Pheochromocytoma and multiple intracranial aneurysms: is it a coincidence?

Case report

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The authors present a case of multiple intracranial aneurysms associated with a pheochromocytoma. The aneurysms were successfully clipped, and a suprarenal tumor located on the left side was totally removed. To the authors’ knowledge this is the fourth reported case of these combined entities in the literature. The authors speculate on the possible etiopathogenesis of the relationship between intracranial aneurysms and attacks of hypertension caused by the presence of neoplasms that discharge acute and irregular levels of catecholamines, especially pheochromocytomas. Perioperative management designed to avoid undesired complications in this rare association is also discussed.

KEY WORDS • pheochromocytoma • intracranial aneurysm

The role systemic hypertension plays in the development of intracranial aneurysms is not debatable. Statistical data and the results of experimental studies indicate an acceleration of aneurysm development in intracranial arteries as a result of hypertension. Additionally, it is well known that there are some hypertensive disorders frequently associated with intracranial aneurysms, such as coarctation of the aorta and polycystic kidney disease. In this article we present a rare case of multiple intracranial aneurysms associated with a pheochromocytoma. The possible role of pheochromocytoma-induced hypertensive attacks in the development of multiple intracranial aneurysms will also be discussed, based on our own case and on three additional cases from the literature.

Case Report

This 48-year-old, right-handed woman was admitted to Hacettepe University Hospital on Friday, January 12, 1996, with the chief complaint of a persistent severe headache with a sudden onset 1 day before admission. The patient had a 10-year history of episodes of flushing, sweating, palpitations, and sudden elevation of blood pressure lasting 10 to 15 minutes. At the time of initial examination, we thought that these symptoms were related to menopause.

Examination. Physical examination of the patient on admission showed a blood pressure of 110/70 mm Hg and a regular pulse rate of 88 beats/minute. Her neurological examination yielded results within normal limits except for neck stiffness. Routine laboratory findings, electrocardiogram, and chest x-ray films proved to be normal. Enhanced and nonenhanced computerized tomography scans of the brain revealed subarachnoid blood in the suprasellar cisterns. A lumbar puncture demonstrated fresh blood in the cerebrospinal fluid at an opening pressure of 150 mm H₂O. Three aneurysms were visualized by means of four-vessel digital subtraction angiography. One aneurysm was located in the anterior communicating artery (ACoA) and two in the middle cerebral arteries (MCAs) both right and left (Fig. 1). Because of the upcoming weekend, the patient was scheduled for surgery on the following Monday. During the first 3 days of hospitalization, her blood pressure varied between 130/90 and 110/70 mm Hg. However, on Sunday night, she suddenly experienced a severe frontal headache, flushing, and sweating. At that time her blood pressure was measured at 230/120 mm Hg; 10 minutes later it returned to normal levels as did the accompanying symptoms. Her family stated that her previous attacks were similar to this one. Therefore, the possible presence of a pheochromocytoma was suspected because of the extreme and temporary nature of the patient’s hypertension. Computerized tomography scanning of the abdomen revealed a large mass in the left adrenal gland, measuring 7 cm in diameter (Fig. 2). The patient’s 24-hour urine vanillylmandelic acid level was 13.6 mg (normal 0–6 mg) and the metanephrine level was 1.09 mg (normal 0.3–0.9 mg). The presumed diagnosis of pheochromocytoma was confirmed by the laboratory findings.
In consultation with colleagues from the departments of endocrinology and anesthesiology, it was determined that a major surgical intervention would place the patient at extremely high risk because of the danger of an acute catecholamine discharge during anesthesia induction and surgical manipulation. Therefore, aneurysm surgery had to be postponed. An extensive preoperative drug regimen was begun immediately, and the patient was given an α-blocker (prazosin hydrochloride, 2 mg twice daily) with a β-blocker (propranolol hydrochloride, 80 mg daily) and she received 3000 ml/day of intravenous fluid (2000 ml 0.09% NaCl and 1000 ml 5% dextrose). Her blood pressure remained stable while this preventive therapy continued for 5 days. Surgical removal of the pheochromocytoma was considered to be life threatening because of the expected blood pressure fluctuation; however, elevated blood pressure can lead to aneurysm rupture, and thus it was decided that the aneurysm surgery should proceed.

