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No evidence of disease activity (NEDA) in MS should include CSF biology — Towards a 'Disease-Free Status Score'

1. Introduction

Since excellent prevention of MS relapses is now obtained with the most recent drugs (i.e. natalizumab), reaching a sustained clinical remission has emerged as an achievable goal in a substantial proportion of patients. The concept of NEDA (*no evidence of disease activity*) was forged by combining two criteria: absence of relapses; absence of confirmed disability progression (no evidence of clinical activity composite); absence of gadolinium-enhancing T1 lesions or new/enlargement of T2 lesions (no MRI evidence of activity composite). The concept was recently extended ('NEDA-4′) to encompass brain atrophy although the reliability of the measure is still a concern in non-expert centres (Kappos et al., 2016). These criteria recapitulate the treatment goals of the relapsing-remitting phase (RR), but do they reliably capture a suboptimal response like a persistent slow-burning neurodegenerative process?

2. Neurodegeneration begins early in MS

MS is a life-long disorder that follows a biphasic curve: ambulation is usually conserved during the RR phase, while impairment preferentially occurs later during the progressive phase (Scalfari et al., 2014). Although inflammation is now prevented by treatments during the early RR phase, uncertainty remains about their preventive effect for a late transition to secondary progression. However, the transition to the progressive phase remains a highly constructed concept and it is often difficult to delineate a clear transition between the two phases (Katz Sand et al., 2014). From a clinical point of view, progression is commonly thought to have occurred if impairment is sustained over 6 months in the absence of relapse, although this definition is still debated. Furthermore, there is no consensus about the value of subjective minimal complaints of impairment as they are commonly received. This period of uncertainty may be as long as 3 years before progression phase is diagnosed (Katz Sand et al., 2014). From a pathological point of view, the two phases are closely intertwined and diffuse signs of progressive neurodegeneration are observed from the onset of MS (Trapp et al., 1998). Even in the absence of new clinical symptoms, this slow-burning degenerative process progressively and irreversibly destroys the brain reserve needed to prevent the consequences of age-related brain atrophy.

3. NEDA is pragmatic but insufficient for assessing disease-free status

Basically, the goal of MS treatments is to avoid long-term impairment. Although no treatment is currently available during the late debilitating progressive phase, a wide range of efficient drugs is now available to treat the RR phase. Disease-status assessment encompasses a combination of clinical and MRI parameters now referred to as NEDA.

In real-life old cohorts of MS patients who were mainly free of treatment, NEDA was achieved in 46% of patients at one year but in less than 10% at 7–10 years (Rotstein et al., 2015; De Stefano et al., 2015a; Uher et al., 2016). In cohorts of patients treated with second-line drugs, NEDA was achieved in no more than 31–47% of patients receiving natalizumab, fingolimod or alemtuzumab for a few years (Kappos et al., 2016; Havrdova et al., 2009; Prosperini et al., 2016). The highest proportion of NEDA (75%) is obtained after autologous stem cell transplantation at three years (Imitola and Racke, 2015).

Obviously, patients not fulfilling the NEDA criteria remain at risk of progression and require more efficient treatments. A major challenge is therefore making the long-term prognosis of the growing number of patients fulfilling these criteria and establishing the most pragmatic objective of apparently complete disease control. Will conversion to the secondary progressive phase still occur in these patients and how can it be predicted? How reliable is NEDA to confirm control of the slow-burning neurodegenerative processes that subsume long-term impairment?

First, NEDA is a useful measure at a given time point but it should be monitored over time, assuming that the proportion of patients fulfilling NEDA declines over time (Rotstein et al., 2015).

NEDA can be used to assess the efficacy of treatment early but cannot predict long-term outcome (University of California SFM-ET et al., 2016). For example, the risk of developing the secondary progressive phase is 7.5% at 8 years in fingolimod-treated patients and is still about 5% in those fulfilling NEDA-4 criteria at one year (Kappos et al., Poster 1217, ECTRIMS 2016). The rate of clinical progression in patients devoid of MRI activity is around 10% after 4 years of natalizumab (Prosperini et al., 2016). Rates of conversion to the progressive phase according to NEDA are still lacking for the other recently introduced drugs.

Lastly, NEDA criteria regarding clinical progression are based on EDSS, which fails to capture subtle clinical changes like cognitive dysfunction, although such changes are observed in more than half of NEDA patients and correlate with late impairment (Damasceno et al., 2016). More comprehensive clinical criteria including multiple scales could be envisioned in NEDA, but such changes would add a level of complexity preventing

