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Measurement of disability in multiple sclerosis

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Abstract

Despite its limitations, the Kurtzke Expanded Disability Status Scale (EDSS) is the gold standard in assessing physical disability in multiple sclerosis (MS). Sustained progression in EDSS has been used widely as the endpoint in therapeutic studies. However, the patients' disability often fluctuates or improves over time; and up to half of the patients with "sustained progression" of EDSS eventually regress to their baseline. It is, therefore, not a sensitive measure to define irreversible progression of disease. The Multiple Sclerosis Severity Score (MSSS) is a useful measure of MS severity, incorporating the EDSS and disease duration. It has some prognostic significance for individuals with mild or severe disease, but is best suited to cross-sectional comparative studies. Cognitive impairment in MS is often considerable, and principally affects the domains of attention, vigilance, processing speed, working memory and executive function. Tests such as paced auditory serial addition test (PASAT) and the symbol digit substitution test (SDT) are therefore quite sensitive to change over time. The Multiple Sclerosis Functional Composite (MSFC), a score combining a measure of lower limb function (timed walk), upper limb function (nine-hole peg test) and cognitive function (PASAT), is useful to detect disability progression in MS trials, as it is sensitive to change over time, but is too time-consuming to become adopted in clinical practice.

INTRODUCTION

Multiple Sclerosis (MS) associated disability not only comprises physical disability, but also cognitive disability and MS-related quality of life impairment, and these are briefly reviewed in this communication. Many other important domains of disability, for example bladder, bowel and sexual dysfunction, fatigue, daytime sleepiness, tremor, depression and caregiver burden are also assessable using clinical scales, but space does not permit further discussion of the relevant assessment methodologies.

PHYSICAL DISABILITY

It has become increasingly important both in the clinical setting and in therapeutic trials to measure disability levels repeatedly in order to assess progression of disability. The Kurtzke Expanded Disability Status Scale (EDSS) remains the gold-standard measure for assessing level of disability.[1] It is an ordinal scale with 19 disease steps between 0 and 10. The scale measures impairment or activity limitation based on the examination of eight functional systems plus ambulation, and is ideally administered by an experienced and EDSS-accredited physician. It does have some limitations, which are well documented. Importantly, it is biased towards locomotor function, is insensitive to change at certain levels and has only moderate inter- and intra-rater reliability.[2-4] An attempt at minimising EDSS measurement error is made by utilisation of the same assessor for repeated EDSS assessments, and by an increasingly standardised set of EDSS definitions, which also underpin an accreditation process for EDSS rater competency.[5]

Identification of sustained disability progression is an important outcome measure in therapeutic trials in relapsing-remitting multiple sclerosis (RRMS). In several recent studies, disability progression has been used as the primary endpoint, underscoring the significance placed on progression events rather than relapses.[6-8] The identification of "sustained disability progression" is based on assessment of repeated EDSS measurements. An increase of 1 point on the EDSS above baseline (or 1.5 EDSS points if the baseline EDSS is 0), subsequently confirmed at repeat assessment either 3 or 6 months later (3 or 6 month confirmed progression) are the most commonly used measures.[6,9-14] The definition may also encompass additional criteria, such as exclusion of confirmation visits during new or ongoing relapses.[7,8]

Difficulties with these definitions arise firstly because relapses may produce neurological changes persisting for many months still followed

by full recovery[15], and secondly because people with RRMS exhibit day-to-day fluctuation in neurological signs and symptoms unrelated to relapses, potentially due to changes in ambient temperature, intercurrent infection and fatigue. The first study to evaluate the reliability of 3 or 6 month confirmed progression to identify long-term sustained progression, comprised a total of 313 patients assessed during clinical trials and reported that only 50% of 3 month sustained progression events persisted to the end of the respective studies.[16] In an attempt to assess the applicability of trial measures to clinical practice, the MSBase study group[17] assessed the rate of long-term return to baseline EDSS after a 3 or 6 month confirmed disability progression event in a large number of frequently assessed MS patients followed prospectively. In this prospectively acquired dataset, 1,137 patients experiencing their first 3 month sustained progression event were identified. As expected, subsequent regression to baseline EDSS was significantly more common in patients with clinically isolated syndrome (CIS)/ RRMS than patients with progressive forms of MS ($p< 0.00001$). In the CIS/RRMS group, 25% of patients regressed back to baseline within 2 years after confirmed progression, 40% within 5 years, and over 50% within 7 years. In the CIS/ RRMS cohort with at least one 6 month sustained progression, 25% of patients had regressed by 3.1 years and 40% by 7.1 years.[18] This study confirms that the application of trial defined sustained disability progression at 3-6 months in clinic-based practice is a relatively insensitive method of identifying permanent disability progression in RRMS.

