

## A study of acromegaly-associated headache with somatostatin analgesia

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## ABSTRACT

To characterise somatostatin analogue responsive headache in acromegaly, hitherto not systematically documented in a significant cohort. Using the UK pituitary network, we have clinically characterised a cohort of 18 patients suffering from acromegaly-related headache with a clear response to somatostatin analogues. The majority of patients had chronic migraine (78%) as defined by the International Headache Society diagnostic criteria. Headache was present at the time of acromegaly presentation and clearly associated temporally with disease activity in all cases. Short-acting somatostatin analogues uniquely resolved pain within minutes and the mean duration of analgesia was 1-6 hours. Patients on long-acting analogues required less short-acting injections (mean 3.7 vs. 10.4 injections per day,  $p=0.005$ ). 94% used somatostatin analogues to control ongoing headache pain. All patients presented with macroadenoma, most had incomplete resection (94%) and headache was ipsilateral to remnant tissue (94%). Although biochemical control was achieved in 78% of patients, headache remained in 71% of them. Patients selected for this study had ongoing headache post-treatment (mean duration 16 years after diagnosis); only 4 patients reached headache remission 26 years (mean, range 14-33) after the diagnosis. Headache in acromegaly patients can be persistent, severe, unrelieved by surgery, long-lasting and uncoupled from biochemical control. We show here that long-acting analogues allow a decrease in the number of short-acting analogue injections for headache relief. Further studies are needed to understand the mechanisms, markers and tumour tissue characteristics of acromegaly-related headache. Until then, this publication serves to provide the clinical characteristics as a reference point for further study.

## INTRODUCTION

Headache can be a feature of pituitary tumours of all sizes and all tumour types. Headache is a particularly characteristic feature of acromegaly, and its management is still suboptimal because its pathophysiology is poorly understood (Arafah et al. 2000; Gondim et al. 2009; Pereira-Neto et al. 2010; Kreitschmann-Andermahr et al. 2013). Growth hormone-secreting pituitary tumours appear to be particularly pro-nociceptive (Abe et al. 1998; Levy et al. 2004b; Gondim et al. 2009; Levy 2011), the prevalence of headache being up to 70% in patients with acromegaly at presentation (Mercado et al. 2004). Somatostatin analogues (SSAs) have an analgesic effect in acromegaly over and above that accounted for by reduction in tumour volume, which has led to authors suggesting that biochemical inhibition of a pro-nociceptive peptide is the mechanism of analgesia (Abe et al. 1998; Levy et al. 2004b; Levy 2011). The apparent absence of an association between tumour volume, cavernous sinus invasion, and intra-sellar pressure with headache as well as its acute relief (Abe et al. 1998; Levy et al. 2004b; Gondim et al. 2009; Dimopoulou et al. 2014) further suggests that headache is not a physical phenomenon, but rather an active endocrine pathophysiological process. Somatostatin analgesia and growth hormone (GH) suppression appear to be ‘uncoupled’, that is to say that somatostatin is observed to cause GH suppression and analgesia but not necessarily both at same time (Levy 2011). This provides a unique human headache model, whereby short-acting octreotide can provide pain relief as well as GH suppression in some patients (Levy 2011). This observation has led to the hypothesis that a pro-nociceptive peptide linked to GH, but not GH *per se*, might somehow link autonomous somatotroph activity to pain. There have been numerous candidate nociceptive peptides proposed, based on headache pathophysiology, including substance P and calcitonin gene-related peptide amongst others (Levy 2011). However, whilst these putative peptides are present in somatotrophs, they have not been reliably correlated with headache in the studies to date. This may be a result of sample size and more

investigation of this nociceptive peptide hypothesis is needed (Levy et al. 2004a). The mechanism of somatostatin analgesia is unknown, but may be correlated with the somatostatin receptor sub-type present within the pituitary tumour. Pasireotide can be effective in patients with acromegaly possibly as a result of its broader somatostatin receptor affinity. We suggest that these interesting clinical observations (up to now in case reports only, Table 1) warrant detailed study to inform further investigation of this area. The place to start before embarking on biochemical, histological and functional radiological studies is to clinically characterise a cohort of acromegaly patients with SSA-responsive headache. Therefore, we recruited a cohort of acromegaly patients with SSA-responsive headache by contacting colleagues working in tertiary pituitary units within the UK in the hope that we would be able to identify a sufficient number to clinically phenotype and then study mechanistic questions in future publications of this cohort.

