Color Visual Evoked Potentials in Children with Type 1 Diabetes: Relationship to Metabolic Control

Yesmino T. Elia,[1,2] *Denis Daneman,*[2,3,4] *Joanne Rovet,*[2,4,5,6] *Mohamed Abdolell,*[7] *Wai-Ching Lam,*[1] *Christine Till,*[5,6] *Vasudha Erraguntla,*[1] *Shehla Rubab,*[1] *Nidhi Lodha,*[1,2] *and Carol A. Westall*[1,2,6]

Purpose. To examine the association between metabolic control (HbA_{1c}) and the chromatic mechanisms of children with type 1 diabetes (T1D), by using the color visual evoked potential (VEP).

Methods. Fifty children with T1D (age range, 6–12.9 years) and 33 age-matched control subjects were tested. VEPs were recorded by placing five electrodes on the scalp according to the International 10/20 System of Electrode Placement. Active electrodes O1, O2, and Oz were placed over the visual cortex. Short-wavelength (S), and long- and medium-wavelength (LM) color stimuli consisted of vertical, photometric isoluminant (1 cyc/deg) gratings presented in a pattern onset (100 ms)– offset (400 ms) mode. Achromatic vertical gratings were presented at 3 cyc/deg. Primary outcome measure was VEP latency. The relationship between S, LM, and achromatic VEP latency, and HbA_{1c} was determined by ANCOVA regression.

Results. S-, LM-, achromatic VEP latencies were not associated significantly with HbA_{1c}. Pubertal status, however, was associated significantly ($P = 0.0114$) and selectively with S-VEP latency. Pubertal children with T1D had delayed (mean delay, 9.5 ms) S-VEP latencies when compared with the prepubertal children with T1D. However, there was no statistically significant difference ($P = 0.1573$) in the effect of pubertal status on S-VEP latency between the T1D and control groups.

Conclusions. Pubertal status rather than HbA_{1c} appears to affect selectively the S-VEP latency of preteen children with T1D. Further study is warranted to determine whether the delay in S-VEP latency in pubertal children with T1D changes over time and whether this change could be a predictive marker for future development of background diabetic retinopathy. (*Invest Ophthalmol Vis Sci.* 2005;46:4107–4113) DOI:10.1167/iovs.05-0178

From the Departments of [1]Ophthalmology and Vision Sciences and [5]Psychology, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada; the [3]Division of Endocrinology and the [6]Brain and Behavior Program, The Hospital for Sick Children, Toronto, Ontario, Canada; and the [2]Institute of Medical Sciences, and the Departments of [4]Pediatrics and [7]Public Health Sciences, University of Toronto, Toronto, Ontario, Canada.

Supported by The Hospital for Sick Children Research Institute Trainees Start-up Fund; the University of Toronto Vision Science Research Program; and the University of Toronto Fellowship, School of Graduate Studies.

Submitted for publication February 10, 2005; revised April 15, 2005; accepted April 26, 2005.

Disclosure: **Y.T. Elia**, None; **D. Daneman**, None; **J. Rovet**, None; **M. Abdolell**, None; **W.-C. Lam**, None; **C. Till**, None; **V. Erraguntla**, None; **S. Rubab**, None; **N. Lodha**, None; **C.A. Westall**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Carol A. Westall, Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, 555 University Avenue, Toronto ON M5G 1X8, Canada; carol@sickkids.ca.

Diabetic retinopathy is one of the long-term microvascular complications of diabetes and a major source of morbidity, causing vision impairment and blindness. In the United States, diabetes is responsible for 8% of legal blindness, making it the leading cause of new cases of blindness in adults aged 20 to 74 years.[1] Each year, approximately 12,000 to 24,000 U.S. residents[1] and 400 Canadians[2] become blind as a result of diabetes. As such, one of the primary goals of managing children with type 1 diabetes (T1D) is to avoid the future risk of diabetic retinopathy by maintaining blood glucose levels close to the normal range.[2] The Diabetes Control and Complications Trial[3] used fundus photography to examine the retinal vasculature of adolescents with T1D (age range, 13–17 years) and demonstrated a close relationship between metabolic (blood glucose or HbA_{1c} levels) control and the onset and progression of retinopathy. Those in the intensive treatment group who maintained good blood glucose control (low HbA_{1c} levels) showed a 53% decreased risk of the development of diabetic retinopathy when compared with the conventionally treated group, whose HbA_{1c} levels were higher.[3]

Before the onset of the microvascular lesions of diabetic retinopathy, the neural retina of the diabetic eye undergoes subtle functional changes that are undetectable by fundus photography.[4–6] However, electrophysiologic techniques have served to detect early neuroretinal functional changes that occur in T1D.[7] For instance, prepubescent children with T1D and no sign of diabetic retinopathy show significantly reduced focal ERG responses compared with control subjects.[8] These findings suggest that diabetes has an early and selective effect on the neural retina before the appearance of microvascular complications.

One functional change previously shown to precede the appearance of overt retinopathy, one that may reflect early neuroretinal dysfunction in T1D, is a change in color vision.[6,7] Color vision is a central or foveal function that may be impaired by any retinal disease that affects the neural retina[9] or the neural pathway to the visual cortex.[6,10,11] Specifically, a change or deficit in the short-wavelength chromatic pathway that is responsible for blue–yellow color discrimination has been described in both adults[7,9,10,12–16] and adolescents[16–20] with T1D who have no evidence of retinopathy. More important, the short-wavelength deficit found in adults with T1D is associated with elevated long-term glucose control or HbA_{1c} levels[21–23] and elevated short-term ambient blood glucose levels (blood glucose levels at time of color vision testing).[11,24]

The color visual evoked potential (VEP), which assesses the integrity of the neural pathways responsible for color vision, is a useful electrophysiologic indicator of early color vision changes in T1D.[10,11] Crognale et al.[10] demonstrated that the latency of the short-wavelength (S)-VEP response of adults with T1D is delayed compared with that of control subjects, whereas Schneck et al.[11] observed in adults with T1D that the delay in S-VEP latency is associated with an increase in ambient blood glucose levels.

