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Influences of Chorion Type on Saccadic Eye Movements in Twins

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Purpose. The influence of genetic and prenatal environmental factors on characteristics of saccadic performance were evaluated in young monozygotic (MZ) twins (8-19 years old) of known chorion type.

Methods. Saccadic eye movements were recorded using an infrared system. Saccadic latency, accuracy, and parameters of amplitude-peak velocity exponential equation (main sequence) were quantified.

Results. Intraclass correlations of saccadic parameters differed significantly from zero for monochorionic and dichorionic MZ twins. The within-pair mean squares were significantly less, and intraclass correlations were significantly higher in monochorionic than in dichorionic twins for latency and were similar for other saccadic parameters (accuracy, slope of main sequence, and peak velocity for 15° saccades).

Conclusions. These findings confirmed previous reports that saccadic parameters of MZ twins are significantly correlated and indicated that similarity of these parameters seen in MZ twins may be driven both by genetic and by prenatal environmental factors. (*Invest Ophthalmol Vis Sci.* 1998;39:2186-2190)

Saccades are high-velocity eye movements for rapid and accurate refixations. The function of voluntary saccades in primates is to bring the image of a target from the periphery onto the fovea. Tests of saccadic eye movements are commonly used to evaluate patients with neurologic, ophthalmologic, and psychiatric disorders and to evaluate the effects of drugs.[1-4] There are several reports describing genetic influences on the saccadic system. Abnormalities of saccadic performance have been reported in patients with schizophrenia and their first-degree relatives.[5,6] Iacono and Lykken[7] have shown that normal monozygotic twins produce similar patterns of eye movements. In previous studies from our group,[8,9] we examined saccadic eye movements in healthy monozygotic (MZ) and dizygotic (DZ) twins and found that the intraclass correlations for saccadic characteristics (latency, accuracy, and peak velocity) were highly significant for identical twins and were not significantly different from zero for fraternal twins. The disparity between MZ and DZ intraclass correlations suggested either gene interactions or inequality of environmental covariances of MZ and DZ twins. The prenatal environment might be a nongenetic factor that contributes to greater similarities in MZ twins. Monozygotic co-twins share all their nuclear genes, but MZ pairs may differ in their placentation. Two thirds of monozygotic twins have a common chorion (monochorionic pairs, MZ-MC) and, as a result, may have a more similar early environment than MZ twins with dichorionic placentation (MZ-DC).[10] A comparison of MZ-MC and MZ-DC twin pairs offers an opportunity to assess an early environmental influence on development. Several studies[10-13] have compared MZ-MC and MZ-DC twin pairs and found that the performance of MZ-MC twins was more similar than MZ-DC twins in several behavioral and cognitive tasks.[11,12]

In a previous study,[8] we evaluated possible genetic influences over the control of saccadic eye movements, comparing MZ and DZ twins. In the current investigation we examined the saccadic eye movements in two groups of MZ twins (monochorionic and dichorionic) to search for evidence of prenatal environmental influences.

Methods

Seventeen pairs of young monochorionic MZ (MZ-MC) twins and 16 pairs of dichorionic MZ (MZ-DC) twins were tested, and data were analyzed. The details of ascertaining the twins, their zygosity testing, and their placental typing were described in detail by Ramos-Arroyo et al.[14] Zygosity was determined using 16 genetic marker systems, and it was estimated that a pair of like-sexed twins who were concordant for all these markers had a probability of 99.8% of being monozygotic. The placentas were examined grossly and microscopically at the time of delivery to determine the type. No twins had neurologic or ophthalmologic disorders. MZ-MC twins (age range, 9-18 years; mean age, 13.2 ± 2.7; 4 boys and 13 girls) and MZ-DC

