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Study on Morphological Lesions of Diabetic Retinopathy by Using Fundus Fluorescein Angiography

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Abstract

Background: The prevalence of diabetes among the population is varied and different in different parts of the world. In India it has been reported form 4-28%.There is prevalence of 6.7% of retinopathy in patients of NIDDM at the initial diagnosis of diabetes. *Methods:* The present study was conducted at Narayana Medical College Hospital, Nellore for a period of two years. The cases included in the study were 50 diabetic patients with retinopathy changes of both sexes with different age groups. Those included were selected from the patients attending the department of medicine for the treatment of diabetic mellitus, and referred to department of ophthalmology for evaluation, known diabetic patients who attended the ophthalmology outpatient department directly for the ophthalmic evaluation were also included in the study. *Result:* The mean age of the study subjects was 55.65 years with standard deviation (SD) of 11.3 years. 30 right eyes (60%) showed non proliferative diabetic retinopathy (NPDR) whereas in 29 left eyes (58%) showed NPDR. The lesions noticed on FFA of the right and left eyes in patients under study are almost same for Microaneurysm, Microaneurysm with haemorrhages, Ischemic maculopathy except hard exudates, intra retinal microvascular abnormalities ,venous beading and Neovascularization. *Conclusion:* From the present study, it was concluded that fundus fluorescein angiography is useful in differentiating the lesions and classifying the diabetic retinopathy. In addition this technique had a major contribution in establishing the cause of unexplained loss of visual acuity.

Keywords: Diabetic Retinopathy; Non Proliferative Diabetic Retinopathy; Proliferative Diabetic Retinopathy; Fundus Fluorescein Angiography.

Introduction

In both developed and developing countries, diabetic retinopathy is a leading cause of blindness and visual impairment [1].

The prevalence of diabetes among the population is varied and different in different parts of the world. In India it has been reported form 4-28% [2]. There is prevalence of 6.7% of retinopathy in patients of NIDDM at the initial diagnosis of diabetes.

In diabetic retinopathy, the angiogram is helpful in make out the extent of ischemia, location of micro aneurysms, presence of intra retinal microvascular abnormalities which can only be confirmed on angiogram; neovascularization and the extent of macular edema [3].

In India retinopathy was detected in 52% of patients with NIDDM of over 25 years duration [4]. Among this NPDR was seen in 41% & PDR in 10.3% patients.

Predisposing Factors

Duration of diabetes appears to be the most important factor in the precipitation of retinopathy, while diabetic retinopathy is also correlated with its severity, proteinuria, renal disease, insulin usage and

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decreased uric acid level. There is less evidence on the influence of age at onset, gender, associated hypertension, cardiovascular disease, serum cholesterol, serum triglycerides and high density lipoprotein. Adequate control of diabetes has been found to delay the retinopathy in many studies but not all.

Aggravating Factors

Humoral factors like onset of puberty and pregnancy can result in Progression of diabeticretinopathy [5].

Types of Diabetic Retinopathy

Non Proliferative Diabetic Retinopathy (NPDR)

This is the effect of ischemia on the retina and refers to the changes taking place within the retina. These consist of microaneurysms, superficial and deep haemorrhages, hard and soft exudates. The NPDR stage with macular edema is an important cause of impartment of vision.

Proliferative Diabetic Retinopathy (PDR)

This is the response of retina to ischemia and is seen in the form of new vassels, which can be seen on the disc as New Vessels at Disc (NVD) and New Vessels Elsewhere (NVE) in the retina.

The Proliferative phase can be complicated by vitreous hemorrhage, retinal detachment, which is important causes of visual impairment changes, and treatable maculopathies.

The NPDR needs no local treatment, only regular follow-ups are advised for early detection and treatment of proliferative changes, and treatable maculopathies.

Proliferative diabetic retinopathy needs treatment by means of photocoagulation in which the hypoxic areas, which stimulate the neovascularization, are thoroughly destroyed.

Fundus Fluorescien Angiography (FFA)

Fluorescein angiography provides a baseline on which subsequent changes can be easily projected and documented. Fluorescein angiography acts as a guide for further evaluation of the condition and it's management.

Fluorescein angiography is the technique of injecting a yellowish dye into a patient's antecubital vein, then photographically stimulating this dye with a blue green light at certain wavelengths to induce fluorescence, in the retinal vascular system of the human eye, and recording this fluorescence on photographic film using a fundus camera. Unlike, fundus photography, which is purely documentary, fluorescence angiography is a diagnostic test yielding information about the patient's ocular health otherwise unavailable to the ophthalmologist.

