Malignant hypertension (MHT), also known as accelerated-malignant hypertension or malignant-phase hypertension, is the most severe form of arterial hypertension. It is defined clinically as high blood pressure (BP) levels associated with lesions of the retinal fundus (flame-shaped hemorrhages, exudates, or cotton wool spots, with or without papilledema). Despite the availability of a vast range of antihypertensive agents, MHT continues to be a significant clinical challenge. Although its prevalence is very low, the absolute number of new cases has not changed over the past decades. While the role of the activation of the renin–angiotensin–aldosterone system and endothelial dysfunction in the pathogenesis of MHT has been well described, recent studies have indicated that the immune system may also play an important role in the development of this condition. Patients with MHT are characterized by pronounced target organ damage, including structural and functional cardiac abnormalities. MHT is frequently complicated by renal insufficiency and end-stage renal disease. The survival rates for patients with MHT have improved considerably with increased availability of antihypertensive treatment. However, renal insufficiency and end-stage renal disease still remain a significant cause of morbidity and mortality in this patient group. In conclusion, MHT is not a “vanishing disease” because there is a relatively stable number of new cases per year. Nonetheless, prognosis and survival rates in these patients have improved significantly owing to earlier detection, stricter BP control, lower BP targets, better choice of antihypertensive drugs, and availability of hemodialysis and renal transplantation.

ABSTRACT

Malignant hypertension (MHT), also known as accelerated-malignant hypertension or malignant-phase hypertension, is the most severe form of arterial hypertension. It is defined clinically as high blood pressure (BP) levels associated with lesions of the retinal fundus (flame-shaped hemorrhages, exudates, or cotton wool spots, with or without papilledema). In the 2010 revision of the Dutch guidelines for the management of hypertensive crisis, van den Born et al replaced the term “malignant hypertension” with “hypertensive crisis with retinopathy”, which was followed by Kaplan and Victor in the 2015 edition of Kaplan’s Clinical Hypertension. The authors concluded that the presence of retinopathy may allow other target organs to be included, making the description of this type of emergency more accurate.1-3 MHT is associated with failure in BP autoregulation and develops when the mean arterial pressure (MAP) reaches a critical level of 150 mmHg, as reported in experimental animals. Fibrinoid necrosis appears in the arterial walls, which may be caused by vasoactive factor(s) or may be a non-specific consequence of very high BP.1

In patients with MHT, very high systolic BP, and in particular significantly elevated diastolic BP, are surrogate markers of increased peripheral vascular resistance associated with an increase in MAP, an abnormal nonpulsatile component of BP.4 Even though the introduction of modern multidrug antihypertensive therapy has resulted in better BP control and markedly improved prognosis, MHT is still a life-threatening manifestation of hypertension and represents a clinical entity characterized by high cardiovascular risk and
elevated risk of developing end-stage renal disease (ESRD) in a long-term follow-up.\(^1\)

**Incidence of malignant hypertension** Despite the vast range of antihypertensive agents and effective BP control, MHT remains an important clinical entity. Although its frequency is very low, the absolute number of new cases has not changed much over the past decades, as documented by recent studies.\(^1\)

The study by Lane et al\(^5\) examined the changing demography and survival of 446 patients with MHT attending the City Hospital in Birmingham, United Kingdom, from 1964 to 2006, with a median follow-up of 103.8 months. In this largest prospective analysis in the world literature, the number of new cases of MHT has not changed substantially over 40 years. The study supports the concept that MHT is not a vanishing disease, with a relatively stable number of 2 to 3 new cases of MHT per 100,000 head of population per year.\(^5\) The demography of the disease has not altered during the follow-up, with no significant differences in the mean age at diagnosis, but with a slight predominance in men. It is of note that during the follow-up, there was a significant increase in the proportion of ethnic minorities, including South-Asians and Afro-Caribbeans, and a significant decrease in white Europeans.\(^5\) Another smaller study evaluating European cohorts demonstrated a fairly stable incidence of MHT, with 2 to 3 new cases per 100,000 head of population over the past 30 years.\(^6\)

A recent retrospective cohort study investigated national trends in the United States in hospital admissions for MHT, identifying all hospitalizations between 2000 and 2011 during which a primary diagnosis of MHT was recorded.\(^7\) The results clearly demonstrated a much higher rate of increase in the number of hospitalizations with a primary discharge diagnosis of MHT during this time period. The rate of annual hospitalizations for MHT remained stable before 2007, but then started to significantly increase at an estimated rate of 2700 per year.\(^7\) One explanation of the results is that the reported data represented a true change in the epidemiology of hypertensive emergencies. Another cause of the change, which is much more likely, is that this abrupt increase resulted from a change in coding practices in the United States.\(^7\)

