impairment in early stages of the disease	54 with MS	Physical disability progression measured by EDSS	PBVC and PVVC longitudinal changes (SIENA)	Greater PVVC reduction was the physical disability predictor factor in the mean term
Horakova et al.[29]	Evaluate the predictive value of gray and white matter atrophy in physical disability	181 with RRMS	Physical disability progression measured by EDSS	Longitudinal and transversal PBVC changes (SIENA y SIENAX)	Decrease in total brain and gray matter volume was associated with greater physical deterioration
Fisher et al.[30]	Assess the impact of gray matter atrophy in physical disability	70 MS	Disability progression measured by EDSS	Measurement of segmental volumes (BPF ad. Hoc software Cleveland Clinic)	Gray matter atrophy related with more physical impairment during follow up
Fisniku et al.[21]	Correlation between brain atrophy and physical disability	73 with CIS followed for 20 years	Physical disability measured by EDSS	Segmental volumes measurements (SIENAX y VBM-SPM2)	Gray matter atrophy correlated with more physical disability in a 20 year follow up
Jasperse et al.[31]	Evaluate the correlation between brain volume changes and physical and cognitive disability	79 with MS	Physical disability measured by EDSS, changes in MSFC	Regional changes in brain volume and PBVC (SIENA)	Central atrophy implied more physical disability, whereas involvement of complex functions correlated with central and peripheral atrophy
Charil et al.[32]	Cortical atrophy relates to physical disability progression	425 with MS	Physical disability progression measured by EDSS	Segmental cortical atrophy (INSECT software)	Atrophy of interconnected areas of the brain might be associated with motor disability in involved patients
Turner et al.[33]	Assess the correlation between changes in brain volume and physical disability after 4 years.	38 with MS	Physical disability progression measured by EDSS	Changes in PBVC and in ventricular volume	More significant brain atrophy during follow up correlated with more physical disability
Bakshi et al.[34]	Evaluate the correlation of changes in brain volume with physical disability	149 with MS	Physical disability progression measured EDSS	Regional atrophy (BPF).	Brain atrophy related to physical worsening in patients with severe involvement

EDSS: expanded disability status scale; PBVC: percentage brain volume change; MSFC: multiple sclerosis functional composite; RRMS: relapsing remitting multiple sclerosis.

(SDMT) and the PASAT test. Atrophy of the anterior segment of the CC has been related to fatigue and its degree of severity[36]. Likewise, Rudick et al.[37] showed a correlation between gray matter atrophy progression and worsening of the MSFC. Table 3 shows the evidence that impact atrophy has on the cognitive field.

Table 3. Brain atrophy in MS and its impact on cognition and fatigue.

