Malignant Hypertension in North West India

A Hospital Based Study

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SUMMARY

One hundred and thirty-five patients with malignant hypertension seen over a period of 11 years (1979 to 1989) at a referral hospital were analyzed to characterize the clinical features and etiology of this disease. Ninety male and 45 female patients with an average age of 38.2 ± 1.4 years were studied. Malignant hypertension was the presenting feature in 68 patients. The etiology included essential hypertension in 88 patients and a secondary cause in 47 patients. Secondary causes included a renovascular etiology in 20 patients, renal parenchymal disease in 19, pheochromocytoma in 6 and Conn's syndrome and adrenal carcinoma in one patient each. Among the 20 patients with renovascular hypertension, Takayasu's arteritis was seen in 15 (75%). The mean age of patients with essential hypertension was 41.7 + 1.14 years while the mean age in patients with secondary hypertension was 33.2 + 1.96 years. Duration of preexisting hypertension was longer in essential hypertensives (2.42 + 0.45 years) than in patients with secondary hypertension (1.27 + 0.41 years, $p < 0.05$). Raised serum creatinine was seen in 93 patients. Seventy-seven patients had left ventricular hypertrophy on ECG. Ninety-six patients were followed for a period ranging from 18 months to 10 years (mean 32 months). Sixteen patients died during hospital stay while 6 patients died during the follow-up period. The deaths were related to the effects of uncontrolled hypertension including, renal failure (11), stroke (6), congestive cardiac failure (3) and myocardial infarction (1). Male sex, higher age at presentation and deranged renal function at presentation were associated with a poor outcome. Thus, essential hypertension is the most common cause of malignant hypertension in India. Takayasu's arteritis is the most common cause of secondary hypertension. Impaired renal function and poor compliance affect the prognosis of malignant hypertension adversely. (Jpn Heart J **35**: 601–609, 1994)

Key words: Essential hypertension Renal parenchymal disease Renovascular hypertension Takayasu's arteritis Pheochromocytoma Conn's syndrome

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MALIGNANT hypertension as first described by Volhard and Fahr, is a rapidly progressive and fatal syndrome, if left untreated.[1] The presence of papilledema has been considered a sine qua non of malignant hypertension.[2] Patients with retinal hemorrhages and exudates without papilledema have been described as having accelerated hypertension.[3] However, many authors classify as malignant hypertension, cases of hypertension with retinal hemorrhages and exudates with or without papilledema,[4–6] thus including grade III and IV retinopathy of Keith Wagener Barker classification.[7–9] Although it may result from any form of hypertension, renal disease appears to be a predominant cause of malignant hypertension.[10] Racial factors are also important, as underlying renal disease appears to be less frequent in blacks.[11] The poor prognosis, which in the past resulted in the death of all patients within 5 years and over 80% in the first year,[12] has certainly improved following the availability of effective antihypertensive drugs.[13,14]

The present study was aimed at examining the underlying disorders responsible for malignant hypertension, its prognosis and the factors influencing the prognosis in Indian patients, in view of the paucity of this information from the Indian subcontinent.

Subjects and Methods

Of 6,665 hypertensives seen over a period of 11 years at the Postgraduate Institute of Medical Education and Research, Chandigarh, 135 patients were found to have malignant hypertension. A detailed clinical examination was performed in all patients. Laboratory investigations included complete hemogram, urine analysis and blood urea, serum creatinine, blood sugar, serum calcium, serum phosphorus and serum electrolyte levels. All patients had an estimation of 24 hour urinary protein excretion, standard 12 lead ECG and a chest skiagram. Special investigations including ultrasonography of the abdomen, intravenous urography, angiography, CT of the abdomen and urinary vanillyl mandelic acid, urinary and plasma norepinephrine, epinephrine, cortisol and aldosterone levels indicated. Patients who did not have any clinical or laboratory evidence of underlying disease responsible for their hypertension were defined as suffering from essential hypertension. From 1976 to 1985, parenteral nitroprusside, diazoxide and reserpine were used for the rapid reduction of blood pressure. From 1986 onwards, sublingual nifedipine was the predominant drug used for this purpose. Maintenance drug therapy for these patients included diuretics, beta blockers, clonidine, methyldopa, calcium channel blockers, hydralazine and angiotension converting enzyme inhibitors, usually in combination of 2 or more. Minoxidil was used to stabilize the blood pressure in resistant patients. Surgical intervention

was performed as required. All patients were asked to attend a special clinic for a regular follow-up. Twenty-three patients were lost to follow up and 22 patients died.

The generated data were subjected to appropriate statistical analysis, and the chi-square test was applied to quantify the magnitude of intergroup differences for the respective parameters. The unpaired 't' test was applied to determine the differences in measurable quantities at the 5% level of significance.

