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The clinical characteristics of headache in patients with pituitary tumours

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The clinical characteristics of 84 patients with pituitary tumour who had troublesome headache were investigated. The patients presented with chronic (46%) and episodic (30%) migraine, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT; 5%), cluster headache (4%), hemicrania continua (1%) and primary stabbing headache (27%). It was not possible to classify the headache according to International Headache Society diagnostic criteria in six cases (7%). Cavernous sinus invasion was present in the minority of presentations (21%), but was present in two of three patients with cluster headache. SUNCT-like headache was only seen in patients with acromegaly and prolactinoma. Hypophysectomy improved headache in 49% and exacerbated headache in 15% of cases. Somatostatin analogues improved acromegaly-associated headache in 64% of cases, although rebound headache was described in three patients. Dopamine agonists improved headache in 25% and exacerbated headache in 21% of cases. In certain cases, severe exacerbations in headache were observed with dopamine agonists. Headache appears to be a significant problem in pituitary disease and is associated with a range of headache phenotypes. The presenting phenotype is likely to be governed by a combination of factors, including tumour activity, relationship to the cavernous sinus and patient predisposition to headache. A proposed modification of the current classification of pituitary-associated headache is given.

Keywords: pituitary tumour; headache; migraine; cluster headache

Abbreviations: IHS = International Headache Society; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

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Introduction

The clinical presentation of pituitary adenomas is dependent upon both structural and functional properties of the tumour (Adams, 2002). It is unclear whether headache, a common symptom of pituitary disease (Abe *et al.*, 1998), is a structural or functional consequence of pituitary disease. Although dural stretch and cavernous sinus invasion are widely considered the mechanisms of headache in pituitary disease (Forsyth and Posner, 1993), the evidence suggests that this is not the case (Abe *et al.*, 1998; Levy *et al.*, 2004). Headache is a recognized feature of small, non-invasive functional tumours, particularly prolactinomas (Abe *et al.*, 1998; Millan Guerrero and Isais Cardenas, 1999), and pituitary tumour size itself is unrelated to headache (Levy *et al.*, 2004), both of which suggest that tumour activity may be important in some forms of pituitary tumour-associated headache.

The presentation and mechanisms of headache in pituitary disease have not been widely investigated. Abe and colleagues (1998) described the headache characteristics in 19 patients with pituitary tumours, reporting generalized and predominantly bilateral frontal headache (Abe *et al.*, 1998). However, with the advent of a systematic classification of headache (Headache Classification Committee of The International Headache Society, 1988) and its subsequent revision (Headache Classification Committee of The International Headache Society, 2004), the opportunity exists to carefully phenotype the headache seen with pituitary tumours. This effort has the prospect of providing clinical information with which to manage such patients and may provide some insights into the primary headaches that are manifest with pituitary disease. The aim of this study was to describe prospectively the

phenotypic characteristics of pituitary tumour related headache in a large series of patients. Moreover, we sought to correlate the headache presentations with the tumour biology. We have presented the data in preliminary form (Levy *et al.*, 2003*c*), where we note the range of primary headache phenotypes that may be found in this patient group.

Subjects and methods

We studied 84 consecutive patients presenting with pituitary tumour and troublesome headache between February 2001 and August 2003. An interview was conducted by a physician trained in headache, during which a questionnaire was completed that required detailed documentation of headache characteristics and response to treatment. Probing beyond the questionnaire ensured detailed documentation of the clinical phenotype. Ongoing treatment responses were documented for the duration of the study. The information was entered prospectively onto an electronic database (Microsoft Access, 2003).

Headache

Headache characteristics collected were laterality, site, severity and quality of pain, attack duration, frequency and associated symptoms, and timing of headache, as well as triggers and alleviating factors. We recorded response of the headache to surgery, radiotherapy and medical treatment. In each case, an attempt was made to classify the headache in line with the International Headache Society Diagnostic Criteria (Headache Classification Committee of The International Headache Society, 1988), taking account ultimately of the revised second edition (Headache Classification Committee of The International Headache Society, 2004). We were mindful of the introductory remarks in the classification that acknowledge the issue of classification where some trigger activates an underlying primary headache type.

