Original Article

Trends in the Pathophysiological Characteristics of Malignant Hypertension

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The aim of the present study is to investigate the pathophysiological characteristics of a number of recent cases of malignant hypertension (MHT) and to compare them to the characteristics of earlier cases. Patients with MHT (age 25–76, mean 44 ± 2 years) who were admitted to our hospital from 1984–1999 were retrospectively studied. All of the patients had either grade III or IV retinopathy and diastolic blood pressure levels higher than 120 mmHg. The observations in this study were compared to previously reported findings regarding 59 MHT patients who were admitted from 1971–1983. Of the 37 recent MHT patients, 20 had essential hypertension (EHT) as the underlying disease, 13 had chronic glomerulonephritis (CGN), and the remaining 4 presented with other diseases including pyelonephritis and renovascular hypertension. A positive family history of hypertension was more prevalent in the EHT patients than in other patients, and persistent proteinuria, microhematuria, and anemia were more prevalent in the CGN patients. These characteristics were similar between the recent and previous cases. Within 4 weeks after admission, hemodialysis was initiated in 3 of the 13 patients (23%) with CGN and 2 of the 20 (10%) patients with EHT. The prevalence of renal death at 1 year after admission was 30%, which was lower than the prevalence in the previous cases (42%). Grade IV retinopathy was seen in 45% of the patients admitted from 1984–1999, significantly less than in the patients admitted from 1971–1983 (66%, $p < 0.05$). In addition, left ventricular hypertrophy was less frequently observed on electrocardiogram in the recent cases (67%) than in the previous cases (88%, $p < 0.05$). Our results suggest that the recent cases of MHT demonstrate less severe organ damage.

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Key Words: malignant hypertension, essential hypertension, chronic glomerulonephritis, hemodialysis, left ventricular hypertrophy

Introduction

Malignant hypertension (MHT) is a life-threatening disease which is histologically characterized by the fibrinoid necrosis of arterioles. The clinical definition of MHT is severe hypertension accompanied by bilateral retinal hemorrhage and/or exudates, with or without papilloedema (1–7). If untreated, the prognosis of MHT is poor, with an 80% mortality rate during the first 2 years after diagnosis (5, 6, 8, 9). The importance of early diagnosis is emphasized as many pa-

tients tend to develop clinical symptoms only during the latter stages of the disease, often presenting with cardiac or renal failure. Early detection, treatment and careful follow-up of patients with MHT are therefore essential, and lack of compliance may have serious consequences. We have previously reported the pathophysiological characteristics of patients with MHT who were admitted to our hospital from 1971–1983, and we found that essential hypertension (EHT) and chronic glomerulonephritis (CGN) were two of the major underlying diseases leading to MHT (7, 10). The purpose of the present study is to investigate the pathophysiological

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Table 1. Profiles of Patients with Malignant Hypertension Resulting from EHT and CGN

	EHT	CGN
Number of patients (M:F)	20 (14:6)	13 (6:7)
Age (years)	44±3	42±3
Ocular fundi (KW III:IV)	10:10	8:5
Family history	19 (95%)	8 (61.5%)*
Duration of hypertension (years)	14.5±2.5	4.7±0.9*
Systolic blood pressure (mmHg)	228±8	211±4
Diastolic blood pressure (mmHg)	137±4	131±4
Heart rate (beats/min)	90±4	88±6

Values are means±SE. * $p < 0.05$ vs. EHT. EHT, essential hypertension; CGN, chronic glomerulonephritis; KW, Keith-Wagener-Barker's classification.

Table 2. Laboratory Findings on Admission of Malignant Hypertension Cases Resulting from EHT and CGN

	EHT	CGN
ECG findings		
LVH	11/15 (73.3%)	5/9 (55.6%)
ST-T change	7/15 (46.7%)	4/9 (44.4%)
Hematuria	4/12 (33.3%)	8/10 (80%)*
Proteinuria	11/12 (91.7%)	10/10 (100%)
Hemoglobin (g/dl)	13.3±0.7	9.6±0.5*
Hematocrit (%)	39.8±2.2	29.1±1.2*
Serum		
Sodium (mEq/l)	140±1	140±1
Potassium (mEq/l)	3.8±0.2	4.4±0.3*
Creatinine (mg/dl)	2.9±0.8	7.4±1.8*
Urea nitrogen (mg/dl)	34±6	57±10*

Values are means±SE. * $p < 0.05$ vs. EHT. EHT, essential hypertension; CGN, chronic glomerulonephritis; LVH, left ventricular hypertrophy.

characteristics of more recent cases of MHT and to compare them to those of previous cases.

