

**Thunderclap headache without hypertension in a patient with pheochromocytoma**

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## Abstract

Pheochromocytoma is a well-known, catecholamine-producing tumor characterized by hypertension, headache, hyperglycemia, hypermetabolism, and hyperhydrosis. About 65% of cases of pheochromocytoma were shown to be associated with hypertension.

A case of pheochromocytoma that presented with thunderclap headache (TCH) and palpitations is reported. The patient never showed hypertension during the course of the disease. Paroxysmal headache and palpitations led to the identification of the underlying condition, and the final diagnosis was confirmed by histopathological examination of a surgical specimen. Pheochromocytoma should be identified as a less common though important cause of TCH.. In addition, due to its lack of utility in identifying this disorder, negative cranial imaging may impede further investigation of extracranial lesions that may be the cause of a patient's headache. According to the International Classification of Headache Disorders (ICHD)-II, headache attributed to pheochromocytoma usually develops concomitantly with an abrupt rise in blood pressure. In our case, however, hypertension was never observed, even when the patient was symptomatic. This is the first report of a case of pheochromocytoma with TCH without hypertension.

**Keywords: Pheochromocytoma, thunderclap headache, hypertension, palpitation**



## **Introduction**

Thunderclap headaches (TCHs) is characterized by a sudden onset of severe head pain that peaks within one minute of onset. Although benign primary TCHs are described in the ICHD-II, TCHs are considered to be symptomatic of subarachnoid hemorrhages, and their importance in diagnosis of acute illness by exclusion is specially mentioned.

In a case with a chief complaint of sudden headaches, we succeeded in detecting the presence of a pheochromocytoma because of the accompanying palpitations. There is a danger of laxness in the differential diagnosis of TCH cases once the possibility of subarachnoid hemorrhage is excluded. We present a case that may affect the long-term prognosis of TCH patients in which the decisive factor in the differential diagnosis of TCH was detected by abdominal imaging rather than head imaging.

## **Case**

The patient was a 33-year-old Japanese woman.

Chief complaint: Sudden intense headaches and palpitations.

Past medical history: The patient had experienced migraines without aura since her early 20s. She had right ovarian cysts resected at 26 years of age and a myomectomy at 32 years of age.

Family history: No family history of headaches, thyroid tumor, or hyperparathyroidism

was present.

Current medical history: On the Xth of X year, while resting after lunch, the patient experienced sudden intense palpitations immediately followed by a severe pulsating headache. Although there was no nausea or vomiting, the patient described it as the "worst headache of my entire life." After continuing for about an hour, the headache gradually disappeared with rest. Because a similar attack occurred on the following day, the patient was seen at the neurosurgery department at her local hospital two days after initial occurrence. A cranial CT scan was performed the same day. Due to the relatively short duration of her headache, negative neurological examination, and negative brain CT scan, the patient was judged to have no abnormalities or need a lumbar puncture. ~~, and received prescriptions for~~ The neurosurgeon prescribed loxoprofen, etizolam, but to little effect.

Ten days after examination, the patient underwent an outpatient migraine examination because of similar, frequent, intense headaches.

Current illness: The patient had a normal blood pressure and heart rate on physical examination. There were no special neurological findings.

Laboratory findings: There were no abnormalities on standard blood and urine tests; thyroid functions were also normal. iPTH levels were 43 pg/ml, blood noradrenaline levels were 1340 pg/ml, adrenaline levels were 61 pg/ml, and dopamine levels were 21 pg/ml. Because noradrenaline levels were significantly elevated, abdominal ultrasonography was performed. A well-defined, roughly spherical tumor, with a diameter of 3.6 cm and partial cystic degeneration, located within the left adrenal gland was found. With these findings, the patient was strongly suspected of having

pheochromocytoma and was hospitalized for detailed examinations in the metabolic internal medicine department. Urinary normetanephrine and metanephrine levels were significantly elevated (2593  $\mu\text{g/ml}$ ). On MIBG scintigraphy, an area of high uptake corresponding to the left adrenal gland was detected (Figure 1). ~~There were no abnormalities on cranial MRI.~~ Cranial MRI was done on the 7<sup>th</sup> day of her admission, two days after the most recent headache attack.