## MATERIALS AND METHODS

We contacted twenty departmental leads of tertiary UK Endocrine Units who contribute to the UK Acromegaly Database to see if they had patients under their care that (i) had a diagnosis of acromegaly, (ii) headache was a significant feature of their presentation, and (iii) there was clear short-acting SSA responsiveness in terms of analgesia for the headache (Howlett et al. 2013). Eighteen patients were identified and confirmed to have a current or previous history of use of short-acting SSA with its abolishing effect on acromegaly-associated headache. These patients were diagnosed with acromegaly between 1987 and 2020. Baseline clinical characteristics and details of specific interventions for the treatment of acromegaly and headache response were collated (Tables 2 and 3) chronological features of headache and exacerbations or improvements with each treatment modality were documented as described previously in a study of acromegaly-associated headache [6]. Headache phenotype was

assessed using an adapted validated headache questionnaire used previously in the investigation of acromegaly-associated headache (Levy et al. 2005b). This questionnaire has been shown to accurately quantitate the severity of the headache and the impact of the headache has on quality of life, based on previous work comparing prospective quantitative headache scores in a cohort of patients with pituitary tumours and headache (Levy et al. 2004b). The International Headache Society definition for pituitary disease related headache is categorised under International Headache Society diagnostic category 7.4.3, where headache is attributed to pituitary hypersecretion, onset is in parallel with other pituitary symptoms and improves with specific treatment of that pituitary disorder (Olesen 2018). Pain severity was quantified on a numerical pain scale, ranging from 0 (no pain) to 10 (most severe pain possible). The study was approved by the Cambridge East Research Ethics Committee and the patients' consent to have their data analysed and recorded was given. Statistical analysis was performed using Statistica (version 13, <http://statistica.io>), the Welch's t-test was used (normality assumption fulfilled by the Shapiro-Wilk Test). Significance was taken a  $p < 0.05$ , data are expressed as mean, median and range.

## RESULTS

### *Patients (Table 2)*

Of the 18 patients with acromegaly and headache at presentation, 14 had current headache, with ongoing significant alleviation after somatostatin injection (classified as 'persistent headache' group). Four of 18 patients had headache that remained in remission after successful treatment of acromegaly ('headache remission' group). More than half of the patients had elevated prolactin at baseline. Sixteen out of 18 patients used self-administered short-acting octreotide to relieve headache. Five patients used octreotide more than ten times a day, all of them had radiotherapy (6-32 years ago). Two did not have headache any more at the time of the study,

so gradually decreased the octreotide dose and ceased octreotide treatment. In these patients no components of dependency were reported.

### *Acromegaly treatment*

All 18 patients in the study had macroadenomas; in 2 cases the pre-operative scans were not available, but their current scan showed residual tumour with MRI cavernous sinus invasion. All patients had undergone transsphenoidal surgery. On post-operative imaging, residual tumour was visible in 94.1% of patients. One patient had no obvious post-operative residuum, but had biochemical evidence of persistent disease requiring second- and third-line treatment. All patients required second-line treatment: 22.2% patients underwent repeat surgery, radiotherapy was given in 88.9% and in 11.1% patients a second course of radiotherapy was needed. Medical treatment for the whole group included cabergoline (22.2%), pegvisomant (33.3%), and long-acting SSA (77.8%). Of the patients on long-acting SSAs, 6 were treated with long-acting octreotide and 8 with long-acting lanreotide, and one later switched to long-acting pasireotide. Following multimodal treatment, 83.3% of patients had at least one pituitary axis deficiency (Table 2 and 3). 77.8% of patients had biochemical control according to Endocrine Society guidelines (n=5 in remission off treatment; n=9 on drug treatment for acromegaly), whereas the remaining 22.2% were not controlled (3 on medical treatment, and 1 awaiting multidisciplinary team decision) (Katznelson et al. 2014).

