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Objective characterization of the relative afferent pupillary defect in MS

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ABSTRACT

Objective: To develop an objective and precise neurophysiologic method from which to identify and characterize the presence and magnitude of relative afferent pupillary defects (RAPD) in patients with MS.
Methods: Binocular infrared pupillometry was performed in 40 control subjects and 32 MS patients with RAPDs, using two precisely defined sequences of alternating light flashes (right–left and left–right). We analyzed three distinct pupillary metrics in response to light stimulation. These included percent diameter change (DC), constriction curve area (CCA), which measures change in diameter over time, and the phase-plane curve area (PCA) which measures change in diameter with change in velocity. Direct and consensual response ratios (for each eye) were computed and analyzed for each metric in response to both the first flash (i.e. first phase) and second flash (i.e. second phase) of the 'swinging flashlight' test.
Results: Second flash pupillary response metric asymmetry ratios yielded the highest discriminatory power for RAPD detection. Receiver operating characteristic areas under the curve for each of the pupillary metric response asymmetry ratios were as follows: diameter change: 0.97; constriction curve area: 0.96; phase-plane curve area: 0.95 ($p<0.0001$ for all comparisons compared to normal subjects). The sum of these three squared ratios (SSR) yielded a combined metric with the greatest discriminatory power (receiver operator characteristic area under the curve = 0.99).
Conclusions: Second flash (i.e. the second phase of the swinging light test) pupillary metric response asymmetry ratios are highly sensitive and specific for the confirmation and characterization of an RAPD in patients with MS. This objective neurophysiologic method may be useful for studying the relationship between a stereotyped reflex, and nervous system architecture, with potential ramifications for detecting and monitoring neuroprotective and restorative effects of novel agents in MS treatment trials.

1. Introduction

Pupillary testing is perhaps the most important bedside examination technique in suspected acute optic neuritis [1,2]. Initially, each pupil is illuminated individually and the constriction responses are evaluated and compared. The affected side in unilateral acute optic neuritis will usually reveal a diminished pupillary response to direct illumination, indicating altered afferent transmission along the optic nerve, but a normal consensual response in the affected eye upon illumination of the contralateral eye, signifying an intact efferent response on the side of the acute optic neuritis. Then the swinging flashlight test is employed where illumination of the normal eye results in brisk direct and consensual pupillary responses, whereas swinging the light to the affected eye results in either dilation (i.e. pupillary escape from constriction) of both pupils, or a brief period of constriction followed by dilation; confirming the presence of a relative afferent pupillary defect (RAPD). The strength of the RAPD can be semi-quantitatively characterized (as log units) at the bedside using neutral density light filters placed in front of the healthy or less affected eye, and adjusting the light transmittance via changes in the filter, until the abnormal eye responds identically to a direct and consensual response [3]. In general, an RAPD should be present in acute optic neuritis, on the affected side, unless there is commensurate involvement of the fellow eye [4,5]. Post-chiasmal lesions can be associated with an RAPD, generally on the side of greater visual field loss. In particular, when contralateral to a tract lesion, the

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greater crossing of pupillary light reflex fibers in the chiasm, than those that remain homolateral in the optic tract, has been proposed as an etiologic mechanism [2,6,7]. The pathophysiology of the RAPD results from slowed or blocked transmission of light information to the pretectal olivary nucleus, leading to delayed and/or reduced activation of the Edinger and Westphal parasympathetic nuclei on both sides of the midbrain tegmentum [6].

Kardon and colleagues have demonstrated that computerized infrared pupillometry methods can provide objective parameters for the purpose of standardizing the swinging flashlight test, and to optimize the accuracy of detecting and quantifying the RAPD [8,9]. The application of pupillometry has facilitated the diagnosis of optic neuropathy associated with glaucoma, where measurements of pupil area amplitude have been found to exhibit greater diagnostic utility when compared to constriction velocity [10]. Additionally, a significant correlation has been confirmed between retinal ganglion cell loss, and the presence of an RAPD in patients with unilateral involvement of the optic nerve [11]. In quantifying the relationship between retinal nerve fiber layer degeneration and the development of an RAPD, studies in rhesus monkeys have shown that the pupillary defect does not occur until about 25 to 50% of retinal ganglion cell neurons have degenerated [12].

The goal of this study was to develop an objective, sensitive and highly specific method to identify and characterize the magnitude of RAPDs in MS patients, when compared to the gold standard bedside neurological examination, the swinging flashlight test. The development of highly precise pupillary metrics may facilitate the study of structure–function relationships in the visual system of MS and related disorders such as neuromyelitis optica (NMO). Further, in conjunction with low contrast letter acuity and sensitivity, optical coherence tomography, multifocal visual evoked potentials, and multifocal electroretinography, sophisticated pupillometry testing may advance our ability to detect and monitor the therapeutic properties of putative protective and restorative agents in treatment trials.

