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Brain atrophy in Multiple Sclerosis

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Abstract: Multiple sclerosis (MS) has traditionally been considered to be primarily an inflammatory demyelinating disorder affecting the white matter. Nowadays it is recognized as both an inflammatory and a neurodegenerative condition involving the white and grey matter. Grey matter atrophy occurs in the earliest stages of MS, progresses faster than in healthy individuals, and shows significant correlations with cognitive function and physical disability; indeed, brain atrophy is the best predictor of subsequent disability and can be measured using magnetic resonance imaging (MRI). There are a number of MRI methods for measuring global or regional brain volume, including cross-sectional and longitudinal techniques. Preventing brain volume loss may therefore have important clinical implications affecting treatment decisions, with several clinical trials now demonstrating an effect of disease-modifying treatments (DMTs) on reducing brain volume loss. In clinical practice, it may therefore be important to consider the potential impact of a therapy on reducing the rate of brain volume loss. This article summarizes the knowledge on brain volume in MS.

Keywords: Multiple Sclerosis, Brain Atrophy, Brain Volume Loss

1. Introduction

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS), characterized pathologically by multifocal areas of inflammation and demyelination in the brain and spinal cord that evolve over time, and clinically by a variable course. Most patients develop significant locomotor disability in 15-20 years after onset [1-4]. In approximately 85% of patients who develop MS, clinical onset is characterized by an acute episode of neurological deficit due to a single lesion within the CNS, and is known as a clinically isolated syndrome (CIS) [2, 3].

While long recognized as a feature of late stages and/or particularly severe MS, brain volume loss (atrophy) was recently recognized and understood as occurring early in the majority of patients with MS even in CIS and radiological isolated syndrome (RID) patients [5-8]. (Figure 1) It was thought to reflect the underlying permanent neuronal damage, and is associated with irreversible disease progression and clinical disability [5, 7, 9]. Both, gray matter (GM) and white matter (WM) appear to manifest neurodegeneration, as reflected by tissue atrophy [10-12] and it may be, at least in part, independent of the degree of active inflammation associated demyelination. This has led to considerable interest in the development of protective strategies aimed at preventing degeneration of axons, and thereby slowing or halting the progression of disability in MS.

Atrophy measures are already becoming standard in many MS treatment trials [5]. Atrophy measures are complementary to conventional magnetic resonance imaging (MRI) measures of gadolinium enhancement, T1 hypointense and T2 hyperintense lesion volume.

In contrast to MRI-visible lesions, CNS atrophy is believed to reflect the net effect of severe and potentially irreversible processes such as demyelination and axonal loss. Measurement of the size of CNS structures may provide an indication of the total amount of tissue damage that has occurred up to a given point in time.

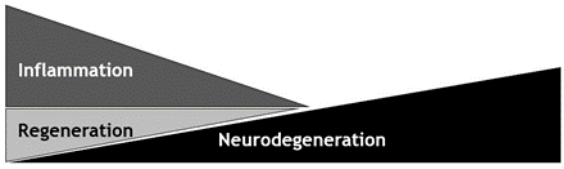

Figure 1. *Evolution in time of the pathophysiology of MS.*

2. Pathophysiology of Atrophy in MS

First of all it is important to understand that the pathology underlying atrophy is the result of multiple mechanisms, and these mechanisms may not be constant over time in individuals and populations. [13] More and less aggressive variations may be associated with disease phenotype and, possibly, histopathology types [14-17]. Disease phenotypes and lesions at various stages are responsible of composite of (transient) volume-gaining (edema by inflammatory demyelination) and volume-losing processes obtained by MRI volumetry. Inflammation and its transiently increased volume effects can confound the interpretation of atrophy measures after successful treatment, when treatment reduces the inflammatory CNS volume, causing a pseudoatrophy [18, 19].

When axonal injury occurs, several potential mechanisms could explain the amplifying functional and structural consequences, the latter resulting in additional volume loss. These include Wallerian degeneration (axonal distal segment) and retrograde or anterograde transneuronal degeneration [20, 21].