The purpose of the present study was to examine the association between long-term metabolic control or HbA_{1c}

levels and the chromatic mechanisms in preteen children with T1D, by using the color VEP technique. The latency of the color VEP was the primary outcome measure of the study.

METHODS

Subjects

Fifty children with T1D were recruited from the Diabetes Clinic at The Hospital for Sick Children (Sick Kids) in Toronto, Canada and 44 met the inclusion criteria. Inclusion criteria were diagnosis of T1D, age between 6 and 12.9 years (mean, 9.1 ± 1.9 [SD]), and duration of diabetes between 1 and 7 years (mean, 3.6 ± 2.1). Exclusion criteria were background diabetic retinopathy (BDR), hemoglobinopathy, inherited or acquired color defects or ocular abnormalities, and any medication or medical condition that affects the retina. Thirty-three age-matched typically developed children or control subjects (mean age, 9.1 ± 1.8 years) were also recruited, to permit exploratory data analysis.

Approval for this study was obtained from the Research Ethics Board at Sick Kids. Parents and/or guardian(s) signed informed consent to confirm their child's participation in the study, whereas children older than 7 years provided oral and written assent. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Vision Examination

Vision was assessed in the Visual Electrophysiology Unit (VEU), Department of Ophthalmology and Vision Sciences, Sick Kids. All children with and without T1D had visual acuities correctable to 20/20 or better. Children with and without T1D had normal scores on the clinical color vision tests: H-R-R Pseudoisochromatic Plates (Hardy, Rand and Rittler, 1991) and Mollon Reffin Minimalist.[25,26] Ophthalmoscopy revealed no retinal abnormalities in children without T1D, and refractive errors ranged from −2.50 to +2.50 D in subjects with T1D and from −3.25 to +3.50 D in those without.

Seven-field stereo color fundus photographs were used to determine whether children with T1D had BDR. Photographs were graded according to the modified Airlie House classification system used in the Early Treatment Diabetic Retinopathy Study.[27] Five children with T1D had BDR: microaneurysms, hemorrhages, and cotton wool spots. Of these five children, one had a history of nephrotic syndrome and another was receiving L-thyroxine (0.1 mg) for hypothyroidism. All five children with BDR therefore were excluded. Another child without BDR was also receiving L-thyroxine (0.1 mg) for hypothyroidism, but was not excluded from the study. No other ocular conditions or systemic conditions that affect vision were found in children with T1D.

Pubertal Status

Pubertal status was assessed both in children with and in those without diabetes by means of a physical development self-rating questionnaire based on the Tanner stages of sexual maturity.[28] The pubertal-assessment questionnaire was scored as follows: Tanner stage 1 was considered prepubertal, whereas Tanner stage 2 and higher represented onset of puberty. Breast development independent of pubic hair status determined pubertal status on the female questionnaire, whereas the most advanced stage of development, either pubic hair or genital development or testicular size, determined pubertal status on the male questionnaire.

Metabolic Control

The most recent HbA_{1c} measurements (i.e., HbA_{1c} measurement taken on day of color VEP testing) were obtained from the Sick Kids diabetes database. HbA_{1c} is an index of blood glucose control over the preceding 3 months.[29] Mean HbA_{1c} levels in the children with T1D was 7.8% ± 0.9%. To control for variations in ambient blood glucose levels during color VEP testing that would influence the study outcome, three blood glucose measurements using the a glucose monitoring system (One Touch Ultra; LifeScan, Burnaby, British Columbia, Canada) were taken.

Color Visual Evoked Potential

Stimuli were created using Vision Research Graphics (VRG) software (Durham, NH) and presented on a rectangular 21-in. RGB color graphics monitor (FlexScan F930; Eizo, Cypress, CA) with 26° × 20° field dimensions. Color stimuli were presented along two axes in CIE color space[30]: the Tritanopic confusion axis stimulated selectively the S-cone pathway, and the axis orthogonal to this stimulated the long- medium-wavelength (LM)-cone pathway. S and LM stimuli passed through white (CIE x-, y-coordinates, 0.33, 0.33). CIE coordinates used were: S-axes $x = 0.3409$, $y = 0.3523$ (greenish-yellow) and $x = 0.2893$, $y = 0.2496$ (purple) and LM-axes $x = 0.3594$, $y = 0.3099$ (red) and $x = 0.3064$, $y = 0.3372$ (green). The cone contrasts for both chromatic stimuli were calculated using the Cole and Hine[31] formula. The respective cone contrasts for S and LM gratings were: S-axis (L = 0.00, M = 0.00, S = 0.39) and L-M-axis (L = 0.06, M = 0.11, S = 0.00). Achromatic stimulus with CIE coordinates $x = 0.3260$, $y = 0.3338$ for white and $x = 0.3250$, $y = 0.3340$ for black was also presented.

