Adolescent Hypertension

II. Characteristics and Response to Treatment

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SUMMARY

Two groups of patients were recognized among 27 black and Latin adolescents who underwent diagnostic evaluation for hypertension. Group I consisted of ten patients, seven of whom had arterial pressures consistently higher than 1 standard deviation above the pressure means of normal adolescents and three had pressures below this level. Group II consisted of 17 patients, 16 of whom had systolic and diastolic pressures greater than 2 standard deviations above the means for their age-sex group. One patient had solely systolic hypertension. An assignable cause for their hypertension was not apparent. Chemical parameters, including plasma renin activity (radioimmunoassay Angiotensin I), were similar to those observed in adult hypertensive patients of the same community. A difference in response to therapy was noted in adolescents compared to adults which may imply differences in the mechanisms involved at this phase of the disease, as has been reported in patients with labile and early hypertension and spontaneously hypertensive rats.

At least three facets of this adolescent hypertension study deserve implementation and investigation: 1) routine blood pressure measurements in high schools, 2) longitudinal evaluation of the indications for and effects of therapy, and 3) intensive inquiry into the hemodynamic and neurohumoral aspects of hypertension in its early unfolding.

Additional Indexing Words:
Prevalence Incidence Primary hypertension
Secondary hypertension Plasma renin activity

THE TRUE PREVALENCE of hypertension in the adolescent population has not yet been established; a variety of reports suggest rates as disparate as 0.9% to 36.2%.

Recent data indicate that methods of hypertension detection which are satisfactory for adults may be invalid for adolescents and suggest that the criteria selected to define hypertension would be more meaningful if related to the means of the systolic and diastolic blood pressures established for this age group. The incidence of essential hypertension in adolescents is unknown but has been assumed to be low, based upon the results obtained in children.

The present study concerns the diagnostic evaluation of adolescents who were found to have arterial pressures of 140/90 mm Hg or above during a blood pressure screening survey in high schools in the Harlem community. The characteristics of hypertension and the response to treatment in this age group are compared to those of adult patients in the same community.

Methods

Twenty-seven black and Latin students, aged 14–19 years (15 males, 12 females), were admitted to the hypertension clinic of Harlem Hospital Center for diagnostic evaluation. Notarized parental consent and detailed explanations of the diagnostic and therapeutic plan preceded formal entry into the clinic.

A thorough history and physical examination formed the basis of the evaluation. Subsequent laboratory investigations were directed specifically toward uncovering secondary forms of hypertension since these have been reported, particularly up to the age of 14 years, as the foremost etiology of hypertension in youth.

Initial blood pressure measurements were made in both arms in the supine, seated, and standing positions and in the left leg, supine, after 15 minutes rest. Serial observations at weekly intervals were made on the left arm with the subject seated and standing. A standard mercury manometer was used and the first and fifth (disappearance of sound) Korotkoff sounds were taken as the systolic and diastolic pressures, respectively. Adult size cuffs were used to cover approximately two-thirds of the upper arm, meeting the criteria for cuff size in children and adolescents. Height (in inches) and weight (in pounds) were recorded at the outset and serial weights were taken; weight reduction and salt restriction were advised according to the individual weight percentile and the amount of salt reported by the patient in his customary diet as well as the observed sodium excretion.

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Assessment of renal function included repeated urinalyses with microscopy of the sediment, urine cultures, endogenous creatine clearance, and rapid-sequence pyelography. Renal arteriography and renal biopsy were procedures reserved for patients suspected of having renal artery stenosis or those with manifestations of renal disease of unknown etiology. A chest X-ray or cardiac series with barium swallow and a 12-lead electrocardiogram was obtained in each subject. Endocrine, collagen-vascular, and other disorders were evaluated by serum electrolytes, fasting blood sugar, serum cholesterol, T₄, plasma cortisol, latex fixation, LE preparations, antinuclear antibody and hemoglobin electrophoresis. Peripheral plasma renin activity was determined by the radioimmunoassay of Angiotensin I. Blood samples were obtained while the subjects were receiving their customary diets, prior to treatment and at noon following four hours of ambulation. A simultaneous 24 hour urine collection was analyzed for sodium as a correlate to the plasma renin value, to assess the adequacy of the urine collection by concomitant creatinine clearance, and to determine the vanilmandelic acid level.