**Pathophysiological mechanisms** Possible pathophysiological mechanisms for the development of MHT have been proposed, including rapidly increasing BP, pressure diuresis and natriuresis, severe renal vasoconstriction, and ischemia (FIGURE 1). In addition, activation of the renin–angiotensin–aldosterone system (FIGURE 2), microangiopathy, hemolytic anemia, and development of retinopathy are observed in MHT. The vascular lesions of MHT include myointimal proliferation and fibrinoid necrosis.\(^8-21\)

**The immune system in malignant hypertension** While the role of endothelial dysfunction and kidney damage in MHT has been addressed by numerous other reviews, recent studies have indicated that the immune system, and in particular T cells, play a crucial role in the development of
immunohistochemical analysis of biopsied renal tissue revealed a higher infiltration of T cells, both CD4+ and CD8+, in patients with hypertensive nephrosclerosis, compared with normotensive controls. In patients with psoriasis treated with mycophenolate mofetil targeting B and T cells has shown to reduce BP. It is possible that immunomodulating agents will emerge in the future as a potential treatment option for patients with MHT, especially in the context of concomitant immune disorders. However, at present, there is no sufficient clinical evidence to support such an approach.

26,27

Clinical features MHT may be accompanied by various symptoms and complications, the most characteristic being microangiopathic lesions or renal dysfunction (Figure 3). Acute lesions in the retinal fundus may include arteriolar spasm, retinal edema, hemorrhages, exudates and papilledema, and engorged retinal veins. In 28% of patients with MHT, van den Born et al.28 found thrombotic microangiopathy, characterized by thromboses of small vessels, intravascular hemolysis with fragmented red blood cells, elevated lactic dehydrogenase, and consumption of platelets. Less common clinical presentations may include fibrinoid necrosis within abdominal arteries producing major gastrointestinal tract infarction with an acute abdomen, necrotizing vasculitis as a feature of lupus, polyarteritis nodosa, or Takayasu arteritis.29-33

Evidence of T cell-derived inflammation in hypertension is also slowly accumulating for humans.26 There is an increased fraction of immunosenescent, cytotoxic T cells in the circulation of patients with hypertension compared with normotensive subjects. Plasma TNF-α and IL-6 levels are correlated with BP, and a immunohistochemical analysis of biopsied renal tissue revealed a higher infiltration of T cells, both CD4+ and CD8+, in patients with hypertensive nephrosclerosis, compared with normotensive controls. In patients with psoriasis treated with mycophenolate mofetil targeting B and T cells has shown to reduce BP. It is possible that immunomodulating agents will emerge in the future as a potential treatment option for patients with MHT, especially in the context of concomitant immune disorders. However, at present, there is no sufficient clinical evidence to support such an approach.26,27
secondary aldosteronism from increased renin secretion induced by intrarenal ischemia. Hypo-
натremia is common and may be severe.1

Multiple markers of inflammation, coagulation, platelet activation, and fibrinolysis were found in the blood of patients with various types of hypertensive emergencies, compared with the levels observed in normotensive controls.2,11

An electrocardiogram usually shows evidence of left ventricular hypertrophy (LVH). Echocardiography may show impaired systolic and dila-
stolic function and delayed mitral valve opening. Regression of these abnormalities usually occurs after lowering of BP by antihypertensive therapy.1

**Identifiable causes of malignant hypertension** In pa-
tients with MHT, after an acute phase, an appro-
priate evaluation of identifiable causes of hyper-
tension should be performed as quickly as possible. It is preferable to obtain the necessary blood and urine samples for required laboratory studies before instituting therapies that may markedly complicate subsequent evaluation. Howev-
er, none of these procedures should delay effec-
tive therapy. MHT usually occurs in patients with long-standing preexisting hypertension and may be associated with a recent cessation of antihyper-
tensive therapy. However, any form of secondary hypertension may progress to MHT.1-3

Renovascular hypertension is the most likely secondary cause, and, in a large series of patients with MHT, renal artery stenosis was the under-
lying cause of hypertension in 3.6% of the cases. It should in particular be sought in younger

patients suspected of fibromuscular dysplasia, or in older patients with extensive atherosclerosis. Idiopathic IgA nephropathy has also been report-
ed as a possible cause of MHT.1,34,35