The absorption peak is 465-490 nm. The emission peak is 520-530 nm. To allow maximal absorption a filter corresponding to the absorption peak of fluorescein dye. i.e., blue filter is kept in the light pathway into the eye. This is the exciter filter. And to filter out other unwanted light a filter corresponding to the emission peak i.e., yellow green filter, is kept in the light pathway to the photographic film. This is the barrier filter. The transmission curves of the filters should be checked for any overlap. If there is overlap pseudofluorescense will result [6].

Fundus fluorescein angiography can be used for, as a screening means for detection of diabetic retinopathy, detection of presence and extent of retinal edema, to differentiate between aneurysm and hemorrhage, to detect maculopathies-Focal, diffuse, and ischemic, to assess the retinal blood flow (Arm retinal circulation) and arterio venous passage, retinal circulation time, to detect area of capillary non-perfusion, to detect presence of new vessels and their extent, and to assess the progression of diabetic retinopathy in a patient.

The detection of preproliferative and proliferative diabetic retinopathy can prevent the complications if these patients are appropriately treated by photocoagulation of the ischemic retina. This study is meant to determine the role of F.F.A. in detection of morphological lesions of diabetic retinopathy especially when subtle changes, which are otherwise difficult to appreciate by ophthalmoscopy or in doubtful causes and to explain the cause for unexplained loss of visual acuity.

Objectives

To determine the morphological lesions of diabetic retinopathy by using fundus fluorescein angiography.

Materials and Methods

The present study was conducted at Narayana Medical College Hospital, Nellore for a period of two years. The cases included in the study were 100 eyes of 50 diabetic patients of both sexes with different

age groups with ophthalmoscopically detectable diabetic retinopathy changes. Those included were selected from the patients attending the department of medicine for the treatment of diabetic mellitus, and referred to department of ophthalmology for evaluation, known diabetic patients who attended the ophthalmology outpatient department directly for the ophthalmic evaluation were also included in the study.

Selection Criteria

Inclusion Criteria

Al l the patients with the history of diabetes confirmed by investigations (RBSValues > 180mg/dl) and among those who have ophthalmoscopically detectable diabetic retinopathy changes.

Exclusion Criteria

Patients of diabetic retinopathy who have media opacities or hazy media due to cataract or other causes, Patients of diabetic retinopathy who have undergone treatment for Diabetic retinopathy by photo – coagulation or other surgeries, allergic to drugs, Porphyrias, end stage kidney disease are excluded from the study.

All these patients were examined and data were recorded in standardized proforma. Visual acuity was recorded and retinoscopy was done in all the cases. Blood glucose and blood urea & serum creatinine were done in all cases and recorded.

The initial examination was started with fundus examination with direct opthalmoscope after papillary dilation with a combination of phenylephrine and tropicamide eye drops (e.g. Itrop plus eye drops). Due care was taken to rule out hypertension in the patient before administration of this eye drops to avoid cardiovascular complications.

The study of diabetic changes in the fundus was performed by non- invasive techniques like direct ophthalmoscopy, slit lamp biomicroscopy using +78D lens, and indirect opthalmoscope with +20D Volk lens. After getting the opinion from the physician regarding the fitness for the fundus fluorescein angiography, the patient was taken up for the procedure.

The patient was explained about the purpose, the procedure, and the possible adverse reactions, which are likely to occur during or immediately after the procedure. He was explained about the management of the likely adverse effect also. Informed consent was taken from the patient. On the day of appointment, the patient was examined and his pupils were dilated with eye drops of a combination of tropicamide and phenylephrine (e.g. Itrop plus). Zeiss FF 450 plus fundus camera was used throughout the study.

The patient was seated comfortably in front of the fundus camera. The antecubital vein was secured and scalp vein set was fixed. On aiming and focusing the camera on the area of primary interest the patient was asked to fix the gaze by looking at the target. Color fundus picture and then red free photographs were taken using green filter. Then pre injection photographs were taken with exciter and barrier filters, if it was found necessary in the fundoscopic examination through fundus camera unit.

3ml of 20% fluorescein dye was injected into the antecubital vein and serial pictures were taken after 7 – 10 sec of post injection for every 10 sec. late films were taken 10 min after injection. All though the procedure, the patient's pulse and general condition was monitored and any reaction was attended to and noted.

After the procedure the patient was made to lie down and relax for 15to 30 minutes. He was also explained about the change in the color of urine and skin. The patient was asked to attend the out- patient department later on a specific date for the report.

