Prognosis of Proliferative Retinopathy in Juvenile Diabetics

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SUMMARY

Fifty-one mostly juvenile-onset diabetic patients with proliferative retinopathy without persistent proteinuria were observed for two to eighteen years (average six years) after proliferative retinopathy had been detected. At the end of five years 10 per cent had died, and about 50 per cent had become blind in both eyes (visual acuity 6/60 or less). Patients with localized, peripheral proliferations had better visual prognosis than patients with pre- or peripapillary proliferations. Hypercholesterolemia appeared to be a poor prognostic sign. It would appear on the basis of reported experience and the present investigation that a surgical procedure on the pituitary gland is a justified therapeutic attempt in juvenile diabetes with retinopathy consisting of either pre- or peripapillary or of widespread proliferations, provided that the patients have not already developed persistent proteinuria. DIABETES *16*:728-33, October, 1967.

During the past ten to twelve years, attempts have been made to arrest the progression of proliferative retinopathy in diabetics by various procedures to ablate or destroy the pituitary gland. These procedures have included (1) transcranial or transsphenoidal hypophysectomy,[1,4,13-15,18,19,22,27] (2) pituitary stalk section,[4,8,11] (3) implantation of yttrium,[9,12] and (4) irradiation by proton rays (heavy particles).[4,17]

After these procedures, arrest and even improvement of the retinopathy have been claimed to occur. It is difficult, however, to assess the effects of these methods, without control data describing the spontaneous course of proliferative retinopathy.[6]

The present investigation was carried out in order to make a retrospective study of the visual prognosis of proliferative diabetic retinopathy in potential candidates for hypophysectomy.

PATIENT MATERIAL

All diabetic patients with proliferative retinopathy treated in the Steno Memorial Hospital, Gentofte, Denmark, during the period 1950 to 1964 were studied. We included not only patients with the more marked cases of vascular or connective-tissue proliferation, but also those who exhibited small, restricted areas of new-formed intraretinal or preretinal vessels with or without connective-tissue proliferation. The diagnosis was made by at least two experienced examiners. All patients who at the time of detection fulfilled the following criteria were selected for further study: (1) age under sixty years, (2) satisfactory renal function with a serum creatinine of less than 1.4 mg. per 100 ml. and no or only intermittent proteinuria, (3) diastolic blood pressure below 100 mm. Hg, and (4) preserved macular function in at least one eye with reading vision. The patients included in the study were those who could be followed for at least two years after proliferative retinopathy had been diagnosed.

Fifty-one patients fulfilled the criteria. Twenty-six were men and twenty-five women. All were followed up in 1964-65. All were on insulin apart from one man whose diabetes had been diagnosed at forty-five years of age.

The average age when proliferative retinopathy was first observed was 36.5 years.

The mean duration of known diabetes when proliferative retinopathy was first observed was 20.6 years.

At the start of the study, four of the fifty-one patients had intermittent proteinuria, and the others none. In three of thirty-nine patients whose serum cholesterol was examined, the levels had been consistently above 300 mg. per 100 ml.

In twenty-two patients the proliferative retinopathy was asymptomatic, while the remaining twenty-nine had noticed visual disturbances. At the first examination the corrected visual acuity in 101 eyes (one eye had previously been enucleated because of glaucoma) was as follows:

	Number of eyes
Good (6/6, 6/9, or 6/12)	76
Impaired (6/18 - 6/36)	14
Blind (6/60 or less)	11

From the Steno Memorial Hospital, Gentofte, Denmark.

The location and extent of proliferation of vessels and connective tissue, are shown in table 3.

Seventeen patients had a mild degree of proliferative retinopathy, i.e., localized peripheral proliferations in one or both eyes. The remaining thirty-four had either pre- or peripapillary proliferations or widespread proliferations in at least one eye.

