European Society of Endocrinology

ESE Clinical Update on Acromegaly 2020

27-29 October 2020

Welcome

Acromegaly continues to present challenges to patients and endocrinologists alike. This series of three dynamic webinars brings us up to date with issues in diagnosis, pathophysiology and management of this debilitating disease.

The European Society of Endocrinology was delighted to welcome experts in the field, who shared their knowledge and experience over the course of three, 2-hour webinar sessions that examined:

- factors in diagnosis, spanning blood tests, physical features, other symptoms and imaging
- the impact of the disease, including the wide range of comorbidities experienced by patients, particularly headache, and the relationship between the disease and socio-economic issues
- disease management, from surgical approaches to the benefits and risks associated with the latest medical treatments, and a look at drugs in development.

This content was richly supported by carefully selected case presentations, and by all important patient perspectives on diagnosis, the burden of disease and management.

We are grateful to all who took part, including attendees, who contributed many pertinent and relevant questions.

This update, like so many events in 2020, had to transfer to an online format in order to go ahead. We were delighted to be able to bring it to you as a series of webinars, and so make it accessible to an even wider audience.

The content is available to attendees and members of ESE at **www.eseondemand.org**.

European Society of Endocrinology

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Chairs and Speakers

ESE thanks all faculty members for their valuable contributions to the ESE Clinical Update on Acromegaly 2020.

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Diagnostic dilemmas in acromegaly

Chairs: **Pia Burman** *(Sweden)* & **Jens Otto Jørgensen** *(Denmark)*

A patient's journey to diagnosis

Sheila Khawaja *Italy*

The first symptoms of acromegaly began in 2002. I have always suffered from migraine headaches but they became very acute and persistent. I finally went to see a migraine specialist in hospital in Trieste. I requested tests and investigations, but these were not done.

Throughout 2002, I was followed by this migraine specialist. Things really started to deteriorate towards summer 2003. I could not see from my left eye any more and had become photophobic. I had headaches 24 hours a day for 28 days a month, so my quality of life had deteriorated considerably.
I could not drive any more and I was gradually isolating myself. I went to my GP and said, 'You know, my shoes don't fit any more and my rings are tight.'

In October 2003, I was diagnosed by magnetic resonance imaging. They told me that I had a pituitary adenoma. I didn't know what that was, but I felt as if I had won the lottery, because finally I understood what was wrong.

Pitfalls of the oral glucose tolerance test in acromegaly

Katharina Schilbach *Senior Research Fellow, Faculty of Medicine, Ludwig-Maximilians University, Munich, Germany*

There are a number of pitfalls in the use of the oral glucose tolerance test (OGTT) in the diagnosis and follow-up of acromegaly.

How to perform the OGTT correctly
Since it is an evaluation of glucose metabolism, the patient should fast before the test. First, blood is drawn for glucose, growth hormone (GH) and (if needed) insulin. The patient then drinks or eats 75g or 100g glucose. After 30, 60, sometimes 90, 120 and 180mins, blood is taken to test for GH. It is important to understand that, by definition, the lowest GH concentration is 'the nadir', no matter at what time it occurs. Some centres use 75g glucose and others use 100g; GH concentrations may be assessed with either dose.[1]

Can the OGTT can be used in patients with glucose disturbances, as is very often the case in acromegaly? The answer is a clear 'yes'. One study measured GH in patients with normal glucose tolerance, in patients with impaired fasting glucose and in patients with impaired glucose tolerance. There was no difference in the fasting GH concentration.[Insert ref?]

Until recently, two cut-off values were applied to the measurement at the nadir: 1µg/l in the diagnosis of acromegaly and 0.4µg/l for persistent GH excess after surgery. However, a recent consensus guideline[2] states that the nadir for diagnosis should be revised to 0.4µg/l, taking into account the use of ultrasensitive GH assays and different factors which influence GH concentration.

Ultrasensitive GH assays
The pituitary secretes different isoforms of GH, as well as dimers and oligomers. Ultrasensitive assays need two features:

a) to use the recommended standard which contains over 96% 22kDa GH

b) to use antibodies which are specific for the 22kDa isoform.

Analysis of some old samples from acromegaly patients using a modern assay showed a high correlation between the results from the old and new assays, but the difference was up to 50%, and was more pronounced at higher hormone concentrations.

Other factors
Many other factors influence GH concentration, including high body mass index (BMI), thyroid disturbances, acute critical illness, and some physiological states such as sleep, physical activity and stress. Oral oestrogens strongly increase GH concentrations.

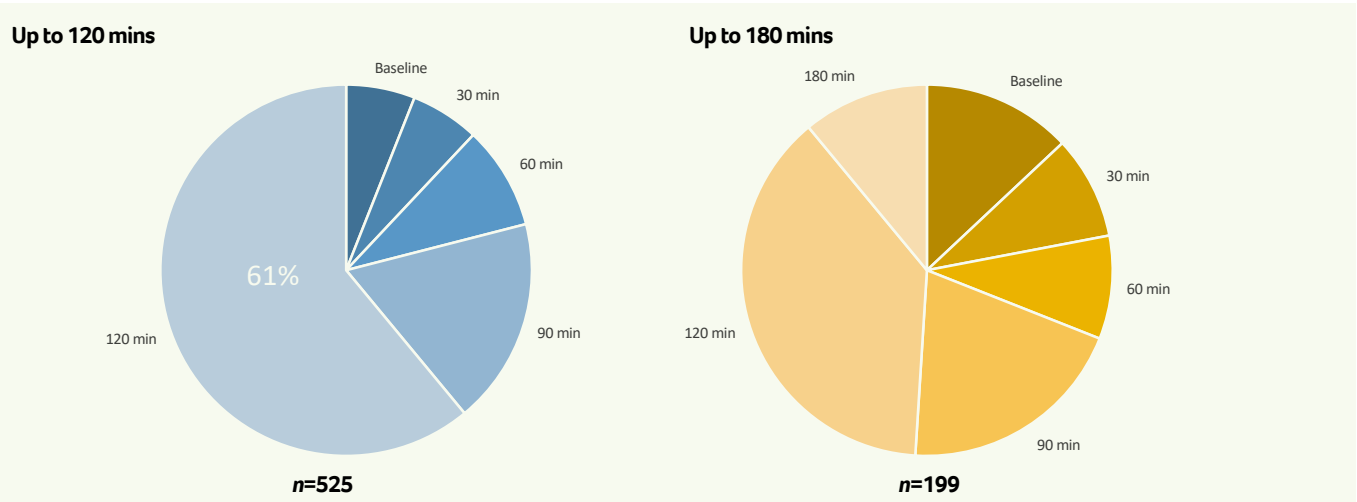
A large study in Munich used a modern assay and more than 500 participants to look at the factors influencing the GH nadir.[3] Those with the greatest effect were BMI, oral oestrogens and the patient's sex. There is a negative correlation between BMI and GH nadir, with higher BMI leading to lower GH nadir concentrations.

The male subjects clearly showed the lowest nadir (mean 0.09µg/l). Premenopausal women taking oral contraceptives had the highest nadir concentration (mean 0.55µg/l). Menstrual cycle phase did not make a difference to the GH nadir.

With further analysis, it was possible to derive cut-offs for the mean nadir values for males and females, and for different BMI subgroups (normal, overweight and obese). Values for males and postmenopausal females were the same (normal weight 0.4µg/l; overweight 0.2 µg/l). In premenopausal females, normal weight subjects had a slightly higher cut-off, while in females taking oral contraceptives it was much higher. The OGTT should be avoided for females on oral contraceptives.

How long should OGTT take?
In the cohort described above, most subjects had their nadir at 120mins. The second most common timepoint was 90mins (around 20%). Among a subgroup of 200 subjects, only 11% exhibited their nadir after 120mins. In a young, slim woman, this extra hour might be necessary to see the nadir, because the GH nadir and the baseline GH correlate quite well.

In summary
In the diagnosis of acromegaly, the OGTT can be performed with either 75g or 100g glucose. It can be used in patients with impaired glucose tolerance as well as in type 2 diabetes, if the blood sugar is well controlled. The official



Only 11% of participants were found to exhibit the GH nadir after 120 mins during an OGTT

cut-off value for GH is 0.4µg/l, but biological and pharmacological factors influence GH concentration and should be considered.

Further comments in Q&A

- There are no good data regarding this test in patients on insulin treatment. Katharina Schilbach does not use this test in patients on high doses of insulin, but will perform it on those taking oral antidiabetes drugs. Jens Otto Jørgensen added that he used it irrespective of the patient's diabetes status, but would perhaps be more careful when doing the final interpretation.
- Dr Schilbach has insufficient data to state whether the OGTT can differentiate between a GH-secreting tumour and an ectopic one, but believes ectopic acromegaly will not suppress in the OGTT.
- Regarding GH cut-offs after surgery, we should generally respect the cut-off of 0.4µg/l, but if a patient is overweight or obese we should have a second look and, if the nadir is only a little below 0.4µg/l, monitor this patient more closely than a patient with a normal BMI.
- Contraceptive use should be stopped one cycle (4 weeks) before using the test.

REFERENCES

1. Arafat *et al.* 2011 *Clinical Endocrinology* **75** 685–691.
2. Giustina *et al.* 2020 *Reviews in Endocrine & Metabolic Disorders* **21** 667–678.
3. Schilbach *et al.* 2019 *European Journal of Endocrinology* **181** 55–67.

Pitfalls in the diagnosis of acromegaly

Peter Kamenicky *Professor of Endocrinology, Bicêtre Hospital, and Paris-Saclay University, France*

The diagnostic algorithm for acromegaly may be found in the 2014 guidelines.[1] It starts with clinical suspicion of the disease, and this will lead to biochemical testing. The screening test is insulin-like growth factor-1 (IGF-1) measurement, and then biochemical confirmation is the growth hormone (GH) nadir during oral glucose tolerance test (OGTT).

Finally, we search for the source of GH excess, usually by pituitary magnetic resonance imaging (MRI).

