Phaeochromocytoma with nocturnal elevation of blood pressure

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Summary

A 47-year-old woman with phaeochromocytoma showed blood pressure changes characterized by the regular appearance of hypertension at night. The urinary excretion of catecholamines and their metabolites showed augmentation roughly parallel with the elevation of the blood pressure. During normotensive periods, the urinary excretion of catecholamines and their metabolites was elevated. The findings suggested that the pressor effect of catecholamine hypersecretion was compromised to a certain degree and that the regular nocturnal appearances of hypertensive paroxysm conceivably resulted from a spontaneous cyclic augmentation of the catecholamine secretion from the tumour.

Introduction

Phaeochromocytoma is a tumour arising from the chromaffin tissue which secretes catecholamines. The hypertension of this disorder is either paroxysmal or sustained, and has been generally thought to be resulting from either episodic or continuous secretion of catecholamines from the tumour (Crout, Pisano and Sjoerdsma, 1961; Gifford *et al.*, 1964; Sheps *et al.*, 1966). In certain cases, however, increased secretion of them was not accompanied by hypertensive episodes (Sato *et al.*, 1971; Taubman, Pearson and Anton, 1974). In the following communication, a patient with phaeochromocytoma with nightly occurrence of hypertension is described, in whom the relation between hypertension and catecholamine secretion was sought by measurements of urinary catecholamines and their metabolites in timed urine samples and of the blood pressure every two hours for 2 consecutive days before and after the removal of the tumour.

Case report

A 47-year-old housewife was referred to the authors for evaluation of hypertension of about 3

years' duration. Her hypertension was characterized by a marked variation of its level, the blood pressure being high in the morning and almost normal in the afternoon. She had had frequent headache, worse on awakening and in the early morning. She had excessive perspiration and frequent post-prandial epigastric fullness as well. She had been admitted to hospital elsewhere for a gastric ulcer 4 months previously. There was no family history of phaeochromocytoma or related disorders.

The patient was a well developed, well nourished woman, who weighed 62 kg and was 159 cm in height. Her blood pressure on one occasion was 170/120 mmHg in the supine position and 122/80 mmHg in the upright position. A few small haemorrhages as well as moderate degree of arteriolar spasm were observed in the fundi. The skin was warm and moderate perspiration was noted over the anterior chest. The rest of the physical examination was unremarkable.

Urinalysis showed ++ proteinuria and ++ glycosuria. Haemoglobin was 15.7 g/dl and haematocrit was 47.2%. The chest X-ray revealed left ventricular enlargement and an ECG showed left ventricular hypertrophy. Urinary excretion of free catecholamines, free and conjugated (total) metanephrine and normetanephrine (hence, total metanephrines, tMN) and vanilmandelic acid (VMA) for 3 consecutive days were as follows: free adrenaline, 0, 80, 20 µg/day; free noradrenaline, 2325, 2095, 2632 µg/day; tMN, 4600, 5000, 3700 µg/day; VMA, 14.8, 20.0, 14.6 mg/day; phentolamine mesylate elicited hypotensive reaction when injected i.v. in the hypertensive phase. The i.v. injection of glucagon caused a significant elevation of blood pressure during the hypertensive phase but the same dose caused a lesser degree of hypertensive response when given in the normotensive phase (Fig. 1). The abdominal angiography disclosed a vascular mass in the vicinity of the right adrenal gland. The oral cholecystogram failed to visualize the gall bladder but an ultrasonic echogram of it suggested the presence of multiple small grains.

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FIG. 1. Blood pressure response to glucagon in hypertensive and normotensive phases. ●—●, in hypertensive phase. ●---●, in normotensive phase.

Her blood pressure (BP) varied widely as seen in Fig. 2, and had a daily peak from late in the evening until the following morning. She was relatively free from symptoms but she complained of headache and perspiration in the morning. On laparotomy a mass was found in the right adrenal gland, partly situated deep behind the inferior vena cava, which was excised. The removed mass was round and 6 cm in diameter, 38 g in weight. The histology of the tumour was consistent with that of pheochromocytoma. Postoperatively, BP was stabilized at the normal level. The patient, however, was troubled by persisting nausea and vomiting of variable severity, recurrence of the gastric ulcer and at least one episode of acute cholecystitis, which necessitated subtotal gastrectomy with Bilroth II anastomosis and cholecystectomy. She recovered from the second laparotomy and was discharged.

Special studies

Because of the marked variation of BP during 24 hr, the relation between BP and urinary excretion

of catecholamines and their metabolites were studied before and after the removal of the tumour.

Materials and methods

BP was measured in the supine position using a sphygmomanometer every 2 hr for two consecutive days before and after the resection of the pheochromocytoma. On the days when BP was measured every 2 hours, urine was collected every 4 hours in a jar containing hydrochloric acid. The aliquots of 4-hr urine specimens were stored at -20°C until the time of analysis. To make urine collection exactly every 4 hours, the patient was instructed by a nurse to void at the end of each 4-hr period. Urinary free catecholamines (fCA) were measured by trihydroxyindol method using a commercial alumina column according to the manufacturer's instruction the results of which were expressed as μg of noradrenaline. tMN was measured by the method of Pisano (1960) and VMA measured by the method of Pisano Crout and Abraham (1962).