Stimulus parameters were chosen to optimize the chromatic response and differentiate between the chromatic and achromatic VEP responses.[32–38] Chromatic and achromatic stimuli were vertical sinusoidal wave gratings of 1 and 3 cyc/deg respectively. Low spatial frequency for chromatic gratings was chosen to minimize chromatic aberration. Chromatic stimuli were presented at photometric isoluminance. Both chromatic and achromatic stimuli were presented in an onset (100 ms)–offset (400 ms) mode at a repeat rate of 2 Hz. The offset mode, composed of a uniform field, was equated in mean luminance and chromaticity (36.50 cd/m^2) to the onset mode. S and LM stimuli were presented at 40% contrast. Achromatic stimulus was presented at 90% Michelson contrast.[39] Mean luminance and chromaticity (36.50 cd/m^2) were identical for all three stimuli.

To extract cortical responses to color stimuli, we placed 6-mm diameter gold disc electrodes (Genuine F-E5GH; Grass Instrument Division, Astro-Med, Inc., West Warwick, RI) equipped with protected terminals (Safelead; Grass) on the scalp according to the international 10-20 system of electrode placement.[40] Three active electrodes were placed over the occipital or visual cortex in positions Oz, O1, and O2, whereas two additional electrodes were positioned on nonvisual areas of the cortex at Pz (ground) and Cz (reference).[40] Color VEPs were recorded monocularly with a viewing distance of 75 cm. Results are reported for the right eye only.

Sample Size Calculation and Statistical Analysis

A sample size calculation using a multiple linear regression power analysis (Power & Sample Size, NCSS/PASS; Statistical and Power Analysis Software, Kaysville, UT) with a power of 0.8, an α of 0.05, and an estimated $\rho_{est} = 0.4$ determined that 44 subjects with T1D were needed for the study. ANCOVA regression was used both for the primary analysis to examine the relationship between S-VEP latency and HbA_{1c}, and for the exploratory analyses: (1) to evaluate the interaction term between the effect of pubertal status on S-VEP latency and group, and (2) to examine the relationship between LM- and achromatic VEP latencies and HbA_{1c}. A computer (SAS software; SAS Institute Inc., Version 8.0) was used to perform the statistical analysis and produce the graphics (S-Plus, 6.2, Academic Site Edition; Insightful, Corp. Seattle, WA) software was used for graphics.

RESULTS

In analyzing the VEP data, latency served as the main measure because it is a more reliable parameter than amplitude; and also, among typically developed subjects, VEP latency shows less interindividual variation than does amplitude.[11,33] Figure 1

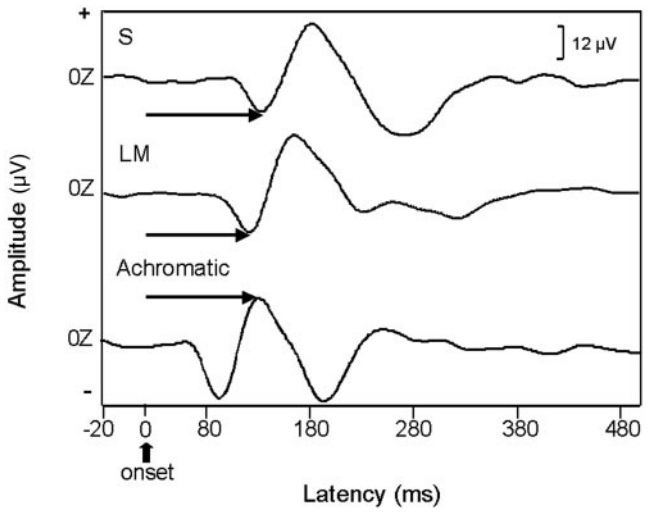

FIGURE 1. Color VEP data from an 11-year-old control subject to S (*top*), LM (*middle*), and achromatic (*bottom*) stimuli. *Arrow*: the measure of latency (in milliseconds), from pattern onset (0 ms) to the peak of the response.

shows the characteristic waveforms for the three axes: S, LM, and achromatic.

The latency for chromatic onset–offset VEP data was measured from pattern onset (time of stimulus presentation at 0 ms) to the trough of the first negative component, which is often followed by a positive component.[33] For achromatic onset–offset stimuli, latency was measured from pattern onset to the peak of the first positive component.[39]

The relationship between S-VEP latency and HbA_{1c} across T1D subjects was determined. The results of the ANCOVA regression modeling S-VEP latency as a function of HbA_{1c} after adjustment for sex, pubertal status, duration of diabetes, and average ambient blood glucose levels during VEP testing, are summarized in Table 1.

ANCOVA Regression

S-VEP Latency Versus HbA_{1c}. The results shown in Table 1 indicate no statistically significant association between S-VEP latency and HbA_{1c} in preteen children with T1D. The Pearson correlation coefficient between S-VEP latency and HbA_{1c} was $\rho = 0.134$ ($P = 0.3905$). The relationship between S-VEP latency and HbA_{1c} in the children with T1D is shown in Figure 2. The covariates of sex, disease duration, and average ambient blood glucose during VEP testing were also not found to be associated significantly with S-VEP latency.

TABLE 1. ANCOVA Regression Modeling S-VEP Latency as a Function of HbA_{1c}

Parameter	Estimate	Standard Error	*P*
Intercept	131.10	14.98	<0.0001
HbA_{1c}	1.76	1.93	0.3662
Sex: female vs. male	3.21	3.61	0.3788
Pubertal Status: prepubertal vs. pubertal	−9.52	3.57	0.0114*
Disease duration	−0.44	0.79	0.5827
Average blood glucose	−0.02	0.28	0.9288

Data are from children with T1D after adjustment for the covariates sex, pubertal status, disease duration, and average ambient blood glucose levels during VEP testing.

* Statistically significant.

