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Direct Ophthalmoscopy *versus* Detection of Hypertensive Retinopathy: A Comparative Study

José Albuquerque de Figueiredo Neto, Guilherme Lima Palácio, Allison Nobrega dos Santos, Pamela Suelen Serra Chaves, Germana Viana Gomes, Tassiane Soares Cabral

Universidade Federal do Maranhão, São Luiz, MA - Brazil

Abstract

Background: Detection of hypertensive retinopathy (HR) with direct ophthalmoscopy is part of the assessment of hypertensive patients. Its use has been questioned because of its subjectivity and high interobserver variability.

Objective: To determine the prevalence of HR in hypertensive patients under outpatient monitoring, the correlation between diagnosis and ophthalmoscopy and angiography, and to correlate it with other target organ damages.

Methods: An observational, analytical and cross-sectional evaluation of 99 patients. Direct ophthalmoscopy and angiography performed by two investigators independently. Classification of RH, as described by Keith, Wagener and Barker.

Results: The prevalence of HR of any grade was higher than 90.0% by both methods. On ophthalmoscopy, we observed grade I abnormalities in 51.0%, grade II in 43.0%, with one patient with grade III HR. On angiography, we observed grade I abnormalities in 42.0% and grade II in 52.0%. We detected three patients with grade III HR, two of which were not detected by ophthalmoscopy. Observers' agreement for the presence and severity of HR was poor with direct ophthalmoscopy and good with angiography. Renal dysfunction, ECG abnormalities (ventricular hypertrophy, pathological Q wave, repolarization abnormalities), and history of stroke were observed in 70.0%, 27.0% and 10.0% of patients, respectively. There was no relationship between the severity of HR and other target organ damages.

Conclusion: We observed a high prevalence of HR using both methods. Observers' agreement for the diagnosis and determination of the severity of HR was better with angiography. In our sample, there was no association of the severity of HR with other target organ damages. (Arq Bras Cardiol 2010; 95(2): 215-222)

Key words: Ophthalmoscopy; retina/injuries; hypertension.

Introduction

Hypertensive retinopathy (HR) is a condition characterized by a spectrum of retinal vascular signs that develop in people with hypertension[1]. Its detection with direct ophthalmoscopy (DO) is part of the assessment of hypertensive patients[2], but its use has been questioned due to its high subjectivity and interobserver variability[3].

The Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the V Brazilian Guidelines on Hypertension list HR as a marker of target organ damage. Therefore, it is a criterion for prescription of treatment[4,5].

Classic studies on retinal abnormalities in hypertension are currently questioned due to some factors[6,7]: inclusion of patients untreated or uncontrolled, diagnosis made only with the DO and association of HR with mortality in studies where there was no control of other risk factors currently known, which may act with confusion factors[8-11].

Recent studies using angiography[12-17] showed high reproducibility in the evaluation of microaneurysms, hemorrhages, arteriovenous crossing abnormalities, focal or generalized arteriolar narrowing. However, few studies have compared the sensitivity and reproducibility between DO and angiography in the detection of HR[18].

Another issue in the study of HR is that some signs seem to be associated with certain clinical conditions[19].

We performed this study because of the importance of hypertension as a cause of morbidity and mortality, lack of data on the prevalence of HR in our environment, the absence of studies comparing DO with angiography in diagnosis and the uncertainty regarding the usefulness of its detection in the evaluation of cardiovascular risk and associated target organ damages.

The objectives were to determine the prevalence of RH in patients monitored in a League of Hypertension of a University

Hospital; to evaluate the correlation between DO and digital angiography (DA) in detecting RH; to study the association of HR with other target organ damages.

Methodology

Type of study

Analytical cross-sectional study conducted from June to December/2008 in a League of Hypertension of a University Hospital.