### *Headache*

Headache started at the same time as the first symptom of acromegaly in the majority of patients (72.2%), suggesting acromegaly-associated headache as defined by International Headache Society diagnostic criteria. These criteria are a strictly defined set of symptoms that allow clinicians to categorise headache, and are the starting point to all headache management (Olesen

2018). Three patients developed headache after the diagnosis of acromegaly, and two of these experienced headaches immediately post-operatively. 94.4% of patients considered that their headache was related to acromegaly, and 77.8% reported it to be the worst aspect of the disease, confirming that the cohort was the population we wished to study. In line with previous reports, 77.8% of our patients had an International Headache Society diagnosis of acromegaly-associated chronic migraine. In 6 cases the headache was classified as migraine with aura, in 2 as migraine with cranial autonomic features, and in 1 case as post-traumatic migraine. The remaining 4/18 (22.2%) patients presented with an International Headache Society diagnosis of pituitary tumour-associated headache, where the headache was relatively featureless, while chronologically clearly correlated with the activity of acromegaly. Mean headache severity was 5.9 (median 5.5, range 3-9) out of a scale of 0-10. For 94.4% of patients, the headache was side-locked (i.e. always having headache on the same side) and the pain was ipsilateral to residual cavernous sinus disease.

#### *Somatostatin analogue responsiveness*

All patients reported that short-acting octreotide improved headache within 1-5 minutes of injection and that the effect wore off after a few hours (range 1-6 hours). The mean dose of octreotide was 114.4 µg/injection (median 100, range 20-500). Patients on short-acting analogues alone (8/18) required a mean of 10.4 injections per 24 hours (median 12, range 3-16). This was statistically more than the number of injections in those patients taking a combination of short- and long-acting analogues: they required 3.7 (median 4; range 0-7) injections per 24 hours. This suggests that the use of long-acting SSA may play a preventative role in headache, whilst short-acting SSA are used as abortive agents by patients. When not on short-acting SSA treatment, the majority of patients (88.9%) had chronic daily headache, rather than episodic headache, chronic daily headache being defined as having more than 15 headache

days in a calendar month. 83.3% of the patients could predict when the next SSA injection was due based on the strength of their headache. One patient developed tolerance and tachyphylaxis with short-acting octreotide with unacceptable headache symptoms, and went on to achieve successful pain relief with pasireotide.

### *Response to other interventions*

Generally, treatment for acromegaly-associated headache other than SSA injections were ineffective. These included NSAIDs, opiates and migraine-specific treatments including the range of triptans (serotonin (5-hydroxytryptamine, 5-HT) 5-HT<sub>1D</sub> receptor agonists) that reduced severity during exacerbations, but were far less effective than short-acting SSAs. No patients reported triptans to be effective, whilst two reported improvement after cannabis and one after Botox injections. 27.8% reported transient headache relief with surgery alone, 22.2% after radiotherapy and 5.6% with pegvisomant. None of the 4 patients using dopamine agonist reported headache relief associated with this medication.

## DISCUSSION

Somatostatin receptors were found in dorsal horn afferent neurons, spinal interneurons, and in the ascending and descending pathways (Stine et al. 1982; Shimada et al. 1985; Dean 2001).

These locations in the central nervous system have a role in pain transmission or inhibition (it can have dual effect on neurons; depending on the modality of pain signalled); therefore, somatostatin analogues would be expected to have an effect on pain (Chapman and Dickenson 1992; Dean 2001; Jung et al. 2008). Octreotide was found to have an analgesic effect in different types of pain and in various way of administration. Subcutaneous injection was used in cancer



and pancreatic carcinoma pain, bone pain from metastatic carcinoid and hypertrophic pulmonary osteoarthropathy (Conno et al. 1994; Johnson et al. 1997; Dean 2001; Katai et al. 2005). Epidural somatostatin was successfully implemented in analgesia of upper abdominal surgery and cancer pain (Taurà et al. 1994; Beltrutti et al. 2000). Intratracheal octreotide infusion was sufficient in cancer pain intraventricular could be potentially useful in patients with head and neck cancer exhibiting local nonopioid-sensitive pain (Candrina and Galli 1992; Penn et al. 1992). Intravenous infusion of octreotide was found to cause pain relief after major abdominal surgery and cluster headache (Sicuteri et al. 1984a; Caleri et al. 1987; Dahaba et al. 2009).

Somatostatin's effect on headache has been reported previously. In cluster headache, octreotide reduced the pain intensity and the duration both intravenously and subcutaneously (Sicuteri et al. 1984b; Caleri et al. 1987; Matharu et al. 2004). In migraine type of headache, this effect seems to be controversial, found by some authors but not confirmed by others (Kapicioğlu et al. 1997; Levy et al. 2005a; Miller et al. 2009).