2. Methods

2.1. Study subjects

We studied the pupillary responses of 40 control subjects (mean age 35.08 ± 9.74 years; 68% female), as well as 32 MS patients (mean age; 43.51 ± 9.66 years; 84% female). All MS patients were confirmed to have experienced an attack of unilateral optic neuritis within 6 months of testing, and bedside examination revealed a corresponding RAPD on the affected side (all confirmed by a single examiner; EMF). Subjects were between 18 and 65 years of age, were recruited from the Clinical Center for Multiple Sclerosis at the University of Texas Southwestern Medical Center at Dallas, and had no evidence of other ophthalmologic conditions. All participants provided informed and written consent prior to the beginning of study procedures. Consent was obtained according to the Declaration of Helsinki (BMJ 1991; 302: 1194). The protocol was approved by the Investigational Review Board of the University of Texas Southwestern Medical Center.

2.2. Protocol

Pupil metrics were measured using an infrared, binocular pupillometry device (NeurOptics, Santa Barbara, California). Two distinct protocols were used. Each protocol consisted of two consecutive monocular white light flashes of 14 μW intensity that were 2000 ms in stimulus duration, with a 250 ms gap latency between stimuli (i.e., during the stimulus transition or 'swing' phase of the simulated swinging flashlight test). One protocol presented the first flash stimulus to the right eye and the second flash stimulus to the left eye, while the other protocol reversed this sequence. We were specifically interested in analyzing the differences in pupil metrics when the RAPD eye was illuminated with the first flash versus the second flash of the infrared pupillography paradigm of the swinging flashlight test.

Our objective was to design a stimulation sequence that would mimic the clinical gold standard bedside swinging flashlight test, but with well-defined and highly precise stimulus characteristics, capable of provoking stereotyped and reproducible responses. While the stimuli were delivered monocularly, direct and consensual pupillary responses were recorded binocularly and simultaneously with infrared pupillometry, at a sampling rate of 30 Hz.

All testing was performed under uniform dark conditions, following 10 min of dark adaptation. Each protocol sequence was repeated seven times, and the mean values for the pupillary metrics were obtained. We analyzed the pupillary response metrics of the two eyes and developed asymmetry ratios (i.e. we compared the pupillary responses between the two protocols). For each eye, this included the usual first-flash (i.e. first phase) metrics of change in pupillary diameter (percent), and maximum constriction velocity, as well as the newly elucidated second-flash (i.e. the second phase of the swinging flashlight test) asymmetry ratios (AR) for pupillary diameter change (DC-AR), the constriction curve area (CCA-AR), which measures change in diameter over time, the phase-plane curve area (PCA-AR), which measures the change in diameter with the change in velocity, independent of time, and constriction velocity maximum (CVM-AR).

2.3. Data analyses

Statistical analysis of the data consisted of utilizing receiver operating characteristic (ROC) curves for the asymmetry ratios, depending upon pupillary responses to the first versus the second illumination stimulus. These curves plot the true-positive rate (sensitivity) on the y-axis and the false-positive rate (specificity) on the x-axis, as the cutoff threshold is varied for the measurement being examined. The area under each ROC curve was calculated for each pupil metric to identify the predictive strength of each pupil metric in detecting an RAPD. The area under the curve (AUC) indicates the strength of the test and will range from 0.5 (non-discriminatory) to 1.0 (perfect discrimination). The optimal cutoff points for each variable were chosen so that the false-positive rate did not exceed 0.05, ensuring that a type II error was present no more than 5% of the time. The application of a phase-plane analysis strategy (PCA-AR) as defined earlier, was also employed in order to develop normal and pathophysiologic pupillometry signatures of the RAPD. All values are reported as means ± SD.

3. Results

3.1. Swinging flashlight test

We investigated the metrics of constriction and pupillary dilation in both normal subjects [Fig. 1], and in MS patients who had an RAPD [Fig. 2]. The first half of the waveform corresponds to the pupillary reflex in response to the direct first flash stimulus. The consensual second flash stimulus of the swinging flashlight test generates analogous transmission properties and measured metrics, as the light is transitioned to the opposite side [Figs. 1 and 2].

The two protocols – each with a different stimulus sequence (left–right and right–left) – elicited similar responses from the control subjects, as shown in Fig. 1. However, in MS patients with an RAPD, there were distinctive differences between these two protocols with respect to the direct and consensual responses [Fig. 2]. Specifically, when the first phase of the swinging flashlight test illuminated the affected eye, we observed a reduced direct and consensual pupillary response when compared to the responses elicited when the first phase of the test illuminated the normal (or less affected) eye. During the swinging flashlight test, when the abnormal eye was illuminated