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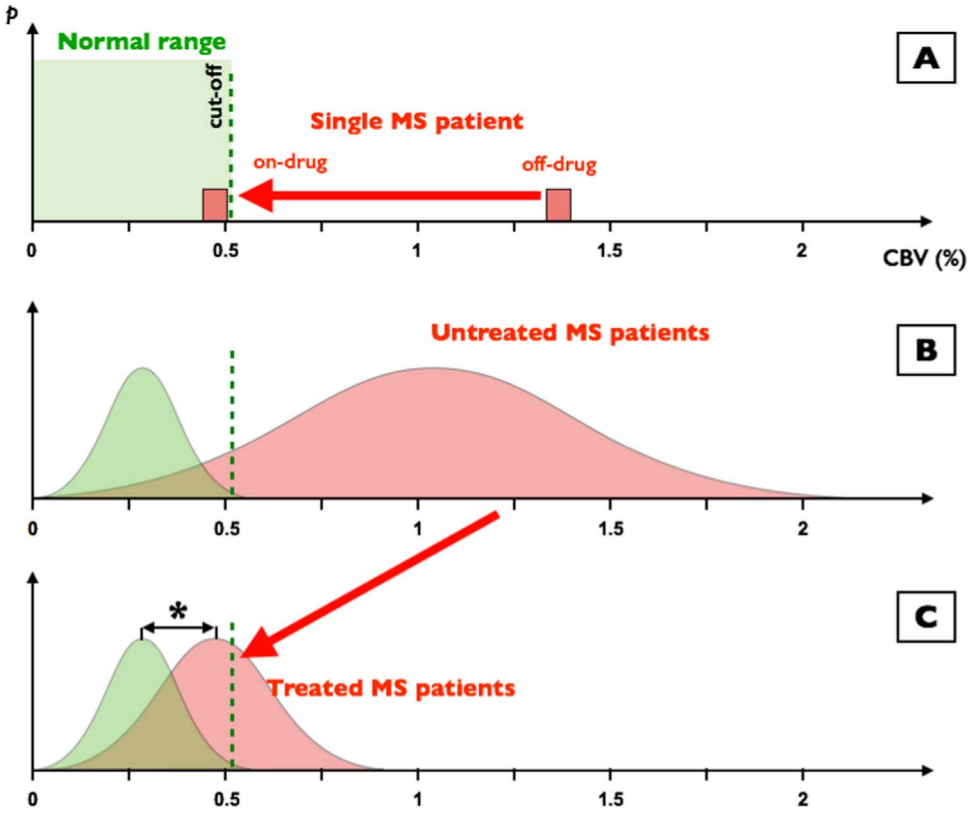

Fig. 1. Limits of brain atrophy measures. Single measure may fall in the normal range (below the cut-off)(A), although the rate of atrophy is still in the higher quantile of the expected age-related rate (B), suggesting erroneously that atrophy has returned to normal value. Only regression toward the mean of atrophy rates in cohorts of treated patients would discriminate still excessive rates (*) from those of healthy controls (C).

large-scale use in clinical practice.

Therefore patients fulfilling the NEDA criteria are 'relapse-free' patients who may not be considered as reaching a 'disease-free' status, since a progressive phase may occur later. As a consequence, patients devoid of relapse but with slowly developing subclinical impairment and brain atrophy over the years would be inappropriately classified as fulfilling the NEDA criteria while beginning a secondary progressive phase. Therefore other criteria are still needed for predicting a sustained remission or a complete recovery.

4. Assessing brain atrophy progression is necessary but provides late post-hoc information

Neurodegeneration is usually assessed by volumetric MRI parameters demonstrating progressive brain atrophy, which is correlated to motor and cognitive impairment. Much of the subtle cognitive dysfunction is captured by the follow-up of brain atrophy (Damasceno et al., 2016). The yearly (age-dependent) brain volume loss (BVL) in healthy controls follows a Gaussian distribution at a lower rate than in MS patients, with a suggested cut-off of −0.5% BVL/year to discriminate the overlapping of MS patients with healthy controls (HC) (De Stefano et al., 2016). The atrophy rate is similar across the subtypes of untreated MS patients (De Stefano et al., 2010). In relapse-free treated patients, it decreases to approximately the higher cut-off of HC.

NEDA-4 criteria now encompass brain atrophy follow-up (Kappos et al., 2016). In the pooled population of fingolimod trials, NEDA-4 was reached in 19% of treated patients (vs 5% in the placebo group) for a threshold of BVL equal to 0.4% (which is above the mean BVL in HC: 0.1–0.3%) (Kappos et al., 2016).

Although monitoring brain atrophy rate (apart from technical limitations so far) is of major importance to evaluate the efficacy of treatments in cohorts, it carries an intrinsic limitation for monitoring MS treatments at the level of single patients. The rate of brain atrophy of treated MS patients might still be excessive even if it reaches the cut-off for the normal range (Fig. 1). Moreover, it may take years to demonstrate a persistent, excessive but small rate of atrophy, so clinicians are able to obtain *post-hoc* information. However, real-time information is required for modifying treatments.

5. Designing a future 'disease-free status score'

5.1. Towards an early predictive score

Brain atrophy is the anatomical consequence of microscopic multiple diffuse CNS inflammatory lesions leading to neuronal and glial loss. The immune reaction in MS is trapped mainly in the intrathecal compartment (Meinl et al., 2008), so assessment of biomarkers in CSF is essential for assessing the persistence of intrathecal inflammation. The correlation between the biological parameters of neurodegeneration in CSF and long-term impairment has received little attention, especially in relapse-free MS patients, but one may expect that patients demonstrating a complete normalization of these biological inflammatory parameters would be at far lower risk than those with signs of persistent processes. Demonstrating this correlation involves two major obstacles: the ability to obtain excellent control of the RR phase is recent; long-term impairment becomes