The features, which were observed, were presence of microaneurysms, retinal edema , capillary dropouts, IRMA, new vessels, maculopathies – focal, diffuse or/ and exudative.

The microaneurysms were appreciated by the hyperflurescents acculardilatations at the terminal ends of the capillaries especially seen around the macula in the arterio venous phase of angiogram. The retinal edema is detected late and slow accumulation of the dye due to leak. Retinal capillary drop out is seen as hypoflurescence. IRMA is seen in the background and are the shunts between the arerioles and venules. The presence of new vessels was detected by the early anterio venous phase. The maculopathics are detected by low late leak pattern in the macular, paramacular area and enlargement of FAZ in the presence of hypoflurescence.

Results

Age and Sex Distribution

The mean age of the study subjects was 55.65 years with standard deviation (SD) of 11.3 years. The youngest was 21 years old and the oldest, 80 years old. There were almost three times as many males as

female patients.

The 51-60 years age group contained the majority of patients (48%). This was followed by the 61- 70 group that accounted for 22% of diabetics. On an average the female patient was 1 year younger than the male counterpart (Table 1).

Family History of Diabetes

11 patients (22%) gave the family history of diabetes; 8 of these were males and 3 females. About equal proportion of male and female patients gave the family history of diabetes.

History of Alcohol/Tobacco consumption

5 patients (10%) gave the history of alcohol consumption. All these, were males. 6 patients (12%) were abusing tobacco. All these, again were males.

Co-Morbodity

In 40 patients (80%), there was no associated systemic disease. In 10 patients (20%) diabetes was associated with hypertension.

Treatment Modality

45 patients (90%) were on oral hypoglycaemic agents. 4 patients(8%) were on insulin therapy. A 72 year old male diabetic was on both Insulin and oral hypoglycaemic therapy.

Treatment Regularity

Treatment in as many as 41 patients (82%) was regular. Therapy in the case of the rest 18% was irregular.

Visual Acuity

Right Eye

In the right eye of 16 diabetic patients (32%) the vision was 6/6 – 6/9. In 4 patients the right eye was economically blind (3/60 or worse). The remaining right eyes had loss of vision of various Intermediary degrees.

Left Eye

Vision in left eye was normal (6/6) in 16 patients. In 4patients the left eye was economically blind (3/60 or worse). The remaining left eyes had loss of vision of various intermediary degrees.

Ophthalmoscopic Findings

Right Eye

30 right eyes (60%) showed no – proliferative diabetic retinopathy (NPDR). Of these mild and moderate cases were 14(28%) and 10(20%) respectively, 6(12%) were severe NPDR. In 11 patients (22%), ophthalmoscopy revealed NPDR associated with clinically significant macular edema (CSME). Whereas in 9 cases (18%) proliferative diabetic retinopathy (PDR) was detected (Table 2).

Left Eye

The Table 2depicts, 29 eyes (58%) showed NPDR. Of these 14 (28%) were mild, 11 (22%) were moderate and 4 (8%) were severe NPDR. Ophthalmoscopy revealed NPDR with CSME in 12 patients (24%) whereas, in 9 patients (18%) PDR was detected (Table 2).

Systemic Hypertension with Diabetic Retinopathy

While 91% of the diabetics with hypertension showed severe retinopathy changes, only about 55% of non-hypertensive patients had such changes (Table 3).

Fundus Fluorescein Angiography Findings

The lesions noticed on FFA of the right and left eyes in patients under study are almost same for Microaneurysm, Microaneurysm with haemorrhages, Ischemic maculopathy except H/MA+IRMA+ venous beading and Neovascularisation (Table 4).

Table 1: Age and sex distribution of diabetic patients

Age group (years)	Male		Female		Total	
	Number	Percent	Number	Percent	Number	Percent
21-30	1	2.7	1	7.7	2	4
31-40	3	8.1	0	0	3	6
41-50	5	13.5	3	23.1	8	16
51-60	19	51.4	5	38.4	24	48
61-70	7	18.9	4	30.8	11	22
71 and above	2	5.4	0	0	2	4
TOTAL	37	-	13	-	50	-
MEAN	55.41	-	54.33	-	55.65	-
SD	11.26	-	10.97	-	11.63	-

Table 2: Ophthalmoscopic findings of right and left eye

Diagnosis	Right eye		Left eye	
	Number of cases	Percent	Number of cases	Percent
Mild NPDR	14	28	14	28
Moderate NPDR	10	20	11	22
Severe NPDR	6	12	4	8
NPDR with CSME	11	22	12	24
PDR	9	18	9	18
TOTAL	50	100	50	100