Results

Of 135 patients with malignant hypertension, 90 were males and 45 were females (Table I). Essential hypertension was found in 88 (65.2%) patients while 47 (34.8%) had an underlying cause (Table II). Table III compares the clinical features of patients with essential hypertension and those with secondary hyper-

Table I. Age and Sex Distribution of Patients with Malignant Hypertension

Age (years)	Males	Females	Total (%)	Essential hypertension	Secondary hypertension
13–19	4	2	6 (4.4)	0	6
20–29	15	10	25 (18.5)	10	15
30–39	25	7	32 (23.8)	22	10
40–49	31	16	47 (34.8)	37	10
50–59	10	8	18 (13.3)	13	5
60–72	5	2	7 (5.2)	6	1
Total	90	45	135	88	47

Table II. Etiology of Malignant Hypertension in 135 Patients

Diagnosis	Male	Female	Total *n*	Total (%)
A. Essential hypertension	60	28	88	(65.2)
B. Secondary hypertension	30	17	47	(34.8)
(a) Renal parenchymal	15	4	19	(14.1)
Chronic glomerulonephritis	7	1	8	(6.0)
Chronic pyelonephritis	1	1	2	(1.5)
Diabetic nephropathy	1	2	3	(2.2)
Obstructive uropathy	2	–	2	(1.5)
Congenital renal anomaly	3	–	3	(2.2)
Renal cell carcinoma	1	–	1	(0.7)
(b) Renovascular hypertension	10	10	20	(14.8)
Takayasu's arteritis	6	9	15	(11.1)
Isolated renal a. stenosis	3	–	3	(2.2)
Renal artery aneurysm	1	1	2	(1.5)
(c) Endocrine disorders	5	3	8	(6.0)
Pheochromocytoma	4	2	6	(4.4)
Conn's syndrome	1	–	1	(0.7)
Adrenal carcinoma	–	1	1	(0.7)

Table III. Clinical Features of Essential versus Secondary Hypertension

Parameter	Essential HT ($n = 88$)	Secondary HT ($n = 47$)	Significance
Age	41.69 ± 1.14	33.2 ± 1.96	$p < 0.05$
Sex (M:F)	2.14:1	2:1	NS
Asymptomatic	4 (4.5)*	0 (0.00)	NS
Dyspnea	46 (52.3)	18 (38.3)	NS
Visual symptoms	41 (46.6)	20 (42.5)	NS
Epistaxis	2 (2.3)	0 (0.00)	NS
Altered sensorium	7 (8.0)	1 (2.1)	NS
Blood Pressure			
Systolic	205.7 ± 1.85**	207.4 ± 1.74	NS
Diastolic	133.5 ± 1.83	135.6 ± 1.81	NS
Asymmetry of pulses	0 (0.00)	8 (17.0)	$p < 0.05$
Bruit over vessels	0 (0.00)	6 (12.8)	$p < 0.05$
Congestive cardiac failure	16 (18.2)	20 (21.3)	NS
Fundus			
Grade III	47 (53.4)	22 (46.8)	NS
Grade IV	41 (46.6)	25 (53.2)	NS
Hypertension<1 year	46 (52.3)	41 (87.2)	$p < 0.05$
Hemoglobin<10 g%	31 (35.2)	19 (40.4)	NS
Serum creatinine>2 mg%	52 (59.1)	41 (87.2)	$p < 0.05$
Proteinuria>500 mg/24hr	54 (61.4)	44 (93.6)	$p < 0.05$
LVH***	51 (58.0)	26 (55.3)	NS
Cardiomegaly	28 (52.3)	25 (53.2)	$p < 0.05$

* Figures in parenthesis are percentages. ** Values are Mean ± SEM, LVH = Left ventricular hypertrophy.

tension.

Examination of optic fundii revealed grade III changes in 69 (51.1%) patients and grade IV changes in 66 (48.9%). There was no significant difference in age, level of systolic and diastolic blood pressure, etiology, serum creatinine, left ventricular hypertrophy and mortality between those with grade III and those with grade IV retinopathy (Table IV).

Clinical features: The predominant complaints included headache in 101 (75%) patients, dyspnea in 64 (47%), visual symptoms in 61 (45%) , palpitations in 50 (37%) and anorexia in 21 (16%). In 4 (3.7%) patients, malignant hypertension was detected on routine pre-operative evaluation. Of 6 patients with pheochromocytoma, intermittent episodic rises in blood pressure were recorded in four and paroxysmal flushing was observed in three patients. Among the 15 patients with Takayasu's arteritis, 8 had asymmetrical pulses, 9 had bruits over vessels and one patient had evidence of aortic regurgitation. Periodic paralysis was the presenting feature in one patient with Conn's syndrome.

