



Malignant hypertension and multiorgan damage: mechanisms to be elucidated and countermeasures

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Extreme elevation of blood pressure is called malignant hypertension or a hypertensive emergency and causes acute vascular damage in target organs; it was recently represented as a hypertensive crisis with multiorgan damage [1]. In malignant hypertension, patients may have a fatal course if blood pressure-lowering treatment is not started immediately. Therefore, evaluation and quick and accurate diagnosis are important. Blood pressure is usually measured when the patient goes to the hospital complaining of an illness. If the blood pressure is abnormally elevated, it is easy to suspect the presence of malignant hypertension. After that, it is important to determine and evaluate the occurrence of widespread organ damage.

In the current issue of *Hypertension Research*, Mishima and Funayama et al. demonstrated close relationships and concurrency among hypertensive acute organ damage to the brain, eyes, and kidneys [2]. This is a very interesting subject for all general physicians, emergency physicians, cardiologists, nephrologists, neurologists, and ophthalmologists. The present study is an effort to bring together a sufficient number of cases over the years. The prevalence of malignant hypertension is extremely low in the general population. Over 50 years of observation in the United Kingdom has revealed ~1–2 new cases per 100,000 population per year [3, 4]. In Asia, including Japan, the epidemiologic investigation of malignant hypertension has been insufficient, and the exact frequency is still unknown.

In the present study, the authors defined malignant hypertension as systolic blood pressure >200 mmHg and diastolic blood pressure >120 mmHg before antihypertensive treatment [2, 5]. Other researchers have

adopted diastolic blood pressure >130 mmHg as the inclusion criteria for malignant hypertension [6]; therefore, at present, there is confusion about the diagnostic criteria for malignant hypertension. However, the blood pressure of the patients in the present study was $222 \pm 18/142 \pm 16$ mmHg at presentation, which is surprisingly close to that of the Birmingham study reported by Lane et al. [4], which was a representative clinical study of malignant hypertension.

The incidence of posterior reversible encephalopathy syndrome in the pediatric population in the U.S. is 0.04% [7], but the incidence of reversible encephalopathy in the general adult population is still unknown. In adults, the incidence of reversible encephalopathy after bone marrow transplantation or in patients with systemic lupus erythematosus is known, but it is not very high. Therefore, reversible encephalopathy is considered to be extremely rare in the general adult population [8]. However, 12 of 20 patients with malignant hypertension in the present study had reversible encephalopathy [2]. This accumulation of a relatively large number of patients with reversible encephalopathy led the authors to propose the concept of “hypertensive reversible encephalopathy syndrome”. The concept of hypertensive reversible encephalopathy syndrome is meaningful in that the lesions are likely to occur in the brainstem and neurological symptoms are mild. As described by the authors in the present study, very few hypertensive reversible encephalopathy syndrome patients had vasospasm [2]. This is interesting because it suggests that hypertensive reversible encephalopathy syndrome and posterior reversible encephalopathy syndrome have different etiologies. The vertebral and basilar arteries are considered to be vulnerable to autonomic dysregulation. The behaviors of the vertebral and basilar arteries in relation to abnormal blood pressure may differ depending on race. It is hoped that future research in many other countries and races will be conducted.

Fortunately, only approximately half of the cases in the present study had cerebral microbleeds, but none had significant bleeding that led to sequelae. However, it is known that once cerebral microbleeds occur, they remain in place and can be detected for more than a year [9]. In other words,

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just because cerebral microbleeds were found in a patient with a certain disease, we do not know that they were due to that disease. Although the patients in the present study were relatively young, the number of cerebral microbleeds in this population was higher than that in elderly patients with atrial fibrillation [10], which makes it easy to imagine a relationship between malignant hypertension and cerebral microbleeds. It seems that rapid treatment by multiple specialists, mainly for blood pressure reduction therapy, was successful.