Methods

A total of 37 MHT patients were admitted to our hospital between 1984 and 1999. Twenty of these patients had EHT, 13 had CGN, 1 had renovascular hypertension and 1 had pyelonephritis as the underlying disease. The underlying disease in the remaining 2 cases could not be clinically determined. All of the patients had either grade III or IV retinopathy associated with diastolic blood pressure (DBP) levels higher than 120 mmHg on admission. The diagnosis of the underlying disease was based on a carefully taken history, physical examination, and laboratory and radiological studies. Histological evaluations of renal biopsy samples were performed in 8 patients. Four of these eight had proliferative glomerulonephritis, 2 had IgA nephropathy, and the remain-

ing 2 had hypertensive nephrosclerosis. CGN was diagnosed using the following criteria: the histological findings for the biopsy, a history of acute or chronic glomerulonephritis, proteinuria with or without hematuria antecedent to the hypertension, persistent proteinuria even after successful treatment of the hypertension, or microscopic findings such as granular casts, red cell casts, *etc.* Thus, 33 MHT patients who presented with either EHT or CGN as an underlying disease were included in the analysis of the pathophysiological characteristics of MHT and were compared with the 59 MHT patients who were admitted from 1971–1983 (7, 10).

Statistical Analysis

Values are presented as mean±SE. The differences in the variables between the EHT and CGN groups were compared by one-way ANOVA. A chi-square test was also utilized when appropriate. *P*-values less than 0.05 were considered to be significant.

Results

Patient profiles are presented in Table 1. There were no differences in gender, age or funduscopy findings between the EHT and CGN groups. The known duration of hypertension was significantly longer and the prevalence of positive family history of hypertension was significantly higher in the EHT group than in the CGN group. Systolic blood pressure (SBP), DBP and heart rate were comparable between the two groups. Four out of 20 EHT patients (20%) and 2 out of 13 CGN patients (15%) were taking antihypertensive drugs on admission, although detailed information on the drugs and the duration of medication was not available. The laboratory findings are outlined in Table 2. Hematuria revealed by dipstick testing and anemia (< 10 g/dl) were significantly more prevalent in the CGN group. Eleven EHT patients and 5 CGN patients had left ventricular hypertrophy (LVH) as defined by the criteria of Sokolow and Lyon. Among them, 7 EHT and 3 CGN patients had both LVH and ST-T changes. The prevalence of LVH and/or ST-T changes observed on ECG, and proteinuria defined as dipstick proteinuria of greater than +1, were comparable between the two groups. However, serum potassium, creatinine and urea nitrogen levels were significantly higher in the CGN group. Antihypertensive treatment was initiated in all patients immediately after admission. Depending on the clinical situation, intravenous and/or oral administration of antihypertensive drugs, such as Ca antagonists, diuretics, angiotensin-converting enzyme (ACE) inhibitors, β -blockers and other classes of antihypertensive drugs were used until a diastolic pressure of 100–110 mmHg was achieved. Within 4 weeks of admission, hemodialysis (HD) was initiated in 3 of 13 patients (23%) with CGN and 2 of 20 patients (10%) with EHT. Laboratory findings at 4 weeks after admission were analyzed in all patients except those who underwent HD (Table 3). Both

Table 3. Laboratory Findings at 4 weeks after Admission in Cases of Malignant Hypertension Resulting from EHT and CGN

	EHT (n=18)	CGN (n=10)
Systolic blood pressure (mmHg)	159±8	142±4
Diastolic blood pressure (mmHg)	94±3	87±3
Heart rate (beats/min)	72±3	72±4
Hematuria	1/15 (6.7%)	4/8 (50%)*
Proteinuria	5/15 (33.3%)	8/8 (100%)*
Hemoglobin (g/dl)	13.0±0.6	10.1±0.5*
Hematocrit (%)	39.3±1.7	30.6±1.1*
Serum		
Creatinine (mg/dl)	1.9±0.3	4.3±1.0*
Urea nitrogen (mg/dl)	26±3	49±10*

Values are means±SE. * $p < 0.05$ vs. EHT. EHT, essential hypertension; CGN, chronic glomerulonephritis.

