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Capturing saccades in multiple sclerosis with a digitized test of rapid number naming

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Abstract

The King–Devick (K–D) test of rapid number naming is a visual performance measure that captures saccadic eye movements. Patients with multiple sclerosis (MS) have slowed K–D test times associated with neurologic disability and reduced quality of life. We assessed eye movements during the K–D test to identify characteristics associated with slowed times. Participants performed a computerized K–D test with video-oculography. The 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) and its 10-Item Neuro-Ophthalmic Supplement measured vision-specific quality of life (VSQOL). Among 25 participants with MS (age 37 ± 10 years, range 20–59) and 42 controls (age 33 ± 9 years, range 19–54), MS was associated with significantly longer (worse) K–D times (58.2 ± 19.8 vs. 43.8 ± 8.6 s, $P = 0.001$, linear regression models, accounting for age). In MS, test times were slower among patients with

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Compliance with ethical standards

Ethical standards This human study has been approved by the appropriate ethics committee and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest No author has received any financial compensation or consultant fees from King Devick Test, Inc. No author has other disclosures pertinent to this study.

higher (worse) Expanded Disability Status Scale scores ($P=0.01$). Average inter-saccadic intervals (ISI) were significantly longer in MS participants compared to controls (362 ± 103 vs. 286 ± 50 ms, $P=0.001$), and were highly associated with prolonged K–D times in MS ($P=0.006$). MS participants generated greater numbers of saccades ($P=0.007$). VSQOL scores were reduced in MS patients with longer (worse) K–D times ($P=0.04$ – 0.001) and longer ISI ($P=0.002$ – 0.001). Patients with MS have slowed K–D times that may be attributable to prolonged ISI and greater numbers of saccades. The K–D test and its requisite eye movements capture VSQOL and make rapid number naming a strong candidate efferent visual performance measure in MS.

Keywords

Multiple sclerosis; King–Devick Test; Rapid number naming; Saccades; Inter-saccadic Interval

Introduction

Neuro-ophthalmic manifestations are common in multiple sclerosis (MS) [1]. Involvement of the afferent visual pathways is well recognized in the form of optic neuritis (ON), which represents the first demyelinating event in 20% of cases and occurs at some point during the course of disease in 50–75% of patients [1–5]. Acute ON is associated with spontaneous improvement, with high contrast visual acuity improving to 20/40 or better in greater than 90% of patients [6]. However, even in the setting of what is said to be ‘good recovery’, clinically meaningful reductions in vision-specific quality of life, visual function and thinning of the retinal nerve fiber and ganglion cell layers of the retina have been demonstrated [7, 8]. Such afferent visual deficits also occur frequently in the absence of acute ON, representing a sub-clinical involvement of the visual pathway [9].

Ocular motor abnormalities are also frequent in MS, and often occur subclinically. Found in 24–84% of patients [10–12], ocular motor deficits result in lower scores for vision-specific quality of life [11]. Efferent manifestations are often chronic and persistent [13], including saccadic dysmetria, internuclear ophthalmoplegia (INO), ocular motor cranial nerve palsies, disorders of the vestibulo-ocular reflex (VOR), pathologic gaze-evoked nystagmus, and acquired nystagmus in central gaze position [10, 13, 14]. Saccadic dysmetria is found in as many as 91% of patients and includes those without overt visual symptomatology [10].

Though performance measures, such as low-contrast letter acuity for afferent vision, are commonly used in MS in clinical practice and as outcome measures in clinical trials, there are currently no widely utilized performance measures that capture efferent visual dysfunction in MS. The King–Devick (K–D) test is a rapid number naming task that has been validated as a sensitive performance measure for sideline detection of concussion [15–18]. The K–D test is a simple visual-verbal task that requires saccades and interleaved fixations. In patients with MS, K–D test times have been shown to be prolonged, i.e., a slowing of the time required to name the numbers on the test cards [19]. The purpose of this investigation was to determine the eye movement characteristics that underlie prolonged K–D test times for rapid number naming in MS using infrared video-oculography. We also

sought to examine how K–D scores (test times and number of errors) and eye movement measures relate to vision-specific quality of life and neurologic impairment.