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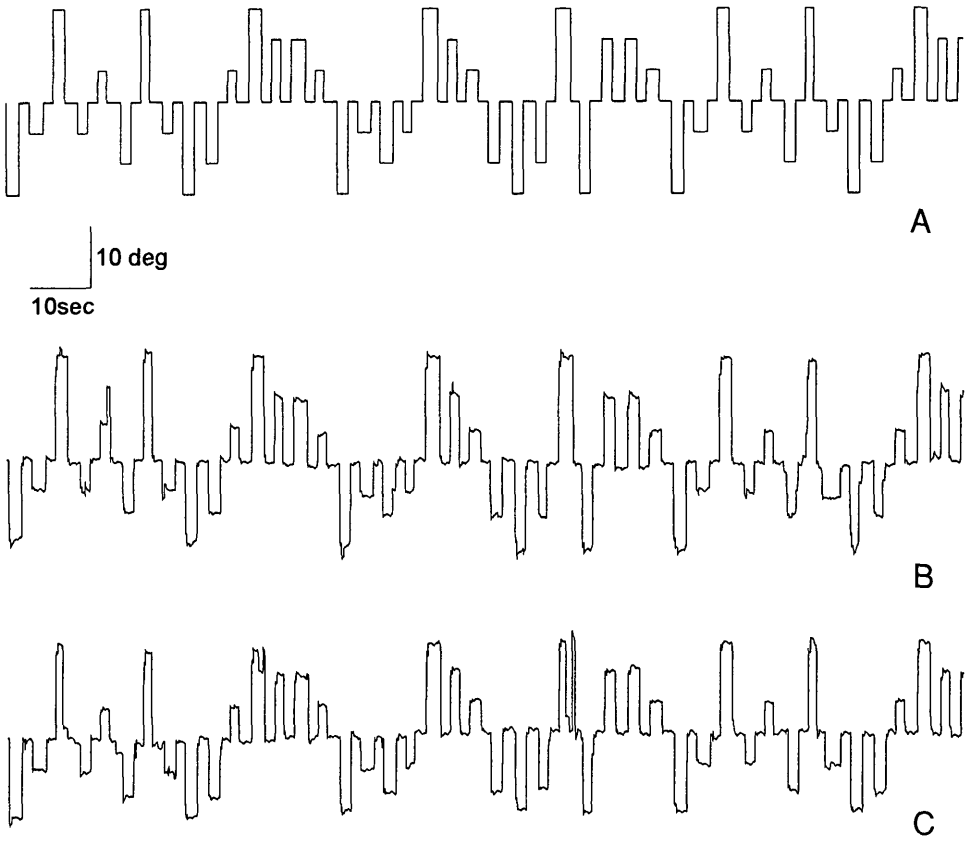

FIGURE 1. Example of typical records (from first trial). **(A)** Target position; **(B, C)** eye position of MZ-MC twins.

twins (age range, 8–19 years; mean age, 12.7 ± 2.8; 6 boys and 10 girls) had similar age distributions. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Written informed consent was obtained from parents (guardians) of twins after the procedures had been explained to them.

Subjects were seated 1 meter from a stimulation bar where a green light-emitting diode was illuminated at 1 of 7 locations (−15°, −10°, −5°, 0°, 5°, 10°, and 15°). Horizontal eye movements were recorded binocularly using infrared spectacles (OBER2 system) and digitized at 250 Hz for off-line analysis. A head restraint discouraged head movements. Two series of similar saccadic tasks were presented, separated by 5 minutes of rest. A calibration trial preceded every series.

Saccadic Task

A target moved randomly from center (0°) to one of the other six positions and after a randomized time interval returned to center. The time intervals between target jumps varied pseudorandomly over the interval of 1.4 to 2.4 seconds. There were 57 center-periphery and 57 periphery-center target jumps in each series that were divided equally between ±5°, ±10°, and ±15°. Subjects were asked to follow the target jumps "as rapidly as possible." We considered the center-periphery and periphery-center saccades as two different groups of saccades (random and semipredictable), because periphery-center movements were at least in part predictable[15] (future position of target was known) and because of possible differences between centripetal and centrifugal movements.

For data analyses and graphical presentation of results, interactive programs were written using Matlab and Microsoft Visual C++. The digitized eye position signal was differentiated. The algorithm of saccade identification was based on a combination of the Kalman filter algorithm[16] and an algorithm for defining the saccade threshold. Data from the right eye were used. Only the primary (first) saccades at an interval of 100 to 400 msec after the target moved were considered. Latency (L), accuracy (Ac), amplitude (A), and peak velocity (V) were calculated for every primary saccade. The accuracy was defined as the fraction of saccadic amplitude divided by target amplitude. Amplitude and peak velocity data were fitted with a least squares regression algorithm to an exponential equation (main sequence[17]), $V = B^*(1 - \exp[-CA])$, where B and C are constants. We calculated the slope of this curve at $A = 0$ as slope $= B^*C$. We calculated the peak velocity of 15° amplitude saccades as $V15 = B^*(1 - \exp[-C^*15])$. Because we did not find significant differences between the latencies, accuracies, slopes, or $V15$s for rightward and leftward saccades, we combined the data for rightward and leftward saccades.

