Diabetic Retinopathy in Identical Twins

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SUMMARY

The prevalence and features of diabetic retinopathy have been examined in twenty-three pairs of identical twins—thirteen concordant (both diabetic) and ten discordant (one diabetic, one not)—who have had diabetes for at least fifteen years. In the concordant pairs retinopathy was more common (present in twenty-three out of twenty-six individuals) and more severe (seven blind or partially sighted) and a family history of diabetes was more frequent than in the discordant pairs (retinopathy in five out of ten, none blind). In twelve out of the thirteen concordant pairs the progression and severity of retinopathy was strikingly similar in the two twins and was correlated only with the duration of diabetes. In the thirteenth pair after twenty years of diabetes, one was blind and the other had normal eyes, although they showed no obvious differences in control or other features. It seems that genetic factors may be important in the etiology and time of appearance of diabetic retinopathy. DIABETES *22*:613-18, August, 1973.

The etiology of diabetic retinopathy is unknown. It is generally assumed that the condition is related to the biochemical disorders of diabetes. However, there is a possibility that constitutional factors, which have some bearing on the etiology of diabetes itself, may also influence the appearance of its complications.

In order to test this suggestion we have examined identical twins one or both of whom has diabetes. Since identical twins have the same genetic make-up, any difference between them must be due to environmental factors; similarities, on the other hand, may be due either to genetic factors alone or to the effects of a shared environment.[1]

MATERIALS AND METHODS

We have described elsewhere[1] our clinical material which consists of ninety-six pairs of identical twins, sixty-five concordant (both diabetic) and thirty-one discordant (one twin diabetic, the other not). Since retinopathy is uncommon in the early years of diabetes, we have restricted the present study to those twins who have been diabetic for at least fifteen years. This group consists of thirteen concordant pairs (twenty-six diabetic individuals) and ten discordant pairs (ten diabetic individuals).

Evidence that the twins were identical comes from clinical history and examination and has been confirmed by testing for the blood groups ABO, CDE, MN, S, P, Lu, K, Le^a, and Fy^a. The chance that a pair of twins concordant for all these blood groups are not monozygotic is less than 3 per cent.[2] Three pairs—two concordant and one discordant (Nos. 11, 12, and 16; see tables 4 and 5)—could not be blood grouped. Nevertheless strong presumptive evidence of their monozygosity was obtained from photographs and from a questionnaire similar to that used by Cederlöf et al.[3] which correlates closely with the results of blood grouping.

In all the concordant pairs the twin in whom diabetes was first diagnosed has had the disease for at least fifteen years, but in two pairs the other twin has had diabetes for a shorter time, nine and fourteen years; in the other eleven pairs both twins have been diabetic for over fifteen years, as have all the diabetic members of the discordant pairs.

The age at diagnosis and the duration of diabetes is similar for the concordant and discordant pairs (table 1). Most of the twins were young at the onset of diabetes, the mean age being about twenty-six in both groups. Both concordant and discordant twins had been diabetic for a long time (mean twenty-three years). The average age of the twins at the time of examination was the same for both groups, forty-nine. Most of the twins were insulin-dependent; only three were treated without insulin—both twins of one pair and one twin of another concordant pair.

A detailed medical history was taken and full physical examination carried out on all the living twins; both members of pair 12 and one member of pairs 11 and 16 had died before the present study was undertaken. However, pairs 11 and 12 had been examined before

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TABLE 1

Age at diagnosis and duration of diabetes in concordant and discordant pairs

Twins	No. of pairs	No. of diabetic individuals	Mean age at diagnosis of diabetes	Range	Mean duration of diabetes	Range
Concordant (both diabetic)	13 (7 F 6 M)	26	25.7	5-52	23.3	9-43
Discordant (only one diabetic)	10 (7 F 3 M)	10	27.3	4-44	21.9	15-31

their deaths and full hospital records and fundus photographs were available. Information about the dead twin of pair 16 was obtained from hospital records.