Methods

Study participants

A convenience sample of participants with MS was recruited during new or established patient visits at the Comprehensive MS Care Center at NYU. Patients were not invited based on particular clinical features, extent of disease, or presence of symptoms. As appropriate for clinical diagnosis at the MS Center, the diagnosis was confirmed by standard clinical and neuroimaging criteria [20]. Patients with comorbid ophthalmic disease unrelated to MS, with exception of corrected refractive error allowing for clear visualization of K–D test cards, were excluded from the study. MS disease duration, current disease-modifying therapies, history of optic neuritis (ON) in either eye, presence of ocular motor findings on examination, and presence of brainstem or cerebellar white matter lesions on MRI were ascertained at the study visit and by chart review. The Expanded Disability Status Scale (EDSS) was performed by a single study investigator using standard methodology (CH). Disease-free control participants were recruited from among NYU staff or friends and relatives of patients; some participants in both the MS and control groups are part of an ongoing longitudinal collaborative study of visual outcomes in MS. Written informed consent was obtained from each participant and all study protocols were approved by the NYU School of Medicine Institutional Review Board (IRB).

Vision-specific quality of life questionnaires

The 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) was administered using established scoring methods [21, 22]. A 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ- 25 was also administered; this scale was designed to target aspects of vision not captured by the NEI-VFQ-25 in patients with MS [23].

Infrared oculographic eye movement recordings

All MS and control participants completed a 13-point spatial calibration procedure, followed by one trial of reading three computer-generated K–D test cards (Fig. 1a) while undergoing eye movement recording using infrared video-oculography (Eyelink 1000+, SR Research, Ontario Canada). The system recorded binocularly with a sampling frequency of 500 Hz and a spatial accuracy of approximately 0.5°. Eye movement data were analyzed off-line using custom Matlab software. Data between card presentations were automatically identified for exclusion and manually confirmed, and data within 100 ms of a blink were excluded. During the recording, participants were asked to read the K–D numbers aloud as quickly as possible from the three test cards projected on a computer screen in sequential order; the total test time constituted the summary score.

Total K–D test times and numbers of errors were recorded. Analyses of saccade velocity, acceleration, amplitude, duration, spatial accuracy, and associations between these measures were completed for two sets of saccades (for all saccades performed, and for ‘task-specific’ saccades required for specifically naming the K–D numbers). Task-specific saccades

included those required to progress from one number to the next (defined as saccades with a horizontal amplitude of at least 2°) and oblique saccades representing the transition between lines during reading (defined as a horizontal amplitude of at least 10° and a vertical amplitude of at least 0.5°, Fig. 1b). Intersaccadic intervals (ISI), defined as the time between task-specific saccades and incorporating both fixation duration and saccade latency, were also analyzed. The median ISI was determined for each individual participant for all task-specific saccades across the three test cards. Median ISI were averaged across participants, due to substantial positive skew in the distribution of these values for all participants. The mean ISI from all of these, however, fit assumptions for an underlying normal distribution and, therefore, the mean was reported. The full methodology for K–D eye movement analysis and recording procedures has been described in detail and was applied in this investigation [24].

Statistical analyses

The capacity for MS vs. control group status of participants to predict K–D total test time, ISI, numbers of saccades, and vision-specific quality of life scale scores was determined using linear regression models, accounting simultaneously for age. These models were used since there was age imbalance between the two groups of participants in this convenience sample. Linear regression techniques were also used to examine associations of K–D test time with saccade measures and other factors in the study.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics for patients with MS and disease-free control participants are presented in Table 1. These investigations included 25 participants with MS (age 37 ± 10 years, range 20–59, 72% women) and 42 disease-free controls (age 33 ± 9 years, range 19–54, 71% women). Ten participants with MS had ocular motor abnormalities noted on clinical examination by a neuro-ophthalmologist, and ten had a history of acute optic neuritis (ON). All but one patient was classified in the clinical study record as having relapsing-remitting MS (RRMS). The single patient with secondary-progressive MS (SPMS) had a K–D test time of 70.3 s (greater than the overall MS mean of 58.2 s, but well within the overall MS cohort range of 34.7–117.8 s). In terms of clinical findings, the patient with SPMS had a history of ON, gaze-evoked nystagmus, and impaired smooth pursuit, similar to several other patients with a RRMS phenotype.