Na+ channels and axonal degeneration

The available evidence suggests that Na+ channels are important participants in axonal degeneration in MS. Nav1.6 are the predominant Na+ channel isoform found in axonal membranes in the CNS in mature nodes of Ranvier [22, 23]. When an axon is demyelinated acquires higher and diffuse expression of Nav1.6 producing a persistent Na+ current that can drive the Na+–Ca2+ exchanger to operate in a reverse mode, importing Ca2+ and triggering secondary cascades and axonal damage [23, 24]. In addition, NO-induced mitochondrial damage, changes in mitochondrial gene expression, and hypoxia/ischaemia due to perivascular inflammation seem to contribute to axonal energy failure, which in turn leads to loss of function of Na+/K+ ATPase and impaired ability of the axon to maintain resting potential and to export Na+ [25, 26]. Great Ca2+ influx into the axon triggers calcium-induced calcium release from internal stores, and the activation of NO synthase, proteases and lipases. Nav1.6 channels are also involved in the activation of microglia and macrophages, which contribute to the production of NO, and in phagocytosis by these cells [27].

It is also possible that some axons degenerate in MS in the absence of demyelination. Therefore, if the inadequacy of ATP supply in MS occurs in neurons in which axons are not demyelinated, the axons might be suffered Ca2+-mediated injury [26, 27].

3. Methods for Measuring Brain Atrophy

The MRI methods available to measure brain volume fall into two main categories: longitudinal or cross-sectional segmentation-based (cross-sectional) and registration-based (longitudinal) techniques. Longitudinal methods measure change in brain volume over time by comparing two MRI scans acquired at different time points [28]. Cross-sectional methods measure brain volume at a single time point using a single MRI scan (Table 1).

Segmentation techniques can measure the whole brain volume or any specific brain structure. Within the segmentation-based method is the BPF, which measure the ratio between brain parenchymal tissue with the total intracranial volume (cerebrospinal fluid and brain tissue). BPF is an automatic method that takes into account the variability of head size [29]. The quantitative two dimensional measures of lateral or third ventricular volume/width can be used easily in daily practice [30].

In the registration-based method, serial scans of the patients are compared, the SIENA is an automatic method registration-based with longitudinal purpose and limited regional analysis. SIENAX is its cross sectional variant [31].

The other method is the voxel-based morphometry (VBM) which allows the entire brain to be explored regional with cross sectional or longitudinal purposes [32, 33].

BPF and SIENA are the most frequently used methods to measure brain volume in clinical practice and in MS trials [34-36].

Table 1. *Most common MRI methods to measure brain volume loss in MS.*

Ventricular volumes (VV)
Structural Image Evaluation, using Normalisation of Atrophy (SIENA)
Structural Image Evaluation, using Normalisation of Atrophy - cross sectional (SIENAX)
Brain Parenchymal Fraction (BPF)
Voxel-Based Morphometry (VBM)

4. Which is the Annual Rate of Atrophy and is Stable Process over Time

As healthy people age, brain volume decreases as part of a normal process. It has been estimated that this rate of annual brain volume loss in healthy subjects ranges from 0.1% to 0.3% [34, 37]. Studies have shown that the rate of brain volume loss in patients with MS is higher, ranging from 0.5% to 1.3% annually [12, 38-42].

The rate of brain atrophy in an individual patient may be affected by a number of factors, MS phenotype, toxic agents, genetic factors and the presence of MS inflammatory lesions. Patients with the apolipoprotein E-ε4 genotype showed an annual increase in brain volume loss five times higher than in patients without this genotype [43], although other studies could not show this relation with brain atrophy [44].

The estimates of brain atrophy rates have varied between studies when compared different MS subtypes. Many studies have shown higher or similar [9, 38, 41, 45, 46] atrophy progression in secondary progressive MS (SPMS) patients when compared to those at earlier stages of MS. De Stefano et al, [39] found heterogeneity in percent brain volume change (PBVC) across MS subtypes and different stage disease. Interestingly, however, this heterogeneity disappeared when PBVC values were corrected for the baseline normalized brain volume (NBV). This suggests that the rate of atrophy progression is very similar in the different MS subtypes and, at late disease stages, does not seem to show nonlinear

progression [9] or a true acceleration [39]. For the patients with CIS, brain atrophy rates are greater in patients who are worsening clinically. This indicate that measures of brain atrophy should have relevance on clinical progression. Perhaps measures of gray matter atrophy could show correlation with measures of cognitive impairment [47, 48].

5. How Early Begins the Atrophy and which is the Gray Matter Damage

MS was traditionally considered to be primarily a white matter disorder, it has become apparent during the last decade that brain atrophy and specially grey matter atrophy, occurs from the earliest stages. Many studies support the idea of an early onset of whole brain atrophy, specially grey matter atrophy, in the first year after CIS and predicts conversion in MS [49-51].

Filippi et al [40] found that in early MS, mean whole brain NAA was reduced by 22% compared with healthy controls ($p < 0.0001$) and this change did not correlate with T2-lesion volume (diffuse damage). This finding suggests that widespread irreversible axonal pathology is independent of MRI-detectable inflammation and is present at early stages of disease, perhaps even before diagnosis [40, 52, 53].

