# 58 Hypertensive Encephalopathy

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## Overview

Fortunately, hypertensive encephalopathy, a once common disorder in hospital emergency rooms and a not infrequent cause of death, has become a medical rarity. Nonetheless, its unexpected occurrence and life-threatening nature require rapid recognition and effective treatment. Moreover, the manifestations of this abnormality are being encountered with increasing frequency among the pediatric and obstetric populations and thus a familiarity with the definition, signs, symptoms, etiology, mechanisms, pathogenesis, diagnosis and treatment of hypertensive encephalopathy is required for a broad spectrum of clinical practice. This chapter will briefly review each of those components in separate sections.

## Definition, signs and symptoms

Contrary to popular misconception, there is no numerical level of blood pressure that can be used to define or exclude hypertensive encephalopathy, since it can occur at blood pressures as low as 150/100 mmHg and not be present in individuals with levels exceeding 250/150 mmHg. An explanation for this lack of numerical criteria will be more evident when the mechanisms for the abnormality are described subsequently. Therefore, any level of blood pressure elevation inappropriately high for the individual and associated with neurological target organ alterations qualifies to be considered hypertensive encephalopathy. A wide spectrum of neurological changes may be present in the syndrome, including severe headaches, visual aberrations (typically blurring or amaurosis fugax), drowsiness, confusion, nausea, vomiting, seizures, transient focal neurological deficits, and stupor or frank coma. Not all of these findings are required, and often more than one is present. The presence of severe (Grade III or IV) hypertensive retinopathy provides confirmation of the pressure-related nature of the abnormality (Figure 58.1). It is often difficult to differentiate hypertensive encephalopathy from the presentation of a hypertensive individual suffering a stroke. Often the separation of the two requires confirmation by imaging techniques and/or the resolution of the symptoms with blood pressure reduction.

## Etiology, mechanisms and pathogenesis

Rather than resulting from vasospasm and reduced cerebral perfusion, current evidence indicates that hypertensive encephalopathy is associated with cerebral vasodilatation.[1] It is believed that the sequence of vascular response to an increase in pressure is to induce vasoconstriction in order to limit increases in blood flow, a process called autoregulation. However, there is a limit to the range of autoregulatory capacity. When exceeded, vasodilatation occurs and blood flow increases. In the brain, this leads to dilation of the tertiary arteries and arterioles with an associated increase in flow and in microvascular pressure. A disruption of the blood–brain barrier occurs because of endothelial dysfunction, resulting in cerebral edema and neurological symptoms.[1] Another important component is the rapidity of increase in blood pressure as well as the severity. The cerebral circulation is thought to adapt to chronic, less severe elevation of pressure at the expense of predisposition to stroke due to arterial occlusion or rupture.[2]

Historically, hypertensive encephalopathy most commonly resulted from longstanding untreated hypertension, which then caused a vicious circle of renal disease leading to higher blood pressure and yet higher pressures until end-organ failure, including the brain, ensued. Today, it is much less common to observe truly unrecognized or untreated hypertension as the cause. In fact, hypertensive encephalopathy is being encountered more frequently in the pediatric population. Some of the reported etiologies in such patients (Table 58.1) have included chemotherapy for a variety of neoplastic conditions, transplantation, transfusion, HIV, neonatal hyperthyroidism, sarcoidosis, post-streptococcal glomerulonephritis, renal vascular hypertension due to Takayasu's arteritis, aortitis or coarctation of the

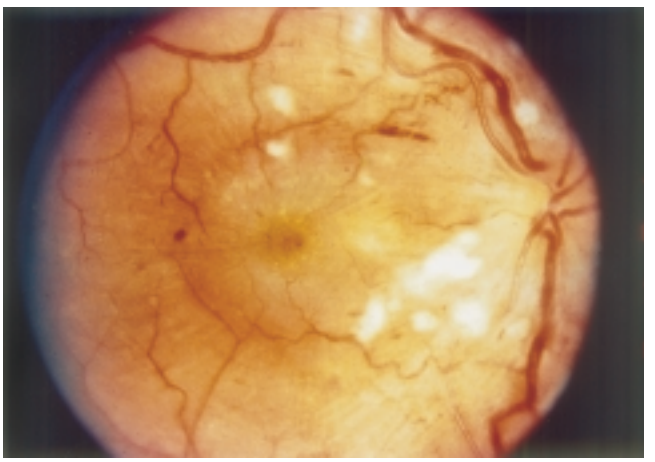

**Figure 58.1** Fundus photography shows disc edema extending to the macula, nerve fiber layer opacification and a nerve fiber layer hemorrhage, and cotton wool spots.