COURSE

The patients were examined regularly by ophthalmoscopy in the Steno Memorial Hospital at intervals of six to twelve months. In addition, the majority were repeatedly examined by our ophthalmological adviser, Professor H. Ehlers, M.D. Retinal photos were obtained in many cases.

The patients were followed for periods of two to eighteen years with an average of six years. Five patients died during the observation period, after two, three, five, eight, and nine years, respectively. Three died in uremia, one of pulmonary embolus, and one of unknown cause, presumably coronary occlusion.

TABLE 1

The ages of patients when proliferative retinitis was diagnosed

Number of patients	Age (yrs.)
1	<20
16	21 - 30
16	31 - 40
12	41 - 50
6	51 - 60

TABLE 2

Duration of known diabetes when proliferative retinitis was diagnosed

Number of patients	Duration (yrs.)
9	<15
16	15 - 20
13	21 - 25
10	26 - 30
3	31 - 35

TABLE 3

The location and extent of proliferation

	Number of eyes
No proliferation	16
Peripheral only	35
Peripapillary	29
Extensive proliferations	13
Proliferations and massive vitreous bleeding	8

During the observation period fifteen patients developed persisting proteinuria, three after one year, four after two years, three after three years, two after five years, two after six years, and one after eight years. Nine patients developed uremia (serum creatinine permanently beyond 1.4 mg. per 100 ml., two after one year's, one after two years', three after three years', two after seven years', and one after nine years' period of observation.

In addition to the three patients who had hypercholesterolemia (more than 300 mg. per 100 ml.) at the start of the study, two others developed hypercholesterolemia in the course of the observation period. The diastolic blood pressure rose above 100 mm. Hg in three patients.

Figure 1 illustrates the patients' visual acuity during the observation period. Loss of vision increased in the course of the years, and at the end of four to five years half the patients were blind in both eyes. At the end of ten years almost one half of the observed patients had died. Of the seven patients remaining alive, five were blind in both eyes, and two were blind in one eye with reading vision preserved in the other.* In the seventeen patients with proliferative retinopathy of a mild degree, i.e., only localized, peripheral prolifera-

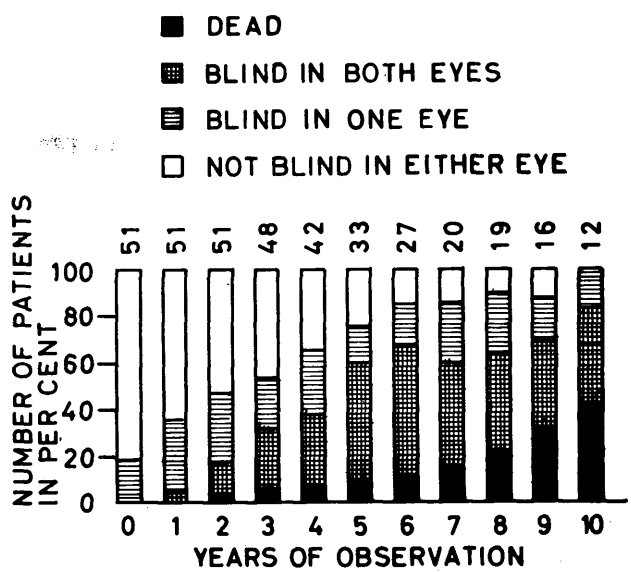

FIG. 1. Prognosis for vision and life in diabetics with proliferative retinopathy. The figures above the columns represent the number of patients observed.

*In the diagrams the observation period for the patients who had died is prolonged beyond the time of death up to 1964, when the analysis was completed.

tions in one or both eyes, the visual prognosis was better than that in the remaining patients who had, in at least one eye, pre- or peripapillary proliferations or more severe proliferative changes (figure 2).