Tumour

Tumour size and the presence or absence of cavernous sinus invasion were also documented, using MRI with coronal and sagittal T1-weighted spin echo with maximum slice thickness of 3 mm before and after gadolinium-base contrast medium. Tumour size was classified according to maximum tumour diameter into the categories of microadenoma ($\leq$10 mm) and macroadenoma (>10 mm). Cavernous sinus invasion was diagnosed on the basis of radiological appearance and treated as present or absent, and the laterality of cavernous sinus invasion was documented using standard radiological criteria (Cottier *et al.*, 2000).

Disability

Headache-related disability was assessed using a migraine disability assessment score (MIDAS) questionnaire (Lipton *et al.*, 2001).

Results

Patient demographics

Of the 84 subjects interviewed, 60 were female (71%) and 24 male (29%). The mean age was 44 $\pm$ 1.4 years (Table 1). The commonest tumour associated with headache was prolactinoma (n = 31; 37%), followed by growth hormone-secreting pituitary tumour (n = 28; 33%), non-functioning adenoma (n = 20; 24%), adrenocorticotrophic hormone-secreting pituitary tumour (n = 4; 5%) and TSHoma (n = 1; 1%). Full details are shown in Table 1.

Tumour characteristics

For the whole group, 55 tumours were macroadenomas (65%) and 29 were microadenomas (35%). Eighteen tumours (21%) were associated with cavernous sinus invasion (Table 1). Macroadenomas were commoner in the non-functioning adenoma (100%) and acromegaly groups (68%), whilst microadenomas were commoner in the Cushing's (100%) and prolactinoma (52%) groups (Table 2).

Headache characteristics

Laterality

Sixty patients (71%) had unilateral headache, which was side-locked in 53 (88%), while it was side-variable in seven (12%; Table 3). Seventeen patients (20%) reported both bilateral

Table 1 Patient demographics and tumour characteristics

Characteristic	Patients *n* (%)
Sex	
Female	60 (71)
Male	24 (29)
Age (mean $\pm$ SD)	44 $\pm$ 1.4
Tumour type	
Prolactinoma	31 (37)
Acromegaly	28 (33)
Non-functioning adenoma	20 (24)
Cushing's disease	4 (5)
TSHoma	1 (1)
Tumour characteristics	
Macroadenoma	55 (65)
Microadenoma	29 (35)
Cavernous sinus invasion	18 (21)

Table 2 Characteristics of each tumour subtype

	Macroadenoma (*n*)	Microadenoma (*n*)	Cavernous sinus invasion (*n*)
Acromegaly (n = 28)	19	9	7
Prolactinoma (n = 31)	15	16	6
NFA (n = 20)	20	0	4
Cushing's (n = 4)	0	4	0
TSHoma (n = 1)	1	0	1
Total (n = 84)	55	29	18

NFA, non-functioning adenoma.

Table 3 Laterality and site of headache

Characteristic	Patients *n* (%)
Laterality	
Strictly unilateral	60 (71)
Side-locked	53 (63)
Side-variable	7 (8)
Bilateral and unilateral	17 (20)
Strictly bilateral	7 (8)
Site	
Orbital/retro-orbital	66 (79)
Frontal	54 (64)
Temple	30 (36)
Parietal	19 (23)
Vertex	26 (31)
Occiput	24 (29)
Nasal	4 (5)
Cheek	4 (5)
Teeth	4 (5)
Jaw	3 (4)
Ear	3 (4)
Neck	4 (5)

and unilateral headache, whilst seven (8%) described exclusively bilateral symptoms. Of the 18 patients with cavernous sinus invasion, 10 (56%) experienced headache ipsilateral to the side of invasion.

Site

The commonest location of headache was the orbital/retro-orbital (79%) and frontal (64%) region. Twenty-nine per cent of patients had headache involving non-trigeminal territory and in 71% the trigeminal territory was exclusively involved (Table 3).

Severity

Ten patients (12%) graded their headache as moderate, 55 (65%) severe, 17 (20%) very severe and two (2%) excruciating. No patients graded their headache mild (Table 4).

Quality

The commonest quality of pain was described as throbbing (63%). Sharp, dull pressure and tightening pain were all noted by some patients (Table 4).

Duration and frequency

The median duration of headache exacerbation was 7 h (range 15 s to 96 h; Table 5). The median attack frequency was 20 per month (range 1–30).

Using the definition of chronic daily headache as 15 headache days or more per month (Welch and Goadsby, 2002), the frequency of chronic daily headache was 53%. Twenty-five patients (30%) used paracetamol (acetaminophen)- or codeine-containing agents on more than 10 occasions per month, and were defined as having medication overuse.

