Familial Aggregation of Severity of Diabetic Retinopathy in Mexican Americans From Starr County, Texas

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OBJECTIVE — Diabetic retinopathy is a major cause of blindness. To determine whether retinopathy itself or only its severity aggregates in families, we examined the occurrence and severity of diabetic retinopathy in Mexican-American siblings with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Using stereoscopic fundus photography of seven standard fields, we measured retinopathy in 656 type 2 diabetic patients from 282 Mexican-American families from Starr County, Texas. Retinopathy severity was scored using the Early Treatment of Diabetic Retinopathy Study system and classified as no retinopathy, early nonproliferative diabetic retinopathy (NPDR-E), moderate-to-severe nonproliferative diabetic retinopathy (NPDR-S), or proliferative diabetic retinopathy (PDR).

RESULTS — Of 249 siblings of randomly selected probands with retinopathy, 169 (67.9%) had retinopathy, compared with 95 of 125 siblings of unaffected probands (76.0%; $P = 0.11$). Proband retinopathy class was associated ($P = 0.03$) with sibling retinopathy class, with significant odds ratios (ORs) for NPDR-E versus no retinopathy (OR 0.57 [95% CI 0.35–0.93]) and PDR versus NPDR-E (2.02 [1.13–3.63]); the contrast of NPDR-S versus NPDR-E approached significance (1.78 [0.99–3.20]). With the more severe classes (PDR and NPDR-S) combined in one group and the less severe ones (none and NPDR-E) in another, more severe proband retinopathy was associated with more severe sibling retinopathy (1.72 [1.03–2.88]).

CONCLUSIONS — More severe diabetic retinopathy showed evidence of familial aggregation, but the occurrence of diabetic retinopathy per se did not. The factors involved in the onset of diabetic retinopathy may differ from those involved in its progression to more severe forms.

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Diabetic retinopathy, a frequent complication of both type 1 and type 2 diabetes, is the fifth most common cause of blindness in the U.S. (1). Some retinopathy occurs in virtually all type 1 and 60% of type 2 diabetic patients affected ≥20 years, although severe proliferative retinopathy is more frequent in type 1 diabetes. The underlying causes of diabetic retinopathy have not yet been elucidated, although tight control of hyperglycemia can retard its development and progression (1–4).

Numerous studies have examined specific genes or chromosomal regions in relation to the risk for diabetic retinopathy. Evidence of linkage between regions on chromosomes 3 and 9 and occurrence of retinopathy has been reported in Pima Indians with type 2 diabetes (5). Polymorphisms in a number of genes have been associated with diabetic retinopathy, although few associations have been replicated (6). Exceptions are aldose reductase (7–14) and the insertion/deletion polymorphism of the ACE gene (15,16), although meta-analysis did not support the latter association (17).

Despite studies relating genetic variation to risk of retinopathy, the extent to which diabetic retinopathy aggregates in families has not been clearly established. Concordance for retinopathy was found in 35 of 37 identical twins concordant for type 2 diabetes but in only 21 of 31 concordant for type 1 diabetes, suggesting a stronger genetic effect in type 2 diabetes (18). In families from the Diabetes Control and Complications Trial, risk of any retinopathy in relatives of subjects with retinopathy was not significantly higher than in relatives of subjects without it. However, the risk of severe retinopathy was higher among relatives of subjects with severe retinopathy than among relatives of those with mild or moderate retinopathy (19). In 322 South-Indian families having two or more siblings with type 2 diabetes, retinopathy prevalence was approximately three times higher in siblings of probands with retinopathy than in siblings of probands without it (20). In preliminary data collected in the early 1980s from 46 Mexican-American diabetic sibling pairs from Starr County, Texas, we found the prevalence of diabetic retinopathy in siblings of probands with retinopathy to be twice that in siblings of unaffected probands. We have now examined aggregation of diabetic retinopathy in a much larger sample of sibships from this same Mexican-American population.