Scores for the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25), and 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 were reduced in patients with MS ($P < 0.001$ for both scales, linear regression models accounting for age) (Table 1; Fig. 2). These scores were also reduced among patients with MS who had longer (worse) K–D test times ($P = 0.04$ – 0.001) and longer inter-saccadic intervals (ISI) ($P = 0.002$ – 0.001).

King–Devick (K–D) test measures

MS was associated with significantly longer (worse) K–D test times (58.2 ± 19.8 vs. 43.8 ± 8.6 s, $P = 0.001$, linear regression models, accounting for age) (Table 2; Fig. 2). In MS, reading times were slower among patients with higher (worse) EDSS scores ($P = 0.01$, accounting for age).

Number naming errors on the K–D test were a median of 0 for both the MS and control cohorts. One patient with MS skipped a line of five numbers, and another incurred five separate number naming errors. The latter patient had a long MS disease duration and an extensive neuro-ophthalmic history (33-year history of RRMS, an EDSS score of 6.5, gaze-evoked nystagmus on examination and a history of bilateral ON).

Eye movement analyses

There were differences between MS participants and controls for average saccadic peak velocity, acceleration, and deceleration for task-specific saccades (Table 2). However, these differences are not meaningful for further analysis, as saccadic peak velocity, acceleration, and deceleration physiologically vary by saccade amplitude and cannot be assessed in aggregate. A more standard method of assessment, called the main sequence analysis, takes saccade amplitude into consideration and plots relationships between saccade amplitude and peak velocity and between saccade amplitude and duration. These main sequence plots were similar for MS participants and controls for task-specific saccades (Figure C— online only).

Average inter-saccadic intervals (ISI) for task-specific saccades were significantly longer in MS participants compared to controls (362 ± 103 vs. 286 ± 50 ms, $P = 0.001$) and were highly associated with prolonged reading times in MS ($P = 0.006$, accounting for age). MS participants also required greater numbers of overall saccades during the K–D task ($P = 0.007$), but task-specific saccade numbers were similar between the two groups ($P = 0.05$, accounting for age).

There were no significant differences in percentages of wrong directional saccades (i.e. right to left) for MS participants vs. disease-free controls (Table 2). Patients with MS did have larger numbers of saccades under the 2-degree task-specific cut-off.

Discussion

Results of this investigation demonstrate that MS is associated with prolonged test completion times for the K–D test of rapid number naming when digitized for infrared video-oculography. Such slowing of K–D test times is associated with longer ISI and increased overall numbers of saccades during the examination, suggesting a potential role for both eye movement and attention-related mechanisms. Importantly, prolonged K–D test times and ISI also reflected worse vision-specific quality of life among MS participants. Eye movement abnormalities with electronic recordings showed the above abnormalities in MS even in the absence of clinically evident findings such as internuclear ophthalmoparesis.

A previous study by Moster et al. first showed that prolonged total K–D testing times in MS, assessed using the printed performance measure test cards only, were associated with

reduced binocular low- and high-contrast letter acuity, history of acute ON in either eye, and retinal nerve fiber layer (RNFL) thinning as measured by optical coherence tomography (OCT) [19]. The present study adds significantly to the MS vision literature by including direct quantified objective assessment of ocular motor measurements during the K–D test. This serves to further elucidate ocular motor patterns underlying slowing of K–D test performance in MS.