Timing

No recordings of early morning or diurnal headache were made.

Table 4 Severity and quality of headache

Characteristic	Patients *n* (%)
Severity	
Mild	0 (0)
Moderate	10 (12)
Severe	55 (65)
Very severe	17 (20)
Excruciating	2 (2)
Quality	
Throbbing	53 (63)
Sharp	29 (35)
Dull	21 (25)
Pressure	19 (23)
Stabbing	15 (18)
Tightening	13 (15)
Boring	6 (7)
Burning	3 (4)
Aching	3 (4)

Table 5 Duration, frequency and associated features

Characteristic	Patients
Median duration (range)	7 h (15 s to 96 h)
Median attack frequency per month (range)	20 (1–30)
Chronic daily headache: *n* (%)	45 (53)
Analgesia overuse: *n* (%)	25 (30)
Associated symptoms: *n* (%)	
Nausea	49 (58)
Vomiting	18 (21)
Photophobia	60 (71)
Osmophobia	20 (24)
Restlessness	12 (14)
Aggravation with movement	64 (76)
Cranial autonomic symptoms: *n* (%)	
Ptosis	16 (19)
Eyelid oedema	10 (12)
Conjunctival injection	22 (26)
Lacrimation	29 (35)
Nasal blockage	10 (12)
Rhinorrhoea	6 (7)
Facial sweating	6 (7)
Facial flushing	2 (2)

Associated symptoms

The frequency and distribution of associated symptoms are shown in Table 5. The commonest associated symptoms were photophobia (71%) and nausea (58%). During an exacerbation, 64 patients (76%) preferred to lie still during an attack, 12 (14%) felt restless and preferred to move around, whilst eight (10%) had no preference (Table 5).

Forty-two patients (50%) reported one or more cranial autonomic features in association with headache exacerbations (Table 5), the commonest of which were lacrimation (35%) and conjunctival injection (26%).

Triggers

The frequency and distribution of headache triggers are shown in Table 6.

Table 6 Triggers and family headache history

Characteristic	Patients *n* (%)
Triggers	
Stress	54 (64)
Exertion	22 (26)
Hunger	34 (40)
Alcohol	22 (26)
Bright lights	15 (18)
Family history of headache disorder	41 (49)

Alleviating factors

Non-pharmacological alleviating factors included fresh air (1%), the use of a warm bath (2%), caffeine ingestion (1%), sleep (1%) and acupuncture (1%).

Pharmacological alleviating factors that were recorded included the use of serotonin 5-hydroxytriptamine 1B/10 (5-$HT_{1B/10}$) receptor agonists (13%) and non-steroidal anti-inflammatory agents (14%). Three patients (4%) found indomethacin more helpful than other anti-inflammatory agents.

Family history

Forty-one patients (49%) reported a family history of a headache disorder (Table 6).

International Headache Society (IHS) Classification (Headache Classification Committee of The International Headache Society, 2004)

There were broadly two groups of patient diagnoses: those with phenotypes that mapped well onto accepted IHS primary headache diagnoses ($n = 73$) and those that did not ($n = 11$). For the former we used the general principle that a trigger may activate a primary headache, and thus diagnosed the patients.

Of the former group, the commonest diagnosis was chronic migraine ($n = 39$), followed by episodic migraine ($n = 25$). Other headache diagnoses included short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT; $n = 4$), cluster headache ($n = 3$), hemicrania continua ($n = 1$) and isolated primary stabbing headache ($n = 1$). Twenty-two patients (26%) had primary stabbing headache as a second headache diagnosis (Table 7). SUNCT syndrome was only seen in patients with prolactin- and growth hormone-secreting tumours, and primary stabbing headache was also more common in these two groups (87%).

Of the group that did not map well onto an accepted IHS primary headache diagnosis, three patients were compatible with the current criteria (7.4.4) for headache attributed to pituitary disease (Table 8). Of the remaining eight patients, two experienced featureless headache, which did not fit with tension-type headache because the severity interfered with daily activities and the timing of headache was associated with the onset of pituitary disease, but the treatment of the tumour did not absolutely resolve the headache (Criterion D; Table 11). In six patients, it was not possible to classify the headache phenotype in accordance with the IHS criteria (Table 8). These patients had a mixture of migrainous (throbbing, nausea, photophobia, phonophobia) or cranial autonomic symptoms. These patients stood out in our group's experience with the particular mixture of symptoms and may represent a unique headache type seen in association with pituitary tumours. The IHS headache diagnoses within each tumour subtype are shown in Table 9.

