RETINAL MANIFESTATIONS IN HAEMATOLOGICAL DISORDERS

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ABSTRACT

BACKGROUND AND OBJECTIVES

To analyse the prevalence of retinal involvement in systemic haematological disorders.

METHODS

This was a cross-sectional non-interventional study done on 259 patients with pre-diagnosed haematological disorders from June 2010 to August 2012. Patients with other systemic disorders or ocular diseases were excluded. A complete haematological work up and ocular examination was done.

RESULTS

Among 259 patients, spectrum of haematological disorders identified included anaemia 150 (57.91%), thrombocytopenia 78 (30.12%) and haematological malignancies 31 (11.97%).77(51.3%) patients of anaemia, 37(47.4%) patients of thrombocytopenia and 12(38.7%) patients of haematological malignancies showed retinal abnormalities. Flame shaped haemorrhages was the commonest presentation.

CONCLUSIONS

There was significant association of anaemia and thrombocytopenia with fundus findings and the fundus findings increased with increasing severity.

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INTRODUCTION

Haematological disorders affect millions of people world over and especially in India, representing a major public health concern due to potential for significant morbidity and mortality.

In haematological disorders, abnormalities can occur in the blood flow, in the rheology and in the actual cellular components of the blood. Since the eye, as well as the entire afferent and efferent visual system, has a robust vascular supply, it is not surprising that hematologic diseases may result in visual dysfunction. The specific manifestation of a particular disorder is dependent upon which cell line is involved, the type of dysfunction and the characteristics of the target tissue.

The blood itself, which is contained within vessels, can have a profound effect on the retinal vascular appearance. In fact, as the walls of healthy retinal arterioles and veins are normally transparent, it is the actual blood column that we see. Retinal findings in haematological disorders may yield useful information about the diagnosis and course of the disease and can be of crucial importance in detecting ophthalmic complications that could be sight threatening. Ocular fundus is the only window where vascular changes whether in haematological disorders or otherwise as well, can directly be visualized in vivo.

Changes in ocular fundus were recognized and described in patients with blood diseases during the latter part of the 19th century. Liebrich (1863) was cited by Gowers in 1904 as the first to describe retinal haemorrhages in acute Leukemia.

MATERIAL AND METHODS

This cross-sectional non-interventional descriptive study was conducted from June 2010 to August 2012 in

the Department of Ophthalmology. Two hundred and fifty nine patients with pre-diagnosed haematological disorders were enrolled. Patients having diabetes, hypertension, dense cataractous changes and other media opacities, previous trauma, ocular surgery or treatment which could affect the eye were excluded from the study. A proforma was devised to include patient's demographical data, a brief medical history, ophthalmic history and fundus examination with a haematological profile. All patients underwent detailed examination of the anterior and posterior segment which included visual acuity, slit lamp evaluation of anterior segment, intraocular pressure, retinal examination using direct and indirect ophthalmoscope and slit lamp biomicroscopy. Fundus photography and FFA documentation was done with fundus camera (Zeiss VisucamNM/FA). Optical Coherence tomography (OCT) scanning using Cirrus HD-OCT was performed in cases with positive findings. Complete haematological profile including haemoglobin levels, total leucocyte count, differential leucocyte count, erythrocyte sedimentation rate, platelet count, peripheral blood smear, bone marrow study and lymph node biopsy was obtained from the patients records.

Patients of anaemia and thrombocytopenia were graded according to their severity (anaemia-on basis of hemoglobin concentration[1] into mild(Grade 1), moderate(Grade II) and severe(Grade III), and thrombocytopenia - on the basis of platelet concentration[2] into mild(Grade I), moderate(Grade II) , severe(Grade III) and very severe(Grade IV).