The aim of this observational study was to characterise the clinical response and phenotype of a unique, well-defined cohort of patients with acromegaly with headache clearly responsive to SSA, in order to provide a preliminary clinical model for further study because the prime objective of octreotide was the control of GH and IGF-1. We therefore did not study acromegalic patients who did not have somatostatin responsive headache. Our data represent a carefully-phenotyped unique cohort with a long follow-up (range 6-33 years). We found that patients used less SSA injections when using a combination of short- and long-acting SSAs, suggesting that when the effects of long-acting SSAs wore off, short-acting agents were

required for breakthrough pain. More often than not, patients could predict when breakthrough pain would occur just before each injection, and this is a useful model for biochemical and functional imaging studies of acromegaly-associated headache going forward. In line with previous studies, the phenotype of acromegaly-associated headache was mostly chronic migraine (Musolino et al. 1990; Pascual et al. 1991; Donangelo et al. 2004; Levy et al. 2005b; Marina et al. 2015). The majority of patients (77.8%) achieved biochemical control from acromegaly following multimodal treatment, including surgery, radiotherapy and medical treatments. Despite this, headache was still an ongoing issue suggesting that this may be an overlooked area of morbidity, even when patients are deemed to be in biochemical remission. While the presence of headache often correlates with biochemical and tumour control of acromegaly, lack of correlation between headache and biochemical control has also been reported. The headache can be relieved by SSAs without biochemical control of acromegaly (Popovic et al. 1988; Siculo et al. 1990; Musolino et al. 1990; Pascual et al. 1991; Donangelo et al. 2004; Marina et al. 2015), or the other way round, headache can persist despite GH control (Musolino et al. 1990; May et al. 1994; Donangelo et al. 2004). We believe that the latter situation might be underreported, as previous studies were not concentrating on headaches as a key outcome. Our data shows that that in the SSA-responsive patient group, the majority of the patients had headaches despite biochemical control of acromegaly. The rapid response to short-acting SSA within minutes is in line with previous case reports (Williams et al. 1987; Siculo et al. 1990; Musolino et al. 1990; Donangelo et al. 2004). We found the duration of analgesic action was less than 6 hours, similar to its action on hormone release. It is known that abortive headache treatments respond better to drugs with a short half-life which fits with our new observation about how patients use short- and long-acting SSA in headache associated with acromegaly.

Williams et al., presented two cases with no headache cessation after short-acting SSA (Williams et al. 1987). In these cases, relatively small doses of octreotide were used compared to other cases listed in Table 1 and that they were the only patients after external beam radiotherapy rather than surgery, without tumour mass reduction. This might suggest that the headache effect of SSAs, even if not correlated to biochemical control, is dependent on tumour related properties such as proximity to the cavernous sinus or somatostatin receptor status of the tumour itself. We reported a patient with acromegaly whose headache responded only to octreotide and not lanreotide (Levy et al. 2003). The other cases of SSA resistant headaches comprised examples of the advantage of second generation SSA over first generation. Considering the role of the somatostatin receptors within the tumour, we found one patient from the current study who had an improved biochemical and analgesic response to pasireotide over octreotide and lanreotide. Pasireotide analgesic effect in acromegaly related headaches (not responding to another long-acting SSA) has been previously observed, suggesting that additional somatostatin receptor affinity may lead to increased analgesic action (Marina et al. 2015; Lovato and Kapsner 2018). Unfortunately, pasireotide was not available at the time of study for all patients.

Rapid timing of action (headache relief) after subcutaneous administration of octreotide (comparable to intravenous administration) suggests a direct somatostatin receptor mediated

