Journal of the Neurological Sciences xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

The natural history of brain volume loss among patients with multiple sclerosis: A systematic literature review and meta-analysis

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ARTICLE INFO

Article history:
Received 29 December 2014
Received in revised form 15 June 2015
Accepted 9 July 2015
Available online xxxx

Keywords:
Multiple sclerosis
Systematic literature review
Meta-analysis
Brain volume loss
Disease progression
Atrophy
Disease-modifying treatment

ABSTRACT

Background: Multiple sclerosis has been associated with progressive brain volume loss.
Objective: We aimed to systematically summarize reported rates of brain volume loss in multiple sclerosis and explore associations between brain volume loss and markers of disease severity.
Methods: A systematic literature search (2003–2013) was conducted to identify studies with ≥12 months of follow-up, reported brain volume measurement algorithms, and changes in brain volume. Meta-analysis random-effects models were applied. Associations between brain volume change, changes in lesion volume and disease duration were examined in pre-specified meta-regression models.
Results: We identified 38 studies. For the meta-analysis, 12 studies that reported annualized percentage brain volume change (PBVC), specified first-generation disease-modifying treatments (e.g., interferon-beta or glatiramer acetate) and used Structural Image Evaluation of Normalized Atrophy algorithm were analyzed. The annualized PBVC ranged from −1.34% to −0.46% per year. The pooled PBVC was −0.69% (95% CI = −0.87% to −0.50%) in study arms receiving first-generation disease-modifying treatments (N = 6 studies) and −0.71% (95% CI = −0.81% to −0.61%) in untreated study arms (N = 6 studies).
Conclusions: In this study, the average multiple sclerosis patient receiving first-generation disease-modifying treatment or no disease-modifying treatment lost approximately 0.7% of brain volume/year, well above rates associated with normal aging (0.1%–0.3% of brain volume/year).

Contents

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http://dx.doi.org/10.1016/j.jns.2015.07.014
0022-510X/

1. Introduction

Multiple sclerosis (MS) is a chronic, progressive inflammatory autoimmune disease of the central nervous system that results in neurological dysfunction characterized by myelin destruction and axonal loss [1]. It affects over 400,000 Americans and more than 2.1 million people worldwide [2].

Magnetic resonance imaging (MRI) is an important tool for diagnosing and monitoring MS through the quantification of lesions in the brain [3]. The Structural Image Evaluation of Normalized Atrophy (SIENA) algorithm is one of the common brain volume algorithms used in longitudinal studies [4]. The rate of brain volume loss (BVL) in MS has been suggested as a potential marker of MS disease progression [3]. In patients with MS, one study reported that BVL occurs at a rate of 0.6% to 1% per year [5]. In a study that examined a cohort of untreated MS patients across subtypes for a median follow-up time of 14 months; it was found that BVL progressed relentlessly throughout the course of the disease at a rate largely independent of subtype, after adjusting for baseline brain volume [6].

Over the past decade, published studies in MS have reported BVL as a measurement of disease burden and discussed the possible factors that influence the rate of BVL. To understand the natural history of BVL in MS patients, this systematic literature review aimed to examine published longitudinal studies (2003–2013) that reported BVL and to develop consensus estimates of the annualized rate of BVL in MS stratified by type of treatment. In addition, it is unclear whether BVL continues at a constant rate throughout the disease course [7]. In particular, disease modifying treatments (DMTs), study population, study design, disease duration, and imaging techniques may impact rates of observed BVL. This study explored the associations between BVL and other features that may impact measured rates of BVL.

2. Methods

2.1. Study selection criteria

We included clinical trials and longitudinal observational studies that reported changes in brain volume measurements in MS patients, had at least 12 months of follow-up time, and specified the brain volume algorithm that was used. For clinical trials, we excluded studies if a placebo or non-MS control group was not reported.

2.2. Search strategy

We searched Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), NHS Economic Evaluation Database (NHS EED) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) for studies published in English between January 2003 and September 2013. We hand-searched references of included reviews from 2013 and reviewed clinical trial registry to identify additional studies that were not indexed in the electronic databases. The complete search strategies and results of the strategy are found in the online Supplemental materials.

2.3. Study selection process and data extraction

Two independent reviewers applied the inclusion criteria and assessed the quality of the data collected using a standardized methodology. Each reviewer evaluated the data from the eligible studies and electronically entered the information into an Excel database developed specifically for the review with prepared fields. Disagreements between reviewers were resolved by consensus or by arbitration through a third party, referring to the original sources.

We collected information on the study design, population, comparisons or treatment groups, sample size, duration of follow-up, brain volume algorithm, average baseline characteristics of patients, MS type, MS disease duration, and reported changes in BVL over the specified time period (Table 1). For brain volume measures, we extracted information for percent brain volume change (PBVC), brain parenchymal fraction (BPF), white matter fraction (WMF), and grey matter fraction (GMF). In addition, we recorded T1-hypointense lesion volume (LV) and T2-hyperintense LV data. We extracted average patient baseline characteristics such as age, disease duration, and Kurtzke Expanded Disability Status Scale (EDSS).

2.4. Risk of bias assessment

We developed a quality assessment form for each type of study design based on the Cochrane Handbook report of low, unclear, and high risk of bias [8]. For studies in which participants were randomized, we assessed biases such as selection, performance, detection, attrition and reporting using an assessment tool from the Cochrane Handbook [8]. For observational studies, we adapted the Newcastle-Ottawa Scale to assess the following biases: selection, attrition, detection and information [9]. The form can be found in the online Supplemental materials section.

2.5. Statistical analyses

When percentage brain volume measures were not provided, we calculated the percentage change by subtracting the baseline and follow-up absolute brain volume measures. We divided the absolute difference by the baseline brain volume measures and multiplied by 100 to obtain the percentage change. For studies that did not annualize percentage brain volume measures, we annualized them by dividing the percentage brain volume measure change by the duration of the follow-up period. We estimated the standard error by dividing the standard deviation of the brain volume measures by the square root of the reported sample size.

We computed a pooled estimate of the annual rate of BVL among studies that reported mean PBVC and used the SIENA algorithm, to facilitate comparability across studies. To better characterize the natural history of brain volume loss in MS, we focused on studies that examined patients treated with first-generation DMTs (e.g., interferon-beta [IFN] or glatiramer acetate [GA]). Heterogeneity across studies was assessed via the I^2 statistic, which quantifies the degree of heterogeneity and describes the percentage of total variation across studies due to heterogeneity rather than chance [10]. We used meta-analysis with random-effects [11] to pool annualized PBVC across studies. In addition, we examined the pooled annualized PBVC by patients receiving first-generation DMT and untreated patients, respectively.

To examine the relationship between study-level reported annualized mean PBVC and the annualized mean changes in T1LV or T2LV, we conducted random-effects meta-regression analysis to allow between-study variance not explained by the covariates by assuming that the true effects follow a normal distribution around the linear

Please cite this article as: T. Vollmer, et al., The natural history of brain volume loss among patients with multiple sclerosis: A systematic literature review and meta-analysis, J Neurol Sci (2015), http://dx.doi.org/10.1016/j.jns.2015.07.014