Pheochromocytomas Occurring in 3 Members in a Family

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SATO, T., SATO, Y., SAKUMA, H., KOBAYASHI, K., MIURA, Y., YOSHINAGA, K. and WATANABE, H. Pheochromocytomas Occurring in 3 Members in a Family. Tohoku J. exp. Med., 1975, 115 (3), 263-269 — Three members of a kindred exhibiting bilateral adrenal pheochromocytomas are presented together with previously reported 15 familial cases in Japan. The rate of tumor growth, the stage of asymptomatic or chemical pheochromocytoma and the importance of urinary catecholamine assay for detection and diagnosis in this type of tumor are particularly emphasized. —— familial pheochromocytoma; urinary catecholamine assay; hypertension

Familial occurrence of pheochromocytoma has been established recently as a significant phenomenon (Steiner et al. 1968). Up to date, more than 300 cases of pheochromocytoma proved at either surgery or autopsy have been reported in Japan (Yoshinaga 1973). Among them, seven separate families affected with pheochromocytoma have been described (Miura et al. 1968; Sato et al. 1971; Shiraiwa et al. 1971; Ando et al. 1971; Nishio et al. 1972; Kondo et al. 1974; Mori et al. 1974).

It is the purpose of this paper to record an additional family in which 3 members out of 5 siblings had bilateral adrenal pheochromocytomas and to discuss the problems concerning tumor growth, urinary catecholamine excretion at an asymptomatic stage of the disease and usefulness of catecholamine determination for the correct diagnosis.

CASE REPORTS

Case 1. Y.S., a 24-year-old male plasterer, was admitted first to the Tohoku University Hospital in 1961 with chief complaint of sudden loss of vision. Family history was nothing particular, except that his father died of brain hemorrhage at the age of 54. Father was hypertensive and diabetic for years. Five siblings were all well at this time.

The blood pressure was 200/130 and phentolamine (Regitine) test was positive.

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A 24-hr collection of urine revealed abnormally high catecholamine excretion, 165 µg of epinephrine (E) and 3,200 µg of norepinephrine (NE). Normal values of E and NE in our laboratory were 0–10 µg and 10–50 µg/day, respectively. Abdominal exploration revealed a right adrenal tumor, weighing 27 g, and this was extirpated. Histologically, the tumor was a typical benign pheochromocytoma. The left adrenal gland was thought to be normal. Postoperatively, the blood pressure returned to normal and histamine stimulation resulted in no significant rise in blood pressure. However, urinary excretion of catecholamines was slightly high (approximately 140 µg/day in NE). The patient was discharged and had not visited our clinic until April, 1974. This case was reported in part elsewhere by one of the present authors (Sato et al. 1964).

In 1970, at the age of 33 and 9 years after the operation, his youngest sister underwent adrenalectomy in another hospital as mentioned below. He came to that hospital to make an inquiry about sister's sickness. At that time, his urine was sent to our laboratory together with the sister's specimens for the analysis of catecholamine. His urinary catecholamines were proved again to be elevated (156 µg/day), but he refused further examinations.

On April 5, 1974, the patient, at the age of 37, entered the Tohoku University Hospital with a short history of the right hemiparesis and difficulty in speech. Since about 6 months before the onset of the present illness, there had been occasional stiff neck, heat intolerance and sweating despite at the cold season. On admission, the patient weighed 57 kg and was 167 cm tall. The blood pressure was 212/120 with pulse rate of 74. The skin was warm. Retinal examinations revealed hypertensive changes graded KW-I and the thyroid gland contained no palpable tumors. [131I]Thyroid scincigram showed no abnormality. Right hemiparesis with accelerated tendon reflex was found, but he was able to walk. The rest of physical examinations were normal. Blood count, blood urea nitrogen, serum cholesterol and fasting blood sugar were all normal. But an oral glucose tolerance test showed a diabetic pattern. Serum electrolytes including Na, K, Cl, Ca and P were within the normal range. X-ray film of the chest was normal, but electrocardiogram revealed a slight left ventricular hypertrophy. The basal metabolic rate was +8%. Abnormal output of urinary catecholamines and their end metabolite were found (E, 26 µg; NE, 393 µg; VMA, 9.1 mg/day). Upper normal value of VMA was 7.0 mg/day in our laboratory. Intravenous pyelography disclosed normal function and configuration of the kidney and urinary tract. Retroperitoneal gas insufflation and laminography revealed a small suprarenal mass on the left.