Brain atrophy rates are higher in those CIS patients who subsequently develop MS compared with those who remain CIS [50, 53-55]. In the ETOMS (Early Treatment of Multiple Sclerosis) trial, a difference in median annual PBVC was found between patients who developed clinical definitive MS (CDMS) versus patients who did not (0.92% and 0.56%, respectively) [56]. Pérez-Miralles et al [57] also found similar results, those patients with a second attack had larger PBVC change (-0.65% versus +0.059%; $p < 0.001$) concluding that global brain and grey matter volume loss occurred within the first year after a CIS and predicts conversion to MS.

Several studies show that gray matter volume loss in MS occurs early in the disease, both deep gray (eg. thalamus) as well as the cortical gray matter [58-60]. Dalton et al [54] showed that progressive gray matter, and not white matter atrophy, was seen in the population progressing to a diagnosis of MS after a CIS and is related to physical disability and cognitive impairment.

It was reported that neocortical atrophy was a prominent feature of relapsing remitting MS (RRMS), and suggested that neocortical atrophy occurs in the earliest stages of MS and is even seen when white matter lesion accumulation is minimal [12, 39, 57, 59]. Many studies have shown that in MS patients there is diffuse cortical atrophy and thinning of the cerebral cortex. Sailer et al. [61] showed that the mean overall thickness of the cortical ribbon in MS patients was 2.30 mm, compared with 2.48 mm in healthy controls. In addition, patients with severe disability and/or long-standing course showed marked focal thinning of the motor cortex (mean 2.35 mm vs 2.74 mm) [61]. Other studies of early MS showed greater atrophy of gray matter than of white matter [51, 59, 62].

It has been shown that the normalised thalamic volume in MS patients was decreased by an average of 17%, compared with healthy controls, and the mean width of the third ventricle was increased by two-fold [11].

It is unknown whether these losses are due to focal or more diffuse gray matter pathology, nor the relative contribution of direct axonal injury nor retrograde degeneration [61, 63, 64].

The pattern of cortical atrophy in patients with RRMS were found in the anterior cingulate cortex, the insula and the transverse temporal gyrus [65]. This pattern differs from that seen in normal ageing, in which, the atrophy occurs mainly in the primary motor and premotor cortices, the prefrontal cortex and the calcarine cortex [66].

6. Clinical Signification

One of the MRI measures that have been proposed to assess MS progression (physical and cognitive disability) is the estimation of brain and spinal atrophy [5, 41, 48, 67-71]. Due to a relative short follow-up periods of 6 months to 3 years, previous longitudinal studies in MS have not shown consistent or strong relation between brain atrophy and disability [30, 72, 73].

Gray matter atrophy correlates and predicts both physical and cognitive disability in MS patients [74-78].

Fisher et al [6] showed the relation between atrophy progression and later neurologic disability, suggesting that atrophy progression during RRMS is clinically relevant and may be used as useful marker for disease progression. Amato et al. have shown that in patients with radiological isolated syndrome, 27.6% of patients have signs of cognitive impairment similar to those of RRMS [79]. Fisniku et al [80] showed that GM, but not WM, fraction correlated with expanded disability status scale ($p < 0.001$) and MS Functional Composite scores ($p < 0.001$). Corpus Callosum (CC) atrophy was associated with cognitive impairment measured with the verbal fluency test (VFT), Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT). The atrophy of the anterior CC segment was significantly associated with fatigue severity and poor outcome in the long-term memory test [81]. Using various cognitive tests, localized cortical atrophy in the prefrontal, parietal, temporal and insular regions has been associated with deficits in verbal memory, information processing speed and attention [82, 83]. Sailer et al. [61] showed significant negative correlations between Expanded Disability Status Scale (EDSS) scores and global cortical thickness ($p= 0.011$) and the mean thickness of the motor cortex ($p= 0.001$). Similary, in a case-control study there were significant negative correlations between EDSS scores and the thickness of the right parahippocampal ($p \leq 0.01$), left lateral occipital ($p \leq 0.01$) and left postcentral cortex ($p \leq 0.001$), and between EDSS scores and the volumes of the right caudate ($p \leq 0.01$) and right nucleus accumbens ($p \leq 0.01$) [84]. Rudick et al. [85] found a correlation between progression of grey matter atrophy and Multiple Sclerosis Functional Composite (MSFC) scores, but not between atrophy and EDSS scores.