In all the twenty living pairs we carried out ophthalmoscopic examination after pupillary dilation. Eight of the thirteen concordant and seven of the ten discordant pairs were also examined by our colleague, Mr. Geoffrey Davies, who was unaware at the time of examination whether these twins were concordant or discordant. We classified the fundus appearances as follows: [1] Normal; [2] Microaneurysms only; [3] Hemorrhages and exudates; or [4] Proliferative retinopathy.

In all but one of the discordant pairs the unaffected twin had an oral glucose tolerance test and all were within normal limits. The unaffected member of the remaining pair (pair 16) died from carcinoma of the breast twenty-four years after the onset of diabetes in her twin. An oral glucose tolerance test five years before her death was normal and there was no record of overt diabetes during her terminal illness. Repeated testing of the other nine unaffected twins over a period of two to six years has shown no deterioration in glucose tolerance, and for this and other reasons we suspect that most of these twins will not develop diabetes, i.e. are not "prediabetics."[1]

RESULTS

The unaffected discordant twins. We have not detected any abnormalities in the eyes of the nine non-diabetic members of discordant pairs whom we were able to examine; the tenth had died.

Comparison of concordant and discordant twins. Among the concordant twins twenty-three out of the twenty-six diabetic individuals showed some degree of retinopathy compared to only five out of ten diabetic members of the discordant pairs (table 2). The severity of retinopathy was strikingly different in the two groups (table 3). Among the concordant twins were eleven individuals who showed retinitis proliferans; five of these were blind and two partially sighted, with vision less than 6/60 in both eyes (table 4). Among the discordant twins, only one had retinitis proliferans and she retained good vision (table 5).

TABLE 2

Prevalence of retinopathy

	Concordant	Discordant
Retinopathy present	23	5
Retinopathy absent	3	5
	26	10

Considering only the more severe degrees of retinopathy (i.e. hemorrhages and exudates or proliferative retinopathy), we find that twenty-one of the twenty-six concordant twins were affected compared to only three of the ten diabetic discordant twins. Because of the small numbers these differences do not reach conventional levels of statistical significance,* but they suggest

*The significance of the difference between five out of ten affected discordant twins and eleven out of thirteen concordant pairs in whom both twins have retinopathy is—$P = 0.17$ (using Fischer's exact test). The difference between five out of ten discordant twins and twelve out of thirteen concordant pairs in whom either both or one twin has retinopathy is—$P = 0.052$.

TABLE 3

Comparison of the severity of retinopathy in concordant and discordant twins

	No.	Without retinopathy	With retinopathy: Microaneurysms only	Hemorrhages and/or exudates	Proliferative retinopathy
Concordant	26	3	2	10	11 (5 blind, 2 partially sighted)
Discordant	10	5	2	2	1 (normal vision)

TABLE 4

Retinopathy in twin pairs concordant for diabetes

Case No.	Sex	Age at onset of diabetes	Duration of diabetes at time of study	Family history (First degree)	Ocular complications of diabetes
1A	F	7	43	Father	Proliferans. Vitreous hemorrhage. Blind.
1B		9	41		Proliferans. Vitreous hemorrhage. Partially sighted.
2A	M	10	31	Mother	Proliferans. Vitreous hemorrhage. Blind. Rubeosis.
2B		17	24	Brother	Proliferans. 6/6 vision.
3A	M	16	28	0	Hemorrhages and exudates.
3B		17	27		Hemorrhages and exudates.
4A	F	27	31	0	Hemorrhages and exudates.
4B		32	26		Hemorrhages and exudates.
5A	M	29	34	0	Proliferans. Vitreous hemorrhage. Blind.
5B		38	25		Proliferans. Vitreous hemorrhage. Blind.
6A	M	19	19	0	Proliferans. Vitreous hemorrhage. Partially sighted.
6B		21	17		Hemorrhages and exudates. Cataract.
7A	M	11	18	0	Proliferans. Vitreous hemorrhage.
7B		19	9		Hemorrhages and exudates.
8A	F	5	18	0	None
8B		6	17		None
9A	M	40	23	Father	Hemorrhages and exudates.
9B		40	23		Hemorrhages and exudates.
10A	F	41	20	Father	None
10B		41	20		Proliferans. Vitreous hemorrhage.
11A	F	44	15	Father	Proliferans. Vitreous hemorrhage. Blind. Rubeosis.
11B		44	19		Proliferans. Rubeosis.
12A	F	49	19	0	Hemorrhages and exudates.
12B		52	14		Hemorrhages and exudates.
13A	F	11	20	0	Microaneurysms only.
13B		11	20		Microaneurysms only.

that retinopathy may be both more common and more severe in the concordant group.