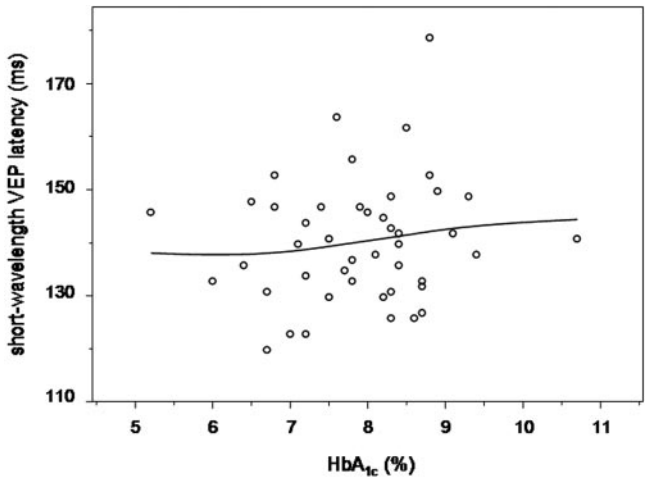

FIGURE 2. S-VEP latency as a function of HbA_{1c} across subjects with T1D (a smoother was used instead of a line from a regression model because a linear regression would force a straight line, irrespective of the actual relationship between S-VEP latency and HbA_{1c}).

An association between S-VEP latency and pubertal status was found to be statistically significant. The mean S-VEP latency of pubertal T1D children ($n = 22$, 144.27 ± 12.24 ms) was delayed significantly when compared with prepubertal children with T1D ($n = 20$, 134.75 ± 8.65 ms; Fig. 3).

Sample S-VEP waveforms of pubertal and prepubertal children with T1D are provided in Figures 4A and 4B, respectively.

To explore further the statistically significant association between S-VEP latency and pubertal status, we computed the interaction term examining the difference in pubertal status effect on S-VEP latency after adjusting for sex between the T1D and control groups. ANCOVA regression results for the interaction term (pubertal status × group) are summarized in Table 2.

Interaction Term Pubertal Status × Group. The pubertal status effect on S-VEP latency was greater in the T1D group than in the control group (estimate value = 6.67). However, this effect was not significant. After a Bonferroni adjustment

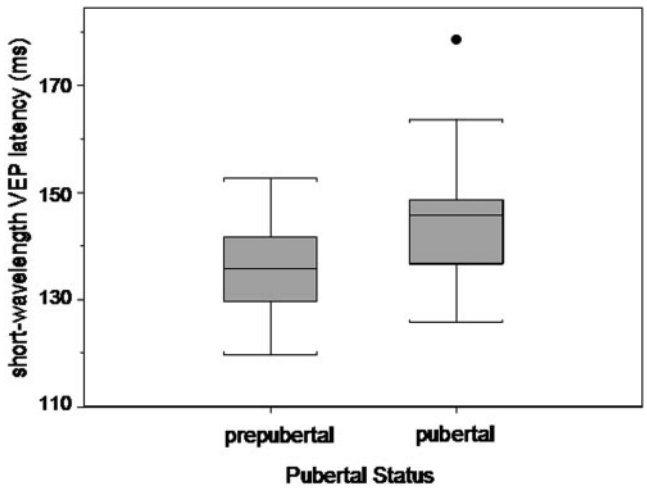

FIGURE 3. Pubertal status versus S-VEP latency in children with T1D. Pubertal status is categorized into two variables: prepubertal and pubertal. The *line* in the *middle* of the *boxes* represents the median of the distribution. Medians: prepubertal = 134.70 ms; pubertal = 145.68 ms. The data point outside the top fence for the pubertal group represents an outlier.

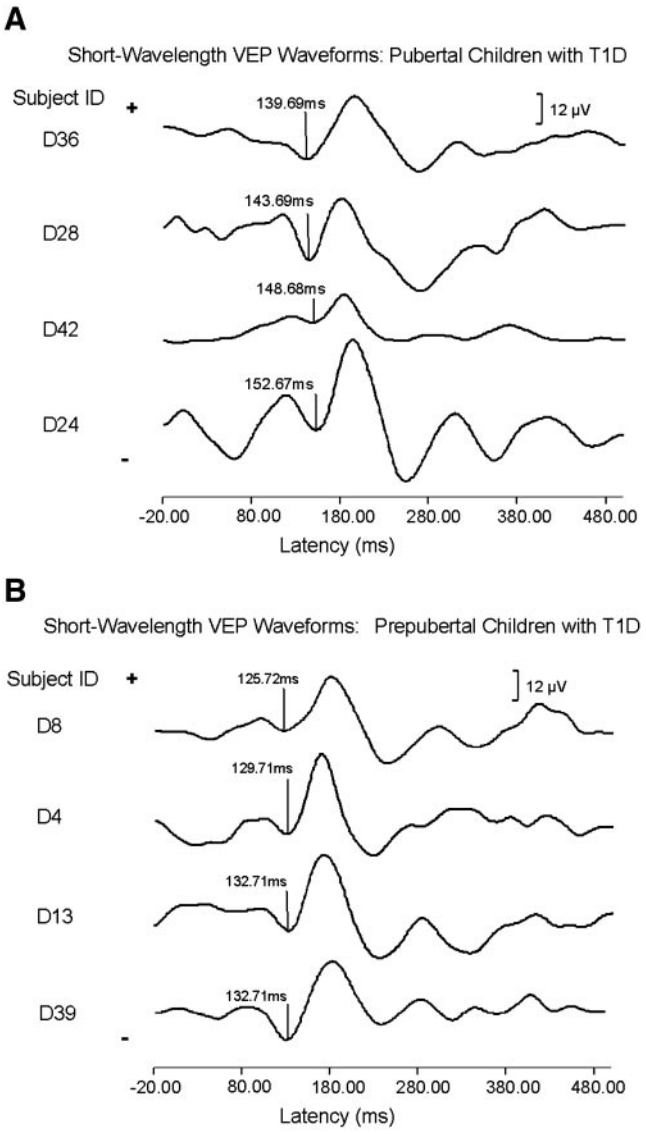

FIGURE 4. Sample S-VEP waveforms of (**A**) pubertal and (**B**) prepubertal children with T1D.

for multiple testing, left eye results were similar to right eye results.