Cognitive impairment, affecting attention, memory and information processing speed, may be present in up to 70% of MS patients [86, 87], and within first years in the disease [88]. In a study of patients with RRMS, the cognitive impairment was correlated with significantly smaller normalised brain volumes and normalised neocortical grey matter volumes than those with normal cognition [89]. Cortical atrophy appears to be a good predictor of cognitive impairment, because even mild impairment has been shown to be associated with significant cortical thinning [90]. Significant correlations have also been reported between cognitive impairment and thalamic atrophy [91].

The deep gray matter volumes (basal ganglia and especially the thalamus) are correlated with disability and cognitive impairment, with information processing speed [91, 92], fatigue [81, 93] and EDSS scores [94, 95].

7. Treatments

In general, prospective studies with interferon- (IFN) β and glatiramer acetate (GA) have shown limited and inconsistent evidence for a beneficial effect on brain atrophy (Table 2).

Table 2. *Brain volume outcomes*

Treatment	Phase	Duration	Clinical type	*n*	Results
Placebo controlled trials					
IFN-ß 1b SC	Phase III	5 years	CIS	468	NS
IFN-ß 1b SC	Phase III	3 years	SPMS	718	NS
IFN-ß 1a IM	Phase III	2 years	RRMS	172	NS
IFN-ß 1a SC	Phase III	2 years	CIS	309	NS
GA	Phase III	1.5 years	RRMS	207	SIG
GA	Phase III	5 years	CIS	409	SIG (early vs delayed tx)
Natalizumab	Observational	2 years	RRMS	39	SIG (WM)
Natalizumab	Phase III	2 years	RRMS	942	NS
Fingolimod	Phase III	2 years	RRMS	1272	SIG
Laquinimod	Phase III	2 years	RRMS	1331	SIG
Laquinimod	Phase III	2 years	RRMS	1106	SIG
Teriflunomide	Phase III	2 years	RRMS	1088	NS
DMF	Phase III	2 years	RRMS	540	SIG (bid), NS (tid)
DMF	Phase III	2 years	RRMS	681	NS
Active comparator controlled trials					
IFN-ß 1b SC (vs GA)	Phase III	3.5 years	RRMS	2244	NS
IFN-ß 1a IM (dose comparison)	Phase III	3 years	RRMS	189	SIG
GA (vs INF ß)	Post hoc	2 years	RRMS	86	SIG (GM)
GA (vs IFN ß)	Retrospective	5 years	RRMS	275	SIG
Daclizumab (vs IFN, GA)	Post hoc	11 years	RRMS	70	SIG
Natalizumab (vs IFN ß)	Pilot study	1.5 years	RRMS	26	SIG
Alemtuzumab (vs IFN-ß 1a SC)	Phase II	3 years	RRMS	334	SIG
Alemtuzumab	Phase III	2 years	RRMS	840	SIG
Alemtuzumab	Phase III	2 years	RRMS	581	SIG
Fingolimod	Phase III	1 year	RRMS	1292	SIG

bid: twice daily, CIS: clinically isolated syndrome, DMF: dimethyl fumarate, GA: glatiramer acetate, GM: grey matter, IFN: interferon, IM: intramuscular, NS: not significant, SIG: significant, RRMS: relapsing remitting MS, SPMS: secondary progressive MS, tid: three times daily, WM: white matter

Today we know that the pathophysiology of MS involves inflammation, neurodegeneration and the failure of the repair mechanisms. Classically the disease modifying treatments have controlled the inflammatory component of the disease. Recently, various trials have begun to evaluate the rate of brain volume loss have yielded mixed results for the reasons mentioned above.

The need of drugs not only against the inflammatory process is obvious, but also we need drugs that prevent or reduce the progression of brain atrophy and/or facilitate the repair mechanisms.

Currently, there is no disease modifying therapy available that completely stop the evolution from RRMS to the progressive phase of the disease.

Zivadinov et al, [96] investigated the effects of intravenous methylprednisolone on brain atrophy and disability progression of 88 patients with RRMS. Patients received either pulsed intravenous methylprednisolone (IVMP) (1

g/day for five days with oral prednisone taper) every four months for three years and then every six months for two subsequent years, or IVMP (1 g/day for five days with oral prednisone taper) only for relapses, without other disease modifying drugs. At the end of the five-year period, treatment with pulsed IVMP significantly slowed development of T1 black holes ($p < 0.0001$), slowed brain atrophy and disability progression ($p = 0.003$) [96].

For subcutaneous interferon β 1a, [97] [61], a study of 519 patients over two years with relapsing MS, found no treatment effect. For IFN β 1b (8 MIU subcutaneous) in relapsing MS, no large trial data are available.