Figure 1 presents typical records. Saccades were made in response to more than 85% of target jumps, and such consistent saccadic response was typical for 33 pairs of twins included in the study. Two pairs of twins, children, were excluded from the study, because they did not follow the

Table 1. Latency of Random Saccades

	MZ-MC	MZ-DC
Mean (msec)	179.6	176.1
Among-pair mean squares	1110	646
Within-pair mean squares	65	210
Intraclass correlations	0.885*	0.541†

MZ-MC, monozygotic twin (group) with monochorionic placentation; MZ-DC monozygotic twin (group) with dichorionic placentation.

* $P < 0.01$.

† $P < 0.05$.

Table 3. Latency of Semipredictable Saccades

	MZ-MC	MZ-DC
Mean† (msec)	170.6	166.2
Among-pair mean squares	687	431
Within-pair mean squares	114	201
Intraclass correlations	0.702*	0.379†

MZ-MC, monozygotic twin (group) with monochorionic placentation; MZ-DC, monozygotic twin (group) with dichorionic placentation.

* $P < 0.01$.

† $P < 0.05$.

instructions, and the number of saccades was too small to get reliable saccadic characteristics.

Statistical Analysis

The latency, accuracy, slope, and *V*15 of random and semipredictable saccades of MZ-MC and MZ-DC twins were compared using methods described by Williams et al.[18] We determined whether the saccadic parameters were normally distributed within the twins of each chorion type using the Kolmogorov-Smirnov test. Latencies and accuracies for random and semipredictable saccades were normalized by logarithmic transformations. There were no violations from normality in slope or *V*15. The comparisons of the saccadic parameters included the following: mean of MZ-MC = mean of MZ-DC (*t*-test, $P < 0.05$), total variances of MZ-MC = total variances of MZ-DC (F test[19]), the within-pair mean squares of MZ-MC = within-pair mean squares of MZ-DC, intraclass correlations of MZ-MC = intraclass correlations of MZ-DC, and intraclass correlations of MZ-MC and MZ-DC = 0. The intraclass correlations were calculated using the among-pair (AMZ) and within-pair (WMZ) mean squares variances by the formula zMZ = (AMZ − WMZ)/(AMZ + WMZ). The hypothesis that rMZ-MC = rMZ-DC was tested by comparing Z transformation of rMZ-MC and rMZ-DC. The hypotheses that rMZ-MC and rMZ-DC = 0 were tested using one-tailed F ratios (AMZ/WMZ).

Results

We calculated the product-moment correlations of latency, accuracy, slope, and *V*15 between the first and second trial results to evaluate the variability of saccadic characteristics in our children's data set. The correlation coefficient, averaged over four parameters (latency, accuracy, slope, and *V*15), was 0.79 for random saccades. The reliability was in good agreement with results obtained for adults.[7,20] We compared latency, slope and *V*15 of random saccades with the same parameters of semipredictable saccades (*t*-test for paired comparisons, $P < 0.05$). To avoid effects of correlation between twins, one subject (randomly selected) from each twin pair was included in the data set. We found that latency was greater and *V*15 was less statistically significant ($P < 0.05$) for random than for semipredictable saccades. The difference in slope didn't reach a statistically significant level. The results of comparison were the same for the first and second trials. The difference in velocities probably corresponded to difference in direction between random (centrifugal) and semipredictable (centripetal) saccades.

