# Cranial Autonomic Symptoms in Patients with Pituitary Adenoma Presenting with Headaches

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**Abstract-** Different types of symptomatic trigeminal autonomic cephalalgias (TACs) have been reported in patients with pituitary adenoma. We investigated the significance of the presence of cranial autonomic symptoms (CAS) in patients with pituitary adenoma presenting with headaches. The records of patients with pituitary adenoma from 1998 to 2004 in our headache clinic were reviewed including headache profile, presence or absence of CAS, and the characteristics of the pituitary adenoma. CAS were ascertained if one or more autonomic symptoms defined for the diagnosis of TACs in the International Classification of Headache Disorders, 2nd edition (ICHD-2) was identified. Thirty-three patients (24F/9M) with pituitary adenoma presenting with headache were recruited for this study: 18 with CAS (55%) and 15 without. Chronic migraine was the most common headache phenotype (n=16, 48%). Three patients were diagnosed as hemicrania continua-like and three, cluster headache-like. In the group with CAS (CAS+), the sides of the tumor were significantly concordant with the sides of headaches (kappa=0.58, $p<0.001$) and those of CAS (kappa=0.67, $p<0.001$). However, this relationship was not demonstrated in those without CAS (CAS-) (kappa=0.07, p=0.61). Compared with the patients in the CAS- group, the patients in the CAS+ group had higher frequencies of macroadenoma (78% vs. 40%, p=0.027) and acromegaly (50% vs. 7%, p=0.009). The presence and absence of CAS in pituitary adenoma-associated headache were associated with different characteristics of the underlying pituitary adenomas including side concordance and incidence of acromegaly and macroadenoma. The pathogeneses for headache might differ between these two groups.

**Key Words:** Acromegaly, Pituitary adenoma, Trigeminal autonomic cephalalgias

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## INTRODUCTION

Headache is a common presentation in patients with pituitary adenomas. The incidence ranges from 33% to 72%[(1)]. In contrast, in a large-scale clinic-based neuroimaging study with CT or MRI of the brain, although the most common neoplasm, pituitary tumor was found in only three out of 1,876 patients (0.16%) with chronic headaches[(2)]. Another study reported that 10% of the normal adult population had asymptomatic pituitary adenoma on MRI scans[(3)]. Although some studies reported improvement of headache after the pituitary tumor

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was removed[1,4,5], in some cases, the causal relationship between headache and pituitary adenoma is not always clear. Therefore, physicians face a clinical dilemma of whether a pituitary tumor revealed by the neuroimaging studies is related to any given patient's headache syndromes. The decision is even more difficult when the pituitary tumor is a microadenoma[6].

A variety of headache phenotypes have been reported to be associated with pituitary adenoma. The most frequently reported headache phenotypes were migraine and different types of trigeminal autonomic cephalalgias (TACs)[4,7,8]. The latter is a newly proposed headache group recognized by the International Classification of Headache Disorders, 2nd edition (ICHD-2) (2004), including cluster headache, paroxysmal hemicrania and short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)[9,10]. However, the exact underlying mechanisms for pituitary adenoma-associated headache are still unknown. Both mechanical and neuro-endocrinal factors have been implicated although the results were conflicting and non-conclusive[1,4,7,11]. A very recent study found that pituitary tumor-associated headache was not related to tumor size or cavernous invasion, rather it was more related to a positive family history of headache[5]. In the ICHD-2[9], headache attributed to hypothalamic or pituitary hyper- or hyposecretion (code 7.4.4) was first defined (Table 1). Of note is that in this proposed diagnostic scheme, only neuro-endocrinal dysfunction is considered to be responsible for the pituitary adenoma-related headache[4,9].

To explore the relationship of headache and pituitary adenoma, we compared the demographics, headache profiles and tumor characteristics between patients with or without cranial autonomic symptoms (CAS). The presence or absence of CAS were stressed because CAS have been considered a requisite for the diagnosis of TACs[9]. We postulated that the underlying mechanisms might differ between those with and without CAS in patients with pituitary adenoma-related headache.