In study of 227 patients with relapsing MS no atrophy was detected with GA, over the nine-month double-blind phase of the study [18].

In TEMSO trial changes of brain volume did not differ significantly among the three study groups (teriflunomide 7 mg vs placebo, p=0.19; teriflunomide 14 mg vs placebo p=0.35) [98].

Dimethyl fumarate (BG-12) presents inconsistent data relating to the decrease in brain volume loss in the two published trials against placebo. In the CONFIRM study the difference fail to reach statistical power [99]. In the DEFINE study the difference was significant in the 240 mg twice daily arm, but not in 240 mg three times daily arm [100].

Decreases in brain atrophy in RRMS patients have also been reported with laquinimod [101].

Fingolimod have shown consistent data about decrease brain volume loss in its three pivotal trials and their extensions (Figure 2). In FREEDOMS trial, [102] fingolimod significantly reduced the brain volume loss over 2 years, compared with placebo (relative reduction, 35%; $p<0.001$), in the FREEDOMS II [103] trial patients given placebo had increased brain volume loss compared with those given fingolimod at months 6, 12, and 24 (relative reduction, 33%; $p<0.001$), and in the TRANSFORMS trial, [104] fingolimod treatment resulted in a significantly lower rate of brain atrophy than intramuscular IFNβ-1a (relative reduction, 32%; $p<0.001$).

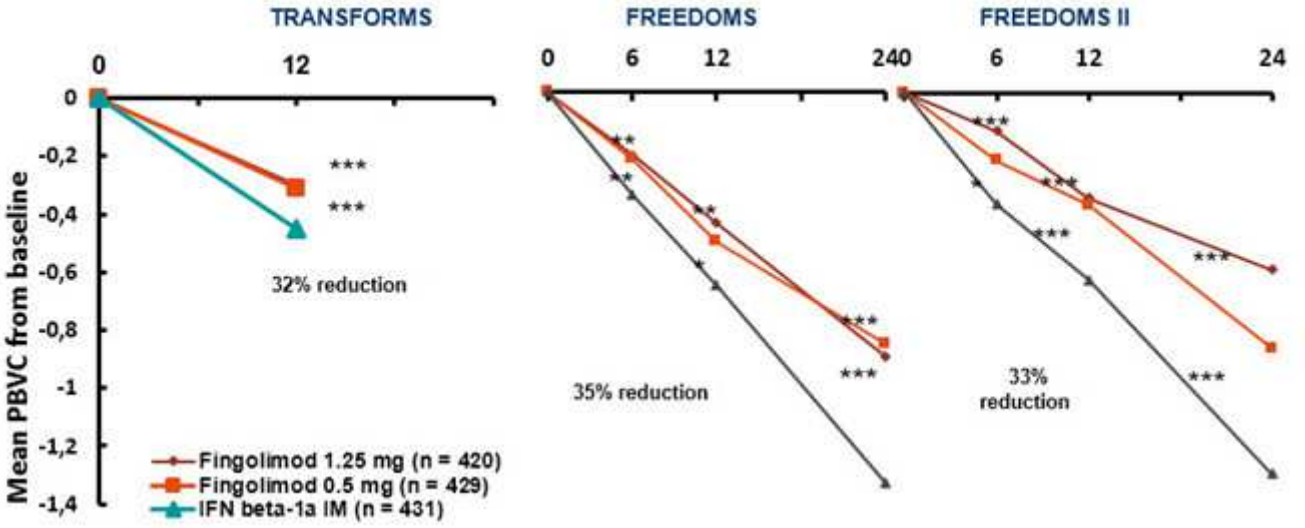

Figure 2. *Brain volume loss in phase III trials of Fingolimod (*p=0.05, **p=0.01, ***p=0.001).*

8. Conclusion

MS was historically considered as an inflammatory disease of the white matter (focal damage). Today there is much evidence that supports, in addition, the affection of the gray matter and neurodegenerative mechanisms, which are at least partially independent of the inflammation.

The atrophy of the GM develops faster than WM atrophy and predominates in early disease stages. The neurodegenerative mechanism, produces permanent damage and appears to correlate with physical and cognitive disability of the patient.

Given this, it is vital the early treatment of MS with drugs that control the inflammatory component and reduce the rate of brain volume loss.

Conflict of Interests

Dr. Gustavo Seifer is Medical Scientific Liaison (MSL) for Novartis Argentina.

Dr. Gaston Kuperman is Medical Manager for Novartis Argentina.

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