Differential Diagnosis of Hypertension

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Accepting that hypertension occurs in an estimated 20% of the adult population in the United States (1) and that it is a leading risk factor in the development of vascular disease (2, 3), physicians are being challenged to assume a more pragmatic approach to the differential diagnosis of hypertension than has been promoted in the past.

Detection. The levels of blood pressure defining hypertension vary, but 140/90 in patients under age 40 and 160/95 in patients over age 40, are generally accepted (1). Such elevated recordings in the office, screening program, or upon admission to the hospital should be followed by three successive recordings made by the physician or trained nursing personnel to definitely determine that the patient has hypertension and that the original reading was not falsely elevated because of emotional factors surrounding the initial examination. Bed rest for hospitalized patients will yield normal blood pressure recordings, and an initial recording which is elevated should be followed by repeated recordings after the patient has returned to normal daily living.

Recording of the blood pressure, though simple, should be properly performed to avoid categorizing a patient in a group already challenging the system's ability to evaluate and treat those in need. With the use of two sets of stethophones connected to a single diaphragm, it is quite easy to instruct office personnel in proper auscultation of the blood pressure. When the mercury manometer is used, the meniscus should be at point 'O' when deflated, and the mercury column should fall freely with a good air flow into the top of the manometer. Aneroid manometers should be standardized with a Y-tubing against a mercury manometer for accuracy. The bladder of the blood pressure cuff should be placed over the brachial artery, and the bell or diaphragm of the stethophone over the pulsating vessel in the anticubital fossa. The patient should be resting for at least five minutes and the blood pressure initially recorded in the supine or sitting position. The cuff should be inflated until the radial pulse can no longer be felt and then deflated at approximately 2 to 3 mm/second. The initial sound (phase I) is recorded as the systolic pressure, with the point of disappearance (phase V) coinciding best with intra-arterial diastolic pressure (4). Where phase V is over 5 mm lower than the point of muffling (phase IV), both numbers should be recorded. Patients with bruits in their arms due to partial stenosis of the artery, as well as those with aortic insufficiency and hyperkinetic circulations from other causes, may not have disappearance of Korotkoff's sounds until near 'O'. In these instances, phase IV, or muffling, is used as the diastolic pressure.

Recordings should be made in both arms, where up to 10 mm Hg difference in pressure may be normally noted; greater differences should suggest the possibility of some intra-arterial obstruction to that extremity. In patients who are markedly obese, a thigh cuff should be used in the upper arm and may be more accurate than recording the blood pressure in the forearm. Pumping the cuff up rapidly, keeping the recording arm elevated, as well as allowing 15 seconds or more between recordings, will prevent venous engorgement, which might affect the arterial pressure.

In addition to blood pressure determinations lying and sitting, the blood pressure should be recorded

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immediately after the patient assumes the standing position and one minute after. The degree of postural drop in blood pressure may be marked in lean patients, particularly in the older age group, and greatly influences not only the patient's further evaluation but also the selection of therapy.

Etiology. In the past, an estimated 10% to 15% or more of hypertensives have been defined as having curable causes, though Gifford (5) found that less than 6% of 5,000 hypertensive patients at the Cleveland Clinic have potentially curable forms of hypertension. In the average primary medical practice, the figure for curable hypertension may be even less, perhaps 2%; that is, over 98% of patients may have hypertension which is either essential or due to renal parenchymal disease.

Essential Hypertension. In essential hypertensives, the age at which hypertension was first detected, or when normal blood pressure was last documented, should be sought. Essential hypertension usually begins at the third and fourth decade of life and progresses through the years. A family history of hypertension, or vascular complications related to hypertension, is often obtained. The Systems Review should be directed at detecting evidence of organ damage such as cerebrovascular insufficiency, vision impairment, arteriosclerotic heart disease, as well as claudication. Most patients will either be entirely asymptomatic or present with manifestations of target organ dysfunction as the main complaint.

An ophthalmoscope, which can be carried in the breast pocket, facilitates funduscopy, and most patients will be found to have normal fundi or perhaps grade I changes due to arteriolosclerosis manifested by an increased light reflex ("copper wire changes"), with occasionally more advanced changes of A-V nicking and compression, all of which relate more to the duration of hypertension, rather than to its severity. Rarely, one will see retinal hemorrhages, exudates, and/or papilledema in the patient with accelerated, "malignant" hypertension. Bruits over the carotid arteries indicate the likelihood of atherosclerotic plaques in these vessels and suggest not only the degree of atherosclerosis present, but should also alert the physician to possible side effects with future drug therapy which might cause postural hypotension and neurological complications. A diffuse left ventricular impulse over the precordium suggests left ventricular hypertrophy due to hypertension, or dilatation as a result of a dyskinetic area of the left ventricle affected by ischemic heart disease. An S-4 gallop sound is heard in patients with more severe hypertension. Palpation of the abdominal aorta for an aneurysm, as well as the pulses in the lower extremities, add further to the evaluation of the total vascular picture.