Results

Before the removal of pheochromocytoma there was a marked variation of BP, high in the late evening and until the following morning, which was no longer observed after the resection of the tumour. Urinary excretion of catecholamines and their metabolites was elevated all day pre-operatively and was further augmented nightly; this paralleled with paroxysms of hypertension (Fig. 3). Postoperatively the urinary excretion of catecholamines was reduced to the normal level and no apparent diurnal variation was noted.

Discussion

The hypertension of pheochromocytoma has been considered to be due to the excessive secretion of catecholamines from the tumour. However, the exact relation of hypertension to catecholamine hypersecretion remained to be determined. The urinary excretion of catecholamines (in certain

FIG. 2 Profiles of blood pressure before and after removal of pheochromocytoma. Broken lines indicate midnight.

FIG. 3. Profiles of blood pressure and urinary excretion of catecholamines and their metabolites before and after removal of pheochromocytoma. Shaded areas indicate postoperative results; BP, blood pressure; fCA, free catecholamines; tMN, total metanephrines; VMA, vanilmandelic acid. Broken lines indicate midnight.

cases, metanephrines also) was known to increase following pressor responses to histamine in subjects with pheochromocytoma (Gifford *et al.*, 1964). Nevertheless, Sato *et al.* (1971) found elevated urinary excretion of catecholamines in five patients with surgically proved pheochromocytoma during the pre-operative normotensive periods. Taubman *et al.* (1974) reported a case of pheochromocytoma without hypertension despite numerous measurements of BP, whose diagnosis was confirmed by elevated plasma as well as urinary levels of catecholamines and by surgery. In the present case the augmented urinary excretion of catecholamines during the paroxysms of hypertension could be considered as reflecting augmented secretion of noradrenaline from the tumour although the actual plasma level was not measured. Elevated urinary excretion of catecholamines during the normotensive periods suggests that the patient acquired a certain tolerance to the pressor effect of catecholamines. Reduced blood volume in certain patients with this condition (Sjoerdsma, Engelman and Waldman, 1966; Tarazi, Dustan and Frohlich, 1970) or reduced pressor response to circulating noradrenaline (Torikai, 1969) might be operative in preventing

the development of hypertension of pheochromocytoma to a limited extent. Excessive secretion of catecholamines, however, could not be comprised and the paroxysm of hypertension might ensue.

A variety of physiological changes was reported as being associated with the initiation of the paroxysms of hypertension in subjects with pheochromocytoma (e.g. twisting of the trunk, bending forward, assuming a decubitus position) as cited by Hermann and Mornex (1964). None of these appeared responsible for the paroxysms in the present case because of the regularity of the hypertensive episodes. The nocturnal elevation of BP and supposedly of catecholamine secretion would rather be due to a spontaneous cyclicality of the catecholamine secretion from the tumour.

Finally, the authors stress the importance of frequent measurements of BP, even throughout the night, to detect pheochromocytoma with paroxysmal hypertension.

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References

- CROUT, J.R., PISANO, J.J. & SJOERDSMA, A. (1961) Urinary excretion of catecholamines and their metabolites in pheochromocytoma. *American Heart Journal*, **61**, 375.
- GIFFORD, R.W., KVALE, W.F., MAHER, F.T., ROTH, G.M. & PRIESTLEY, J.M. (1964) Clinical features, diagnosis and treatment of pheochromocytoma: A review of 76 cases. *Proceedings. Mayo Clinic*, **39**, 281.
- HERMANN, H. & MORNEX, R. (1964) *Human Tumours Secreting Catecholamines*. p. 3. Pergamon Press, London.
- PISANO, J.J. (1960) A simple analysis for normetanephrine and metanephrine in urine. *Clinica chimica acta*, **5**, 406.
- PISANO, J.J., CROUT, J.R. & ABRAHAM, D. (1972) Determination of 3-methoxy-4-hydroxymandelic acid in urine. *Clinica chimica acta*, **7**, 285.
- SATO, T., ONO, I., MIURA, Y. & YOSHINAGA, K. (1971) Increased catecholamine excretion during normotensive phase in paroxysmal type of pheochromocytoma. *Japanese Heart Journal*, **12**, 214.
- SHEPS, S.G., TYCE, G.M., FLOCK, E.V. & MAHER, F.T. (1966) Current experience in the diagnosis of pheochromocytoma. *Circulation*, **34**, 473.
- SJOERDSMA, A., ENGELMAN, K. & WALDMAN, T.A. (1966) Pheochromocytoma. *Annals of Internal Medicine*, **65**, 1302.
- TARAZI, R.C., DUSTAN, H.P. & FROHLICH, E.D. (1970) Plasma volume and chronic hypertension. *Archives of Internal Medicine*, **125**, 835.
- TAUBMAN, I., PEARSON, O.H. & ANTON, A.H. (1974) Asymptomatic catecholamine-secreting pheochromocytoma. *American Journal of Medicine*, **57**, 953.
- TORIKAI, T. (1969) [Aspects of hormones and hypertension. *Japanese Journal of Society of Internal Medicine*, **58**, 578 [in Japanese].