If the patient has a typical clinical picture, diagnosis of acromegaly should not be a problem. However, the first pitfall in diagnosis is to increase awareness of this rare disease among GPs and the different specialists involved in managing the complications and co-morbidities of acromegaly. The journey to diagnosis can sometimes be quite long and is not really straightforward. Facemasks should be removed!

Patients with a mild clinical picture may not look acromegalic at first sight. In order to interpret the clinical signs, development over the years is very important. Ask your patients to bring photos with them. This is especially important in the milder cases.

It is very important to know when the disease began. Why this diagnostic delay? Many symptoms of acromegaly are attributed to ageing. The development of the clinical picture is frequently very slow and insidious, so the family do not notice it. Accompanying symptoms, such as headache and fatigue, are quite non-specific. Very often, it is several symptoms together which orient the diagnostic procedure. The co-morbidities associated with the diagnosis, such as hypertension and diabetes, are also very common in the general population.

The main symptoms leading to diagnosis are depicted in the Table.[2] The most important ones are the dysmorphic features and headache. Symptoms such as those relating to the carpal tunnel and sweating are less likely to lead to diagnosis. We do not currently have a useful screening strategy.

Patients may also be referred to you because their GP thinks they have acromegaly, but actually they do not have it. So this can be a pitfall in clinical diagnosis, but it will be corrected on biochemical screening since IGF-1 will be normal in these patients.

IGF-1 measurement

According to Katznelson *et al.*,[1] IGF-1 should be measured in all patients with typical clinical manifestations of acromegaly. It should be considered in those without the typical features of acromegaly but with conditions that may be associated with the disease (e.g. sleep apnoea syndrome and hyperhidrosis), and in those with a pituitary mass, in order to rule out somatotroph tumours. Measurement of IGF-1 is also recommended in patients with a genetic predisposition to pituitary tumours.

The main initial symptoms leading to diagnosis of acromegaly.[2] The most common ones are the dysmorphic features and headache.

Symptom
Acral changes
Headache
Amenorrhoea
Diabetes mellitus
Dental
Carpal tunnel
Visual
Sexual dysfunction
Galactorrhoea
Arthralgia
Chest pain
Hypertensive crisis
Dizziness
Increased weight
Gynaecomastia
Weakness
Sleep apnoea

In general, IGF-1 is a good diagnostic tool in screening for acromegaly. Out of 332 patients from the Bicêtre series, only 13 (4%) had normal IGF-1 values. With a reliable assay and good age-related reference values for IGF-1, the sensitivity and specificity are 95–99% for the diagnosis of acromegaly.

Despite this, IGF-1 measurement is not perfect. There are conditions other than GH hypersecretion that can influence IGF-1 concentrations. For example, anorexia nervosa and fasting will increase GH and decrease IGF-1; poorly controlled diabetes, obesity, liver disease, exogenous oestrogens and hypothyroidism also affect serum IGF-1 levels. The oestrogen status is very important, not only for interpreting GH values, but also for IGF-1 values. Other factors that will increase IGF-1 include pregnancy, puberty and adolescence.

Assays

It is important to know which IGF-1 assay your laboratory uses. Chanson *et al.* compared six different methods of IGF-1 measurement in 107 patients with either acromegaly or GH deficiency.[3] Some patients with mild disease were classified, according to the method used, either as normal controlled or as abnormal uncontrolled. Patients with moderate acromegaly may have borderline normal IGF-1 values and normal subjects may have marginally elevated IGF-1 values.

It is generally agreed that the cut-off values in biochemical confirmation of the disease (the nadir GH concentration during OGTT) are lower than those proposed in the guidelines.[1] This test may not be necessary to confirm the diagnosis in very typical cases, but is more useful in borderline or mild presentations.

Sometimes, though not very often, acromegaly is caused not a pituitary adenoma but by ectopic secretion of GHRH or (extremely rarely) GH. For instance, nothing was visible on pituitary MRI in one young woman with acromegaly, and she was found to have ectopic secretion of GHRH from an appendicular carcinoid. In another example, a man with multiple endocrine neoplasia type 1 had subtle clinical features of acromegaly and a gonadotroph pituitary adenoma. He also had a mass in the pancreas with metastases to the lymph nodes. After extensive surgery, his GHRH levels dropped back to normal.

Conclusions

The diagnostic procedure of acromegaly begins with clinical suspicion. IGF-1 concentration is our tool for biochemical screening; it is a very good tool, but is influenced by factors other than GH secretion, such as diabetes and oestrogen status. The utility of GH under OGTT in typical cases is questionable. Robust GH and IGF-1 assays and normative data for interpretation are necessary. In patients without convincing images on pituitary MRI and in those with MEN-1 syndrome, ectopic GHRH secretion should be considered.

REFERENCES

1. Katznelson *et al.* 2014 *Journal of Clinical Endocrinology & Metabolism* **99** 3933–3951.
2. Nachtigall *et al.* 2008 *Journal of Clinical Endocrinology & Metabolism* **93** 2035–2041.
3. Chanson *et al.* 2016 *Journal of Clinical Endocrinology & Metabolism* **101** 3450 –3458.

[^{11}C]Methionine PET imaging

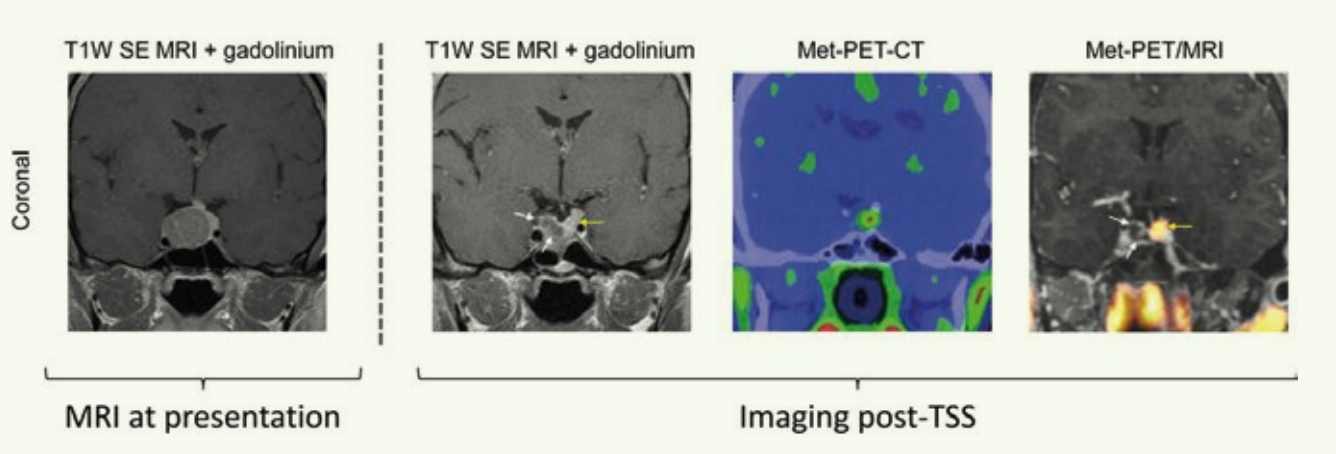
Mark Gurnell *Professor of Clinical Endocrinology, Wellcome–MRC Institute of Metabolic Science, University of Cambridge, UK*

In the Endocrine Society treatment guidelines from 2014, surgery features at the outset, but then disappears off the radar.[1] However, the latest consensus group publication recognises a main role for surgery in early treatment, and also includes it as an option later on.[2] We shouldn't always discount this option. It is important to consider how to make informed decisions about which patients should have further surgery, or stereotactic radiosurgery, for example. To address these possibilities, surgeons really need to know exactly where the tumour is.

Limitations of conventional MRI

Whilst magnetic resonance imaging (MRI) will undoubtedly remain the mainstay of our cross-sectional imaging approach to pituitary tumours, it is not perfect. In acromegaly, perhaps our biggest challenge is when the first treatment has been attempted and the patient either has persistent disease or develops recurrent disease. It can be difficult to disentangle post-treatment change on the scan from what might be residual tumour. Then, of course, there is the challenge of the frequently encountered incidentalomas, which may not be the cause of the patient's presentation.

Imaging can sometimes be limited when trying to interpret the situation either pre- or post-therapy. For example, one woman had an effective transsphenoidal resection with normalisation of IGF-1, but the imaging shows an abnormal signal resembling



Acromegaly in remission after transsphenoidal surgery (TSS). Post-operative MRI suggests a significant right-sided tumour remnant (white arrows), with normal gland (contrast enhanced, yellow arrow) displaced superiorly to the left. However, Met-PET/MRI demonstrates tracer uptake only at the site of the normal gland and confirms no residual functioning tumour at the site of the suspected remnant reported on routine clinical MRI. Met-PET-CT, [^{11}C]methionine-PET-CT; Met-PET/MRI, co-registered [^{11}C]methionine-PET-CT and MRI; SE, spin echo; T1W, T1 weighted. Reproduced by permission from *European Journal of Endocrinology* 175 485–498.[3]

residual tumour. Another case achieved a very good result soon after transsphenoidal decompression but, after 1 year, IGF-1 rose to a level similar to the value at presentation. However, MRI showed very little change, so where is the recurring disease? Less commonly in acromegaly, we are sometimes unable to see the lesion, even at the outset.

Molecular tracers

For some time, there has been interest in using molecular tracers, in the domain of positron emission tomography (PET) imaging or functional imaging, to try and detect potential *de novo* or recurrent disease, and a whole host of pituitary tumour subtypes. Different approaches have revolved around targeting a particular receptor's expression on the surface of the adenoma, looking at metabolic aspects of tumour biology, or characterising the amount of amino acid uptake and ultimately peptide synthesis.

Methionine has advantages for imaging the sella. It has a favourable target-to-background ratio compared with other tracers, it has higher uptake in the pituitary compared with the background brain and, actually, the chemistry is relatively simple to undertake.