SBP and DBP levels were higher in the EHT group than in the CGN group, although the difference was not statistically significant. Persistent proteinuria was seen in 5 patients with EHT, which was significantly less frequent than in the CGN group (8 patients). Similarly, in the CGN group, hematuria and anemia were more prevalent, and serum creatinine and urea nitrogen levels were significantly higher.

These observations were comparable to the characteristics identified in the cases of MHT that we had previously examined and reported on. A chronological comparison of the pathophysiological characteristics of MHT is presented in Table 4. The gender distribution and the proportion of cases with EHT or CGN as the underlying disease in MHT were comparable between the recent and previous cases. The age at which MHT was diagnosed tended to be higher (45 ± 7 years) in the recent cases. Grade IV retinopathy was seen in 45% of the patients admitted from 1984–1999, which was significantly less frequent than in those admitted from 1971–1983 (66%, $p < 0.05$). In addition, LVH was less frequently observed on ECG in recent cases (67%) than in the previous cases (88%, $p < 0.05$). Within 1 year after admission, 1 patient who belonged to the EHT group among the recent cases died of heart failure. HD was initiated in 6 of 13 patients (46%) with CGN and 3 of 17 patients (18%) with EHT in the recent cases. The prevalence of renal death at 1 year after admission was significantly higher in the previous cases with CGN; HD was initiated in 88% of those patients ($p < 0.01$).

Discussion

MHT has been reported to be less common in developed countries, predominantly due to the availability of effective antihypertensive medication (1, 3, 4, 6, 8, 9, 11, 12). Indeed, β -blockers and vasodilators were predominantly used in our previous cases (7, 10), while Ca antagonists and ACE in-

Table 4. Comparison of the Pathophysiological Characteristics between Recent and Previous Cases of Malignant Hypertension

	1971–1983 (10)	1984–1999
Number of patients (M:F)	59 (42:17)	33 (20:13)
Age	38±6	45±7
Antihypertensive therapy before admission	21 (35.6%)	6 (18.2%)
Ocular fundi (KW III:IV)	20:39	18:15*
EHT:CGN	33:26	20:13
ECG findings		
LVH	49/56 (87.5%)	16/24 (66.7%)*
ST-T change	34/56 (60.7%)	11/24 (45.8%)
Hematuria	26/59 (44.1%)	12/22 (54.5%)
Proteinuria	52/59 (88.1%)	21/22 (95.5%)

* $p < 0.05$ vs. 1971–1983. KW, Keith-Wagener-Barker's classification; EHT, essential hypertension; CGN, chronic glomerulonephritis; LVH, left ventricular hypertrophy.

hibitors were increasingly used in the recent cases. Furthermore, clinicians have become more aware of the necessity of treating hypertension, and patient compliance has improved due to the greater efficacy and tolerability of new pharmaceuticals (11, 13). In fact, the incidence rate of MHT in the present study (approximately 2.2 cases per year) seems to be lower than in the previous study (4.9 cases per year) (7, 10). Nevertheless, 37 cases with MHT were admitted to our hospital during the past 13 years.

Although 20% of EHT patients and 15% of CGN patients were on antihypertensive medication in the present study, the average SBP and DBP levels on admission were surprisingly similar to the cases in our previous report (10). An overall downward trend in mean serum creatinine levels at the time of initial presentation has been reported in MHT patients over a 24-year survey period (9). This trend is consistent with our observation that the serum creatinine levels of our recent patients with EHT (2.9 ± 0.8 mg/dl) and CGN (7.4 ± 1.8 mg/dl) tended to be lower when compared to earlier cases (3.7 ± 0.6 and 10.8 ± 1.3 mg/dl, respectively) (10). Furthermore, we found that grade IV retinopathy and LVH on ECG were less frequent in the recent cases than in the previous cases. The most frequent symptom on admission was visual disturbance, with headache being the next most frequent. None of the recent cases showed symptoms suggesting hypertensive encephalopathy or congestive heart failure, which were occasionally seen in the previous cases. These findings may suggest that the more recent cases of MHT are being diagnosed before severe organ damage occurs. This trend may be partly attributable to the early detection of hypertension by prevailing health examination systems or the increased recognition of patients with hypertension.

