

Headache in Pheochromocytoma

Masahiko Watanabe
*Department of Neurology,
University of Tsukuba
Japan*

1. Introduction

Two motives have combined to make me write a paper on headache in patients with pheochromocytoma. First, I would like to contribute to the clinical practices of both endocrinological clinicians who are working with patients with pheochromocytoma and neurologists who are performing headache consultations by elucidating the clinical characteristics of headache in patients with pheochromocytoma. Second, I will discuss the stereotypy of current diagnostic criteria provided by "The international classification of headache disorders," 2nd edition (ICHDII)(1) by reviewing the literature concerning the mechanism of headache attributed to pheochromocytoma.

Pheochromocytoma is a rare tumor arising from the chromaffin tissue. Although it is well-known to produce catecholamine, the tumor is frequently disclosed incidentally by autopsy or adrenal imaging.(2)-(3) The representative clinical features are characterized by the pentad of symptoms known as the "5Hs", that is headache, hypertension, hyperglycemia, hypermetabolism, and hyperhydrosis. Among these symptoms, which are attributed to the overproduction of catecholamine by the tumor, headache is important for four reasons. First, it is one of the most frequent symptoms.(4)(5)(6)(7) Second, it is frequently the presenting symptom.(8) Third, it may be the only symptom.(9)(10) Fourth, it may be the presenting symptom of a life-threatening disease with a histopathologically confirmed tumor.(11)(7)

2. Clinical characteristics of headache attributed to pheochromocytoma

Paroxysmal headache occurs in 51-80% of patients with pheochromocytoma. The most characteristic feature of the headache is its rapid onset. It nearly always seems to reach its peak within minutes, sometimes within one minute (thunderclap headache).(10)(12-14) It usually occurs spontaneously, but recurrent severe headaches may occur after voiding in patients with bladder pheochromocytoma.(13, 15)

An important feature of the paroxysmal headache is its short duration. In 50% of patients it lasts for less than 15 minutes, and in 70% its duration is less than one hour.(4) However, in patients with migraine, it may last longer.(8)

The headache was nearly always bilateral, (8) affecting any part of the head. The occipital, nuchal-occipital, and frontal-occipital regions are the predominant locations.(4) The headache is generally described as throbbing, pulsating, or bursting in quality, and is

moderately to very severe in intensity.(8) As in the other patients with pheochromocytoma, headaches are frequently associated with palpitation and perspiration. Other features include apprehension and/or anxiety, often with a sense of impending death, tremor, visual disturbances, abdominal or chest pain, nausea, vomiting, and occasionally paraesthesia. The face can blanch or flush during attack.

The headaches are sometimes worse when lying down and sometimes made worse by moving.(8) Stress maneuvers such as coughing, sneezing, bending, and straining commonly aggravate the pain.(4) Measurement of blood pressure before and after onset of the headache revealed a sudden increase in both systolic and diastolic blood pressure.(8)

3. Diagnosis of headache attributed to pheochromocytoma

Diagnostic cues are usually provided by additional symptoms attributed to sympathetic activation, such as diaphoresis, palpitation, apprehension, and/or anxiety. The diagnosis is established by the demonstration of increased excretion of catecholamines or catecholamine metabolites, and can usually be verified by analysis of a single 24-hour urine sample collected when the patient is hypertensive or symptomatic.

4. Differential diagnosis

The typical case with the full-blown syndrome (5Hs) is not difficult to diagnose, but in some cases of pheochromocytoma, the symptoms are very subtle or absent except for severe headache. The most important point is to include pheochromocytoma in the differential diagnosis of a case with episodic headache. Further, careful history taking with close attention to sympathetic autonomic features will guide physicians to the right path.

Development of radiology enables us to exclude most secondary headache disorders easily, but in all primary headaches and some secondary headaches, brain imaging studies reveal no changes. In the case of pheochromocytoma, normal brain imaging is not the end but the starting point for the differential diagnosis.