Anaemia: on basis of hemoglobin concentration[1]

Sub Group	Haemoglobin level			
	Non anaemia	Mild(I)	Moderate(II)	Severe(III)
Non pregnant women(15-49 years)	12.0 g/dl and above	10.0-11.9g/dl	7.0-9.9g/dl	below 7.0 g/dl
Men (15-49 years)	Above 12.9 g/dl	12-12.9 g/dl	9-11.9 g/dl	Less than 9 g/dl

Thrombocytopenia- on the basis of platelet concentration[2]-

Platelets count	Grade
$\geq$ 75,000/mm3	I (mild)
<75,000 – 50,000/mm3	II (moderate)
<50,000 – 25,000/mm3	III (severe)
<25,000/mm3	IV (very severe)

RESULTS

Of 259 patients enrolled in the study, a total of 150 (57.91%) subjects were confirmed cases of anaemia (Group I), 78(30.12%) subjects were of Thrombocytopenia (Group II) and 31(11.97%) were patients of haematological malignancies(Group III). Fundus abnormalities were maximally observed in 77 cases of anaemia (GroupI,51.3%) whereas they were minimal (12) in haematological malignancies (Group III, 38.7%) (Table-1).However, on comparing the data statistically, no significant intergroup difference was observed (p=0.430). The mean age of patients was maximum in Group III (41.05±14.61; range 19-65 years) while it was minimum in patients of Group II (28.76±13.08; range 8-75 years) (Table-2). Majority of patients were males in all the three groups. The severity of anaemia was graded according to haemoglobin levels defined by WHO.[1]

Table 1: Prevalence of Fundus Abnormalities

S.No.	No. of cases with fundus abnormalities %	No. of cases without fundus abnormalities%
Group I (Anaemia) (n=150)	51.3	48.67
GroupII (Thrombocytopenia) (n=78)	47.4	52.56
GroupIII(Haematological malignancies) (n=31)	38.7	61.29

Table 2: Demographic Characteristics

S.No	Group	Mean Age+SD(range) (in years)	Male %	Female %
1	I (n=150)	33.86±12.88	57.33	42.67
2	II (n=78)	28.76±13.08	57.69	42.31
3	III (n=31)	41.05±14.61	54.84	45.16

Majority of subjects had grade III anaemia {82 (54.67%)}. It was observed that 34 (22.67%) patients each, were suffering from grade II anaemia and grade I anaemia. Out of total 150 cases of anaemia there were 77 (51.3%) with posterior segment abnormalities. Majority of cases{61 (74.39%)}of grade III anaemia presented with fundus abnormalities whereas in grade I and grade II anaemia, most of the patients had no fundus abnormality and this difference was statistically significant (p=0.000). Background haemorrhage {54(36%)} was the most common finding followed by Retinal vein dilatation {37(24.5%)}. On optic disc examination, pale color was observed in 6(4.1%) cases(Table-3).

Table 3: Distribution of fundus changes according to severity of anaemia

S.No.	Posterior segment abnormalities	Grade I (mild) (n=34)		Grade II (moderate) (n=34)		Grade III (severe) (n=82)		P value (Chi-square test)
		No.	%	No.	%	No.	%	
1	Optic disc							
	i) Pale color	0	0	6	18.18	0	0	0.027
	ii) Blurred margins	0	0	0	0	0	0	_
	iii) Cup abnormalities	0	0	0	0	0	0	_
2	Background							
	i) Haemorrhage	3	9.09	0	0	51	62.96	<0.001
	ii) Exudate	0	0	0	0	3	3.7	_
	iii) Any lesion	0	0	3	9.09	0	0	0.171
3	Retinal vessels							
	i) Retinal artery attenuation	0	0	0	0	0	0	_
	ii) Retinal vein dilatation/ tortuosity	3	9.09	6	18.18	27	33.33	0.248
4	Macular abnormalities	0	0	0	0	0	0	_

