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Binocular low-contrast letter acuity and the symbol digit modalities test improve the ability of the Multiple Sclerosis Functional Composite to predict disease in pediatric multiple sclerosis

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ABSTRACT

Background: Outcome measures to capture disability, such as the Multiple Sclerosis Functional Composite (MSFC), were developed to enhance outcome measurements for clinical trials in adults with multiple sclerosis (MS). The MSFC initially included three components: a timed 25-foot walk [T25FW], 9-hole peg test [9HPT], and the Paced Auditory Serial Addition Task [PASAT]. Modifications to the original MSFC, such as adding binocular low-contrast letter acuity (LCLA) or substituting the symbol digit modalities test (SDMT) for the PASAT, improved the capacity to capture neurologic impairment in adults. Similar outcome scales for pediatric MS have not yet been established.
Objective: To determine whether the three-component MSFC or a modified MSFC with LCLA and the SDMT better identifies neurological deficits in pediatric MS.
Methods: We evaluated 5 measures (T25FW, 9HPT, Children's PASAT [ChiPASAT], SDMT, and binocular LCLA [Sloan charts, 1.25% contrast]) in children with MS (disease onset < 18 years) and healthy controls. To be able to compare measures whose scores have different scales, Z-scores were also created for each test based on the numbers of standard deviations from a control group mean, and these individual scale scores were combined to create composite scores. Logistic regression models, accounting for age, were used to determine whether the standard 3-component MSFC or modified versions (including 4 or 5 metrics) best distinguished children with MS from controls.
Results: Twenty pediatric-onset MS subjects, aged 6–21 years, and thirteen healthy controls, aged 6–19 years, were enrolled. MS subjects demonstrated worse scores on the 9HPT ($p=0.004$) and SDMT ($p=0.001$), but not the 25FTW (adjusted for height, $p=0.63$) or the ChiPASAT ($p=0.10$): all comparisons adjusted for age. Decreased (worse) binocular LCLA scores were associated with MS (vs. control status, $p=0.03$, logistic regression; $p=0.08$, accounting for age). The MSFC composite score for the traditional 3 components did not differ between the groups ($p=0.28$). Replacing the ChiPASAT with the SDMT (OR 0.72, $p=0.05$) better distinguished MS from controls. A modified MSFC-4 with the SDMT replacing the ChiPASAT and including binocular 1.25% LCLA had the greatest capacity to distinguish pediatric MS from controls (OR 0.89, $p=0.04$, logistic regression). Including all 5 metrics as a composite MSFC-5 did not improve the model ($p=0.18$).
Conclusions: A modified MSFC (25FTW, 9HPT, SMDT, and binocular 1.25% LCLA) is more sensitive than the traditional MSFC or its components to capture the subtle impairments that characterize pediatric MS and should be validated in order to be considered for future pediatric MS trials.

1. Introduction

Standardized tools that reliably quantify neurologic impairment in pediatric multiple sclerosis (MS) have not been

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established. MS clinical trials in adult patients have used the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Although the EDSS incorporates eight Functional Systems scores (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, cerebral, and ambulation), the EDSS summary score itself is heavily influenced by ambulation status. Gait impairment and sustained disability in children with MS are less common than in adults; thus the EDSS may not be a sensitive metric for pediatric MS. In one observational study of 76 pediatric MS patients, baseline mean EDSS scores were 1.4 ± 0.8 and did not change (mean of 1.2 ± 0.9) after a mean follow-up of 30 months (standard deviation 15 months) irrespective of treatment (Ghezzi et al., 2005). Another study of 84 pediatric MS and 258 adult MS patients demonstrated a >2 fold higher relapse rate in the pediatric MS group but median EDSS scores did not differ between the groups, and remained low (median 1.5, range 0–8) over a 6-year period (Benson et al., 2014).

The Multiple Sclerosis Functional Composite (MSFC), consisting originally of a timed 25-foot walk (T25FW), a 9-hole peg test (9HPT), and Paced Auditory Serial Addition Task (PASAT), was developed as an outcome tool for adults to capture the most relevant dimensions of function and disability, including ambulation, arm function, and cognition (Rudick et al., 1997, 2002; Cutter et al., 1999). The MSFC is brief and can be administered by a non-clinician. Compared to the EDSS, MSFC and its component scores are more reliable and correlate better with disease stage than does the EDSS (Polman and Rudick, 2010). The Children's PASAT (ChiPASAT) has been adapted for children ages 8–15 years (Johnson et al., 1988; Dyche and Johnson, 1991) and replaces the PASAT when using the MSFC for younger MS patients.

