HYPERTENSIVE BRAIN DISEASES.
11. HYPERTENSIVE ENCEPHALOPATHY

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IN THE year 1928, two important concepts were introduced in the study of hypertension. Keith et al used the term "malignant hypertension" in severely hypertensive patients with papilledema, retinal hemorrhages, and exudates whose prognoses were worse than those with less retinopathy. Oppenheimer and Fishberg introduced the term "hypertensive encephalopathy" when they described a syndrome of transient neurological disturbances with seizures, aphasia, confusion, headache, visual loss, and hemiplegia in a 19-year-old patient with severe hypertension. Oppenheimer and Fishberg categorized these disturbances as hypertensive encephalopathy (HE), that it became an acceptable entity.

**Definition**

HE is a clinical syndrome of acute and transient focal or generalized neurologic dysfunction that occurs in patients with systemic hypertension. The neurological abnormalities are reversible when blood pressure is lowered. Consequently, the diagnosis should be limited to hypertensives whose sudden rise in blood pressure is associated with multifocal neurologic dysfunction which cannot be explained by other structural or metabolic diseases such as cerebral hemorrhage or uremia.

**Epidemiology**

HE is uncommon, even in large series of patients with malignant hypertension. In one study of 190 patients with malignant hypertension, 73 had neurologic symptoms but only one had classic HE. Accurate figures on mortality are unavailable because many episodes are transient and do not receive the attention of physicians. The long-term outlook is determined by the hypertension rather than by the neurologic dysfunction.

**Pathogenesis and Pathology**

In their original report, Oppenheimer and Fishberg attributed the changes observed in their patients to generalized cerebral arterial spasm. Their evidence was supported by the presence of retinal arterial spasm, cerebral edema, and pale cerebral hemispheres at autopsy. Later, this theory of "vasoconstriction" was supported experimentally by producing a sudden rise in the blood pressure and showing pallor in the cerebral cortex with diffuse constriction of the pial vessels in encephalopathic animal brains. The original vasospasm hypothesis was then questioned later, and Robertson et al reported foci of cerebral infarctions in 4% of rats that became hypertensive by the adrenal regeneration technique. In normotensives there is an autoregulation system of the cerebral blood flow (CBF) with upper and lower limits. Both the upper and lower limits are shifted to higher levels in chronic stable hypertensives. If there is an acute rise in the blood pressure, the autoregulation is overridden with an increase in the CBF. In HE, the upper limit of autoregulation is exceeded with a "breakthrough," leading to a passive increase in CBF and "forced vasodilatation."
tion leads to vascular necrosis and disruption of blood brain barriers to water, solutes, and proteins. This process includes the retina and optic nerve. In fatal cases, autopsy showed brain swelling with diffuse fibrinoid necrosis, thrombosis of cerebral arterioles, microinfarcts, and petechial hemorrhages in brain parenchyma.

Relation to Malignant Hypertension

Malignant hypertension is a syndrome associated with a progressive rise in the blood pressure in hypertensive patients. It may be related to the onset of hypertension in apparently normotensive individuals. The syndrome is characterized by progressive retinopathy with arteriolar spasm, hemorrhages, exudates and papilledema, deteriorating renal function with proteinuria and hematuria, and frequently, microangiopathic hemolytic anemia. Encephalopathic features are unusual, but there may be nonspecific neurological dysfunctions such as headache and drowsiness. Blood pressure varies between 160 to 250 mm Hg in systole and 100 to 150 mm Hg in diastole; this depends upon the previous condition of the patient. The pathogenesis is thought to be excessive sodium loss which leads to activation of renin and angiotensin. This results in necrotizing vasculitis and a further increase in the blood pressure with more renal ischemia. The absence of encephalopathic features and the presence of uremia differentiate malignant hypertension from HE.

Clinical Features

The hypertensive patient initially starts feeling with a headache which begins occipitally, but soon it becomes generalized and may be associated with nausea and vomiting. Later, the patient becomes restless, confused, and disoriented with defective memory and impaired high intellectual function. Myoclonic twitches in the extremities and focal convulsions can be observed. The patient may also have dysphasia, hemianopic visual loss, or cortical blindness. These neurological phenomena change with time and may shift from one side to another and from extremity to extremity. Lastly, without treatment, the cerebral functions deteriorate and the patient becomes stupor and comatose. Fundal examination shows hypertensive retinopathy with arteriolar narrowing, hemorrhages, and exudates. Papilledema may or may not be present. Blood pressure varies, but usually it is 120 to 150 mm Hg diastolic and 200 to 300 mm Hg systolic. General examination may show left ventricular hypertrophy and/or congestive heart failure.

Diagnosis

HE can be caused by hypertension from a variety of causes, including glomerulonephritis, pheochromocytoma, eclampsia, primary aldosteronism, and essential hypertension. HE should be differentiated from the following conditions: (1) uremic encephalopathy - the patient is in renal failure with depressed alertness, impaired intellect, and delirium. Sometimes myoclonus, asterixis, or convulsions may occur but usually resolve after dialysis; (2) cerebral infarction and cerebral or subarachnoid hemorrhage - in these cases, the patient usually shows persistent, profound, focal neurologic deficit with less disturbed awareness and rarely has seizures. The blood pressure may be normal or high but not to the same extent as in HE; and (3) other conditions which include intracranial tumors, particularly of the posterior fossa, delirium tremens, meningitis, acute intermittent porphyria, and traumatic or chemical injury to the brain such as lead poisoning and carbon monoxide intoxication; in these circumstances, it is very unusual for the blood pressure to be high.