A total of 78 patients of Thrombocytopenia comprised the Group II of the present study. For the purpose of study the patients were further sub grouped as having mild, moderate, severe and very severe thrombocytopenia. Maximum number of the subjects 29 (37.18%) had severe type of thrombocytopenia followed by very severe type in 27 (34.61%). Moderate type of thrombocytopenia was present in 14 (17.95%) subjects and only 8 (10.26%) subjects had mild type of thrombocytopenia. It was observed that with increasing severity of thrombocytopenia, the proportion of subjects with fundal abnormalities increased. There were 37 (46.94%) cases who had posterior segment abnormalities. In gradeI no fundal abnormality was found. In grade II, it was 14.28%(2), whereas in Grade III it was 27.59%(8). In grade IVfundus changes were found in all the subjects. This

difference among different grades of thrombocytopenia was statistically significant ($p<0.001$). Retinal vein dilatation/tortuosity was the most common finding 32(40.8%) followed by pale color of optic disc 6(8.2%). Background haemorrhage was found in 5(6.1%) subjects (Table-4). Retinal Haemorrhage is a common complication associated with thrombocytopenia. Although in mild thrombocytopenia no fundal abnormalities were observed, but in all the cases with very severe presentation retinal haemorrhages were present, 11.7% had Roth's spot, 5.8% had flame shaped haemorrhage and 5.8% had dot and blot haemorrhage. Among different severity grades of thrombocytopenia, retinal vein dilatation/ tortuosity was observed to be significantly higher in mild to moderate grades of thrombocytopenia and pale optic disc colour also showed statistically significant differences.

Table 4: Prevalence of fundus changes in relation to severity of thrombocytopenia

S.No.	Posterior segment abnormalities	Grade I (Mild) (n=8)	Grade II (moderate) (n=14)	Grade III (Severe) (n=29)	Grade IV (very severe) (n=27)	P value (Chi-square test)
		No. /%	No. / %	No. /%	No/ %	
1	Optic disc					
	i) Pale color	0	0	0	6 (23.5%)	0.042
	ii) Blurred margins	0	0	0		_
	iii) Cup abnormalities	0	0	0		_
2	Background					
	i) Haemorrhage	3	0	0	5 (17.6%)	0.111
	ii) Exudate	0	0	0		_
	iii) Any lesion	0	0	0		_
3	Retinal vessels					
	i) Retinal artery attenuation	0	0	0		_
	ii) Retinal vein dilatation/ tortuosity	0	2 (11.1%)	8 (27.8%)	22 (82.4%)	<0.001
4	Macular abnormalities	0	0	1 (3%)	1 (3.7%)	0.492

A total of 31 patients comprised the group of haematological malignancies (Group III) in the present study. Majority of subjects were of chronic myeloid leukemia (14, 45.16%). A total of 5 (16.13%) subjects were of acute myeloid leukaemia, 1 (3.23%) subject had multiple myeloma, 3 (9.68%) of Acute Lymphoid Leukaemia, 2 (6.45%) Chronic Lymphoid Leukaemia, 2 (6.45%) Hodkins Lymphoma and 4 (12.90%) patients of Non-Hodgkins lymphoma. There were 40% cases who had posterior segment abnormalities. Retinal vein dilatation {11(35%)} was the most common finding followed by background haemorrhage {5,(15%)}. There were 3 (10%) patients who were found to be having blurred margins on optic disc examination (Table-5). Fundal abnormalities were found in more patients of CML malignancy {7, (50%)} as compared with AML {5, (20%)}, ALL {1, (33.33%)}, CLL {1, (50%)}, {1, (50%)}and NHL {1, (25%)}patients and this difference was statistically not significant. Overall incidence of retinal abnormalities was positive in 47.46% of subjects with haematological disorders. The changes were maximum in Group I {77, (51.3%)} and minimum in Group III {12 (38.7%)}. This difference was statistically significant (p=0.024).