RESEARCH DESIGN AND METHODS

— Mexican-American families from Starr County, Texas, having two or more siblings with type 2 diabetes

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Abbreviations: NPDR-E, early nonproliferative diabetic retinopathy; NPDR-S, moderate-to-severe nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Statistics for selected variables by probands' status*

	Random probands		Duration-based probands	
	Probands	Nonprobands	Probands	Nonprobands
Discrete variables				
Sex				
Male	109 (38.7)	149 (39.8)	117 (41.5)	141 (37.7)
Female	173 (61.3)	225 (60.2)	165 (58.5)	233 (62.3)
Retinopathy				
No	89 (31.6)	110 (29.4)	48 (17.0)	151 (40.4)*
Yes	193 (68.4)	264 (70.6)	234 (83.0)	223 (59.6)
Continuous variables				
Age (years)	58.2 ± 10.2	59.0 ± 9.7	58.9 ± 9.7	58.5 ± 10.1
BMI (kg/m^2)	31.4 ± 6.2	31.1 ± 6.2	30.6 ± 5.6	31.8 ± 6.6*
Glucose (mg/dl)	191.9 ± 69.8	186.2 ± 67.5	194.7 ± 73.3	184.2 ± 64.4†
HbA_{1c} (%)	10.8 ± 3.8	10.2 ± 4.1	10.6 ± 4.3	10.4 ± 3.7
Age at diagnosis (years)	49.2 ± 10.5	50.2 ± 10.7	45.6 ± 9.7	52.9 ± 10.2*
Type 2 diabetes duration (years)	9.1 ± 7.4	8.9 ± 7.2	13.3 ± 7.8	5.7 ± 4.7*
Retinopathy score	31.5 ± 19.7	31.1 ± 18.4	37.6 ± 19.0	26.5 ± 17.5*

Data are *n* (%). *$P < 0.05$; †$P < 0.10$ for probands vs. nonprobands.

were eligible for the study. Diabetes classification was based on National Diabetes Data Group guidelines from 1979 wherein individuals currently treated for diabetes having fasting glucose ≥140 mg/dl on more than one occasion or having an abnormal glucose tolerance test were considered to have diabetes. A diagnosis of type 2 diabetes was excluded if age at diagnosis was <30 years, BMI was <30 kg/m^2, and insulin had been used continuously since diagnosis. Subjects were enrolled through the Family Blood Pressure Program, as previously described (21).

Retinopathy grading

Stereoscopic color fundus photographs of seven standard fields of each eye were scored using the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification system (22). Scores for the more severely affected eye were used to classify diabetic retinopathy as follows: 10–12: normal or nondiabetic retinopathy; 15–37: early nonproliferative diabetic retinopathy (NPDR-E); 43–53: moderate-to-severe nonproliferative diabetic retinopathy (NPDR-S); 60–85: proliferative diabetic retinopathy (PDR).

Analyses

We used contingency tables and logistic regression to compare the prevalence and severity of retinopathy among siblings of probands classified by retinopathy status. With logistic regression, generalized estimating equations were used to account for correlations among family members, using proportional odds models for polytomous outcomes (23–25). Because neither individuals nor families were selected on the basis of retinopathy, the usual definition of a proband as an affected individual through whom a family is ascertained was not applicable. We used two different methods to designate probands. In the first method, one proband was selected at random from each family; in the second, the proband in each family was the sibling who had had diabetes the longest. Wilcoxon's rank-sum tests and χ^2 tests were used to compare probands and nonprobands. Note that in contingency table and logistic regression analyses, the retinopathy status of the proband was an attribute of each family; the probands themselves were not included in the analyses. Statistical analyses were performed using SAS software (SAS Institute, Cary, NC).

RESULTS

— Complete retinopathy and covariate data were available for 656 subjects from 282 sibships. There were 214 sibships of size two (75.9%), 49 sibships of size three (17.4%), 14 sibships of size four (5.0%), and five sibships of size five (1.8%). Of the total sample, 398 subjects were female (60.7%) and 258 were male (39.3%). Some degree of retinopathy was present in 457 subjects (69.7%).