Rarely, primary hyperaldosteronism may be associated with MHT, as documented by a small number of cases. A recent report described a 22-year-old patient with MHT, associated with primary hyperaldosteronism and LVH mimicking hypertrophic cardiomyopathy.35,36 Primary al-
dosteronism is typically defined by an increased plasma aldosterone level and suppressed plasma renin activity through a negative feedback mech-
anism. Hence, primary aldosteronism and MHT are at opposite ends of the renin spectrum, and their coexistence is thought to be very rare.36,37

There have also been sporadic reports of MHT in patients with pheochromocytoma and renin-
secreting tumors.38-40

It is of note that, in most cases, MHT is accom-
ppanied by various life-threatening symptoms, signs, and associated complications. However, it is not uncommon to see patients denying any pri-
or symptoms in the end stages of the hyperten-
sive disease. In such cases, MHT is often unre-
cognized until a later stage in the progress of the disease, when clinical symptoms are becoming ap-
parent and patients are symptomatic.1

**Impact of malignant hypertension on the heart** A few studies have confirmed that structural and func-
tional cardiac abnormalities are present in pa-
tients with MHT, indicating features of cardiac damage and compensatory remodeling. However,
Long-term renal outcome Although the survival rate of patients with MHT has considerably improved with the introduction of antihypertensive therapy, MHT is frequently complicated by renal insufficiency, and ESRD still remains a significant cause of morbidity and mortality in this patient group. The STAT study demonstrated that, in patients hospitalized with acute severe hypertension, the presence of acute kidney injury was associated with a greater risk of serious outcomes, including mortality and additional end-organ damage.

A retrospective analysis of 120 patients with MHT conducted in the Netherlands showed that patients with MHT had a markedly increased risk of ESRD after the acute phase. During a median follow-up period of 67 months, 31% of the patients reached the primary endpoint (ESRD), 15% reached the secondary endpoint (all-cause mortality), and 24% required kidney replacement. After the acute phase, initial serum creatinine levels and BP during follow-up were the main predictors of future ESRD.

In another retrospective study, Gonzalez et al reported on long-term renal outcomes in a cohort of 197 patients with MHT. Renal involvement was a major component of MHT, with 63% of the patients presenting with acute renal function impairment. The probability of renal survival in the entire cohort was 84% and 72% after 5 and 10 years of follow-up, respectively. The study confirmed that the severity of renal failure at presentation, worse BP control during follow-up, and severity of proteinuria were important prognostic factors for long-term renal outcomes.

In another study, van den Born et al reported a relatively high prevalence of microangiopathic hemolysis in patients with MHT and showed that, in those subjects, microangiopathic hemolysis was an important indicator of both renal insufficiency and recovery. It has been reported that, when intensive antihypertensive therapy was started in patients with MHT, renal function remained unchanged or improved in nearly half of those with initial renal insufficiency. In one series of 54 patients with MHT requiring dialysis, 22% of the subjects recovered sufficient renal function to allow withdrawal of dialysis.

Considering that the activation of the renin–angiotensin–aldosterone system is an important pathogenic mechanism in MHT and that drugs affecting the system have specific antiproteinuric properties, a long-term treatment of patients with MHT should be based mainly on this type of agents.

Management MHT is a hypertensive emergency, and patients should receive immediate antihypertensive treatment owing to a high risk of renal failure, stroke, myocardial infarction, and heart failure.

Following the 2013 guidelines on hypertension from the European Society of Hypertension and European Society of Cardiology, the current treatment is based on agents that can be administered by intravenous infusion and titrated according to response, avoiding abrupt falls in BP and excessive hypotension.

The goal of the immediate therapy should be to lower diastolic BP to approximately 110 mmHg. There is a consensus opinion to reduce MAP by no more than 25% during the acute phase in order to avoid cerebral hypoperfusion. Labetalol, sodium nitroprusside, nicardipine, nitrates, and furosemide are listed among the most frequently used intravenous drugs. However, due to the low incidence of MHT, there are no data to document which of these drugs is best, or whether their use is followed by a decrease in morbidity and mortality in this group of patients.

The study by Immink et al showed a significant difference in the decrease of systemic vascular resistance during the administration of sodium nitroprusside and labetalol (43% and 13%, respectively) in patients with MHT. These may be attributed to differential effects of these drug classes on systemic vascular resistance and heart rate in patients with MHT. It has also been recognized that antihypertensive drugs differ in their capacity to reduce central BP, whereas their effects on peripheral BP may be similar.