Functional imaging in indeterminate scans

In one case, the surgeon was convinced that he had resected the tumour, but a scan suggested that there might be residual tumour. [^{11}C]Methionine PET–computed tomography (CT) was undertaken. Using PET–CT alone was not good enough here, the PET and CT need to be merged together with MRI, so essentially co-registering, or alternatively using PET–MR, as a way of bringing together the functional and anatomical information. Normal tracer uptake by residual normal gland at the left side of the sella could be seen. However, the area that was suspected to be a site of possible residual tumour, based on the radiological characteristics alone, showed no uptake.

Another patient appeared to have a good surgical result, but had a significant amount of residual acromegaly. Volumetric MRI identified two areas which took up tracer quite noticeably. This directed the surgeons to remove a significant amount of residual tumour and the patient achieved remission.

The ACROPET study of 30 patients included 4 with no residual disease in whom a possible tumour had been questioned on a scan (see figure), and 26 with equivocal imaging whose biochemistry clearly showed that they had residual disease.[3] All had PET: the 4 patients in remission had negative scans, and all but one of the patients with active disease had a positive scan. An important lesson was learned here, as the patient with the negative scan was taking suppressive somatostatin analogues.

This study allowed 14 patients to go to further surgery, and the findings could guide the management in terms of radiotherapy. Some patients elected to stay on medical therapy. Of the surgical cases, 7 achieved complete remission, and the other 7 had IGF-1 levels less than twice the upper limit of normal. Importantly, there were no neurovascular injuries in this series, even though many of these tumours were lateral. There was a single additional pituitary hormone deficit in one patient.

***De novo* cases**

A recently published paper described a series of patients with lateral disease that had previously been deemed unresectable, but all of whom saw improvement following PET-guided surgery.[4] They all had raised IGF-1 levels, which came down into the normal range or to a level less than 1.2 times the upper limit, which may be considered respectable given their starting points.

One of these patients had had two transsphenoidal approaches and radiotherapy 15 years earlier and was on maximum somatostatin analogue. An area towards the posterior aspect of the sella attracted attention: it was debatable by MRI, but clearly very abnormal by PET. A 3D reconstruction was brought CT, MRI and PET together, to show exactly where the remnant was hidden and the important structures nearby. The neurosurgeon and ENT surgeon successfully located the lesion. It is very unlikely that they would have performed surgery without seeing the target by PET. The patient subsequently had an IGF-1 well within control, without any requirement for medical therapy.

Another patient in the series with clear active disease (a large macroadenoma) had a good result on first surgery. The PET tracer was a little more medial than would have been expected from the MRI. Modelling showed where the tumour was in relation to the carotid and, quite remarkably, the surgeons could put this patient into remission, without the need for medical therapy.

Conclusions

MRI should remain the cornerstone of management. However, repeat surgery could figure in modern management algorithms. Scenarios might include patients with persistent disease following incomplete surgery, and those who have had multiple treatments over many years but who still have active disease or are intolerant of the medications. PET may be the guiding light that is needed to provide reassurance that the right area will be targeted in these patients, for whom further investigation is going to be higher risk.

Molecular imaging is an emerging technique which is relevant to all pituitary tumour subtypes but which has particular relevance to acromegaly. [^{11}C]Methionine is a very useful tracer. It is really important to always merge the anatomical imaging with the functional imaging. Some new algorithms are being developed to help potentially provide more precise targets. We can also bring our

endocrine expertise to the table here, because endocrine suppression can distinguish between adenomas and normal pituitary tissue if there is any doubt.

Further comments in Q&A

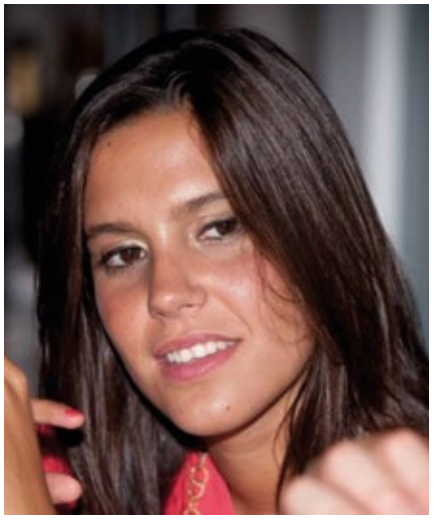
- Somatostatin analogues suppress methionine uptake, so you have to discontinue treatment if you want to perform [^{11}C]methionine-PET. Sandostatin and lanreotide Autogel should be stopped for 12 weeks. For dopamine agonists 4 weeks is sufficient. GH receptor antagonism is fine to continue. The main thing is to show that the disease has reactivated and IGF-1 and GH have risen.
- Lesions down to about 2mm have been detected using this methodology; those were in patients with Cushing's.
- [^{11}C]Methionine was chosen as a tracer that would work across tumour subtypes. It works nicely in prolactinomas, thyrotrophin-secreting adenomas, and in a significant proportion of Cushing's (it is not perfect in Cushing's, partly because of background uptake by the normal gland).
- You can see patients with an elevated IGF-1 but not GH after surgery because in the early post-operative period a GH/IGF-1 disconnect exists. Sometimes IGF-1 takes a little longer to achieve its new set point. If you intervene before IGF-1 has had maybe 12 weeks to find its place, you may act on something when there is not residual disease. The GH is correct in that setting.
- Regarding the choice of IGF-1 assay, it is most important that you get to know the assay you are going to use and how it performs.

REFERENCES

1. Katznelson *et al.* 2014 *Journal of Clinical Endocrinology & Metabolism* **99** 3933–3951.
2. Giustina *et al.* 2020 *Reviews in Endocrine & Metabolic Disorders* **21** 667–678.
3. Koulouri *et al.* 2016 *European Journal of Endocrinology* **175** 485–498.
4. Bashari *et al.* 2020 *Neurosurgical Focus* **48** E8.

Case presentation: Ectopic acromegaly caused by a pancreatic neuroendocrine tumour

Sara Donato *Endocrine Fellow, Portuguese Institute of Oncology, Lisbon, Portugal*



This clinical case of ectopic acromegaly was caused by a pancreatic neuroendocrine tumour. Acromegaly is usually caused by a pituitary adenoma, but can also be caused by ectopic production of growth hormone-releasing hormone (GHRH) or, even more rarely, by ectopic secretion of GH. Ectopic acromegaly may cause important diagnostic dilemmas, because of confusing pituitary findings on MRI and because the serum GHRH assay is not widely available.

A 71-year-old female presented with macroglossia. She had an acromegalic face, needed a larger ring size and her shoe size was enlarged. She had diabetes, hypertension and obstructive sleep apnoea syndrome. She had elevated insulin-like growth factor-1 (IGF-1) on biochemical evaluation, and GH secretion was not suppressed on oral glucose tolerance test (OGTT). So her acromegaly was confirmed biochemically.

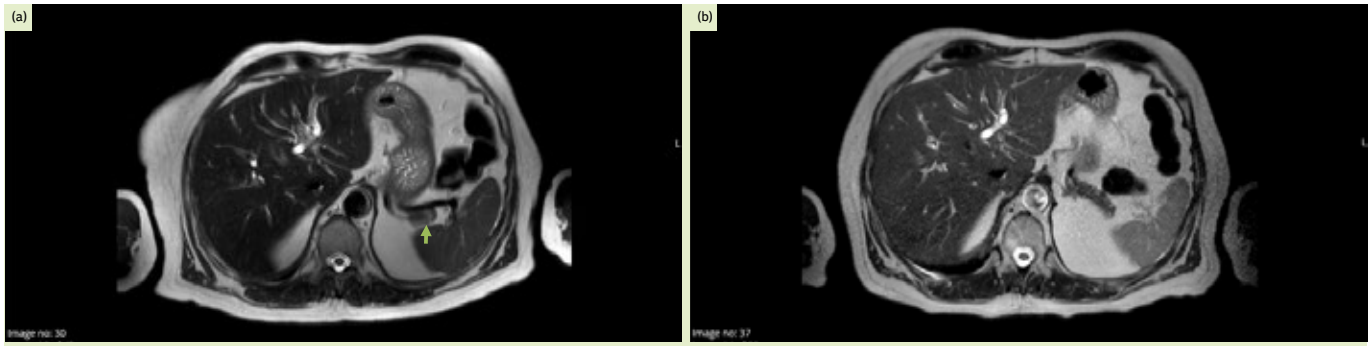
Pituitary MRI was performed, but did not detect an adenoma, although there was some asymmetry. At that point, the possibility of ectopic acromegaly was raised. Since ectopic acromegaly is usually caused by a neuroendocrine tumour, the decision was taken to perform a PET scan with a high sensitivity for these tumours. Intense uptake was observed at the pancreas, and so abdominal MRI was performed, which revealed a pancreatic mass. This suggested ectopic acromegaly caused by a pancreatic neuroendocrine tumour. Evaluating GHRH was delayed by COVID-19.

Treatment was initiated with lanreotide 120mg every 6 weeks, and 6 weeks after first administration both GH and IGF-1 were in the normal range, and the GHRH result was normal.

A pancreatic neuroendocrine tumour, such as was found in this case, is a common cause of ectopic acromegaly. Production of GHRH does not usually normalise with medical therapy, so we hypothesised that the ectopic acromegaly was due to a GH-producing pancreatic neuroendocrine tumour. An ultrasound-guided endoscopy was undertaken to confirm this, in order to collect more samples of GH, IGF-1 and GHRH. However, this was also postponed for several months because of COVID-19.

The patient was feeling much better by then. She described a reduction in hand and feet size, and was breathing and sleeping better.

Somatostatin receptor-specific PET scans have high sensitivity in identifying neuroendocrine tumours. Somatostatin analogues can control GH secretion, but usually have only modest effects on tumour mass. Doubt persists about whether this is a GH- or GHRH-secreting tumour. Acromegaly was apparently due to a pancreatic neuroendocrine tumour with an excellent clinical and biochemical response to therapy. But we cannot exclude the presence of a small adenoma, because of the asymmetry on pituitary MRI.



Abdominal MRI scan (a) before treatment, showing an 8mm nodule on the pancreatic tail, and (b) after 5 months of treatment with lanreotide.

