Hypertensive Encephalopathy

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HYPERTENSION produces most of its damage to the brain as a result of elevations of systolic blood pressure of varying severity for long periods of time. However, severe, acute hypertension can rapidly produce drastic and life-threatening situations. Hypertensive encephalopathy (HTE) is a syndrome which develops following a sudden but sustained elevation of systemic blood pressure to high levels and has characteristic clinical and pathological features which are clearly different from those of chronic hypertension. HTE usually occurs with little warning, as in eclampsia or acute nephritis. Less commonly, it results from an abrupt elevation of pressure in patients with chronic essential hypertension that has entered an accelerated or malignant phase.

Oppenheimer and Fishberg, who were the first to recognize HTE, identified the elevation of pressure as the essential causative factor, thereby separating the syndrome from the neurological consequences of uremia and other metabolic and toxic conditions with which it had previously been confused. HTE is considered to occur less frequently than in previous decades because of improved treatment of such antecedent conditions as acute nephritis, eclampsia, and malignant hypertension. However, the few carefully documented cases in the literature probably reflect an underestimation of its frequency in recent years. Clinicians must remain alert to the significance of early symptoms of HTE, a condition which is potentially fatal but which can be reversed completely by adequate treatment.

Pathogenesis

The most ominous pathological component of HTE is cerebral edema, which is due to increased vascular permeability and may be focal or generalized. It is characterized by an increase in brain weight, flattening of the gyri, compression of ventricles, and in some cases herniation of the cerebellum through the foramen magnum. Confusion in the literature about the presence of brain swelling in HTE has arisen from descriptions of patients who either had not met the clinical criteria for HTE or who survived the encephalopathic period and came to autopsy after the acute pathological changes had subsided.

Acute fibrinoid necrosis, similar to that found in renal disease, is usually present in penetrating cerebral arteries. Petechial hemorrhages, perivascular exudates, and military infarcts are frequent. The brains of patients with longstanding hypertension will show additional vascular changes such as medial hypertrophy, hyalinization, and atherosclerosis.

The specific reason for blood pressure elevation appears to be unimportant because a wide variety of conditions have been reported to cause HTE. Eclampsia, acute nephritis, and sudden elevation of pressure in patients with chronic essential hypertension are well-recognized causes. Pheochromocytoma, Cushing's syndrome, ACTH toxicity, and renal artery thrombosis have also been responsible. The blood pressure elevation following limb lengthening operations (presumably the result of peripheral nerve influences) is an unusual but well-documented cause. Another uncommon circumstance, but one with close similarities to laboratory models of HTE, is the rebound hypertension with encephalopathy which has been reported one to three hours after completing an infusion of saralasin acetate (sar'ala'-angiotensin II) during the investigation of patients suspected of having renin-dependent forms of hypertension.

The usual response of cerebral resistance vessels to change in systemic blood pressure is to maintain cerebral blood flow (CBF) constant by autoregulation, i.e., to constrict in response to increased pressure (Bayliss response) and dilate when pressure falls. In normoten- sive individuals (average resting mean pressure 90 mm Hg), there is a wide range of mean systemic pressure (60 to 120 mm Hg) over which autoregulation can be maintained. The rapidity and the eventual height of the blood pressure rise relative to baseline are the most important factors determining whether HTE develops. Symptoms appear at lower pressure levels in patients previously normotensive, such as children with acute nephritis or pregnant women with eclampsia. Since autoregulation is set higher in patients with chronic hypertension, the blood pressure may rise to 250/150 or above before symptoms appear. This factor may explain why HTE appears to be more common in previously normotensive patients.

Initially it was postulated that in response to a severe pressure rise, there was intense reflex vasoconstriction (excessive Bayliss response), causing decreased CBF, ischemia of cerebral vessels, increased permeability of the blood-brain barrier, and cerebral edema. However, recent studies have suggested that it may not be regions of vessel narrowing which are at fault but areas of abnormal vasodilation that represent a "breakthrough" of autoregulation. These latter observations suggest that there are regions of resistance vessels where smooth muscle contractility is overcome by in-
creased intraluminal pressure, leading to vascular damage and subsequent cerebral edema. CBF studies in patients with acute hypertension have documented areas of increased CBF and have been used to support the "breakthrough" hypothesis. However, the resolving power of the CBF techniques used is insufficient to exclude the possibility of the presence of small regions of low flow within areas of high flow. Both theories may apply, and there may be an admixture of regions of excessive constriction and dilation, each contributing to disturbed function.