Malignant hypertension was the first presentation of hypertension in 68 (50.5%) patients. In the remaining 67 (49.6%) patients, hypertension was detected 1 month to 17 years prior to the development of a malignant phase.

Table IV. Comparison of Patients with Grade III and IV Retinopathy

Parameter	Grade III retinopathy ($n = 69$)	Grade IV retinopathy ($n = 66$)	Significance
Age	39.8±1.41*	37.66±1.46	NS
Blood pressure			
Systolic	207.6±1.68	211.2±1.7	NS
Diastolic	133.2±1.48	134.5±1.96	NS
Etiology			
Essential	47 (68.1)**	41 (62.1)	NS
Renal parenchymal	11 (15.9)	8 (12.1)	NS
Renovascular	8 (11.6)	12 (18.2)	NS
Endocrine	3 (4.3)	5 (7.6)	NS
Serum creatinine>2 mg%	46 (66.7)	47 (71.2)	NS
LVH	40 (58.0)	37 (56.1)	NS
Deaths	10 (14.5)	12 (18.2)	NS

* Values expressed as Mean±SEM. ** Values in parentheses are percentages.

Underlying hypertension was present for 2.42 ± 0.45 years in patients with essential hypertension, 1.27 ± 0.41 years in those with renal parenchymal disease and 3.2 ± 0.2 months in those with renovascular disease ($p < 0.05$).

Laboratory investigations: Serum creatinine was abnormal in 93 (68.9%) patients and 38 (40.9%) of these had severe renal failure (serum creatinine more than 8 mg%). Sixty (66.6%) of the 90 patients investigated had significant 24 hour urinary protein excretion (more than 500 mg). On ECG examination, 77 patients had left ventricular hypertrophy, 14 patients had evidence of myocardial ischemia and 4 patients had myocardial infarction. Radiographic findings included cardiomegaly in 53 patients and congestive cardiac failure in 13 patients.

Sixty-five patients were admitted to the hospital on presentation while the rest were treated on an outpatient basis. 68.9% of patients had a pretreatment systolic blood pressure (SBP) of over 190 mmHg. After adequate treatment, SBP was reduced to less than 150 mmHg in 75.6% of these patients. Pretreatment diastolic pressure of more than 115mmHg in all patients was reduced to less than 100 mmHg in 93.6% of these patients on follow up.

Follow up: Outcome in 135 patients with malignant hypertension is shown in the Figure. Of 52 patients with grade III retinopathy, the retinal changes improved in 35, remained unchanged in 15 and deteriorated in 2 patients. In 38 patients with grade IV retinopathy, papilledema disappeared in 1 to 4 months. However, its reappearance in two patients was attributed to uncontrolled hypertension due to poor compliance with drugs.

Twenty-five of 35 patients who had normal serum creatinine on presentation maintained adequate renal function on follow-up while in 9 patients, it deteriorated. Fifty-five patients had an elevated serum creatinine on initial presentation. In 14 (25.4%) patients, renal function improved as evidenced by a

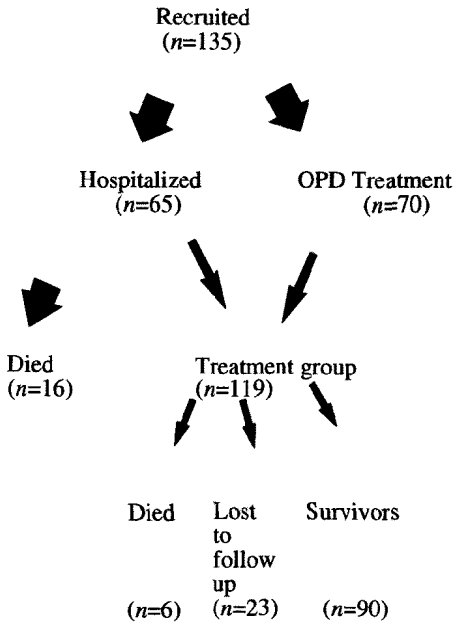

Figure. Outcome of 135 patients with malignant hypertension

Table V. Factors Affecting Survival

Parameter	Patients who survived ($n = 90$)	Patients who died ($n = 22$)	Significance
Age	37.5±1.39#	44.3±1.56#	$p < 0.05$
Sex (M:F)	1.65:1	10:1	$p < 0.05$
Fundus			
Grade III	49 (54.4)*	10 (45.5)	NS
Grade IV	41 (45.6)	12 (54.5)	NS
LVH	54 (60.0)	18 (81.8)	NS
Serum creatinine>8 mg%	8 (8.9)	11 (50.0)	$p < 0.05$
Stroke	13 (14.4)	6 (27.3)	NS
Congestive cardiac failure	22 (24.4)	3 (13.6)	NS
Myocardial infarction	2 (2.2)	1 (4.5)	NS

* Values in parentheses are percentages. # Values expressed as Mean ± SEM.

gradual decline in serum creatinine while in 26 (47.3%) patients there was a gradual rise.