***Table 1.*** *Diagnostic criteria of headache attributed to hypothalamic or pituitary hyper- or hyposecretion (code 7.4.4) in the International Classification of Headache Disorders, 2nd edition (ICHD-2)*

| Headache attributed to hypothalamic or pituitary hyper- or hyposecretion |
|---|
| A. Bilateral, frontotemporal and/or retro-orbital headache fulfilling criteria C and D; |
| B. At least one of the following:<br>1. prolactin, growth hormone (GH) and adreno-corticotropic hormone (ACTH) hypersecretion associated with microadenomas < 10mm in diameter.<br>2. disorder of temperature regulation, abnormal emotional state, altered thirst and appetite and change in level of consciousness associated with hypothalamic tumor; |
| C. Headache develops during endocrine abnormality |
| D. Headache resolves within 3 months after surgical resection or specific and effective medical therapy |

## METHODS

We retrospectively reviewed patients with pituitary adenoma, who visited our headache clinic at Taipei-Veterans General Hospital (VGH) from 1998 to 2004 based on our computer database of headache patients. Our headache clinic has been operating since 1996. A headache registration system was established in 1997. Each patient completed a structured headache intake form when he/she first visited the headache clinic. The headache intake form contained demographic data and headache characteristics including headache pattern, location, frequency, intensity, duration, precipitating factors, accompanying symptoms and all items pertaining to CAS (see the following).

To be included in the study, patients had to show pituitary adenoma on their magnetic resonance imaging (MRI) examinations of the sella performed on 1.5 T units. We analyzed gadolinium-enhanced coronal images with emphasis on the sella, obtained through spin-echo T1-weighted images with TR 700 ms, TE 15 ms, a 192 $\times$256 acquisition matrix, a 20-cm field of view and 3-mm slice thickness. A neuroradiologist (Lirng JF) independently recorded the locations (left, right, middle or bilateral) and the maximum size in diameter of the pituitary adenoma and also determined if there was cavernous sinus invasion based on their MRIs. In order to eliminate any bias, the neuroradiologist was blinded to

clinical pictures of any of the patients in the study. In this study, microadenoma was defined as pituitary adenoma with a maximum diameter ≤ 10 mm and macroadenoma, >10 mm.

One author (Hung CW) reviewed the charts and the intake forms including headache profile, family history, clinical characteristics, endocrinology survey, and treatment modalities. The diagnosis of acromegaly was determined by clinical features and the blood tests. The presence of CAS in this study was defined as the patients reporting having at least one the following signs based on the criteria of TACs proposed by the ICHD-2, including conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, frontal or facial sweating, miosis or ptosis[8]. These signs were considered relevant only when they accompanied headache attacks. The presence of these signs was ascertained if they were recorded in the intake form and also confirmed by the physicians. They were recorded as left side, right side or bilateral.

The surgical pathology was also recorded. At our hospital, immunochemistry staining was routinely used for final diagnoses of pituitary adenomas[12]. For those with pathological diagnoses of plurihormonal adenomas, i.e. tumors capable of producing two or more hormones that differ in chemical composition, immunoreactivity, and biological effects, all hormone combinations in the adenoma were recorded[12].

**Statistical methods**

All statistical analyses were carried out using the SPSS for Windows 11.0. In this study, we divided the patients into 2 groups based on the presence or absence of CAS. For those with CAS, we designated them as the CAS+ group and those without as the CAS- group. We used the $\chi^2$ or Fisher's exact and Student's *t*-tests, as appropriate, to compare the frequency distribution of categorical variables or continuous variables between groups. The sides of pituitary adenomas were determined as right, left or bilateral (note: central location of the tumor was calculated into bilateral location). As for the headaches or CAS, the sides were determined as one-sided (side-locked or predominantly one-sided (>80% over one side)) as left or right or bilateral (equal side-shifting, both sides, central, or generalized). For concordance, both the kappa statistic and agreement (%) were calculated to compare the sides of headache, autonomic signs and pituitary adenoma. The adequacy of the kappa coefficient was evaluated using the following descriptive ranges: a kappa of 0.40 to 0.59 was considered to be moderate, a kappa of 0.60 to 0.79 was considered to be substantial, and a kappa d0.80 was considered to be excellent agreement[13]. All these tests were two-tailed and a $P$ value < 0.05 was considered statistically significant.