Laboratory studies should include a CBC and an SMA-12, or at least a cholesterol, 2 hr. p.c. sugar, 16 hr. fasting triglyceride level, and a urinalysis. A baseline electrocardiogram and P-A radiograph of the chest for evidence of left ventricular hypertrophy or enlargement should be obtained and used for comparison with future studies.

Chronic Renal Disease. Proteinuria, particularly when accompanying or preceding the onset of hypertension by history, or when associated with a history of glomerulonephritis or repeated pyelonephritis, suggests primary renal disease as the cause for hypertension. An abnormal urinary sediment including white blood cells, red blood cells, and/or casts further suggests such an etiology. An elevated creatinine, with intravenous pyelogram (IVP) demonstration of kidneys which are contracted, polycystic, or with typical changes of chronic infection may also serve to document this etiology.

Renal Artery Stenosis. Of the curable forms of hypertension, renal artery stenosis probably represents the larger group, though it still represents a small number of patients in the average practice. The abrupt onset of hypertension, particularly in the age groups below 40, and particularly in females, more likely suggests fibromuscular disease of a renal artery. The rather abrupt onset of hypertension in older age groups that were previously normotensive also suggests a stenotic lesion, but one due to atherosclerosis. Hypertensive patients under therapy who are increasingly difficult to control might also be suspected of having renal artery stenosis. The history, except in regard to the progression of the hypertension itself, is usually unrevealing. It should be noted that renal artery stenosis is not often seen in blacks. The presence of vascular spasm on funduscopy suggests a more acute onset of hypertension.

A rapid sequence IVP revealing delayed appearance of contrast media by one kidney suggests that it is inadequately perfused. A difference in kidney size is significant if the left kidney is more than 1.5 cm shorter than the right, or if the right kidney is 2.0 cm or more shorter than the left, the right kidney being normally shorter than the left. Aortography should be performed if pyelography suggests unilateral renal disease, and even when the IVP is normal, if the clinical

picture is strongly suggestive, since there are significant numbers of false-negative IVP's. On physical examination, systolic bruits in the epigastrium are not sufficiently reliable in the diagnosis of renal artery stenosis, though a systolic murmur with a diastolic component would be strongly suggestive. The demonstration of stenosis in a renal vessel does not mean that such a kidney is inadequately perfused, or that inadequate perfusion is the cause of the patient's hypertension, since renal artery stenosis may exist in normotensive patients.

Plasma renin vein assays may also be normal or elevated. It is, therefore, necessary to obtain renal vein renin ratios by catheterization of each of the renal veins. Following a period of salt deprivation, and three hours after 80 mg of furosemide by mouth, if the renin level from the suspected kidney is 1.5 to 2 times that of the anatomically normal kidney, and particularly if the contra-lateral kidney renin level is lower than the peripheral plasma renin, then the suspected kidney is probably contributing to the hypertension. Further confirmation is available by the administration of an analog of angiotensin II, the potent vasopressor responsible for the hypertension in renal artery stenosis, that can be used to block angiotensin II. When the analog produces a clear-cut lowering of blood pressure when given intravenously, this would further support the suspicion that renal artery stenosis is causing the hypertension (6). This analog is saralasin acetate and is still under investigation for general use.

Primary Aldosteronism. An even more rare cause of hypertension is primary aldosteronism. Such patients may present with a history of weakness, muscle cramps, and paresthesias, but will more likely be detected by the finding of hypokalemia. When such is documented on repeated determinations of the serum potassium in a patient who has not been on diuretics or a low-salt diet or who does not have other clinical causes for hypokalemia, such as diarrhea, vomiting, and so forth, then a 24-hour urine sample for total potassium should be obtained. If the patient has been off diuretics for at least three days and the potassium excretion exceeds 30 to 40 mEq in 24 hours, then excessive aldosterone effect must be considered. Such patients must be on an adequate salt intake diet before urinary measurements of potassium are made, as well as the analyses of plasma renin and aldosterone levels, which will be needed to further confirm this diagnosis. High levels of aldosterone, accompanied by abnormally low levels of renin, are diagnostic of this disease, but do not determine whether such are due to an isolated adenoma of the adrenal cortex or to bilateral nodular hyperplasia. Visualization of the adrenal glands prior to surgery is recommended since patients with bilateral adrenal hyperplasia present a more serious problem for surgical, as well as subsequent endocrine management, and such patients usually respond quite well to medical management with spironolactone.