Last, the relationships between LM- and achromatic VEP latencies, and HbA_{1c} across T1D subjects were determined. After adjustment for sex, disease duration, pubertal status, and average ambient blood glucose levels during VEP testing, neither LM- ($n = 39$, $P = 0.6057$) nor achromatic ($n = 45$, $P = 0.7250$) VEP latencies were significantly associated with HbA_{1c}. Moreover, covariates including pubertal status were not significantly associated with either LM- or achromatic-VEP latency.

DISCUSSION

The primary objective of this study was to examine the association between HbA_{1c} and color vision in preteen children with T1D—specifically, the S chromatic pathway. We hypothesized that the S-VEP latency would be associated with HbA_{1c} levels after adjustment for the covariates sex, pubertal status, duration of diabetes, and average ambient blood glucose levels during VEP testing. However, S-VEP latency was not found to be associated significantly with HbA_{1c} levels in this cohort of children with T1D. Furthermore, LM- and achromatic VEP latencies also were not associated with HbA_{1c} levels.

One possible explanation for the lack of association between HbA_{1c} levels in preteen children with T1D and their S-VEP latencies, contrary to the findings in adults with T1D,[11,21–24] is that preteen children with T1D, unlike older individuals with T1D, generally maintain good blood glucose control and low HbA_{1c} levels (<8%).[3,41,42] As such, children with T1D generally show decreased frequency and/or severity of diabetic retinal complications compared with older individuals with T1D.[3] The range of HbA_{1c} levels in the participants in the present study may have been too restrictive to obtain a significant correlation between S-VEP latency and HbA_{1c} levels. Indeed, 52% of the diabetes sample in the present study demonstrated good blood glucose control (<8% HbA_{1c}), whereas 39% were in the 8% to 9% HBA_{1c} range. Only 9% had an extremely elevated level (>9% HbA_{1c}).

Instead, we found an association between pubertal status and S-VEP latency in the T1D group. The pubertal T1D group had significantly delayed S-VEP latencies when compared with the prepubertal T1D group. There are several possible explanations for this finding.

A luminance (nonchromatic) artifact resulting from a large field stimulus and/or testing at photometric isoluminance[35,36,38,43] may have contaminated the data. A luminance artifact would appear as an early (approximately 100 ms) positive peak preceding the first negative component or chromatic response.[33] S-responses are more vulnerable to luminance contamination than LM-responses.[36,38,43] The most likely sources of luminance artifact under such conditions are chromatic aberration[35,36,43] and varying macular pigmentation among subjects.[38,43]

Testing with a 3° circular stimulus field along with a restricted number of spatial cycles (3–6 spatial cycles) minimizes luminance artifact in S-VEP responses.[35,36,38,44] We attempted to collect S-VEP responses using a 3° circular blue–yellow stimulus on the most compliant children with and without diabetes (ages, ~6–12years). The data collected in this age group were unrepeatable and unreliable. However, we managed to collect S-VEP data on the children by using a 9° circular field. When comparing the morphology of S-VEP responses from the 26° × 20° rectangular stimulus and the 9° circular field stimulus, we found that responses to either stimulus produced a predominantly chromatic waveform (i.e., no significant positive peak; Fig. 5). Most important, stimulus field size did not affect S-VEP latency significantly. The test–retest variability for our large 26° × 20° rectangular stimulus, which is defined as mean S-VEP latency difference (trial 1minus trial 2) ± 1 SD, was 5.77 ± 4.40 ms. The mean difference in S-VEP latency ($n = 8$, 4.26 ± 2.11 ms) between the 26° × 20° and 9°

TABLE 2. ANCOVA Regression Modeling the Interaction Term Pubertal Status × Group

Parameter	Estimate	Standard Error	*P*
Intercept	143.17	2.65	<0.0001
Sex: female vs. male	2.89	2.33	0.2203
Pubertal status: prepubertal vs. pubertal	−9.85	2.99	0.0016*
Group: control vs. diabetes	−5.79	3.03	0.0603
Pubertal status × group	6.67	4.66	0.1573

The difference in pubertal status effect (difference in mean S-VEP latency between the pubertal and prepubertal subgroups) on S-VEP latency between the T1D and control groups after adjusting for sex. Main effects in the model are pubertal status and group.

* Statistically significant.

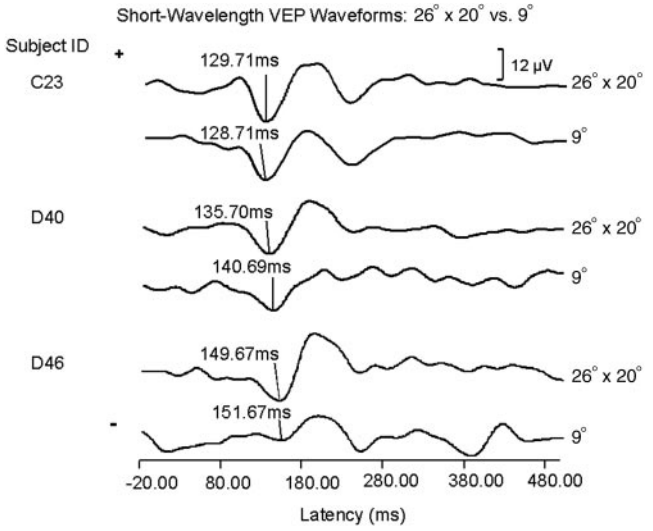

FIGURE 5. Sample S-VEP waveforms from one control subject (C23) and two children with T1D (D40, D46) comparing the time to respond (latency) to short-wavelength stimuli of different sizes and shapes: 26° × 20° rectangular field versus 9° circular field.

stimulus fell within the test–retest variability of the 26° × 20° stimulus, confirming that S-VEP latency was not affected by our large field stimulus.