## RESULTS

**Study participants**

During the study period, 33 consecutive patients (9 men, 24 women, mean age 41.7±14.8, range 23-76 years) with pituitary adenoma were retrospectively collected from our headache clinic database. They accounted for 0.6% of total headache patients (33/5,162). The mean duration of headache was 8.8±10.0 years. The major reasons for initial MRI examinations were intractable headaches (n=21), amenorrhea or oligomenorrhea (n=5), acromegaly (n=5) and galactorrhea (n=2). Eighteen patients comprised the CAS+ group and had at least one autonomic sign (55%) and the others, designated the CAS- group (n=15) did not have autonomic signs. Of the CAS+ group, the frequencies of different autonomic signs were as follows: lacrimation (n=17, 94%), conjunctival injection (n=2, 11%), eyelid edema (n=5, 28%), ptosis (n=6, 33%), nasal stuffiness (n=3, 17%) or rhinorrhea (n=4, 22%). A high proportion of patients in both groups reported a family history of a headache disorder (41% in CAS+ and 59% in CAS- groups). Neurological and ophthalmologic examinations showed cranial nerve palsy in two patients (CAS+ n=1, CAS- n=1) and visual field defects in four patients (CAS+ n=3; CAS- n=1).

**Headache profile**

Table 2 shows the detailed headache profile and characteristics of the pituitary adenoma in each patient. Except for one patient in the CAS- group, all patients

suffered from very frequent headaches (≥15 days/month). Overall, 14 patients (78%) in the CAS+ group and 10 (67%) in the CAS- group reported daily headaches. Frontotemporal or retro-orbital headache was reported in 7 patients (47%) among CAS- group and 14 patients (78%) among CAS+ group (p=0.064). The headache characteristics did not differ between the two groups of patients including throbbing headaches, exacerbation during physical activities, and accompanied nausea, vomiting, photophobia and phonophobia. A phenotype diagnosis of headache profile was given based on the ICHD-2[9] (Table 2). The most common headache diagnosis in patients without CAS (n=15) was chronic migraine (n=5, 33%). Among patients with CAS (n=18), the most common headache diagnoses were chronic migraine or probable chronic migraine (n=10, 56%), hemicrania continua-like (n=3, 17%, none of them responsive to indomethacin) and cluster headache-like (n=3, 17%). Probable chronic migraine (n=6) was diagnosed because of superimposed medication overuse[9].

**Tumor characteristics: neuro-radiological features, hormonal profile and pathology**

Based on MR imaging measurements, the frequency of macroadenoma among patients with CAS (n=14, 78%) was higher than those without CAS (n=6, 40%) (p=0.027). The frequencies of cavernous sinus invasion did not differ between the patients in these two groups (CAS+ n=4 (22%) vs. CAS- n=2 (13%), p=0.51). Of note, the patients in the CAS+ group had a higher frequency of acromegaly than those in the CAS- group (9/18 (50%) vs. 1/15 (7%), Fisher's exact test, p=0.009).

Based on the surgical pathology results in 19 patients, the most frequent histopathology was plurihormonal adenoma (n=7, 37%) especially in the CAS+ group. Based on the immunochemistry staining, GH-secreting adenoma (somatotroph adenoma) was more common in the CAS+ group than CAS- group with a trend of significance (9/12 (75%) vs. 2/7 (29%), Fisher's exact test, p=0.07). The frequency of prolactin-secreting adenoma did not differ between the two groups (CAS+ 6/12 (50%) vs. CAS- 2/7 (29%), Fisher's exact test, p=0.633).

**The agreement between the sides of pituitary adenoma and those of headache or cranial autonomic signs (CAS)**

Ten patients (56%) in the CAS+ group and 6 patients (40%) in the CAS- group presented with unilateral or predominantly unilateral headaches (Table 3). In this study, those reporting unilateral headaches but equal side-shifting (n=2) were grouped into the bilateral location group for the side concordance analysis. Among patients in the CAS+ group, the sides of headaches (72% agreement, kappa=0.58, p<0.001) and autonomic signs (78% agreement, kappa=0.67, p<0.001) were significantly concordant with tumor locations (Table 3). Only 4 of the 18 patients in the CAS+ group showed side discrepancy. In contrast, among the patients in the CAS- group, the side concordance was very poor between the locations of headaches and those of the tumor (33% agreement, kappa=0.07, p=0.61).

