# Anesthesia and von Hippel-Lindau Disease Associated with Pheochromocytoma

Yuko HOSHINO, Hidefumi OBARA, Katsuya MIKAWA
and Seizo IWAI

(Key words: Hippel-Lindau disease, anesthesia, pheochromocytoma resection)

Von Hippel-Lindau disease is characterized by the association of retinal angiomatosis with cerebellar hemangiomas. But the disease may manifest a variety of distinct lesions, more than 25 of which have been identified. Von Hippel-Lindau disease described here was associated with pheochromocytoma. We report on the rare case of anesthesia and discuss the potential anesthetic problems.

## Case Report

The patient, a 31-year-old male, was admitted for investigation of recurring headaches and shoulder stiffness of several years duration. He also complained of weakness and numbness of the lower extremities which had appeared about three months prior to admission. He had known about his hypertensive condition, but had not sought treatment. The family history was unremarkable. Physical examination revealed hypertension (170/100 mmHg), hypesthesia of the left leg, and paresthesia of an area corresponding roughly to TH8 and TH9. Cranial nerves were intact. Laboratory findings showed polycythemia (Hb:18 g/dl, Ht:55%) and elevated plasma catecholamine levels. Urinary vanillylmandelic acid (VMA) was 47.2 mg/24 hours (normal:13 mg/24 hours) and urinary noradrenaline was 2800 $\mu$g/24 hours (normal:70 $\mu$g/24 hours). The chest roentgenogram and intravenous pyelogram were normal. The electrocardiogram showed complete right bundle branch block. Computed tomography of the head was normal. Computed tomography of the abdomen revealed a mass in the left adrenal gland region. Aortography and selective adrenal angiography showed a 8×7 cm mass in the region of the left adrenal gland and a 2.5×1.5 cm tumor in the region of the right adrenal gland, which was considered compensatory hypertrophy. Fluorescein angiography showed bilateral retinal hemangiomas. Myelography revealed an obstruction corresponding to TH12 and L1. Spinal angiography showed a mass of tortuous vessels. Thyroid function was normal. A diagnosis of pheochromocytoma with von Hippel-Lindau disease was made and pheochromocytoma excision planned. The patient was started on daily oral doses of prazosin (8 mg) and propranolol (30 mg). The night before the operation, propranolol was discontinued.

The patient was premedicated orally with diazepam (10 mg) two hours prior to surgery, and intramuscularly with scopolamine (0.4 mg) and hydroxyzine (100 mg) one hour preoperatively. Two intravenous infusions, a right radial artery line, and a Swan-Ganz catheter via the right internal jugular vein were set in before anesthesia. The electrocardiogram was monitored. At this time BP was 182/104 mmHg, HR 94 bpm, central venous pressure (CVP) was 10 mmHg, and pulmonary artery pressure (PAP) was 12 mmHg. Anesthesia was induced with

*Department of Anesthesiology, Kobe University School of Medicine, Kobe, Japan*

*Address reprint requests to Dr. Hoshino: Department of Anesthesiology, Kobe University School of Medicine, Kusunoki-cho, Chuo-ku, Kobe, 650 Japan*

150 mg of thiamylal and 6 mg of pancuronium intravenously, and enflurane (2%) by mask. Sodium nitroprusside was started at 5 μg/kg/min by intravenous microdrip infusion. After 8 minutes, the BP was 125/80 mmHg. The oral cavity was sprayed with 2% xylocaine and the tracheal cavity with 4% xylocaine. Systolic arterial blood pressure increased to 160 mmHg with each manoeuvre, but returned to 120 mmHg within a few minutes. When the BP fell to 110/70 mmHg, intubation was performed with no blood pressure changes. PAP was 9 mmHg. Anesthesia was maintained with enflurane (1–3% inspired concentration) and nitrous oxide (50–70%) in $O_2$. Sodium nitroprusside was infused up to 1.5 μg/kg/min as required. The patient was preloaded with 2000 ml of plasma and 800 ml of Ringer's lactate solution before removal of the tumor. PAP increased gradually to 16 mmHg, but BP remained stable. During manipulation of the tumor, BP was 115/70 mmHg; removal of the tumor did not decrease arterial blood pressure. Sodium nitroprusside was stopped after tumorectomy. Duration of the surgery was four hours, and no arrhythmias were noted throughout the procedure. Blood loss was estimated at 2120 ml and 1200 ml of blood was transfused. An additional 400 ml of Ringer's lactate solution was required. Perioperative urine output was 1520 ml. Preoperative and postoperative hematocrit values were 55% and 33%, respectively.