The results of our pilot work are similar to those of Rabin et al.[33] Both studies showed that using a large-field monitor does not alter the VEP waveform (no positive peak = no luminance contamination), nor does it change significantly the latency (time to respond to stimulus) of the negative-going component. Furthermore, even though testing at photometric isoluminance has been reported to contaminate chromatic responses, small deviations from perceptual isoluminance minimally distort the shape of the chromatic waveform; and, most important, latency the main measure of the color VEP is not altered significantly.[33] Consequently, the delay in S-VEP responses found in the pubertal children with T1D does not appear to arise as a result of luminance contamination.

Second, the effect of the pubertal status, per se, must also be examined. Because the interaction term was not statistically significant, the delay in S-VEP latency in the pubertal children with T1D may not be a phenomenon that is confined to the diabetes group. However, this study was not designed to compute the interaction term. With sufficient power and sample size, the difference in pubertal status effect on S-VEP latency between the two groups may have been significant and confined to the diabetes groups, as pubertal status effect on S-VEP latency was greater in the diabetes group than in the control group.

Furthermore, the neural pathways that process chromatic information are not mature or adultlike until the onset of puberty, which occurs usually between 12 and 14 years.[45] At this time, the morphology of the chromatic VEP waveform changes from a positive-negative to the classic negative-positive, causing a subtle shift in latency ((i.e., earlier or shorter).[45] However, because earlier latencies were not seen in pubertal children with T1D, the effect of pubertal status on S-VEP latency in the diabetes group is unlikely to be due to maturation of the visual system.

Alternatively, pubertal status may be a marker of blood glucose elevations, which in turn may contribute to the observed significant association between pubertal status and S-VEP latency in the diabetes group. Major changes in the hormonal environment of adolescents with T1D during puberty are thought to be responsible for reduced metabolic control and increased HbA_{1c} levels during this stage of development.[3,41,42,46] Poor metabolic control is often attributed to abnormalities in the growth hormone/insulin-like growth factor (GH/IGF)-1 axis, which cause spontaneous hypersecretion of GH and reduction of circulating IGF-1.[47,48] Consequently, insulin sensitivity or the ability of insulin to stimulate glucose uptake into peripheral tissues may be reduced in adolescents with T1D, thereby resulting in poor metabolic control.[47,48] However, because mean HbA_{1c} in the pubertal group (HbA_{1c}, 7.8%; range: 6%–10.7%) was similar to that of the prepubertal group (HbA_{1c}, 7.8%; range: 6.5%–9.5%), metabolic control in the present study does not seem to explain the S-VEP latency delay in pubertal children with T1D.

S-cone sensitivity reduction or S-deficiency in adults with T1D is associated with duration-dependent lens yellowing.[49] The lenses of young adults (median, 30 years) with T1D, with a long disease duration (median, 21 years), become yellow at an accelerated rate when compared with those of nondiabetic control subjects.[50] Moreover, premature lens yellowing in T1D has been attributed in part to elevated blood glucose levels, which may lead to the accelerated glycosylation of lens proteins.[50,51] In the present study, however, the pubertal children with T1D were young (mean age, 10 years), had good glucose control (mean HbA_{1c}, 7.8%), and had a short disease duration (mean disease duration, 4.3 years), and therefore this explanation is unlikely.

Last, the retina is an insulin-sensitive tissue.[52] Retinal electrophysiology has demonstrated a dose-dependent reduction in the amplitudes of both the a- and b-wave components of the electroretinogram after administration of insulin in vitro.[53] Abnormal levels of insulin are needed by children with T1D, which are typically increased to control for elevation in HbA_{1c} during puberty.[42,48,54] As insulin dosage administered in units per kilogram body weight does not increase significantly during the early stages of puberty,[41,42] changing insulin levels during puberty is an unlikely explanation of delayed S-VEP latency.

In light of recent findings by Verrotti et al.,[55] which showed an association between delayed VEP latencies in response to a luminance pattern-reversal stimulus and high HbA_{1c} levels (mean HbA_{1c}, 9.4%) in adolescents between the ages of 10 to 19, it is important to study the chromatic mechanisms of older adolescents as well as young adults with T1D. Because the short-wavelength deficit in T1D is a functional change that arises before the onset of diabetic retinopathy it is also important to determine whether the S-VEP latency delay in pubertal children with T1D changes over time and whether this change could be a predictive marker for the onset of background diabetic retinopathy.

In summary, pubertal status, rather than metabolic control, disease duration, sex, and average ambient blood glucose during VEP testing, appears to delay S-VEP latency in pubertal children with T1D. Factors such as chromatic VEP maturation, hormonal milieu, hyperopic refractive error, lens yellowing, hypoglycemia, and attention deficits cannot explain the delay in S-VEP latency of pubertal children with T1D. However, further investigation into the pubertal status effect on S-VEP latency in the diabetes group is needed, since this effect seemed to be greatest in the diabetes group, even though the interaction term was not found to be statistically significant.

