



The John Whitaker
Research Track
Platform Presentation



VALIDATION OF AN AMBULATION-SPECIFIC VISUAL ANALOG SCALE (VAS) USING THE LIFEWARE SYSTEM

Background: When defining a clinically meaningful change in ambulation in multiple sclerosis (MS), consideration of the patient's perspective is crucial. Subjective visual analog scales (VASs) represent potentially promising complements to objective clinical measures. The LIFEware System (LIFEware) has been widely embraced as a valid, reliable patient-oriented measure of functional status.

Objective: To validate the VAS as a measure of patient-perceived change in ambulation using the MSPhysical component of LIFEware.

Design/Methods: Data from 90 MS patients (mean age: 47.8+/-10.5yrs; mean EDSS: 2.9+/-1.7) were studied. Patients reported change in ambulation by marking a horizontal 10cm line anchored by word descriptors (ie. "much worse"). Scored on a scale of 0-100, VAS scores ≤ 25 were arbitrarily selected to represent meaningful worsening. Patient-perceived problems rising from a low seat (GETUP), stair climbing (STAIRS), standing (STAND), fatigability (FTG) and using right (RLL) and left (LLL) lower limbs were assessed and compared to data available from previous evaluations (med. 442.5 days). Functional changes detected by VAS and MSPhysical item scores were dichotomized (ie. 'worse' or 'no change/better').

Results: Patient-perceived worsening was reported by 27.8% of patients via the VAS. Worsening functional status was detected in 14.4-31.1% of patients according to changes in MSPhysical item scores. Statistically significant correlations between VAS and the following MSPhysical item scores were observed: GETUP ($r=.46, p<.05$), STAIRS ($r=.40, p<.05$), STAND ($r=.42, p<.05$), FTG ($r=-.23, p<.05$), RLL ($r=-.44, p<.05$) and LLL ($r=-.34, p<.05$). Chi square analyses of independence demonstrated no statistically significant differences between VAS and any MSPhysical item scores ($p>.05$).

Conclusion/Discussion: Patient-perceived changes in ambulation detected by the VAS appear to reflect patient-reported functional status captured by the MSPhysical items of LIFEware. While further validation is warranted, incorporating complementary patient-oriented measures when attempting to define clinically meaningful changes may provide valuable insight into the diverse impact of MS.

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AN INVESTIGATION OF PATIENTS WITH MS THAT IMPROVE OVER A FIVE-YEAR PERIOD

This study used the MS Physical measure, which is a composite of patient reported outcomes of disability and limitations (within the LIFEware® System) and the EDSS to assess functional change longitudinally in patients with Multiple Sclerosis (MS). Data were obtained from the Jacobs Neurological Institute, the largest site within the New York State Multiple Sclerosis Consortium. There were 751 patients assessed at enrollment and 5-year follow-up. The study objectives were two-fold: first, to investigate what proportion of patients improved over a 5-year period, as compared to staying the same or worsening, second, to determine which factors were associated with an improvement in function over time. Patients were classified into three groups: improved, stayed the same, or worsened, based on differences between baseline and 5-year follow-up scores. All groups were equal in terms of EDSS and MS Physical rating at baseline. Overall, 7% of patients improved in functioning over a 5-year period, 23% remained the same and 70% worsened. There was no significant difference in patient age, age of MS onset, age of MS diagnosis, duration of MS, education level, marital status, family history, sex or race in patients who improved as compared to those who stayed the same or worsened. Patients classified as relapsing/remitting were significantly more likely to have improved at 5-year follow-up, and patients classified as secondary progressive were significantly more likely to have worsened at 5-year follow-up ($\chi^2=57.04$ (df=8), $p<.01$). Patients who were employed were significantly more likely to have stayed the same or improved at 5-year follow-up compared to those not employed ($\chi^2=17.98$ (df=6), $p<.01$). In conclusion, a small percent of patients improved over a 5-year period using two measures, the MS Physical and the EDSS. Employment at baseline through 5 years was associated with patients who improved.

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THE EFFECT OF EXHAUSTIVE EXERCISE ON COGNITIVE FUNCTION IN INDIVIDUALS WITH MS

Background: Approximately 54-65% of individuals with MS experience cognitive impairment at some point during their disease course. Until recently, it was thought that only individuals with significant disease progression experienced cognitive impairment; however there is now sufficient evidence that cognitive impairment can occur among individuals with mild MS. Numerous researchers have suggested that global fatigue may impact cognition. Research has demonstrated that among healthy individuals an acute bout of exercise improves cognitive functioning.

