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EDITORIAL

Malignant hypertension: does this still exist?

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Malignant hypertension (MHT) is the most severe form of hypertension. It was originally defined by two major features: extremely high blood pressure with the diastolic blood pressure above 130 mmHg at the time of the diagnosis and hypertensive retinopathy grades III or IV in the Keith et al.'s classification [1].

More recently, the definition of MHT has been reconceptualized to emphasis multi-organ damage [2, 3]. Indeed, overall prognosis in patients with MHT mainly depends on the function of kidney, brain, and heart [3]. As the earlier diagnosis and appropriate antihypertensive treatment result in significant improvement of prognosis [4], it is of the utmost importance to set reliable diagnostic criteria. Hence, the proposed new definition presents MHT as a group of disorders with out of range elevation in blood pressure with the concomitant damage of at least three different target organs [3]. Considering the disease entity in a broader perspective will allow to increase the detection and estimate the real prevalence of this hypertensive emergency.

The principals of prompt detection, systemic evaluation, and effective management are the key to improve the long-term prognosis.

Epidemiology

In general population the prevalence of MHT is relatively low with annual incidence rate of around 2 per 100,000 of Caucasian population [5, 6]. Greater disease predisposition and worse prognosis is observed in the Afro-American population (7.3 new cases per 100,000 of population per year) [6]. There is also no significant difference in MHT prevalence between developed and developing countries [7, 8].

As a hypertensive emergency MHT might develop in patients with prior history of essential hypertension, but in up to 60% cases MHT occurs *de novo* with no differences in signs and symptoms or long-term survival [9].

In the past, MHT had an unfavorable prognosis and without adequate treatment, mortality rate in MHT was around 80% at 2 years [10]. Importantly, 5-year survival among MHT patients has improved dramatically over the decades and for patients diagnosed after 1997 it is now more than 90% [11]. When compared malignant and non-MHT all-cause mortality is higher, with kidney failure as the main cause of death among patients with MHT [12, 13]. Nevertheless, since the new, more effective anti-hypertensives are in use, current prognosis performs better [2]. Despite the overall decrease, the prevalence has been roughly stable for the last 40 years [4].

Diagnostic difficulties

MHT may pose a diagnostic challenge whilst early diagnosis is essential for prompt treatment [3, 14]. As emphasized, the MHT has a significantly worse prognosis than the non-MHT, and it appears this difference is mainly due to renal insufficiency resulting in end-stage renal disease. Moreover, the main diagnostic problem is caused by the lack of obvious symptoms which flag out patients who require further investigation, that is fundoscopy. The latter is an essential examination required to establish an initial diagnosis based on the original criteria. Thus, retinal

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fundoscopy should be performed in all patients presenting with severely increased blood pressure on examination [2]. It is due to the fact that typical retinal changes are dynamic, start to regress immediately upon the implementation of the antihypertensive treatment and do not persist for longer than 2–3 months [2, 15].

Although in some cases, when patients present with extreme signs of blood pressure elevation, such as hypertensive encephalopathy and MHT is suspected, Grade 3–4 ocular changes might be absent during their initial examination [16]. There are also other disorders which might cause papilledema or retinal hemorrhages, such as severe anemia, ineffective endocarditis, or connective tissue disorders [17]. Not to mention also diabetic retinopathy, which is a leading cause of sight impairment and retinal changes [18]. All the above disrupt and complicate the differential diagnosis. As the clinical presentation of MHT is often delayed, the presence of ocular fundus changes before initiating treatment should not be a determinant [3]. Moreover, changes in the vision correspond to the renal function impairment [19, 20].

The common cause of the described alternations is systemic microvascular dysfunction. An important pathological feature of MHT is endothelial dysfunction and fibroid necrosis of arterioles, that obviously concerns various tissues and affects many organs, especially key ones, that is kidney, heart, and brain [2, 21]. This premise lay the foundation for the evolution of definition in which the concept of multi-organ damage, described as hypertensive target organ damage (TOD), was introduced [2, 3, 21]. Other diagnostic criteria required are the presence of damage of at least three different target organs (kidney, heart, brain, and small vessels) and out of range elevation in systolic and diastolic blood pressure.