Table 7 Headache characteristics (IHS classification)

Characteristic	Patients *n* (%)
Chronic migraine	39 (46)
Episodic migraine	25 (30)
SUNCT	4 (5)
Cluster headache	3 (4)
Hemicrania continua	1 (1)
Primary stabbing headache†	23 (27)
Other‡	1 (13)

†Lone diagnosis in one patient; ‡See Table 8; SUNCT = short-lasting unilateral neuralgiform headache, conjunctival injection and tearing.

Treatment characteristics

Surgery

Fifty-five patients (65%) underwent hypophysectomy, of whom 50 had transphenoidal and five transcranial approaches (Table 10). Twenty-seven patients (49%) reported an improvement in headache following surgery, 20 (36%) experienced no change in symptoms, and eight (15%) reported worsening of headache.

Radiotherapy

Sixteen patients underwent radiotherapy, of whom one experienced an improvement in headache, the remainder reporting no change in symptoms (Table 10). The median time to follow up from radiotherapy was 5 years (range 2–13 years).

Somatostatin analogues

Octreotide

Twelve patients received octreotide 100 μg, of whom seven reported a reduction in headache frequency and severity (Table 10). Of those that experienced improvement in headache, four had treated migraine, two reported an improvement in featureless headache, and one reported a reduction in the frequency and severity of SUNCT-like attacks. After several months of octreotide administration, three patients experienced rebound headache. One patient developed a dependency syndrome, requiring 12 injections per day. Four patients received both octreotide and lanreotide during treatment, three of whom reported a preferential response to octreotide in terms of headache.

Table 8 Patients with potentially secondary headache phenotypes (Headache Classification Committee of The International Headache Society, 2004)

Case	Age/sex	Effect of surgery	Tumour characteristics			Headache characteristics							
			Histology	Size	Cavernous sinus invasion	Site	Quality	Severity	Mvt	Nausea	Photo	Phono	Cranial autonomic
Featureless headache phenotypes													
GS	74/M	Better	NFA	Macro	–	Orbital/retro-orbital	Continuous dull	Moderate	–	–	–	–	–
GW	84/F	Better	NFA	Macro	–	Retro-orbital/vertex	Continuous pressure	Moderate	–	–	–	–	–
PC	65/M	Medical Rx only better	Prolactin	Macro	Right	Strict right	Orbital/parietal/vertex Tight/sharp 2 h stabbing exacerbations	Severe	–	–	–	–	–
NE	31/F	Worse	Prolactin	Macro	–	Frontal	Episodic 3 h dull	Moderate	–	–	–	–	–
MN	37/F	Worse	Acro	Macro	Left	Strict left retro-orbital	Continuous dull ache	Severe	–	–	–	–	–
Headaches with mixed migraine/trigeminal autonomic cephalalgia phenotypes													
LD	29/F	Better	Somato	Macro	Left	Strict left retro-orbital/frontal	Continuous pressure plus stabs	Severe	+	–	+	+	Lacrimation
IT	50/M	Better	Acro	Macro	–	Uni/bilateral temporal/vertex	Ache/boring/dull	Very severe	+	+	+	–	Lacrimation
SB	38/M	Better	Prolactin	Macro	Left	Strict left orbital/retro-orbital	Continuous boring/dull 30–60 exacerbations	Severe	R	–	+	–	Lacrimation, ptosis
PT	52/F	Better	NFA	Macro	–	Bilateral frontal	Continuous dull/throbbing 60 min exacerbations ± visual aura	Severe	R	–	–	–	Lacrimation
CW	51/F	Better	Cushing's	Micro	–	Bilateral generalized	Episodic (4–48 h) pressure	Severe	–	–	–	+	–
BP	73/M	Worse	Prolactin	Macro	Left	Strict left orbital/maxilla/jaw	Continuous sharp plus stabs	Very severe	–	+	+	–	Nasal block, ptosis

Acro = acromegaly; Macro = macroadenoma; Mvt = headache worsened with physical activity; NFA = non-functioning adenoma; phono = phonophobia; photo = photophobia; Prolactin = prolactinoma; R = restless or agitated during exacerbations; Somato = somatomammotroph.