Mortality: Of 65 hospitalized patients, 16 died during their first hospital stay. The causes of death were severe renal failure (8), stroke (5), congestive cardiac failure (2) and myocardial infarction (1). During the follow-up, 6 patients passed away. Of these, one had essential hypertension and five had secondary hypertension (Takayasu's aortoarteritis-3, diabetic nephropathy-1, malignant pheochromocytoma-1). The causes of death in this group included uremia in

three patients and congestive cardiac failure and stroke in one patient each. In one patient the cause was unrelated to hypertension.

Autopsy was performed in 16 subjects who died during hospitalization. On autopsy, 5 of 8 patients with severe renal failure had grade III or IV changes in the kidneys (Saltz et al).[15] Glomerular scarring was present in one patient. In the remaining 3 patients, renal histology revealed grade II arteriolar changes and minor interstitial changes. All 5 patients who had developed stroke showed evidence of brain infarction.

The patients who died were predominantly males ($n = 20$) with a higher age as compared to those who survived ($p < 0.05$). A significantly greater number of patients who died had severe renal failure (Table V, $p < 0.05$).

Discussion

This study presents our experience with malignant hypertension in 135 patients in a tertiary care hospital in the north west part of India. In developed countries with the advent of effective antihypertensive drugs, malignant hypertension has become uncommon.[14] The present data reveal that of the 6,665 hypertensives registered in a clinic treating hypertensive patients during this 11 year period, 2.02% had malignant hypertension. The patient group is selective and does not reflect the incidence of malignant hypertension in the general population of hypertensives. The commonest cause of malignant hypertension was essential hypertension, accounting for 65.2% of patients. The predominance of essential hypertension in this study indicates that early detection and control of essential hypertension has yet not become effective in India.

An autopsy study of malignant hypertension in the Bantu population in Johannesberg[11] showed a similarly high prevalence of essential hypertension, while studies from developed countries reveal secondary causes to be dominant.[12,14] It was revealing that 68 (50.3%) patients reported for the first time with malignant hypertension and were not aware of having hypertension. Malignant hypertension most often supervenes in patients with pre-existing hypertension, rather than presenting as a *de novo* event. This suggests that hypertension often remains undetected for a long time in India.

Secondary hypertension was responsible for 34.8% of cases in this study. Takayasu's arteritis (TA) involving the renal arteries was the commonest secondary cause. This is consistent with experience in India and similar observations have been reported from several other south Asian countries.[16–18] The pathogenetic mechanism of hypertension in TA include renal ischemia, loss of vascular compliance and disturbances in the baroreceptor mechanism producing hyperreninemia.

Essential and secondary malignant hypertension differed in their age distribution. The average age (41.69 ± 1.14 years) of patients with essential hypertension was higher as compared to that of patients with secondary hypertension (33.2 ± 1.96 years). It is quite possible that the malignant phase in essential hypertension develops after a prolonged period while in patients with secondary hypertension the malignant phase supervenes rather quickly during the course of the disease. In this study the mean duration of hypertension before the onset of the malignant phase in those with essential hypertension was higher than that of patients with secondary hypertension. Kawazoe et al had a similar experience although in their study the duration of hypertension was much longer in both groups as compared to the present study.[19] The relatively shorter duration of clinical hypertension in our study is possibly related to the late detection of hypertension in our population. Treatment significantly improved the overall prognosis as a result of a reduction in diastolic blood pressure in the majority of our patients. But 17.8% of patients did continue to have moderate hypertension on follow-up, a finding similar to the observation by Yu et al[20] and it reflects poor patient compliance.

The patients with grade III and grade IV retinopathy did not differ in their clinical picture, etiology of hypertension or the outcome. Our findings support the view that there is no inherent difference in grade III and grade IV retinopathy with respect to clinical behavior and the presence or absence of papilledema does not influence the prognosis in this group. Impaired renal function, higher age at presentation and male sex were associated with a poor prognosis. These findings are consistent with those reported in other studies.[5,20–23]

Thus, analysis and follow-up of these patients with malignant hypertension confirms that essential hypertension continues to remain the most common cause of malignant hypertension in India. A public education program stressing early detection, treatment and follow-up of hypertension will reduce the incidence of malignant hypertension and its associated morbidity and mortality.

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