Acknowledgments

The authors thank Carole Panton, Assistant Director of the VEU, for invaluable comments and criticisms after reviewing the manuscript; Thomas Wright, research technologist, for excellent technical assistance with the color VEP and for help with the illustrations; ophthal-

mic imaging specialists Leslie MacKeen and Cynthia Vandenhoven for obtaining fundus photographs in the children with T1D; Joyce Robinson, Administrative Assistant in the Division of Endocrinology, for helping to identify the children with T1D who were eligible to take part in the study; and all the participants for their cooperation in the study.

References

1. American Diabetes Association. http://www.diabetes.org/diabetes-statistics/eye-complications.jsp. Accessed 2004.
2. Canadian Diabetes Association. Clinical Practice Guidelines. www.diabetes.ca/cpg2003. Accessed 2004.
3. Diabetes Control and Complications Trial (DCCT). Effects of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus. *J Pediatr*. 1994;125:177–188.
4. Bresnick GH. Diabetic retinopathy viewed as a neurosensory disorder. *Arch Ophthalmol*. 1986;104:989–990.
5. Ewing FM, Deary IJ, McCrimmon RJ, Strachan MW, Frier BM. Effect of acute hypoglycemia on visual information processing in adults with type 1 diabetes mellitus. *Physiol Behav*. 1998;64:653–660.
6. Lieth E, Gardner TW, Barber AJ, Antonetti DA. Retinal neurodegeneration: early pathology in diabetes. *Clin Exp Ophthalmol*. 2000;28:3–8.
7. Ewing FM, Deary IJ, Strachan MW, Frier BM. Seeing beyond retinopathy in diabetes: electrophysiological and psychophysical abnormalities and alterations in vision. *Endocr Rev*. 1998;19:462–476.
8. Greco AV, Di Leo MA, Caputo S, et al. Early selective neuroretinal disorder in prepubertal type 1 (insulin-dependent) diabetic children without microvascular abnormalities. *Acta Diabetol*. 1994;31:98–102.
9. Yamamoto S, Kamiyama M, Nitta K, Yamada T, Hayasaka S. Selective reduction of the S cone electroretinogram in diabetes. *Br J Ophthalmol*. 1996;80:973–975.
10. Crognale MA, Switkes E, Rabin J, et al. Application of the spatiochromatic visual evoked potential to detection of congenital and acquired color-vision deficiencies. *J Opt Soc Am A*. 1993;10:1818–1825.
11. Schneck ME, Fortune B, Switkes E, Crognale M, Adams AJ. Acute effects of blood glucose on chromatic visually evoked potentials in persons with diabetes and in normal persons. *Invest Ophthalmol Vis Sci*. 1997;38:800–810.
12. Kinnear PR, Aspinall PA, Lakowski R. The diabetic eye and colour vision. *Trans Ophthalmol Soc UK*. 1972;92:69–78.
13. Roy MS, McCulloch C, Hanna AK, Mortimer C. Colour vision in long-standing diabetes mellitus. *Br J Ophthalmol*. 1984;68:215–217.
14. Bresnick GH, Condit RS, Palta M, et al. Association of hue discrimination loss and diabetic retinopathy. *Arch Ophthalmol*. 1985;103:1317–1324.
15. Hardy KJ, Lipton J, Scase MO, Foster DH, Scarpello JH. Detection of colour vision abnormalities in uncomplicated type 1 diabetic patients with angiographically normal retinas. *Br J Ophthalmol*. 1992;76:461–464.
16. Kurtenbach A, Flogel W, Erb C. Anomaloscope matches in patients with diabetes mellitus. *Graefes Arch Clin Exp Ophthalmol*. 2002;240:79–84.
17. Verrotti A, Lobefalo L, Chiarelli F, et al. Colour vision and persistent microalbuminuria in children with type-1 (insulin-dependent) diabetes mellitus: a longitudinal study. *Diabetes Res Clin Pract*. 1995;30:125–130.
18. Kurtenbach A, Schiefer U, Neu A, Zrenner E. Preretinopic changes in the colour vision of juvenile diabetics. *Br J Ophthalmol*. 1999a;83:43–46.
19. Kurtenbach A, Schiefer U, Neu A, Zrenner E. Development of brightness matching and colour vision deficits in juvenile diabetics. *Vision Res*. 1999;39:1221–1229.
20. Giusti C. Lanthony 15-Hue Desaturated Test for screening of early color vision defects in uncomplicated juvenile diabetes. *Jpn J Ophthalmol*. 2001;45:607–611.
21. Muntoni S, Serra A, Mascia C, Songini M. Dyschromatopsia in diabetes mellitus and its relation to metabolic control. *Diabetes Care*. 1982;5:375–378.
22. Trick GL, Burde RM, Gordon MO, Santiago JV, Kilo C. The relationship between hue discrimination and contrast sensitivity deficits in patients with diabetes mellitus. *Ophthalmology*. 1988;95:693–698.
23. Hardy KJ, Scarpello JH, Foster DH. Relation between blood glucose control over 3 months and colour discrimination in insulin dependent diabetic patients without retinopathy. *Br J Ophthalmol*. 1995a;79:300.
24. Volbrecht VJ, Schneck ME, Adams AJ, Linfoot JA, Ai E. Diabetic short-wavelength sensitivity: variations with induced changes in blood glucose level. *Invest Ophthalmol Vis Sci*. 1994;35:1243–1246.
25. Mollon JD, Astell, S., Reffin JP. A minimalist test of colour vision. In: Drum B, Morelan JD, Serra A, eds. *Colour Vision Deficiencies X.* Dordrecht, The Netherlands; Kluwer Academic Publishers; 1991:59–67.
26. Shute RH, Westall CA. Use of the Mollon-Reffin minimalist color vision test with young children. *J AAPOS.* 2000;4:366–372.
27. Early Treatment Diabetic Retinopathy Study. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98:786–806.
28. Morris N, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. *J Youth Adolesc*. 1980;9:271–280.
29. Gabbay KH, Hasty K, Breslow JL, et al. Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. *J Clin Endocrinol Metab*. 1977;44:859–864.
30. Smith VC, Pokorny J. Spectral sensitivity of the foveal cone photopigments between 400 and 500 nm. *Vision Res*. 1975;15:161–171.
31. Cole GR, Hine T. Computation of cone contrasts for color vision research. *Behav Res Methods Instr Comput.* 1992;24:22–27.
32. Kulikowski JJ, Murray IJ, Parry NRA. *Electrophysiological Correlates of Chromatic-Opponent and Achromatic Stimulation in Man.* Dordrecht, The Netherlands: Kluwer Academic Publishers; 1989;145–152.
33. Rabin J, Switkes E, Crognale M, Schneck ME, Adams AJ. Visual evoked potentials in three-dimensional color space: correlates of spatio-chromatic processing. *Vision Res*. 1994;34:2657–2671.
34. Robson AG, Kulikowski JJ. Verification of human visual evoked potentials (VEPs) elicited by gratings containing tritanopic pairs of hues (Abstract). *J Physiol*. 1995;485:22.
35. Kulikowski JJ, Robson AG, McKeefry DJ. Specificity and selectivity of chromatic visual evoked potentials. *Vision Res*. 1996;36:3397–3401.
36. Kulikowski JJ, McKeefry DJ, Robson AG. Selective stimulation of colour mechanisms: an empirical perspective. *Spat Vis*. 1997;10:379–402.
37. Robson AG, Kulikowski JJ, Korostenskaja M, Neveu MM, Hogg CR, Holder GE. Integration times reveal mechanisms responding to isoluminant chromatic gratings: a two-centre visual evoked potential study. In: Mollon JD, Pokorny J, Knoblauch K, eds. *Normal or Defective Colour Vision.* London: Oxford University Press; 2003.
38. Robson A, Holder GE, Fitzke FW, Moreland JD, Kulikowski JJ. Subject-specific macular pigmentation influences the selectivity of chromatic VEPs (Abstract). 41st International Symposium of the International Society for Clinical Electrophysiology of Vision (ISCEV), Nagoya, Japan, April 2003.
39. Harding GF, Odom JV, Spileers W, Spekreijse H. Standard for visual evoked potentials 1995. The International Society for Clinical Electrophysiology of Vision. *Vision Res*. 1996;36:3567–3572.
40. Jasper. Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalogr Clin Neurophysiol*. 1958;10:370–375.
41. Daneman D, Wolfson DH, Becker DJ, Drash AL. Factors affecting glycosylated hemoglobin values in children with insulin-dependent diabetes. *J Pediatr*. 1981;99:847–853.
42. Mortensen HB, Robertson KJ, Aanstoot HJ, et al. Insulin management and metabolic control of type 1 diabetes mellitus in child-