The left adrenal area was explored on May 7, 1974 and a benign pheochromocytoma weighing 10 g was extirpated. The tumor contained 0.44 mg of E and 3.55 mg of NE per g of wet tissue. Postoperative course was uneventful and he has returned to his job.

Case 2. M.K., a 26-year-old house wife, the youngest sister of Case 1 and Case 3, was admitted to the Yonezawa City Hospital in March 1970, for evaluation
of her hypertension. Past history revealed hypertensive episodes for the last 3 years. During the first pregnancy in 1968, she had frequent hypertensive crises. She obtained a male baby in mature birth. Thereafter, frequent hypertensive attacks with headache and palpitation continued. In 1970, in the 7th month of the second pregnancy, frequency and severity of the attacks increased gradually. She complained of pulsating headache, excessive sweating, puffy eyes and occasional convulsions. It terminated in premature birth of a healthy male baby at the 9th month. After delivery, the blood pressure was still read at 240/130. Since repeated VMA tests (Sato et al. 1961) gave positive results, the diagnosis of pheochromocytoma was strongly suspected.

Physical examinations of the head, eyes, lips, tongue and neck revealed no abnormality. Skin was normal and no palpable mass was found in the abdomen. The white blood cell count was 10,800. Hemoglobin and hematocrit were 83 and 41%, respectively. Urinalysis showed one plus protein, but no sugar. Serum cholesterol increased to 312 mg/100 ml. Normal blood sugar curve was found after oral glucose tolerance test. Serum electrolytes including Na, K, Cl and Ca, serum total protein and blood urea nitrogen were all within the normal range. The basal metabolic rate was +7%. Chest X-ray film and electrocardiogram were normal. Both Regitine and tyramine tests were positive. A 24-hour urine specimen which had been sent to our laboratory contained 74 μg of E, 1,054 μg of NE and 23 mg of VMA. We reported, therefore, that these values were all diagnostic for pheochromocytoma and recommended to consult a surgeon about transabdominal incision because of possible bilateral occurrence of the tumor, and to take urine specimens from other members of her family because the patient was a member of familial cases. On retroperitoneal pneumography, bilateral suprarenal small masses were found as expected.

On December 23, 1970, bilateral adrenal tumors, weighing 25 g in the right and 20 g in the left adrenal gland, were found and successfully removed. Histological diagnosis was the typical benign pheochromocytoma. E content of the left tumor was 0.37 and NE content 3.21 mg/g of wet tissue. A report of this case was published in 1974 (Sato et al.).

During 4 years since the operation, the blood pressure has remained normal and the patient has been asymptomatic. No tumors in the neck have arisen up to the time of this report.

Case 3. K.H., a 32-year-old house wife, elder sister of Case 2, was admitted to our clinic on May 10, 1974. She was normotensive and complained of only slight headache in the morning. When her sister had adrenalectomy in 1970, relatively high urinary excretion of catecholamine (200 μg/day in average) was already observed in this case. However, she refused further examinations because of no distress and being busy in children care. The patient had had two normal deliveries.

On admission, physical examinations revealed a well developed, well nourished woman in no distress. Ophthalmological examinations of fundi were normal and
the heart was normal. There was no palpable mass in the neck and in the abdomen. The blood pressure was 120/70 and pulse rate was 72/min. Results in blood count, urinalysis, chest X-ray study, electrocardiogram and basal metabolic rate were all within the normal limits. No cold nodules in the thyroid scan were found. Blood chemistry including serum cholesterol, electrolytes, fasting blood sugar and blood urea nitrogen were normal. Analysis of a 24-hour urine revealed abnormal excretion of catecholamines, 14 µg of E and 250 µg of NE. However, VMA was normal (5.0–5.5 mg/day). Retroperitoneal pneumography with tomograms showed a small suprarenal mass on the left. During her hospitalization, the blood pressure elevated to 170/100 in only one occasion. It disappeared spontaneously after several minutes.

On July 26, 1974, she underwent adrenalectomy and a small, well encapsulated, oval tumor, 8.5 g in weight, was found arising from the left adrenal gland. This was extirpated leaving behind more than one third of apparently normal adrenal cortex. The right adrenal gland was enlarged as a whole, and was removed. Histological diagnosis was a benign pheochromocytoma. On chemical assay, E and NE contents in the left tumor were 0.36 and 2.52 mg/g, respectively.

After the operation, urinary excretion of catecholamine returned to normal and the patient was freed from the headache. Replacement therapy of the steroid withdrew 3 months later.

**DISCUSSION**

This is the eighth kindred of familial pheochromocytoma in Japan. The present cases showed several interesting points, as mentioned below.