Pheochromocytoma. Most patients with pheochromocytoma will be symptomatic with fluctuating blood pressure due to the intermittent discharge of catecholamines. Headaches, nervousness, palpitations, and sweating are the usual symptoms. These patients are rarely overweight, and the presence of obesity would make the diagnosis unlikely. Laboratory studies are usually not necessary to exclude this diagnosis, but if suspected, a metanephrine screening test of the urine should be obtained. If this is positive, free catecholamines can be measured in a 24-hour urine sample. Drugs and dietary factors, which complicate measurement of VMA, make this test of limited value.

Cushing's Disease. The typical Cushingoid features, together with evidence of carbohydrate intolerance, make this diagnosis one to be considered, though the overwhelming majority of such patients suspected on this basis, will turn out not to have the disease. Measurement of plasma cortisol on a 7 AM specimen, after administration of 1.0 mg dexamethasone at bedtime the night before, if supressed below normal values, all but excludes completely such a diagnosis.

Coarctation of the Aorta. Simple palpation of the pulses in the lower extremities and comparing their volume and time of onset with that in the radial or carotid pulse is usually all that is necessary to lead one to consider the possibility of coarctation. If there is a pulse lag and diminished or absent pulses in the legs, then the blood pressure should be recorded, if possible, in the arm and thigh. Normally, the thigh blood pressure exceeds the arm blood pressure and if the opposite is evident, then the diagnosis of coarctation will need to be pursued further.

"The Pill." The use of oral contraceptives may cause reversible hypertension and is probably one of the more common causes of curable hypertension among the others mentioned, in the average population. Discontinuing oral contraceptives will result in the return of blood pressure to normal within several months.

Classification of Hypertensive Patients by Renin Assay. Renin is produced and released by the juxtaglomerular apparatus in the kidney in response to the pressure in the afferent arteriole and by the sodium level in the macula densa of the kidney. Normal physiological factors which lower renal artery pressure cause increased renin release, whereas factors which increase renal artery pressure cause a decrease in renin levels. Similarly, diminished sodium effect, such as seen in salt depletion, results in increased renin release, whereas increased sodium effect on the blood pressure is associated with suppressed renin levels (7). The compensatory mechanisms for restoration of normal pressure and sodium effect on the blood pressure come about through renin influence on the production of more, or less, angiotensin II, the potent vasopressor circulating agent. Angiotensin II further influences the release of aldosterone from the adrenal cortex which when increased results in increased sodium and fluid retention as a result of its effect on the renal tubule (8).

Plasma vein renin assay (PVRA) is actually a measurement of the amount of angiotensin I (the inactive precursor of angiotensin II) formed from a substrate over a given period of incubation time. Renin levels are expressed as ng/cc/hr of incubation and are commercially available by radioimmunoassay techniques. Such plasma renin activity is compared with those determined to be within the low, normal, or elevated levels for the particular laboratory. Reliable PVRA requires that the sodium-volume status of the patient not be disrupted by outside influences such as diets, and so forth, and most of the commonly used hypertensive drugs, as well as oral contraceptives, must be omitted temporarily to obtain diagnostic and unprovoked results. Approximately 25% to 30% of patients with essential hypertension will have low renin levels, whereas a somewhat smaller number will have high renin levels, with a slight majority having normal renin levels (9). Determination of renin levels in patients with essential hypertension has been advanced by some who have studies to indicate that renin may be toxic to the vascular system and should be treated with renin-lowering drugs (10, 11) such as propranolol or methyldopa. Other studies do not confirm this (9). Others have proposed a diagnostic trial of antihypertensive drugs with known effect on renin activity, as a better approach than using the renin levels per se; that is, a propranolol or methyldopa response suggesting increased renin hypertension, whereas diuretic responsiveness would suggest low or normal renin levels.

Conclusion. The overwhelming majority of hypertensive patients have essential hypertension, which is a potent risk factor in producing vascular disease. Overall, it must be stated that the differential diagnosis of hypertension is a relatively minor factor in approaching the tremendous challenge of detecting and adequately treating the overwhelming majority of patients who are now undetected, untreated, or inadequately treated.

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