**Table 58.1 Common causes of hypertensive encephalopathy in children**

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| HIV | Hemolytic–uremic syndrome |
| Neonatal hyperthyroidism | Guillain–Barré syndrome |
| Sarcoidosis | Pheochromocytoma |
| Post-streptococcal glomerulonephritis | Cancer chemotherapy |
| Aortitis | Organ transplantation |
| Coarctation of the aorta | Transfusion |
| Renal vascular hypertension (Takayasu's arteritis, neurofibromatosis) | |
| Amoxapine overdosage | |

**Table 58.2 Common causes of hypertensive encephalopathy in adults**

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|---|---|
| Pre-eclampsia/eclampsia | Baroreflex failure after endarterectomy |
| Renal vascular hypertension | Cyclosporine administration |
| Pheochromocytoma | Cocaine |
| Glomerulonephritis | Amphetamines |
| Hemolytic–uremic syndrome | Sympathomimetic agents |
| Systemic lupus erythematosus | Erythropoietin administration |

aorta, hemolytic–uremic syndrome, Guillain-Barré syndrome and amoxapine overdose. Five children with α-1 antitrypsin deficiency who received liver transplantation and had evidence of pre-transplant glomerulonephritis developed severe hypertension after transplantation, and four had hypertensive encephalopathy.[3] The apparent common denominator physiologically appears to be excessive vasoconstriction resulting from activation or increased responsiveness to pressor substances, including the renin–angiotensin system, catecholamines and sympathomimetic substances, and the vascular effects of drugs.

Among pregnant women the pre-eclampsia/eclampsia syndrome has been viewed as a form of hypertensive encephalopathy. It is important to recognize that as many as half of the cases of eclampsia may occur in the 48 hours following delivery. A recent study of cerebral perfusion in women with pre-eclampsia and eclampsia found increased cerebral perfusion pressure and decreased cerebrovascular resistance in the women with eclampsia compared to those with less severe disease (pre-eclampsia).[4] These findings confirm the concept that eclampsia, just as non-pregnant hypertensive encephalopathy is viewed, represents a failure of cerebral autoregulation in the face of the increase in pressure resulting in increased cerebral blood flow.

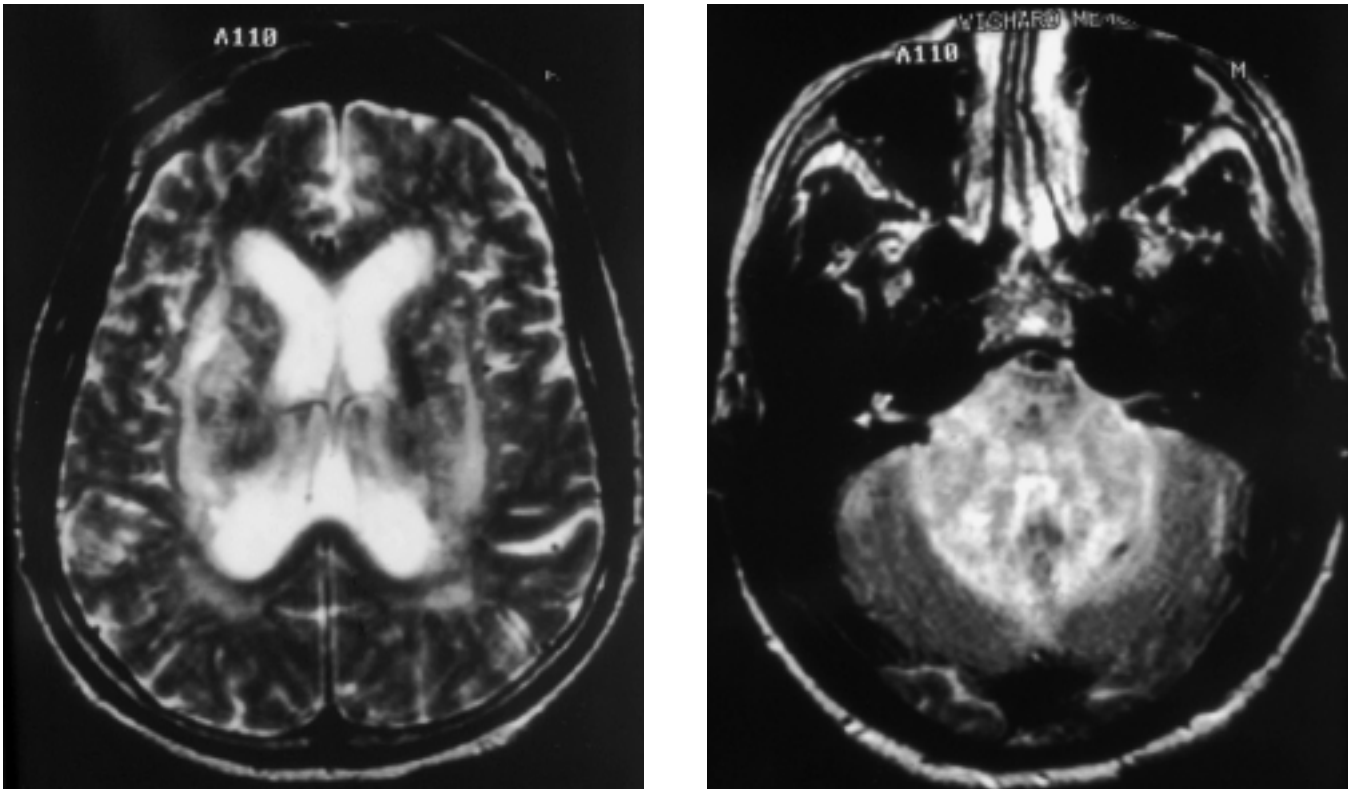
In adults an increasing number of etiologies for hypertensive encephalopathy have been identified (Table 58.2). Some investigators have preferred the descriptive name of reversible posterior leukoencephalopathy syndrome (RPLS) for this disorder. Among the associated findings have been thrombotic thrombocytopenic purpura,[5] renovascular hypertension, glomerulonephritis, hemolytic–uremic syndrome, baroreflex reflex failure following carotid endarterectomy, systemic lupus erythematosus and, most recently, erythropoietin administration.[6] The mechanism whereby the latter induces hypertension and encephalopathy is not clearly understood. Cyclosporine toxicity has also been reported in association with hypertensive encephalopathy.[7] The mechanism for this effect appears to be due to activation of the sympathetic nervous system that is also implicated in hypertensive encephalopathy resulting from cocaine or amphetamine abuse and phenylpropanolamine.[8]