Table 3: Incidence of PDR & NPDR in patients with and without Glycemic control

Glycemic Control	PDR	NPDR	Total
Controlled	3	34	37
Uncontrolled	9	4	13
Total	12	38	50

Table 4: Fundus fluorescein angiography findings in right and left eyes

Lesions	Right eye		Left eye	
	No. of cases	Percentage	No. of cases	Percentage
Microaneurysms only	15	30	15	30
MA+ haemorrhages	10	20	10	20
H/MA+IRMA+venous beading	4	8	3	6
Macular edema				
Exudativemaculopathy	8	16	10	20
Ischemicmaculopathy	2	4	2	4
Neovascularisation	11	22	10	20

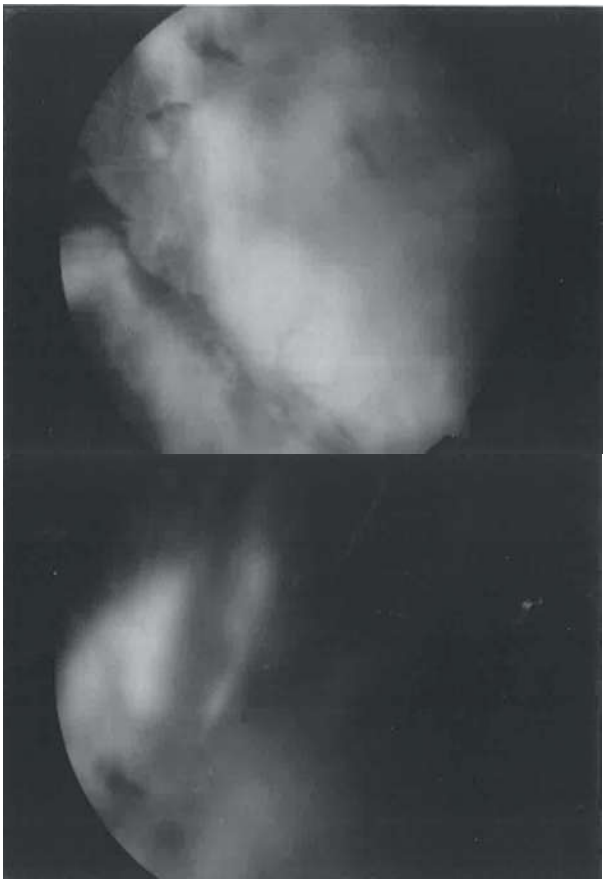

Fig. 1: Hyperfluorescent leaks over disc and hypofluorescent pre-retinal hemorrhages

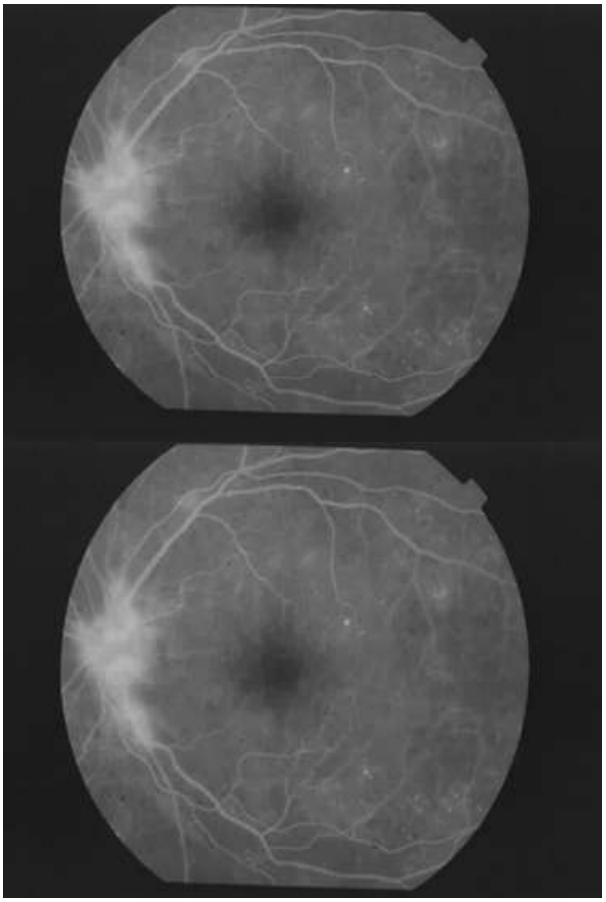

Fig. 2: Hyperfluorescent leaks over disc and elsewhere

Discussion

The mean age of the present study subjects was 55.65 years with a standard deviation of (SD) of 11.13 years. In a similar study conducted by Ramsevak V. et al [7] who have studied 775 cases, the mean age was 72.1 years. Another study conducted by Gonzalez Villalpando C. et al [8] where 231 patients were examined. The mean age was 62.4 years.