In the present study, seven patients did not show any of the three hypertension-related symptoms: reversible encephalopathy syndrome, serous retinal detachment, or proteinuria. Mishima and Funayama et al. speculated that this was due to the patient's early consultation. However, all patients already had retinopathy. This clearly implies that retinopathy precedes all findings and symptoms. In fact, malignant hypertension has long been a focus of attention in relation to retinopathy. A recent review has also emphasized the importance of performing retinal fundoscopy on patients with severe hypertension during the initial presentation [6]. It has also been pointed out that patients with genuine malignant hypertension occasionally have low diastolic blood pressure with systolic hypertension and ocular symptoms [6]. Mishima and Funayama et al. clearly showed how important ophthalmologic examination is for the rapid diagnosis of malignant hypertension.

The pathophysiology of malignant hypertension or hypertensive emergency is gradually being clarified due to the accumulation of research. In the present study, Mishima and Funayama et al. performed a matrix analysis and found a strong association between reversible encephalopathy syndrome, serous retinal detachment, and proteinuria [2]. The authors concluded that the underlying analogous pathophysiology in malignant hypertension is capillary leakage due to capillary hyperperfusion following the disruption of pressure regulation in the arterioles.

There are still problems to be solved. Hypertensive emergency requires immediate treatment in an intensive care unit for intravenous administration of a short-acting anti-hypertensive and continuous blood pressure monitoring. On the other hand, conservative treatment is recommended for hypertensive urgency, which is acute severe hypertension without organ damage [1]. The Correspondence by Koracevic et al. published this year in *Hypertension Research* defined the problem [11]. The problem is that there is no established treatment recommendation during the time required to distinguish between hypertensive emergency and urgency, that is, to detect organ damage. To prevent irreversible organ damage in patients with acute severe hypertension, this real-world problem needs to be urgently resolved.

Furthermore, according to the present study, untreated essential hypertension was the most common cause of the

underlying etiology. Essential hypertension contributes significantly to the pathophysiology of malignant hypertension, and with the aging population, malignant hypertension could become even more common worldwide, especially in developing countries [6]. To prevent the development of malignant hypertension, we must stop ignoring hypertension. An ophthalmologic examination must be performed immediately to evaluate multiorgan damage in patients with malignant hypertension. It is hoped that no one will suffer from the sequelae of malignant hypertension in the future.

Compliance with ethical standards

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

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References

1. Peixoto AJ. Acute severe hypertension. *N Engl J Med*. 2019;381:1843–52.
2. Mishima E, Funayama Y, Suzuki T, Mishima F, Nitta F, Toyohara T, et al. Concurrent analogous organ damage in the brain, eyes, and kidneys in malignant hypertension: reversible encephalopathy, serous retinal detachment, and proteinuria. *Hypertens Res*. 2020. Epub ahead of print. <https://doi.org/10.1038/s41440-020-0521-2>.
3. Lip GY, Beevers M, Beevers G. The failure of malignant hypertension to decline: a survey of 24 years' experience in a multi-racial population in England. *J Hypertens*. 1994;12:1297–305.
4. Lane DA, Lip GY, Beevers DG. Improving survival of malignant hypertension patients over 40 years. *Am J Hypertens*. 2009;22:1199–204.
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–52.
6. Shantsila A, Lip GYH. Malignant hypertension revisited—does this still exist? *Am J Hypertens*. 2017;30:543–9.
7. Thavamani A, Umaphathi KK, Puliyl M, Super D, Allareddy V, Ghorri A. Epidemiology, comorbidities, and outcomes of posterior reversible encephalopathy syndrome in children in the United States. *Pediatr Neurol*. 2019;103:21–6.
8. Hinduja A. Posterior reversible encephalopathy syndrome: clinical features and outcome. *Front Neurol*. 2020;11:71.
9. Saito T, Kawamura Y, Sato N, Sugiyama E, Okada M, Takeuchi T, et al. Cerebral microbleeds remain for nine years: a prospective study with yearly magnetic resonance imaging. *J Stroke Cerebrovasc Dis*. 2018;27:315–20.
10. Saito T, Kawamura Y, Tanabe Y, Asanome A, Takahashi K, Sawada J, et al. Cerebral microbleeds and asymptomatic cerebral infarctions in patients with atrial fibrillation. *J Stroke Cerebrovasc Dis*. 2014;23:1616–22.
11. Koracevic G, Lovic D, Zdravkovic M, Stojanovic M, Djordjevic D. How should we treat very high blood pressure until we distinguish between hypertensive emergency and urgency? *Hypertens Res*. 2020;43:470–2.