Saccade characteristics

In this study, the relation between saccade amplitude and peak velocity and between saccade amplitude and duration revealed no differences between our heterogeneous cohort of MS participants vs. disease-free control participants. The common MS clinical eye movement sign of inter-nuclear ophthalmoplegia (INO), characterized by adduction slowing in the affected eye [25], occurs at some point in 17–68% of patients [10–12, 26]. In the present study, only three participants (12%) were clinically documented to have an INO, with two of the three patients having bilateral INO. While patients with MS may also rarely have ocular motor nerve palsies, such as 6th nerve palsy [27], or supranuclear gaze palsies that result in slowing of saccades, no patient in our study had these clinical findings. The number of patients with INO in this study was too small for specific sub-stratified analyses investigating the capacity of the K–D test to identify individuals with INO; however, assessment of this aspect of the K–D and other visual performance tests will be of interest in future studies.

Inter-saccadic intervals (ISI)

Traditionally, saccade latency or reaction time is defined as the interval between a visual stimulus being presented and the initiation of a saccade [28]. In the standard spiral-bound card and in our digitized version of the K–D test, all numbers are displayed simultaneously for each card. Thus, true saccadic latency cannot be determined in this paradigm. The ISI, which is a measure of time between saccades, is a composite of saccade latency and other parameters, such as duration of time in fixation for each number [24, 29]. One of the most notable results of this study was the prolongation of the ISI, which contributed substantially to K–D total test time lengthening. This was illustrated by the associations between prolonged ISI duration and increased K–D test times within the MS cohort, accounting for age. We cannot determine in this study if the ISI prolongation during K–D testing in MS is due to prolonged saccadic latency or excessive fixation, or if both contribute. However, we hypothesize that both of these factors have a role in increasing K–D test times.

Saccade paradigms that require a higher cognitive load and increased attention, such as anti-saccades (instruction to participant is to look in the opposite direction to a flashed target) and memory-guided saccades (saccade is made to the remembered location of a previously present target), have been shown to have prolonged latencies in patients with MS compared to controls [30]. Though a simplification, there are generally two main categories of saccades: (1) reflexive saccades to fixate a suddenly appearing object of interest, which originate in the parietal lobe; and (2) those that require more of a cognitive demand to perform, for which frontal lobe circuits (including the frontal eye fields and dorsolateral prefrontal cortex) are critical [31]. The saccades required to perform the K–D test are likely

more similar to the higher cognitively loaded saccades. Shifting attention from one target to the next in the context of scene viewing and reading is a three-step process, requiring disengagement from the initial target, moving attention to the next target, and finally engaging the new target. Thus, it is reasonable to hypothesize that saccadic latency during K–D performance could be prolonged in MS.

In addition to saccadic latency, the ISI incorporates fixation time; thus, attentional and cognitive factors mediating the flow of information are required to facilitate task completion. MS is known to cause cognitive deficits in up to 40–60% of adult patients [32], even early in the disease. Affected domains include information processing speed, attention, memory, and executive functions [33]. Of these, delayed information processing is one of the most commonly observed deficits [34–36]. Further, while language skills are often relatively intact in MS, deficits of rapid retrieval are common, as they are highly dependent on processing speed [37]. Interestingly, poor patient performance on the Paced Auditory Serial Addition Task (PASAT, a neuropsychological inhibition task) in MS patients has been significantly associated with prolonged latencies of cognitively demanding saccade eye movement tasks [30].

Another factor for consideration in prolongation of the ISI is fatigue. Fatigue is one of the most frequent symptoms in MS, reported in 65–95% of adult patients with MS [38–41]. While fatigue may overlap with mood disturbance and cognitive dysfunction, it can also occur independently [42, 43]. While studies of the K–D test in athletes having sustained concussion have shown no change in test performance after exercise or fatigue alone [15], the neurobiology of MS-related fatigue is likely mechanistically different. For example, a study that involved a repetitive saccade task in MS patients found that saccadic latencies were significantly longer in fatigued vs. non-fatigued patients. Furthermore, fatigued MS patients had a significantly decreased saccade peak velocity and amplitude compared to non-fatigued MS patients [44]. We hypothesize that ISI prolongation in MS is multifactorial, with contributions from increased saccade latency and other eye movement abnormalities, cognitive factors and fatigue. Future studies will be required to assess the relative contributions of each of these entities to abnormal K–D performance and ISI prolongation in MS.