The twenty-six concordant twins and the ten diabetic discordant twins have been compared with respect to factors which might account for the increased severity of retinopathy in the concordant group. We have found no differences in body weight, blood pressure, insulin dosage or serum cholesterol between concordant and discordant twins nor, in the concordant pairs, between the first- and second-diagnosed twins.

There was, however, a striking difference in family history of diabetes between the concordant and discordant twins, five of the thirteen concordant pairs but none of the ten discordant pairs having a diabetic parent (table 6).*

Another factor which might explain a difference between the severity of retinopathy in the two groups of twins is the control of their diabetes. This is notoriously difficult to measure, especially in retrospect. Nevertheless, we have made the attempt and have found no difference between the concordant and discordant twins in [1] the interval between onset of symptoms and the diagnosis of diabetes, [2] frequency of emergency hospital admission for ketoacidosis or [3] degree of glycosuria in those twins (thirteen concordant and eight discordant) for whom adequate data exist.

Progression of retinopathy in concordant pairs. The nature and severity of retinopathy in the concordant pairs is, with one exception, strikingly similar.

In one pair (No. 8) both twins have normal fundi. They are of considerable interest. They developed diabetes at the ages of five and six, and both have always had unstable diabetes which is badly controlled by any criteria. Each has had over twenty hospital admissions for ketoacidosis, and one was a heroin addict for two years. In spite of having diabetes for eighteen and seventeen years, respectively, neither twin shows any retinopathy.

Nine pairs have similar types of retinopathy, either simple or proliferative (Nos. 1, 2, 3, 4, 5, 9, 11, 12, and 13 in table 4). In two pairs (Nos. 6 and 7) the retinopathy is different in degree, one twin showing prolifer-

*We have not been able to examine the affected relatives of the twins and do not know whether any also had diabetic retinopathy.

TABLE 5

Retinopathy in the diabetic twins of pairs discordant for diabetes

Case No.	Sex	Age at onset	Duration	Family history (1st degree)	Ocular complications of diabetes
14.	M	25	21	0	Scattered microaneurysms.
15.	F	4	29	0	Hemorrhages and exudates.
16.	F	34	24	0	Hemorrhages and exudates.
17.	F	20	30	0	Proliferans.
18.	F	44	17	Sister	None.
19.	M	36	15	0	None.
20.	F	13	16	0	None.
21.	F	38	25	0	None.
22.	F	24	20	0	A few microaneurysms.
23.	M	34	17	0	None.

ative retinopathy, the other simple, but in both pairs the twin with simple retinopathy has not had diabetes as long as the one with proliferative changes. In pair 7, one twin had hemorrhages and exudates after fifteen years of diabetes and proliferative retinopathy after eighteen years. The other twin has had diabetes for only nine years and already shows hemorrhages and exudates. In pair 6 the difference in diabetes duration is only two years; both twins show extensive hemorrhages and exudates but the twin in whom diabetes was first diagnosed also shows some neovascularization which is not present in his twin.

TABLE 6

Family history of diabetes

	Number of pairs	Number with diabetic parent
Concordant	13	5
Discordant	10	0

In eight of the pairs for whom it is possible to date the onset of hemorrhages and exudates accurately the duration of diabetes at the time these ocular changes occurred was strikingly similar (table 7). Retinopathy seems to be discovered earlier in the twin in whom diabetes is recognized last, although this may be merely a reflection of a tendency for the second twin to be examined after the discovery of retinopathy in the first. In pair 11 (table 4) the interval may be more apparent than real since it was difficult to date the onset of diabetes precisely in the index twin and the second twin had not had her eyes examined for several years before retinopathy was discovered.