Case 1 was initially thought to be usual or sporadic type of pheochromocytoma and contralateral adrenal gland was apparently normal at that time. However, questions remained in his slightly high excretion of urinary catecholamines despite normalization of his high blood pressure and negative histamine provocation test (Sato et al. 1964). The patient had had no contact with us and never been determined for his blood pressure until the time of sister’s operation. At this time, 9 years after the surgery, his urinary excretion of catecholamine was still high and the blood pressure was around 170/100. Existence of bilateral pheochromocytomas in his sister strongly suggested that he had probably another tumor in the other side of adrenal gland, but he refused further examinations again because he was asymptomatic. Elapsing another 4 years, total 13 years after the operation, he developed hypertensive cerebrovascular accident and was finally admitted to our clinic. Pheochromocytoma in the contralateral side which had grown to 10 g was found and removed. Discernible symptoms of pheochromocytoma appeared only about 6 months before the final admission.

Case 1 discloses evidence that there is a tumor having such a slow rate of growth. During this 13 years, slightly high excretion of catecholamine into the urine had continued without any characteristic symptoms and he had worked as a plasterer as usual. This stage, therefore, could be considered as “chemical pheo-
<table>
<thead>
<tr>
<th>Family No.</th>
<th>Case No.</th>
<th>Place (year)</th>
<th>Age</th>
<th>Sex</th>
<th>Pheochromocytoma</th>
<th>Medullary thyroid cancer</th>
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<td>I^1</td>
<td>1</td>
<td>Sendai (1968)</td>
<td>37</td>
<td>F</td>
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<td>3</td>
<td>* (1971)</td>
<td>44</td>
<td>F</td>
<td>* ( * )</td>
<td>*</td>
<td>Father died of gastric hemorrhage</td>
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<tr>
<td></td>
<td>4</td>
<td>*</td>
<td>26</td>
<td>F</td>
<td>* ( * )</td>
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<td></td>
<td>15</td>
<td>M</td>
<td>* ( * )</td>
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<td>31</td>
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<td>28</td>
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<td>30</td>
<td>F</td>
<td>* ( * )</td>
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F, female; M, male; ?, not mentioned.
The reference numbers are shown together with the Family No.
chromocytoma.” An additional example was Case 3. Slightly high output of urinary catecholamine had continued for more than 4 years, but she also had been asymptomatic and normotensive. These observations indicate that, for many years, there is an abnormal stage in catecholamine secretion prior to developing symptoms as pheochromocytoma. Normotensive state in these cases, despite relatively high excretion of urinary catecholamine, could be explained by a phenomenon of tachyphylaxis against catecholamine. It has been well known that the blood pressure response to catecholamine decreased spontaneously with time. In any way, detection of such asymptomatic or chemical pheochromocytoma might be difficult, but the urinary catecholamine assay, not VMA alone as in Case 3, would be the most conclusive procedure.

In Case 2, an actual proposita of this familial pheochromocytoma, symptoms aggravated progressively during the course of pregnancy. Since repeated VMA tests (Sato et al. 1961) were positive, pheochromocytoma rather than toxemicia of pregnancy or eclampsia was strongly suspected and bilateral pheochromocytoma consecutively removed. It should be kept in mind that pheochromocytoma with pregnancy is extremely hazardous to both mother and fetus unless the disease is correctly diagnosed and properly treated (Fox et al. 1969). Detection of Case 2 had led us to examine other members of this family to discover additional tumor cases.

Including the present family, 8 families affected with pheochromocytoma have been reported in this country, making a total of 18 cases. Clinical data in these patients are summarized in Table 1. Of these 18 cases, 12 were female and 6 male. Thus, female was affected more than twice as often as male. The age distribution was concentrated between ages of 20 and 30. Pairs of two siblings, sisters or sister and brother, were most frequent. There was one family (Family No. VII) affected in two generations, sisters and son (Mori et al. 1974). Two thirds of these patients had bilateral adrenal pheochromocytomas and more than one fourth had medullary carcinoma of the thyroid gland (Sipple’s syndrome). In the latter group, parathyroid tumor was found in one case (Furukawa et al. 1972).

It should be emphasized that even when a patient with pheochromocytoma seems to be usual or sporadic type, particular important things are taking family history in detail and estimating urinary catecholamine in other family members in order to detect additional tumor cases one after another and to prevent the vascular accident. If familial pheochromocytoma is seen, it should be necessary to search the adrenal tumor bilaterally and the tumor in the neck. Moreover, all members of the family including children should be examined and followed up periodically.

References


Familial Pheochromocytomas