## DISCUSSION

Pituitary adenoma-associated headache is a rare diagnosis among our headache patients. Although many of them presented with frequent and severe migraine headaches, a large proportions of them also showed features of CAS (54%). Our study found that, among patients in the CAS+ group, there was moderate to substantial side concordance between pituitary adenoma and headache and CAS. In addition, compared with those without CAS, patients with CAS had higher frequencies of macroadenoma and acromegaly. However, these findings were not demonstrated in patients without CAS.

The headache syndromes were not fully described in patients with pituitary adenoma until recently[1,4,14] although the association has been considered existent for long. In a review article in 1991, autonomic signs were not mentioned as part of this headache syndrome[14]. In fact, most patients were reported as case reports. Cluster headache[4,7,15-17] and SUNCT[18] were reported previously but hemicrania continua was only reported recently[4]. Nevertheless, CAS were not studied systematically until very recently, when a study reported 50% patients with pituitary adenoma-associated headache had CAS[4]. In

***Table 2.*** *Demographics, headache profile and characteristics of pituitary adenoma of the study patients*

| No. | Age / sex | Locations of headache | VNS | Duration of attacks | Headache frequency | Throbbing | Exacerbation by physical activities |
|---|---|---|---|---|---|---|---|
| **Without cranial autonomic signs (CAS-)** | | | | | | | |
| 1 | 43/M | Vertex | 10 | Cont | Daily | N | N |
| 2 | 23/F | Bil T | 8 | 4-24 hours | Daily | Y | Y |
| 3 | 29/F | Bil T | 7 | Cont | Daily | Y | Y |
| 4 | 70/M | O | 3 | 4hrs | 4 Ds/wk | N | N |
| 5 | 39/F | Whole head | 10 | 1-2 Ds | 4 Ds/wk | N | N |
| 6 | 23/F | Whole head | 4 | Cont | Daily | N | N |
| 7 | 35/F | Vertex | 4 | 4hrs | 5 Ds/wk | N | Y |
| 8 | 23/F | Rt T | 8 | Hrs | 1 Ds/M | Y | N |
| 9 | 43/F | Rt O | 4 | Cont | Daily | Y | N |
| 10 | 60/M | Shift sides | 8 | 1-2 Ds | 4 Ds/wk | N | N |
| 11 | 30/M | Lt retroorbital | 10 | Ds | Daily | N | N |
| 12 | 54/F | Lt FT | 2 | Cont | Daily | N | N |
| 13 | 42/F | Vertex | 10 | Cont | Daily | Y | N |
| 14 | 23/F | Whole head | 7 | Cont | Daily | Y | N |
| 15 | 38/F | Bil T | 8 | Cont | Daily | Y | Y |
| **With cranial autonomic signs (CAS+)** | | | | | | | |
| 16 | 46/F | Bil T | 3 | Cont | Daily | Y | Y |
| 17 | 39/F | Bil T | 10 | Cont | Daily | N | Y |
| 18 | 40/F | Bil TP | 8 | Hrs | Daily | Y | N |
| 19 | 48/F | Whole head | 10 | Cont | Daily | N | Y |
| 20 | 45/F | Whole head | 10 | Cont | Daily | Y | Y |
| 21 | 76/M | Rt retro-orbital | 8 | 30 min-4 hrs | 5 Ds/wk | N | Y |
| 22 | 28/F | Shifting sides | 7 | 1-2 Ds | 5 Ds/wk | Y | N |
| 23 | 39/F | Lt T | 3 | Cont | Daily | Y | N |
| 24 | 38/F | Lt O | 8 | Cont | Daily | N | N |
| 25 | 50/F | Lt T | 7 | Cont | Daily | Y | Y |
| 26 | 32/F | Lt T | 10 | Cont | Daily | Y | N |
| 27 | 25/M | Whole head | 5 | 30 min | 5 Ds/wk | N | N |
| 28 | 75/M | Rt FT | 8 | Cont | Daily | N | Y |
| 29 | 49/F | Bil T | 9 | Cont | Daily | Y | N |
| 30 | 47/M | Rt FT | 4 | Cont | Daily | N | N |
| 31 | 43/F | Rt FT | 8 | 1-2 hours | Daily | N | Y |
| 32 | 61/F | Lt retroorbital | 8 | 1-2 hours | Daily | Y | Y |
| 33 | 20/M | Lt F | 8 | 3 hours | 5 Ds/wk | N | N |