Sample

For convenience purposes, patients were selected as they came for routine medical appointments, observing the exclusion criteria of the study, namely:

a. Diabetes mellitus;

b. Media opacity (scarring, vitreous hemorrhage, cataract);

c. Retinal detachment;

d. Lack of systemic clinical data in the medical records of the League of Hypertension.

We examined 131 consecutive patients. We excluded 32 patients: one, because of double evaluation, three because of media opacity on ophthalmological test, 6 due to insufficient data in their files and 22 have developed diabetes. We evaluated 99 patients.

Data collection

Performed by clinical and ophthalmological tests, namely:

a. Clinical examinations - the patients underwent systemic clinical examination for the presence of risk factors for cardiovascular disease and categorization of their blood pressure as for severity, according to the V Brazilian Guidelines on Hypertension[4].

b. Routine laboratory tests - urinalysis, potassium and creatinine, fasting glucose, total cholesterol, LDL, HDL and triglycerides - in accordance with the V Brazilian Guidelines on Hypertension[4].

c. 12-lead electrocardiogram assessed abnormalities consistent with left ventricular hypertrophy (Cornell criteria), and assessment of the presence of pathological Q wave and ventricular repolarization abnormality.

The cleareance estimated of creatinine was calculated according to Cockcroft-Gault formula. Decreased renal function was defined as smaller than 60 ml/min.

Ophthalmologic examination was performed, including visual acuity, biomicroscopy and applanation tonometry. Direct ophthalmoscopy was also performed with coaxial ophthalmoscope 3.5 V (Welch Allyn, Skaneateles Falls, United States) and angiography with equipment CF60 UVi (Canon, Tokyo, Japan) with digital system Eye Q Pro (Canon, Tokyo, Japan) after pulilar dilation with 1.0% tropicamide eye drops. The images were obtained in the field of 60 degrees, centered on the macula.

Each patient underwent fundoscopy by two ophthalmologists, with similar experience and independently.

Angiographies were also interpreted by these physicians without prior knowledge of patients' clinical conditions, independently. In a second step, a new interpretation was made by consensus. We performed classification of HR as described by Keith, Wagener and Barker[6].

Statistical analysis

Data were analyzed using Epi Info 3.4.3 (2007). Quantitative variables were presented as averages and standard deviation. Qualitative variables were presented as frequencies and percentages.

As for fundus and angiography findings, we measured the Kappa coefficient of agreement among examiners. Agreement was considered poor in cases of Kappa coefficient smaller than 0.20; weak, between 0.21-0.40; moderate between 0.41-0.60; good between 0.61-0.80; and very good when it was higher than 0.80.

To test the association between risk factors and severity of HR, we used Fisher's exact test. A significance level of 5.0% was adopted.

Ethical aspects

Data were collected after approval by the Research Ethics Committee (Process 33104-178/2007) and the patients signed a consent form.

Results

We evaluated 99 patients whose demographics are presented in Table 1.

Analysis of the presence of risk factors for cardiovascular diseases revealed that they had no risk factor in addition to hypertension in 9.1% of the cases, one or two factors in 45.5% and three or more risk factors or cardiovascular disease in 24.2%. (Table 2).

As for the time of diagnosis of hypertension, 42.4% of patients were younger than 6, 21.2% between 6 and 10, and 36.4% were older than 10. There was no association between the time of diagnosis and the presence of retinopathy (p > 0.05).

Staging of hypertension can be seen in Table 3.

The frequency of target organ damages is shown in Table 4.

The prevalence of HR using DO and digital angiography, as well as the consensus of angiography by both observers are shown in Table 5.

The coefficient of agreement for the presence of HR with DO was poor, with Kappa equal to 0.22 CI 95% [0.38 to 0.83].

However, there was a good coefficient of agreement for the presence of HR with digital angiography, with Kappa value equal to 0.66 CI 95% [0.00 to 1.37].

When we evaluated observers' coefficient of agreement in distinguishing grade I or grade II retinopathy through DO, this proved to be poor, with Kappa equal to 0.33 CI 95% [0.13 to 0.52].