Author	Aim of the study	N patients with RMMS	Result variable	Brain atrophy measurement (software used)	Comment
Cruz Gómez et al.[38]	Correlation between brain atrophy and fatigue	60	Fatigue measured by fatigue severity scale	Segmental atrophy by VBM-SPM8	In patients with fatigue there was a reduction in segmentary gray and white matter volume when compared to controls
Amato et al.[39]	Evaluate the relationship between cognitive reserve and brain atrophy in patients with RRMS	52	Cognitive reserve was assessed through a score that included education, IQ and pre morbid activities	Segmental brain volumes and longitudinal PBVC changes (SIENAX and SIENA)	The cognitive reserve might compensate structural damage, however, with damage and atrophy progression, this compensation is lost
Batista et al.[40]	Determine if atrophy of the thalamus and basal ganglia play a role in the speed to process information in RRMS (SPI)	86	Complete neuropsychologic tests, PASAT and SDMT.	Segmentary subcortical subglobal volumes (SIENAX and FIRST)	Information processing alterations was related to greater atrophy of subcortical structures that include the thalamus and the caudate
Calabrese et al.[41]	Evaluate if atrophy of cortical and deep gray matter structures relates to fatigue in patients with RRMS	152	Fatigue measured by the fatigue impact scale	Segmental subcortical volumes (FreeSurfer)	Segmental atrophies were related to greater fatigue in RRMS
Pellicano et al.[42]	Assess the correlation between cortical and subcortical regional atrophy in RRMS.	24	Fatige measured by the fatigue impact scale	Cortical and subcortical segmental brain atrophy (FreeSurfer)	Parietal cortex atrophy was significantly related to fatigue in patients with RRMS
Sumowski et al.[43]	Evaluate the effect of brain atrophy on the cognitive reserve	38	Information processing	Third ventricle enlargement (manual processing)	Brain atrophy showed negative effects on information processing that was partially attenuated by the cognitive reserve
Mineev et al.[44]	Assess correlation between cognitive deterioration and brain atrophy	65	Extended neuropsychologic assessment	Manually measured brain volumes	Greater brain atrophy correlated with greater cognitive involvement in patients with RRMS
Sanchez et al.[45]	Evaluate the correlation between brain atrophy and cognitive deterioration in RRMS	52	Extended neuropsychologic assessment.	Subcortical global and segmental atrophy (manual processing of the bicaudate space and of the third ventricle diameter)	Central ventricle atrophy was the best predictor for global cognitive deterioration in this group of patients with RRMS
Houtchens et al.[46]	Assess if thalamic atrophy correlates with cognitive deterioration in RRMS	79	Extended neuropsychologic assessment.	BPF and subcortical brain volumes using JIM software	Thalamic atrophy might be a sensitive biomarker of neurodegeneration and cognitive impact
Tekok-Kilic et al.[47]	Evaluate the correlation between gray matter atrophy and cognitive involvement in RRMS	59	Extended neuropsychologic assessment.	Brain segmental volumetry (SABRE software)	Thalamic atrophy might be a sensitive biomarker of neurodegeneration and cognitive impact
Tedeschi et al.[48]	Assess the correlation of fatigue with white and gray matter atrophy	222	Fatige measured by the fatigue impact scale	Brain total and segmental volumes	Greater fatigue was observed with greater brain atrophy
Sanfilipo et al.[49]	Evaluate correlation of gray and white matter atrophy with cognitive deterioration in RRMS	40	Extended neuropsychologic assessment	Cortical and subcortical brain total and segmental volumes (SPM99)	Gray and white matter atrophy contribute independently to cognitive deterioration in RRMS
Lazeron et al.[50]	Assess the correlation between brain atrophy and cognitive deterioration in RRMS	82	Rao short battery tests	Segmental and total brain volume (BPF local software)	Cognitive deterioration in MS depends moderately on brain structural damage
Edwards et al.[51]	Evaluate the association between cognitive deterioration and supra – tentorial brain atrophy.	40	Extended neuropsychologic assessment	Segmental and total brain volume (BPF)	White matter atrophy correlated with worse cognitive performance, probably reflecting the effect of axonal subcortical damage and myelin loss
Zivadinov et al.[52]	Evaluate if cognitive deterioration in early stages of MS correlates with brain volume loss	53 in early disease stages	Extended neuropsychologic assessment	Total brain volume (semiautomatic local program)	In early stages of the disease, cognitive deterioration correlated signifcantly with total brain volume loss probably due to axonal loss

RRMS: relapsing remitting multiple sclerosis; PVBC: percentage brain volume change.

Table 4. Pivotal studies and the effect on brain atrophy and physical disability60.