The burden of acromegaly

Chairs: **Sebastian Neggers** *(The Netherlands)* & **Peter Kamenicky** *(France)*

A patient's view of morbidity in acromegaly

Sheila Khawaja *Italy*

I compare my journey to a rollercoaster ride. The symptoms that I had were headaches and constant pain all over my body. The complete loss of control of my life was the thing that impacted me the most. Another issue was having to accept that I would never look the way I looked before.

Acromegaly really changes your facial features completely and, at the height of my disorder, I could not look at myself. I would dress myself and brush my teeth with my eyes closed. I just could not accept what was happening to my face, to my body, and that was the hardest aspect to get over. The headaches would take one half of my head and were so strong that my eyes were watering, and it felt like I was always sniffing. Despite me trying to say I was OK, everyone could see the pain in my face.

I couldn't touch the back of my head; you couldn't touch my hair.

The only thing that would help it was a combination of two drugs: pegvisomant and octreotide. That was my magic cocktail. Right now, I have finally accepted the way I am.

Determinants of morbidity and mortality in acromegaly

Philippe Chanson *Professor of Endocrinology, University of Paris-Saclay, and Head, Department of Endocrinology and Reproductive Diseases, Bicêtre Hospital, France*

Some of the co-morbidities seen in acromegaly include dysmorphic syndrome, hypertension, colon cancer, arthropathy and sleep apnoea.

Hypertension

Between 11 and 54% of patients with acromegaly are hypertensive, according to registry data.[1] There are clearly two main mechanisms: endothelial dysfunction and dysregulation of arterial tone, and also total body water, plasma volume and extracellular water increase. Growth hormone (GH) exerts an antinatriuretic effect on the kidney. Overexpression of the epithelial sodium channel (ENaC) is related to the excess of GH not only in the kidney, but also at other sites where it is expressed, particularly the mucosa. This improves after treatment of acromegaly, after reduction of GH.

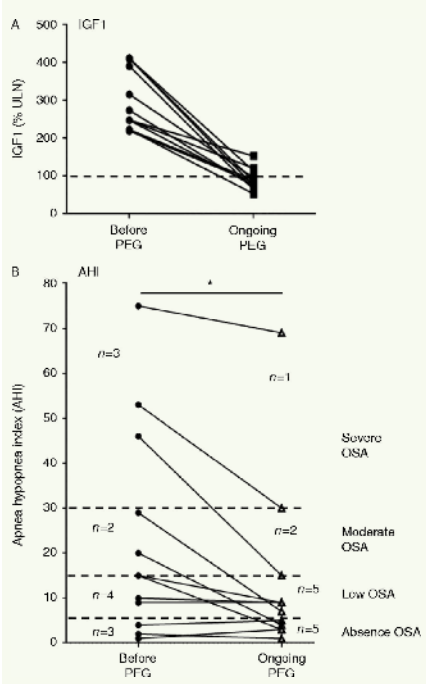
When looking at hypertension and vascular changes during treatment of acromegaly, the clinical improvement parallels the decrease in insulin-like growth factor-1 (IGF-1), but it is not sufficient. Treatment of acromegaly is able to normalise hypertension in only half the patients, so there remain other determinants of hypertension in these patients. The type of antihypertensive treatment that should be used when treating the patient with acromegaly is unknown.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) can be best assessed by polysomnography. Various degrees of severity are indicated by the apnoea–hypopnoea index (AHI): <5 normal, 5–20 mild, 20–30 moderate and >30 severe. Sleep apnoea contributes to morbidity and probably also to mortality in acromegaly.

Sleep apnoea is of the obstructive type in these patients, particularly due to skeletal modifications and soft tissue swelling and mucosal hypertrophy. Sleep apnoea, and particularly OSA, is very common in acromegaly. Reviewing series that have been published showed 69% of patients had OSA at the time of diagnosis, when assessed by polysomnography. It is interesting that when you treat the patient there is often an amelioration and even disappearance of OSA.

After effective treatment of acromegaly, about 60% of patients have a normalised AHI.[2] This means that the OSA remains in 40% of patients with acromegaly; this is further proof that GH and IGF-1 are important determinants of the co-morbidities, but they are not the only determinants. In general, there is clinical improvement in parallel to the decrease in IGF-1. In many patients, there is improvement, even if the index does not normalise (Figure).



Effect of pegvisomant (PEG) on AHI in 12 patients. Clinical improvement parallelled the decrease in IGF-1. Reproduced by permission from *European Journal of Endocrinology* **173** 693–702.[4]

Obesity and weight gain, which may complicate the treatment of acromegaly, have also been shown to be important determinants of OSA. A decrease in weight was found to be associated with an improvement in AHI. In contrast, in those whose AHI worsened, there was often a gain in weight after the effective treatment of acromegaly.

To summarise, treatment of acromegaly improves OSA, decreases its severity and sometimes cures it, but about 40% of patients still have OSA after treatment. We propose polysomnography after treatment, and continuous positive airway pressure might be indicated in these patients. There are many questions, for instance, is it as effective in acromegaly as in those without it? Sometimes there are problems with compliance, as masks may be inadequate masks due to the dysmorphic syndrome.

Cardiac effects of acromegaly

Cardiomyopathy in these patients may be studied by echocardiography or magnetic resonance imaging (MRI). The main features of this cardiac disease include cardiac hypertrophy, which is often associated with diastolic dysfunction, and eventually systolic dysfunction. This cardiomyopathy can occur in the absence of hypertension, diabetes and coronary disease, and is really the effect of GH or IGF-1 on the myocardium. There is an effect on the muscle but also oedema.

We have studied this by MRI, looking at the T2 relaxation time of the myocardium, which reflects the myocardial oedema. We treated 15 patients with acromegaly, performing MRI just before surgery and shortly afterwards, and comparing the results with controls. The T2 relaxation time was significantly longer in patients when compared with normal controls, but it decreased very quickly (within a few days) after treatment of acromegaly. This timescale is not sufficient for a decrease in the muscle hypertrophy of the myocardium, and is probably related to a decrease in the myocardium's water content.

Many studies with different drugs show that the left ventricular mass index (LVMI) and left ventricular ejection fraction (LVEF) improve after treatment of acromegaly, but some factors may interfere with this improvement.[3] Young patients showed LVMI and left ventricular mass at levels similar to those of controls after treatment of acromegaly, but this was not the same in older patients. This is also true for LVEF. Treatment of acromegaly improves myocardial hypertrophy and cardiac dysfunction in the early stages, but the improvement depends on age, the presence of hypertension and the duration of disease.

Coronary heart disease

The prevalence of clinical coronary heart disease in France, Belgium and Italy is low, at just 4–7%, so clearly it is not a big problem. Congestive cardiac failure is seen, but these stages of cardiac myopathy are very rare nowadays. We found that it was present in only 3% of all patients, and the prognosis is poor, even if there is an improvement upon treatment initially.

In conclusion

If we summarise the different effects of treatment, clearly we are able to reduce morbidity, but we cannot really eliminate it, even if patients with acromegaly are treated effectively.

In recent years, the standardised mortality rate is no longer significantly increased. This is probably related to improvements in treatment: patients with controlled GH and IGF-1 do not have increased mortality. (However, in patients who are uncontrolled, an increased mortality rate remains.) Mortality is in general reduced to the expected age- and sex-adjusted rates, and the cardiac and vascular mortality is no longer the leading cause of death. There is probably an exception for cerebrovascular mortality, which is related to previous radiotherapy and remains high. Cancer has become the first cause of death in many studies.

Further comments in Q&A

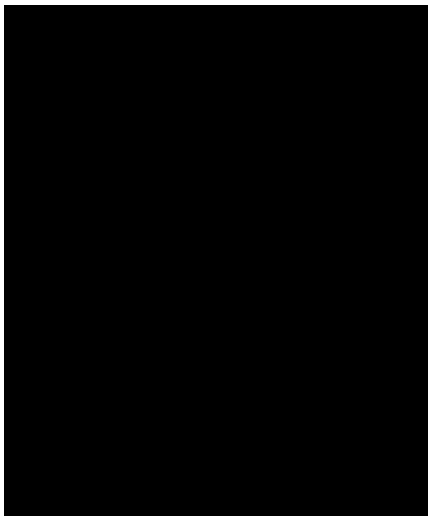
- With regard to the characteristics of osteoporosis in patients with acromegaly, there is some controversy about an increased fracture rate in acromegaly: some teams find an increase, others do not. When patients do not have hypogonadism, they may have a normal or even increased bone mineral density (BMD). Hypogonadism, when present, clearly decreases the BMD.
- The possibility of improvement of central sleep apnoea upon treatment (in contrast to peripheral sleep apnoea) is unknown.
- Improvement in acromegaly upon treatment is related to the duration of acromegaly. For all the co-morbidities, the duration of acromegaly must be taken into account, as this fixes the complications. When the disease is long-standing and pretty much incidental, then aggressive treatment is unlikely to have much impact on complications.
- The improvement in cardiovascular mortality is more a general background effect than the effect of our treatment. Ischaemic heart disease has improved in many populations. The increase in cancer mortality suggests it is general cancer mortality rather than one particular type of cancer. Jakob Dal commented that a study on cancer in the Danish cohort showed the overall hazard ratio was only about 1.1; it was driven mainly by colorectal cancer.

REFERENCES

1. Maione *et al.* 2017 *European Journal of Endocrinology* **176** 645–655.
2. Attal & Chanson 2010 *Journal of Clinical Endocrinology & Metabolism* **95** 483–495.
3. Colao *et al.* 2004 *Endocrine Reviews* **25** 102–152.
4. Kuhn *et al.* 2015 *European Journal of Endocrinology* **173** 693–702.

The socio-economic impact of acromegaly

Jakob Dal *Department of Endocrinology and Diabetes, Aarhus University, Denmark*



Acromegaly is associated with significant morbidity, psychological distress and a decreased health-related quality of life, and this is probably even worse in female patients. The onset of acromegaly is insidious, with a diagnostic delay of 5–10 years. We have previously examined the incidence, prevalence, complications and long term prognosis of acromegaly in Denmark.[1] A recent study by Lenders *et al.* showed that female patients may have a longer diagnostic delay, a worse quality of life and a higher prevalence of hypertension and diabetes than male patients with acromegaly.[2] The Danish data show that female patients have double the risk of heart failure, diabetes and sleep apnoea compared with male patients.