4.1 Cluster headache and other trigeminal autonomic cephalgia

Among the primary headaches, cluster headache is most similar to pheochromocytoma headache. An episodic pattern of occurrence, sudden onset, rapid evolution, short duration, and severity characterize both headaches. However, cluster headache is strictly unilateral and has parasympathetic autonomic system features, while pheochromocytoma headache is usually bilateral and has sympathetic autonomic system features. In addition to the difference in autonomic features, its unilaterality is also characteristic of cluster headache. Pain is usually more localized to the orbital area in patients with cluster headache. If these two diseases are confounded, highly critical outcomes may follow. In one reported cases, for example, dihydroergotamine, an agent sometimes used to treat cluster headache, was administered erroneously to a patient with pheochromocytoma, causing a hypertensive crisis and posterior reversible encephalopathy syndrome.(16)

4.2 Migraine

Because migraine is one of the commonest headache disorders, it is always included in the differential diagnosis of headache disorders. Classical migraine with aura will be no diagnostic problem, but a bilateral episodic headache without aura, should be differentiated

from other disorders, including pheochromocytoma. Particularly, if the history of headaches is short and their duration is brief, it will be a diagnostic challenge. Nausea is usually associated with both types of headache. Magnetic resonance imaging of the brain is useless in the differential diagnosis of these two. Careful history taking with particular attention to additional features, including scotoma, photophobia, and sympathetic autonomic symptoms reveals the correct diagnosis.

4.3 Thunderclap headache (TCH)

Thunderclap headache (TCH) is defined as a severe head pain with sudden onset, reaching its maximum intensity in less than 1 minute and lasting from 1 hour to 10 days. Subarachnoid hemorrhage is by far the most common and most dangerous cause of thunderclap headache, but numerous other diseases involving the vasculature of the central nervous system, such as ischemic stroke, cerebral venous thrombosis, cervical arterial dissection, acute hypertensive crisis, retroclival hematoma, pituitary apoplexy, and the non-vascular structures of the central nervous system, such as spontaneous intracranial hypotension, third ventricle colloid cyst, and intracranial infection are found on the list of the diseases to be excluded in the differential diagnosis. Therefore, TCH is a particularly important symptom in differential diagnosis by cranial imaging. However, it is also important to bear in mind that many other diseases associated with TCHs, such as pheochromocytoma(10, 12-14) and myocardial infarction, cannot be detected by cranial imaging and may have serious outcomes.

4.4 Tension-type headache (TTH)

Tension-type headache (TTH) is the most common type of primary headache, and its lifetime prevalence in the general population is estimated to be from 30% to 78%. TTH is subdivided into episodic and chronic subtypes. Episodic TTH is further subdivided into frequent and infrequent subtypes. Frequent episodic TTH may be a candidate for the diagnosis of pheochromocytoma. It is usually bilateral and non-throbbing in nature. The intensity of the headache is mild to moderate, and it is not aggravated by routine physical activity. It lacks nausea, vomiting, arterial hypertension, or other sympathetic autonomic features (palpitation, perspiration, pallor, tremor, or anxiety).

4.5 Headache attributed to arterial hypertension

Mild (140-159/90-99 mmHg) or moderate (160-179/100-109 mmHg) chronic arterial hypertension does not cause headache.(17) Ambulatory blood pressure monitoring in patients with mild to moderate hypertension has shown no convincing relationship between blood pressure fluctuations over a 24-hour period and the presence or absence of headache.(18) However, paroxysmal hypertension may cause headache. "Headache attributed to hypertensive crisis without hypertensive encephalopathy" is defined as a bilateral pulsating headache that may be precipitated by physical activity and associated with a hypertensive crisis. A hypertensive crisis is defined as a paroxysmal rise in systolic (to ≥ 180 mmHg) and/or diastolic (to ≥ 120 mmHg) blood pressure but without clinical features of hypertensive encephalopathy. Further, headache that develops during a hypertensive crisis should resolve within one hour after normalization of blood pressure.(1) The mechanism of this type of headache is not fully understood. Failure of baroreceptor reflexes (after carotid endarterectomy or subsequent to irradiation of the neck) is thought to

be a one of the mechanisms. Although it shows no sympathetic autonomic features, the rest of the characteristics of this headache are quite similar to pheochromocytoma headache. Again, it is important to ask the patient about their present and past history of sympathetic autonomic symptoms (palpitation, perspiration, pallor, tremor, or anxiety) and neck surgery.