In that same analysis of severity of HR between grades I and II, there was a good agreement when using the digital angiography, with Kappa equal to 0.70 CI 95% [0.55 to 0.84].

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Table 1 - Demographic aspects and cardiovascular risk factors of the patients included in the research protocol of hypertensive retinopathy, from June to December/2008, HU-UFMA

Risk factors	n	(%)
Smokers		
Yes	12	12.1
No	87	87.9
Dyslipidemic		
Yes	62	62.6
No	37	37.4
HFDCV*		
Present	68	68.7
Absent	31	31.3
Heart disease		
Yes	20	20.2
No	79	79.8
CVA **		
Yes	10	10.1
No	89	89.9
History of nephropathy		
Yes	40	40.4
No	59	59.6
Hypercholesterolemia (> 200 mg/ml)		
Yes	47	47.5
No	52	52.5
Hypertriglyceridemia (> 150 mg/ml)		
Yes	61	61.6
No	38	38.4

*HFDCV - family history of cardiovascular disease, **CVA - cerebral vascular accident (stroke).*

No relationship was found between the severity of HR and the stages of hypertension on examiners' consensus through digital angiography (Table 6).

Renal dysfunction was present in 20.2% of the patients. No relationship was found between the degree of retinopathy and the severity of renal dysfunction (Table 7).

We analyzed the electrocardiograms of 90 patients and observed electrocardiographic abnormalities in 27.3% of them. No relationship was found between the degree of retinopathy and ECG abnormalities (Table 8).

History of stroke was present in 10 patients in the sample. However, no relationship was established between positive history of stroke and severity of HR.

There was no association between race and severity of HR.

Table 2 - Staging of hypertension and target organ damage of patients included in the research protocol of hypertensive retinopathy, from June to December/2008, HU-UFMA

Variables	n	(%)
Hypertension stage		
Optimal, normal or borderline	43	(43.4)
Stage I	21	(21.2)
Stage II	20	(20.2)
Stage III	11	(11.1)
Isolated systolic hypertension	04	(4.1)
Target organ damage	n	(%)
CVA	10	10.1
Nephropathy (clearance < 60 ml/min)	20	20.2
Hypertrophy or ischemia on electrocardiogram	27	27.3

Table 3 - Prevalence of hypertensive retinopathy according to the classification of Keith, Wagener and Barker, according to the method diagnosed by observers 1 and 2 and consensus of angiography in the research protocol of hypertensive retinopathy, from June to December/2008, HU-UFMA

Examination	0	I	II	III	I – III	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n
Ophthalmoscopy						
Observer 1	5 (5.1)	51 (51.5)	43 (43.4)	0 (0)	94 (94.9)	99
Observer 2	3 (3.0)	41 (41.4)	54 (54.6)	1 (1)	96 (97.0)	99
Angiography						
Observer 1	1(1)	45 (45.5)	50 (50.5)	3 (3)	98 (99)	99
Observer 2	2 (2)	32 (32.3)	62 (62.7)	3 (3)	97 (98)	99
Consensus	2 (2)	42 (42.4)	52 (52.6)	3 (3)	97 (98)	99

Table 4 - **Classification of hypertensive retinopathy according to the second stage of hypertension using the consensus among examiners in digital angiography in the research protocol of hypertensive retinopathy, from June to December/2008, HU-UFMA**

Classification of HR	Classification of hypertension					
	Optimal normal borderline	Stage 1	Stage 2	Stage 3	Isolated systolic	Total
Normal	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
Grade I	20 (20.2)	6 (6.1)	10 (10.1)	3 (3)	3 (3)	42 (42.4)
Grade II	19 (19.2)	14 (14.1)	10 (10.1)	8 (8.1)	1 (1)	52 (52.6)
Grade III	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)	3 (3)
TOTAL	43 (43.4%)	21 (21.2%)	20 (20.2%)	11 (11.1%)	4 (4.1%)	99 (100%)