effect (Sicuteri et al. 1984b; Caleri et al. 1987; Williams et al. 1987; Popovic et al. 1988; Sicolo et al. 1990; Musolino et al. 1990; Pascual et al. 1991; Schmidt et al. 1993; May et al. 1994; Levy et al. 2003; Donangelo et al. 2004; Matharu et al. 2004; Marina et al. 2015; Lovato and Kapsner 2018). Both effect on vasculature and on neuron activation could be considered here. Somatostatin receptors have been described in human blood vessels and endothelial cells (Curtis et al. 2000). Vasoconstriction has been previously reported in response to somatostatin (Caleri et al. 1987), similar to oxygen and triptans, well-known agents reducing headaches via vasoconstriction (Drummond and Anthony 1985; Group 1991; Mampreso et al. 2009). The distribution of somatostatin receptors in the nervous system was mentioned already; however, the post-receptor effect is puzzling (Stine et al. 1982; Shimada et al. 1985; Dean 2001). Release of substance P from peripheral trigeminal nerve endings gives a similar effect observed in cluster headaches (Caleri et al. 1987). However, no association between the presence of substance P in pituitary adenoma specimens and headache was observed (Levy et al. 2004a). We found that headache is uncoupled from GH secretion, but this does not rule out the hypothesis of activation of still an unknown nociceptive peptide.

Our patients and previously published cases (Table 1) were relatively young at the time of acromegaly diagnosis (especially those with persistent headache). They all presented with a macroadenoma. The average time of diagnostic delay in our group was noticeably longer in patients within the headache persistent than in the headache remission group. It is known that sparsely granulated adenomas occur more commonly in younger patients and are typically rapidly growing, larger tumours. In the literature, only two cases of somatostatin responsive headache with adenoma granulation assessment were reported, and they both were sparsely

granulated lesions (Marina et al. 2015). It remains to be determined whether there are any other histological, biochemical or somatostatin receptor expression features related to and responsible for headache; however, it was beyond the scope and goals of this study.

In all cases, headache was localised ipsilateral to the residual tissue, suggesting that a combination of structural and biochemical features are linked to headache (Donangelo et al. 2004; Marina et al. 2015; Lovato and Kapsner 2018). The cavernous sinus has significant neurovascular structures for head pain, including the trigeminal ganglion and internal carotid artery, which are likely to cause symptoms when irritated either chemically or physically or both. The hypothesis is that somatostatin aborts the activation of such neurovascular structures within the cavernous sinus. Another issue is that two of our patients developed headaches only after surgery. In previously reported cases of SSA responsive headaches, in one the headache appeared after transcranial intervention, and in the other case after radiotherapy (Popovic et al. 1988; Pascual et al. 1991). Triggering or compressing the structures suspected to be responsible for headache (as the effect of changing the rheology of the cavernous sinus structures or packing after surgery, and oedema after radiotherapy) stays in line with this observation. The majority of patients (77.8%) were in biochemical control of acromegaly following multimodal treatment. All our patients who were in headache remission were biochemically controlled, but headache remained a significant ongoing morbidity despite disease remission in 71.4% of patients. In patients with general headache reduction, older age, longer follow-up time, and longer follow-

up time after radiotherapy were observed. At least some of this could be explained the late effect of radiotherapy.

The scope and construction of our study do not allow us to draw clear conclusions about octreotide related dependency. Patients using octreotide with the highest frequency, could discontinue octreotide when headache severity decreased. The question of octreotide dependency in headache is beyond the scope of this study.

In summary, in this report of a unique, SSA-responsive, acromegaly-associated headache patient cohort with prolonged follow-up, we found that the majority of the patients had macroadenoma with cavernous sinus invasion; the ipsilateral pain was reduced by SSAs; the combination of long-acting SSAs with short-acting analogues produced better pain relief as judged by short-acting analogue injection frequency. The headache often persisted for many years even in patients who were biochemically controlled of their acromegaly. We hope that further studies will clarify the mechanism of the headache and will help to better manage these patients.

**Declarations:***Availability of data and materials*

All data generated or analysed during this study are included in this published article.

*Ethical approval*

This study was approved by the Cambridge East Research Ethics Committee (MREC 06/Q0104/133).

The patients consent to have their data analysed and recorded was given.

*Conflict of Interest*

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Table 1. Studies on SSA responsive headaches acromegaly-associated headache