Operation. The patient underwent surgery on January 22, 1996. The ACoA aneurysm (which caused the subarachnoid hemorrhage [SAH]) and the right MCA aneurysm were clipped via a right pterional craniotomy. While the patient was still anesthetized, a left pterional craniotomy was performed and the left MCA aneurysm was also clipped. Throughout the surgery, which lasted approximately 5 hours, the patient’s blood pressure remained stable.

Postoperative Course and Second Operation. The patient awakened from the operation with no neurological deficit, and her postoperative course was uneventful. Ten days after the aneurysm surgery, she underwent adrenalectomy for total removal of the pheochromocytoma. Histopathological examination revealed the typical appearance of a pheochromocytoma. Seven days later, the patient was discharged in good condition, receiving no antihypertensive therapy.

Discussion
We would like to emphasize two points in this article:

1) the possible role of hypertension induced by a pheochromocytoma in the development and rupture of multiple intracranial aneurysms; and 2) the importance of the preoperative diagnosis and perioperative management of a patient undergoing major surgery for a ruptured aneurysm in the presence of a pheochromocytoma.

The role systemic hypertension plays in both the formation and rupture of intracranial aneurysms has been discussed extensively in the neurosurgical literature. McCormick and Schmalstieg questioned the association of cerebral aneurysms and systemic hypertension but found no correlation in the 250 patients they studied. Andrews and Spiegel investigated this relationship in 212 cases but found that blood pressures were not elevated to a statistically significant extent in their patients with aneurysms compared with the general population. However, it is well known that intracranial aneurysms are more frequently found in patients with various hypertensive diseases, such as coarctation of the aorta and polycystic kidney disease. It has also been clearly demonstrated in experimental studies that high blood pressure influences the development of intracranial saccular aneurysms.

Sekhar and Heros summarized available histological data on a number of congenital factors implicated in the pathogenesis of saccular aneurysms and suggested that acquired factors, such as degenerative changes, hemodynamic stress, atherosclerosis, and hypertension, may also play a role. Risk factors for the development and rupture of intracranial saccular aneurysms were identified in a case–control study of autopsy subjects by de la Monte, et al. They found a high degree of correlation between systemic hypertension and development of saccular aneurysm (p < 0.001). According to their study, the presence of systemic hypertension and atherosclerosis are two of the major risk factors associated with the development of saccular aneurysms. Most recently, Taylor and colleagues extensively analyzed the risk factors for cerebral aneurysm formation and rupture in 20,767 elderly patients. According to their study, hypertension is an independent risk factor for SAH that is caused by rupture of a previously intact aneurysm.

All of these results strongly suggest that systemic hypertension plays a major role in the development and sub-

**Fig. 1.** Right carotid angiogram delineating three intracranial aneurysms.

**Fig. 2.** Abdominal computerized tomography scan revealing a 7-cm-diameter adrenal mass.
sequent rupture of intracranial aneurysms. By extrapolation, hypertension might also be associated with an increased incidence of multiple aneurysms compared with their occurrence in normotensive patients. Kwak and associates\textsuperscript{14} found hypertension in 45% of patients harboring aneurysms and the incidence of multiple aneurysms in this group was higher than that of single aneurysms. Østergaard and Høeg\textsuperscript{15} stated that the most important factor in explaining multiplicity of intracranial aneurysms is the presence of hypertension. We retrospectively reviewed our own aneurysm series. We found that the incidence of hypertension was 39% in patients with a single aneurysm and 61% in patients with multiple aneurysms. In addition three of the four patients with pheochromocytomas (two from the literature and the one we present here) had multiple aneurysms. Although no definitive conclusions can be drawn about the relationship of multiple intracranial aneurysms to pheochromocytomas based on these cases, we believe that excessive alterations in hemodynamic forces due to hypertensive attacks may be a causative factor in the formation and rupture of these aneurysms. Even though presence of an underlying congenital or acquired defect in the vascular wall cannot be ruled out in this small group of patients, hypertensive attacks should not be overlooked as a potential cause of aneurysm formation.

