Characterization of Early Stages of Diabetic Retinopathy

Importance of the breakdown of the blood-retinal barrier

In an excellent clinical overview on diabetic retinopathy, Davis (1) describes the natural course of diabetic retinopathy, considering the presence of retinal capillary microaneurysms as the earliest reliable sign. He affirms that "when the number of microaneurysms in an eye exceeds 10, fluorescein angiography usually demonstrates retinal capillary abnormalities, consisting of capillary dilatation, capillary nonperfusion (capillary dropout), and/or focal fluorescein leakage from microaneurysms or more diffuse leakage from capillaries (1)."

Since 1974, the late Daniel Toussaint and myself have shown that microaneuryms could be preceded by a functional abnormality characterized by the appearance of fluorescein leaks secondary to an increased permeability of the pigment epithelium and retinal capillaries (2,3). These leakages are different from those seen later in the disease in the (pre) proliferative stage. Even though our first studies were published in French (not English), in 1978, Arnall Patz, from the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital, in fairness, wrote in *The New England Journal of Medicine* that "Drs. Dorchy and Toussaint have pioneered in the use of fluorescein angiography in the study of diabetic retinopathy and have defined early changes observed in patients with juvenile-onset diabetes. . . Their observations of capillary leakage as a result of vascular incompetence before specific morphologic lesions occur represent an important contribution (4)". However, nearly two decades later, it is difficult to persuade some diabetologists or ophthalmalogists of the importance of fluorescein leaks as an incipient functional abnormality.

Previously, we published a longitudinal study of 161 type I diabetic children and adolescents to investigate, by retinal fluorescein angiography, the nature of the initial vascular changes in childhood diabetes, their frequency, and their occurrence (5). The criteria for inclusion were to have had at least one normal angiogram no more than 3 yr before the occurrence of the first observed angiographic changes or to have one normal eye. The different types of significant retinal abnormalities isolated or not, as well as the mean duration of diabetes and age, are shown in Table 1 (5) Although capillary nonperfusion was rarely an initial lesion, occurring after a longer duration of diabetes and at a later age than the other abnormalities, no significant difference could be found between the various types of lesions for either the patient's age at onset or the duration of diabetes. The type of initial lesion was also unrelated to sex, age at onset of diabetes, or long-term glycemic control evaluated by mean values of GHb from either the onset of follow-up or from 1977 onwards, when the method became available. Retinopathy was not found in children <12 yr of age and was detected only after at least 3 yr of diabetes. However, we published the case of a boy with Mauriac syndrome who had become diabetic at 19 mo of age and showed retinopathy at 11 yr of age (6). The longest retinopathy-free period was 16 yr. The mean interval between the onset of retinopathy in the two eyes was 1.2 yr with a maxima of 6 yr. In conclusion, if microaneurysms, isolated or associated with other abnormalities, are the most frequently observed lesion (65% of the eyes), leakages were seen in 52% of the eyes, and in the absence of other lesions, in 18% of cases. We also observed in a 14-yr-old adolescent a rare manifestation of capillary permeability involving the optic disc capillaries, resulting in transient leakage at the level of the optic nerves, consecutive to rapid improvement in the degree of control (7).

After 20-yr of experience in retinal fluorescein angiography, from a practical point of view, our findings indicate that, even when used to search for discrete signs of retinopathy, fluorescein angiography should not be performed in patients <12 yr of age or in youths whose diabetes has lasted for <4 yr, regardless of the fact that this technique seems to pose no risk to children. As a diabetologist in charge of children and adolescents, I believe fluorescein angiography provides important objective information for diabetes management and convincing arguments for teenagers to maintain good metabolic control of their disease. Incipient fluorescein leaks are reversible functional abnormalities, re-

Table 1—*Frequency, mean duration of diabetes, age at occurrence, and types of significant lesions in 118 eyes of 69 children affected by initial diabetic retinopathy*

Type of lesion	Eyes (%)	Eyes with single type of lesion (%)	Mean duration of diabetes (yr)	Mean age (yr)
Microaneurysms	65	31	8.1	16.6
Leakage	52	18	8.3	16.5
Hemorrhages	25	8	7.6	15.9
Areas of capillary nonperfusion	11	0	9.2	18
Capillary remodelling	6	1	9	16.4
All lesions	100	58	8.2	16.4

lated to long-term metabolic control, whereas microaneurysms represent irreversible anatomical lesions.

HARRY DORCHY, MD, PHD

FROM THE CHILDREN'S UNIVERSITY HOSPITAL, REINE FABIOLA, UNIVERSITY OF BRUSSELS, BELGIUM.