Table 5: Distribution of various fundus findings according to type of haematological malignancy

S.No.	Posterior segment abnormalities	AML	CML	Multiple myeloma	ALL	CLL	HL	NHL	P value (Fisher exact test)
		No. /%	No. / %	No. / %	No/ %	No/ %	No/ %	No/ %	
1	Optic disc								
	i) Pale color	0	0	0	0	0	0	0	_
	ii) Blurred margins	0	2(14.3)	0	0	0	1(50)	0	0.621
	iii) Cup abnormalities	0	0	0	0	0	0	0	_
2	Background								
	i) Haemorrhage	0	0	3(21.4)	1(33.3)	1(50)	0	1(25)	0.469
	ii) Exudate	0	0	0	0	0	0	0	_
	iii) Any lesion	0	0	0	0	0	0	0	_
3	Retinal vessels								
	i) Retinal artery attenuation	0	0	0	0	0	0	0	_
	ii) Retinal vein dilatation/ tortuosity	1(20)	6(42.9)	0	0	1(33.3)	1(50)	1(25)	0.493
4	Macular abnormalities	1(20)	0	0	0	1(33.3)	0	0	0.492

IIIUSTRATIONS :

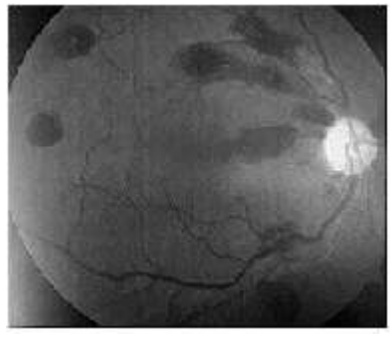

Fig1. Fundus Photo of Anaemia (Grade III)

Fig.2. Fundus Photo of
Right eye Thrombocytopenia (Grade IV)

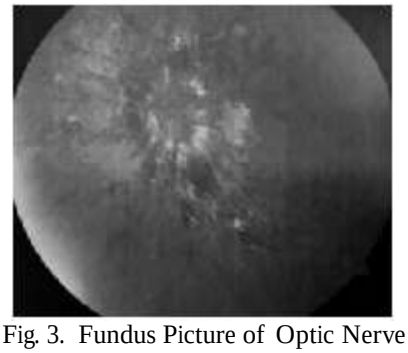

Fig. 3. Fundus Picture of Optic Nerve involvement in CML

DISCUSSION

Haematological diseases encompass wide spectrum of disorders that can present with varied ocular, especially retinal manifestations. Indeed, ocular manifestations may be the initial indication of an underlying haematological disorder. Blood disorders are one of the major health problems presenting with variable clinical manifestations. Nutritional anaemia remains the commonest haematological abnormality especially in the third world nations.

Among anaemic patients background related abnormalities, haemorrhage was the most common abnormality encountered in 54(36%) patients. There were 3(2.0%) patient with exudates. Retinal vein dilation/tortuosity was observed in 37(24.5%) patients (Table-3). In other studies retinal vascular changes was 28.56% and haemorrhages were 19.04%[3] whereas another study had found venous fullness and venous tortuosity in 18% and 24% of their series, thus venous dilation and tortuosity is one of the common retinal findings and is in consonance with present result[4]. Similarly in the current study 6(4.1%) patients had pale optic disc which is in correlation with the study done by Kataria VC et al[5] (1983) in a series of 40 patients of anaemia, 18 patients had pale disc. In a study by Aisen et al.[6] 20% of anaemic patients had haemorrhage whereas in another study, incidence of retinal haemorrhage was observed to be 14% and presence of tortuous veins, exudates and disc oedema were the other retinal abnormalities encountered[7]. In the current study ocular disc involvement was in 6(4.1%), haemorrhage in 54(36)%, exudates in 3(2%) and retinal vein dilatation/tortuosity in 37(24.5%) patients of anaemia. Thus the observations in present study are in consonance with the findings of other studies.[3,6,7]

Fundus changes were most common among severe (grade III) anaemia patients {61, (74.39%)} followed by 35.3%(12) involvement in moderate (grade II) and minimum {3, (8.82%)} in mild (grade I) anaemi , akin with the findings of Shaheen et al. who encountered no retinal abnormality in mild category of anaemia and maximum incidence in severe category of anaemia (34.2%).[7] The findings in present study are also in agreement with the findings of Merin and Freund (1968)[8] who reported the incidence of retinal abnormalities to be higher in severe anaemia (31.8%) as compared to moderate anaemia (13.3%).