Developers of the MSFC and MS outcomes committees have incorporated low-contrast letter acuity as a visual outcome component for inclusion in the MSFC. The original MSFC did not include a test of vision since high-contrast visual acuity, the only visual measure available in the clinical trial data sets used to develop the MSFC, did not detect changes over time. Routine clinical tests of high-contrast visual acuity, typically assessed by wall-mounted Snellen charts (and as adjudicated in the EDSS), do not maximally capture visual dysfunction in adult patients (Rudick et al., 1997). Pediatric MS patients with optic neuritis typically recover high contrast visual acuity. In one study of 38 pediatric MS patients with optic neuritis, 95% of patients demonstrated complete recovery (Snellen visual acuity of 20/20) (Taimur et al., 2014). As expected, high-contrast (Early Treatment Diabetic Retinopathy Scale [ETDRS]) scores also do not differ between pediatric MS subjects with optic neuritis and controls (Waldman et al., 2014). Low-contrast letter acuity (LCLA), where the subject views letters of progressively smaller size as well as reduced contrast to the background (ie: grey letters as opposed to black) is a more sensitive tool to detect subtle visual impairment (Balcer et al., 2000). In adult clinical trials of natalizumab, LCLA, in comparison to high-contrast acuity, differentiated treated patients from those patients in the placebo arms and identified patients with worsening visual impairments despite no change in the EDSS (Balcer et al., 2012; Chahin et al., 2015).

We have recently demonstrated the ability of LCLA to capture visual dysfunction in 22 pediatric MS patients, although only the more stringent 1.25% contrast distinguished patients from controls (Waldman et al., 2014). With the recent launch of several clinical trials of new therapies in pediatric MS populations, and with the imperative to better appreciate the impact of MS onset during childhood, we evaluated the MFSC and its components, the SDMT and LCLA in a cohort of pediatric MS patients in order to determine which combination of tests best captured measurable neurological impairment.

2. Methods

2.1. Study eligibility

Children with relapsing-remitting MS (presenting with a first attack prior to age 18 years) were recruited from the Pediatric MS Program at the Children's Hospital of Philadelphia as a convenience sample between 2007 and 2012. The diagnosis of MS was established using the 2007 International Pediatric MS Study Group criteria (Krupp et al., 2007). Healthy children without neurologic, ocular, or systemic disease were recruited by local advertisement, and were required to have normal corrected visual acuity.

For MS subjects, all testing was performed at least 30 days after a relapse and 6 months or more from an attack of optic neuritis. The children were assessed for a history of optic neuritis in one or both eyes. We considered optic neuritis to have occurred if detailed chart review identified documentation of: decreased high-contrast letter acuity, pain with eye movement, color desaturation, and/or visual field abnormalities lasting at least 24 h, with or without optic nerve swelling or enhancement visualized on magnetic resonance imaging. EDSS scores were obtained retrospectively from neurology office notes using a standardized, reliable algorithm developed by one of the authors (SC).

2.2. MSFC, SDMT, and LCLA

The MFSC was administered according to the Administration and Scoring Manual (Fischer et al., 2001), including two timed trials of both the T25FW and 9HPT (dominant and non-dominant hand). The PASAT was replaced with the ChiPASAT, which was administered via a computerized program (Dr. Robert J. McInerney and Associates, Canada). The written SDMT was completed using a standardized protocol (Smith, 1973) in 90 s, and the number of correct responses was recorded. High (Early Treatment Diabetic Retinopathy Study [ETDRS] 3.2 m charts, Lighthouse Low Vision Products, Long Island, NY) and low-contrast letter acuity (Sloan 1.25% contrast 2 m charts, Precision Vision) were recorded using the patient's own correction, standardized testing protocols at the appropriate viewing distance, and a retroilluminated viewing cabinet. Cycloplegic refraction was not performed. Binocular acuity scores, rather than monocular scores with each eye separately, were included to capture visual function with both eyes together. This is analogous to testing arm and leg function using performance measures of T25FW and 9HPT.

2.3. Analyses

Summary scores for function tests were calculated as follows. For the T25FW, the times for the 2 trials were averaged; for the 9HPT, the times for the 4 trials (2 trials each of the dominant and non-dominant hands) were averaged. The number of correct responses in the allotted time was determined for the ChiPASAT (3 min) and the SDMT (90 s). For the binocular LCLA (1.25% contrast) charts, the number of letters identified correctly (maximum 70) was recorded. Each functional test was compared between MS subjects and disease-free controls using logistic regression. The analyses were repeated adjusting for age (and height for the T25FW). Z-scores were also created for the MS patients on each performance measures using the data from the disease-free controls as the reference population; Z-scores in this study represent the standard deviation from the control group mean.

Composite Z-scores were also created to allow for comparisons of combinations of tests with regard to capacity to distinguish MS patients vs. controls, although we acknowledge that the composite Z-score is less widely used than perhaps originally anticipated. The composite Z-scores for each patient were calculated using the