Table 9 International Headache Society (IHS) Classification (Headache Classification Committee of The International Headache Society, 2004) diagnoses for each tumour type

	CM	EM	SUNCT	CH	HC	PSH	Other†
Acromegaly (*n* = 28)	15	6	2	1	0	8	3
Prolactinoma (*n* = 31)	11	13	2	0	1	12	4
NFA (*n* = 20)	11	4	0	2	0	3	3
Cushing's (*n* = 4)	1	2	0	0	0	0	1
TSHoma (*n* = 1)	1	0	0	0	0	0	0
Total (*n* = 84)	39	25	4	3	1	23	11

†Not definable by IHS criteria (see Table 8). CM = chronic migraine; EM = episodic migraine; SUNCT = short-lasting unilateral neuralgiform headache, conjunctival injection and tearing; CH = cluster headache; HC = hemicrania continua; PSH = primary stabbing headache; NFA = non-functioning adenoma.

Table 10 Headache response to pituitary management (number of patients)

	Improvement	Exacerbation	No change
Surgery			
Transphenoidal	23	8	19
Transcranial	4	0	1
Radiotherapy	1	0	15
Somatostatin analogue			
Sandostatin	7	0	5
Octreotide LAR	4	0	2
Lanreotide	1	0	3
Dopamine agonist			
Cabergoline	9	3	11
Bromocriptine	3	6	13
Quinagolide	0	2	0

Octreotide LAR

Six patients received octreotide long acting release (LAR) 20 mg per month, of whom four reported a reduction in headache frequency and severity (Table 10). Two patients reported headache recurrence 1 week prior to the following injection. No patient on octreotide LAR developed tachyphylaxis or a dependency syndrome.

Lanreotide

Four patients received lanreotide 30 mg every 2 weeks. One patient experienced reduction in headache frequency and severity on lanreotide, the remaining three reporting no change in symptoms (Table 10). The single patient who experienced improvement in headache on lanreotide did not experience benefit from octreotide.

Dopamine agonists

Cabergoline

Cabergoline (dose range 0.25–4 mg per week) was prescribed in 23 patients. Nine patients reported a reduction in headache severity and frequency on cabergoline, 11 experienced no change, and three reported an exacerbation in symptoms (Table 10). Of the three patients who reported an exacerbation in symptoms, one experienced a change from episodic to chronic migraine, one underwent a change from episodic migraine to persistent unilateral indomethacin-responsive headache, classified as hemicrania continua, and one experienced a severe and reproducible exacerbation of SUNCT-like syndrome that lasted for 12 h and is reported in detail elsewhere (Levy *et al.*, 2003*b*).

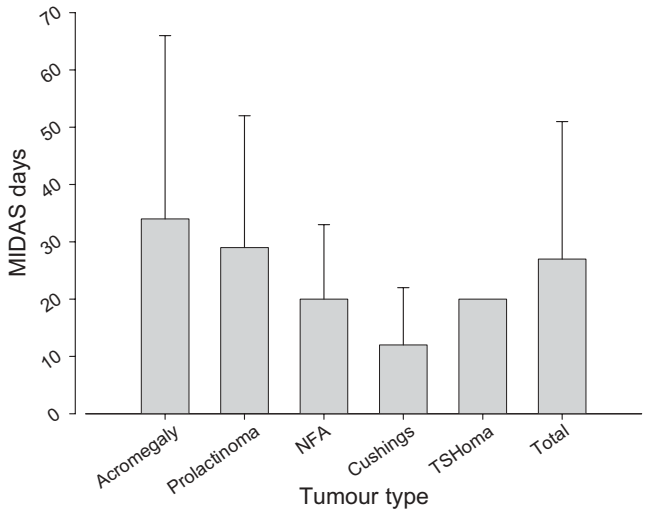

Fig. 1 Distribution of MIDAS scores amongst tumour types with the mean and SD shown for each tumour and for the group as a whole (total).

Bromocriptine

Twenty-two patients received bromocriptine (dose range 2.5–22.5 mg per day). Of these, three patients experienced a reduction in headache frequency and severity, 13 reported no change, and six reported headache exacerbation (Table 10). Of the six patients who reported headache exacerbation, five experienced worsening migraine, and one experienced severe exacerbation of SUNCT lasting 12 h, which is reported in detail elsewhere (Levy *et al.*, 2003*b*).