A period of observation in which six recordings of diastolic blood pressure were observed at 95 mm Hg or greater was required prior to treatment. When weight reduction was occurring in obese subjects the period of observation was extended. The initial treatment sequence paralleled that established for the adult hypertensive clinic population without reference to the pretreatment plasma renin level. Spironolactone 50 mg daily was prescribed, except in two patients who received spironolactone 300 mg/day at the outset, and in one patient in whom the dose was increased to attempt enhanced natriuresis. Alpha-methylldopa, in 250 mg increments, was added if control was not achieved after four weeks. The development of gynecomastia in two young men after eight months of spironolactone therapy (50 mg/day) led to an alternate protocol of propranolol 50 to 120 mg daily, with the addition of hydralazine 100 to 200 mg daily if necessary.

A two-way analysis of variance was performed to test the differences in chemical parameters between patients with low, normal, and high plasma renin activity.

Results

Serial measurements of blood pressure in the 27 students permitted separation into two groups: 1) in ten students, the majority of blood pressure readings were less than 140/90 mm Hg; and 2) in 17 students, the blood pressures were consistently higher than 140/90 mm Hg. Further analysis revealed that patients in group I had blood pressures that varied about the level of one standard deviation above the means observed in a large sample of adolescents. Six females and one male had readings consistently above this level (females: 123/82 mm Hg; males: 132/85 mm Hg). Weight reduction in two of these female students resulted in a blood pressure decline below this level. Three additional males had blood pressures which were invariably below 132/85 mm Hg. Plasma renin activity in relation to urinary sodium excretion was within the range of normal subjects in all students in group I.

In group II, 16 of the 17 students had blood pressures consistently higher than two standard deviations above the means observed in this age group (females: 135/92 mm Hg; males: 145/95 mm Hg). One male patient had solely systolic hypertension. Nine students had normal, four had high, and three had low plasma renin activity (fig. 1). Although aldosterone levels were not measured, serum potassium measurements of 4 mEq/L or more were present in the low renin patients, suggesting that hyperaldosteronism was an unlikely cause of their hypertension.

The proportion of students who had a family history of hypertension or who were overweight was similar in students in group I and group II. Five of group I students and eight of group II students had a family history of hypertension. One student in each category had no knowledge of their family history. Thirteen students were over the 97th percentile of weight for their age (group I: 5, group II: 8) but they were not invariably the same patients as those having a family history of hypertension.

Diagnostic evaluation in both groups revealed no endocrine or collagen-vascular disease. Hemoglobin AA was present in all subjects. Coarctation of the aorta was not found in any of the patients on physical examination or chest X-ray. Rapid sequence pyelography disclosed a minor degree of unilateral dilatation at the ureteropelvic junction in one patient.
and bifid renal pelves in another patient, both males. Calyceal blunting was absent and urinary sediment and cultures were consistently negative. Four patients in group I and two patients in group II failed to have pyelograms performed. None of these patients had high plasma renin activity. Urinalyses, urine cultures, and creatinine clearances were normal in all patients. Normal electrocardiograms were observed in all patients in group I and in 14 of 17 patients in group II. Low voltage of the lateral T waves was noted in three patients (high: 1; normal: 2 renin patients).

Comparative analysis of the blood pressures and chemical parameters of patients in group II (persistent hypertension) was made with respect to the level of plasma renin activity. There was no significant difference in either the systolic (low: 147 ± 15 mm Hg; normal: 149 ± 8 mm Hg; high: 138 ± 5 mm Hg) or diastolic (low: 107 ± 6 mm Hg; normal: 107 ± 11 mm Hg; high: 102 ± 6 mm Hg) blood pressures among the renin subgroups. Serum cholesterol (low: 188 ± 18; normal: 168 ± 20; high: 191 ± 13 mg/100 ml) and blood urea nitrogen (low: 16 ± 2.5; normal: 12 ± 3.8; high: 11 ± 2.0 mg/100 ml) were not significantly different among the renin categories. Although the difference in urinary sodium excretion did not achieve statistical significance, low renin patients excreted less sodium (88 ± 37 mEq/24 hrs) than normal (166 ± 67 mEq/24 hrs) or high (189 ± 141 mEq/24 hrs) renin patients. All patients were continuing their customary sodium diets during the measurement. No such differences were observed in creatinine clearance (low: 98 ± 4; normal: 119 ± 18; high: 118 ± 23 ml/min/m²).