4.6 Intracranial pheochromocytoma

Brain metastases of pheochromocytoma are extremely rare, and intracranial lesions are the only sites of metastasis in patients with adrenal pheochromocytoma. Mercuri et al. reported a primary meningeal pheochromocytoma that presented with headache, vomiting, and arterial hypertension.(19) Laboratory studies revealed high plasma catecholamines (norepinephrine and epinephrine). The tumor was resected, and histopathological examination confirmed the diagnosis. Six years follow-up after surgery showed that the patient was neurologically intact with normalized blood pressure and catecholamine values. This case is a very rare exception in which cranial imaging study provided the crucial information to make a diagnosis of headache attributed to pheochromocytoma.

4.7 Spontaneous intracranial hemorrhage due to pheochromocytoma

Park et al. reported an 18-year-old man who presented with a sudden onset of headaches, followed by left hemianopsia.(20) He had experienced palpitations and chest discomfort during physical exertion for two years prior to admission. A brain CT scan showed intracerebral hemorrhage in the left frontoparietal area. Hypertension in the form of paroxysmal attacks led the authors to suspect pheochromocytoma. Evaluation of a 24-h urine specimen showed elevated vanillylmandelic acid and metanephrine levels. Abdominal CT demonstrated a para-aortic mass, and ¹³¹I-metaiodobenzylguanidine (MIBG) scintigraphy showed high uptake in the same area. This case typically showed that cranial imaging is useless to make a correct diagnosis of headache caused by pheochromocytoma.

4.8 Pheochromocytoma crisis induced by glucocorticoids

Pheochromocytoma crisis (PC) is a rare life-threatening endocrineological emergency that may present spontaneously or can be elicited by triggers, including certain medications that trigger the release of catecholamines by tumors. Acute and rapidly progressive hemodynamic disturbances result from the actions of high quantities of catecholamines secreted by the tumor. Hypertensive crisis, cardiac ischemia, cardiogenic shock, and end-organ failure may occur. Some patients show headache concomitant with hypertension. Many drugs can cause adverse reactions in patients with pheochromocytoma, but we also have to keep in mind that a high-dose dexamethasone suppression test (DST) may precipitate PC in cases with incidental adrenal masses.(21)

5. Headache and hypertension

Recording of blood pressure before and after the onset of the headache revealed a sudden increase in both systolic and diastolic blood pressure.(8) Probably because of this single sign, the diagnostic criteria proposed in “The international classification of headache disorders, 2nd edition (ICHD-II)” included concomitant hypertension as a mandatory item for the diagnosis of headache attributed to pheochromocytoma.(1) However, in some patients, very

high blood pressures were observed without concomitant headache.(8) In addition, observation of normal or low blood pressure in pheochromocytoma cases is not particularly rare,(22) and it is known that catecholamine concentrations in circulating blood are not well correlated with blood pressure. There were other cases in which hypertension was not observed despite confirmation of urinary catecholamine metabolite elevation.(23)

6. Mechanism of headache in patients with pheochromocytoma

The mechanism of headache associated with pheochromocytoma is not fully understood. According to the International Classification of Headache Disorders; 2nd Edition (ICHDII), the diagnosis of headache attributed to pheochromocytoma is established by fulfillment of the following two conditions. First, headache develops concomitantly with an abrupt rise in blood pressure. Second, headache resolves or markedly improves within 1 hour of normalization of blood pressure. However, not a small number of patients who were demonstrated to have pheochromocytoma by biochemical or radiological examination and/or histopathological findings of their surgical specimens showed typical headache without hypertension.(14, 23) Therefore, hypertension is not the only factor in headache pathogenesis.(24)

6.1 Catecholamines and headache

The human cerebral circulation is innervated by sympathetic nerves. The sympathetic system contains the transmitters noradrenaline, neuropeptide Y (NPY), and possibly adenosinetriphosphate (ATP) and is a vasoconstrictor pathway.(25) The cranial vessels are also innervated by the trigeminal nerve. This system is marked by the presence of calcitonin gene-related peptide (CGRP), substance P, and neurokinin A. It is a vasodilator pathway(26) via antidromic release upon activation as well as having a primary involvement in sensory function.(27)