Structural damage to the blood-brain barrier is not required to produce cerebral edema in the presence of hypertension. Cerebral arterioles and capillaries become abnormally permeable to protein-bound dyes within a few seconds of the induction of severe acute hypertension in experimental animals. Pinocytotic vesicles have been observed to transport large molecular markers through the structural components of the blood-brain barrier during periods of hypertension. Passage of protein molecules by pinocytosis may be an important factor leading to the extravascular accumulation of protein rich fluid, thereby promoting the passage of water into the brain and the development of cerebral edema.

The seizures of HTE may introduce complicating metabolic factors. Convulsions produce a rise in blood pressure and are often accompanied by apnea and anoxemia.

**Clinical Characteristics**

HTE was a diagnosis adopted with enthusiasm following its initial description. It was often used indiscriminately to describe all manner of cerebrovascular events occurring in the presence of hypertension, including episodes we now recognize as transient ischemic attacks. The diagnosis of HTE is descriptive, and it should be applied only to a characteristic syndrome which develops during sudden sustained elevation of blood pressure and which can be reversed by prompt blood pressure reduction.

Blood pressure elevation usually occurs 12 to 48 hours before the onset of symptoms although often the interval cannot be documented accurately. A generalized headache which increases steadily in severity and which may lead to considerable restlessness is usually the first symptoms. Skin pallor has been commented on in the early stages. Nausea, vomiting, and visual blurring are common. A complaint of loss of vision in the presence of normal pupillary reactions should suggest cortical blindness. The patient may complain of focal neurological symptoms such as fleeting numbness or tingling in the arms or legs. The seriousness of the situation may not be appreciated until the appearance of focal or generalized convulsions.

The patient is often drowsy and slightly confused when first examined, and there may be a degree of neck stiffness. Papilledema may be present with flame-shaped retinal hemorrhages and exudates. Vasoconstriction of retinal arteries is described, but changes in vascular caliber are usually due not to spasm but to structural change at the same vascular site. Drowsiness and stupor will proceed to coma if the significance of the associated hypertension remains unrecognized and untreated.

The electroencephalogram will reflect an impaired level of consciousness by loss of normal alpha activity. Slow waves may be prominent in the occipital areas in patients with cortical visual symptoms.

Compression of the lateral ventricles in the CAT scan is an indication of cerebral edema. Symmetrical, well-demarcated, low density areas in the cerebral white matter, presumably representing edema, have been reported during encephalopathy with clearing following treatment.

Lumbar puncture should be avoided in patients suspected of having increased intracranial pressure. Unwitting examination of the CSF in patients with HTE often (but not always) reveals elevated pressure, a mild pleocytosis, and elevated protein.

The presence of blood pressure elevation to high levels, headache, papilledema, diffuse disturbance of sensorium, seizures, and the relatively mild nature of transient focal neurological symptoms comprise a characteristic picture of HTE. However, differential diagnosis may include a variety of intracranial disorders such as cerebral infarction, embolism, intracerebral or subarachnoid hemorrhage, subdural hematoma, encephalitis, or brain tumor. The CAT scan is now a precise aid in the identification of regions of brain hemorrhage or infarction.

In hypertensive patients, who are particularly liable to cerebral thrombosis, arterial hypertension may be a consequence of a cerebral lesion. Transient elevations of blood pressure may accompany transient ischemic attacks. Therefore, the significance of hypertension in the presence of a variety of acute neurological symptoms should be carefully assessed. As a general rule, the elevation of blood pressure in HTE will be much greater than that encountered in other conditions.