M: male; F: female; Rt: right; Lt: left; Bil: bilateral; T: temporal; O: occipital; F: frontal; P: parietal; VNS: verbal numerical scale (0-10); Cont: continuous. D: day; wk: week; Y: yes; N: no.

***Table 2.*** *Demographics, headache profile and characteristics of pituitary adenoma of the study patients (continue)*

| No. | Nausea or vomiting | Photophobia and phonophobia | Diagnosis of headache phenotypes | Acromegaly | Pathology by immunochemistry staining |
|---|---|---|---|---|---|
| **Without cranial autonomic signs (CAS-)** | | | | | |
| 1 | N | Y | TTH | + | Plurihormonal (GH, PRL, ACTH) |
| 2 | Y | Y | CM | - | |
| 3 | Y | Y | CM | - | |
| 4 | N | N | CTTH | - | Gonadotroph |
| 5 | Y | N | Probable migraine | - | Somatotroph |
| 6 | N | N | CTTH | - | |
| 7 | Y | Y | Probable migraine | - | |
| 8 | Y | Y | Migraine without aura | - | |
| 9 | Y | N | CM | - | |
| 10 | Y | Y | CM | - | TSH |
| 11 | Y | Y | Unclassified | - | Corticotroph |
| 12 | N | N | CTTH | - | Null cell |
| 13 | Y | Y | pCM with pMOH | - | |
| 14 | Y | Y | CM | - | |
| 15 | N | N | Probable migraine | - | |
| **With cranial autonomic signs (CAS+)** | | | | | |
| 16 | Y | N | pCM with pMOH | - | Prolactinoma |
| 17 | Y | Y | pCM with pMOH | - | |
| 18 | N | Y | CM | + | Plurihormonal (GH, PRL) |
| 19 | Y | N | pCM with pMOH | - | |
| 20 | Y | N | pCM with pMOH | - | Plurihormonal (ACTH, PRL, alpha-subunit) |
| 21 | N | Y | Probable migraine | + | Plurihormonal (GH, PRL, ACTH, TSH, FSH, LH, alpha-subunit) |
| 22 | Y | Y | pCM with pMOH | - | |
| 23 | N | N | HC like | + | Plurihormonal (GH, PRL, ACTH) |
| 24 | Y | Y | CM | + | Somatotroph |
| 25 | Y | Y | pCM with pMOH | - | |
| 26 | Y | N | CM | - | |
| 27 | N | Y | Unclassified | + | Somatotroph |
| 28 | Y | N | HC like | - | Gonadotroph |
| 29 | Y | Y | CM | + | Plurihormonal (GH, PRL) |
| 30 | N | N | HC like | + | Plurihormonal (GH, alpha-subunit) |
| 31 | N | Y | Cluster headache | + | Somatotroph |
| 32 | Y | N | Cluster headache | - | |
| 33 | N | N | Cluster headache | + | Somatotroph |

TTH: probable tension-type headache; CM: chronic migraine; CTTH: chronic tension-type headache; HC: hemicrania continua; p: probable; MOH: medication overuse headache; PRL: prolactin; TSH: thyroid stimulation hormone; GH: growth hormone.