ADDRESS CORRESPONDENCE TO HARRY DORCHY, MD, PHD, HÔPITAL UNIVERSITAIRE DES ENFANTS REINE FABIOLA, UNIVERSITE LIBRE DE BRUXELLES, AVENUE JJ CROCQ, 15-B 1020 BRUXELLES, BELGIQUE.

TYPE I DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS.

References

1. Davis MD: Diabetic retinopathy: a clinical overview. *Diabetes Care* 15:1844–74, 1992
2. Toussaint D, Dorchy H: Exploration angiofluorescéinique de la rétinopathie diabétique infantile. Etude préliminaire. *Bull Soc Belge Ophtalmol* 168:783–800, 1974
3. Dorchy H, Toussaint D, Devroede M, Ernould C, Loeb H: Diagnostic de la rétinopathie diabétique infantile par angiographie fluorescéinique. Description des lésions initiales. *Nouv Presse Med* 6:345–47, 1977
4. Patz A: Retinal vascular diseases (reply to a letter). *N Engl J Med* 299:1017–8, 1978
5. Verougstraete C, Toussaint D, De Schepper J, Haentjens M, Dorchy H: First microangiographic abnormalities in childhood diabetes—types of lesions. *Graefe's Arch Clin Exp Ophthalmol* 229:24–32, 1991
6. Dorchy H, Van Vliet G, Toussaint D, Ketelbant-Balasse P, Loeb H: Mauriac syndrome: three cases with retinal angiofluorescein study. *Diabete Metab* 3:195–200, 1979
7. Dorchy H, Toussaint D, Verougstraete C, Lemiere B: Transient acute disc swelling associated with improved metabolic control in an adolescent with type I diabetes: role of dexamethasone therapy. *Eur J Pediatr* 143:187–90, 1985

Response to Dorchy

I appreciate Dr. Dorchy's comments and am sorry that my characterization of the capillary microaneurysm as "the hallmark of diabetic retinopathy and its earliest reliable sign" may have seemed unfair to him or dismissive of the pioneering fluorescein angiographic studies he and his collaborators have published over the years.

In the table in Dr. Dorchy's letter, 18% of eyes in which the initial stage of retinopathy was observed had only fluorescein leakage, whereas 31% had only microaneurysms (1). However, two other commonly observed lesions, characterized as "between the stages of clear absence and definite presence" were excluded from this analysis, namely, "microaneurysm-like spot dilatations" (present in 52% of eyes) and "focal capillary dilatations" (present in 49% of eyes). Both of these lesion types are beautifully illustrated in the paper, and I suspect many observers would agree with me that the authors are probably being overly conservative in excluding them from the microaneurysm category. To be counted as a microaneurysm, a lesion had to be at least as large as a 65-μm reference spot. Even to be counted as a microaneurysm-like spot dilatation, a lesion had to be at least as large as a 45-μm spot. If microaneurysm-like spot dilatations and/or focal capillary dilatations were included as microaneurysms, I suspect that substantially >31% of eyes would be classified as having only microaneurysms and substantially <18% as having only fluorescein leakage. If so, results might not be very different from those reported by the Diabetes Control and Complications Trial (Table 1) (2), which were the basis for my statement that "when the number of microaneurysms in an eye exceeds 10, fluorescein angiography usually demonstrates retinal capillary abnormalities, consisting of capillary dilation, capillary nonperfusion (capillary dropout), and/or focal fluorescein leakage from microaneurysms or more diffuse leakage from capillaries (3)."

I commend Dr. Dorchy and his collaborators for their important contributions. Fluorescein angiography has played an important role in advancing our knowledge of diabetic retinopathy. Currently, however, I find little clinical need for it, except to guide photocoagulation treatment of diabetic macular edema.

MATTHEW D. DAVIS, MD

FROM THE DEPARTMENT OF OPHTHALMOLOGY, UNIVERSITY OF WISCONSIN, MADISON, WISCONSIN.

Table 1—*Presence of LK, D, and/or LS in field 2F fluorescein negative of rapid series eye compared with number of microaneurysms detected in field 2F negative of same eye

	Microaneurysms in field 2F fluorescein negative (*n*)						
LK, D, or LS	0	1	2	3–5	6–10	≥11	Total
None	181	30	11	24	7	13	266
Questionable	2	1	1	2	1	8	15
LK (no D or LS)	0	0	0	1	5	12	18
D (±LK, no LS)	0	0	1	1	2	6	10
LS (±LK, ±D)	0	0	0	1	0	10	11
Total	183	31	13	29	15	49	320

*Rapid series eye indicates the eye photographed at ~1 frame/s during the transit of fluorescein dye through the retinal vasculature.