Year	Trial	Control arm	Treatment arm	N	Brain volumen measurement	Effect of atrophy *
1999	MSCRG[61]	Placebo	IFNb-1ª 6 MIU	301	BPF	0.50
2006	AFFIRM[62]	Placebo	Natalizumab	942	BPF	0.56
2006	SENTINEL[63]	IFNb-1ª 30 Mcg	IFNbeta 1-a 30 mcg + natalizumab 300 mg	1171	BPF	0.77
2008	REGARD[64]	GA	IFNbeta-1a-44 mcg	764	SIENA	1.28
2009	BEYOND[65]	GA	IFNbeta-1a-250	1347	SIENA	0.90
			IFNbeta-1a-500	1345		0.80
2010	FREEDOMS[58]	Placebo	FTY 0.5 mg	843	SIENA	0.63
			FTY 1.25 mg	847		0.55
2010	CLARITY[66]	Placebo	Cladribine 3.5 mg	870	SIENA	0.81
			Cladribine 5.25 mg	893		0.81
2011	TEMSO[55]	Placebo	Teriflunomide 7 mg	728	BPF	1.0
			Teriflunomide 14 mg	721		1.0
2012	DEFINE[56]	Placebo	BG-12 240 mg t.i.d	818	SIENA	0.70
			BG-12 240 mg 3 daily	824		0.83
2012	CONFIRM[57]	Placebo	BG-12 240 mg t.i.d	722	SIENA	0.94
			BG-12 240 mg 3 daily	708		0.97
			GA	713		0.84
2012	MSCARE-I[67]	IFNbeta-1ª	Alemtuzumab	821	BPF	0.50
2012	MSCARE-II[68]	IFNbeta-1ª	Alemtuzumab	1187	BPF	0.63
2012	FREEDOMS-II[69]	placebo	FTY 0.5 mg	757	SIENA	0.70
			FTY 1.25 mg	757		0.52

GA: glatiramer acetate; *The effect of atrophy is over physical disability at two years follow-up estimated as R2 .

IMPACT OF DISEASE MODIFYING THERAPIES ON BRAIN ATROPHY

Based upon these findings, there is a clear need to identify medication not only for the inflammatory process but also for preventing brain atrophy progression and neurodegeneration. Currently, the effect of medication on MS and its secondary impact on brain atrophy is under investigation. However, in some phase III clinical trials the brain atrophy biomarker has become a primary assessment outcome.

In a study that included 519 patients with RRMS for a two-year period, the subcutaneous administration of interferon b- 1a[53], found no effect of treatment on brain atrophy when compared to placebo. In another study that used glatiramer acetate in the evaluation, there were no differences in brain atrophy during follow-up in the placebo arm[54]. In studies that used teriflunomoide no significant changes in brain atrophy were found when compared to the placebo arm, whereas in those studies that assessed fingolimod and BG-12 (FREEDOMS and TRANSFORMS and DEFINE studies) showed significant differences in atrophy rate reduction when compared with no treatment or active drug[55,56,57,58,59]. In a recent meta-analysis conducted by Sormani et al.[60], the researchers were able to demonstrate the impact of controlling degenerative activity with the current available MS treatments. This degenerative activity was reflected in the atrophy (Table 4). The main findings of the overall analysis showed that a greater reduction in brain atrophy led to reduced disability progression in the two-year follow-up period assessed[60]. Brain atrophy might also have a greater predictive value than conventional MRI findings in preventing physical disability progression (lesional load in T2).

CONCLUSION

In this review we describe the current available evidence regarding brain atrophy and its consequence in MS patients. MS has traditionally been considered a white matter inflammatory disease. Today, there is a large body of evidence that supports the hypothesis that gray matter involvement and the neurodegenerative mechanisms are at least partially independent from inflammation in this disease.

The neurodegenerative mechanism creates permanent damage and correlates with physical and cognitive disability. Therefore, it is important to treat MS in the early stages to decrease the loss of brain volume and its consequences. Some issues should be overcome in order to increase it´s use and confidence, like the influence that brain water content could have on the measurement as well as the cut off value of annual brain atrophy that should be used in daily clinical practice for example. Regarding the first issue, many research lines addressed the issue and showed that the inclusion of pseudo T2 sequences as well as frequent MR scans can serve as a marker of changes in bulk brain water content and thus can help to investigate the presence of pseudoatrophy in multiple sclerosis vs. real brain volume loss in order to better characterize the