***Table 3.*** *The concordance of the sides of headache, cranial autonomic signs and pituitary adenoma in patients with and without CAS*

| | Sides of pituitary adenoma | | | Side concordance analysis | | |
|---|---|---|---|---|---|---|
| | Right | Left | Bilateral or central | Agreement | Kappa | *P* value |
| *CAS+ group* | | | | | | |
| **Sides of headaches** | | | | 72% | 0.58 | < 0.001 |
| Right | 4 | 0 | 0 | | | |
| Left | 1 | 4 | 1 | | | |
| Bilateral, central or side shifting | 1 | 2 | 5 | | | |
| **Sides of cranial autonomic signs** | | | | 78% | 0.67 | < 0.001 |
| Right | 5 | 0 | 1 | | | |
| Left | 0 | 4 | 0 | | | |
| Bilateral | 1 | 2 | 5 | | | |
| *CAS- group* | | | | | | |
| **Sides of headaches** | | | | 33% | 0.07 | 0.61 |
| Right | 1 | 1 | 0 | | | |
| Left | 1 | 2 | 1 | | | |
| Bilateral, central or side shifting | 4 | 3 | 2 | | | |

CAS: cranial autonomic signs.

line with this study, we found autonomic signs were not uncommon (55%) in our patients with lacrimation being the most common. Among our CAS+ group, three patients were diagnosed as cluster headache-like and three, hemicrania continua-like, but none of our patients presented with SUNCT. However, overall, chronic migraine was still the most common headache phenotype, which concurred with a recent report[4]. The reasons that most of our patients had to be diagnosed as migraine but fail to fulfill the criteria of TACs were: longer durations of headache, frequent accompaniment of migrainous features, and the hierarchical diagnostic classification algorithms defined by the ICHD-2. Nevertheless, we are not sure if the presence of CAS in our patients with pituitary adenomas could be considered as an atypical form of TACs[19].

Our study found a significant lateralization concordance between pituitary adenoma and headache and CAS among patients in the CAS+ group. In addition, compared with those without CAS, we also demonstrated higher frequency of macroadenoma in patients with CAS. These findings imply that a structural factor of the pituitary adenomas could be a possible pathogeneses for headache in patients with CAS. Whether the responsible pituitary adenomas influence the surrounding structures, such as pituitary fossa, hypothalamus[4] or cavernous sinus, to induce both headaches and CAS, is an issue which deserves further study.

When compared with the CAS- group, the patients in the CAS+ group had a higher frequency of acromegaly. In fact, headache has been considered as one of the major manifestations of acromegaly even though the related headache characteristics have not been specified. Octreotide, a somatostatin analog, which is used to treat patients with acromegaly[20], was reported to be effective in treatment of acromegaly-associated cluster headache[21]. We do not know whether the acromegaly-related hormones (growth hormone or Insulin-like growth factor-1) were associated with headache among patients with CAS+[22]. The presence of CAS is considered the hallmark for the diagnosis of different TCAs[9,10]. Hypothalamus, the chief source of

somatostatin within the central nervous system[23], has been demonstrated to be responsible for TACs[24-26]. Intriguingly, a recent clinical trial showed subcutaneous octreotide was effective in treatment of cluster headache[27], a major diagnostic entity of TACs. Therefore, hypothalamus has been postulated to link pituitary adenoma and its associated headaches in a recent study[4].

There are several potential limitations to the present study. First, the extrapolation of the data obtained from the headache clinics to those of neurosurgical or endocrinological services may be unwarranted. However, the clinical characteristics of our patients were quite similar to those reported very recently in a neurosurgical unit[4]. Our findings at least represent a subset of the more intractable headache patients with pituitary adenomas. Second, we did not adopt the ICHD-2 criteria for the diagnosis of pituitary adenoma-associated headaches. It is because the newly proposed criteria are not fully examined[4] and, moreover, the causal relationship was not easily ascertained in some of our patients. Third, similar to previous studies[4], patients with pituitary adenoma only accounted for a small portion of patients in the headache clinic. Therefore, studies recruiting a larger sample size of patients are in need to reach more solid conclusions.

## CONCLUSION

The presence and absence of CAS in pituitary adenoma-associated headache were associated with different characteristics of underlying pituitary adenomas including side concordance and percentages of acromegaly and macroadenoma. The role of pituitary adenoma in the pathophysiology of headache characteristics might differ among patients with and without CAS. Unlike previous studies, our study first divided patients into those with and without CAS for analyses, which might better delineate the clinical correlates with pituitary adenomas.

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