It is hardly possible to connect throbbing headache with the direct action of the strong vasopressor, noradrenalin, which usually causes hypertension in patients with pheochromocytoma. Lance et al. studied the relationship between the main subtype of catecholamine produced by the pheochromocytoma and clinical symptoms of patients. They concluded that the presence or absence of headache or quality of the headache did not bear any relationship to the ratio of norepinephrine to epinephrine secreted.(8) Intravenous infusion of norepinephrine into a patient susceptible to migraine at a sufficient concentration to raise the systolic blood pressure 10 to 40 mmHg is not sufficient to produce headache. Wolff et al. administered such infusions on 116 occasions to 35 patients with vascular headaches of the migraine type, with abolition or reduction in intensity of headache in 93 instances. In these cases, the diameter of the temporal artery and the amplitude of its pulse wave were observed to diminish as the headache abated.

6.2 Neuropeptides and headache

It seems quite plausible that strong vasodilator peptides produced by pheochromocytoma, such as adrenomedullin(28) and CGRP(23) can cause episodic vascular headaches characterized by throbbing in patients with pheochromocytoma. The headache-inducing property of CGRP has been studied in one double-blind controlled trial.(29) The headache was pulsating in quality and resolved within 1 hour after ingestion of CGRP. In addition, a

recent study showed that a CGRP antagonist is effective in the acute treatment of migraine.⁽³⁰⁾ To elucidate a possible role of CGRP in the pathological mechanism of pheochromocytoma headache, a trial using a CGRP antagonist in patients with pheochromocytoma headache should be performed.

7. Conclusion

It is very important to understand the characteristics of the headache attributed to pheochromocytoma because it is one of the most frequent symptoms of a disease that is frequently neglected clinically. It is also important to consider during headache consultation because both neurological and radiological examinations of the brain will provide little information for the correct diagnosis.

The mechanism of the headache in patients with pheochromocytoma is not fully understood. In addition to the arterial hypertension, vasodilator peptides produced by the tumor may play important roles.

8. References

- [1] Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia*. 2004;24 Suppl 1:9-160.
- [2] Kopetschke R, Slisko M, Kilisli A, Tuschy U, Wallaschofski H, Fassnacht M, et al. Frequent incidental discovery of pheochromocytoma: Data from a german cohort of 201 pheochromocytoma. *Eur J Endocrinol*. 2009 Aug;161(2):355-61.
- [3] Manger WM. The protean manifestations of pheochromocytoma. *Horm Metab Res*. 2009 Sep;41(9):658-63.
- [4] Thomas JE, Rooke ED, Kvale WF. The neurologist's experience with pheochromocytoma. A review of 100 cases. *JAMA*. 1966 Sep 5;197(10):754-8.
- [5] Loh KC, Shlossberg AH, Abbott EC, Salisbury SR, Tan MH. Pheochromocytoma: A ten-year survey. *QJM*. 1997 Jan;90(1):51-60.
- [6] Mannelli M, Ianni L, Cilotti A, Conti A. Pheochromocytoma in Italy: A multicentric retrospective study. *Eur J Endocrinol*. 1999 Dec;141(6):619-24.
- [7] Manger WM, Gifford RW. Pheochromocytoma. *J Clin Hypertens (Greenwich)*. 2002 Jan-Feb;4(1):62-72.
- [8] Lance JW, Hinterberger H. Symptoms of pheochromocytoma, with particular reference to headache, correlated with catecholamine production. *Arch Neurol*. 1976 Apr;33(4):281-8.
- [9] Udayakumar N, Sivaprakash S, Chandrasekaran M. Headache as the only sign of pheochromocytoma: An analysis. *Indian J Med Sci*. 2007 Nov;61(11):611-3.
- [10] Sanyal K, Fletcher S. Headache as a sign of pheochromocytoma. *Emerg Med J*. 2009 Jan;26(1):71.
- [11] Verrijcken A, Scirot R, Dubois CL. From trivial headache to life-threatening disease. *Int J Cardiol*. 2011 Jan 7;146(1):e7-9.
- [12] Heo YE, Kwon HM, Nam HW. Thunderclap headache as an initial manifestation of pheochromocytoma. *Cephalalgia*. 2009 Mar;29(3):388-90.