temporal pattern of brain volume change in affected patients. The other issue mentioned is the cut off value in annual brain volume loss. De Stefano et al. demonstrates that different values of annual PBVC could define a pathological range at different levels of specificity (ie, 'pathological' rates could be defined as above -0.52% with a specificity of 95%, above -0.46% with a specificity of 90% and above -0.40% with a specificity of 80%) and interestingly, increasing age did not influence in such cut-off values. Establishing cut-offs will allow to discriminate between physiological and pathological rates in patients with MS, however is currently a difficult task in MS.

Despite the relevance that brain volumetric has demonstrated, it´s use has not yet being translated into clinical practice. However, advances in computational

technology are paving the way for a more disseminated use in MS as well as other neurological disorders.

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000;343(13):938-52. doi:10.1056/NEJM200009283431307
2. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. Axonal transection in the lesions of multiple sclerosis. N Engl J Med. 1998;338(5): 278-85. doi:10.1056/NEJM199801293380502
3. De Stefano N, Airas L, Grigoriadis N, Mattle HP, O'Riordan J, Oreja-Guevara C et al. Clinical relevance of brain volume measures in multiple sclerosis. CNS Drugs. 2014;28(2):147-56. doi:10.1007/s40263-014-0140-z
4. Filippi M, Agosta F. Imaging biomarkers in multiple sclerosis. J Magn Reson Imaging. 2010;31(4):770-88. doi:10.1002/jmri.22102
5. Perez-Miralles F, Sastre-Garriga J, Tintore M, Arrambide G, Nos C, Perkal H et al. Clinical impact of early brain atrophy in clinically isolated syndromes. Mult Scler. 2013;19(14):1878-86. doi:10.1177/1352458513488231
6. Rojas JI, Patrucco L, Míguez J, Besada C, Cristiano E. Brain atrophy in radiologically isolated syndromes. J Neuroimaging. 2015;25(1):68-71. doi:10.1111/jon.12182
7. Coleman MP, Perry VH. Axon pathology in neurological disease: a neglected therapeutic target. Trends Neurosci. 2002;25(10):532-37. doi:10.1016/S0166-2236(02)02255-5
8. Bjartmar C, Trapp BD. Axonal degeneration and progressive neurologic disability in multiple sclerosis. Neurotox Res. 2003;5(1-2):157-64. doi:10.1007/BF03033380
9. Craner MJ, Damarjian TG, Liu S, Hains BC, Lo AC, Black JA et al. Sodium channels contribute to microglia/macrophage activation and function in EAE and MS. Glia. 2005;49(2):220-9. doi:10.1002/glia.20112
10. Evangelou N, Konz D, Esiri MM, Smith S, Palace J, Matthews PM. Size-selective neuronal changes in the anterior optic pathways suggest a differential susceptibility to injury in multiple sclerosis. Brain. 2001;124(9):1813-20. doi:10.1093/brain/124.9.1813
11. Simon JH. Brain atrophy in multiple sclerosis: what we know and would like to know. Mult Scler. 2006;12(6):679-87. doi:10.1177/1352458506070823
12. Filippi M, Absinta M, Rocca MA. Future MRI tools in multiple sclerosis. J Neurol Sci. 2013;331(1-2):14-8. doi:10.1016/j.jns.2013.04.025
13. Filippi M, Valsasina P, Rocca M. Magnetic resonance imaging of grey matter damage in people with MS. Int MS J. 2007;14(1):12-21.
14. Bermel RA, Bakshi R. The measurement and clinical relevance of brain atrophy in multiple sclerosis. Lancet Neurol. 2006;5(2):158-70. doi:10.1016/S1474-4422(06)70349-0