With randomly chosen probands, there were no statistically significant differences between probands and nonprobands in key characteristics (Table 1). With probands selected on the basis of diabetes duration, however, the situation was different. Duration-based probands necessarily had longer mean diabetes duration than nonprobands ($P < 0.001$) and had been diagnosed at younger ages ($P < 0.001$). As expected, retinopathy prevalence (59.6%) and severity scores (mean ± SD 37.6 ± 19.0) in duration-based probands were significantly higher than in nonprobands (40.4% and 26.5 ± 17.5, respectively; $P < 0.001$ for both). Less predictably, mean BMI was significantly lower in duration-based probands than in nonprobands ($P = 0.017$). The combination of obesity and long-term diabetes may increase mortality, lowering average BMI among survivors of long-term diabetes (26). Alternatively, late-stage or long-term diabetes may be associated with some degree of weight loss (27,28). Both types of probands yielded similar results in analyses of familial aggregation. We hereafter focus on results based on randomly chosen probands, noting any differences found with duration-based probands.

Whether a proband's siblings had any retinopathy was independent of whether the proband was affected: 169 of 249 siblings of retinopathy-affected probands had retinopathy themselves (67.9%), compared with 95 of 125 siblings of unaffected probands (76.0%; $P = 0.110$).

Table 2—*Observed and expected numbers of nonprobands by severity of retinopathy in randomly assigned probands*

Retinopathy in proband	Retinopathy in nonproband			
Four groups*	PDR	NPDR-S	NPDR-E	None
PDR				
Observed	5	16	16	10
Expected	5	11	17	14
NPDR-S				
Observed	13	18	25	23
Expected	8	18	30	23
NPDR-E				
Observed	8	21	47	47
Expected	13	28	46	36
None				
Observed	13	30	52	30
Expected	13	28	47	37
Three groups†		Severe	Mild	None
Severe				
Observed		52	41	33
Expected		42	47	37
Mild				
Observed		29	47	47
Expected		41	46	36
None				
Observed		43	52	30
Expected		41	47	37
Two groups†		Severe		Mild or none
Severe				
Observed		52		74
Expected		42		84
Mild or none				
Observed		72		176
Expected		82		166

*$0.05 < P < 0.10$; †$P < 0.10$.

To assess whether the severity, rather than the occurrence, of retinopathy might show evidence of familial aggregation, we cross-tabulated retinopathy classes of probands and their siblings (Table 2). Although an overall χ^2 test of independence (ignoring familial relationships) only approached significance ($P = 0.066$), comparisons of observed and expected numbers (expected numbers derived under the hypothesis of independence between the retinopathy status of probands and their siblings) illustrates certain patterns. Fewer siblings of probands with mild retinopathy (NPDR-E) had more severe retinopathy than expected, either NPDR-S (8 observed vs. 13 expected) or PDR (21 observed vs. 28 expected). However, more of these siblings than expected had no retinopathy (47 observed vs. 36 expected). More siblings of probands with NPDR-S had PDR than expected (13 observed vs. 8 expected) and more siblings of probands with PDR had NPDR-S than expected (16 observed vs. 11 expected). However, for both proband classes, the observed numbers of siblings with the same level of retinopathy severity as the proband matched expectations. These comparisons suggest that severely affected probands are more likely to have severely affected siblings, whereas mildly affected probands more likely have mildly affected siblings.

With the more severe retinopathy classes (PDR and NPDR-S) combined, the overall hypothesis of independence was rejected ($P = 0.015$). Probands with severe retinopathy again had more siblings with severe retinopathy than expected; however, probands with mild retinopathy had more siblings with no retinopathy than expected (Table 2). With the two less severe classes also combined in one group, the hypothesis of independence was again rejected ($P = 0.018$).

As another test of familial aggregation, we restricted analyses to sibling trios drawn from the 68 sibships of size three or greater (randomly selecting one trio from each sibship of size four or greater). We randomly selected one pair from each trio, counted the number in each pair who were concordant either for retinopathy prevalence or severity, and tested whether pairs with two affected members were more likely to have a third sibling similarly affected. As there were only three pairs with neither member affected, we grouped these with the pairs having only one affected member. Pairs in which both siblings had retinopathy, whether mild or severe, were no more likely to have a third affected sibling than were pairs with zero or one members affected (Table 3) ($P = 0.762$). However, pairs in which both members had some degree of retinopathy were more likely to have a third sibling with severe retinopathy ($P = 0.038$). Furthermore, pairs in which both members had severe retinopathy were significantly more likely to have a third sibling with severe retinopathy, whereas pairs in which neither member had severe retinopathy were less likely to have a severely affected sibling ($P = 0.028$).