Table 5 - **Severity of hypertensive retinopathy and renal function in the research protocol of hypertensive retinopathy from June to December/2008, HU-UFMA**

Renal function	Classification of Keith, Wagener and Barker (1939) on angiography (consensus)				
	Normal n (%)	Grade I n (%)	Grade II n (%)	Grade III n (%)	TOTAL n (%)
Normal (CI > 90 ml/min)	0 (0)	15 (15.1)	15 (15.1)	0 (0)	30 (30.3%)
Light dysfunction (90 ml/min < CI < 30 ml/min)	2 (2)	16 (16.2)	29 (29.3)	2 (2)	49 (49.5%)
Moderate dysfunction (60 ml/min < CI <30 ml/min)	0 (0)	9 (9.1)	6 (6.1)	1 (1)	16 (16.2%)
Severe dysfunction (CI < 30ml/min)	0 (0)	2 (2)	2 (2)	0 (0)	4 (4%)
TOTAL	2 (2%)	42 (42.4%)	52 (52.6%)	3 (3%)	99 (100%)

Table 6 - **Abnormalities on electrocardiogram and severity of hypertensive retinopathy in the research protocol of hypertensive retinopathy from June to December/2008, HU-UFMA**

ECG	Keith-Wagener classification on angiography (consensus)				
	Normal n (%)	Grade I n (%)	Grade II n (%)	Grade III n (%)	TOTAL n (%)
Normal	1 (1.1)	28 (31.1)	33 (36.7)	1 (1.1)	63 (70)
Abnormal	1 (1.1)	8 (8.9)	16 (17.8)	2 (2.2)	27 (30)
TOTAL	2 (2.2)	36 (40%)	49 (54.5)	3 (3.3)	90 (100%)

Table 7 - **Relationship between history of stroke and severity of hypertensive retinopathy in the research protocol of hypertensive retinopathy from June to December/2008, HU-UFMA**

CVA	Keith-Wagener classification on angiography (consensus)				
	Normal n (%)	Grade I n (%)	Grade II n (%)	Grade III n (%)	TOTAL n (%)
Positive history	0 (0)	3 (3)	7 (7.1)	0 (0)	10 (10.1)
Negative history	2 (2)	39 (39.4)	45 (45.5)	3 (3)	89 (89.9)
TOTAL	2 (2)	42 (42.4)	52 (52.6)	3 (3)	99 (100)

Discussion

International guidelines consider the retinal findings differently. For the European Society of Hypertension and the European Society of Cardiology, grade III and IV HR as classified by Keith, Wagener and Barker, is regarded as an associated clinical condition[6,20]. The International Society of Hypertension of the World Health Organization and the Guidelines of the British Society of Hypertension consider grades III and IV of Keith, Wagener and Barker as target organ damage[21,22]. The National Committee on Prevention,

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Table 8 - Severity of hypertensive retinopathy according to race in the research protocol of hypertensive retinopathy from June to December/2008, HU-UFMA

Race	Keith-Wagener classification on angiography (consensus)				
	Normal n (%)	Grade I n (%)	Grade II n (%)	Grade III n (%)	TOTAL n (%)
White	2 (2)	11 (11.1)	12 (12.1)	0 (0)	25 (25.3)
Brown	0 (0)	16 (16.2)	24 (24.2)	3 (3)	43 (43.4)
Black	0 (0)	15 (15.1)	16 (16.2)	0 (0)	31 (31.3)
TOTAL	2 (2)	42 (42.4)	52 (52.6)	3 (3)	99 (100)

Detection, Evaluation and Treatment of Hypertension in the United States and the V Brazilian Guidelines on Hypertension consider the presence of any sign of retinopathy as target organ damage[4,5].