There is one exceptional pair. After twenty years of diabetes one is blind from proliferative retinopathy, the other has normal eyes:

Violet and Iris (pair 10) are women now aged sixty who have had diabetes for twenty years. Their father had mild diabetes for several years before his death at age seventy-eight, but it is not known if he had retinopathy.

Violet presented at the age of forty with a two week history of pruritus vulvae and thirst and was found to have a fasting blood sugar of 320 mg./100 ml. Her diabetes was satisfactorily stabilized on PZI 14 U. daily. Microaneurysms and exudates were noted after nine years of diabetes, and after fourteen years her vision was seriously impaired by bilateral macular exudates. After seventeen years neovascularization was observed and she had her first vitreous hemorrhage. Further vitreous hemorrhages followed in both eyes and she is now blind twenty years after diabetes was diagnosed.

Iris, at the time her sister developed diabetes, had had pruritus vulvae for three months. She was found to have a fasting blood sugar of 310 mg./100 ml. and

TABLE 7

Time of appearance of background and proliferative retinopathy in affected concordant twins: In most pairs the duration of diabetes is about the same in each twin when retinopathy is first observed

	Duration of diabetes at which hemorrhages and exudates were first observed		Duration of diabetes at which proliferative retinopathy was first observed	
Pair No.	1st twin	2nd twin	1st twin	2nd twin
1.	35	32	36	33
2.	Not known	Not known	20	23
3.	26	24	None	None
4.	30	22	None	None
5.	22	20	25	22
6.	Not known	8	20	(16)*
7.	11	9	15	(10)*
9.	25	25	None	None
10.	9	None	15	(20)*
11.	7	14	10	15
12.	15	13	None	None

* No proliferative changes. Figures in parentheses indicate duration of diabetes at time of study.

Neither twin of pair 8 had retinopathy; both twins of pair 13 had microaneurysms only.

was stabilized at a different hospital on PZI 20 U. daily. After twenty years of diabetes, she has normal optic fundi.

The course of diabetes in this pair of twins is summarized in table 8. They have attended different diabetic clinics and have lived apart since early adult life. Both were put on insulin immediately after diagnosis, and attempts have been made to stabilize each of them on oral hypoglycemic drugs. Each twin independently put herself back on to insulin because of poor urine tests. Both have tested their urine once a day and have conscientiously adhered to their diets. Full records are available for Violet, the twin with retinopathy. They cover a period of twenty years and show a very high standard of diabetic control, the number of urine tests showing 2 per cent glycosuria being only 10 out of 228. Few blood tests were done.

Iris, the twin with normal eyes, did not attend a clinic for the first ten years after diagnosis but the records of thirty-four clinic visits in the next ten years show excellent control.

Neither twin is overweight, has suffered from diabetic ketosis or shows any other diabetic complication. We have not been able to find any difference between them which might account for such a strikingly dissimilar degree of diabetic retinopathy.

TABLE 8

A pair of identical twins, diabetic for twenty years, with strikingly dissimilar eyes

	Violet	Iris
Fundi in 1972	Bilateral retinitis proliferans (blind)	Normal
Age at diagnosis of diabetes	40	40
Duration of symptoms at time of diagnosis	2 weeks	3 months
Fasting blood sugar at time of diagnosis	320 mg./100 ml.	310 mg./100 ml.
Started on insulin	Immediately	Immediately
Initial insulin dosage	PZI 16 U.	PZI 20 U.
Insulin dosage in 1972	PZI 16 U.	Lente 52 U.
Hospital admissions for ketoacidosis	0	0
Diet	2000 cal.	1800 cal.
*Urine tests showing 2 per cent sugar	10/228	1/34
*Urine tests showing 1 per cent sugar	29/228	0/34
*Blood sugars > 200	1/8	13/34
*Blood sugars > 300	0/8	2/34
Pregnancies	0	2
Menopause	49	49
Blood pressure:		
At diagnosis	140/90	114/70
In 1972	155/90	160/80
Serum cholesterol	325 mg./100 ml.	300 mg./100 ml.