15. Paolillo A, Coles AJ, Molyneux PD, Gawne-Cain M, MacManus D, Barker GJ et al. Quantitative MRI in patients with secondary progressive MS treated with monoclonal antibody Campath 1H. Neurology. 1999;53(4):751-7. doi:10.1212/WNL.53.4.751
16. Okuda DT, Siva A, Kantarci O, Inglese M, Katz I, Tutuncu M et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. PLoS One. 2014;9(3):e90509. doi:10.1371/journal.pone.0090509
17. De Stefano N, Stromillo ML, Rossi F, Battaglini M, Giorgio A, Portaccio E et al. Improving the characterization of radiologically isolated syndrome suggestive of multiple sclerosis. PLoS One. 2011;6(4):e19452. doi:10.1371/journal.pone.0019452
18. Di Filippo M, Anderson VM, Altmann DR, Swanton jk, Plant GT, Thompson AJ et al. Brain atrophy and lesion load measures over 1 year relate to clinical status after 6 years in patients with clinically isolated syndromes. J Neurol Neurosurg Psychiatry. 2011;81(2):204-8. doi: 10.1136/jnnp.2009.171769
19. Filippi M, Rovaris M, Inglese M, Barkhof F, De Stefano N, Smith S et al. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9444):1489-96. doi:10.1016/S0140-6736(04)17271-1
20. Fisher E, Rudick RA, Simon JH, Cutter G, Baier M, Lee JC et al. Eight-year follow-up study of brain atrophy in patients with MS. Neurology. 2002;59(9):1412-20. doi:10.1212/01.WNL.0000036271.49066.06
21. Fisniku LK, Chard DT, Jackson JS, Anderson VM, Altmann DR, Miszkiel KA et al. Gray matter atrophy is related to long-term disability in multiple sclerosis. Ann Neurol. 2008;64(3):247-54. doi:10.1002/ana.21423
22. Sailer M, Fischl B, Salat D, Tempelmann C, Schönfeld MA, Busa E et al. Focal thinning of the cerebral cortex in multiple sclerosis. Brain. 2003;126(8):1734-44. doi:10.1093/brain/awg175
23. Jacobsen C, Hagemeier J, Myhr KM, Nyland H, Lode K, Bergsland N et al. Brain atrophy and disability progression in multiple sclerosis patients: a 10-year follow-up study. J Neurol Neurosurg Psychiatry. 2014;85(10):1109-15. doi:10.1136/jnnp-2013-306906
24. Hofstetter L, Naegelin Y, Filli L, Kuster P, Traud S, Smieskova R et al. Progression in disability and regional grey matter atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2014;20(2):202-13. doi:10.1177/1352458513493034
25. Zivadinov R, Havrdová E, Bergsland N, Tyblova M, Hagemeier J, Seidl Z et al. Thalamic atrophy is associated with development of clinically definite multiple sclerosis. Radiology. 2013;268(3):831-41. doi:10.1148/radiol.13122424
26. Popescu V, Agosta F, Hulst HE, Sluimer IC, Knol DL, Sormani MP et al. Brain atrophy and lesion load predict long term disability in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2013;84(10):1082-91. doi:10.1136/jnnp-2012-304094
27. Rojas JI, Patrucco L, Besada C, Bengolea L, Cristiano E. Brain atrophy at onset and physical disability in multiple sclerosis. Arq Neuropsiquiatr. 2012;70(10):765-8. doi:10.1590/S0004-282X2012001000003
28. Lukas C, Minneboo A, Groot V, Moraal B, Knol DL, Polman CH et al. Early central atrophy rate predicts 5 year clinical outcome in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2010;81(12):1351-6. doi:10.1136/jnnp.2009.199968

29. Horakova D, Dwyer MG, Havrdova E, Cox JL, Dolezal O, Bergsland N et al. Gray matter atrophy and disability progression in patients with early relapsing-remitting multiple sclerosis: a 5-year longitudinal study. J Neurol Sci. 2009;282(1-2):112-9. doi:10.1016/j.jns.2008.12.005

30. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol. 2008;64(3):255-65. doi:10.1002/ana.21436

31. Jasperse B, Vrenken H, Sanz-Arigita E, Groot V, Smith SM, Polman CH et al. Regional brain atrophy development is related to specific aspects of clinical dysfunction in multiple sclerosis. Neuroimage. 2007;38(3):529-37. doi:10.1016/j.neuroimage.2007.07.056

32. Charil A, Dagher A, Lerch JP, Zijdenbos AP, Worsley KJ, Evans AC. Focal cortical atrophy in multiple sclerosis: relation to lesion load and disability. Neuroimage. 2007;34(2):509-17. doi:10.1016/j.neuroimage.2006.10.006

33. Turner B, Lin X, Calmon G, Roberts N, Blumhardt LD. Cerebral atrophy and disability in relapsing-remitting and secondary progressive multiple sclerosis over four years. Mult Scler. 2003;9(1):21-7. doi:10.1191/1352458503ms868oa

34. Bakshi R, Benedict RH, Bermel RA, Jacobs L. Regional brain atrophy is associated with physical disability in multiple sclerosis: semiquantitative magnetic resonance imaging and relationship to clinical findings. J Neuroimaging. 2011;11(2):129-36. doi:10.1111/j.1552-6569.2001.tb00022.x

35. Amato MP, Hakiki B, Goretti B, Rossi F, Stromillo ML, Giorgio A et al. Association of MRI metrics and cognitive impairment in radiologically isolated syndromes. Neurology. 2012;78(5):309-14. doi:10.1212/WNL.0b013e31824528c9

36. Yaldizli O, Penner IK, Frontzek K, Naegelin Y, Amann M, Papadopoulou A et al. The relationship between total and regional corpus callosum atrophy, cognitive impairment and fatigue in multiple sclerosis patients. Mult Scler. 2013;20(3):356-64. doi:10.1177/1352458513496880

37. Rudick RA, Lee JC, Nakamura K, Fisher E. Gray matter atrophy correlates with MS disability progression measured with MSFC but not EDSS. J Neurol Sci. 2009;282(1-2):106-11. doi:10.1016/j.jns.2008.11.018

38. Cruz Gómez AJ, Ventura Campos N, Belenguer A, Ávila C, Forn C. Regional brain atrophy and functional connectivity changes related to fatigue in multiple sclerosis. PLoS One. 2013;8(10):e77914. doi:10.1371/journal.pone.0077914

39. Amato MP, Razzolini L, Goretti B, Stromillo ML, Rossi F, Giorgio A et al. Cognitive reserve and cortical atrophy in multiple sclerosis: a longitudinal study. Neurology. 2013;80(19):1728-33. doi:10.1212/WNL.0b013e3182918c6f

40. Batista S, Zivadinov R, Hoogs M, Bergsland N, Heininen-Brown M, Dwyer MG et al. Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis. J Neurol. 2012;259(1):139-46. doi:10.1007/s00415-011-6147-1

41. Calabrese M, Rinaldi F, Grossi P, Mattisi I, Bernardi V, Favaretto A et al. Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing-remitting multiple sclerosis. Mult Scler. 2010;16(10):1220-8. doi:10.1177/1352458510376405

42. Pellicano C, Gallo A, Li X, Ikonomidou VN, Evangelou IE, Ohayon JM et al. Relationship of cortical atrophy to fatigue in patients with multiple sclerosis. Arch Neurol. 2010;67(4):447-53. doi:10.1001/archneurol.2010.48

43. Sumowski JF, Chiaravalloti N, Wylie G, Deluca J. Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. J Int Neuropsychol Soc. 2009;15(4):606-12. doi:10.1017/S1355617709090912

44. Mineev KK, Prakhova LN, Il'ves AG, Kataeva GV, Petrov AM, Reznikova TN et al. Characteristics of neurological and cognitive status in patients with multiple sclerosis in relation to the location and volumes of demyelination foci and the severity of brain atrophy. Neurosci Behav Physiol. 2009;39(1):35-8. doi:10.1007/s11055-008-9086-2