Pheochromocytomas are rare, endocrinologically active tumors of the adrenal medulla that produce a variety of catecholamines, the sudden release of which may cause hypertensive crises.\textsuperscript{4,9} Common features of hypertension, paroxysmal in 40% of cases, include episodes of palpitaton, sweating, flushing, and anxiety.\textsuperscript{21,22} Clinically, a few patients may be asymptomatic. In a review by Melicow,\textsuperscript{17} only 17 of 100 patients with pheochromocytoma displayed no clinical symptoms suggestive of the disease. Pheochromocytomas account for approximately 0.1% of all cases of hypertension in the general population.\textsuperscript{15}

Although the association of coarctation of the aorta and polycystic kidney disease with intracranial aneurysms is well known, such an association with pheochromocytoma is exceedingly rare. We presume the rarity of this entity is related to the frequency of primary disease in the general population. The incidence of pheochromocytoma is only 0.95 per 100,000 person-years.\textsuperscript{5} We believe that because of this low incidence pheochromocytoma has not come to attention as a causative factor for intracranial aneurysms until now. To date, only three cases have been reported in the English-language literature.\textsuperscript{5,8,13} In 1933 Hick\textsuperscript{13} described a patient with severe SAH from an ACoA aneurysm. She died a few hours after admission. A pheochromocytoma was found during autopsy. Browne and Meyer\textsuperscript{8} reported an interesting case of a 34-year-old man with three intracranial aneurysms and a pheochromocytoma. The patient died as a result of SAH and autopsy revealed a large pheochromocytoma on the right side. The last case, reported by DeSouza, et al.,\textsuperscript{a} was that of a 13-year-old boy who had two intracranial aneurysms. This patient was examined preoperatively because of hypertension, and a right adrenal tumor was demonstrated angiographically and biochemically. Both intracranial and retroperitoneal lesions were treated surgically, and the patient was discharged in good condition. In addition, Hasegawa and colleagues\textsuperscript{13} reported a patient with a catecholamine-secreting malignant schwannoma who also had multiple intracranial aneurysms. Although this patient did not have a pheochromocytoma, the clinical presentation was similar to these three cases mentioned previously. This 51-year-old man had a history of episodic hypertension and elevated levels of catecholamine in serum and in 24-hour urinary excretion. He was surgically treated for thoracolumbar schwannomatosis. Approximately 40 days after the operation, he suffered a severe SAH. Cerebral angiography revealed three intracranial aneurysms. He was surgically treated for the aneurysms but died 6 days after this operation.

Because of the low incidence of pheochromocytoma, a neurosurgeon may never have the opportunity to observe a case of aneurysm associated with pheochromocytoma; however, knowledge of the association is extremely important in handling such a case properly because it is difficult to control intraoperative fluctuations in blood pressure caused by the tumor releasing catecholamines at the onset of anesthetic induction and continuously throughout the procedure. If unsuspected pheochromocytomas that manifest intraoperatively or shortly thereafter are not handled expeditiously, they may cause fatal hypertensive crises. When a pheochromocytoma is suspected, laboratory tests provide a definitive diagnosis. The differential diagnosis includes thyrotoxicosis, drug use, anxiety attacks, and cardiovascular deconditioning.\textsuperscript{22}

In an early series reported by Apgar and Papper,\textsuperscript{2} approximately 50% of patients with pheochromocytoma died during the early postoperative period. Of 54 patients in the Mayo Clinic study found to have a pheochromocytoma at autopsy, the tumor had not been suspected in 41. Of this subgroup 27% died of cardiovascular crises triggered by minor operations for unrelated disease.\textsuperscript{25} Once a pheochromocytoma has been diagnosed in a patient, adequate preparation must be undertaken prior to surgery. Such preparation involves the use of α-blockers (phe-noxybenzamine hydrochloride or prazosin hydrochloride) and also in some patients β-blockers (propranolol hydrochloride) in addition to adequate fluid intake.\textsuperscript{4} As an anesthetic agent, phentolamine or sodium nitroprusside has proved to be extremely useful in controlling the hypertensive crises that may occur during surgery even in patients who have been fully “blocked” by α- and β-blockers.

Conclusions

Our suggestion is that patients harboring intracranial aneurysms, especially those with multiple aneurysms and paroxysmal hypertensive attacks, should be carefully examined for the possible presence of an irregular catecholamine-secreting entity, specifically pheochromocytoma. If such a linkage is ever suspected, all precautions should be taken to avoid undesirable ends.

References

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