In this study, using DO and considering the presence of any sign of retinopathy, we observed prevalence above 90.0%, with grade I abnormalities in 51.0% and grade II in 43%. One patient had grade III HR. No patient with grade IV was found. The most common findings were diffuse arteriolar narrowing and arteriolar wall opacification, and pathologic arteriovenous crossing. Considering only advanced damages (Grade III and IV), the prevalence of HR would be 1.0%.

In the Framingham Eye Study, with DO, in a general population aged 52-85, the prevalence of retinopathy was 0.8%, excluding patients with diabetes. The concept of retinopathy included only advanced forms such as retinal hemorrhages and exudates, without considering arteriolar wall abnormalities[18].

McDonough, Garrison and Hames[23], using DO, evaluating 2,210 people, found that 2.2% had retinopathy defined as the presence of microaneurysms, hemorrhages or exudates. On evaluation of earliest signs of retinopathy, 34.0% had generalized or focal arteriolar narrowing, and 13.2%, pathological AV crossings[23].

Besharati et al[24] studied 213 hypertensive patients with DO and found a prevalence of 39.9%, considering any sign of retinopathy. In those with mild hypertension, the prevalence was 25.3%; in patients with moderate hypertension, 34.5%; and those with severe hypertension, prevalence was 84.6%. The most common findings were arteriolar narrowing (35.13%), pathologic arteriovenous crossing (17.12%) and cotton wool spots (9.0%)[24].

In this study, the coefficient of agreement for the diagnosis and severity of HR showed a weak agreement, using DO.

Using DO in assessing hypertensive patients results in imprecision and interobserver variability. It is particularly imprecise in people with mild to moderate hypertension[2,8].

In this study, the detection of HR using angiography was higher than 90.0%, with grade I abnormalities in 42.0% and grade II in 52.0%. Three patients with grade III HR were detected, two of which were not detected by DO. No patient with grade IV was observed. Considering only advanced damages (Grade III and IV), the prevalence of HR would be 3.0%.

Using angiography and standardized methodology for documenting and defining the various signs of HR, epidemiological studies have shown a prevalence ranging from 2-15.0% in the general population[10,12,25-27].

The Beaver Dam Eye Study[12], using angiography, evaluated 2,375 non-diabetics aged 43-86, finding a focal arteriolar narrowing in 14.0%, retinopathy in 8.0%, and pathological AV crossings in 2.0%. When hypertensives were excluded, there was focal arteriolar narrowing in 11.0%, retinopathy in 6.0% and pathological AV crossings in 2.0%. Therefore, it can be inferred that retinal microvascular abnormalities are common in nondiabetic populations, although they are more prevalent in patients with hypertension[12].

In the Blue Mountains Eye Study[27], 3,275 non-diabetic individuals underwent angiography. The prevalence of retinopathy was 9.9%. The Atherosclerossis Risk in Communities (ARIC) Study[25] studied 9,300 individuals older than 49, without diabetes, using angiography. The prevalence of focal arteriolar narrowing was 6.0%, retinopathy of 3.0% and pathological AV crossing of 6.0%.

The higher prevalence of retinopathy observed in these studies, compared to the Framingham study, may be due to the higher sensitivity of photographic assessment techniques against ophthalmoscopy. However, these studies did not include the earliest sign of HR, the generalized arteriolar narrowing[13].

In this study, the coefficient of agreement for the detection and assessment of the severity of HR using angiography was higher than that found using DO.

Cuspidi et al[28] evaluated 197 patients with grade I and II hypertension (73.0%) without pretreatment, using digital angiography, with two independent observers. The overall prevalence of retinal changes was 84.3% and 84.7% respectively.

In this study, there was no correlation of retinopathy with age, sex, time of diagnosis and stage of hypertension. Data from the Beaver Dam and ARIC study suggest that the prevalence of arteriolar narrowing and pathological AV crossing seem to be directly related with age. The prevalence of retinopathy was also age-dependent in the Blue Mountains study[12,24,26].