Tables 1, 2, 3, and 4 summarize the results obtained for latency, accuracy, slope, and *V*15 for random and semipredictable saccades. The characteristics, obtained from first and second trials, were very similar, and the results shown in the tables represent data averaged over the two trials. Table 1 shows MZ-MC and MZ-DC means, among-pair mean squares, within-pair mean squares, and intraclass correlations for latency of random saccades. There were no significant differences in mean latency between MZ-MC and MZ-DC twins. The hypothesis of equal latency variances of MZ-MC and MZ-DC twins was not rejected. The within-pair mean squares were greater for MZ-DC twins than for MZ-MC ($P < 0.05$). Both intraclass correlations were significantly greater than 0 (rMZ-MC, $P < 0.01$; rMZ-DC, $P < 0.05$). The intraclass correlation of MZ-MC twins was significantly greater than that of the MZ-DC twins ($P < 0.05$). Table 2 contains MZ-MC and MZ-DC means, among-pair mean squares, within-pair mean squares, and intraclass correlations for accuracy, slope, and *V*15 of random saccades. There were no significant differences in mean

Table 2. Accuracy, Slope, and Velocity of 15° Saccade (Random Saccades)

	MZ-MC			MZ-DC		
	Accuracy	Slope	*V*15	Accuracy	Slope	*V*15
Mean	0.93	59.7	435.7	0.92	60.5	410.8
Among-pair mean squares	0.118	135	4463	0.100	82	4111
Within-pair mean squares	0.039	39	1388	0.039	19	1349
Intraclass correlations	0.509†	0.552*	0.528*	0.445†	0.626*	0.507†

*V*15, velocity at 15° saccade; MZ-MC, monozygotic twin (group) with monochorionic placentation; MZ-DC, monozygotic twin (group) with dichorionic placentation.

* $P < 0.01$.

† $P < 0.05$.

TABLE 4. Accuracy, Slope, and Velocity of 15° Saccade (Semipredictable Saccades)

	MZ-MC			MZ-DC		
	Accuracy	**Slope**	***V*15**	**Accuracy**	**Slope**	***V*15**
Mean	0.93	58.9	475.4	0.92	57.5	455.6
Among-pair mean squares	0.115	127	5154	0.098	94	3888
Within-pair mean squares	0.037	46	978	0.035	26	1273
Intraclass correlations	0.486*	0.469*	0.680†	0.483*	0.573*	0.514*

MZ-MC, monozygotic twin (group) with monochorionic placentation; MZ-DC, monozygotic twin (group) with dichorionic placentation; *V*15, velocity at 15° saccade.

* $P < 0.01$.

† $P < 0.05$.

of accuracy, mean of slope, or mean of *V*15 between MZ-MC and MZ-DC twins. The hypotheses of equal variances of accuracy, slope, and *V*15 were not rejected. All intraclass correlations were significantly greater than 0 (MZ-MC accuracy $P < 0.05$, slope and *V*15 $P < 0.01$; MZ-DC slope $P < 0.01$, accuracy and *V*15 $P < 0.05$). There were no significant differences in within-pair mean squares or intraclass correlations between MZ-MC and MZ-DC twins. Tables 3 and 4 present the same data for semipredictable saccades. The pattern of results was similar to that for random saccades. For all four saccadic parameters there were no significant differences between means of MZ-MC and MZ-DC twins, intraclass correlations were significantly greater than 0, and the hypotheses of equal variance were not rejected. The within-pair mean squares were less and the intraclass correlation was greater for MZ-MC than for MZ-DC twins (Table 3), although these differences did not reach statistical significance ($P = 0.1$ and $P = 0.16$, respectively). The within-pair mean squares and intraclass correlations of accuracy, slope, and *V*15 were similar for MZ-MC and MZ-DC twins (Table 4).

Accardo et al.[21] found that children in the primary school age range had latencies similar to those of adults but higher peak velocities for random saccadic tasks. To decrease the possible influence of age on our results, we adjusted *V*15 and slope for age by linear regression analysis and repeated the analysis for adjusted data. The results obtained from the adjusted data repeated the same pattern we found on the raw data sets.

DISCUSSION

Intraclass correlations of MZ-MC and MZ-DC twins were statistically significantly different from 0 for latency, accuracy, slope, and *V*15 of random and semipredictable saccades. These results replicated our results from a previous study[8] in which all saccadic measures showed significant MZ correlations. The latency of random saccades (Table 1) showed a significant effect of chorion type. Total variances for this saccadic parameter were equivalent for MZ-MC and MZ-DC twins, but the within-pair mean squares and intraclass correlations were significantly different (Table 1). The latency of semipredictable saccades (Table 3) also showed similar influences of chorion type. In contrast, the accuracy, slope, and *V*15 showed no significant association with chorion type either for random (Table 2) or semipredictable saccades (Table 4). The intraclass correlations of these parameters were similar for both types of twins.