Socioeconomic data from nationwide studies in acromegaly are scarce and rarely focus on gender differences. We wanted to use the Danish nationwide registries for our research. They have advantages in that they are population-based, have complete follow-up and, as every Danish citizen has a unique identification number, different registries can be used to gather a lot of data on each patient. It is also easy to make a comparison cohort. In Denmark there are five centres that treat acromegaly, and the information from them was collated to find all the patients. The records were checked to see if the patients really had the disease, and different clinical variables that were not available in our registry were picked out.

Study objectives

Our aim was to study the different socio-economic factors in acromegaly. These included retirement, different social security benefits, annual income, co-habitation, separation, parenthood and education level. All patients with acromegaly diagnosed from 1977 to 2010 were identified, and they were matched to a control group (citizens with the same birthdate and gender).

Our cohort comprised 576 cases with acromegaly, with a median age at diagnosis of 47 years (range 10–89). The gender split was approximately 50 male:50 female. Females had lower IGF-1 levels, which has been shown previously. Comparing younger versus older patients (50% of the cohort in each group), the younger group showed larger adenomas and higher IGF-1 levels, which is also well known.

Results

Cox regression showed an increased hazard ratio (HR) of 1.43 for patients being retired. In the 5-year period prior to diagnosis there was also an increased HR for retirement of 1.15. Conditional logistic regression gave an odds ratio above 1 for retirement before diagnosis, which kept increasing after diagnosis. Linear regression showed that the difference in retirement between patients and their controls was significantly higher in females compared with males. The difference between the genders increased significantly until 15 years after diagnosis.

Patients with acromegaly showed no increased use of social security benefits prior to diagnosis, but there was an increased use in the first 3 years after diagnosis. The difference between patients and their controls was significantly higher among females compared with males, and this tendency towards an increase persisted for up to 15 years.

There was no difference in annual income between patients with acromegaly at diagnosis and the reference population. However, in the 15 years following diagnosis, the difference increased significantly, with a higher income among those with acromegaly. There was no difference between the genders. This may be because patients with low income, manual labour jobs are more prone to retire than those with high income jobs.

Our studies have previously shown that, in the last 20 years, there is no significant increase in mortality associated with acromegaly. This current study showed an increased mortality (HR 1.43), probably because the data extend back to 1977.

Education was not significantly decreased among the group with acromegaly, possibly because of the quite high age at diagnosis. There was no increase in separation associated with acromegaly, but there were decreases in cohabitation (HR 0.69) and parenthood (HR 0.56). Parenthood was also significantly decreased in the 5 years before diagnosis of acromegaly (HR 0.71). There was no significant difference between genders for these parameters, but females tended to have a worse outcome than males, especially regarding cohabitation and parenthood.

Younger patients were comparable with older patients in most respects though retirement risk was higher in the younger group and the risk of separation was higher among the older group.

Subgroup analysis

We defined various subgroups. The remission subgroup included patients having an IGF-1 level lower than 2SD above normal at 2–3 years after diagnosis. The non-remission subgroup comprised patients with an increased IGF-1 at 3–5 years after diagnosis. The surgery subgroup included patients who were treated with surgery only, and the final subgroup for hypopituitarism had patients who had received replacement therapy with pituitary hormones at some point.

The subgroup analysis examined retirement, separation, cohabitation and parenthood (see Table). The most notable pattern was seen in the remission group compared with the non-remission group. The highest rates of retirement were found among the hypopituitarism group, which makes sense since these patients probably have more severe disease, with larger adenomas, and are probably treated more frequently with radiotherapy.

Conclusions

In conclusion, socioeconomic status is impaired in patients with acromegaly even before diagnosis. Females, and those without disease remission, have worse outcomes. Early diagnosis and effective treatment of acromegaly could be important in mitigating the negative impact on patient-related outcomes.

Further comments in Q&A

- It is unclear why female patients do worse. Females have an increased risk of co-morbidities, which could affect their ability to work. Also, females have a worse quality of life score regarding self-image and relationships, which could impact their social life, parenthood and so forth.
- The mean number of children per woman or man with acromegaly could have been calculated, but we did not do that. The frequency of pregnancy increased during the follow-up period, probably due to better treatment of acromegaly, but also fertility treatment.

REFERENCES

1. Dal *et al.* 2016 *European Journal of Endocrinology* **175** 181–190.
2. Lenders *et al.* 2020 *European Journal of Endocrinology* **182** R67–R82.

Subgroup analysis: see description of the subgroups in the text (HRs values are shown, with 95% CIs in parentheses)

	Remission	*P* value	Non-remission	*P* value	Surgery only	*P* value	Hypopituitarism	*P* value
Retirement	1.19 (0.92-1.54)	0.18	1.47 (1.02-2.11)	0.04	1.39 (1.05-1.86)	0.02	1.85 (1.38-2.47)	<0.01
Separation	0.70 (0.36-1.34)	0.83	1.08 (0.59-1.96)	0.80	1.25 (0.71-2.21)	0.45	0.85 (0.51-1.45)	0.56
Cohabitation	1.11 (0.59-2.09)	0.75	0.50 (0.22-1.21)	0.09	0.39 (0.16-0.94)	0.04	0.63 (0.38-1.05)	0.07
Parenthood	0.63 (0.30-1.33)	0.23	0.55 (0.23-1.34)	0.19	0.55 (0.26-1.16)	0.128	0.60 (0.33-1.00)	0.05

Acromegaly and headache

Miles Levy *University Hospitals of Leicester NHS Trust, Leicester, UK*

General perspectives

Activation of the trigeminal nerve causes the trigeminovascular reflex, which is the basis behind all headache. Headache can either be primary or secondary. Primary means you have a normal brain scan, with no other pathology.

Migraine is the commonest example. If you do a functional magnetic resonance imaging (MRI) scan, you will see activation of the ipsilateral brain stem and that will cause loss of descending inhibition of pain. So, the pain comes first and then, after that, you get the trigeminovascular reflex. It used to be thought that migraine was a disease of the blood vessels but it is, in fact, a disease of the central nervous system (CNS) with secondary vascular changes. Because of the anatomical relationship of the pterygopalatine ganglion, you often get autonomic activation to do with the same reflex.

The rarer forms of primary headache occur in the ipsilateral hypothalamus, which is an organ of interest because that is the basis of all the trigeminal autonomic cephalgias (including cluster headaches). Ipsilateral hypothalamic activation is the hallmark of the trigeminal autonomic cephalgias.

Secondary headache implies other pathology, which is essentially irritation of the meninges, by blood or pus, or increased cerebrospinal fluid (CSF) pressure, for example. A haemorrhage in a pituitary tumour is painful probably because of cytokines from the blood in the cavernous sinus.

Pituitary headache

It seems there is no correlation between the size of tumour and headache. Some patients have very small microadenomas but significant headaches. Others, who have very large non-functional tumours, may not have any headache at all. They present with optic chiasma problems or hypopituitarism but not necessarily pain.

Does pain result from invasion of the neurovascular structures: the cavernous sinus, the internal carotid artery, the trigeminal ganglion? Again, there is no clear correlation between just cavernous sinus invasion and pain, although we will certainly have patients who have ipsilateral pain to cavernous sinus invasion. It seems that it is not related just to the physical presence of the lump.

Acromegaly seems to be the most pronociceptive co-morbid condition of all the pituitary tumours. Is that because of secretion of a peptide that causes trigeminovascular irritation? We are talking about hormonal mechanisms, and we know that somatostatin analogues (SSAs) can give immediate analgesia. Pain must somehow be related to growth hormone (GH), but it can be uncoupled from GH: there may be an, as yet unidentified, pronociceptive peptide for which we still need to hunt.

Pituitary headache occurs in about 50–70% of pituitary tumours. It is much more common in secretory tumours, particularly in those secreting GH. Molecules such as substance P, calcitonin gene-related peptide and neuropeptide Y are all associated with primary headache and present in pituitary tumours, but there is no association with pituitary headache.

Does the analgesic effect of SSAs depend on the receptor subtypes present in the individual patient? Note also that the somatostatin receptor heterodimerises with the opiate receptor.[1] They are expressed together and may have synergistic effects on CNS pain.

Acromegaly headache phenotypes

Migraine is by far the commonest headache phenotype, followed by a relatively high prevalence of trigeminal autonomic cephalgias (TACs), which are rare headache syndromes in the general population. The third phenotype to know is the International Headache Society (IHS) pituitary headache. It is important to be able to phenotype headaches (see Table).

Example case presentations

Case 1

A 23-year-old woman presented to neurologists with headache. It was always right-sided and there were significant cranial autonomic features, but migrainous features as well. So IHS migraine, with autonomic features.

The patient was diagnosed with early acromegaly. She had a GH-secreting adenoma and thus an indication for surgery.

Acromegaly headache phenotype

Migraine

Migraine is defined as follows.

1. At least five headache attacks lasting 4–72h:
   - unilateral location
   - pulsating quality
   - moderate or severe intensity
   - aggravated by routine physical activity.

2. During headache, at least one of:
   - phonophobia and photophobia
   - nausea and/or vomiting.

On functional MRI, migraine appears as a disorder of ipsilateral brain stem activation, not a disorder of the blood vessels.

Trigeminal autonomic cephalgias

TACs are characterised by autonomic symptoms: ipsilateral ptosis, conjunctival congestion, lacrimation, nasal stuffiness or rhinorrhoea. These headache syndromes can be characterised according to how long they last:

- SUNCT/SUNA last for seconds, though patients may have 20 attacks a day
- paroxysmal hemicrania lasts for about 30 minutes, and is more common in women
- cluster headaches lasts hours, and are much more common in men
- hemicrania continua is a persistent unilateral pain.