The prevalence of retinopathy was higher in males, when adjusted for age, both in the Beaver Dam and in the ARIC study. However, in the Blue Mountains, no difference was found[11,25,27].

In literature, it is reported that generalized arteriolar narrowing and pathologic arteriovenous crossings can be observed more commonly in patients with longer duration of diagnosed hypertension, representing signs of chronic vascular damage. On the other hand, focal arteriolar narrowing, retinal hemorrhages, microaneurysms and cotton wool spots are believed to be related to the current level of hypertension[13,19].

The distribution of the severity of HR in this study, according to the classification of Keith, Wagener and Barker was presented as follows: Grade I - 42 patients (42.4%), grade II - 52 patients (52.6%), grade III - 3 patients (3%) and grade IV - no patient.

The high frequency of early signs of retinopathy, including grades I and II of Keith, Wagener, and Barker, and the low frequency of intense signs, grades III and IV, may be related to the duration of hypertension and treatment and regular control of blood pressure[6].

In this study, renal dysfunction was observed in 20.2% of patients. However, no association was established between renal dysfunction and the presence and severity of HR. In the ARIC study, individuals with retinopathy (odds ratio 2.0; confidence interval 95.0%, 1.4-2.8), microaneurysms (OR, 2.0, CI 95.0%, 1.3 - 3.1), retinal hemorrhages (OR, 2.6, CI 95.0%, 1.6-4.0), cotton wool spots (OR 2.7, CI 95.0%, 1.6-4.8) and pathologic arteriovenous crossings (OR 1.4, CI 95.0%, 1.0-1.9) were more likely to develop renal dysfunction than individuals without retinal abnormalities[11].

The study found electrocardiographic abnormalities consistent with left ventricular hypertrophy, presence of pathological Q waves and ventricular repolarization abnormalities in 27.0% of patients. Gillum[29] noted that retinal arteriolar narrowing detected by ophthalmoscopy determined two to six-fold increased likelihood of developing ischemic heart disease, after controlled analysis for hypertension, diabetes and hypercholesterolemia.

Duncan et al[30] demonstrated that the presence of RH in men doubled the chance of ischemic heart disease (relative risk 2.1; confidence interval 95%, 1.0 - 4.2). On the other hand, the ARIC study[31] reported a correlation between generalized arteriolar narrowing and ischemic heart disease in women (relative risk 2.2, confidence interval 95%, from 1.0 to 4.6) but not in men (relative risk 1.1, confidence interval 95%, 0.7 - 1.8).

The limitations of this study should be highlighted. The number of patients evaluated may have been insufficient to demonstrate the relationship between specific signs of HR

and target organ damage. The prevalence of abnormalities was higher than usually reported in the literature, and may have resulted from bias, given the subjectivity of defining abnormality in vascular diameters. Accurate methods of measurement may change these estimates. Another aspect is that the population of patients studied was of a League of Hypertension under regular clinical treatment and monitoring, which could explain the low frequency of more severe signs of HR.

The relevance of this study should also be emphasized. The scarcity of studies on the subject in our country and the region makes the familiarization of frequency of HR signs in the population studied to serve as a parameter for other studies. This study is also useful in showing the profile of fundus findings in patients under regular treatment, mostly classified in the early stages of HR. The high frequency signal casts doubt on its relevance in the risk stratification of hypertensive patients. These findings were not proportional to the frequency of other target organ damages. The work also is unique in comparing HR diagnosing techniques, once we do not find in literature and other studies comparing DO and angiography in detecting HR. Superior fundus findings open discussions on the role of this diagnostic technique in assessing hypertensive patients.

Conclusion

HR is frequent in hypertensive patients being treated in primary care programs. The diagnostic agreement among ophthalmologists is higher in the analysis of angiographies than on direct ophthalmoscopy. The lack of association between retinal abnormalities and other evidence of target organ damage may be related to the small sample size.

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