Purpose: This study examined cognitive functioning before and after a maximal exercise test in persons with mild MS to determine if fatigue resulting from acute exercise would adversely affect cognitive functioning.

Methods: The sample was 25 females with RRMS (mean EDSS score 2.5) and 15 matched healthy controls. Participants completed computerized versions of the Erikson's Flanker Task and Stroop Color Word Task immediately before and after a maximal exercise test on a cycle ergometer.

Results: Repeated measures ANOVAs revealed no group differences in reaction time or accuracy on the Flanker and Stroop tasks. A significant time main effect for reaction time responses indicated faster reaction time following the exhaustive bout of exercise. T-tests showed that individuals with MS had improved reaction time on both cognitive tasks (range of $d = .62 - 1.02$) and these findings were consistent with the controls (range of $d = .75 - 1.32$).

Conclusion: Among this sample of mildly impaired individuals with MS, exhaustive exercise had no deleterious effect on reaction time or response accuracy during cognitive tasks. Moreover, exhaustive exercise was associated with significant improvements in reaction time for both the Flanker and Stroop tests. This initial research finding suggests that vigorous exercise may be beneficial for cognitive functioning. Exercise might be an instrumental means for maintaining and improving cognitive function among individuals with mild MS.

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IL-12 AND IL-23 INDUCE DISTINCT TYPES OF EAE

The IL-12 p40 family of cytokines (composed of IL-12p70 and IL-23) plays a critical role in the development of experimental autoimmune encephalomyelitis (EAE). However, the relative contributions of IL-12 and IL-23 to the pathogenic process remain to be elucidated. Here we show that activation of uncommitted myelin-reactive T cells in the presence of either IL-12p70 or IL-23 confers encephalogenicity. Adoptive transfer of either IL-12p70 or IL-23 polarized cells into naïve syngeneic hosts resulted in an ascending paralysis that was clinically indistinguishable between the two groups. However, histological and RT-PCR analysis of central nervous system (CNS) tissues revealed distinct histopathological features and immune profiles. While IL-12p70 driven disease was characterized by macrophage rich infiltrates and prominent NOS2 upregulation, neutrophils and G-CSF were prominent in IL-23 driven lesions. The monocyte attracting chemokines CXCL9, 10, and 11 were preferentially expressed in the CNS of mice injected with IL-12p70 modulated effectors, whereas the neutrophil attracting chemokines CXCL1 and CXCL2 were upregulated in the CNS mice given IL-23 modulated effectors. Treatment with anti-IL-17 or anti-GM-CSF inhibited EAE induced by transfer of IL-23 polarized, but not IL-12p70 polarized, cells. These findings indicate that autoimmunity can be mediated by distinct effector populations that employ disparate immunological pathways to achieve a similar clinical outcome.

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IDENTIFICATION OF A NOVEL SOLUBLE TREM-2 PROTEIN IN THE CEREBROSPINAL FLUID AND ITS ASSOCIATION WITH MULTIPLE SCLEROSIS AND CNS INFLAMMATION

Triggering receptor expressed on myeloid cells 2 (TREM-2) is a membrane-bound receptor expressed on some myeloid cells including microglia and macrophages. Engagement of TREM-2 on these cells has been reported to reduce inflammatory responses and, in microglial cells, to promote phagocytosis. TREM-2 function is critical within the central nervous system (CNS) as its genetic deficiency in humans leads to neurodegeneration with myelin and axonal loss. Blockade of TREM-2 was shown to worsen the mouse model for multiple sclerosis (MS). In the present study, a soluble form of TREM-2 protein has been identified. Soluble TREM-2 protein (sTREM-2) was detected in human cerebrospinal fluid (CSF), and was significantly elevated in subjects with MS and other inflammatory neurologic diseases compared to subjects with non-inflammatory neurologic diseases. In contrast, levels of sTREM-2 in the blood did not differ among the groups. Furthermore, TREM-2 receptor expression was demonstrated on a subset of CSF monocytes and was also highly expressed on myelin-laden macrophages in the CNS tissue in active demyelinating MS lesions. Elevated levels of sTREM-2 might inhibit the anti-inflammatory function of the membrane-bound receptor in MS. Therefore sTREM-2 is a possible target for future therapies. (L. Piccio is a fellow of the National MS Society FG 1665-A-1).

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