Familial Pheochromocytoma Associated with Von Recklinghausen’s Disease

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We report a 19-year-old woman who presented with headache, vomiting, and elevated blood pressure; pheochromocytoma and von Recklinghausen’s neurofibromatosis were diagnosed. Her mother had the same skin lesions and was also found to have pheochromocytoma. Both patients underwent surgical resection and the postoperative courses were uneventful; the daughter subsequently married and delivered a healthy child. Although both pheochromocytoma and von Recklinghausen’s disease are derived from neuroectoderm and are inherited disorders, concomitant familial occurrence of these two diseases is very rare, only three families have been reported previously worldwide. (Internal Medicine 33: 110-114, 1994)

Key words: neurofibromatosis, hypertension

Introduction

von Recklinghausen’s disease, an inherited disorder derived from neuroectoderm, may rarely be associated with pheochromocytoma. Familial pheochromocytomas are seen in about 5% of patients with pheochromocytoma (1). We experienced a family, in which pheochromocytomas were found in two consecutive generations. In both patients the findings were associated with von Recklinghausen’s neurofibromatosis.

Case Report

Case 1

This patient was a 19-year-old woman who had had café-au-lait spots on the skin since birth (Fig. 1); she first noticed subcutaneous nodules at the age of 15. She was well until 1986 when she was admitted to our institution because of headache, vomiting, and excessive sweating. Her mother and her younger brother also had café-au-lait spots on the skin and subcutaneous nodules. Her family had no history of hypertension. On admission, her blood pressure was 208/110 mmHg, and café-au-lait spots and subcutaneous nodules on the skin were widespread. A fundoscopic examination showed bilateral papilledema. Cardiac examination revealed accentuated first and second sounds in the right second intercostal space. No masses were noted on abdominal palpation. Because of the extremely high blood pressure, papilledema and profuse sweating, we considered a diagnosis of pheochromocytoma. Endocrinological examination revealed a remarkable increase of catecholamine levels: 13,700 pg/ml plasma noradrenaline, 1190 pg/ml plasma adrenaline, 1100 μg/day urine noradrenaline, and 231 μg/day of urine adrenaline. Plasma cortisol, renin, and aldosterone levels were also increased, but slightly. The 75-gram oral glucose tolerance test revealed impaired glucose tolerance. Abdominal computed tomography and ultrasonography of the abdomen demonstrated a mass measuring 5x4x3 cm in size in the left adrenal gland, and the renal arteriography revealed a

Fig. 1. A nevus and café-au-lait spot on the skin of the back (case 1).
hypervascular lesion over the left kidney.

Hypertension was controlled with 6 mg of prazosin (a-blocker), 100 mg of atenolol (β-blocker), and 40 mg of nifedipine (calcium antagonist). The left adrenal mass was resected; it weighed 50 g and measured 5.5×4.5×2.5 cm. The surface of the tumor was dark brown and the cut side was reddish-brown (Fig. 2). Histologically, the tumor was classified as pheochromocytoma with no evidence of malignancy (Fig. 3). The patient’s blood pressure and plasma catecholamine levels were normalized one month after operation (Fig. 4a).

Case 2

This patient, a 44-year-old woman, the mother of case 1, was hospitalized on suspicion of familial pheochromocytoma. Three years prior to admission, she had experienced an episode of headache and vomiting, but she had no history of hypertension. She had had café-au-lait spots and subcutaneous nodules all over the skin since childhood (Fig. 5). Apart from the skin lesions and minimal hypertensive change in the fundi, physical examination showed no significant findings; blood pressure was normal 142/80 mmHg. Laboratory examinations showed increased levels of catecholamines in both plasma and urine, with no other hormonal abnormality. Abdominal computed tomography and echography showed a mass of 7×6×5 cm above the left kidney, whereas 131I adosterol adrenal scintigraphy showed a hot spot in the right, but not in the left, adrenal gland. 131I MIBG (metaiodobenzyl guanidine) scintigraphy showed uptake in the left adrenal gland (Fig. 6). After admission, she experienced headache and nausea on three occasions, associated with episodes of high blood pressure, of up to 180–200/100–120 mmHg; plasma catecholamines during these episodes were higher than when she recovered. A left adrenalectomy was performed; the tumor weighed 200 g and measured 7.0×7.5×5.4 cm (Fig. 7). Histologically, the tumor was classified as pheochromocytoma with no malignancy (Fig. 8). Blood pressure and catecholamine levels were within normal levels three days after the operation (Fig. 4b). Table 1 summarizes the catecholamine levels in the plasma, urine, and tumor in cases 1 and 2. The postoperative courses were uneventful for both patients.