Taken together, in the absence of definite evidence, clinicians must continue to administer
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Parenteral drugs to markedly lower elevated BP in patients with a hypertensive emergency. However, this should be done carefully, under close supervision, and with the choice of drugs that allow for a gradual reduction in BP that have no inherent toxicity, and that provide the ability to back down if the target organ function deteriorates.\textsuperscript{1-3}

Prognosis If left untreated, the 1-year survival rate has been reported to be only 10% to 20%, with most patients dying within 6 months. Effective treatment has led to a substantial improvement in the survival rate, with the rate at 5 years reaching between 60% and 75% in developed countries. However, in developing countries such as Nigeria, the prognosis appears to be considerably worse, with 1-year survival rates of only 37.5%.\textsuperscript{1,14,50-55}

The results from the largest prospective registry of 446 patients with MHT attending the City Hospital in Birmingham, United Kingdom, clearly showed a significant improvement in the 5-year survival rates, from 32% before 1977 to as much as 91% for patients diagnosed between 1997 and 2006 (\textbf{Figure 4}).\textsuperscript{5}

The mortality rate was similar among white Europeans and African-Caribbeans, but significantly lower among South-Asians. The best independent predictors of overall survival were age, decade of MHT diagnosis, serum creatinine levels at presentation, and follow-up systolic BP.\textsuperscript{5}

In addition, a retrospective cohort study that investigated national trends in the United States in hospital admissions for MHT showed a decrease in the mortality rate by 36% among patients diagnosed with MHT after 2007.\textsuperscript{7}

The study by Amraoui et al\textsuperscript{50} documented that, despite a considerable improvement in the survival rate over the past decades, patients with a history of MHT remain at increased risk, and the annual incidence of all-cause mortality was higher in MHT patients compared with that in normotensive and hypertensive controls.

Taken together, despite satisfactory BP control with modern antihypertensive therapy, MHT continues to be an important clinical entity and may significantly contribute to an increase in total cardiovascular risk.\textsuperscript{1,14,50-55}

Summary In summary, MHT is not a “vanishing disease”, having a relatively stable number of cases per year, but its prognosis and survival rates have significantly improved owing to earlier detection, tighter BP control, lower BP targets, better choice of antihypertensive drugs, and availability of hemodialysis and renal transplantation. However, despite the vast range of antihypertensive agents and effective BP control, MHT remains a significant clinical challenge.

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ARTYKUŁ POGŁĄDOWY

Nadciśnienie tętnicze złośliwe – nowe aspekty starej jednostki klinicznej

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leczenie, nadciśnienie tętnicze złośliwe, patogeneza, występowanie

STRESZCZENIE
Nadciśnienie tętnicze złośliwe (malignant hypertension – MHT), nazywane także przyspieszonym nadciśnieniem tętniczym złośliwym lub fazą złośliwą nadciśnienia tętniczego, jest najcięższą postacią nadciśnienia tętniczego. Definiuje się je jako istotnie podwyższone wartości ciśnienia tętniczego z towarzyszącymi zmianami na dnie oka (plomykowate wybroczyny, wysięki, ogniska waty, z lub bez obrzęku tarczy nerwu wzrokowego). Pomimo dostępności licznych leków hipotensyjnych MHT pozostaje ważnym problem klinicznym. Częstość jego występowania jest bardzo niska, jednak bezwzględna liczba nowych przypadków nie zmieniła się na przestrzeni ostatnich dekad. Chociaż rola aktywacji układu renina-angiotensyna-aldosteron i dysfunkcji śródbłonka w patogenezie MHT została dobrze udokumentowana, wyniki ostatnich badań wskazują, że także układ odpornościowy może odgrywać istotną rolę w rozwoju tej choroby. Chorzy z MHT charakteryzują się nasilonymi powikłaniami narządowymi nadciśnienia tętniczego, w tym nieprawidłowościami strukturalnymi i funkcjonalnymi serca. Częstymi powikłaniami MHT są upośledzenie funkcji nerek oraz schyłkowa niewydolność nerek. Przeżycie chorych z MHT poprawiło się znacząco wraz ze zwiększeniem dostępności leczenia hipotensyjnego, niemniej jednak upośledzenie funkcji nerek i rozwój schyłkowej niewydolności nerek wciąż stanowią istotną przyczynę chorobowości i śmiertelności w tej grupie chorych. Podsumowując, MHT nie jest „znikającą chorobą”, ponieważ charakteryzuje się stałą liczbą nowych przypadków rocznie. Rokowanie i przeżycie pacjentów z MHT poprawiło się natomiast znacząco w wyniku wcześniejszego rozpoznania, ścisłej kontroli ciśnienia tętniczego, niższych wartości docelowych ciśnienia tętniczego, większego wyboru leków hipotensyjnych oraz zwiększenia dostępności leczenia nerkozastępczego i transplantacji nerek.