Until recently, there has been no method of assessing and comparing disease severity in MS with a single assessment at a single point in time. The Global Multiple Sclerosis Severity Score (MSSS) was originally devised with this exact aim: to allow comparisons of relative disease severity at all EDSS levels for a given disease duration, using a single clinical assessment at a single point in time.[19] It was derived from analysis of Kurtzke EDSS scores stratified by disease duration on 9,872 European individuals with MS. It includes cases with MS ranging from one year to more than thirty years from disease onset, producing yearly severity scores. The score is the decile of the EDSS within the range of MS patients at the same disease duration. In order to validate this concept, the authors assessed the stability of the MSSS over time using two French longitudinal cohorts and found that, although the mean change in MSSS in the groups was zero, there were significant changes in an individual's MSSS rank over time. They concluded that the MSSS was a useful measure of disease severity in studies of groups of MS cases, but was not suitable to track individuals' progress over time. Subsequently, however, the global MSSS has begun to be used in outcomes studies, but appropriate validation in an independent dataset was still required.

For this reason, the MSBase study group assessed the stability of the MSSS in 6,100 patients with 38,683 EDSS scores from onset of first symptom to 15 years disease duration.[20] The analysis demonstrates an increasing rank correlation between MSSS at 0 and 5 years ($r=0.66$), 5 and 10 years ($r=0.80$) and 10 and 15 years ($r=0.88$). MSSS rank stability increased with disease duration, probably due to reduced influence of relapses and non-relapse fluctuations on EDSS. MSSS at 5 years from diagnosis was highly predictive of MSSS at 10 years, and therefore is likely to be of prognostic value in individuals. The predictive value of MSSS scores (i.e. MSSS rank stability) in all prospectively assessed 5 year intervals (0-5, 5-10 and 10-15 years) was weakest for EDSS scores between 1.5-2.5, but much stronger at higher or lower disability levels.

COGNITIVE DISABILITY

The burden of cognitive impairment in multiple sclerosis is considerable, and particularly it is of crucial significance in employment outcomes and social disability.[21] Cognitive dysfunction is not strongly correlated with the EDSS score[22], and it is unusual for it to be formally assessed and followed by repeat measures over time in routine clinical practice. As might be expected from a multifocal CNS disease, the most frequently reported cognitive impairments are apparent in tests measuring attention, vigilance, processing speed, working memory and executive function. It is for this reason that tests such as the paced auditory serial addition test (PASAT) and the symbol digit substitution test (SDT), which represent tasks that draw on precisely these cognitive functions, namely vigilance, processing speed and working memory, are the most sensitive of all cognitive tests in detecting abnormalities in people with MS.[23] Interestingly, abnormalities in the PASAT performance in MS patients typically reflect a much greater loss of processing speed than accuracy, illustrating particularly significant deficits in processing speed in MS patients.[24]

Unfortunately, these tests are still too cumbersome and time-intensive to be truly useful in routine clinical practice. However, a new generation of patient self-administered, computer based testing paradigms is emerging (for an example, see www.cogstate.com) and this may pave the way for much more widespread cognitive monitoring in clinical practice in the near future.

MSFC: A MULTI-DOMAIN DISABILITY MEASUREMENT TOOL

In clinical trials, efforts by the United States National Multiple Sclerosis Society's Advisory Committee on Clinical Trials to improve upon the responsiveness of the EDSS to detect disability change in patients in a 2 year time-frame led to the development of the Multiple Sclerosis Functional Composite (MSFC), a score combining a measure of lower limb function (timed walk), upper limb function (nine-hole peg test) and cognitive function (PASAT). The scores for each test are normally distributed, and are highly responsive to change over 2 years, thus producing much greater statistical power to detect change in the context of clinical trials.[25] However, unlike the EDSS, the MSFC is not based on the routine neurological examination, and thus requires considerable additional time and a relatively high level of training to perform. Therefore, it is unlikely that the MSFC will ever be widely used outside the clinical trial domain.

MS-RELATED QUALITY OF LIFE (QoL)

Generic health-related QoL instruments, foremost amongst them the SF36 and SF12 health surveys, are validated in many languages and have been widely used in a broad range of diseases including MS. However, they lack specificity for MS-related QoL change.[26] More recently, many groups have developed and validated MS-specific QoL instruments, and their responsiveness to change over time is currently being assessed in prospective cohort studies. These tools are derived from interviews with MS patients, and serially refined to a manageable number of individual items. Three examples include the MS quality of life instrument – MSQLI[27], MSQOL-54 and the MS international quality of life questionnaire (MusiQol).[28] Serial comparative assessments of QoL and physical disability measures do suggest that they are not highly correlated with each other.[29] Therefore, QoL assessment captures an additional disability dimension beyond physical scales. Unfortunately, there is a great proliferation of different tools, and, unlike the EDSS, no generally accepted QoL instrument in MS has emerged, significantly reducing the chance of meaningful cross-cohort comparisons.[30]

In this brief overview, we have highlighted the importance of serial EDSS assessments for tracking physical disability progression in MS. The application of the MSSS allows a rapid assessment of relative rank of any given EDSS score in comparison to peers with similar disease duration. Cognitive impairment in MS causes major morbidity for patients and families, and therefore monitoring of cognition is likely to become much more widespread in clinical practice. This is likely to be aided by more widespread availability of computer-based psychometric assessment tools that are patient self-administered. Quality of life is a composite measure of disease and non-disease related factors, and a large number of free tools are currently available. However, none are widely used in clinical practice at the present time.

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