The pathophysiology of MHT is complex and varies with its underlying disease (1, 3–7, 9–11). According to a report

from an Indian hospital, the most common cause of MHT is EHT, which accounts for 65.2% of all MHT patients (4). The present study also shows that EHT is the most common underlying disease in MHT, present in 54% of our patient population. Secondary hypertension includes renal parenchymal hypertension, renovascular hypertension and chronic pyelonephritis, in which CGN is the most common cause of MHT (4, 9). There are a number of differences between EHT and CGN in terms of clinical manifestations (4, 6, 7, 10, 11). First, EHT and CGN patients differ in their age distributions. Our previous study showed that EHT patients were older than CGN patients (10). Since the known duration of hypertension was longer in EHT patients (7.6 years) than in CGN patients (3.8 years), a longer time period might be required for hypertension to develop into a malignant phase in EHT patients. In the present study, however, the average ages of EHT and CGN patients were comparable. The CGN patients in the present study were approximately 8 years older than in the previous cases. Although the reason for this is not clear, the recent trend toward a delay in the development of MHT in CGN patients may be, at least in part, due to an increased understanding of the illness and the adoption of lifestyle modifications that can mitigate it. Second, patients with EHT had lower initial serum urea and creatinine levels than did patients with CGN. Within 4 weeks after admission, HD was initiated in 23% of CGN patients and 10% of EHT patients. Within 1 year, HD was initiated in 46% of CGN patients and 18% of EHT patients. Our previous study showed that HD was introduced in 9% of EHT patients and 88% of CGN patients at 1 year (10), suggesting a poor renal survival rate in the latter. This trend toward a decreased incidence of renal death in the recent cases may be attributable to the development of antihypertensive therapy. In contrast with the poor renal survival rate, the 5-year mortality rate was significantly lower in CGN patients than in EHT patients in the cases previously reported (10). The recent cases of MHT should be followed-up in order to clarify the long-term prognosis of MHT in patients kept under strict blood pressure control with various kinds of antihypertensive medication.

In conclusion, recent cases of MHT demonstrate less severe organ damage in comparison with MHT cases from our previous study. The long-term prognosis of MHT should be

determined in a future study.

References

1. Sesoko S, Ishikawa Y, Ishii M: Etiology and management of malignant hypertension. *Compr Ther* 1988; **14**: 19–24.
2. Bales A: Hypertensive crisis. How to tell if it's an emergency or an urgency. *Postgrad Med* 1999; **105**: 119–130.
3. Kitiyakara C, Guzman NJ: Malignant hypertension and hypertensive emergencies. *J Am Soc Nephrol* 1998; **9**: 133–142.
4. Sharma BK, Singh G, Sagar S: Malignant hypertension in north west India. A hospital-based study. *Jpn Heart J* 1994; **35**: 601–609.
5. Lip GYH, Beevers M, Beevers DG: Does renal function improve after diagnosis of malignant phase hypertension? *J Hypertens* 1997; **15**: 1309–1315.
6. Lip GYH, Beevers M, Beevers DG: Complications and survival of 315 patients with malignant-phase hypertension. *J Hypertens* 1995; **13**: 915–924.
7. Kawazoe N, Eto T, Abe I, *et al*: Pathophysiology in malignant hypertension: with special reference to the renin-angiotensin system. *Clin Cardiol* 1987; **10**: 513–518.
8. Clough CG, Beevers DG, Beevers M: The survival of malignant hypertension in blacks, whites and Asians in Britain. *J Hum Hypertens* 1990; **4**: 94–96.
9. Lip GYH, Beevers M, Beevers G: The failure of malignant hypertension to decline: a survey of 24 years' of experience in a multiracial population in England. *J Hypertens* 1994; **12**: 1297–1305.
10. Kawazoe N, Eto T, Abe I, *et al*: Long-term prognosis of malignant hypertension; difference between underlying diseases such as essential hypertension and chronic glomerulonephritis. *Clin Nephrol* 1988; **29**: 53–57.
11. Scarpelli PT, Livi R, Caselli GM, *et al*: Accelerated (malignant) hypertension: a study of 121 cases between 1974 and 1996. *J Nephrol* 1997; **9**: 207–215.
12. Suzuki H, Nakamoto H, Nemoto H, *et al*: Control of blood pressure and prevention of end-organ damage in patients with accelerated hypertension by combination with arotinolol and extended release nifedipine. *Hypertens Res* 2000; **23**: 159–166.
13. Edmunds E, Beevers DG, Lip GYH: What has happened to malignant hypertension?: a disease no longer vanishing. *J Hum Hypertens* 2000; **14**: 159–161.