When the patient was returned to his room, cardiovascular measurements showed a hyperdynamic pattern, with BP 162/82 mmHg, HR 104 bpm, PAP 12 mmHg, and cardiac output 10 litres/min. Nifedipine (10 mg) was administered sublingually when the systolic arterial blood pressure rose above 160 mmHg. By the 6th post-operative day, the patient's arterial blood pressure had decreased to and remained at 130/80 mmHg without medication. The postoperative period was uneventful.

## Discussion

In 1904 von Hippel established retinal angiomatosis as a distinct clinical entity[1], and in 1926 Lindau first reported on the complex of multiple hemangiomas in the central nervous system (CNS) and viscera[2]. Lindau also noted that 20% of the cases of retinal angiomatosis had associated hemangiomas of the cerebellum or medulla oblongata, and were often associated with cysts of the pancreas, kidney and liver, hypernephroma, and renal cell carcinoma. The combination is now known as von Hippel-Lindau disease, and is defined as a complex of at least one CNS hemangioma and at least one visceral tumor. Von Hippel-Lindau disease is known as an autosomal disorder which is familial. Medullary carcinoma of the thyroid, familial multiple endocrine neoplastic syndromes, carcinoids and neurofibromatosis occur together frequently in this disease. Boland has suggested that these diseases originate from neural crest maldevelopment[3].

Though more than 25 different lesions have been noted in association with von Hippel-Lindau disease[4,5], only 6 of these lesions commonly produce significant consequences[6]: retinal angioma (64%); cerebellar (69%), medullary (11%), and spinal (8%) hemangioblastoma; renal cell carcinoma (22%); and pheochromocytoma. The association of pheochromocytoma and von Hippel-Lindau disease is not common, but 62 cases have been reported to date[7,8]. In more than one-third of the 62 cases, pheochromocytoma occured in both adrenal glands or multiple locations. These tumors may also arise outside the abdomen such as intrathoracically[7], which suggests that they may arise at any place along the sympathetic chain. The first anesthetic problem is to identify the tumors, such as pheochromocytoma, which may develop in many locations and may be multiple. The number and location of the other lesions comprising Lindau disease should be looked for precisely preoperatively.

The second problem is to maintain intracranial pressure (ICP) and renal function as well as arterial blood pressure, since the most common causes of death

are cerebellar hemangioblastoma and renal cell carcinoma[4,6]. In the presence of cerebellar hemangioblastoma, ICP is often chronically elevated[9]. Hematoma, meningitis and hydrocephalus are frequent post-operative complications[4,6,9]. The mortality rate during surgery or in the immediate postoperative phase is about 15%[9]. In the presence of renal cell carcinoma, death results from renal failure, metastatic disease, and uremia[4,6]. The choice of anesthetic is influenced by the above mentioned factors, the patient's condition, and the consideration that the patient may require repeated surgery for recurrent tumors.

In our patient, retinal hemangiomas, spinal hemangioma and pheochromocytoma were found, but no hemangiomas of the cerebellum or medulla oblongata and no kidney disease were found. We used enflurane without incident. Enflurane has been recommended for pheochromocytoma resection, because it does not produce cardiac sensitization to catecholamines[10]; however, it causes a dose-dependent increase in cerebral blood flow, although arterial blood pressure remains stable[11], and causes both an increased production of cerebrospinal fluid (CSF)[12] and an increased resistance to CSF outflow[13]. Furthermore, it may produce renal toxicity in patients with pre-existing kidney disease due to the metabolization of inorganic fluoride[14]. Therefore, if cerebellar hemangioblastoma or kidney disease exist, enflurane should not be used. Recently, isoflurane has been recommended for pheochromocytoma resection[15], but it also has some risk of increasing ICP[16].