* Figures obtained from examining all available hospital records which in the case of Iris are few as she did not attend a clinic for the first ten years after diagnosis; Violet has attended hospital regularly and has had many urine but few blood tests.

DISCUSSION

Although there are nearly fifty detailed case reports of diabetes in identical twins, in only one pair was an abnormal appearance of the fundus noted.[4]

Fischer,[5] in a study of ten diabetic sibships, considered that the predisposition to proliferative retinopathy was inherited. Caird, Pirie, and Ramsell[6] did not support this conclusion although they found that the children of parents with retinopathy seemed to show a slightly increased tendency themselves to develop retinopathy.

Since the unaffected twins in our discordant pairs show little sign of becoming diabetic[1] it seems reasonable to conclude that the etiology of diabetes in the affected twin is predominantly non-genetic. In the concordant pairs, on the other hand, genetic factors probably play a large, though not necessarily the only, part in the etiology of the diabetes. The greater frequency and severity of retinopathy in the concordant than in the discordant twins in the present series suggests that genetic factors may also be important in the etiology of diabetic retinopathy. This seems to be supported by the striking similarity in the type and progression of the retinopathy in all but one of the thirteen concordant pairs.

The alternative explanation—that the similarity of retinopathy is due to similarity of environment—does not seem likely. Ten of the thirteen pairs have lived apart for most of their diabetic lives, including, in eight cases, the first five years after diagnosis which, it has been suggested,[7,8] may be the most important period.

We cannot refute the suggestion that the difference in retinopathy between concordant and discordant pairs may be due to difference in diabetic control; we can only say that we have found no evidence of it. And in the one pair with strikingly dissimilar eyes (pair 10), control of diabetes, insofar as this can be measured, appeared to be good in both. In this pair, at least, it seems that another explanation of the difference in retinopathy is needed.

In spite of collecting this relatively large series of twins we are still not in a position to meet Cahill's[9] requirement for settling the controversy about the relation between control of diabetes and its complications—

i.e. identical twins of whom one is well and the other poorly controlled. We suspect that we never shall be, because of the rarity of such cases and the difficulty of assessing control.

There have been reports of retinopathy apparently antedating the metabolic abnormalities of diabetes. It is difficult to assess these reports because in many of them proof of the absence of diabetes is inadequate. The only two cases where the patient had unequivocally normal glucose tolerance were reported by Levine[10] and Linnar et al.[11]

If there are any patients who might be expected, because of their heredity, to show diabetic retinopathy without diabetes it is the unaffected identical twins of diabetics. We have not found any sign of retinopathy in the nine unaffected identical twins of diabetics reported here.

In our opinion a more probable explanation for the rare cases where retinopathy appears to precede diabetes is that these individuals are in fact latent diabetics who have had sustained hyperglycemia in the past which has later remitted.

Comparison of retinopathy in discordant and concordant twins. There is a widespread assumption that "idiopathic" diabetes mellitus is an etiologically homogeneous disorder which is inherited. This assumption is, we believe, unsound[1] and has been made less secure by the discovery that diabetes can be caused by viral infections of the pancreas in mice[12] and by circumstantial evidence that the Coxsackie B_4 virus may be implicated in some cases of juvenile diabetes in man.[13]

If a wholly environmentally determined form of diabetes does exist, one would expect to find it in the diabetic twins of discordant pairs. The fact that five of ten of our discordant twins showed retinopathy suggests that it is the condition of diabetes itself rather than any genetic factors which leads to the retinopathy. This is supported by the finding of diabetic retinopathy in hemochromatosis[14] and other types of secondary diabetes.[15,16] Nevertheless the retinopathy in our discordant cases—as in hemochromatosis, also—is conspicuously mild. Although half the cases were affected, in only one out of ten of these twins who had had diabetes for twenty-three years was there any proliferative retinopathy. This is in striking contrast to the concordant pairs in whom retinopathy was at least as common as one might expect in a general diabetic clinic population and, perhaps, rather more severe.[8]

We are left, therefore, with the tentative conclusion that the frequency and severity of diabetic retinopathy is, in part, influenced by inherited factors, but that it can also occur, though less severely, in "nongenetic" diabetics.

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