The mean age in the first study is more when compared to the remaining three studies due to the reason that the patients selected for the study are only of type 2 diabetes mellitus when compared to the patients of the other three studies where in the patients are of both type I and type 2diabetes mellitus.

Ophthalmoscopic Findings:

In our study we found more case of mild/moderate NPDR than other studies. This may be due to the fact that we had exclusion criteria of not including the patients having hazy media and the patients who had already undergone photocoagulation.

In the study conducted b Bertram et.al [9], 48 patients (9.8%) had already undergone laser photoco-agulation, 13 panretinal scatter, 18 with focal photocoagulation and 17 with both.

The NPDR category in the study conducted by Ramsevak V. et al [7] is 212.4% which is also less when compared to the present study. This is because they have screened the patients of diabetes mellitus patients who attended the ophthalmlic clinic for the first time for the evaluation.

Role of Irregular Treatment and Poor Glycemic Control:

In our study we had 13 patients who were irregular in their treatment. This can be considered a factor, which lead to poor glycemic control the grade of retinopathy of these patients are tabulated according to the duration of diabetes as follows.

In a study conducted by RM Voutilainen – Kaunisto, et. al [10] who studied progress of retinopathy with respect to poor glycemic control in 133 patients observed of retinopathy changes in 55% of patients after 5 years. They concluded, in the diabetic patients, poor glycemic control was the most important predictive factor for the development of retinopathy. It was directly associated with HbA1C values in their by their study.

Another study conducted by Kingsley LA et. al [11] showed significant differences in glycosilated hemoglobin values in patients with and without retinopathy changes. The number of microaneurysms was positively associated with individual mean glycosilated hemoglobin (HbA1C).

Detailed study of dilated ophthalmoscopy, biomicroscopy wherever needed, was followed by fluorescein angiography.

Fundus Fluorescein Angiography Findings

The microaneurysms were appreciated better both in the number, position and in relation to vasculature. This was is consensus with the study conducted by Friberg TR et. al [12], who studied 101 patients, about twice as many microaneurysms were detected on the FFA as on the colour photography. Also FFA showed microaneurysms in 57% of the eyes that had no detectable microaneurysms on colour photography.

However the study conducted by Niesel P. et al [13] states that the described method of quantitative evaluation of diabetic retinopathy quantifies the progression of retinopathy. Accurate quantitative analysis of the comparison between the ophthalmoscopic quantitative analysis of the comparison between the ophthalmoscopic quantification and angiographic quantification was difficult because of the cumbersome nature of counting especially by ophthalmoscopy, lack of accuracy and interpretation problems.

In a study conducted by Helstedt, et. al [14], it is concluded that although microaneurysms in fluorescein angiography and red spots in color or red free photographs all reflect the degree of retinopathy, about half of the red dots in photography don't represent open micro aneurysms in fluorescein angiography.

Ischaemicmaculopathy was better appreciated by fluoresce in angiography than by ophthalmoscopy. Widening of FAZ was also better delineated with fluorescein angiography than by ophthalmoscopy.

In a study conducted by Smith RT et. al [15] they studied 34 diabetic patients with clinically significant macular edema (CSME) by fundus photography, fluorescein angiography and vitreous fluorophotomertry observed that all the three investigations together best predicted visual acuity. They also concluded that by performing fluorescein angiography it is possible to quantitative macular ischaemia.

Clinically significant macular edema (CSME) was observed better by fluorescein angiography than by ophthalmoscopy. The study conducted by Kylstra JA et al [16] where 100 patients were studies by six retina specialists also concluded that the use of FA

improves the accuracy of treatment planning of CSME. Fluorescein angiography was also more accurate is exact localization and extent of neovascularization. This finding was in concurrence with the one observed by Jain BA, et al [17] who studies 25 patients of diabetic retinopathy by ophthalmoscopy and fundus fluorescein angiography.

Conclusion

From the present study, it was concluded that fundus fluorescein angiographyis useful in differentiating the lesions and classifying the diabetic retinopathy. It is useful in assessing the severity of characteristics like capillary loss and to explain the unexplained loss of visual acuity.

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