hood and adolescence in 18 countries. Hvidore Study Group on Childhood Diabetes. *Diabet Med*. 1998;15:752–759.

43. Moreland JD, Robson AG, Soto-Leon N, Kulikowski JJ. Macular pigment and the colour-specificity of visual evoked potentials. *Vision Res*. 1998;38:3241–3245.
44. Robson AG, Kulikowski JJ. Verification of human visual evoked potentials (VEPs) elicited by gratings containing tritanopic pairs of hues (abstract). *J Physiol*. 1996;485:22P.
45. Crognale MA. Development, maturation, and aging of chromatic visual pathways: VEP results. *J Vision*. 2002;2:438–450.
46. Sargeant DT, Achtenberg J, Davis JE. Increased haemoglobin A1C in insulin dependent diabetes during puberty (abstract). *Diabetes.* 1980;29:177A.
47. Acerini CL, Williams RM, Dunger DB, et al. Metabolic impact of puberty on the course of type 1 diabetes. *Diabetes Metab*. 2001; 27:S19–S25.
48. Hamilton J, Daneman D. Deteriorating diabetes control during adolescence: physiological or psychosocial? *J Pediatr Endocrinol Metab*. 2002;15:115–126.
49. Tregear SJ, Knowles PJ, Ripley LG, Casswell AG. Chromatic-contrast threshold impairment in diabetes. *Eye*. 1997;11:537–546.
50. Lutze M, Bresnick GH. Lenses of diabetic patients "yellow" at an accelerated rate similar to older normals. *Invest Ophthalmol Vis Sci*. 1991;32:194–199.
51. Williams RH, Larsen PR. *Williams Textbook of Endocrinology.* 10th ed. Philadelphia: WB Saunders; 2003;chap 31.
52. Reiter CE, Gardner TW. Functions of insulin and insulin receptor signaling in retina: possible implications for diabetic retinopathy. *Prog Retin Eye Res*. 2003;22:545–562.
53. Gosbell A, Favilla I, Jablonski P. The effects of insulin on the electroretinogram of bovine retina in vitro. *Curr Eye Res*. 1996; 15:1132–1137.
54. Dunger DB. Diabetes in puberty. *Arch Dis Child*. 1992;67:569–570.
55. Verrotti A, Lobefalo L, Trotta D, et al. Visual evoked potentials in young persons with newly diagnosed diabetes: a long-term follow-up. *Dev Med Child Neurol*. 2000;42:240–244.