These tests, however, did not explicitly account for correlations among family members. We therefore used logistic regression with generalized estimating equations to account for correlations among siblings. With only proband retinopathy status as a predictor, four-, three-, and two-group retinopathy classifications all yielded statistically significant evidence of familial aggregation of retinopathy severity ($P = 0.019$, $P = 0.013$, and $P = 0.033$, respectively). Because other factors may influence risk of diabetic retinopathy, we tested potential covariates including age, sex, BMI, hypertension status, fasting blood glucose, HbA_{1c}, and diabetes duration. Only the last two factors were consistently significant and included in our final models (Table 4); hypertension status was also significant but because its inclusion did not affect inferences regarding proband's

Table 3—*Retinopathy status of randomly chosen member of sibling trio vs. number of siblings with a given retinopathy status in the remaining pair*

	Retinopathy status of third sibling	
Status (pair vs. sibling)	Affected	Unaffected
Affected vs. affected		
Two affected pair members		
Observed	9	22
Expected	10	21
One or no affected pair member		
Observed	12	25
Expected	11	26
Affected vs. severity*		
Two affected pair members	Severe	None or Mild
Observed	16	15
Expected	12	19
One or no affected pair member		
Observed	10	27
Expected	14	23
Severity vs. severity*		
Two affected pair members		
Observed	7	2
Expected	3	6
One affected pair member		
Observed	9	16
Expected	10	15
No affected pair member		
Observed	10	24
Expected	13	21

*$P < 0.05$.

retinopathy status, we present results for models without it. HbA_{1c} and, especially, diabetes duration had larger effects than did proband's retinopathy status, emphasizing the importance of glycemic control and diabetes duration in retinopathy. However, evidence of familial aggregation of more severe retinopathy remained, even after accounting for the effects of glycemic control, diabetes duration, and correlations among siblings. With covariates included, an overall χ^2 test for the proband's retinopathy status, using four groups, only approached significance ($P = 0.055$). However, overall tests for both three and two retinopathy groups were significant ($P = 0.028$ and $P = 0.046$, respectively). Because the global test for three groups was significant, we tested all pairwise contrasts between groups. The contrast for probands with severe retinopathy (PDR or NPDR-S) relative to those mildly affected (NPDR-E) was significant ($P = 0.014$; odds ratio = 1.89 [95% CI 1.14–3.15]), even with a Bonferroni adjustment for multiple testing ($\alpha = 0.017$). With two groups (PDR or NPDR-S vs. normal or NPDR-E), the risk of severe retinopathy in siblings of severely affected probands was modestly increased (1.71 [1.03–2.84]).

Models using duration-based probands gave generally similar results, though the effect of diabetes duration was reduced somewhat. Using duration-based probands lowered the mean and the variance of diabetes duration in nonprobands (Table 1), attenuating the effect of disease duration in the models. In models with HbA_{1c} and diabetes duration as covariates, the effect of retinopathy status was significant with four groups ($P = 0.044$), but not with three ($P = 0.057$) or two ($P = 0.101$). However, in each case, estimated coefficients for the retinopathy groups were similar to those obtained with randomly chosen probands.

CONCLUSIONS — Overall, we found evidence of familial aggregation of the severity of diabetic retinopathy. The occurrence of severe diabetic retinopathy in one sibling predicts increased risk of severe retinopathy in other siblings with type 2 diabetes, even after other risk factors for retinopathy such as diabetes duration and poor glycemic control are taken into account. However, we found no evidence that the occurrence of retinopathy per se aggregates in Mexican-American families with type 2 diabetes. Familial aggregation of the severity, but not the occurrence, of diabetic retinopathy may indicate that the biological factors that determine its severity are different from those that determine its onset.