The association of polycythemia with CNS hemangioblastomas is the last problem. Polycythemia in this disease is presumably related to erythropoietic activity of the tumor cyst fluid[17], and the incidence is 17%[6]. If analysis of the peripheral blood reveals a hemoglobin level in excess of 18.0 g/dl, the tumor is almost certainly a hemangioblastoma[9]. Our case had also associated with polycythemia, but it occurs in occasional causes with renal cell carcinoma and pheochromocytoma[5].

In summary, von Hippel-Lindau disease may manifest a variety of distinct lesions[4,5]. Preoperative detailed examination and careful anesthetic management are necessary with the attention of the presence of CNS hemangioblastomas, the increased intracranial pressure, renal dysfunction, and polycythemia.

(Received Oct. 27, 1986, accepted for publication May 29, 1987)

## References

1. von Hippel E: Üeber eine sehr seltene Erkrankung der Netzhaut. Arch f Ophth 59:83–106, 1904
2. Lindau A: Cysts in cerebellum: Structure, pathogenesis and relations to angiomatosis of retina. Acta Path Microbiol Scand. supp 1:1–128, 1926 (in German)
3. Bolande RP: The neurocristopathies: A unifying concept of disease arising in neural crest maldevelopment. Hum Pathol 4:409–429, 1974
4. Horton WA, Wong V, Eldridge R: von Hippel-Lindau disease: Clinical and pathological manifestations in nine families with 50 affected members. Arch Intern Med 136:769–777, 1976
5. Melmon KL, Rosen SW: Lindau's disease: Review of the literature and study of a large kindred. Am J Med 36:595–617, 1964
6. Hardwig P, Robertson DM: von Hippel-Lindau disease: A familial, often lethal, multi-system phakomatosis. Ophthalmology 91:263–270, 1984
7. Hoffman RW, Gardner DW, Mitchell FL: Intrathoracic and multiple abdominal pheochromocytomas in von Hippel-Lindau disease. Arch Int Med 142:1962–1964, 1982
8. Lee KR, Wulfsberg E: Neurocutaneous syndromes: Pheochromocytomas associated with von Hippel-Lindau syndrome. J Kans Med Soc 78:120–121, 1977
9. Jeffreys R: Clinical and surgical aspects of posterior fossa hemangioblastoma. J Neurol Neurosurg Psychiatry 38:105–111, 1975
10. Janeczko GF, Ivankovich AD, Glisson SN, Heyman HJ, El-Etr AA, Albrecht RF: Enflurane anesthesia for surgical removal of pheochromocytoma. Anesth Analg 56:62–67, 1977

11. Todd MM, Drummond JC, Shapiro HM: Comparative cerebrovascular and metabolic effects of halothane, enflurane and isoflurane (abstract). Anesthesiology 57:A332, 1982
12. Artru AA, Nugent M, Michenfelder JD: Enflurane causes a prolonged and reversible increase in the rate of CSF production in the dog. Anesthesiology 57:255–260, 1982
13. Artru AA: Effects of enflurane and isoflurane on resistance to reabsorption of cerebrospinal fluid in dogs. Anesthesiology 61:529–533, 1984
14. Mazze RI, Calverley RK, Smith NT: Inorganic fluoride and nephrotoxicity: prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 46:265–271, 1977
15. Suzukawa M, Michaels IAL, Ruzbarsky J, Kopriva CJ, Kitahata LM: Use of isoflurane during resection of pheochromocytoma. Anesth Analg 62:100–103, 1983
16. Grosslight K, Foster R, Colohan AR, Bedford RF: Isoflurane for neuroanesthesia: Risk factors for increases in intracranial pressure. Anesthesiology 63:533–536, 1985
17. Waldmann TA, Levin EH, Baldwin M: The association of polycythemia with a cerebellar hemangioblastoma: The production of an erythropoiesis stimulating factor by the tumor. Am J Med 31:318–324, 1961