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 cephalalgia

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. 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. 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.

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. 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. However, in some patients, very
high blood pressures were observed without concomitant headache. In addition, observation of normal or low blood pressure in pheochromocytoma cases is not particularly rare, 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.

### 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. Therefore, hypertension is not the only factor in headache pathogenesis.

#### 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. 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 neuropeptide A. It is a vasodilator pathway via antidromic release upon activation as well as having a primary involvement in sensory function.

It is hardly possible to connect throbbing headache with the direct action of the strong vasopressor, noradrenaline, 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. 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 and CGRP 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. 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

The book is divided into six sections. The first three sections focus on the pathophysiology of the disease, showing anatomo- and histopathological aspects, experimental models and signaling pathways and programmed cell death related to pheochromocytoma. The fourth discusses some specific aspects of clinical presentation, with emphasis on clinical manifestations of headache and heart. The fifth section focuses on clinical diagnosis, laboratory and imaging, including differential diagnosis. Finally, the last section discusses the treatment of pheochromocytoma showing clinical cases, a case about undiagnosed pheochromocytoma complicated with multiple organ failure and other cases about catecholamine-secreting hereditary tumors. Thus, this book shows the disease "pheochromocytoma" in a different perspective from the traditional approach. Enjoy your reading.

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