Renal abnormalities are the most common evidence of TOD and constitutes an independent determining factor in prognosis [22]. MHT exerts various impacts on the kidney, from elevated serum creatinine and proteinuria to acute renal failure as a first presentation of MHT [23, 24]. Moreover, renal ischemic changes are aggravated by hemolysis and low plate platelet count, resulting from thrombotic microangiopathy [3, 25].

In the heart, the impairment of cardiac structure and function is so evident that it is referred as hypertensive heart disease [26]. It includes left ventricular hypertrophy, cardiomegaly, systolic and diastolic dysfunction, and finally heart failure [9, 27]. Even atrial fibrillation is said to be a certain presentation of TOD [27].

Prevention of neurological deficits is a crucial goal in MHT treatment, especially because of their often-asymptomatic course and limited diagnostic possibilities. However, the most life-threatening condition, hypertensive encephalopathy, is a rare emergency with sudden onset of symptoms that facilitates differential diagnostics [2, 28].

Treatment

The hypertensive emergencies require immediate intervention to lower blood pressure [29]. It is important to reduce the blood pressure in appropriate pace, which is ~20–25% decrease within several hours [30]. Too rapid blood pressure reduction may result in severe multi-organ ischemia caused by hypoperfusion and failure of autoregulation mechanisms [16, 31]. The conventional "normal" level of blood pressure should not be aimed at acute presentation with MHT [32]. First line pharmacological agents are labetalol and nicardipine. Alternatively nitroprusside and urapidil can be used as safe and effective treatment of MHT [30], as recommended by the ESC position document. Labetalol is an alpha 1 adrenergic receptor and nonselective beta-adrenergic receptor blocker. Its main advantage is capacity to both maintenance of cardiac output and reduction of peripheral resistance with preservation of cerebral, renal, and coronary blood flow [33]. Nicardipine, a dihydropyridine derivative calcium channel blocker with cerebral and coronary vasodilatory activity, increases stroke volume and coronary blood flow and it is especially recommended for patients with coronary artery disease[34]. Alternatively, some groups use very low oral dose of angiotensin-converting enzyme inhibitors [35] or renin–angiotensin system blockers [36] titrated over 48 h, to prevent excessive fall in blood pressure. Although the preferable therapeutic approach for each patient depends on clinical presentation, the optimal clinical care is often be provided in the intensive care units to ensure adequate monitoring and treatment adjustments [37].

New definition

The original definition of MHT was focused only on visual disturbance and did not include other evidence of organ damage [1]. Such TOD, especially the severity of renal impairment, is pivotal in overall prognosis [38]. Along with the development of techniques for TOD assessment, a new definition has been widened to include the presence of impairment in at least three different organs including kidney, heart, brain, and microangiopathy [3]. They constitute various clinical presentations of the same disease entity [2, 3].

The current 2018 ESC/ESH Guidelines for the management of arterial hypertension present new, broadened approach to the hypertensive emergencies [29]. A collective group of "hypertension urgencies and emergencies" was distinguished with a strong emphasis on magnitude of organ damage, described as hypertension-mediated organ damage [29]. Besides, the term of "malignant hypertension" was clarified as it refers to the poor prognosis when untreated

[29]. It characterizes the condition of severe hypertension with concomitant retinopathy, microangiopathy, disseminated intravascular coagulation, encephalopathy, acute heart failure, or acute deterioration in renal function [29]. Updated guidelines also offer greater range of diagnostic possibilities depending on target organs affected and symptoms, divided on common and specific tests [29]. Hence, common diagnostic tests including 12-lead ECG, hemoglobin, platelet count, fibrinogen, creatinine, eGFR, urine albumin:creatinine ratio were included for routine testing with fundoscopy as a crucial part of the diagnostic workup. Specific tests such as troponin, CK-MB, echocardiography, CT or MRI brain, urine drug screen, etc., undeniably contribute to improvement in general management of MHT [2, 39].

Conclusions

Although general improvements in diagnosis of MHT has been made, this is still a common emergency, especially in the developing countries due to the growing population, undiagnosed hypertension, and low level of health care services. Moreover, the diagnosis is established when the target organ impairment occur therefore this condition is related to much worse outcome than the nonmalignant forms of hypertension [3].

Despite better prognosis and significantly improved survival rates, patients with MHT remain at high risk. Not only do they require special attention during hospitalization, but also after discharge, which include screening for secondary hypertension and frequent follow-up visits.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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