## Diagnosis

As previously mentioned, the signs and symptoms of hypertensive encephalopathy can frequently not readily be differentiated from those related to stroke in a hypertensive individual. Cerebral imaging often provides a rapid means of separating them (Figure 58.2). Upon CT or MRI scanning, the presence of hypodense areas, representing edema, particularly in the parieto-occipital area but occasionally involving the cerebellum and brain stem, are strongly suggestive of hypertensive encephalopathy. The imaging picture seen in stroke is usually quite different, although occasionally no changes are immediately evident.

## Treatment

The signs and symptoms of hypertensive encephalopathy are typically responsive to lowering of blood pressure within hours or, sometimes, days. The major caveats in the treatment of elevated blood pressure in patients with central nervous system symptoms, whether likely due to hypertensive encephalopathy or stroke, are to avoid overly rapid or precipitous reduction in blood pressure and to ensure




(a) (b)

**Figure 58.2** Axial T2 weighted MRI shows extensive areas of bilateral hyperintensities in the corona radiata and peritrigonal regions (a), and diffuse edema in the pons and cerebellar white matter (b).

careful and frequent assessment of neurological status as well as that of other end-organs. Despite the immediate and dramatic efficacy of rapidly acting agents, they should only be used with resources for monitoring and controlling the magnitude of blood pressure reduction achieved to avoid further end-organ compromise, failure or death. This typically requires intra-arterial monitoring if intravenous agents are chosen in order to maintain systolic blood pressure in a range of 160–200 mmHg when it is above 200 on entry, or above 140 when it is initially less than 200 mmHg. Such intravenous agents would include sodium nitroprusside, labetalol, a combined alpha and beta adrenergic blocking agent, angiotensin-converting enzyme inhibitors such as enalapril, and calcium channel entry blockers such as diltiazem. Sodium nitroprusside (Nipride®) is given by intravenous infusion beginning at a rate of 0.5 μg/kg per minute and increasing up to a dose of 10 μg/kg per minute. The blood pressure response is noted immediately but requires constant monitoring. Nitroprusside is not innocuous, since it can cause thiocyanate toxicity. Thus it should only be employed sufficiently long to reduce a markedly elevated pressure, and other antihypertensive agents should be instituted, preferably orally, in order to permit discontinuation of the nitroprusside drip. Without other antihypertensive therapy blood pressure will rise within minutes after discontinuation of the infusion. Intravenous labetalol (Normodyne®) is typically given as an initial 20-mg bolus, which should exert a maximal effect on blood pressure within 5 minutes. Additional boluses can be given after 5–15 minutes of observation until the desired reduction in pressure is obtained. Again, constant monitoring of pressure is required and care must be taken to avoid rapid positional changes, since the alpha blockade can result in postural hypotension. The duration of effect of intravenous labetalol is variable, but generally persists for hours after a total cumulative administration of 200–400 mg. An angiotensin-converting enzyme inhibitor, enalapril (Vasotec®) is available in intravenous form as enalaprilat for emergent use. It is administered as a 1.25-mg bolus infused over a 5-minute period. A blood pressure response can be anticipated within 10–15 minutes, with a duration of action of about 6 hours. Monitoring of blood pressure is required, and attempts made to convert the patient to oral antihypertensive medications are also necessary. The calcium channel entry blocker, diltiazem (Cardizem®) is available in intravenous form. The usual initial dose is 20 mg given over a 2-minute period with repeat dosing after 15 minutes if the response is not adequate. Because of its effect to reduce heart rate, intravenous diltiazem is typically used for the control of arrhythmias. Therefore attention must be paid to heart rate and rhythm as well as to blood pressure when this agent is used. Esmolol (Brevibloc®) is a