Patients with pituitary headache have more TACs than the general population. Activation of the ipsilateral hypothalamus is important in these syndromes.

IHS pituitary headache

This is just a description of headache attributed to pituitary hypersecretion. It is characterised as a bilateral frontotemporal or retro-orbital headache associated with prolactin, GH, acromegaly or Cushing's. The headache develops at the same time as the endocrine presentation and resolves within 3 months of either surgery or medical treatment.

Very unfortunately, she had a CSF leak mid-operation. The disease went into remission clinically and biochemically, but the patient noticed that the headache had changed. The cranial autonomic headache had completely disappeared, but she had developed postural

headache which was worse on standing, worse at the end of the day and better with caffeine. This new low CSF pressure headache eventually improved and went away.

Headache changes in real time, and you need to phenotype the headache every time you see the patient. Headache may be a good clinical marker of GH activity, but migraine is very common in young women. Any change to the internal physiology can trigger migraine, so you must carefully differentiate what is causing it.

Case 2

A 29-year-old woman developed secondary amenorrhoea, with headache which was left-sided, retro-orbital and migrainous with no autonomic features. It was unresponsive to analgesia.

We wrote up and published this case because she was also acromegalic.[2] After surgery, she had persistent headache, and the migraine was identical to the presentation. She was not in remission. We gave her octreotide to control the acromegaly and her headache completely disappeared. When we tried changing her to lanreotide the GH was controlled but her headache was not. We put her back on to octreotide at her request and the headache went away.

What we observed here was that both octreotide and lanreotide controlled the GH very nicely, but only octreotide controlled the headache. Therefore, we suggested that there was an uncoupling between GH and headache. Comparing receptor affinity, octreotide binds better than lanreotide to receptor 3. We hypothesised that maybe receptors 2 and 5 are coupled to GH and receptor 3 is coupled to pain.

Further comments in Q&A

- Regarding whether the frequency and intensity of headaches have anything to do with the growth velocity of the pituitary tumour, a couple of studies are looking at intrasellar pressure and whether there is a link between this and headache. It is probably related to a combination of physical and biochemical characteristics.
- It is worth considering the use of oral versus parenteral drugs in headache. Cluster headache responds very well to intramuscular sumatriptan but not to oral sumatriptan. If the patient had a very difficult acute headache, the parenteral version might work better, because there is a critical change in the blood brain barrier during even primary headache.
- I am sure the thing to do is to manage acromegaly exactly as you always would do, but just to consider whether the patient has primary headache, in which case there is a role for the neurologist. The question for us as endocrinologists is whether we really think the headache and acromegaly go hand in hand. These patients often fall between the cracks of neurology and endocrinology and end up getting a bad deal. It would be great if specialists talked more to each other. Philippe Chanson added that he thought the relationship between endocrinologists and neurologists or pain specialists is not so easy with acromegaly patients.
- Some of the cytokines are elevated and there does seem to be a link with headache. Steroids are a fantastic treatment for all kinds of primary and secondary headache, probably as a result of the suppressive effect on inflammatory cytokines.

REFERENCES

1. Somvanshi & Kumar 2014 *PLoS One* **9** e85193.
2. Levy MJ *et al.* 2003 *Headache* **43** 794–797.

Case presentation: A patient with headache

Sebastian Neggers *Associate Professor of Medicine and Endocrinology, Erasmus University Medical Center, Rotterdam, The Netherlands*

This case is of a woman who was 55 years of age. She had been quite young when she was diagnosed with acromegaly. Her main two complaints at that time (1984) were bitemporal hemianopia and headache. She was operated on in 1985, and also received post-operative radiation. Although the post-operative computed tomography scan looked quite good, her insulin-like growth factor-1 (IGF-1) levels were still elevated, and she still had headaches. She was given subcutaneous octreotide, which controlled her headaches completely and her IGF-1 well.

Magnetic resonance imaging about 10 years ago showed an empty sella, but she still had high IGF-1 levels. She was switched to long-acting somatostatin analogues, but these rendered her headaches uncontrollable. Many other drugs and drug combinations were tried, but none worked as well as subcutaneous octreotide: she used on average 500µg 8–10 times a day. This was the only way she could control her headaches, but clearly it was a disruptive routine for her.

Dr Neggers saw her for the first time in 2012. After some persuasion, she switched to pasireotide LAR 40mg every 4 weeks. That controlled her IGF-1 very well, so well that she became growth hormone (GH)-deficient. Her headaches were gone, and she did not use her subcutaneous octreotide any more.

The question then was, what should we do? We tried many pasireotide dosing options to try to improve the GH deficiency while controlling the headaches. In the end, we settled on pasireotide 20mg every 4 weeks, and accepted that she might have GH deficiency. We explained to her what the issues might be with that; she agreed, and has been treated now for 6 years. She is satisfied with the arrangement, and her quality of life has increased significantly.

Further comments in Q&A

- Miles Levy remarked that the case describes a patient who responds really well to a long-acting drug, which goes against all headache pharmacology. This suggests we must be looking at an endocrine explanation: pasireotide must be having an endocrine suppressive effect on a peptide.
- Peter Kamenicky added that he clearly would accept a slight GH deficiency rather than inject short-acting octreotide 10 times a day. The IGF-1 level may be a consequence of her previous radiotherapy and is not really linked to her quality of life, but the headaches are very debilitating.

The current and future landscape in acromegaly management

Chairs: **Maria Chiara Zatelli** *(Italy)* & **Niki Karavitaki** *(Italy) (Denmark)*

Acromegaly treatment: a patient's experience

Sheila Khawaja *Italy*

The treatments were a combination of injections and pills. At the very beginning, I became diabetic and I had to take insulin shots for 18 months. Gradually, that was replaced with pills and, eventually, the diabetes disappeared. My doctor was surprised; I was not reacting as per the textbooks.

Many drugs were tried in an attempt to find the right cocktail for me, and because my quality of life was so miserable the doctor eventually prescribed the combination of octreotide and pegvisomant. At one point the administration in the hospital refused to give me a drug, because they did not believe I had this disorder. My endocrinologist was very upset and called his colleague in another hospital. I was shuttling between the hospitals to collect the drug from the hospital pharmacy, which was not convenient for a patient.

Gradually, the drug doses were reduced, some were replaced, some were taken away and eventually it was possible to manage without pegvisomant.

I do not remember having any adverse effects at all. I think it was just burdensome to have so many meds to take at different times of the day, to be so careful and to keep everything at the right temperature. It was quite a chore when I was travelling. I had to travel with a pegvisomant ice cooler, and I always had problems with the airlines.

Case presentation: management of acromegaly

Osamah Hakami *Queen Elizabeth Hospital, Birmingham, UK*

This case examines the approach to take when remission from acromegaly is not achieved by surgery. The patient was a 19-year-old female, who was seen by her GP for a 10-month history of secondary amenorrhoea and a 5-month history of headache. Her prolactin was elevated, and pituitary magnetic resonance imaging (MRI) showed a large pituitary macroadenoma with optic chiasma compression, significant cavernous sinus invasion and encasement of the right internal carotid artery (see Figure).

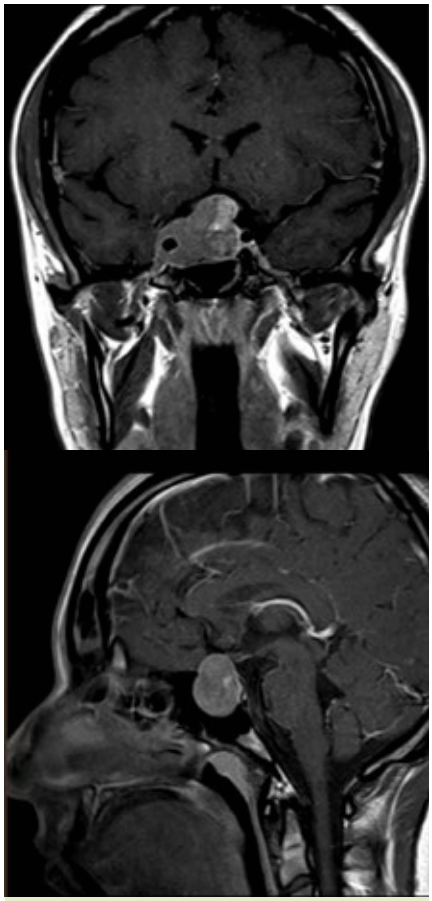
In August 2017, she was referred to our pituitary service. Her headaches were moderate to severe, enough to affect her daily life, but she had no symptoms of acromegaly or Cushing's disease, and did not report any visual manifestations. Her past medical history was not significant.

Clinically, she did not have any signs of acromegaly. On neuro-ophthalmic review, she had bilateral superotemporal visual loss. Hormonal assessment revealed an insulin-like growth factor-1 (IGF-1) level twice the upper limit of normal, and elevated growth hormone (GH) which failed to suppress on oral glucose tolerance test. She was oestrogen-deficient, but her thyroid function was normal.

In October 2017, she underwent transsphenoidal surgery, and the sellar and suprasellar components of the tumour were removed. Pathology confirmed the presence of a sparsely granulated tumour with high prolactin activity. Because she was young, genetic testing was offered, but it came back negative for *AIP*.

Post-operatively, her vision returned to normal; her adrenocorticotrophin (ACTH), thyrotrophin and prolactin remained normal. However, she had persistent acromegaly biochemically. At 3-month follow-up MRI in December 2017, the presence of a significant residuum within the right cavernous sinus was confirmed. In February 2018, her IGF-1 and GH remained significantly elevated and she was started on long-acting octreotide.

After a further 4 months, her GH and IGF-1 levels remained elevated, with no significant response to the somatostatin analogue, and pituitary MRI showed growth of the residuum.



MRI on presentation showed a large pituitary macroadenoma with optic chiasma compression, significant cavernous sinus invasion and encasement of the right internal carotid artery.

A second transsphenoidal surgery for further debulking was performed in August 2018, and was followed by proton beam radiotherapy.