The visual prognosis for the individual eyes depends

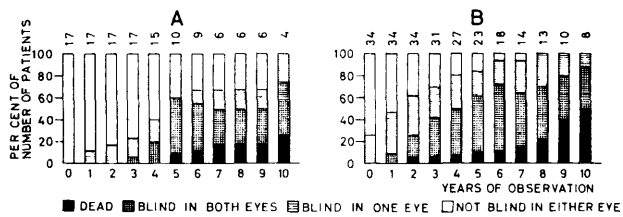

FIG. 2. Prognosis for vision and life in diabetics with proliferative retinopathy. A—peripheral proliferations only. B—more widespread proliferations. The figures above the columns represent the number of patients observed.

upon the extent and localization of the proliferative changes. Among eyes with localized peripheral proliferations half had become blind in five to six years, while the corresponding period was two to three years for

FIG. 3. Prognosis for vision in eyes of diabetics with proliferative retinopathy in relation to the extent of proliferations. A—eyes with peripheral proliferations only. B—eyes with peripapillary proliferations. The figures above the columns represent the number of patients observed.

eyes with pre- or peripapillary proliferations (figure 3).

The relation of visual prognosis to sex, age at diagnosis of the proliferations, age at diagnosis of diabetes, and duration of known diabetes is illustrated in figure 4.

It appears that prognosis is independent of sex, duration of known diabetes, and age at diagnosis of diabetes, while apparently patients under thirty-five years

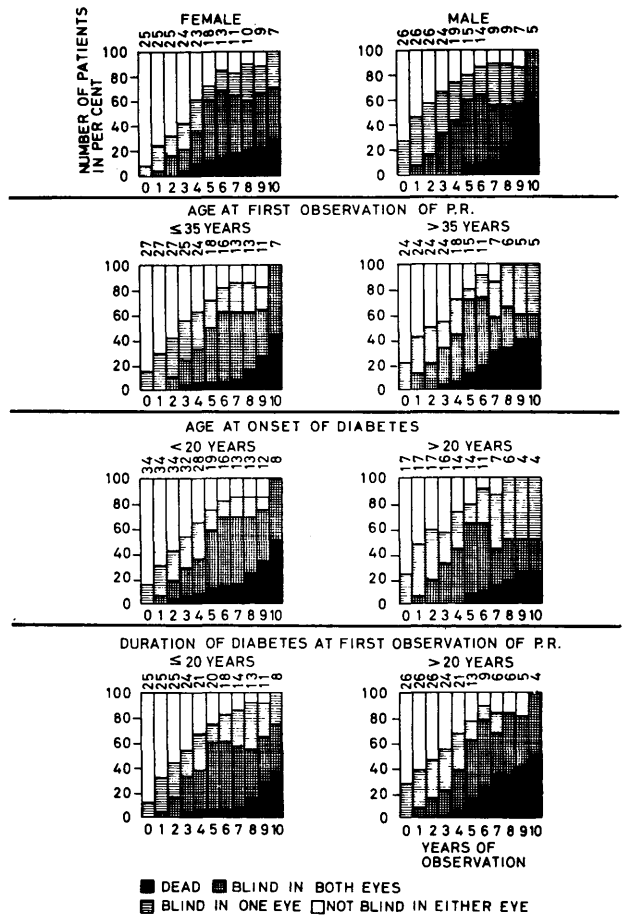

FIG. 4. Prognosis for vision and life in diabetics with proliferative retinopathy in relation to: (1) sex; (2) age at detection of proliferative retinitis; (3) age at diagnosis of diabetes; (4) duration of known diabetes at detection of proliferative retinitis. The figures above the columns represent the number of patients observed.

of age are somewhat better than those who are over thirty-five years of age when the proliferative retinopathy is diagnosed. This impression is in agreement with the findings of Caird and Garrett.[5]

The three patients who had hypercholesterolemia at the onset of the observation period became blind in both eyes at the end of six months, one year and five years, respectively. Of four patients with intermittent proteinuria at the commencement of the observation period, three were blind in both eyes at the end of two, eight, and ten years, while the fourth patient had retained vision in both eyes at the end of three years.