Association of other related complications or other altered haematological parameters which might also affect the outcome, depending upon their severity, cannot be ruled out[9] In present study owing to limitations, no such relationship could be explored.

The relevance of thrombocytopenia becomes more important with the recent outbreaks of dengue fever in

this part of country. Almost all the cases of thrombocytopenia (group II) included in this study were of dengue fever origin. Thrombocytopenia among dengue fever is of transient nature i.e. the thrombocytopenia is generally not of a long duration. The incidence of fundus abnormalities in different categories of thrombocytopenia showed that with an increasing severity of thrombocytopenia, the incidence of fundal abnormalities increased. There were 5(6.1%) cases with retinal haemorrhage whereas retinal vein dilatation/ tortuosity was present in 32(40.8%) cases. Optic disc pallor was observed in 6(8.2%) cases. Overall posterior segment abnormalities were present in 37(47.4%) patients and 2(6.7%) patients had macular involvement (Table-4). In a study by Teoh et al. (2006) haemorrhage (77%) and retinal vasculitis (23%) were observed as the most common fundal involvement findings[10]. In present study the lower incidence of haemorrhage could be attributed to timely administration of proper medication and anti-haemorrhagic drugs to these patients. (All the patients included in the present study were hospital admitted, who were being managed medically and haematologically). Retinal vein tortuosity in thrombocytopenia was the most common finding in present study and was seen to be increasing with increasing severity of thrombocytopenia.

The findings of the study are in concurrence with the findings of Kapooret al.[11] (2006) who observed the incidence of retinal haemorrhage in thrombocytopenia to be 3.7%. In present study this was slightly higher at 5.08% in all grades of thrombocytopenia.

Amongst all the 31 patients of haematological malignancies, only 12 (38.7%) patients showed fundus involvement (Table-5). In another study a slightly higher incidence of retinal involvement was observed in 34 out of 53 patients of AML (64.2%).[12] In present study there were only 5 cases of AML. Of these only 1 had fundal findings in the form of retinal veins dilatation and tortuosity. The difference between our findings and that of Karesh et al could be because of the difference in sample size and that ours is not a specialised centre for treatment of haematological malignancies.

Among the three groups there was no significant difference of optic disc parameters except for blurred margins which were present in 3 (10%) cases of haematological malignancies. The incidence of haemorrhage was observed to be significantly lower in thrombocytopenia patients as compared to anaemic and haematological malignancy groups ($p=0.001$).

The findings in the present study suggest that the fundal involvement in haematological disorders seems to be a time-dependent disease. In transient diseases (such as thrombocytopenia) where the patient is under medication the incidence is low as compared to diseases with prolonged illness (such as haematological malignancies) or where the disease remains latent for a prolonged duration (such as anaemia).

Retinal haemorrhage and retinal vein dilatation is the most common finding that was observed in present study. The fact that the ocular manifestations might have been suppressed by continuing treatment cannot be denied especially in cases of thrombocytopenia and haematological malignancies where use of anti-haemorrhagic drugs is a common practice.

An understanding of the retinal manifestations of various blood diseases is useful for ophthalmologists because of the frequency with which these patients are seen, not only for ophthalmic complaints but also for routine examination. Retinal manifestations can also be the earliest manifestation of undiagnosed haematological disorders. The ophthalmic examination may also give some insight into the extent of the disease and may, in some cases, shed light on its severity and prognosis.

The trends obtained in present study show that the fundal involvement in haematological disorders is quite high and especially so in common disorders like anaemia. This high incidence of retinal involvement in anaemic subjects indicate the need for a larger and systematic study preferably an interventional one so as to know whether the change in anaemic status as a result of interventions brings about a change in status of retinal abnormalities. One of the limitations of the study was that all the patients of thrombocytopenia were from amongst dengue fever patients who were under medication; hence the results might be confounded. In view of this limitation, and considering the low incidence of thrombocytopenia a larger study with longer duration is recommended to support or disapprove the observation of the present study.

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