Quinagolide

Two patients received quinagolide therapy. One experienced worsening migraine whilst the other reported an exacerbation in SUNCT identical to the cabergoline and bromocriptine responses described above (Table 10).

Disability

MIDAS questionnaires were completed in 69 patients. The highest MIDAS scores were seen in the acromegaly and prolactinoma groups (Fig. 1). The mean MIDAS score for the whole group was 27 $\pm$ 24 days. Forty-eight per cent of patients with pituitary tumour-associated headache had severe levels of disability (Fig. 2).

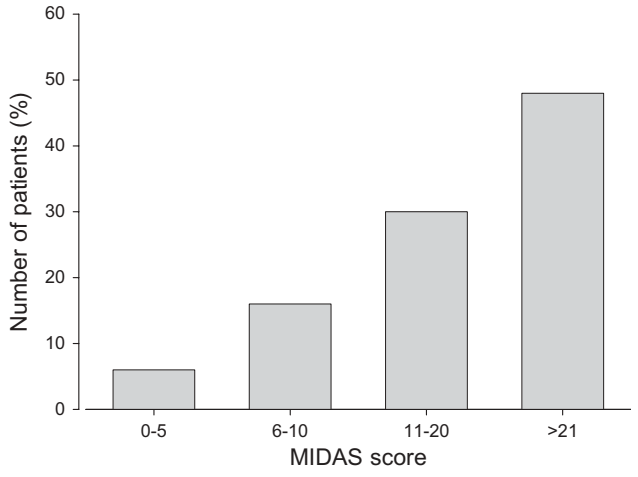

Fig. 2 Distribution of MIDAS scores by conventional grading cut-offs in patients with pituitary tumour and headache. The distribution is right-shifted in comparison with primary headache populations sampled from the population.

Discussion

Headache is a common and disabling aspect of pituitary disease. Our cohort most often reported migraine, but we also saw cluster headache, SUNCT and hemicrania continua. Some patients had unclassifiable headaches which may be new forms of secondary headache specific to pituitary tumours that have not hitherto been recognized. No particular tumour type produced a specific headache syndrome. The observation that 48% of patients had MIDAS scores within the severe range suggests that disability due to pituitary headache is considerable (Lipton *et al.*, 2001). Pituitary tumour-related headache is an important, common issue that requires careful history to facilitate correct diagnosis and thus optimal management.

The improvement in headache following surgery in 49% of cases implies a causal link between the tumour and presence of headache, although it is difficult to control for the confounding variables of the anaesthetic, or indeed natural history. Furthermore, the abolition of headache in 64% of acromegalics who were prescribed somatostatin analogues suggests a link between tumour activity and headache. Octreotide appeared to be more beneficial than lanreotide for headache, although one patient responded preferentially to lanreotide. It is possible that the somatostatin receptor status of the tumour is important in predicting headache response (Levy *et al.*, 2003*a*). Somatostatin analogues are known to interfere with the opioidergic system (Connor *et al.*, 2004), which may partly explain their analgesic action (Otsuka *et al.*, 1998). Alternatively, pharmacokinetic differences may explain the improved efficacy of octreotide because it has a quicker onset of action and is given subcutaneously as opposed to intramuscular lanreotide. Although some patients in our cohort who had migraine headache reported a useful therapeutic effect with octreotide we found in a double-blind placebo controlled trial that it was not useful in acute migraine in patients without pituitary disease (Levy *et al.*, 2005). In contrast, we have recently established that octreotide is useful in the acute treatment of cluster headache (Matharu *et al.*, 2004). In this regard, and mindful of the similar areas of the brain involved in both conditions, the posterior hypothalamus (May *et al.*, 1999; Goadsby, 2002), the fact that some of our SUNCT patients reported utility of octreotide deserves further study. Octreotide dependency has been reported previously (May *et al.*, 1994; Popovic *et al.*, 1988) and we observed this in our cohort as a potential complication in the management of pituitary-related headache.