Despite numerous studies of associa-

Table 4 —*Odds ratios for diabetic retinopathy status of siblings of randomly chosen probands*

	Reference group	Odds ratio	95% CI
Four retinopathy classes			
$HbA_{1c} \geq 10.1\%$	<10.1%	2.16	1.40–3.05
Diabetes duration ≥11 years	<11 years	5.47	3.50–8.55
PDR	No diabetic retinopathy	1.14	0.64–2.03
NPDR-S	No diabetic retinopathy	0.95	0.53–1.70
NPDR-E	No diabetic retinopathy	0.57	0.35–0.93
Three retinopathy classes			
$HbA_{1c} \geq 10.1\%$	<10.1%	2.39	1.60–3.58
Diabetes duration ≥11 years	<11 years	5.98	3.76–9.51
PDR or NPDR-S	No diabetic retinopathy	1.06	0.63–1.79
NPDR-E	No diabetic retinopathy	0.56	0.33–0.94
Two retinopathy classes			
$HbA_{1c} \geq 10.1\%$	<10.1%	2.11	1.31–3.40
Diabetes duration ≥11 years	<11 years	5.46	3.30–9.04
PDR or NPDR-S	NPDR-E or no diabetic retinopathy	1.71	1.03–2.84

Data are from logistic regression models accounting for familial correlations, proportional odds model with cumulative logits.

tions between diabetic retinopathy and variants in candidate genes, evidence for familial aggregation of diabetic retinopathy is surprisingly limited. For instance, in twin studies, most retinopathy-concordant twins had no retinopathy; only 4 of 68 pairs were concordant for severe retinopathy (18). Given that retinopathy and diabetes duration are strongly related, concordance for lack of retinopathy may be less informative than concordance for its presence, because some subjects with no retinopathy at the time of a study may develop it later. It has been suggested that because most patients with type 2 diabetes eventually develop retinopathy, there may be little genetic variation in susceptibility to diabetic retinopathy per se, even if genetic variation affects its severity (19). However, in a sample of South-Indian families having two or more siblings with type 2 diabetes, the odds ratio for retinopathy among siblings of probands with retinopathy relative to siblings of unaffected probands was 3.37, even after adjusting for age, diabetes duration, systolic blood pressure, proteinuria, and HbA_{1c} (20). This does not accord either with our findings or those of the Diabetes Control and Complications Trial study (19). However, the South-Indian sample may have been biased toward families more concordant for retinopathy, because only siblings who were patients at a regional diabetes clinic and had received retinal examinations as part of their clinical care were eligible. If diabetic patients without retinopathy are less likely to have visual problems and to receive retinal examinations (29), potentially unaffected siblings would have had a higher probability of being excluded from the study.

One factor that might obscure evidence of familial aggregation of diabetic retinopathy in our population is the very high retinopathy prevalence in our sample. Almost 70% of our subjects had some retinopathy; of 282 sibships, only 20 (7.1%) contained no affected members. In the studies of monozygotic twins, 35% of those with type 2 diabetes had retinopathy (18). In population-based studies, estimates of retinopathy prevalence in Mexican Americans with type 2 diabetes have ranged from ~33 to 48% (30–33). In 118 diabetic individuals from Starr County selected without regard to whether any family members had type 2 diabetes, the prevalence of retinopathy was 45% (C.L.H., D.M.H., V.H.G., B.E.K.K., R.K., unpublished observations), much less than that in our family sample.

This difference in retinopathy prevalence between family-based and population-based samples is not surprising. To increase the number of families likely to be carrying high-risk alleles for diabetes, we enrolled only families in which at least two siblings had type 2 diabetes, which would tend to select for longer disease duration. As disease duration is the paramount risk factor for diabetic retinopathy, retinopathy prevalence is likely to be higher in families selected for diabetes than in diabetic subjects from the general population.

Overall, our findings are consistent with observations suggesting that a familial component for risk of diabetic retinopathy is related more to its severity than to its onset (19). That most subjects with diabetes of more than 20 years' duration develop retinopathy also suggests that familial factors do not play a major role in its onset. The mechanisms underlying the onset of mild retinopathy may differ from those involved in its progression to more severe forms. Retinopathy comprising one or two microaneurysms is found in 7% of the general nondiabetic population and 11% of hypertensive individuals (34,35). Factors that can accompany diabetes even in the absence of severe hyperglycemia, such as hypertension, may be more important in retinopathy onset, whereas factors associated with severe or long-term hyperglycemia, such as ischemia and hypoxia associated with increased levels of vascular endothelial growth factor, may be more important in progression of retinopathy to more severe forms. Genetic or environmental factors shared within families may have more impact on advanced microvascular complications of diabetes, leading to familial aggregation of more severe retinopathy rather than retinopathy onset. In studying the genetic factors affecting diabetic retinopathy, it may be preferable to focus on more severely affected individuals.

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