Patients in group I were considered potential candidates for the development of hypertension and serial blood pressure measurements were continued. Group II patients were considered to have primary hypertension. One patient with solely systolic hypertension and one obese patient with an excessive salt habit continue under observation and five patients discontinued clinic visits. Treatment was initiated in the remaining ten patients according to the protocol for adult patients. Five patients were started on spironolactone 50 mg daily (low renin: 1; normal renin: 3; high renin: 1). Whereas each of the normal renin patients responded with a 20 mm Hg decline in diastolic pressure, the low renin patient had only a 5 mm Hg reduction and the high renin patient had a 10 mm Hg reduction in diastolic pressure. Normotension was not achieved in any of these patients on this regimen. When spironolactone was increased to 300 mg in one normal renin patient to attempt increased natriuresis, the diastolic pressure rose 5 mm Hg and did not change on a combination of alpha-methyldopa 500 mg and spironolactone 50 mg daily. When propranolol 40 mg and hydralazine 100 mg/day were substituted, the diastolic pressure fell below 1 standard deviation above the means for this age group.

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**Figure 2**

Adolescent hypertension. Response to treatment in relation to the plasma renin activity is depicted as the change in mm Hg from the control level.
Spironolactone 300 mg daily also failed to alter the blood pressure to the desired level in one low renin patient, and he continued to have unsatisfactory control on a combination of alpha-methylldopa 500 mg and spironolactone 50 mg daily. Although a paradoxical response in both blood pressure and plasma renin activity (0.2 to 1.9 ng/ml/hr) was observed on propranolol 120 mg/day, the addition of hydralazine 200 mg daily effected a 30 mm Hg reduction in pressure. Plasma renin activity returned to pretreatment levels at this point. One additional patient was given spironolactone 300 mg daily as initial treatment. Although a satisfactory decline in pressure was noted, she was equally well controlled with propranolol 80 mg daily.

Because of the incompletely satisfactory response to spironolactone and the concern regarding the development of gynecomastia in two young men as well as the possibility of other unknown adrenal influences in the maturing adolescent, the therapeutic regimen was changed to propranolol (six students) or propranolol and hydralazine (three students) (fig. 2). In each instance the diastolic blood pressure was reduced to or below 1 standard deviation above the means of the appropriate age-sex group. There was no apparent relationship between the level of plasma renin activity and the response to therapy. A younger chronologic age did not favor a response to propranolol alone although the duration of hypertension prior to discovery was unknown. However, five of six patients who required only propranolol had diastolic blood pressures of 105 mm Hg or less whereas the three patients who required the addition of hydralazine were all males with diastolic blood pressures of 110 mm Hg or higher.

**Discussion**

Two groups of patients were recognized in 27 adolescents who were among those identified with blood pressures at or above 140/90 mm Hg during a blood pressure survey of 3537 high school students. In group I, seven of ten adolescents had blood pressures consistently greater than 1 standard deviation above the means established for this age group (females: 123/82, males: 132/85 mm Hg) but rarely achieved the 2 standard deviation level (females: 135/92, males: 145/95 mm Hg). Although diagnostic studies were unremarkable and plasma renin activity in relation to urinary sodium excretion was within the range of normal subjects, the possibility of labile or early hypertension seemed possible and continued sequential observations were maintained.

In group II, 16 adolescents (ten males, six females) had sustained systolic and diastolic hypertension and one male had solely systolic hypertension, consistently higher than 2 standard deviations above the established means. Diagnostic evaluation revealed no substantiated cause. Minor variations in the rapid-sequence pyelograms of two male patients were associated with an otherwise entirely normal renal assessment.

An indication for renal biopsy or renal arteriography was not apparent despite the reported preclusion of a renal basis for hypertension in young people. The true prevalence of renovascular hypertension could not be determined in the Cooperative Study of Renovascular Hypertension because of patient selection. In this study, 30% of the patients were black; however, the relative incidence of renovascular disease in these patients was only 8%. In 295 unselected adult black hypertensive patients previously reported, we were unable to identify any significant renovascular abnormalities despite the employment of selective renal arteriography and differential renin measurements in suspected cases. A spectrum of plasma renin activity was observed in patients in group II with sustained hypertension. Comparative analysis of arterial pressures and chemical parameters revealed no statistically significant differences among the renin subgroups, although a reduced sodium excretion was observed in low renin patients. These adolescent patients, therefore, mirrored the findings in adult hypertensive patients of the same community.