Dopamine agonists both alleviated and exacerbated headache, which has previously been observed (Ferrari *et al.*, 1988; Massiou *et al.*, 2002; Levy *et al.*, 2003*b*). This paradoxical observation may be related to a complex interplay of the physical effects on the tumour and the central actions of dopamine agonists. The reduction of tumour size in large prolactinomas may improve headache via structural changes, although there is little evidence for the size of the tumour being generally important (Levy *et al.*, 2004). Alternatively, or in addition, the effects of dopamine agonists on the trigeminovascular system may have deleterious effects on headache. Dopamine agonists share properties with ergot alkaloids (Trabucchi *et al.*, 1978), and ergot alkaloids are known to alter the activity of the trigeminovascular system (Hoskin *et al.*, 1996). It has also been suggested that the dopamine–prolactin axis plays an important role in some primary headaches notably migraine (Peroutka, 1997; Peroutka *et al.*, 1997; Peres *et al.*, 2001) and cluster headache (Goadsby, 2002). This may, in part, explain the unpredictable headache responses observed with dopamine agonists. The exacerbation of headache was dramatic in certain cases, an observation that has been previously observed in association with SUNCT (Ferrari *et al.*, 1988; Massiou *et al.*, 2002; Levy *et al.*, 2003*b*).

In addition to tumour-related factors, the type of headache in pituitary disease is likely to be a result of patient-dependent factors. The finding that 49% of the study group had a family history of headache suggests that they were more predisposed to the primary headaches than the general UK population (Steiner *et al.*, 2003). Migraine is known to have a familial aggregation (Ferrari, 1998), and the development of pituitary tumour-associated migraine, accounting for 75% of presentations in this study, may have been a result of genetic predisposition to migraine in affected patients rather than specific tumour-related factors. As migraineurs have increased sensitivity to changes in the internal or external milieu (Goadsby *et al.*, 2002), the development of the pituitary tumour may have lowered the threshold for attacks in predisposed migraineurs. The presence of a higher proportion of migraine in prolactinomas and growth hormone-secreting tumours suggests that functional activity may be an important trigger.

Cluster headache and SUNCT are relatively rare headache syndromes and the observation of three cases of cluster headache and four cases of SUNCT in our relatively small cohort of 84 patients suggests that these syndromes may be

over-represented in pituitary disease. While it is possible that this is in part referral bias with regard to our unit's headache interest, this was minimized by studying consecutive referrals to the neurosurgery unit, which is unlikely to have this headache-related bias. Cavernous sinus invasion was present in two of the three cluster cases, which may suggest that invasion of local structures is relevant. Although cavernous sinus invasion does not appear to be predictive of headache in pituitary tumours *per se* (Abe *et al.*, 1998; Levy *et al.*, 2002), the sinus does contain pain-producing structures, such as the internal carotid artery and trigeminal nerve and ganglion, invasion of which might be expected to cause pain. There have been several reports of pituitary-associated cluster headache presenting with ipsilateral cavernous sinus tumour invasion (Tfelt-Hansen *et al.*, 1982; Greve and Mai, 1988; Milos *et al.*, 1996; Porta-Etessam *et al.*, 2001). The cavernous sinus has been previously implicated in the pathophysiology of cluster headache (Moskowitz, 1988; Hardebo, 1994), although functional imaging data suggests that ipsilateral hypothalamic activation may be more important (May *et al.*, 1998, 2000; Sprenger *et al.*, 2004). Of the four SUNCT cases, two were prolactinomas and two were growth hormone-secreting tumours, suggesting that tumour activity may be important in pituitary-related SUNCT, although our sample size is small. The dramatic exacerbation of SUNCT with dopamine agonists observed in certain cases further suggests that perturbations in the dopamine–prolactin axis may be important in this headache syndrome. Ipsilateral hypothalamic activation has been demonstrated in primary SUNCT (May *et al.*, 1999) and it is conceivable that specific neuroendocrine pathways involving the dopamine-prolactin and growth hormone axis are capable of activating SUNCT pathophysiology.

The aim of this study was to document the clinical spectrum of pituitary tumour-associated headache. We did not attempt to determine the prevalence of headache in pituitary disease, which would have required recruitment of larger numbers of patients from both the surgical and non-surgical setting in a prospective and consecutive fashion. Because our study was based in a neurosurgical centre, the patient population is likely to have contained relatively larger numbers of macroadenomas compared with a non-surgical centre. This may have given a biased impression of the frequency and quality of headache found in our study, and further work is required to determine the validity of our findings in the generality of patients with pituitary tumours. We observed a significant number of patients who experienced residual headache after treatment of their pituitary tumour and found these patients to present a difficult management problem. Although treatment response was not formally part of the study design, we managed a large number of this cohort and continue to see such patients. We have observed that phenotype-driven medical management markedly improved disability in many patients. There are previous reports that pituitary tumour associated with headache may respond to serotonin-5-$HT_{1B/1D}$ receptor agonists, i.e. triptans (Shah and Freij, 1999; Pascual, 2000). We found that both