45. Sanchez MP, Nieto A, Barroso J, Martín V, Hernández MA. Brain atrophy as a marker of cognitive impairment in mildly disabling relapsing-remitting multiple sclerosis. Eur J Neurol. 2008;15(10):1091-9. doi:10.1111/j.1468-1331.2008.02259.x

46. Houtchens MK, Benedict RH, Killiany R, Sharma J, Jaisani Z, Singh B et al. Thalamic atrophy and cognition in multiple sclerosis. Neurology. 2007;69(12):1213-23. doi:10.1212/01.wnl.0000276992.17011.b5

47. Tekok-Kilic A, Benedict RH, Weinstock-Guttman B, Dwyer MG, Carone D, Srinivasaraghavan B et al. Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis. Neuroimage. 2007;36(4):1294-300. doi:10.1016/j.neuroimage.2007.04.017

48. Tedeschi G, Dinacci D, Lavorgna L, Prinster A, Savettieri G, Quattrone A et al. Correlation between fatigue and brain atrophy and lesion load in multiple sclerosis patients independent of disability. J Neurol Sci. 2007;263(1-2):15-9. doi:10.1016/j.jns.2007.07.004

49. Sanfilipo MP, Benedict RH, Weinstock-Guttman B, Bakshi R. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. Neurology. 2006;66(5):685-92. doi:10.1212/01.wnl.0000201238.93586.d9

50. Lazeron RH, Boringa JB, Schouten M, Uitdehaag BM, Bergers E, Lindeboom J et al. Brain atrophy and lesion load as explaining parameters for cognitive impairment in multiple sclerosis. Mult Scler. 2005;11(5):524-31. doi:10.1191/1352458505ms1201oa

51. Edwards SG, Liu C, Blumhardt LD. Cognitive correlates of supratentorial atrophy on MRI in multiple sclerosis. Acta Neurol Scand. 2001;104(4):214-23. doi:10.1034/j.1600-0404.2001.00270.x

52. Zivadinov R, Sepcic J, Nasuelli D, De Masi R, Bragadin LM, Tommasi MA et al. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2001;70(6):773-80. doi:10.1136/jnnp.70.6.773

53. Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. 1993 [classical article]. Neurology. 2001;57(12 Suppl 5):S10-5.

54. Rovaris M, Comi G, Rocca MA, Wolinsky JS, Filippi M. Short-term brain volume change in relapsing-remitting multiple sclerosis: effect of glatiramer acetate and implications. Brain. 2001;124(9):1803-12. doi:10.1093/brain/124.9.1803

55. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365(14):1293-303. doi:10.1056/NEJMoa1014656

56. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367(12):1098-107. doi:10.1056/NEJMoa1114287

57. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12):1087-97. doi:10.1056/NEJMoa1206328

58. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387-401. doi:10.1056/NEJMoa0909494

59. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402-15. doi:10.1056/NEJMoa0907839

60. Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol. 2014;75(1):43-9. doi:10.1002/ana.24018

61. Rudick RA, Fisher E, Lee JC, Simon J, Jacobs L. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting. Neurology. 1999;53(8):1698-704. doi:10.1212/WNL.53.8.1698

62. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):899-910. doi:10.1056/NEJMoa044397

63. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354(9):911-23. doi:10.1056/NEJMoa044396

64. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008;7(10):903-14. doi:10.1016/S1474-4422(08)70200-X

65. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8(10):889-97. doi:10.1016/S1474-4422(09)70226-1

66. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):416-26. doi:10.1056/NEJMoa0902533

67. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1819-28. doi:10.1016/S0140-6736(12)61769-3

68. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1829-39. doi:10.1016/S0140-6736(12)61768-1

69. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6):545-56. doi:10.1016/S1474-4422(14)70049-3