Severe diabetic retinopathy in adolescents

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SUMMARY This paper reports on 9 patients aged 13-18 years (mean 15.4) with severe diabetic retinopathy. Two patients were prepubertal and 4 were going through puberty. Hypertension was present in 2 patients, while 4 had proteinuria. Severe preproliferative disease was present in 3 patients initially and proliferative retinopathy in the remainder. In 5 this retinopathy was considered to be florid. Two patients seen prior to 1975 had pituitary ablation, while those seen after 1975 were treated by extensive argon and xenon arc photocoagulation. Proliferative lesions regressed in both groups. At the latest follow-up 7 of the 9 patients achieved a final visual acuity of 6/9 or better in at least one eye. One patient became blind. Proliferative retinopathy advances rapidly in adolescents, but photocoagulation, as used now, can maintain vision in most.

Severe diabetic retinopathy is rarely reported under the age of 18 because duration of disease before puberty is not thought to be of significance in the development of microvascular disease. Immerslund¹ and Jackson *et al.*² found no cases of proliferative retinopathy before the age of 18 in juveniles with as long as 17 years' duration of diabetes. Indeed, Jackson *et al.*² found that only 14% of their post-pubertal insulin-dependent diabetics had any evidence of retinopathy. This is in contrast to the studies of Malone *et al.*,³ who found that 75% of their diabetic children had vascular abnormalities noted on fluorescein angiography, with 7% having early proliferative disease in at least one eye. Frank *et al.*,⁴ in a well controlled study, found no retinopathy in young diabetics with 0 to 4 years' duration of diabetes, 27% between 5 and 9 years', and 71% with over 10 years' duration. No proliferative retinopathy was noted in patients under age 18. The purpose of this report is to draw attention to the fact that, although rare, severe retinopathy can occur in adolescent diabetics, even before the onset of puberty, and to discuss possible treatment.

Patients

Between 1965 and 1982 9 adolescents with severe retinopathy were seen in the Hammersmith Hospital (HH) Diabetic Retinopathy Clinic (this represents approximately 0.5% of the new retinopathy patients). Details of the medical and eye data are given in

Tables 1-3. The age of the 9 adolescents ranged from 13 to 18 years (mean 15.4 years), with a mean age at onset of diabetes of 5.7 years. The mean duration of diabetes was 9.7 years. Seven patients were female and 2 were male. They were followed up for a mean duration of 5.1 years (range 1-17 years). At presentation 6 had proliferative retinopathy, 5 with both new vessels on the disc (NVD) and new vessels elsewhere (NVE). Three had severe preproliferative retinopathy characterised by intraretinal microvascular abnormalities (IRMA), cotton-wool spots,

Fig. 1 Comparison of initial and final visual acuity of all patients. Diagonal line is 'no change' line; those between it and the vertical axis improved, those between it and the horizontal axis deteriorated.

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Table 1A No specific treatment for retinopathy initially

Patient	Age			Management		Control		Pubertal status
	Onset	Referral + year	Last visit	Initial	After diag. of DR	Before	After	
1 ♀	5	14 1963	32	BD Sol. Insulin No diet	Sol. and NPH bd 280 g CHO	Poor	→ Fair	Pubertal
2 ♀	14	18 1969 1979	31	Single daily Sol.+PZI	bd Insulin (variable)	Poor	→ Poor Fair	Postpubertal
3 ♂	5	14 1980	16	Single daily NPH	CSII 8/12 tds insulin	Fair	→ Good	Pubertal

DR=diabetic retinopathy. bd=twice daily. tds=3 times daily. CHO=carbohydrate. Sol=soluble. PZI=protamine zinc insulin. NPH=isophane protamine insulin. Diag=diagnosis. PC=photocoagulation. Mac.=macular(r).