Saccade frequency

Though there was no significant difference in task-specific saccade numbers between MS participants and disease-free controls, our MS participants demonstrated greater numbers of saccades overall, specifically those smaller than 2°, to complete the K–D test. We also found the average amplitude of saccades to be smaller in the MS cohort (Table 2). Completing saccades in smaller steps could possibly allow a sequential direction of gaze towards the visual goal, thus, deconstructing the task into smaller and simpler components. The additional saccades in MS patients may also reflect saccadic dysmetria and the need for corrective saccades.

Vision-specific quality of life, EDSS, and K–D correlations

In this study, vision-specific quality of life was reduced in MS patients with longer (worse) K–D test times and longer ISI. Prolonged K–D times were also associated with higher (worse) EDSS scores for MS disability. Abnormal eye movements due to brainstem and cerebellar disease have been shown to be predictive of a worse prognosis in MS [13] and to correlate with increasing EDSS and walking disability [10, 14]. These findings are likely due to the fact that posterior fossa abnormalities are more common in patients with abnormal eye movements, as well as in patients with more severe gait impairment [13]. Infratentorial lesions in MS also predict future disability [45].

In contrast to the above, EDSS scores did not correlate with saccade measures of higher order, cortically driven saccade tasks [30]. These results reflect an overall limitation of the EDSS, in that it may not effectively and comprehensively assess the full spectrum of vision-related deficits. Importantly, many of the abnormal eye movements seen in MS are not scored as part of the EDSS, including phorias of the visual axes not appreciated on motility examination, saccadic dysmetria, subtle INOs, impaired smooth pursuit, impaired VOR, and impaired vergence [10].

Despite a significant association of longer K–D total test times to worse EDSS scores in our study, it is worthwhile to note that, given the categorical nature of the EDSS, a few patients with higher levels of disability may be driving this observation. However, the participant with the highest K–D time (117.8 s) was a 20-year-old with a relatively low EDSS score (3.0) and no afferent or efferent visual dysfunction. He had been diagnosed with MS at age 4 (disease duration 16 years). His ISI was much higher (566 ms) than the average MS cohort average (362 ms) and likely drove his prolonged K–D time. A second participant with a long K–D time had EDSS 6.5 and a K–D time of 86.6 s with five errors had disease duration of 33 years, history of bilateral optic neuritis, impaired smooth pursuit and pathologic gaze-evoked nystagmus. A third participant had EDSS 6.5 and a K–D time of 77.3 s with disease duration 21 years, history of unilateral optic neuritis, unilateral INO, impaired smooth pursuit and pathologic gaze-evoked nystagmus. The fourth participant with a very long K–D time had EDSS 5 and a K–D time of 96.7 s with disease duration 16 years, history of unilateral optic neuritis, and impaired smooth pursuit. Notably, all four of these patients had brainstem or cerebellar lesions on MRI.

Conclusions

Despite a growing literature on the neuro-ophthalmic manifestations of MS, there are no widely utilized simple performance measures that capture the efferent visual system. Scores for the K–D test are associated with vision-specific quality of life and overall disability. We report objective eye movement findings in MS patients during performance of the K–D test that account for prolonged K–D test times, including prolonged ISI values and higher overall number of saccades. The K–D test is an easy to administer, rapid test that may prove to be a helpful performance measure of visual disability; this is analogous to the concept that the timed 25-foot walk is a performance measure that broadly captures aspects of gait performance and mobility in MS. The K–D test is an ideal candidate for future prospective

studies and ideally, the K–D test or similar rapid performance measures [46] could be used longitudinally in the clinical setting and in future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

a Demonstration and test cards for the King–Devick (K–D) test (implemented in a digital paradigm for these investigations). To perform the K–D test, participants are asked to read the numbers on each card from *left to right* as quickly as possible without making errors. The *upper left* shows the demonstration card. Participants are asked to read each of the three test cards in the same manner as the demonstration. The times required to complete each card are recorded in seconds. The sum of the three test card time scores constitutes the summary score for the entire test, the K–D time score. Numbers of errors made in reading the test cards are also recorded; mis-speaks on numbers are recorded as errors only if the

subject does not immediately correct the mistake before going on to the next number [47]. **b** Demonstration of eye tracking tracings of saccades and fixations overlaid on K–D test cards for a representative control participant. *Purple lines* represent ‘task-specific’ horizontal and oblique saccades and *orange circles* represent fixations

