Topical Corticosteroid Response and Retinopathy in Juvenile-onset Diabetes Mellitus

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SUMMARY

In a prospective study, 64 patients with insulin-dependent juvenile-onset diabetes mellitus were followed for eight to 12 years to determine if those with higher spontaneous intraocular pressures (IOPs) would be protected from the development of retinopathy. The patients were also classified initially as high (GG), intermediate (NG), or low (NN) responders on the basis of their IOP response to corticosteroid eyedrops. High responders were found to be considerably in excess (25 per cent) of the proportion found in the general population (6 per cent). Retinopathy developed significantly less often and was less severe in the high (GG) corticosteroid responders. Although the GG diabetics had significantly higher mean baseline IOPs than the less responsive NN and NG groups in each corticosteroid response category, the mean IOP of the group with retinopathy was not significantly different from that without retinopathy. This suggested that factors associated with the GG response other than increased IOP might be important in the relative resistance to diabetic retinopathy. DIABETES *26*:757-59, August, 1977.

An elevation of intraocular pressure (IOP) to over 31 mm. Hg (GG response) after six weeks of topical dexamethasone, 0.1 per cent four times daily, occurs in 6 per cent of the general population but is observed in 25 per cent of patients with diabetes mellitus and 88 per cent of patients with primary open-angle glaucoma.[1,2] Conversely, an 18-20 per cent prevalence of diabetes mellitus or abnormal glucose tolerance is observed in GG responders.[3]

When a series of patients with juvenile-onset diabetes mellitus were studied prospectively for a period of six years, diabetic retinopathy was observed in 14 per cent. Interestingly, diabetic retinopathy occurred in 25 per cent of the NN responders (IOP less than 20 mm. Hg after topical dexamethasone) and in 11 per cent of the NG patients (IOP 20-31 mm. Hg after corticosteroids) but in none of the GG diabetics.[2] These observations suggested the possible predictive value for retinopathy of topical corticosteroid testing in patients with juvenile-onset diabetes mellitus.

We now report a prospective study of the relationship between the topical corticosteroid response and the occurrence of retinopathy in patients with juvenile-onset diabetes mellitus followed for an average of 11 years.

METHODS

Sixty-four patients with juvenile-onset diabetes mellitus, all of whom required insulin for control, were followed for eight to 12 years. The onset of diabetes mellitus was before age 20 years in all, and the mean duration of diabetes was 14.0 years (range 10 to 20 years) (table 1). None of the patients had ophthalmoscopic evidence of diabetic retinopathy at the time of initial eye examination. All patients were classified by their IOP response to topical corticosteroids at the start of the study. No significant differences were noted in age, sex, duration of diabetes, or length of follow-up in the different corticosteroid groups (table 1). All had yearly eye examinations including refraction, slit-lamp biomicroscopy, gonioscopy, applanation tonometry, visual field testing, and ophthalmoscopy with dilated pupils. Photographs of the posterior pole of the retina were taken annually for documentation of the retinal findings. For purposes of this study, the degree of diabetic retinopathy was graded arbitrarily as mild (less than 20 microaneurysms) or moderate to severe (20 or more microaneurysms with or without intraretinal hemorrhages and/or neovascularization of the retina). Statistical analyses employed Yates' corrected chi-square and paired chi-square, the Fisher exact test, or the Student *t*-test.

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TABLE 1

Information on patients with juvenile-onset diabetes mellitus

Corticosteroid classification	NN	NG	GG	Total
Number of patients	23 (36%)	25 (39%)	16 (25%)	64 (100%)
Number of males	11 (48%)	16 (64%)	7 (44%)	34 (53%)
Age (mean ± σ years)	24.7 ± 6.9	26.6 ± 8.8	24.4 ± 7.9	25.3 ± 7.8
Duration diabetes (mean ± σ years)	13.4 ± 2.5	14.9 ± 3.1	13.5 ± 3.5	14.0 ± 3.1
Follow-up (mean ± σ years)	11.1 ± 0.8	11.0 ± 0.8	11.2 ± 1.0	11.1 ± 0.8

NN = IOP <20 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.
NG = IOP 20-31 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.
GG = IOP >31 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.