Table 11 Proposals for modifications to the IHS criteria

Current classification	
7.4.4	Headache attributed to hypothalamic or pituitary hyper- or hyposecretion
Diagnostic criteria	
A	Bilateral, frontotemporal and/or retro-orbital headache fulfilling criteria C and D
B	At least one of the following: (i) prolactin, growth hormone (GH) and adrenocorticotrophic hormone (ACTH) hypersecretion associated with microadenomas <10 mm in diameter (ii) disorder of temperature regulation, abnormal emotional state, altered thirst and appetite and change in level of consciousness associated with hypothalamic tumour
C	Headache develops during endocrine abnormality
D	Headache resolves within 3 months after surgical resection or specific and effective medical therapy
New proposal	
7.4.4	Headache attributed to hypothalamic dysfunction
Diagnostic criteria	
A	Bilateral, frontotemporal and/or retro-orbital headache fulfilling criteria C and D
B	Disorder of temperature regulation, abnormal emotional state, altered thirst and appetite and change in level of consciousness associated with hypothalamic tumour
C	Headache develops when hypothalamic pathology is manifest
D	Headache resolves within 3 months after specific and effective medical therapy
7.4.5	Headache attributed to pituitary disease
Diagnostic criteria	
A	Bilateral or unilateral frontotemporal and/or retro-orbital headache fulfilling criteria C and D
B	Either a functioning or non-functioning pituitary tumour is identified by biochemical testing or appropriate brain imaging (i) with cavernous sinus involvement (ii) without cavernous sinus involvement
C	Headache develops in close temporal proximity to endocrine abnormality or with symptoms attributable to pituitary disease, such as visual loss
D	Headache resolves, or there is marked improvement, within 3 months after surgical resection, or specific and effective medical therapy

acute and preventive phenotype-driven treatment was helpful for many patients. We found that patients with residual ipsilateral cavernous sinus invasion were particularly refractory to medical therapy. Prospective blinded placebo-controlled studies are required to determine the optimum management of the pituitary tumour-associated headache, although in their absence placebo-controlled studies from the underlying primary headache types manifest by these patients seem a very useful guide to their management.

Lastly, based on our relatively large, prospective study with tissue verification of the diagnosis, we make some suggestions as to the classification of headache in patients with pituitary disease (Table 11). Currently, the International Headache Society classifies pituitary and hypothalamic headaches together (Headache Classification Committee of The International Headache Society, 2004). In principle we do not see this as a way forward for research or indeed clinical practice. The disorders are different, the structures distinct and, given the rich phenotypic variation we have seen in pituitary tumour-related headache, it seems reasonable to split these. Given the implications of local involvement of the cavernous sinus from both a local treatment and headache presentation, we feel this should be specified for research and characterization. We suggest that requirement C is insufficient to deal with non-functioning adenomas, which made up nearly one-quarter of the cohort, and could easily present with a manifestation of the tumour, such as visual impairment, that is non-endocrine; thus our suggested amendment. For requirement D we are convinced by our series that the requirement of complete resolution of headache after surgical or indeed endocrine management is not uniformly useful. We have established that for most tumours the headache problem is unrelated to tumour size (Levy *et al.*, 2004), and so it seems appropriate that amelioration of headache after tumour treatment rather than resolution more completely captures the outcome; thus, we have altered section D. We invite centres with substantial throughput to consider these proposals and test them prior to the next edition of the headache classification.

In summary, we have described the headache characteristics observed in 84 patients with pituitary tumour-associated headache. We did not find the presence of cavernous sinus invasion and large tumour size to be a prerequisite for headache. Functioning tumours presented with the most headache-related disability, and the dopamine–prolactin and growth hormone axes were exclusively associated with SUNCT. The majority of cases of pituitary-associated headache presented with migraine, although a wide spectrum of headache presentations was observed. We have found the current classification system good but provide suggestions based on our data for a revision. From a clinical perspective, pituitary-associated headache appears to be a management problem both before and after treatment of the pituitary tumour. From an academic perspective, this subject may represent an interesting opportunity to understand the relative roles of the cavernous sinus and the hypothalamo-pituitary axis in headache.

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