Table 1B No specific treatment for retinopathy initially

Patient	BP mmHg	Medical data			Visual acuity				Retinopathy		Eye treatment
		S urea mmol/l	S creat. µmol/l	Protein U g	Initial R	L	Latest R	L	Initial	Latest	
1 ♀	120/60	6.0	—	2.0	6/6	6/6	6/6	6/6	Pre-PDR	Mild BgR	
2 ♀	100/70	3.0	72	—	6/5 6/24	6/5 6/18	6/5 NPL	6/5 HM	Pre-PDR BgR PDR ThG + mac. oedema		Extensive argon + xenon PC Surgery for ThG
3 ♂	110/80	3.1	77	1.8	6/5	6/5	6/5	6/5	BgR	Pre-PDR	

S urea=serum urea. S creat.=serum creatinine. BgR=background retinopathy. ThG=thrombotic glaucoma. PDR=proliferative diabetic retinopathy. Protein U=protein in urine.

venous beading, and extensive intraretinal haemorrhages and microaneurysms.

Visual acuity on presentation was 6/12 or better in 13 of 18 eyes (72%). During follow-up the visual acuity improved or remained stable in all eyes except those of patient 2. She became blind in both eyes due to thrombotic glaucoma. Seven of 9 patients achieved a final visual acuity of 6/9 or better in at least one eye (Fig. 1).

The diabetic control at presentation was poor in 6 cases but improved in 8 during follow-up. In most cases this improvement occurred after switching from single daily injections of insulin to multiple injections or, more recently, to continuous subcutaneous insulin infusion (CSII). With regard to the patients' pubertal status (Tables 1A, 2A, 3A) at the time of presentation, 2 were prepubertal, 4 were entering puberty, and 3 were postpubertal. The systemic blood pressure was raised in 2 patients, and laboratory values of renal function were normal except for proteinuria in 4

patients (Tables 1B, 2B, 3B). Other systemic illnesses included anorexia nervosa, hyperlipidaemia, and diabetic cardiomyopathy in one patient each. Of the 4 patients who had blood rheology tested 3 had abnormal blood viscosity and one showed abnormal red cell deformability.

TREATMENT

The 9 patients could be categorised into 3 groups according to the type of treatment given initially for the severe retinopathy. In group A (Table 1A, B) no specific eye treatment was given because the retinopathy was at that time of severe background or preproliferative type and diabetic control was poor. In patient 3 the retinopathy improved with better control of the diabetes and hyperlipidaemia. However, in patient 1 the retinopathy became more severe at least temporarily despite optimal control with CSII. In patient 2 the retinopathy initially improved with resolution of the anorexia nervosa

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Table 2A Pituitary ablation

Patient	Age			Management		Control		Pubertal status
	Onset	Referral + year	Last Visit	Initial	After diag. of DR	Before	After	
4 ♀	5	17 1968	30	Single daily lente	bd Insulin (variable), thyroxine, prednisolone	Poor	→ Fair	Postpubertal
5 ♀	10	16 1976	22	Single daily lente	bd Insulin, no replacement	Poor	→ Fair	Early puberty

Table 2B Pituitary ablation

Patient	BP mmHg	Medical data			Visual acuity				Retinopathy		Eye treatment
		S urea mmol/l	S creat. µmol/l	Protein U g	Initial		Latest		Initial	Latest	
					R	L	R	L			
4 ♀	120/70	3.7	69	—	6/5	CF	6/5	HM	R PDR NVD+NVE L TD	R quiescent with RP L Cataract TD	Pituitary ablation (complete)
5 ♀	110/60	6.7	82	—	6/9 6/18	6/9 6/24	6/5	6/5	PDR NVD+NVE	Quiescent with RP	Photocoagulation with argon both eyes, pituitary ablation (incomplete)

NVD=new vessel on optic disc. NVE=new vessel elsewhere. TD=traction detachment. RP=retinitis proliferans.