- [13] Im SH, Kim NH. Thunderclap headache after micturition in bladder pheochromocytoma. *Headache*. 2008 Jun;48(6):965-7.
- [14] Watanabe M, Takahashi A, Shimano H, Hara H, Sugita S, Nakamagoe K, et al. Thunderclap headache without hypertension in a patient with pheochromocytoma. *J Headache Pain*. 2010 Oct;11(5):441-4.
- [15] Mou JW, Lee KH, Tam YH, Cheung ST, Chan KW, Thakre A. Urinary bladder pheochromocytoma, an extremely rare tumor in children: Case report and review of the literature. *Pediatr Surg Int*. 2008 Apr;24(4):479-80.
- [16] Kelley BJ, Samples S, Kunkel R. PRES following administration of DHE in a patient with unsuspected pheochromocytoma. *Headache*. 2008 Sep;48(8):1237-9.
- [17] Kruszewski P, Bieniaszewski L, Neubauer J, Krupa-Wojciechowska B. Headache in patients with mild to moderate hypertension is generally not associated with simultaneous blood pressure elevation. *J Hypertens*. 2000 Apr;18(4):437-44.
- [18] Gus M, Fuchs FD, Pimentel M, Rosa D, Melo AG, Moreira LB. Behavior of ambulatory blood pressure surrounding episodes of headache in mildly hypertensive patients. *Arch Intern Med*. 2001 Jan 22;161(2):252-5.
- [19] Mercuri S, Gazzeri R, Galarza M, Esposito S, Giordano M. Primary meningeal pheochromocytoma: Case report. *J Neurooncol*. 2005 Jun;73(2):169-72.
- [20] Park SK, Lee JK, Joo SP, Kim TS, Kim JH, Kim SH, et al. Spontaneous intracerebral haemorrhage caused by extra-adrenal pheochromocytoma. *J Clin Neurosci*. 2006 Apr;13(3):388-90.
- [21] Rosas AL, Kasperlik-Zaluska AA, Papierska L, Bass BL, Pacak K, Eisenhofer G. Pheochromocytoma crisis induced by glucocorticoids: A report of four cases and review of the literature. *Eur J Endocrinol*. 2008 Mar;158(3):423-9.
- [22] Bravo EL, Tarazi RC, Gifford RW, Stewart BH. Circulating and urinary catecholamines in pheochromocytoma. diagnostic and pathophysiologic implications. *N Engl J Med*. 1979 Sep 27;301(13):682-6.
- [23] Agarwal A, Gupta S, Mishra AK, Singh N, Mishra SK. Normotensive pheochromocytoma: Institutional experience. *World J Surg*. 2005 Sep;29(9):1185-8.
- [24] Piovesan EJ, Moeller L, Piovesan LM, Werneck LC, de Carvalho JL. Headache in patients with pheochromocytoma. influence of arterial hypertension. *Arq Neuropsiquiatr*. 1998 Jun;56(2):255-7.
- [25] Edvinsson L, Owman C, Sjöberg NO. Autonomic nerves, mast cells, and amine receptors in human brain vessels. A histochemical and pharmacological study. *Brain Res*. 1976 Oct 22;115(3):377-93.
- [26] Hong KW, Yoo SE, Yu SS, Lee JY, Rhim BY. Pharmacological coupling and functional role for CGRP receptors in the vasodilation of rat pial arterioles. *Am J Physiol*. 1996 Jan;270(1 Pt 2):H317-23.
- [27] McCulloch J, Uddman R, Kingman TA, Edvinsson L. Calcitonin gene-related peptide: Functional role in cerebrovascular regulation. *Proc Natl Acad Sci U S A*. 1986 Aug;83(15):5731-5.
- [28] Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, et al. Adrenomedullin: A novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun*. 1993 Apr 30;192(2):553-60.

- [29] Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia*. 2002 Feb;22(1):54-61.
- [30] Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, et al. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. *N Engl J Med*. 2004 Mar 11;350(11):1104-10.