RESULTS

Of the 64 patients with juvenile-onset diabetes mellitus, 22 (36 per cent) were classified initially as NN, 25 (39 per cent) as NG, and 16 (25 per cent) as GG responders (table 1). During the eight-to-12-year follow-up, 32 (50 per cent) of the 64 patients developed ophthalmoscopic evidence of diabetic retinopathy. Retinopathy was observed in 14 (61 per cent) of 23 NN responders and in 14 (56 per cent) of 25 NG patients but in only four (25 per cent) of the 16 diabetics in the GG group (table 2). Thus, the GG responders developed significantly less diabetic retinopathy than did the NN and NG groups ($P < 0.05$). Furthermore, moderate to severe retinopathy was observed in nine (19 per cent) of the 48 NN-NG patients but in none of the diabetics classified as GG ($P < 0.05$) (table 2).

As observed in nondiabetic subjects,[4] mean IOP before topical corticosteroids was significantly greater in GG responders (18.5 mm. Hg) than in NG responders (16.6; $P < 0.05$) or in NN responders (14.8; $P < 0.001$). There was no significant IOP difference, however, between the patients with and without retinopathy in each corticosteroid category (table 3).

TABLE 2

Corticosteroid responses and diabetic retinopathy

Category (no. patients)	NN (23)	NG (25)	GG (16)	Total (64)
No. with diabetic retinopathy	14 (61%)	14 (56%)	4 (25%)	32 (50%)
No. mild	9 (39%)	10 (40%)	4 (25%)	23 (36%)
No. moderate to severe	5 (22%)	4 (16%)	0 (0%)	9 (14%)

NN = IOP <20 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.
NG = IOP 20-31 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.
GG = IOP >31 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.
Mild retinopathy = <20 microaneurysms.
Moderate to severe retinopathy = ≥20 microaneurysms with or without intraretinal hemorrhages and/or neovascularization of the retina.

DISCUSSION

In 64 patients with a mean duration of juvenile-onset diabetes mellitus of 14 years, the incidence of diabetic retinopathy is 50 per cent after 11 years of follow-up. This is significantly greater than the 14 per cent observed in the same patients during the first six years of follow-up ($P < 0.0005$) and emphasizes the increase of retinopathy with duration of disease.

In this series moderate to severe retinopathy is noted in nine (19 per cent) of the 48 members of the NN-NG group but in none of the 16 diabetics classified as GG. Thus, not only is the incidence of diabetic retinopathy significantly lower (25 per cent vs. 58 per cent) but, when it occurs, is less severe in GG

TABLE 3

Intraocular pressure and diabetic retinopathy in each corticosteroid category

Classification	NN	NG	GG	Total
IOP (mean ± σ mm. Hg)	14.8 ± 2.1	16.6 ± 2.1	18.5 ± 3.5	16.4 ± 2.9
With retinopathy	15.1 ± 2.6	16.9 ± 2.5	20.0 ± 2.7	16.5 ± 2.9
Without retinopathy	14.2 ± 1.8	16.1 ± 1.3	18.0 ± 3.7	16.3 ± 3.0

NN = IOP <20 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.
NG = IOP 20-31 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.
GG = IOP >31 mm. Hg after topical dexamethasone 0.1 per cent four times daily for six weeks.

responders. It is tempting to attribute the reduced incidence and severity of diabetic retinopathy in the GG group to a higher IOP. Clinically, severe diabetic retinopathy is seldom observed in adult diabetic patients with elevated IOP.[2,5] However, in each corticosteroid response category, the mean IOP of the diabetic group with retinopathy is not significantly different from that without retinopathy. Thus, at least in the patients with juvenile-onset diabetes mellitus, factors associated with the GG response other than the level of IOP may be important in the relative resistance to the development of retinopathy.

Increased prevalences of HLA antigens A1, B8, B18, Bw15, and Cw3 are reported in juvenile-onset diabetes mellitus.[6-8] Interestingly, increased HLA-A1 and B8 are also noted in diabetic microangiopathy.[9,10] In view of the increased prevalence of B12 and B7 in primary open-angle glaucoma[11] and the correlation of HLA-B12 with the corticosteroid response,[12,13] possible further interrelationships between HLA antigens and diabetic retinopathy need investigation.

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