In the course of the study period various attempts to treat the retinopathy were carried out. These consisted of x-ray irradiation of the posterior part of the

eyeballs[16] in eleven cases, injections of deca-durabolin for long periods in ten cases, and long-term anticoagulant medication[28] in twelve cases. It is not believed that these treatments provided any beneficial effects.

DISCUSSION

Although spontaneous remission and arrest of proliferative retinopathy have been observed repeatedly, the condition is generally held to be rapidly progressive in nature. Beetham,[2] for instance, stated that in the course of five years proliferative retinopathy usually has advanced to an extreme degree. In respect to prognosis for life, Root et al.[26] have reported that about 50 per cent of patients with proliferative retinopathy are dead less than five years after the proliferations are detected.

In the present analysis only 10 per cent of the patients had died five years after proliferation was detected, and 50 per cent had become blind in both eyes at the end of five years. The better prognosis, for vision as well as for life, in the present cases may presumably be accounted for by the exclusion of patients with permanent proteinuria. That the presence of nephropathy has great influence on the prognosis for vision and life in patients with proliferative retinopathy is evident in figure 5 which gives data on patients who developed proliferative retinopathy *after* or *at the diagnosis time* of proteinuria. Of these fifteen patients, thirteen had died or become blind in five years. Figure 5 also reveals that retinopathy progresses more rapidly in these patients, since one half the survivors had become blind in two years.

Patients who have only localized or peripheral proliferations in one or both eyes have a better visual prognosis than the other patients (cf., figure 2). This appears to be due predominantly to the fact that peripheral proliferation progresses more slowly than pre- or peripapillary proliferations. This concept is compatible with the findings of Dobree.[10] Although the prognosis in the present material was better than expected, the visual prognosis in patients with pre- or peripapillary and/or with extensive proliferation must be regarded as very poor.

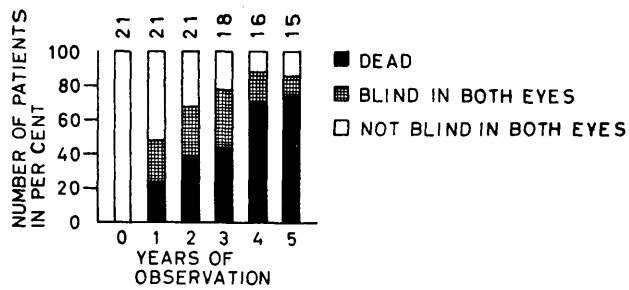

FIG. 5. Prognosis for vision and life in diabetics who developed proliferations after developing persistent proteinuria. The figures above the columns represent the number of patients observed.

Many different treatments have been used to arrest the progression of the proliferative retinopathy. The most extreme approach has been hypophysectomy. The rationale of this treatment is based upon observation of two diabetics whose retinopathy improved after they developed Sheehan's syndrome, and experience with pancreatectomized dogs whose diabetes proved to be more easily controlled after removal of the pituitary gland.[21,23,24]

The lack of somatotrophin and the lack of the diurnal variations in corticosteroids in hypophysectomized individuals have been thought to exert a favorable effect upon the proliferative retinopathy. Since, however, the concentration of somatotrophin is not permanently elevated in juvenile diabetics, and since the majority of patients with combined acromegaly and diabetes do not exhibit retinopathy,[3] this hypothesis may have to be abandoned. Furthermore, the favorable influence of

TABLE 4

Hypophysectomized diabetics with proliferative retinitis observed for two to six years after operation (from the literature)

Number of patients	No progression	Progression	Dead	Cause of death	Author
4	1 (+ 3*)	0	3	Uremia; sepsis; hypoglycemia	Luft (1962; 1955)
1	1	0	0		Lundbaek (1962)
2	2	0	0		Ainslie (1962)
12	7	2 (+ 3*)	4	Hypoglycemia 2 Coronary thrombosis 2	Sjøgren (1962)
6	5	1	1	Gastrointestinal hemorrhage*	Pearson (1964)
25	16 - 19	3 - 6	8		

*Uncertain

stalk-section does not necessarily follow the degree of reduction to somatotrophin.[25] Nevertheless, most authors who have done hypophysectomy are of the opinion that the procedure does help, the progression being arrested in many cases and the proliferative retinopathy even improved in some instances (Bradley et al.[4]).