Publication	No.	Age	Adenoma size	Pain relief	Type of SSA	Time of response	Injections intervals	SA-SSA daily dose (µg)	Surgery	RT	GH and headache reaction	Placebo control	Withdraw syndrome comments
(May et al. 1994)	1	33	NA	Y	SA-SSA	"within minutes"	4-6 hours	800	Y	Y	GH(+) H(-)	N	Y
(Donangelo et al. 2004)	1	53	macroadenoma	Y	SA-SSA	N/A	6 hours	1000	Y	Y	GH(-) H(+)	N	Y
	2	16	macroadenoma	Y	SA-SSA	N/A	N/A	1800	Y (2)	Y	N/A	N	Y
	3	40	macroadenoma	Y	SA-SSA	2-3 min	8 hours	900	Y	Y	GH(+) H(-)	N	Y
(Williams et al. 1987)	1	46	5 mm suprasellar extension*	Y	SA-SSA	2-10 min	up to 6 hours	300	N	Y	N/A	Y	N/A
	2	27	Partially empty sella*	Y	SA-SSA	2-10 min	up to 6 hours	300	N	Y	N/A	Y	N/A
	3	39	macroadenoma	Y	SA-SSA	2-10 min	6-8 hours	300	Y	Y	N/A	Y	N/A
	4	45	Partially empty sella*	N	SA-SSA	No response	No response	300	N	Y	N/A	Y	N/A
	5	68	Partially empty sella*	N	SA-SSA	No response	No response	300	N	Y	N/A	Y	N/A
(Marina et al. 2015)	1	21	macroadenoma	N Y	SA-SSA+LA-SSA; Pasireotide		12 hours	200	Y (2)	N	GH(-) H(-) GH(+) H(+)	N	N/A
	2	33	macroadenoma	Y Y	SA-SSA+LA-SSA Pasireotide	"rapid effect"	12 hours	200	Y (2)	N	GH(-) H(+) GH(+) H(+)	N	N/A
(Popovic et al. 1988)	1	28	macroadenoma	Y	SA-SSA	"several minutes"	2 hours	1500	Y	Y	GH(-) H(+)	Y	Y
(Lovato and Kapsner 2018)	1	22	macroadenoma	N Y	LA-SSA Pasireotide				Y (2)	Y	GH(-) H(-) GH(+) H(+)	N	N/A
(Pascual et al. 1991)	1	31	macroadenoma	Y	SA-SSA	"immediate analgesia"	6 hours	400	Y	N	GH(-) H(+)	Y	N/A

(Levy et al. 2003)	1	29	microadenoma	Y	SA-SSA LA-SSA (Octr) LA-SSA (Lan)	N/A	12 hours**	200	Y	Y	GH(-) H(+) GH(+/-) H(-) GH(+) H(+)	N	N/A
(Musolino et al. 1990)	1	18	N/A	Y	SA-SSA	2 min	2 hours	300	Y (2)	Y	GH(-) H(+)	Y	N/A
	2	24	N/A	Y	SA-SSA	2 min	2 hours	300	Y	N	GH(+) H(-)	Y	N/A
(Schmidt et al. 1993)	1	N/A	N/A	Y	SA-SSA	4-15 min	2,5-8 hours	1500	N/A	N/A	N/A	Y	N/A
	2	N/A	N/A	Y	SA-SSA	4-15 min	2,5-8 hours	500	N/A	N/A	GH(+) H(-)	Y	N/A

No. case number; \* based on CT (notice study from 1987); \*\*with mild headache 1 hour before each octreotide dose; GH(+) biochemically controlled; GH(-) biochemically not controlled; H(+) headache controlled; H(-) headache not controlled. Additionally description of 8 patients with headache relief after SA-SSA without division no division into individual patients and description criteria used in the table (Sicolo et al. 1990).