Fig. 2.

Box plots demonstrating average scores for **a** King–Devick (K–D) total test time and **b** 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) in patients with MS vs. disease-free controls. The *horizontal lines* in the *box* represent the medians, and *boxes* delineate the interquartile range (25th–75th percentiles). *Whiskers* represent the range of observations (represented as *circles*). *P* values are based on linear regression models, accounting for age

Table 1

Demographic and clinical characteristics of study participants

	Patients with multiple sclerosis (MS) (n = 25)	Disease-free control participants (n = 42)
Age [years]	37 ± 10 (20–59)	33 ± 9 (19–54)
Sex [n, % women]	18 (72%)	30 (71%)
MS subtype [relapsing-remitting, %]	24 (96%)	
NEI-VFQ-25 composite score [maximum 100]	83 ± 16 (43–100)	96 ± 6 (69–100)
10-Item Neuro-Ophthalmic Supplement score [maximum 100]	76 ± 20 (73–100)	93 ± 7 (73–100)
Expanded Disability Status Scale (EDSS) score	2.0 (0–6.5)	
MS disease duration [years]	8 (1–33)	
Brainstem or cerebellar MRI lesions [n, % of patients]	18 (72%)	
History of optic neuritis (ON) [n, % of patients]	10 (40%)	
Ocular motor findings on examination [n, %]	10 (40%)	
Internuclear ophthalmoparesis [n, %]	3 (12%) (two manifest bilaterally)	
Misalignment of visual axes [n, %]	2 (8%) (both 6th nerve palsy)	
Gaze-evoked nystagmus [n, %]	4 (16%)	
Nystagmus in central position [n, %]	2 (8%) (one downbeat, one upbeat)	
Smooth pursuit impaired [n, %]	8 (32%)	

NEI-VFQ-25 25 Item National Eye Institute Visual Functioning Questionnaire, *10-Item Supplement* 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25

Table 2

Saccade and intersaccadic interval data for study participants

	Patients with multiple sclerosis (MS) (<i>n</i> = 25)	Disease-free control participants (<i>n</i> = 42)
Saccade numbers		
Numbers of all saccades	164 ± 47	138 ± 18
Numbers of K–D saccades	137 ± 29	124 ± 15
Wrong direction saccade percentage (%)	14%	10%
Temporal measures		
Total King–Devick (K–D) test time [s]	58.2 ± 19.8	43.8 ± 8.6
K–D card 1 time [s]	18.5 ± 5.5	14.3 ± 2.9
K–D card 2 time [s]	19.1 ± 6.2	14.4 ± 2.7
K–D card 3 time [s]	20.6 ± 8.5	15.1 ± 3.3
Duration [ms]	34.5 ± 5.7	32.0 ± 4.0
Peak velocity [°/s]	299.8 ± 57.4	341.6 ± 49.7
Peak acceleration [°/s]	33,568.0 ± 8350.8	38,754.0 ± 6881.6
Peak deceleration [°/s]	28,987.2 ± 6059.5	32,828.7 ± 5659.5
Intersaccadic interval [°/s]	362 ± 101.7	286 ± 49.7
Spatial measures		
Amplitude [°]	7.8 ± 1.1	8.5 ± 0.9
Distance [°]	1.1 ± 0.2	1.0 ± 0.3
X error [°]	0.1 ± 0.3	0.1 ± 0.3
Y error [°]	0.0 ± 0.2	0.1 ± 0.2