Table 3A Photocoagulation

Patient	Age			Management		Control		Pubertal status
	Onset	Referral + year	Last visit	Initial	After diag. of DR	Before	After	
6 ♀	6	16 1977	20	Single daily sol. + PZI	CSII 4/12 bd insulin	Fair	→ very good	Prepubertal
7 ♀	3	15 1979	18	Single daily lente	bd insulin	Poor	→ fair	Pubertal
8 ♂	1	16 1980	17	Single daily lente, bd insulin 3 yr	CSII Atenolol	Poor	→ very good	Post pubertal
9 ♀	2	13 1981	14	Single daily lente	bd insulin, frusemide bd, prazosin TDS, digoxin bd, spironolactone	Poor	→ fair	Prepubertal

(Figs. 2A, B). Ten years later, following erratic control of the diabetes, first macular oedema then proliferative retinopathy developed. Extensive argon and xenon photocoagulation was ineffective in preventing rubeotic glaucoma in both eyes. This lead

to complete blindness despite surgical attempts to control the glaucoma.

The 2 patients in group B (Tables 2A, B) were seen in the late 1960s and mid 1970s. Each had an yttrium-90 implant of the pituitary for severe proliferative

Table 3B Photocoagulation

Patient	BP mmHg	Medical data			Visual acuity				Retinopathy		Eye treatment
		S urea mmol/l	S creat. μmol/l	Protein U g	Initial		Latest		Initial	Latest	
					R	L	R	L			
6 ♀	135/90	6.6	61	—	6/5	6/9	6/6	6/9	R PDR NVD+NVE L RP	R quiescent L RP with mild mac. traction	Extensive argon and xenon
7 ♀	110/70	3.1	68	—	6/36	6/36	6/24	6/18	PDR NVD+NVE with mac. oedema	Quiescent with mac. RPE changes	S/A
8 ♂	165/110	5.4	79	3.2	6/5	6/5	6/5	6/5	Pre-PDR ↓ PDR NVE	Quiescent BgR	S/A
9 ♀	130/100	6.0	69	1.6	6/18	6/18	6/12	6/9	PDR NVD+NVE with mac. oedema	Reduced activity	S/A

RPE=retinal pigment epithelium. S/A=same as above.

retinopathy. In patient 5 argon laser therapy was first attempted, but the proliferative retinopathy became more aggressive in both eyes (Figs. 3A, B). In both patients 4 and 5 the retinopathy regressed following pituitary ablation (Fig. 3C). Both patients had residual areas of retinitis proliferans with mostly fibrous tissue. The vision in the left eye of patient 4 remained poor because of the pre-existing traction retinal detachment involving the macula.

The 2 patients in group C (Tables 3A, 3B) first presented between 1977 and 1981. Three had severe proliferative diabetic retinopathy (PDR) (Fig. 4A), while one had only early NVE with extensive areas of ischaemia. Because of the aggressiveness of the retinopathy and the young age of the patients photo-coagulation with both argon and xenon was performed. Each eye received between 1500 to 3000 argon burns (mean 2264 burns) as well as 300 to 1000

Fig. 2 Patient 2. A: Fluorescein angiogram of right macula at presentation. Note widespread leakage and capillary nonperfusion.

Fig. 2B Same as Fig. 2A but 2 years later, shows only a few leaking microaneurysms.

Fig. 3 Patient 5. A: Fluorescein angiogram of right disc when patient first seen. Shows leakage from new vessels on the disc, venous beading, and dilatation.

xenon burns (mean 565 burns). The retinopathy improved in all cases. In patients 7 and 9 the reduced visual acuity was initially due to macular oedema and ischaemia (Figs. 4B 4C). In patient 7 the oedema resolved, but she remained with subsequent atrophy of the retinal pigment epithelium in both maculae. This accounted for the abnormal final visual acuity. Residual areas of inactive fibrovascular tissue

Fig. 3B From colour photograph of inferior nasal area of patient seen in Fig. 3A, showing deterioration of disc new vessels after argon laser photocoagulation.

Fig. 3C Disc of patient seen in Fig. 3A following pituitary ablation. New vessels on disc have disappeared.

(retinitis proliferans) were noted in patients 6, 7, and 9 (Fig. 4D). In patient 6 visual acuity remained at 6/9 in the left eye due to pre-existing preretinal traction over the macula (Fig. 5).

The general health has been fair to good during the follow-up period in 7 of the 9 patients. The only death occurred in patient 9, due to rapidly progressive nephropathy and cardiomyopathy.