beta-adrenergic blocking agent available for intravenous use, most frequently in arrhythmias and congestive heart failure. Frequently, diuretic administration is also required to combat the fluid retention and intravascular volume expansion that accompanies vasodilatation. Intravenous furosemide can be used for this purpose. Typically an intravenous bolus of 10–40 mg is administered.

If the subject is awake and able to swallow, longer-acting oral medication can often be administered, reducing the need for intra-arterial monitoring. These agents can be expected to begin to reduce pressure within 30–45 minutes, and can generally be safely used when facilities for frequent and careful monitoring of pressure and status are available. In view of the presumed vasoconstrictor mechanism for the disorder, many favor vasodilator drugs such as calcium channel entry blockers, clonidine, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Vasodilatation may seem to be paradoxical in the face of the pathophysiological role proposed for this biological action. However, systemic, rather than cerebral, vasodilatation will lead to a rapid reduction of blood pressure and permit the return of normal cerebral autoregulation. Monitoring blood pressure every 15 minutes, if constant monitoring is not feasible, should provide information regarding the reduction of blood pressure. It is important to recognize that longer-term blood pressure control may require the addition of other classes of drugs, often including diuretics and beta blocking agents, and a commitment to long-term blood pressure monitoring and control. The rate and degree of blood pressure reduction is usually dependent on the clinical status and the initial level of blood pressure elevation. When the pressure is above 200 mmHg systolic the initial therapeutic target should be 160–200 with the pressure maintained at those levels until the stability of neurological status and that of other end-organs is apparent. Moreover, it is often necessary to differentiate hypertensive encephalopathy from stroke by anatomical techniques such as MRI or CT since further reduction in pressure may not always be desirable with the latter. After the diagnosis is clear, particularly if the neurological symptoms show improvement with the initial reduction in pressure, subsequent further reductions to levels of 140 mmHg systolic are warranted. Since hypertensive encephalopathy is often encountered among known hypertensives that have forsaken antihypertensive drug therapy, commitment to compliance with treatment may help decrease the likelihood of a recurrence.

## References


1. Heistad DD, Lawton WJ. Pathogenesis of acute hypertensive encephalopathy. *In:* Izzo JL, Black HR, eds. Hypertension Primer. Philadelphia: Lippincott, Williams & Wilkins, 1999:186–187
2. Phillips SJ, Whisnant JP. Hypertension and the brain. Arch Intern Med 1992;152:938–945
3. Noble-Jamieson G, Barnes ND, Thiru S, Mowat AP. Severe hypertension after liver transplantation in alpha 1 antitrypsin deficiency. Arch Dis Child 1990;65: 1217–1221
4. Williams KP, Wilson S. Persistence of cerebral hemodynamic changes in patients with eclampsia: a report of three cases. Am J Obstet Gynecol 1999;181(5 Pt 1): 1162–1165
5. Bakshi R, Shaikh ZA, Bates VE, Kinkel PR. Thrombotic thrombocytopenic purpura: brain CT and MRI findings in 12 patients. Neurology 1999;52:1285–1288
6. Delanty N, Vaughan C, Frucht S, Stubgen P. Erythropoietin-associated hypertensive posterior leukoencephalopathy. Neurology 1997;49:686–689
7. Schwartz RB, Bravo SM, Klufas RA, et al. Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy: CT and MR findings in 16 cases. Am J Roentgenol 1995;165:627–631
8. Lake CR, Gallant S, Masson E, Miller P. Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. Am J Med 1990;89:195–208