In January 2019, she was started on the GH receptor antagonist pegvisomant due to her lack of response to somatostatin analogues. After 7 months, her IGF-1 finally normalised on pegvisomant 25mg daily, her periods returned and became regular, and her ACTH axis remained normal. Her last MRI scan in June 2020 showed a small residuum in the cavernous sinus which did not grow on pegvisomant.

The long term plan is to take her off medical treatment, following the success of radiotherapy, and to continue monitoring her pituitary function. She will have lifelong follow-up in the pituitary service.

This highlights the aggressive nature of the tumour causing acromegaly in her case. Due to the young age of onset, the acromegaly has significantly affected the patient's social life and sense of well-being. She had significant anxiety about the tumour's prognosis and is apprehensive about requiring lifelong medication.

Further comments in Q&A

- Niki Karavitaki reflected that the diagnosis of acromegaly is devastating in any adult patient but for a young person it may be even worse. This is an important point which may quite often escape adult endocrinologists.

Brief overview and limitations of current surgical approaches

Pietro Mortini *Head, Neurosurgery and Radiosurgery Unit, San Raffaele University Health Institute, Milan, Italy*

Surgical approaches

The transsphenoidal route approaches through the nose: the sphenoid sinus is crossed in order to reach the pituitary fossa. Transcranial approaches are through the skull from above. They are very rare, and are generally used for giant pituitary tumours or tumours that involve the optic pathways. Recently, we developed an orbital approach to the compressed optic nerve. We achieved very good results, with visual improvement in 97.4% of cases after surgery. Even with transcranial surgery, pituitary function is spared in roughly half the patients.

There are three magnification systems in use. The microscope is the oldest, most developed and widely used technique. This equipment gives a direct view of the pituitary, and allows assistance by a second surgeon. Use of an endoscope enables the surgeon to view a reconstructed image, generated by a small camera that is put inside the body. The exoscope is a hybrid between the microscope and the endoscope.

Biology is the most important factor to consider when planning pituitary surgery. It is necessary to define whether the cavernous sinus is displaced or invaded. It is not possible to cure a tumour that has extended into the cavernous sinus, though one which has displaced the cavernous sinus may be cured.

Mortini *et al.* refer to a personal series on microsurgical treatment of growth hormone (GH)-secreting and other tumours in 2145 patients.[1] In GH-secreting tumours, the cure rate is far better for microadenomas than for macroadenomas, and is minimal in invasive tumours. The efficacy of microsurgery is very high, and far superior to endoscopy.

The importance of experience

The surgeon's experience, rather than the technique used, is paramount. The quality of care and the rate of cure are high if a single surgeon does the majority of surgery.[2] Microscopic and endoscopic techniques have similar results in terms of cure. Of course, the experience of the team is significant, and is the reason why hospital volumes are important.

The complication rate is strongly correlated with the surgeon's experience. Data collected from 900 surgeons in 1997 recorded that 86% operated on <200 cases in their lifetime, 9% on 200–500 patients, and 3% on >500 patients.[3] In the first group, there were huge numbers of complications, including anaesthetic complications.

Cases are, however, widely dispersed. One study considering more than 5000 patients in the USA showed the median annual operation rate was 10 per hospital or 3 per surgeon. The number of complications is strongly related to the hospital volume.

Over recent years, endoscopic approaches have become more popular. The conclusion of one paper which looked at data from nearly 6000 patients over 25 years was that there was no evidence to support one pituitary surgical technique over another: both endoscopic and microscopic approaches have the same result in terms of cure, but endoscopic approaches have a higher complication rate. The cost of endoscopic procedures, even in patients without complications, is higher than those using microscopy.

GH-secreting tumours

Despite the extensive surgical resection advocated by endoscopic approaches, the chances of cure of invasive tumour are not remarkably higher. Multimodal therapy is important.

In the only prospective study comparing the outcome of transsphenoidal surgery using microscopy and endoscopy,[4] the outcomes were very similar, but the endoscopic group had a significantly higher risk of complications. Moreover, the extensive surgery advocated in the endoscopic technique is linked to very high complication rates, with cerebral nerve palsies in 27%, and serious blood loss. For endoscopic surgery, the operating time is 95–185min, whereas the mean time for microscopic surgery is <45min. The long duration of surgery has been reported as a risk factor for complications, in particular in patients with acromegaly.

Nasal complications are much more common in patients who have had an endoscopic procedure. After microscopic surgery, 94% have normal nasal function.

Finally, endoscopy has a longer learning curve. There is no clear reason to consider endoscopy better than microscopy. Microscopic techniques are still the gold standard for pituitary surgery, particularly in GH-secreting tumours.

Further comments in Q&A

- From the surgeon's point of view, pretreatment of acromegaly patients using long-acting somatostatin analogues makes no difference, but it is helpful for the anaesthetist, since patients who have been pretreated are in better general condition.
- The patient is prepared the day before surgery. After surgery, they are followed-up for 24 hours. In the absence of complaints such as headache or fever, the patient can be discharged. So their stay is 3 or 4 days maximum. Early discharge is only appropriate if you have an excellent and experienced surgeon.

REFERENCES

1. Mortini *et al.* 2018 *Endocrine* **59** 72–81.
2. Gittoes *et al.* 1999 *Quarterly Journal of Medicine* **92** 741–745.
3. Ciric *et al.* 1997 *Neurosurgery* **40** 225–236.
4. Starke *et al.* 2013 *Journal of Clinical Endocrinology & Metabolism* **98** 3190–3198.

Current medical treatments and their limitations

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There are many goals of treatment in acromegaly. We need to consider acromegaly as an oncological disease, because there is a tumour; so we have to stop tumour growth and hormone excess. One of the main strategies is surgical resection. The other strategy is to try to stop hormone excess using medical therapy. Here, there are a number of different approaches. Furthermore, we have to tailor medical therapy. There is no one strategy that is good for every single patient.

Some considerations are shown in the Table.

Factors to consider when choosing treatment options
Age
• expected span for healthy life
Severity of disease and comorbidity
• tumour size and location • glucose intolerance, cardiovascular complications, headache
Risk/benefit
• effectiveness and adverse effects • health economics: cost versus effect • duration: adherence to treatment

Somatostatin analogues

We have seen good results with the conventional first generation somatostatin analogues (SSAs) that we have used for over 25 years. If patients are treated with SSAs before surgery, almost half gain biochemical control in 1 year. As first-line therapy, they can control growth hormone (GH) and insulin-like growth factor-1 (IGF-1) together. They have good tolerability and can also obtain a significant reduction in tumour mass, sometimes as much as 75% shrinkage.

Cabergoline

Many patients starting with IGF-1 that is not very elevated could benefit from the dopamine agonist cabergoline. Cabergoline monotherapy can completely control IGF-1 secretion. In patients aged 65 and older, the use of cabergoline can be tried before other drugs. Cabergoline is also very efficient in preventing insulin resistance and diabetes.

Appropriate dosages

In the early 1990s, we moved from subcutaneous octreotide to the octreotide LAR formulation. We had previously been able to modify the dosage in terms of individual tolerance and efficacy, but with the LAR we were forced to use one of three doses: 10, 20 or 30mg. We examined how we could modify the dose.[1] If we escalated the patients who were not completely responsive to a 20mg dose at 3 months to a dose of 30 or 40mg, after 2 years only a small minority of patients were not fully controlled. And even the patients whose acromegaly was not completely controlled could have as much as 60% shrinkage of the tumour. The use of SSAs as reference medical therapy for acromegaly probably needs higher dosages than 30mg.

Other approaches

Patients who are not fully responsive to first generation SSAs or cabergoline may be treated with pasireotide (a next generation SSA), pegvisomant (a GH receptor antagonist), or a combination of first generation SSA and pegvisomant.

Experience with pasireotide

Pasireotide (Signifor) was approved for treatment of acromegaly in 2014. The head-to-head study comparing pasireotide versus octreotide as first-line treatment demonstrated pasireotide's superiority. Patients who have resistant acromegaly, or are not fully responsive, are possible candidates for pasireotide. In the PAOLA study,[2] patients were randomised into three groups. One group remained with octreotide or lanreotide, and the others received either 40 or 60mg pasireotide. Only the patients who switched to pasireotide could obtain completely controlled GH and IGF-1, and most had changes in tumour volume.

Pasireotide creates an imbalance between the secretion of insulin and that of glucagon. Consequently, hyperglycaemia, diabetes and glucose-related disease may be observed when patients are treated with pasireotide. This effect is related to the drug itself; it is not a deterioration of glucose tolerance independent of the use of pasireotide.

Pegvisomant

Pegvisomant acts directly on the GH receptor to reduce the effect of GH, and improves glycaemic control quite rapidly. The only problem with pegvisomant is that it does not control tumour size. It appears to be a very safe and efficacious treatment, and is very efficacious in combination with SSAs.

Combination therapies

The combination of an SSA and cabergoline has been found to be very efficient, and is much cheaper than an SSA plus pegvisomant. Up to 80% of patients were completely controlled using this combination therapy. The possibility of combining cabergoline with pegvisomant has also been proposed. Some reduction in IGF-1 has been demonstrated.

Factors affecting disease control

Which factors may contribute to inadequate disease control when using all the drugs and strategies described? These include the characteristics of the individual tumours (some are larger and more aggressive than

others). Secondly, in the past, we have probably used suboptimal dosing of medical therapy. Other factors include adherence to treatment, inertia, cost and availability of drugs and molecular resistance to medical therapy. In this time of personalised medicine, we need to tailor the treatment to each patient. There is no one single strategy that can cover the needs of everybody.

Further comments in Q&A

- Pasireotide and pegvisomant are not prescribed as first-line medical treatment, despite so many patients displaying resistance to SSAs. This is because the regulatory agencies have identified them as more costly, and so should be used as second-line therapy. There is also a question of side effects, until we gain more clinical experience.

REFERENCES

1. Colao *et al.* 2007 *European Journal of Endocrinology* **157** 579–587.
2. Gadelha *et al.* 2014 *Lancet Diabetes & Endocrinology* **2** 875–884.

What is new on the horizon for acromegaly?