Our results suggest an association of chorion type with reaction times but not with the phasic component of the saccadic command (slope of main sequence, peak velocity for 15° saccades) or accuracy. Our results are consistent with the results of Sokol et al.[12] and Rose et al,[11] MZ-MC twins were found to be more similar than MZ-DC twins in other behavioral tests.

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In Vivo Demonstration of Increased Leukocyte Entrapment in Retinal Microcirculation of Diabetic Rats

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Purpose. Leukocytes have been reported to be less deformable and more activated in diabetes. It has also been suggested that they cause microvascular occlusions that may cause diabetic microangiopathy. This study was designed to evaluate in vivo leukocyte dynamics in the retinal microcirculation of diabetic rats.

Methods. Streptozotocin (STZ)-induced diabetic rats 4 weeks after diabetes induction and spontaneously diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats with 6 weeks' duration of diabetes were used in this study. Leukocyte dynamics were observed with acridine orange digital fluorography, using a nuclear fluorescent dye of acridine orange and high-resolution images from a scanning laser ophthalmoscope.

Results. There was no significant difference in capillary leukocyte velocity between the STZ-induced diabetic rats (1.27 ± 0.12 mm/sec, mean ± SD) and nondiabetic control subjects (1.38 ± 0.07 mm/sec) or between OLETF rats (1.31 ± 0.17 mm/sec) and the nondiabetic controls, Long-Evans Tokushima Otsuka (LETO) rats (1.29 ± 0.11 mm/sec). In contrast, the density of leukocytes trapped in the retinal microcirculation was significantly elevated in the STZ-induced diabetic (2.5-fold; $P < 0.01$) and the OLETF rats (2-fold; $P < 0.01$) compared with leukocyte density in the control subjects.

Conclusions. Pharmacologically induced and spontaneously diabetic rats showed increased leukocyte entrapment in the living retina in the early stages of diabetes. In light of the damaging potential of leukocytes, accumulation of leukocytes in diabetic retinas from the preretinopathy stage could cause microvascular occlusions and dysfunction, in turn causing diabetic retinopathy. (*Invest Ophthalmol Vis Sci.* 1998;39:2190-2194)

Capillary obstruction plays an important role as the initiator of the pathogenesis of diabetic retinopathy. Although capillary occlusions, subsequent vascular nonperfusion, and endothelial cell loss in early diabetic retinopathy are well understood clinically and histopathologically, little is known about the causes of the initial capillary occlusion.

In diabetes, leukocytes have been found to be less deformable[1] and more activated.[2] We have also studied the flow behavior of blood cells through microchannels that simulate capillaries and have reported that diabetic leukocytes occasionally plug the microchannels, prolonging the transit time of whole blood.[3] In addition, lower perfusion in the retina has been shown in the early stages of diabetes.[4-6] Thus, leukocytes can become trapped more easily in the retinal capillary bed of diabetes. Recent histopathologic studies have shown increased capillary occlusion and damage by leukocytes in the retina of diabetic rats[2] and in the choroid of patients with diabetes.[7] However, it is difficult to assess in vivo dynamic behavior of leukocytes in the microcirculation from histologic sections. Although an in vivo study recently showed that the incidence of leukocyte plugging increases throughout capillary networks in the skeletal muscle of diabetic rats,[8] no attempts have been made to examine leukocyte dynamics directly in the living retina.

We have recently developed a method called acridine orange digital fluorography that allows us to visualize leukocytes and examine leukocyte dynamics in rat retinal circulation in vivo.[9,10] In the present study, using this method, we investigated the dynamic behavior of leukocytes in the retinal microcirculation of streptozotocin (STZ)-induced diabetic rats, a chemically induced insulin-dependent diabetes mellitus model, and Otsuka Long-Evans Tokushima Fatty (OLETF) rats, a spontaneous model of non-insulin-dependent diabetes mellitus.

Methods

Animals

All animals were managed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. For chemically induced diabetes, a rat model was used in which diabetes was induced by streptozotocin (STZ; Sigma Chemical, St. Louis, MO). Diabetes was induced in 5 Long-Evans rats, weighing

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