Neither the true prevalence of elevated blood pressures nor the incidence of essential hypertension in adolescence has been established as yet. Blood pressure measurements in a large sample of adolescents indicated that methods of hypertension detection in the adult population may not be applied successfully to the adolescent age group. Furthermore, there is a paucity of information in the literature defining the characteristics of hypertension during the interm between prepuberty and maturity. Phasic shifts have been shown in the blood pressures of normal adolescents so that lability of pressures during this period may not be taken, a priori, to represent labile hypertension.

Two studies restricted to adolescents have relevance to the present findings. Masland and coworkers found that 25 of 1795 patients attending an adolescent clinic had hypertension (140/90 mm Hg). In only seven of these were definable causes present and a renal etiology predominated. The remaining patients were diagnosed as "labile" hypertensives because only an occasional blood pressure elevation was observed. In the Evans County epidemiologic study 50 adolescents were designated hypertensive (140/90 mm Hg). Thirty of these patients were available for follow-up seven years later, and 18 continued to have
hypertension. In this group, two deaths from cerebral hemorrhage and four instances of target organ dysfunction occurred in this short period.16 These studies suggest, in the first instance, a higher incidence of essential hypertension, and in the second study, a higher morbidity from uncontrolled hypertension at this age than has been recognized previously.

The prognostic significance of labile hypertension has been disputed in epidemiologic studies. Based upon large samples of adults, neither Thompson nor Pollack et al.18 concluded that transient blood pressure elevations were a harbinger of later hypertension, whereas Stamler19 and Levy et al.20 considered levels of diastolic pressure of 90 mm Hg and 100 mm Hg, respectively, a potential signal of early hypertension. The reasons for this disparity are unclear; however, the importance of hemodynamic studies of labile and early hypertension seems clear in this regard. Frohlich and his coinvestigators21 showed the presence of a hyperkinetic circulation in patients with labile hypertension, manifested by increases in cardiac index and left ventricular ejection rate. This work confirmed the finding of an elevated cardiac index in patients with labile hypertension reported by Eich et al.22 Only few hemodynamic studies have been reported in the adolescent age group. However, Kuramoto and coworkers23 studied patients under 35 years and found a significantly higher cardiac index in those with labile hypertension than in those with fixed hypertension. The results in six patients aged 14–19 years corresponded to those of the adults.

Measurements of cardiac index were not made in either of our two groups of adolescents. However, the response of group II patients (sustained hypertension) to treatment by beta-adrenergic blockade may signify this function as one possible mechanism since the effectiveness of beta-adrenergic receptor blockade in reducing arterial pressure has been shown to be directly related to the height of the initial cardiac index.24 A relation between pretreatment plasma renin activity and response to beta-adrenergic receptor blockade was not evident since adolescents having low, normal, or high plasma renin activity responded equally well, with a decline in arterial pressure to levels 1 standard deviation or below the means of the systolic and diastolic pressures of normal adolescents.

In contrast to the salutary response to beta-adrenergic receptor blockade, spironolactone therapy was less effective. In this respect, the adolescents differed from adult black patients with long-standing hypertension, 40% of whom achieved satisfactory blood pressure levels with spironolactone. Comparative measurements of plasma volume or total body sodium were not available to assess possible differences. A parallel is suggested, however, in the response to diuretic therapy in young spontaneously hypertensive rats reported by Nagaoka et al.25 Hydrochlorothiazide failed to reduce the blood pressure in these animals. This experimental model of hypertension also exhibits a hyperkinetic circulatory state in the early phase of hypertension with a later transition to increased peripheral resistance and normal cardiac index similar to the results in early human hypertension.26 The necessary addition of a vasodilator drug in a few patients may represent transition to a phase of increased peripheral resistance with the possibility of morphologic vascular changes as one mechanism.27

The data suggest that essential hypertension, at least in the black population, has a higher incidence in adolescence than has been emphasized previously. More extensive studies will be required to determine the relative efficacy of antihypertensive drugs and the relation to the underlying array of hemodynamic and neurohumoral influences.

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