Clinical progression: The patient's blood pressure was within the normal range for the duration of this study, including during both headache occurrence and non-occurrence. There were seven headache ~~occurrences~~ during hospitalization of eighteen days. The average blood pressure for this time period was 112.6/66.0 mmHg; no evidence of hypertension was observed. The average heart rate during headache occurrence was 88.0 bpm; however, the patient reported experiencing palpitations three times. We administered prazosin hydrochloride and nifedipine to restore her circulating blood volume. A laparoscopic adrenalectomy was performed two months later, and a macroscopically well-defined, solid tumor, measuring 3x3x2.7 cm, was found in the left adrenal gland.

Histopathology: The tumor consisted of solid and fascicular proliferation of polygonal and rhombic cells. The tumor cells had hyperchromatic round nuclei with a rough chromatin pattern and basophilic cytoplasm. On immunohistochemical analyses, the tumor cells were positive for CD56, chromogranin A, and synaptophysin. From

these results, the tumor was diagnosed as a pheochromocytoma.

Discussion: Thunderclap headaches (TCHs) occur suddenly, with pain intensity peaking in under one minute and continuing from one hour to 10 days. The most dangerous condition associated with headaches meeting these criteria is subarachnoid hemorrhage; however, numerous other diseases involving the vasculature of the central nervous system such as ischemic stroke[1], cerebral venous thrombosis, cervical artery dissection, acute hypertensive crisis, retroclival hematoma, pituitary apoplexy and non-vascular structure of the central nervous system such as spontaneous intracranial hypotension, third ventricle colloid cyst, and intracranial infection[2] are found on the list of diseases that should be excluded in the differential diagnosis. Therefore, TCH is a particularly important symptom in differential diagnosis by cranial imaging. However, it is extremely important to bear in mind that many other diseases associated with TCHs, such as pheochromocytoma [3-6] and, myocardial infarction, cannot be detected with cranial imaging and may have serious outcomes.

Characteristic symptoms accompanying headaches in cases of pheochromocytoma include perspiration, palpitations, anxiety, and facial pallor; headaches are known to occur simultaneously with sudden blood pressure elevation [7].

Other than the present patients, all reported cases of pheochromocytoma with accompanying TCHs have included high blood pressure (Table 1) [3-6]. Although many of the patient's headache occurring while under observation in the hospital were accompanied by palpitations, blood pressure was within normal range during the headaches. Observation of normal or low blood pressure in pheochromocytoma cases is not particularly rare [8], and it is known that catecholamine levels in the circulating blood are not well correlated with blood pressure. There are other cases in which hypertension was not observed, despite confirmation of urinary catecholamine metabolite elevation [9]. Possible reasons for the observation of normal blood pressure in cases with pheochromocytoma (which is a catecholamine-producing tumor) include: 1) reduced circulating plasma volume due to continuous vasoconstriction; 2) individual differences in the catecholamine metabolic rate and related reactions, and 3) the effects of strong vasodilating agents (such as calcitonin gene-related peptides, adrenomedulin,) [10] produced by the tumor [9].

This case study suggests that pheochromocytoma should be included in the differential diagnosis of TCHs with accompanied by palpitations, even when the blood pressure is normal. We would also like to propose that headache occurring concurrently with

sudden blood pressure elevation may be inadequate as diagnostic criteria for headaches caused by pheochromocytoma.

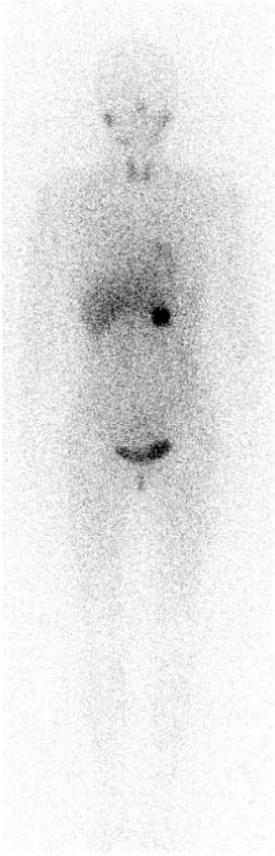
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**Fig. 1** An area of high uptake conforming to the left adrenal gland is seen

**Table 1** Previously reported cases of TCH with pheochromocytoma

Author, year	Age (years)	Sex	Headache	Associated symptoms	Hypertension
Sanyal K, et al. 2009	45	male	sudden, short, excruciating	pulsating sensation in abdomen and chest	+
Heo Y-E, et al. 2008	45	female	explosive, pulsatile, worst of her life	none	+
Im S-H, et al. 2007	37	male	sudden, pulsating, worst of his life	sweating, conjunctival injection, restlessness	+
This case	33	female	sudden, pulsatile, worst of her life	palpitations	-