From the literature we have tried to pick out those patients who have, in general, fulfilled the criteria employed in the present study and who have been followed for a sufficiently long time to permit an impression of the course of the proliferative retinopathy after hypophysectomy (table 4).

In about 70 per cent of these patients the visual acuity or the retinopathy had not progressed two and one-half to six years (average 2.8), after hypophysectomy. Eight patients had died in the course of follow-up, three patients of hypoglycemia. None of the deaths could be ascribed to the hypophysectomy. It should be noted that the preoperative duration of the proliferations in these materials is unknown.

A comparison of our nonoperated cases with those operated upon, listed in table 4, is not justified. Nevertheless, it would appear that successful hypophysectomy may have a favorable effect upon the course of proliferative retinopathy. Whether this could be due to a favorable action upon the retina from changes in hormonal balance, from cutting of nervous pathways between the hypothalamus and the retina as suggested by Wolter,[29] or from other effects remains to be determined. Efforts to prevent the development of proliferative retinopathy by good control of the diabetes must still be looked on as of great importance.[7]

CONCLUSION

In juvenile diabetic patients with proliferative retinopathy without nephropathy the risk of blindness is so great that a surgical procedure on the hypophysis involving relatively little risk, e.g., transsphenoidal hypophysectomy, appears to be justified. Whether or not stalk section, implantation of yttrium, or proton irradiation are preferable to transsphenoidal hypophysectomy is not yet known.

The presence of only peripheral, localized proliferations, however, does not, in general, appear to be sufficient indication for hypophysectomy, as the spontaneous visual course of these patients is relatively favorable. In the presence of persisting proteinuria, the survival time is so short that hypophysectomy is not warranted. Little is known, however, about the influence of hypophysectomy on diabetic nephropathy.

ACKNOWLEDGMENT

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In Vitro Studies on the Nutritive Value of Leaf Proteins

(*Continued from page 721*)

the literature on the biological value of the protein as measured in feeding trials with rats.

The estimated biological values for each of the preceding twelve foodstuffs were 97, 87, 83, 84, 75, 76, 65, 71, 50, 45, 26, and 17, respectively. The calculated values compared favorably with the literature values obtained in feeding experiments (correlation of $r = 0.990$).

The authors state that, although some variation in the estimated biological value by the pepsin-pancreatin index was observed, the values obtained (range = 73 to 89) indicate that the nutritive value of LPC protein would be very good. They further report that little difference was observed in the amino acid composition and estimated biological value of nine species of plants used for preparing leaf protein concentrates. This suggests to them that LPC "... from a large number of plant species growing in different localities would have uniformly high biological value."

Additional research on leaf proteins in animals, as well as humans, would appear desirable, since the present pace of population increase necessitates that additional high quality protein sources be found to combat protein malnutrition. Certainly leaf proteins could be prepared in nearly every country, providing that processing technics were not too complicated.

Furthermore, this work should be extended to animal studies, since some of the earlier literature on studies with animals has indicated that the quality of protein from leaves may vary (S. J. Cowlishaw, D. E. Eyles, W. F. Raymond, and J. M. A. Tilley, J. Sci. Food Agr. 7:768, 1956; Ibid. 7:775, 1956). However, it has been reported by Waterlow (*loc cit.*) that feeding of leaf protein-milk mixtures to protein-malnourished infants resulted in gains in weight equal to those of babies on milk alone at the same protein level.

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