Table 2. Summary of patient characteristics\*

No.	Current persistent headache	Current Age	Sex	AoD	Length of follow-up (years)	Repeat surgery <sup>o</sup>	Number of radiotherapies	Current or past			IGF-1 control	PRL	Currently on treatment	Residual tissue/Cavernous sinus invasion	Pain vs remnant tissue	Pituitary deficiency
								DA	LA-SSA	PEG						
1	NO	39	F	25	14	YES	1	NO	NO	NO	YES	E	NO	Yes/Yes	IPSI	TSH
2	NO	64	F	32	32	NO	1	NO	NO	NO	YES	N/A	NO	N/A	N/A	TSH
3	NO	72	M	39	33	NO	0	YES	YES (2 types)	NO	YES	N/A	LA-SSA	Yes/Yes	IPSI	ACTH, Gn
4	NO	81	F	57	24	NO	1	NO	YES	NO	YES	N	SA-SSA+LA-SSA	Yes/Yes	IPSI	TSH, ACTH
5	YES	47	F	18	29	NO	1	NO	NO	NO	YES	N	NO	Yes/Yes	IPSI	TSH, GH
6	YES	43	M	26	17	NO	2	NO	YES	YES	YES	N/A	SA-SSA+LA-SSA+PEG	Yes/Yes	IPSI	Gn
7	YES	42	F	29	13	NO	2	NO	NO	YES	YES	N/A	SA-SSA	Yes/Yes	IPSI	TSH, ACTH, Gn
8	YES	43	M	33	10	NO	1	NO	YES	YES	YES	E	SA-SSA+LA-SSA+PEG	Yes/Yes	IPSI	TSH, Gn
9	YES	47	F	33	14	YES	0	NO	YES	NO	YES	E	SA-SSA+LA-SSA	Yes/Yes	CL	0
10	YES	48	M	33	15	NO	1	NO	YES	NO	YES	N	SA-SSA+LA-SSA	Yes/Yes	IPSI	ACTH, Gn
11	YES	52	F	35	17	NO	1	NO	YES	YES	YES	N/A	SA-SSA+PEG	Yes/No	No side predilection	TSH
12	YES	61	F	38	23	NO	1	NO	YES	NO	YES	N	SA-SSA+LA-SSA	Yes/Yes	IPSI	TSH, Gn
13	YES	56	F	40	16	NO	1	YES	YES	NO	YES	E	NO	No evident mass/Yes <sup>#</sup>	Not to be estimate	TSH, ACTH, Gn
14	YES	57	F	45	12	NO	1	YES	YES	YES	YES	E	SA-SSA+LA-SSA	Yes/Yes	IPSI	TSH
15	YES	29	F	23	6	NO	1	NO	YES (2 types)	YES	NO	N	LA-SSA	Yes/Yes	IPSI	0
16	YES	56	M	23	33	YES	1	NO	YES	NO	NO	N	SA-SSA+LA-SSA	Yes/Yes	IPSI	TSH, ACTH, Gn
17	YES	41	M	28	13	YES	2	YES	YES	NO	NO	E	SA-SSA+PEG	Yes/Yes	IPSI	ACTH, Gn
18	YES	42	F	35	7	NO	1	YES	YES	NO	NO	N	SA-SSA+NO <sup>o</sup>	Yes/Yes	IPSI	0

\*SA-SSA was administered to all patients at least once in their lives (inclusion criteria) and thus is parameter is not included in the table. AoD, age of diagnosis; <sup>9</sup>All patients had one surgery; DA, dopamine agonist; PRL: E-elevated, N-normal; LA-SSA long-acting somatostatin analogue; SA-SSA, short-acting SSA; Gn, gonadal hormone replacement; #, on pre-operative scan; IPSI, ipsilateral; CL, contralateral; °, patient awaiting pegvisomant treatment; N/A, not available

Table 3. Headache response to treatment

	<b>Whole group (n=18)</b>	<b>Headache remission (n=4)</b>	<b>Persistent headache (n=14)</b>	<b>p-value</b>
Age mean (median; range)	51 years (47.5; 29-81)	64 years (68; 39-81)	47 years (47; 29-61)	0.165
Sex (Female/Male)	12/6	3/1	9/5	
Age at diagnosis of acromegaly mean (median; range)	33 years (33.0; 18.0-57.0)	38.3 years (35.5; 25-57)	31 years (33; 18-45)	0.397
Length of follow-up (median; range)	18 years (16, 6-33).	26 years (28; 14-33)	16 years (14; 6-33)	0.119
Time of diagnosis delay mean (median; range)	5 years (5; 0-14)	2.5 years (2.5; 1-4)	6.1 years (5.5; 0-14)	0.010
Biochemical control	77.8%	100%	71.4%	0.225
Improvement after surgery	5/18 patients	1/4 patients	4/14 patients	
Improvement after RT	4/18 patients	2/4 patients	2/14 patients	
RT	88.9% (16/18)	75% (3/4)	92.9% (13/14)	0.314
Time after RT mean (median; range)	14.1 years (12.5; 5-32)	22 years (21; 13-32)	12 (10; 5-28)	
LA-SSA*	55.6% (10/18)	50% (2/4)	57.1% (8/14)	
DA*	0%	0%	0%	
Pegvisomant*	22.2% (4/18)	0%	28.6% (4/14)	

\*Currently on treatment; LA-SSA, long-acting SSA; RT, radiotherapy; DA, dopamine agonist