**Treatment**

During the acute period the patient should be nursed in an I.C.U. where systemic pressure, airway obstruction, level of consciousness, and seizures can be monitored during treatment. The immediate objective of treatment is to lower systemic blood pressure rapidly but prudently. The desired level of immediate pressure reduction will depend on the patient's history. The autoregulatory range in patients with longstanding hypertension is set higher than in normotensives. Thus, a response to treatment will usually occur when blood pressure is lowered to levels in hypertensive patients that are higher than those required for a response in patients previously normotensive. Under normal conditions cerebral autoregulation is unimpaired in both hypertensive and normotensive patients until mean arterial pressure is reduced by 25 to 30%. With a decline of mean pressure to 40% of baseline levels, symptoms of cerebral hypoperfusion develop. Therefore, a patient with blood pressure of 225/150 mm Hg will suffer a reduction of CBF if blood pressure is lowered to 140/
100 and will develop clinical symptoms if pressure drops further to 100/70. Target values of blood pressure to be reached with treatment should be higher in the elderly and in those with a previous history of hypertension.

The desirable drug to lower blood pressure in HTE should have rapid but reversible action, be free of depressant CNS effects, have a low toxic-therapeutic ratio, and provide a reasonably predictable and controlled reduction of pressure. Sodium nitroprusside is often the initial drug of choice. Like all intravenous drugs used for treatment of severe hypertension, it acts within a few minutes and is unsatisfactory for long-term management. It causes arterial and venous relaxation, providing an increase in venous capacitance so that cardiac output remains unchanged despite a slight increase in heart rate. Special nursing and intensive care facilities are desirable when nitroprusside is used so that it may be given by infusion pump with the rate adjusted according to response. The usual infusion dose is 0.5 to 0.8 μg/kg/min.

Diazoxide is less favored. Although it is more easily administered in an i.v. bolus of 150 to 300 mg, the pressure drop in some patients may be greater than desired, particularly in those already using antihypertensive drugs or in renal failure. Diazoxide was the drug used in a report describing patients who developed permanent blindness following treatment of malignant hypertension; it was thought that too rapid and uncontrollable a drop in blood pressure resulted in occipital lobe infarction.

When blood pressure has been reduced to an acceptable level, a beta-blocker such as propranolol by mouth can be started. Hydralazine may be added as an adjunct, and a diuretic will frequently be needed for long-term management.

During the acute phase of HTE, attention is directed toward lowering the blood pressure. However, cerebral edema is the life-threatening component of HTE, and if symptoms of intracranial pressure persist, it may be necessary to institute treatment specifically directed at reducing cerebral edema. Such treatment may include dexamethasone 4 to 6 mg in every four to six hours or, in the absence of renal disease, hyperosmolar agents such as glycerin or mannitol.

Anticonvulsants should be used during the acute illness. Diphenylhydantoin i.v. in doses adequate to achieve therapeutic serum levels rapidly may be adequate to control seizures although supplementation with barbiturates may be required. Diazepam is much favored as an anticonvulsant for the treatment of repetitive seizures, but it is a drug to be avoided because of its central depressant action. Also, the hypotensive response which it may induce can complicate assessment of the effects of other hypotensive drugs.

With prompt diagnosis and treatment patients usually show a rapid response and resolution of symptoms and signs. Adequate treatment appears to lead to complete recovery in most patients, but long-term follow-up with careful neurological and psychometric assessment of a group of such patients has yet to be reported.

Once the episode of HTE has been resolved, the patient may require long-term management for blood pressure control. As with all forms of hypertension, the record of such medical management is poor. Drugs are now available to deal adequately with the emergency of HTE and the long-term treatment of hypertension, but in one study assessing the efficacy of long-term care, only 27% of patients with malignant hypertension had an average treated diastolic blood pressure less than 100 mm Hg. This dismal situation results from poor surveillance by physicians and lack of treatment compliance by patients.

Hypertension remains the major risk factor for stroke. Maintaining blood pressure within a normal range protects against the development of atherosclerosis in major cerebral and neck arteries and degenerative changes such as hyalinization in small arteries, all of which are precursors of cerebral thrombosis and hemorrhage. It is the responsibility of all physicians to examine blood pressure routinely, treat hypertension when found, and to continue to treat it adequately as long as required. Such attention will do more than anything else to diminish the overall burden of stroke.

References
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