We also examined the younger brother of case 1. His blood pressure was 136/60 mmHg and his plasma and urine catecholamines were within the normal range.

Discussion

Pheochromocytoma is a rare disease which accounts for fewer than 1% of patients with systemic hypertension (2). In 95% of patients, pheochromocytoma is sporadic; in the remaining 5% it is familial (1). Inheritance of familial pheochromocytoma is autosomal dominant with high penetrance (3).

von Recklinghausen’s disease is an inherited disorder characterized by multiple neurofibroma and café-au-lait spots on the skin; the incidence in the general population is one in 3,000 (4). This disorder is also inherited by a dominant trait (5).

von Recklinghausen’s neurofibromatosis is found in about 5% of patients with pheochromocytoma (5). The origin of adrenal medullary chromaffinomas and ganglionic neuroblasts is thought to be a precursor of the sympathogonia, originating from the primitive neuroectoderm or neural crest. von Recklinghausen’s disease is also a disease of neuroectodermal dysplasia. Therefore, a close association between the two diseases, i.e., neurofibromatosis and pheochromocytoma, could be considered, although the incidence of such associations is extremely rare. Attempts have recently been made to analyze the tumorigenesis of hereditary tumors by elucidating the location of abnormal genes. The loss of heterozygosity on chromosomes 1, 11, and 22 has been detected in pheochromocytoma, and the occurrence of multiple endocrine neoplasia type 2 is thought to be related to these chromosomal abnormalities (6–8). However, in type 1 neurofibromatosis, which includes von Recklinghausen’s disease, an abnormality
of 17q11-12, called the NF1 gene, has been detected. This gene has been cloned and is thought to be a tumor suppressor gene (9–11). Xu et al (12) believe that this gene functions as a tumor suppressor gene in the adrenal medulla. They were led to this conclusion by their findings that loss of heterozygosity was seen in 5 of 7 patients who had both pheochromocytoma and von Recklinghausen’s disease. They explained the concomitant occurrence of these two diseases in terms of chromosomal analysis. Differences in the genes causing the conditions may explain why familial pheochromocytoma is often seen in multiple endocrine neoplasia type 2, but is seldom seen with von Recklinghausen’s disease. Unfortunately, chromosomal analysis was not carried out in the present patients. The concomitant occurrence of familial pheochromocytoma and von Recklinghausen’s disease is very rare, only three families having been reported worldwide (13–15). Martin et al (13) reviewed 54 autopsy-proven cases of pheochromocytoma seen

Fig. 4. Clinical course; case 1(a) and case 2(b).

Fig. 5. Subcutaneous nodules in the skin (case 2).
at the Mayo Clinic over the 50-year period from 1928–1987, and reported 2 familial cases of pheochromocytoma and von Recklinghausen’s disease. Svante et al investigated 80 consecutive pheochromocytoma patients operated on from 1956 to 1985 (14), and reported one familial pattern (15). In that case, the mother had both pheochromocytoma and von Recklinghausen’s disease and the daughter had von Recklinghausen’s disease but refused surgery; she was diagnosed with pheochromocytoma only by computed tomography and 131I MIBG scintigraphy. It is important that a meticulous investigation for pheochromocytoma is pursued in patients with von Recklinghausen’s disease and vice versa.

References


Table 1. Laboratory findings

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<th>case 1</th>
<th>case 2</th>
<th>normal range</th>
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<tbody>
<tr>
<td>Plasma adrenaline pg/ml</td>
<td>1,190</td>
<td>1,220</td>
<td>&lt;120</td>
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<td>noradrenaline pg/ml</td>
<td>13,700</td>
<td>807</td>
<td>40–350</td>
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<td>Urine adrenaline µg/day</td>
<td>231</td>
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<tr>
<td>noradrenaline µg/day</td>
<td>1,100</td>
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<td>100–700</td>
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<td>dopamine µg/day</td>
<td>960</td>
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<td>VMA mg/day</td>
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<td>56.4</td>
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<td>Tumor adrenaline µg/g (wet)</td>
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