Neuroradiological Findings

Computed tomography (CT) and magnetic resonance (MR) of brain changes are usually diffused and symmetrical with effacement of ventricles and sulci, due to cerebral edema. In milder cases there is only supratentorial involvement, while in severe cases, the brainstem and cerebellum are also involved. Occasionally, the CT of the brain shows focal white matter and cortical hypodense lesions which may be symmetrical or asymmetrical and often imposed on more diffuse cerebral edema. MR appears to be more sensitive than CT and better defines the anatomy of cerebral involvement with high intensity lesions seen in the white and grey matter. Since cortical...
blindness is not rare, bilateral occipital lesions are well documented. The neuroradiological findings are invariably reversible which usually resolve within several days.23

Management

HE is an acute life-threatening emergency that can end fatally.3,17 It requires hospitalization and prompt reduction of blood pressure. It is one of the hypertensive emergencies in which the antihypertensive therapy should be initiated parenterally. The level to which the blood pressure can be lowered varies; it depends primarily on the state of the patient's renal and cardiac functions. If renal function is reasonably adequate and there is no history of disease of the cerebral or coronary arteries, reduction of blood pressure to normal or even to slightly hypotensive levels can be done without complications.18 However, aggressive over-enthusiastic therapy which lowers the blood pressure to below the lower limits of autoregulation can lead to cerebral ischemia or infarction.18 Reduction of the blood pressure in patients with coronary artery disease or cerebral ischemia carries some risk which must be balanced against the risk of cerebral complications from continued marked elevation of the blood pressure. It is always safe to lower the systolic blood pressure to about 170 mm Hg and the diastolic blood pressure to about 105 mm Hg.

A number of drugs are now available for this purpose. Nitroprusside is the most effective. Its dosage control, potency, and rapidity of action make it the treatment of choice for this emergency. The hypotensive effects of sodium nitroprusside are produced by peripheral vasodilation caused by a direct action on the walls of the blood vessels. Oral antihypertensive medication can be started simultaneously because there is no contraindication to the concomitant use of the two types of treatment.

Intravenous infusion of sodium nitroprusside should be administered by an infusion pump with a microdrip regulator to provide precise measurement of the flow rate. It should be used only when the facilities and equipment for continuous monitoring of blood pressure are available. The average dose is 3...\(\mu\)g/kg/min, and the maximum dose that should be administered is 10...\(\mu\)g/kg/min. The action on the blood pressure is immediate (within minutes), and if the infusion is stopped, blood pressure usually begins to rise immediately and may return to pre-treatment levels in 1 to 10 minutes. When the drug is dissolved in solution (according to the packaging directions), it tends to deteriorate in the presence of light and should be protected by wrapping the container with opaque material. Sodium nitroprusside is rapidly metabolized to cyanide and then converted to thiocyanate. If the infusion is continued for many hours, cyanide toxicity may develop. If increased tolerance to the drug develops, as shown by the need for higher doses, acid-base balance must be monitored because metabolic acidosis is the earliest and most reliable evidence of toxicity. Dyspnea, headache, vomiting, decreased consciousness, absent stretch reflexes, and decreased volume of the pulse are some of the symptoms and signs of cyanide toxicity. Cyanide toxicity can be treated successfully with intravenous injections of hydroxycobalamin.

Other drugs like diazoxide (hyperstat), hydralazine (apresoline), and methyldopa (aldomet) may also be used. Hydralazine hydrochloride (apresoline), in doses of 20 mg, given either intravenously or intramuscularly will also quickly reduce blood pressure. However, the action of hydralazine is not always predictable, and the dosage and frequency of administration needed for a satisfactory change in blood pressure are extremely variable.

Diazoxide, a thiazide derivative related to chlorthiazide, can be used in the treatment of HE. An intravenous dose of 100 to 150 mg, followed 10 to 15 minutes later with a similar dose, produces an immediate hypotensive effect that lasts 8 to 9 hours. Intravenous frusemide is often needed to lower the blood pressure further and prevent salt and water retention. Once the blood pressure has been lowered by parenteral preparations, oral therapy should be instituted to maintain the patient's blood pressure at a reasonable level.

The cerebral manifestations are transient and always reversible with the control of the blood pressure. Specific therapeutic measures are rarely needed. Irritable and restless patients may need a small dose of intravenous anxiolytic drugs such as diazepam. Convulsive attacks are usually well controlled with intravenous diazepam and/or phenytoin in the acute stage, however, long-term anticonvulsant maintenance therapy is no
needed. Intravenous steroids (dexamethasone) are used to decrease the cerebral edema; if it occurs, these drugs have no role in the management of HE and they are not without complications.

Illustrative Case

A 22-year-old female had a sudden rise in the blood pressure during the last weeks of pregnancy due to eclampsia. The highest blood pressure recorded was 200/130 mm Hg. Later, she developed a generalized tonic-clonic seizure. A lower cesarean section was done; upon recovery from the anesthesia, she was found to be blind. Examination revealed dilated pupils with normal light reflex. Fundi showed arteriolar narrowing bilaterally. She had no weakness, and all modalities of sensation were normal. She had no reflex dominance, and the Babinski sign was absent bilaterally. ER of the brain was done (Figure 1). Her blood pressure was well controlled with parenteral hydralazine. Five days later, her condition started to improve, and within a week, her vision was normal.

FIGURE 1A. Initial CT brain showing bilateral low attenuate areas in the parietal lobe (as seen by the arrows).

FIGURE 1B. ER brain one week later; the same area showing no abnormality.

Comments on Neuroradiological Findings

The initial ER of the brain showed small ventricles reflecting the brain edema. There was bilateral, symmetrical, non-enhancing, low density lesions in the occipito-parietal regions. One week later, the ER brain was normal; MR imaging at this stage was also normal and excluded sinus thrombosis.

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References