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There are several optimal clinical outcomes for acromegaly (see Figure) which we must take into consideration as clinicians. Among these, it is important to ask patients how they feel about the management of their condition.

Furthermore, many factors are involved in deciding which medications to use, and we have to think of all of them. Efficacy, availability and safety are essential considerations, but frequency of administration, patient preference and tumour volume are also important, amongst others.

Response to medication

Assessment of disease control in patients treated with long-acting somatostatin receptor ligands (SRLs) varies according to when insulin-like growth factor-1 (IGF-1) levels are measured during the month following injection. This is very important, and a decision and clear recommendation are needed regarding when IGF-1 should be sampled.

Why do some patients have more resistance to octreotide and lanreotide? Clearly it is important to use the right dose. Some features are also particularly relevant, such as sparsely granulated tumours, hyperintensity on magnetic resonance imaging and low levels of somatostatin receptor 2 (SSTR2). The most recent large study looked at data from more than 600 patients.[1] The most important factors for biochemical response were IGF-1 at baseline and body weight. For non-response, relevant factors included age at diagnosis, surgery at baseline and whether the tumour was a macroadenoma.

Regarding predictors of response to pegvisomant, many groups have shown that the dose is essential in both single therapy and in combination treatment. Patients that are older, male, without diabetes, with low IGF-1 at baseline and with normal or low body mass index will respond better to pegvisomant.

The Pituitary Society update to acromegaly management guidelines has recently been published.[2]

Another study has looked at several forms of combination therapy, taking cost-effectiveness into consideration.[3] Low-dose octreotide or lanreotide plus weekly pegvisomant was found to be the cost-effective and also efficacious option for patients requiring combination therapy.

A combination of pasireotide and pegvisomant can yield biochemical control rates exceeding 70%. The addition of pegvisomant did not, however, ameliorate the high rate of pasireotide-induced hyperglycaemia. Patient selection for this combination should be carefully considered, particularly given the high cost. However, if patients are not controlled, then the cost would be even higher, due to the comorbidities.

New drugs in development

None of the following drugs have been approved in Europe, though oral octreotide capsules were approved in the USA by the Food and Drug Administration in June 2020.

Oral octreotide

The OPTIMAL study included patients with acromegaly. They were randomised to either oral octreotide capsule or placebo. Patients were previously controlled on either octreotide or lanreotide, and most were on a medium or high dose.

Results showed that 75% of patients on oral octreotide completed 36 weeks without the need for reversion to prior injectable therapy. The mean IGF-1 was maintained on medication and the median time to loss of response in the placebo group was 16 weeks. With strict IGF-1 criteria, 58% of patients receiving oral octreotide maintained the response at the end of the double-blind placebo-controlled phase, and 90% of the octreotide oral capsule group chose to continue into the extension phase. Interestingly, no new unexpected safety signals were observed.

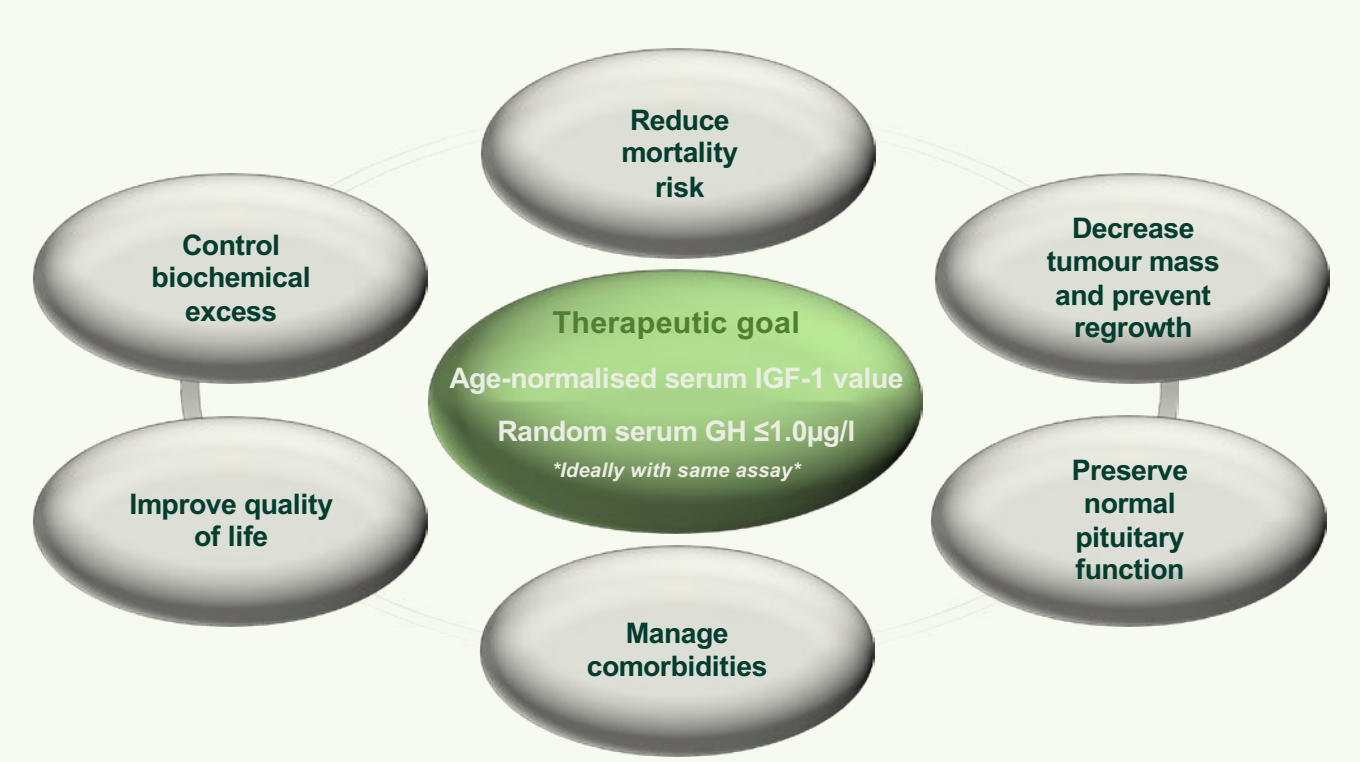
The drug is initiated at a dose of 40mg/day. It is very important to make sure that the patient does not eat for 1 hour before taking the drug or for 2 hours afterwards, to maximise bioavailability. Because most of the patients were found to need a higher dose, we should probably start at 60mg/day, initiate it at the time of previously scheduled injections and uptitrate very quickly, every 2–4 weeks, based on IGF-1 and clinical symptoms.

Paltusotine

Paltusotine is in clinical trials. It is orally bioavailable, just like other traditional oral small molecule drugs, and is a non-peptide. The oral bioavailability is high, about 70%, with a half life of 42–50 hours. Since the absorption is so good, administration could potentially be once a day.

Antisense drugs

Traditional drugs work on a disease-associated protein, while antisense drugs prevent the translation of the receptor itself.



Optimal clinical outcomes in acromegaly. It is also important to ask patients how they feel about the management of their condition.

The new generation of antisense drugs are GalNAC-modified, which markedly increases the potency of hepatocyte targets. IONIS-GHR-L_{RX} is a ligand-conjugated antisense (LICA) drug. This drug is still in phase II and there are no publicly available data, but there are some noteworthy results on safety, given that this is a very interesting mechanism. If we can change the receptor and have a longer half-life medication, this would be potentially very useful for a lot of patients who require combination therapy.

The safety profile for this new generation of antisense drugs has been studied in more than 600 patients, and in more than 200 patients for 6 months or longer. The data are derived from several large studies on anti-sense drugs used to treat various conditions in the USA. A favourable safety and tolerability profile has been observed.

Veldoreotide

The other SRL with a unique SSTR profile is veldoreotide. It shows balanced binding to SSTR2 and -5 (so is similar to pasireotide) but has unique binding to SSTR4. SSTR4 is very important for glucose and has effects on insulin. Several *in vitro* studies from Germany show different effects on insulin with different doses of veldoreotide.

In conclusion

Several medications, some of them approved in the USA, are likely to come to Europe. Many clinical trials are in phase II around the world. Although we are making progress towards personalised therapy, many challenges remain. The most important thing is to reduce the delay in diagnosis because, although there are many treatments, it is very hard to get a good result if the tumour is very large.

Doctors need to understand their patients' needs throughout diagnosis and treatment. Again, the age at which a subject presents could have a huge impact on the patient's life and quality of life. Knowing that you have a tumour and you need treatment for life at an early age is very daunting.

It is helpful to take a multidisciplinary approach, to ask about patient preferences and to understand patient-related factors such as cost and financial worries overall. Quality of life and health economics should be integrated into clinical trials. There is no answer at the moment, but hopefully, by working together, we can reduce complications and restore mortality rates to those of the normal population.

Further comments in Q&A

- Patients to start on pasireotide are selected depending on their glucose control at baseline. When patients have very large tumours, pasireotide and pegvisomant are used to obtain acromegaly control. A patient who has diabetes but does not have a large tumour would be a perfect candidate for pegvisomant.
- Regarding the landscape for the treatment of acromegaly in 5–10 years, the more drugs we have available, the more we can tailor treatment to patients. Some will do much better on one drug than another. The 'perfect treatment' would be an oral medication, an SRL, but it will be hard to control everybody with this: tumours do their own thing. So, we will probably need to add more combinations even though that adds to the cost.
- Rather than waiting to start treatment of comorbidities such as hypertension and arthropathies until after surgery or normalisation of growth hormone/IGF-1, it is best to treat everything aggressively before surgery. Waiting just adds to the years of complications for patients.
- Arthropathy is probably the most difficult co-morbidity to manage.

REFERENCES

1. Coopmans *et al.* 2020 *Journal of Clinical Endocrinology & Metabolism* **105** 2964–2974.
2. Fleseriu *et al.* 2020 *Pituitary* doi: 10.1007/s11102-020-01091-7.
3. Bonert *et al.* 2020 *Journal of Clinical Endocrinology & Metabolism* **105** e3236–e3245.

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