Discussion

The 9 cases reported in the present study are of a much younger age (mean 15.4 years) and with a shorter duration of diabetes (mean 9.7 years) than previous studies have indicated. Among juvenile diabetics the mean age of onset of PDR is said by Beetham⁵ and Deckert *et al.*⁶ to be 29.6 and 36.5 years respectively. This occurred after a mean duration of diabetes of 20.5 years.

The prevalence of PDR among adolescent diabetics is low. Deckert *et al.*⁶ found that only 2% of their juvenile diabetics with PDR were under the age of 20. In more recent studies^{7,8} PDR was seen in only 2 diabetics (age 18 or under) out of the 267 children and young adults examined. These figures are in agreement with the present series of 9 cases, which represent approximately 0.5% of the new retinopathy patients at the Hammersmith Hospital.

Many authors^{2,7-10} believe that good control is essential in preventing the development of severe retinopathy. In 6 of our 9 cases there was a long-standing history of poor diabetic control on

Fig. 4 Patient 7. A: Extensive disc new vessels, widespread haemorrhages, and venous dilatation in right disc area at presentation.

Fig. 4C Same as Fig. 4B but fluorescein angiogram, showing extensive capillary dilatation, small areas of nonperfusion, and leakage.

presentation with severe retinopathy. This is consistent with the series of Valone and McMeel,¹¹ in which 13 of 14 adolescents presenting with severe PDR were poorly controlled. One would therefore expect the retinopathy to improve with good control if diabetic control is of ultimate importance. Yet in all 3 of our cases on CSII the retinopathy continued to progress. It may be that, once diabetic retinopathy

reaches a certain stage, good control is no longer an influencing factor.¹² Optimal metabolic control has recently been shown to increase somatomedin levels while decreasing abnormally high growth hormone levels.¹³ This change in hormonal balance could stimulate progression of the retinopathy as reported in diabetics on CSII¹² and in children treated for Mauriac's syndrome.¹⁴ The role that hormonal

Fig. 4B Right macula showing intraretinal microvascular abnormalities, extensive haemorrhages, and vascular tortuosity at presentation.

Fig. 4D Right disc area 2 years after extensive xenon and argon photocoagulation. New vessels on disc have regressed. Fibrous retinitis proliferans present inferior to the disc.

Fig. 5 Left eye of patient 6 after extensive photocoagulation. Shows retinal striae due to traction from retinitis proliferans on the disc.

changes might play during the onset of puberty is uncertain as well. Despite reports to the contrary¹²⁷⁸ PDR can occur in prepubertal children, as seen in 2 of our cases.

Systemic diseases that have an influence on vascular permeability or platelet aggregation could present an additional factor for the development of severe retinopathy. Abnormal blood viscosity was observed in the few patients who were tested. Other coexistent medical conditions—mostly complications of diabetes—were present in 5 patients, but 4 (patients 4, 5, 6, and 7) did not differ from other juvenile diabetics with only minimal or no retinopathy. Thus no single risk factor could be identified that would account for the severity of the retinopathy at such a young age.

When severe retinopathy does occur in adolescents, it seems to be rapidly advancing in nature. The natural course of the disease can, however, be altered by means of pituitary ablation or photocoagulation. In the early and mid 1970s pituitary ablation was shown to improve visual outcome in young diabetics with florid PDR.¹¹¹⁵ The 2 cases in group B illustrate the effectiveness of this form of treatment. Yet the results in the group C patients show that photocoagulation alone can be equally effective. However, a large number of intense laser burns are needed, and xenon photocoagulation is often required in addition to argon. In young children xenon photocoagulation

may have to be administered under general anaesthesia. After photocoagulation the neovascularisation regressed in all 4 group C patients. Visual acuity improved or remained normal. Thus the visual prognosis can be good if aggressive treatment with both xenon and argon photocoagulation is administered promptly.

We thank the various consultants who have referred the patients to us, in particular Dr J. D. N. Nabarro, Dr T. C. Harvey, Dr P. A. Thorn, and Dr J. Cassar. The illustrations were prepared by Mr S. Aldington.

This work was supported by the Scientific Section of the British Diabetic Association.

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